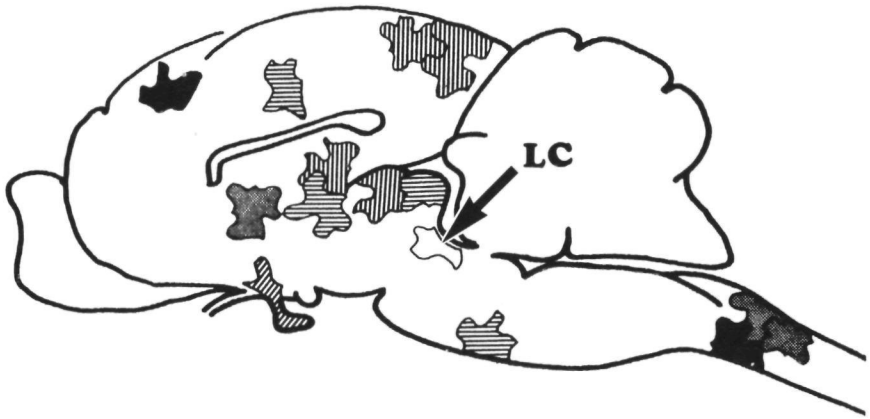
THE NORADRENERGIC LOCUS COERULEUS.

Behavioral effects of intra-cerebral injections,

and a survey of its structure, function and pathology.

Paul A.M. van Dongen

DE NORADRENERGE LOCUS COERULEUS.



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door Paul A.M. van Dongen

THE NORADRENERGIC

LOCUS COERULEUS

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PROEFSCHRIFT

ter verkrijging van de graad van doctor in de wiskunde en natuurwetenschappen van de Katholieke Universiteit van Nijmegen op gezag van de rector magnificus Prof. Dr. P.G.A.B. Wijdeveld volgens besluit van het college van decanen in het openbaar te verdedigen op donderdag 25 september 1980 des namiddags om 4.00 uur

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Table of contents.

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- Van Dongen, P.A.M., C.L.E. Broekkamp, A.R. Cools, 1978, "Atonia after carbachol microinjections near the locus coeruleus in cats", Pharmacol. Biochem. Behav. 8, 527-532.
- Van Dongen, P.A.M., C.L.E. Broekkamp, A.R. Cools, 1979, "Locus coeruleus and substantia nigra. involvement in morphine-induced behavior", Brain Res. Bull. 4, 307-311.
- Van Dongen, P.A.M., A.R. Cools, 1979, "Microinjections of opiate agonists and antagonists in the area of the locus coeruleus in cats. Effects on behavior", in "Catecholamines. Basic and Clinical Frontiers", pp. 1095-1097, eds. E. Usdin, I.J. Kopin, J. Barchas, Pergamon Press, New York.
- Van Dongen, P.A.M., 1980, "Locus ceruleus region: effects on behavior of cholinergic, noradrenergic and opiate drugs injected intracerebrally into freely moving cats", Exp. Neurol. 67, 52-78.

"The locus coeruleus is an exceptional nucleus"

Friede et al. 1963

Iijima 1977, 1978

With thanks to 64 cats, and to my own 2 cats
Iepke and Pikkie, who helped me to understand
the 64 others

SUMMARY.

Introduction. The subject of this thesis is the "locus coeruleus" (LC), a nucleus situated in the brain stem of vertebrates, containing the largest number of noradrenergic cell bodies (NE cells) in the central nervous system of mammals. The thesis contains a review of the literature on the LC (section 1 and 6), my own experimental results (section 2), theoretical consideration on structure and function in the nervous system (section 5), and general conclusions about the "function" of the LC (section 3).

1. Review of the literature on the LC (sections 1 and 6)

The LC cells (section 1.1). In man the LC is conspicious as a blue spot in the floor of the fourth ventricle; the name of this nucleus ("locus coeruleus" means "blue spot") is due to its color, which is caused by the pigment neuromelanin. The number of LC cells varies by species (in man 18,000; in the rat 1600); these cells are medium-sized and all contain norepinephrine (NE)*. In the LC a dense net of capillaries is present. The LC consists in fact of 2 parts: a dorsal part (LCd) and a ventral part (LCv).

Inputs of the LC (section 1.2). The LC receives fibers from (amongst others) hypothalamic nuclei, the reticular formation and raphe nuclei. The afferent fibers contain the activating neurosecretes acetylcholine (ACh) and substance-P, and the suppressing neurosecretes norepinephrine (NE), serotonin (5-HT) and enkephalins. Moreover, estrogens and androgens have an effect on the LC.

* This summary contains a number of rather oversimplified statements; the reader is referred to the complete text for more precise versions of these statements, their precise meanings and limitations.

The activity of the LC (section 1.3). The LC cells are most active during waking, less active during sleep, and inactive during paradoxical sleep. During waking, the LC cells are particularly active in the presence of stimuli indicating something relevant for the animal, such as food, danger, or noxious or novel stimuli. When an LC cell is active it suppresses neighbouring LC cells.

Outputs of the LC (section 1.4). The LC projects to extremely many parts of the central nervous system: I am aware of no other brain nucleus that innervates so many CNS regions. The LCd projects principally to sensory and integrative parts of the CNS such as the various cortical regions, the sensory thalamic nuclei and the cerebellum, while the LCv projects mainly to executive parts of the CNS (hormonal and motor) such as the neurosecretory hypothalamic nuclei, the cerebellum and the ventral spinal cord. Convincing evidence has been presented in the literature that NE is a neurotransmitter and a neuromodulator of the LC, while it probably also secretes dopamine-β-hydroxylase (section 4.3). The LC cells have an effect on neurons, neurosecretory cells, glia cells and cerebral capillaries. The LC cells suppress the maintained activity (which may be considered as noise) of their target neurons, while many stimulus-induced effects ("responses" or signals) remain relatively intact: the signal-to-noise ratio increases as a result of LC's activity. This LC-induced increase in the signal-to-noise ratio is accompanied by extra use of energy, and increases in the cerebral metabolism and blood flow.

The LC in neurology and psychiatry (section 6). In section 6, the findings mentioned in the literature on the involvement of the LC in a number of diseases are reviewed. The LC and/or the central NE transmission are disturbed in a number of diseases: Lewy body disease, diseases with Parkinsonian symptoms, some dementias, Hallervorden-Spatz disease, paranoid schizophrenia, bipolar depression and some forms of endogenous unipolar depression. Probably a disturbance in the LC is a cause of intellectual impairments, dementia and depression. Some speculations are done on the involvement of the LC in dreaming, hallucinations, delusions and confusions.

what was already known.....

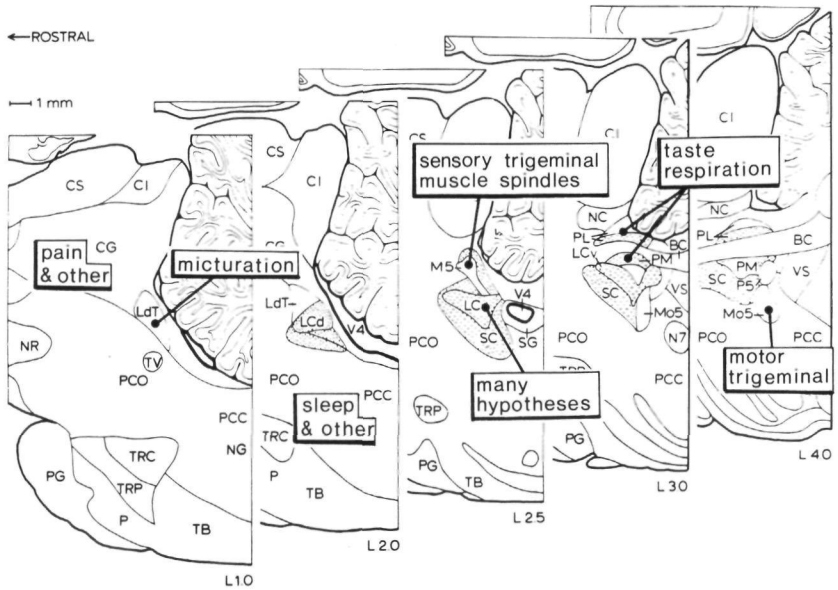


Fig. i Survey of the functional knowledge of the LC, the pontine NE cells and the adjacent dorsal pontine tegmentum, as available at the start of the current study

2. Survey of the experimental results (section 2)

Introduction. The "function" of the LC, and its involvement in behavior is investigated in the current study. Previous studies have already indicated an involvement of the LC in behavior. I have injected the activating ACh agonist carbachol and the suppressing agents clonidine (adrenoceptor agonist), and opiate agonists (morphine, fentanyl) and antagonists (naloxone) into the LC and its adjacent regions; these drugs were injected intracerebrally into freely moving cats. My results are best illustrated by comparing figures i and ii. Since a subgroup of the drug-induced effects has implications for the interpretation of these results, and for the "function" of the LC, they will be mentioned more extensively below.

and the conclusions of this study:

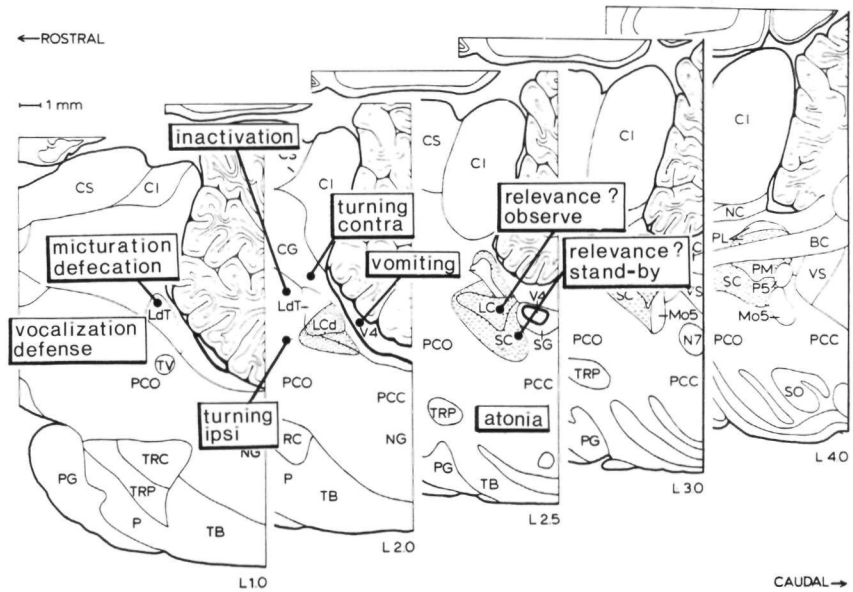


Fig.ii Survey of the functional conclusions that were drawn from the current study

The intracerebral injection technique; clonidine-induced vomiting (section 2.6). Clonidine caused vomiting when it was injected into the fourth ventricle. The amount of clonidine reaching the ventricle when injected into nervous tissue near the ventricle, was too small to cause vomiting. Since the clonidine-induced vomiting was negatively associated with the other drug-induced effects, and since published data indicate that drugs injected in a small volume (0.5 µl as used here) affect a rather restricted region (section 4.2), it has been concluded that the other drug-induced effects found in this study were not due to a proportion of the drug reaching the ventricle.

Carbachol-induced atonia and paradoxical sleep (section 2.1). An often quoted hypothesis on the "function" of the LC is that it causes the relaxation of the large postural muscles (atonia) during paradoxical sleep (PS). In this study, a similar atonia was caused by carbachol injected near the LC, but the carbachol-induced atonia is most probably not caused by the effects of carbachol on the LC cells for the following reasons: 1) it was not the LC but the more ventrally situated caudal pontine reticular formation (PCC) that was the most effective region; 2) the carbachol-induced atonia was not reduced by α- nor β-adrenoceptor blocking agents; and 3) after destruction of the LC the carbachol-induced atonia persisted. The carbachol-induced atonia and most probably also the atonia during PS, appeared to be caused by the PCC and not by the LC.

Carbachol-induced hissing and growling, anxiety (section 2.2). A recently formulated hypothesis is that the LC is involved in the production of behavior associated with fear or anxiety. In this study carbachol injected near the LC caused hissing and growling, characteristic of defense in the cat, or an expression of fear. These defense reactions were caused through the rostral pontine reticular formation (PCO) and not through the LC. Other evidence indicating that the LC is not necessary - and probably not important - for the production of anxiety/defense behavior has also been reviewed.

Carbachol-induced micturation and defecation, stress (section 2.5). In other studies, experimental bilateral destruction of the LC in animals has been reported as causing urogenital disorders and even death. Some authors have suggested that the LC reduces the organism's response to stressors; the cases of death after destruction of the LC have been considered as corroboration of this hypothesis: the LC-lesioned animals were thought to be no longer "stress-tolerant". In this study, carbachol injected near the nucleus laterodorsalis tegmenti (LdT) rather than the LC caused micturation and defecation; my findings are in line with published anatomical data that the LdT causes micturation and defecation. Since I am of the opinion that the cases of death after destruction of the LC region were due to destruction of the LdT rather than of the LC, I do not think that such data support the hypothesis of a "stress-dampening function" of the LC.

Naloxone and morphine-induced behavior (section 2.8). Cats injected with morphine (5 mg/kg i.p.) showed characteristic morphine-induced behavior: repetition of a limited series of movements, and disturbance of the senso-motor co-ordination. In this study, the cats temporarily ceased their stereotyped behavior and their senso-motor co-ordination was restored after an intracerebral injection of the morphine antagonist naloxone into the LC. The conclusion is that observation of, and reaction to, stimuli were restored by naloxone. Since morphine receptors and morphine-sensitive cells are found predominantly in the LC, I have concluded that the naloxone-induced restoration of activity of the LC caused a restoration of the observation of, and the reaction to, stimuli. In my opinion this is the best possible generalization of the LC-induced effects.

3. Theoretical considerations on the meaning of "function" (section 5)

Introduction. I have constructed a framework consisting of strictly defined concepts on structure and function of the nervous system. This was necessary since the keyword "function" appears to be used in several different meanings. Two meanings of the question "What is the function of S?" are particularly relevant in this book: 1) "What does S do?" and 2) "Why did S evolve?". Question 1 must of course be answered, before question 2 can be.

The function of brain region S. The question "What does brain region S do?" is identical to "What effects do inputs of S have on outputs of S?". This question can however be answered at different levels, for instance the molecular or cellular level. When neuroscientists ask "What is the function of brain region S?", the intended meaning is either the question "What does S do at the organ or the behavioral level?", or the question "Why did S evolve?". "What does S do at the organ or the behavioral level?" is identical to "What is represented by the inputs of S outside the CNS, and what are the effects of the outputs of S outside the CNS or outside the organism?".

4. Conclusions on the "functions" of the LC (section 3)

What the LC does at the behavioral level is identical to the generalizations of what is represented and generated by the LC cells' activity. Metaphorically, the LC cells seem to be saying: "Maybe something important is going on; observe what is going on (LCd), and stand-by to react (LCv)". One might ask why the observations and reactions are not always at maximum performance; but one should keep in mind that the LC's actions cost energy, so an economical use of the available energy resources implies that the LC maximizes the brain's performance only when certain stimuli indicate that something important might be going on. The latter statement is the answer to the question "Why did the LC evolve?". Both meanings of the question "What is the function of the LC?" have hereby been taken into consideration, and the answers which are in my opinion the best generalizations of the experimental findings have been presented.

Abbreviations.

The numbers between brackets indicate the most relevant pages.

A6	other name for "locus coeruleus" (18)
ACh	acetylcholine (28 - 29, 175 - 177)
AChE	acetylcholinesterase (176)
ACTH	adrenocorticotropin (32 - 33, 188 - 189)
AMP	adenosinemonophosphate (170)
ANG	angiotensin (32, 188 - 189)
ARAS	ascending reticular activating system (25, 142)
A&S	Amaral and Sinnamon (1977) (extensive review on the LC) (11)
ATP	adenosinetriphosphate (145, 172)
ATPase	adenosinetriphosphatase (170, 171)
BC	brachium conjunctivum (19)
CA	catecholamine
CG	central gray (19, 25, 96)
CGL	corpus geniculate laterale
ChAT	choline-acetyltransferase (28, 176)
CI	colliculus inferior (19)
CNS	central nervous system
COMT	catechol-O-methyltransferase (167)
CS	colliculus superior (19)
CSF	cerebrospinal fluid
DA	dopamine (29 - 30, 188 - 189)
DBH	dopamine-β-hydroxylase (166, 174 - 175)
DOCA	deoxycorticosteron (65)
dopa	3,4-dihydrophenylalanine
E	epinephrine (= adrenaline) (31, 188 - 189)
EEG	electro-encephalogram (60 - 61)
EMG	electromyogram (72)
End	endorphine (32 - 33, 188 - 189)
Enk	enkephaline (33, 188 - 189)
GABA	γ-aminobutyric acid (31)
Glu	glutamic acid (31)
Gly	glycine (31)
5-HIAA	5-hydroxy-indoleacetic acid
HRP	horseradishperoxidase (186 - 187, 191, 200)
5-HT	5-hydroxytryptamine (serotonin) (31, 188 - 189)
KF	nucleus of Kölliker and Fuse (24 - 25)
LC	locus coeruleus (21, 137 - 145)
LCd	locus coeruleus pars dorsalis (19, 22)
LCv	locus coeruleus pars ventralis (19, 22)
LdT	nucleus laterodorsalis tegmenti (19, 25, 99 - 102)
LHRH	luteinizing hormone releasing factor (32, 188 - 189)

β-LPH	β-lipotropin (32 - 33, 188 - 189)
M5	nucleus tractus mesencephali nervi trigemini (19, 24)
MA	monoamine
MAO	monoamineoxidase (167)
MHPG	3-methoxy-4-hydroxyphenylethylene glycol (167)
Mo5	nucleus motorius nervi trigemini (19)
MotX	nucleus motorius nervi vagi
α-MSH	α-melanocyte stimulating hormone (32 - 33, 188 - 189)
N7	nervus facialis (19)
NAD(P)	nicotinamide adenine dinucleotide (phosphate) (62)
NC	nucleus cuneiformis (19)
NE	norepinephrine (= noradrenaline) (19, 30 - 31, 165 - 174, 211 - 213)
NG	nucleus gigantocellularis (19)
NR	nucleus ruber (19)
6-OHDA	6-hydroxydopamine (76)
Oxy	oxytocin (34, 188 - 189)
P	tractus pyramidalis (19)
P5	nucleus sensorius superior nervi trigemini (19)
PB	nuclei parabrachiales (19, 24 - 25)
PCC	nucleus pontis centralis caudalis (19, 69 - 82)
PCO	nucleus pontis centralis oralis (19, 83 - 93)
PG	pontine gray (nuclei pontis) (19)
PHF	paired helical filament (274)
PL	nucleus parabrachialis lateralis (19, 24 - 25)
PM	nucleus parabrachialis medialis (19, 24 - 25)
PNMT	phenylethanolamino-N-methyltransferase (31)
PS	paradoxical sleep (40, 69 - 82)
SC	subcoeruleus region (19)
SN	substantia nigra (115 - 126)
SO	oliva superior (19)
SP	substance P (33, 188 - 189)
SWS	slow wave sleep (40, 69 - 82)
TH	tyrosine hydroxylase (29 - 30, 166)
TRC	nucleus reticularis tegmenti pontis, pars centralis (19)
TRH	thyrotropine releasing factor (32, 188 - 189)
TRP	nucleus reticularis tegmenti pontis, pars pericentralis (19)
TV	nucleus tegmenti ventralis (Gudden) (19)
V4	fourth ventricle (19, 103 - 108)
Vaso	vasopressin (34, 188 - 189)
VIP	vaso-active intestine peptide (34)
VL	nucleus vestibularis lateralis (19)
VS	nucleus vestibularis superior (19)
VTA	area ventralis tegmenti (115 - 126)
W	waking (40, 69 - 82)

0. GENERAL INTRODUCTION.

GENERAL INTRODUCTION

Noradrenergic neurons in the locus coeruleus. The Locus coeruleus (LC) is a small nucleus in the dorsolateral part of the pontine tegmentum (Maeda et al. 1973, Ramon-Moliner and Dansereau 1974a,b, Toyama et al. 1978). Since the discovery that the LC contains the largest number of noradrenergic cell bodies (NE cells) in the central nervous systems (CNS) (Dahlström and Fuxe 1964, Swanson and Hartman 1975, Amaral and Sinnamon 1977), anatomical and functional investigations into the LC have become a rage in science.

Reviews. Nine review articles have been devoted to the LC (Sano 1941, Russel 1955, Amaral and Sinnamon 1977, Nakamura and Iwama 1978, Shimizu 1978, Clark 1979, Ramm 1979, Mason 1979c, Moore and Bloom 1979), 3 of which are unfortunately in Japanese. To avoid exceptionally extensive quotation of references in this book, reference will frequently simply be made to Amaral and Sinnamon's (1977) extensive review, indicated by A&S and a section number. More recent publications or articles of special relevance to the subjects treated here will however be specifically mentioned. Some aspects which were not extensively discussed in these reviews will receive more emphasis in this book: these are an overview of afferent and efferent fibers, afferent putative neurosecretes, structure of inputs and outputs, intrinsic LC circuitry, varicosities as terminals, NE and dopamine-β-hydroxylase (DBH) as neurosecretes of the LC (with a survey of the electrophysiology) and the LC in neurology and psychiatry.

Summary of the composition of this book. The first 3 of the 6 sections of this book have been composed as a coherent entity (see fig. 1).

1. Section 1 reviews the data in the literature on morphology (section 1.1), inputs (section 1.2), intrinsic information processing (section 1.3) and outputs of the LC (section 1.4). (The main subdivision is not the usual - anatomy, neurochemistry and electrophysiology -, but is related to a system approach - input, transfer function and output -.) The choice is made to present a complete but inevitably dull survey of the data in the literature (tables to be found in section 4.6), and a clear, easy to read summary and interpretation of these data (text of section 1).

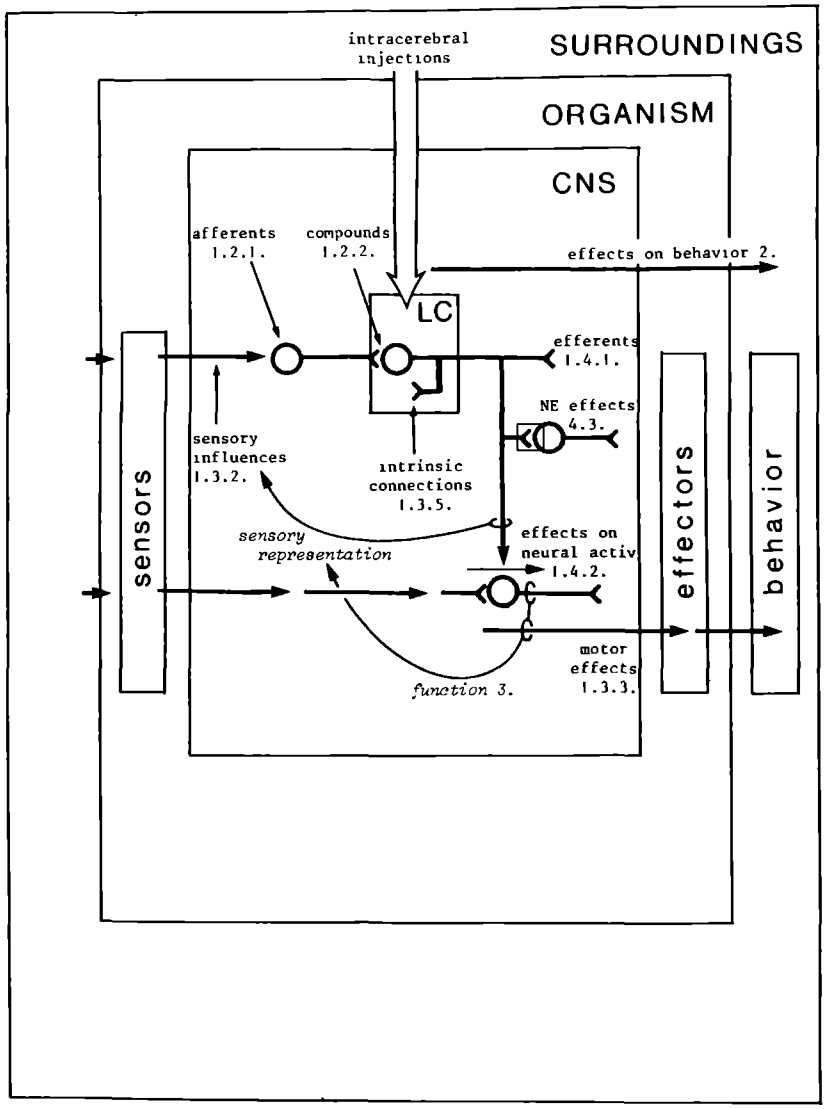


Fig. 1 Diagram of this book; the numbers refer to the sections in which the various subjects are discussed.

2. My experimental results and a discussion of them is presented in section 2: "Experimental results of intracerebral injections".
3. In the general discussion (section 3), some "functions" attributed in the literature to the LC are discussed, followed by a presentation of my functional hypothesis on the LC.
4. The research methods employed, methodological considerations and most tables (7-16) are presented as separate appendices in section 4.
5. Section 5 deals with theoretical aspects of structure and function in the CNS; these considerations were necessary as a basis for my functional hypothesis.
6. The involvement of the LC and the central NE transmission in neurologic and psychiatric diseases is reviewed in section 6.

Pure and applied research. Most of this book deal with pure, non-applied research. Present knowledge about the relevance of the LC and the central NE transmission is too limited for selective therapeutic action, and the syndrome concomitant with disfunction or destruction of the LC, or with manipulation of the central NE transmission in man and animals is complex. A number of drugs, known or suspected to affect the central NE transmission (which reflects mainly the LC activity) quite directly, are used in the treatment of hypertension (clonidine and propranolol), depression (tricyclic antidepressiva), Parkinson's disease (*l*-dopa), psychotic manifestations (haloperidol) and opiate-withdrawal (clonidine). An advance in our knowledge of the LC and the central NE transmission should contribute to the production and application of centrally acting drugs that are more selective therapeutically.

1. REVIEW OF THE LITERATURE ON THE LOCUS COERULEUS.

1.1. The locus coeruleus and the dorsal pontine tegmentum.

SECTION 1.1. TABLE OF CONTENTS

1.1.1. MORPHOLOGY OF THE NORADRENERGIC LOCUS COERULEUS

Pontine NE cells. Cells have been found in the rostrolateral part of the rhombencephalic tegmentum of all vertebrates studied that show green formaldehyde- or glyoxylic acid-induced fluorescence: catecholamine-containing cells (CA cells) (Tohyama 1976). In the rat it has been demonstrated that the CA is norepinephrine (NE)* (section 4.3.1.) and this is most probably the case in the cat and in man (Jones et al. 1977, Farley and Hornykiewicz 1977, Marchand et al. 1979a,b). The NE-containing cells (NE cells**) in the pons of mammals might be homologue with the NE cells in the rostral rhombencephalon of other vertebrates (but see Tohyama 1976).

* Where it has been shown that the CA involved is norepinephrine, the word "norepinephrine" (NE) is used; when the CA involved can be either norepinephrine (NE) or epinephrine (E), the word "(nor)-epinephrine" ((N)E) is used. Receptors for which the presumed endogenous ligand is either NE or E are called "adrenoceptors"; in the CNS pharmacological criteria have not been established as yet to distinguish adrenoceptors with NE as the endogenous ligand from those with E as the endogenous ligand, cf. Cedarbaum and Aghajanian 1977, 1978b.

** For a discussion on whether NE cells do actually release NE as a neurotransmitter, see section 4.3.1.

A proportion of the NE cells in the dorsal pontine tegmentum are clustered in a distinct compact cell group, generally called the "locus coeruleus" (LC)*. In this histochemically demarcated LC non-NE cells are also found (see below), and the NE cells are also found scattered in the pontine tegmentum outside the LC. The localization of the LC and the pontine region containing NE cells is shown in fig. 2.

The LC in mammals. In all the mammals studied a LC has been identified either as compactly aggregated CA cells (marsupials, Crutcher and Humbertson 1978; lagomorphs, Blessing et al. 1978; rodents, A&S, 2.2.1.; primates, A&S, 2.2.3., Jacobowitz and MacLean 1978) or as more scattered CA cells intermingled with non-CA cells (carnivores, Pin et al. 1968, Maeda et al. 1973, Jones and Moore 1974, Chu and Bloom 1974, Ishikawa et al. 1975, Poitras and Parent 1978). Although in all the mammals studied the LC could be identified as a distinct nuclear mass (Russell 1955, A&S 1.), this does not necessarily imply that it is also an entity with regard to its afferent and efferent connections and its "function" (see below "Subdivision of the LC").

Pigmentation. In man and other primates the LC is macroscopically visible as a blue spot in the floor of the fourth ventricle. This blue color is due to the pigment neuromelanine (A&S 2.5.), which is present only in medium-sized LC cells and not in small ones (Forno and Alvord 1974). Neuromelanine is present in CA neurons (Bazelon et al. 1967), and it consists (among others) of chains of non-enzymatically oxidized CAs (Hirosawa 1968, Barden 1969, Rodgers and Curzon 1975, Graham 1978, 1979). Neuromelanine is different from the enzymatically (tyrosinase) formed skin pigment melanine (see Barden 1969), and it is present in the CA cells of albino animals and man (Foley and Baxter 1958, Kastin et al. 1976).

Names of the LC. In the course of time the (nucleus) locus coeruleus (also spelled caeruleus and ceruleus) has had different names (cf. Berman 1968): "substantia ferruginea", "nucleus pigmentosus pontis", "nucleus laterodorsalis tegmenti" (Nomina anatomica 1966), "nucleus dorsolateralis tegmenti" (Russell 1955), and group "A6" (Dahlström and Fuxe 1964).

* For a more precise definition of "LC", see page 21.

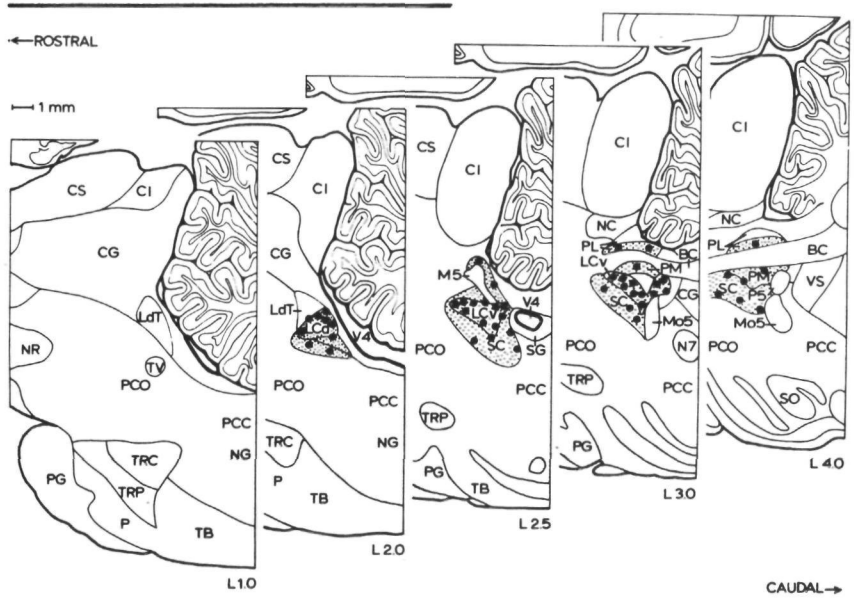


Fig. 2 Localization of the pontine NE cells in the cat, drawn in parasagittal planes, after Berman (1968); the demarcation lines are based on clustering of cells in Nissl-stained sections. The localization of the pontine NE cells was reconstructed from the figures in Pin et al. (1968), Maeda et al. (1973), Jones and Moore (1974), Chu and Bloom (1974) and Poitras and Parent (1978); for abbreviations see pp. 6-7.

The names "LC" and "nucleus laterodorsalis tegmenti" (LdT) have not in this thesis been treated as synonymous: the LC is the distinct nucleus of clustered NE cells in the dorsolateral pontine tegmentum, and the LdT is the nucleus immediately rostromedial to the LC; it can be clearly distinguished from the LC in cholinesterase stained preparations (cf. Maeda et al. 1973, Koelle et al. 1954, Butcher et al. 1977).

Form of the LC cells. The NE cells in the dorsal pontine tegmentum are of medium size; it is probable that all medium-sized LC cells of the rat are NE cells (Swanson 1976b, Shimizu et al. 1979). Two types of NE cells have been described, smaller fusiform cells and larger multipolar cells; both types occur in the LC (A&S 2.2., Grzanna et al. 1977, Shimizu et al. 1978).

Both cell types have long dendrites that branch once or twice and extend outside the boundaries of the LC, especially in the medioventral direction (Swanson 1976b, Shimizu 1978). Spine-like protrusions are found, on which synapses occur, on the dendrites as well as on the somata (A&S 2.3, Tatemichi and Ramon-Moliner 1975, Shimizu et al. 1978). The somatic spines have even been used to distinguish NE cells from non-NE cells (Shimizu et al. 1978). The dendrites of the NE cells contain vesicles similar to exocytotic vesicles with NE and dopamine-β-hydroxylase (DBH) (A&S 2.3, Cimarusti et al. 1979), and these NE-containing dendrites make close contacts with the dendrites and somata of other NE cells (Shimizu et al. 1979). The axons of the LC cells are very thin (0.35 μm, Beaudet and Descarries 1978), and the proximal parts of the axons of the NE cells give off very fine collaterals within the LC (Shimizu and Iwamoto 1970, Swanson 1976b, Shimizu et al. 1978, 1979). Some of these collaterals seem to make contact with the dendrites of other NE cells (Shimizu et al. 1978, 1979): recurrent collaterals. NE terminals are in close contact with the dendrites and somata of the NE cells, but synaptic specializations have not been found (Shimizu et al. 1979). An axon making contact with its cell body of origin has never been described. For further morphological details, the reader is referred to A&S 2. and 2.3.

Non-NE cells in the LC. The monoamine-containing cells (MA cells) of the LC are medium-sized (Dahlström and Fuxe 1964, Swanson and Hartman 1975). Most of the MA cells of the LC are noradrenergic (at least in rodents, primates and carnivores; cf. A&S 2.2. and section 4.3.1); a small fraction of them contain 5-hydroxytryptamine (5-HT or serotonin; cat and monkey, Sladek and Walker 1977, Legér et al. 1978a, Pickel et al. 1977a), or epinephrine (E, monkey, Pearse et al. 1979), but in the rat all MA cells are NE cells. The LC of all mammals investigated also contains small cells (Ramon-Moliner 1974, Swanson 1976b, Shimizu et al. 1978, 1979), which are probably non-MA cells. Since these small cells are occasionally in direct contact with NE cells (Shimizu et al. 1979), they might be LC interneurons. Some cells in the LC contain neurotensin (Uhl et al. 1979b) or substance P (SP) (Ljungdahl et al. 1978a). At present it is uncertain whether the neurotensin or SP cells also contain NE. Some peripheral NE cells also contain somatostatin (Hökfelt et al. 1977c), but no somatostatin cell bodies have been described in the LC (Hökfelt et al. 1978a, Finley et al. 1978). The following compounds are not found in the

cell bodies of the LC, although the technique used was sensitive enough to detect these compounds in other cell bodies: thyrotropin releasing factor (TRH), luteinizing hormone releasing factor (LHRH), angiotensin II (ANG II), β-lipotropin (β-LPH), β-endorphin (β-End), adrenocorticotropin (ACTH), α-melanocyte stimulating factor (α-MSH), enkephalins, vasopressin, oxytocin, somatostatin, vasoactive intestine peptide (VIP) and gastrin (cf. section 1.2.2 for references).

Definition of the "Locus coeruleus". When a CNS region is investigated, a basic question is whether it is an "entity"* (or "system", cf. section 5.2.2) according to anatomical, neurochemical and physiological criteria. I am of the opinion that the pontine NE cells do not form an entity together with the numerous non-NE cells which are found intermingled with them (Ramon-Moliner (1974) regarded these non-NE cells as displaced cells of the central gray and/or reticular formation). I assume however that the pontine NE cells which are clustered in a distinct nucleus do form an entity (neurochemically they are an entity, and also some anatomical and physiological evidence has been presented that these cells are similar, cf. sections 1.2, 1.3.2 and 1.4.1). For these reasons, the following definitions are proposed and used throughout this book:

Locus coeruleus (LC) = the NE cells of the dorsal pontine tegmentum clustered in a distinct nucleus

Locus coeruleus region = that region of the dorsal pontine tegmentum in which the NE cells are clustered; the LC region contains NE and non-NE cells.

Should future research indicate that some or even all non-NE cells in the LC region are interneurons of the LC NE cells, it would have to be concluded that the NE cells, together with their non-NE interneurons, form an entity.

* An "entity" is a "coherent collection of elements"; this is often called a "functional system", but the latter term will be avoided (cf. section 5.2.4, p. 243). An entity is only defined for a specified "level" (section 5.3) of investigation. An entity can be divided into smaller entities (subsystems), or be part of a larger entity.

Subdivision of the LC. Two types of LC cells have been distinguished: smaller fusiform cells and larger multipolar cells (see above). The fusiform cells are situated in the dorsal part of the LC, "LCd", and the multipolar cells are situated in the ventral part of the LC, "LCv" (also called LC pars alpha, LCα) and are also scattered ventrally to the LCv in the subcoeruleus region (SC)*. A subdivision of the LC in LCd and LCv is also suggested on the basis of the afferent and efferent fibers and interaction with hormones (sections 1.2.1, 1.2.2, 1.2.3, and 1.4.1). Table 1 provides a summary of the subdivision of the pontine NE cells into different subsystems. Further anatomical and electrophysiological research is required to determine which subdivision is most appropriate, or in other words, which subsystems are really entities.

Table 1

Subdivision of the pontine NE cells into different subsystems as proposed by various authors

Amaral and Sinnamon 1977		Grzanna and Molliver 1980	
rostral group	subsystem 1	rostral group	subsystem 1
A4	subsystem 1	A4	subsystem 2
LCd	subsystem 1	LCd	subsystem 3
LCv	subsystem 2	LCv	subsystem 4
subcoeruleus	subsystem 2	subcoeruleus	subsystem 5

* The concept "subcoeruleus region" is employed inconsistently in the literature (cf. A&S 2.2.1); in this book, SC is the region in the pons ventral to the LC where NE cells are located; under this definition SC is identical to A7.

Number of LC cells. There are some 1600 LC cells in the rat, 7500 in the rhesus monkey (A&S 2.2.3.), and 18.000 in man (Brody 1976). In the rat, the LCd contains 1400 cells and the LCv 200 cells (Swanson 1976b).

Vascularization. A dense capillary bed has been observed in the LC of the rat and the monkey (but, as yet, not in the cat) (A&S 2.4.). The cell bodies and dendrites of LC NE cells of the rat and monkey appear to be very close to capillaries or small arterioles (Finley and Cobb 1940, Felten and Crutcher 1979), microvilli protruding from the blood vessel wall into the lumen are present (Shimizu and Iwamoto 1970). At the moment it is not certain whether these microvilli are specialized in reacting to compounds in the blood, or in releasing compounds into the blood; since no vesicles characteristic of exocytosis are present near the lumen however (Shimizu and Iwamoto 1970, Felten and Crutcher 1979), it is probable that the capillary bed is an input channel of the LC. Some other highly vascularized brain regions appear to be extra-blood-brain-barrier regions (area postrema, subfornical organ, nucleus supraopticus), but there are no indications that the LC is itself an extra-blood-brain-barrier region (Koella and Sutin 1967). A comparable neuronal-vascular relationship is also found in the serotonergic raphe nuclei and in the dopaminergic substantia nigra (Felten and Crutcher 1979).

1.1.2. THE "FUNCTION" OF THE REGIONS ADJACENT TO THE LC

Introduction. The function* of the regions surrounding the LC will be mentioned briefly. Since it is almost impossible to affect only the LC leaving its surrounding regions unaffected (section 4.2), some knowledge of the function of these areas is necessary for an interpretation of functional investigations. For the demarcation of the nuclei in the dorsolateral pontine tegmentum see Tohyama et al. 1978 and fig. 2, and for a survey of functions see fig. 3.

* The meaning of "function" will be defined in section 5.2.4; here it is used in the meaning "the activity in which this region is primarily involved".

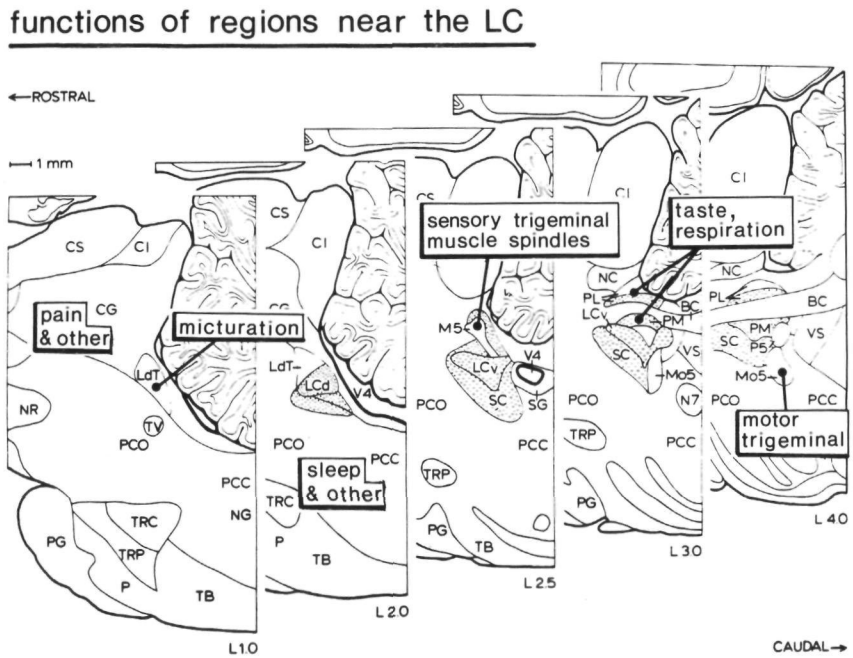


Fig. 3 Functions of regions adjacent to the LC. In this figure, only those "functions" are indicated which are generally accepted as being the "functions" of the regions indicated.

The nucleus mesencephalicus nervi trigemini (MesV). Since the neurons of the MesV are the cell bodies of the muscle spindle afferents of the trigeminal nerve, the function of MesV is receiving and transmitting primary sensory, trigeminal muscle spindle information.

The parabrachial nuclei (PB) and the nucleus of Kölliker and Fuse (KF). In the literature 2 broadly accepted ideas on the function of the PB and KF are to be found: taste and respiration. Taste. The n. parabrachialis medialis (PM) and KF are the relay stations of gustatory information from the nucleus solitarius to the thalamic taste region and the amygdala (Norgren and Leonard 1973, Nomura and Mizuno 1979). Respiration. The PM and KF are regarded as the pontine pneumotaxic center (Bertrand and Hugelin 1971, Bertrand et al. 1973, Vibert et al. 1979, Riche et al. 1979,

Cohen 1979). The extent of the pneumotaxic center is however not simply related to the PM and KF; the region in which pneumotaxic neurons are found does not co-incide with known anatomical regions (cf. Bertrand and Hugelin 1971).

The nucleus laterodorsalis tegmenti (LdT). The laterocaudal part of the LdT projects to the sacral spinal cord, and probably is the pontine micturation center (Satoh et al. 1978a,b, Loewy et al. 1979a); this area is identical to the "Barrington nucleus" (Tohyama et al. 1978).

The pontine reticular formation. The most often quoted function of the reticular formation is the regulation of sleep-wakefulness levels. Manipulations in the pontine reticular formation cause so-called "a-specific", generalized effects (arousal, attention), which led to the concept of the "ascending reticular activating system", and so-called "specific" effects such as eating, drinking, gnawing, pain, changes in respiration and blood pressure, vocalization, attack, defense, grooming and effects associated with motor acts (e.g. Waldbillig 1975, Siegel and McGinty 1978, Bertrand et al. 1973). In my opinion, the reticular formation is not an entity (or a single system), but an aggregate of several systems, which happen to be spatially intermingled, are difficult to delineate anatomically, and which have different functions, some "generalized" and some "specific".

The griseum centrale (CG). Like the reticular formation, the CG is involved in many functions. The most often quoted is the involvement of the ventromedial part of the CG in pain (Kerr and Casey 1978, Schenberg and Graeff 1978), but the following effects are also elicited by manipulations in the CG: vocalization (dorsal and dorsolateral part), self-stimulation (ventral part), escape or defense reactions (dorsal part), respiration, arousal, head and body movements, locomotion, copulation and suppression of the ongoing behavior (Jürgens and Ploog 1970, Wolfle et al. 1971, Bertrand et al. 1973, Waldbillig 1975, Keene and Figueroa 1977, Schenberg and Graeff 1978, Jürgens and Pratt 1979, Sakuma and Pfaff 1979). In my opinion, a subdivision of the CG in a number of systems is necessary for functional statements.

1.2. Inputs of the LC.

SECTION 1.2. TABLE OF CONTENTS

1.2.1. AFFERENT FIBERS OF THE LC

A complete survey of the regions reported as projecting to the LC is presented in table 6 (p. 186) and a generalized and simplified outline is given in fig. 4. Three major groups of afferents are present:

1. hypothalamic so-called neurosecretory nuclei (Hayward 1977): n. paraventricularis, n. arcuatus, n. supraopticus, n. suprachiasmaticus and n. perifornicalis.
2. reticular and raphe nuclei: especially in and around the n. reticularis lateralis (A1 group) and around the nucleus solitarius (A2 group) and in the nuclei raphes dorsalis and pontis.
3. Some sensory nuclei: in particular the vestibular nuclei, the solitarius complex and the spinal trigeminal nucleus; in one HRP study (Gupta et al. 1977), it is suggested that the quantitatively most important afferent connections come from sensory nuclei (visual, auditive, somatosensory and visceral). This is in line with electrophysiological data (section 1.3.2), but it is not in agreement with other HRP studies.

In addition, the following are also found: 4. the cerebellar n. fastigii, 5. a few commissural fibers from the contralateral LC and other parabrachial nuclei, and 6. the area ventralis tegmenti.

No afferent fibers to the LC have been described from 1. the thalamus, and 2. the basal ganglia. The suggestion of Sakai et al. (1977) that the LCd would receive input almost exclusively from the n. raphes dorsalis seems rather extreme to me, and indeed the method used (retrograde HRP transport)

Afferent connections of the LC

Fig. 4 Regions projecting directly to the LC. The contours are redrawn after Nieuwenhuys et al. 1979.
1. N. interstitialis striae terminals, 2. Nn. preoptici, 3. N. paraventricularis, 4. N. lateralis hypothalami, 5. N. perifornicalis, 6. N. arcuatus, 7. N. raphes dorsalis, 8. N. fastigii, 9. N. raphes pontis, 10. around N. reticularis lateralis (A1 catecholaminergic cell group), 11. around N. solitarius (A2 catecholaminergic cell group).

does not justify such a conclusion. Moreover, it is indicated that the projection from the n. interstitialis striae terminalis is also mainly to the LCd (Swanson and Cowan 1979).

The structure of the afferent connections*. Data about the structure of the afferent connections to the LC are unfortunately not available, since it would be interesting to know more about the topography of the afferent connections: are these projections topical, ordered non-topical, or random? (cf. section 1.4.1, fig. 14). If the projections are random, the LC cells are equal and interchangeable with regard to their afferent fibers.

1.2.2. PUTATIVE NEUROSECRETES IN AFFERENT TERMINALS IN THE LC

The putative neurosecretes** in afferent terminals in the LC are summarized in table 7 (p. 188). Comments on the techniques used and the interpretation of table 7 are given there.

Acetylcholine (ACh). ACh and its synthetizing and degrading enzymes (cholineacetyltransferase (ChAT) and acetylcholine-esterase (AChE) respectively) are present in the LC; their ratio to one another is an indication that the LC cells are cholinoceptive (A&S 2.2.1., cf. Guyenet and Aghajanian 1979, Albanese and Butcher 1979). (The relevance of the AChE in the NE cell bodies will be discussed in section 4.3.3.) The technique available for mapping of cholinergic neurons is less reliable: ChAT-immunochemistry is specific but less sensitive, while AChE-histochemistry is sensitive but less specific (cf. Lewis and Shute 1978, McGeer and McGeer 1979, Lehmann and Fibiger 1979). In any case, neurons demonstrated as cholinergic contain histochemically determinable AChE (Lehmann and Fibiger 1979), for this reason regions are called "ACh +" in table 7 when AChE is found in their cell bodies (Parent et al. 1978,

* The concept "structure of input" might seem to be an inconsistent use of these words (cf. section 5.2.2), but the inputs of system S might be an entity, a system S', and the concept "structure of S'" is defined and implies a consistent use of words.

** For definitions of "(putative) neurosecrete", "neurotransmitter" and "neuromodulator", see section 4.3; the unsatisfactory collective term "neuroregulator" for neurotransmitter and neuromodulator (Barchas et al 1978, Watson et al. 1978) has been avoided.

Poitras et al. 1978, Butcher et al. 1978). ACh causes activation* of the LC cells (Bird and Kuhar 1977, Kuhar et al. 1978, Guyenet and Aghajanian 1977, 1979) via muscarinic receptors (cf. Kobayashi et al. 1978); this activation is not influenced by opiate antagonists (Guyenet and Aghajanian 1979)**.

Dopamine (DA). DA and its synthetizing and degrading enzymes (tyrosine-hydroxylase (TH), and monoamineoxidase (MAO) and catechol-O-methyl-transferase (COMT) respectively) are present in the LC (A&S 2.2.1., Saavedra et al. 1976b); these enzymes and DA itself are however also present in the NE- and epinephrine-containing cells, so that extra evidence is necessary before it can be concluded that the LC is dopaminoceptive. A source of such DA terminals*** is probably the area ventralis tegmenti

* The words "activation" and "suppression" are used, when in extracellular single cell recordings respectively an increase or a decrease in the firing rate in the maintained activity is found. The words "excitation" and "inhibition" are used, when in intracellular single cell recordings respectively a depolarization or a hyperpolarization is found with a concomitant increase or decrease in the maintained and evoked activity (cf. Van Gisbergen et al. 1974). Reasons are presented (sections 1.4.2 and 4.3) that the idea that the influence of one neuron on its target neuron is either excitation or inhibition, is an inadequate and incomplete description of the various effects of a neuron on its target neuron. The presently available knowledge on the effects of putative neurosecretes on the LC cells is however limited to the outcome of extracellular recordings, so the description is limited to the concepts "activation" and "suppression".

** This indicates that the effects of ACh are not mediated via an opiate receptor, so that 3 of the possible models for the action of ACh (fig. 5) are rejected. The influence of certain antagonists on the action of other putative neurosecretes is mentioned also as excluding some models of the action of these putative neurosecretes.

*** In this book, "terminal" is used of each enlargement of an axon containing vesicles with the appearance of exocytotic (neurosecretory) vesicles; "synaps" is a terminal with specializations of the membranes of the terminal and/or the target cell. Not all terminals are synapses so the words "presynaptic" and "postsynaptic" are not always appropriate; they are not used here, and "of the terminal" and "of the target cell" are used respectively instead.

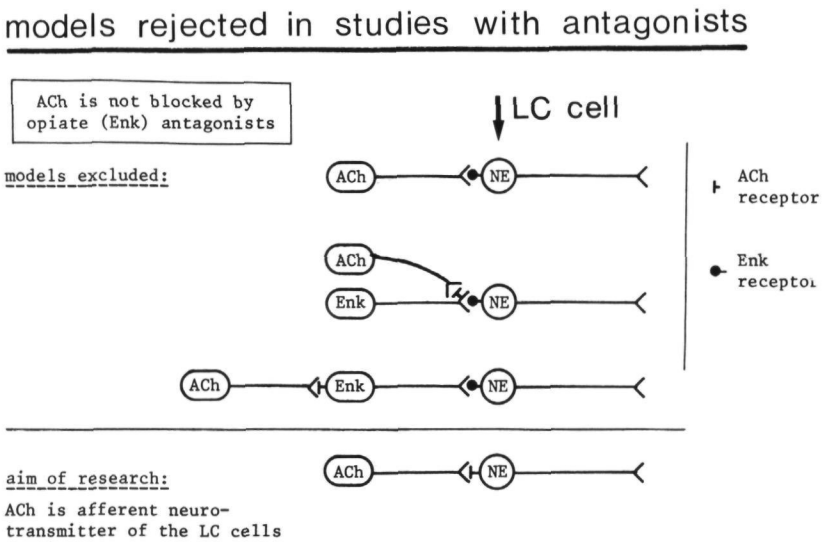


Fig. 5 Models of interactions of various putative neurosecretes tested in studies of antagonists' action. Examples of models which might be rejected when the response to neurosecrete A (here ACh) is not blocked by antagonists of the receptors of neurosecrete B (here Enk) are given.

(A10), while also the substantia nigra pars compacta (A9) and the hypothalamic n. arcuatus might give off DA terminals to the LC. DA causes suppression of the LC, but the receptors involved are pharmacologically characterized as α_2-adrenoceptors (Cedarbaum and Aghajanian 1977a). It is still uncertain whether the LC receives a dopaminergic input.

Norepinephrine (NE). The LC is not only noradrenergic (sections 1.1 and 4.3), but also noradrenoceptive: NE terminals make contact with the dendrites and cell bodies of the LC neurons without synaptic specializations. NE-containing dendrites also make close contacts with LC cells (Shimizu et al. 1979). The most important source of these NE terminals are the adjacent LC cells (see sections 1.1 and 1.3.3), but other possible sources are the contralateral LC and SC (A4, A6 and A7), and the regions around the nucleus lateralis reticularis (A1), the nucleus solitarius (A2) and the region dorsal to oliva superior (A3). NE causes suppression of the LC cells via α_2-adrenoceptors (Cedarbaum and Aghajanian

1977, Guyenet and Aghajanian 1977, Svensson and Usdin 1978, Young and Kuhar 1979), this suppression is not influenced by opiate antagonists (Aghajanian 1978). The NE-induced suppression of the LC cells is at least partly lateral suppression (section 1.3.3).

Epinephrine (E). E, its precursors and its synthetizing and degrading enzymes (TH, DBH and phenylethanolamino-N-methyltransferase (PNMT), and MAO and COMT) are present in the LC (A&S 2.2.1., Saavedra et al. 1976a). Regions which possibly project to the LC, and contain E cell bodies are around the nucleus reticularis lateralis (A1 or C1) and the nucleus tractus solitarii (A2 or C2). E fibers project to the LCv (Hokfelt et al. 1974). E causes suppression of the LC cells via α_2-adrenoceptors in the same way as NE does (Cedarbaum and Aghajanian 1977).

5-Hydroxytryptamine (5-HT, serotonin). Terminals containing 5-HT and its synthetizing enzyme are also found in the LC (Pickel et al. 1977a, Leger and Descarries 1978). None, or few, of the 5-HT terminals make synaptic contacts with identified LC* cells. most of the 5-HT terminals end without synaptic specializations (Pickel et al. 1977a, Leger and Descarries 1978). Most (87%) 5-HT in the LC is present in terminals of neurons of the nucleus raphes dorsalis (Palkovits et al. 1977c, cf. table 7). 5-HT causes suppression of the LC cells (Segal 1979).

γ-Aminobutyric acid (GABA) A fairly large proportion (44%) of the terminals in the LC accumulate ^{3}H-GABA (Iversen and Schon 1973), and are therefore probably GABAergic (Roberts et al 1976b), if these terminals actually are GABAergic, GABA would be quantitatively the most important putative afferent neurotransmitter to the LC cells. The origin of the GABA fibers in the LC is uncertain, it may be that the cerebellar cortex projects to the LC (Snider 1975, but not Sakai et al. 1977, Cedarbaum and Aghajanian 1978a), the cerebellar Purkinje cells are GABAergic (cf Roberts et al. 1976). GABA causes suppression of the LC cells; which is not affected by muscarinic, α_2-adrenoceptor, or opiate antagonists (Cedarbaum and Aghajanian 1977, Guyenet and Aghajanian 1979).

* The term "identified LC cells" is used, when extra histological evidence is presented that the neurons in the LC region really contain NE.

Glutamate (Glu). Glu causes activation of LC cells; this activation is not affected by muscarinic antagonists (Guyenet and Aghajanian 1979). The Glu innervation of the LC has not been further investigated, so it is at the moment uncertain whether the response to Glu is specific, and whether Glu terminals are present. Apart from the hippocampus, no region possibly projecting to the LC is described as glutaminergic (cf. table 7, and Curtis and Johnston 1974, Storm-Mathisen and Opsahl 1978).

Glycine (Gly). Gly suppresses the LC cells; this suppression is not affected by α_2-adrenoceptor antagonists (Cedarbaum and Aghajanian 1978b). The evidence that the LC is glycinoceptive is incomplete.

Thyrotropin releasing factor (TRH). In the LC sparse, single TRH fibers have been described (Hökfelt et al. 1978a). The regions which possibly project to the LC and contain TRH cell bodies, are the nucleus dorsomedialis hypothalami and the nucleus perifornicalis. Cells in the LC do not react to TRH applied iontophoretically (Guyenet and Aghajanian 1977).

Luteinizing hormone releasing factor (LHRH). LHRH fibers have been described near the LC (Silverman and Krey 1978), but it is not certain whether they actually occur in the LC. The regions which possibly project to the LC and contain LHRH cell bodies are the basal hypothalamus (nucleus arcuatus and area retrochiasmatica), the nucleus preopticus medialis and the nucleus medialis septi (cf. table 7 and Hökfelt et al. 1978a, Silverman and Krey 1978).

Angiotensin II (ANG II). ANG II terminals occur in the LC at a low to moderate density (Fuxe et al. 1976b, Chaugaris et al. 1978). The regions which project to the LC and contain ANG II cell bodies, are the nucleus paraventricularis and the area perifornicalis (Hökfelt et al. 1978a).

β-Lipotropin (β-LPH), endorphins (End), melanocyte stimulating factor (MSH) and adrenocorticotropin (ACTH). β-LPH, MSH, End and ACTH occur predominantly in the same cells and even in the same vesicles (Watson et al. 1978, Sofroniew 1979, Bugnon et al. 1979a,b,c, Pelletier 1979); these cell bodies are located in and rostrolaterally to the nucleus arcuatus (cf. table 7). Cells containing α-MSH only, however, have been described in other CNS regions (Swaab and Fisser 1978, Watson and Akil 1979b, but not Jacobowitz and O'Donohue 1978). It is probable that the fibers containing peptides of the LPH series terminate near but not in the LC (cf. Watson et al. 1978, Bloom et al. 1978, Jacobowitz and O'Donohue 1978,

Pelletier and LeClerc 1979, O'Donohue et al. 1979b). The LPH cells of the nucleus arcuatus are not identical to the DA cells of the nucleus arcuatus (Bugnon et al. 1979c).

The enkephalins (Enk). The enkephalins are peptides related to those of the β-LPH series. Over 20 regions have been reported as containing Enk cell bodies (Hökfelt et al. 1977b, Simantov et al. 1977, Uhl et al. 1979a, Glazer and Basbaum 1979), while only a single region (in an near the nucleus arcuatus) contains β-LPH cell bodies. Leucine-enkephalin (Leu-Enk) and methionine-enkephalin (Met-Enk) have a similar distribution, but they are found in different neurons (Hökfelt et al. 1977, Simantov et al. 1977, Larsson et al. 1979). Enk fibers occur in the LC at a moderate density (Simantov et al. 1977, Uhl et al. 1979a), forming predominantly asymmetric synapses on the dendrites of identified LC cells (Pickel et al. 1979). A high density of Enk (opiate) receptors has been described in the LC (Pert et al. 1976, Atweh and Kuhar 1977b, Kuhar 1978). Enk cell bodies are present in the so-called hypothalamic neurosecretory nuclei and in many other regions (cf. table 7, Hökfelt et al. 1977, Uhl et al. 1979a, Glazer and Basbaum 1979). Enk (and morphine) causes suppression of the LC cells (Bird and Kuhar 1977, Young et al. 1977, Guyenet and Aghajanian 1977, 1979, Aghajanian 1978); such suppression is not affected by muscarinic or by α_2-adrenoceptor antagonists.

Substance P (SP). The LC contains a few SP cell bodies and a medium-dense network of SP fibers and terminals (Ljungdahl et al. 1978b); asymmetric SP synapses have been described on the dendrites of identified NE cells of the LC (Pickel et al. 1979). More than 30 regions contain SP cell bodies (Ljungdahl et al. 1978a), some of which possibly project to the LC: these regions include the nucleus solitarius, raphe nuclei and the so-called hypothalamic neurosecretory nuclei and many other nuclei (cf. table 7, Ljungdahl et al. 1978a). 5-HT and SP occur together in single neurons as well as separately in the raphe nuclei pallidus, obscurus and magnus (Hökfelt et al. 1978b, Chan-Palay et al. 1978, Chan-Palay 1979), but morphological differences have been described between SP and 5-HT terminals in the LC (cf. Pickel et al. 1977a, 1979, Leger and Descarries 1978), so it is probable that these compounds do not occur in the same terminals in the LC. Moreover, in contrast to 5-HT, SP and related peptides cause activation of the LC cells; this activation is not influenced by muscarinic or by opiate antagonists (Guyenet and Aghajanian

1977, 1979).

Neurotensin. The LC contains a few neurotensin cell bodies, fibers and terminals (Uhl et al. 1979b). These terminals may have their cell bodies either in and around the nucleus reticularis lateralis, the nucleus raphes dorsalis, or the contralateral dorsolateral pontine tegmentum. Neurotensin causes suppression of half the LC cells (Young et al. 1978, but cf. Guyenet and Aghajanian 1977).

Vasopressin (Vaso) and oxytocin (Oxy). The LC contains Vaso and/or Oxy fibers and terminals (Swanson 1977, Brownfield et al. 1978). Regions which possibly project to the LC, and contain Vaso/Oxy cell bodies, are n. paraventricularis, n. supraopticus and n. suprachiasmaticus (cf. table 7 and Swanson 1977, Choy and Watkins 1977, Buijs et al. 1978, Reaves and Hayward 1979). Most regions contain both Vaso and Oxy, but the compounds are found separately in different cells (Choy and Watkins 1977, Watkins and Choy 1977).

Other neuropeptides. No other neuropeptides in fibers or in terminals in the LC have, as far as I am aware, been described up to the present. Other neuropeptides that might reach the LC are: somatostatin, vasoactive intestine peptide (VIP) and gastrin (Hökfelt et al. 1978a, Finley et al. 1978, Krisch 1978, 1979, Dierickx and Vandesande 1979b).

Survey of the afferent putative neurosecretes. Fig. 6 gives a survey of the afferent putative neurosecretes of the LC and, where possible, their cells of origin and terminals. The putative neurosecretes ACh, NE, SP and Enk probably have a direct action on the LC neurons and the action of each of these 3 compounds is in any case not caused via the receptors of the remaining 2 of these compounds: they are secreted by independent input channels as indicated by electrophysiological and ultrastructural investigations (Pickel et al. 1978, Guyenet and Aghajanian 1979). More knowledge of the afferent putative neurosecretes of the LC is not yet available.

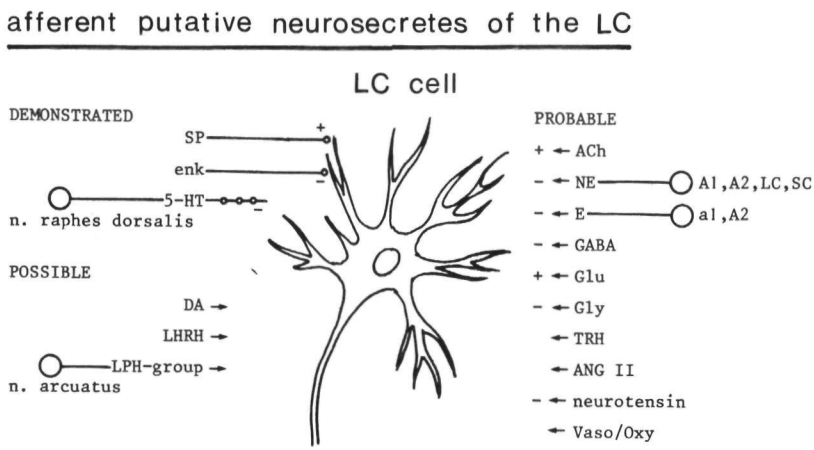


Fig. 6 Afferent putative neurosecretes of the LC and their cells of origin when these are known. For the abbreviations see the text of section 1.2.2 or pp. 6-7.

1.2.3. HORMONAL INPUT OF THE LC

Identified LC cells accumulate estrogens and androgens in their nuclei (fig. 7); estrogens are predominantly accumulated in the LCv (Heritage et al. 1977), while the accumulation of androgens has not yet been described in detail (Stumpf and Sar 1978, Heritage and Grant 1979). Accumulation of androgens and estrogens is a characteristic property of CA cells but is not exclusively to them (Heritage et al. 1977, Heritage and Grant 1979). Accumulation of progesteron or corticosteroid in the LC has not been mentioned (Stumpf 1978). Sex-related differences in NE levels have been described in rats; the NE levels and the behavior of male rats can be feminized either by castration or administration of estrogens (Wilson and Argawal 1979).

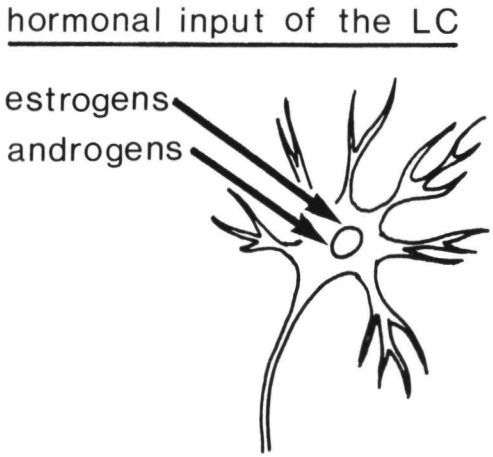


Fig. 7 Hormones which appear to accumulate in the cell nuclei of the LC cells (cf. Heritage et al. 1977, Stumpf and Sar 1978, Heritage and Grant 1979).

1.3. The activity of the LC.

SECTION 1.3. TABLE OF CONTENTS

Introduction

Three types of methods have been used to investigate the activity of the LC cells: single cell electrophysiology, biochemistry and (rarely used) histochemical methods such as karyometry. The interpretation of biochemical measures is difficult, because the different biochemical parameters (the concentrations of NE or its metabolites, the activities of TH and DBH, and the NE uptake) are related in a complicated, and as yet not fully understood, way to the normal activity of the LC cells (cf. Perlow et al. 1978, and section 4.4). Moreover, major changes in the animal's life are necessary to induce a detectable change in biochemical parameters (cf. section 1.3.4). Single cell recordings, on the other hand, can provide a much more detailed view on the relationships between LC activity and the animal's environment and activity, but recording of single LC cells in behaving unanaesthetized animals is difficult, and the first 2* reports have only recently appeared (Foote and Bloom 1979, Jones et al. 1979)**. In this section results yielded by the 3 methods mentioned above will be presented together.

* The data of Chu and Bloom (1973, 1974b) are based on a cell sample consisting of many non-LC cells.

** The LCd of the rat contains 7 times as many NE cells as the LCv (section 1.1), so that the results of single cell electrophysiological methods apply mainly to the LCd.

1.3.1. AFFERENT CNS SIGNALS TO THE LC

Electrical stimulation of many parts of the CNS can elicit orthodromic responses from the LC cells (Nakamura 1977, Takigawa and Mogenson 1977, Igarashi et al. 1979a, Segal 1979). Most of these responses are polysynaptic, but the following are probably monosynaptic. Electrical stimulation of the nucleus spinalis nervi trigemini causes activation of the LC and SC cells (Igarashi et al. 1979a), the neurosecrete involved might be substance P (section 1.2.2). Electrical stimulation of the nucleus raphes dorsalis causes suppression of the LC cells (Segal 1979); the neurosecrete involved is probably 5-HT (section 1.2.2).

1.3.2. LC CELL ACTIVITY AND SENSORY STIMULI

Sensory modalities and convergence. LC and SC cells are activated by visual, auditive, tactile and pain (tooth pulp) stimuli (Takigawa and Mogenson 1977, Nakamura 1977, Igarashi et al. 1979a,b, Foote and Bloom 1979, Jones et al. 1979). (In anaesthetized or decerebrated animals only strong and often noxious stimuli can activate the LC cells (Korf et al. 1974, Cedarbaum and Aghajanian 1978b, Segal 1979).) The LC cells are moreover activated by electrical stimulation of sympathetic visceral afferents (splanchnic nerve), and suppressed by electrical stimulation of parasympathetic visceral afferents (vagus nerve) (Takigawa and Mogenson 1977, Svensson and Thorén 1979). The LC cells are suppressed by an increase in blood volume load via the nervus vagus, no correlation has been found between LC cell activity and blood pressure or heart rate in anaesthetized rats (Svensson and Thorén 1979). A single LC cell is activated by stimulation of many sensory modalities (Takigawa and Mogenson 1977, Nakamura 1977, Igarashi et al. 1979b, Foote and Bloom 1979, Jones et al. 1979). Moreover, a single LC cell has a large somatosensory receptive field (Nakamura 1977). Fig. 8 is a diagram of the different sensory inputs to the LC cells.

Response characteristics. The latencies of LC cell responses vary over a wide range; from 5 to 58 msec (Igarashi et al. 1979b): oligo- and polysynaptic responses occur. The stimulus-induced activation is generally followed by suppression with a duration of more than 500 msec (Cedarbaum and Aghajanian 1978b, Jones et al. 1979, cf. section 1.3.5). The LC re-

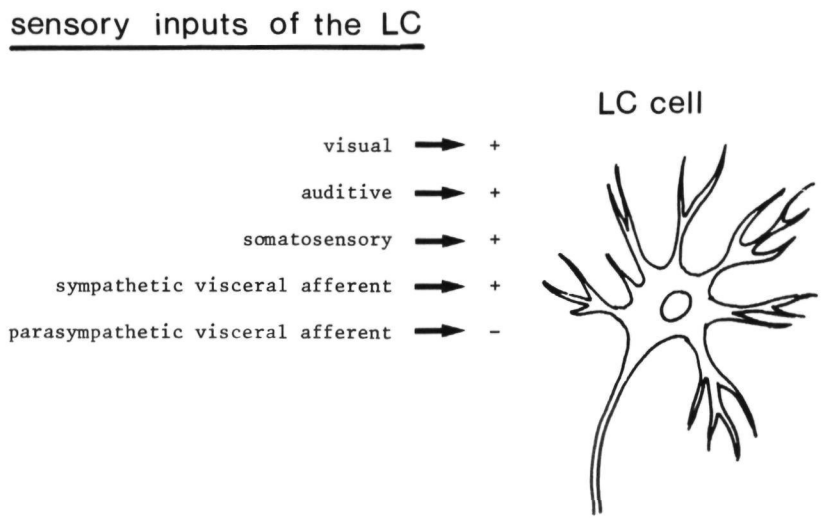


Fig. 8 Diagram of the sensory inputs of the LC cells, and the influence of these inputs (+ = activation; - = suppression)

sponse to prolonged (30 sec) stimulation of the sciatic nerve (probably Aδ- and C-fibers) is however of the sustained type: the highest firing rate is reached immediately after the beginning of the stimulus, followed by a decrease, but the steady firing rate is higher than the pre-stimulus level (Cedarbaum and Aghajanian 1978b). Sustained activation outlasting the duration of a nociceptive stimulus has also been mentioned by Segal (1979). The response to simple stimuli was variable and showed rapid habituation (Foote and Bloom 1979). The suppression after stimulus-induced activation and the rapid habituation on the one hand, and the sustained response type on the other hand may appear to represent conflicting results; a quantitative analysis of the dynamic properties of LC cells and their habituation might serve to clarify such seeming contradiction. More complex, arousal-eliciting stimuli (such as the sight of food) elicited responses from the LC cells which were repeatable as long as the behavioral response was not habituated (Foote and Bloom 1979).

The structure of sensory inputs*. More detailed information on the stimuli that are suitable for influencing LC cells has not yet appeared. The trajectories by which sensory stimuli affect the LC cells are unknown in most cases. Whether all LC cells are identical with respect to their afferent signals, and react in general to the same stimuli, or in other words, whether the LC cells are functionally specialized and receive systematically varied sensory input is also unknown. For functional statements it is necessary to know whether or not the LC cells are functionally differentiated, and whether such eventual functional specialization correlates with the localization of these cells within the LC. These questions are equivalent to those stated in section 1.2.1 about the topography of the afferent connections (see also section 1.4.1, pp. 55-56).

1.3.3. LC CELL ACTIVITY AND MOVEMENTS

No correlation between LC cell activity and specific movements has been found (Foote and Bloom 1979, Jones et al. 1979). Arousal-eliciting stimuli induce orientation movements and activation of the LC cells, but apparently identical movements occur without cell activity, and cell activity occurs without movements. *"In general, LC seems to be on the sensory side of the sensory-motor continuum, demonstrating short latency polysensory responses but no correlation with specific motor acts."* (Jones et al. 1979).

1.3.4. LC CELL ACTIVITY AND MAJOR BEHAVIORAL ACTIVITY

Sleep-wakefulness stadia. LC cell activity in rodents and primates is at its highest level (up to 10 spikes/sec), when the animal is awake (W) and alert, lower during drowsiness and slow wave sleep (SWS) and at its lowest during paradoxical sleep (PS) (Hobson et al. 1975, Foote and Bloom 1979, Jones et al. 1979; see footnote on page 37). Interestingly, the LC cells

* See footnote on page 28.

have a high firing rate during the transition from SWS to W, or from PS to W (Chu and Bloom 1974, McCarley and Hobson 1975, Jones et al. 1979). The size of the nucleus of the LC cells is smaller during sleep than during arousal, indicating a lower cell activity during sleep (Bubenick and Monnier 1972).

Daily rhythms. The NE content of the cerebrospinal fluid (CSF) is highest during awake periods (Ziegler et al. 1976, Perlow et al. 1978); this probably reflects the release of NE from central NE terminals. The other biochemical measures of which day- and night-time values have been published are more complexely related to the central NE release (see section 4.4). Most authors, however, report that the highest NE levels are during the awake period in the whole or parts of the brain in rodents, lagomorphs and primates (Manshardt and Wurtman 1968, Scheving et al. 1968, Friedman and Walker 1968, Asano 1971, Elephtheriou 1974, DiRaddo and Kellog 1975, Hillier et al. 1975, Philo et al. 1977, but not Collu et al. 1973). This circadian rhythm in the activity of central NE is synchrone and in phase with peripheral NE, as reflected in the pineal gland and the blood plasma (Wurtman and Axelrod 1966, Brownstein and Axelrod 1974, Morgan and Reiter 1977, Ziegler et al. 1977a). It has nevertheless been demonstrated that the NE measured in the brain and CSF is of central origin (Ziegler et al. 1977a, Perlow et al. 1978). The relationship between central and peripheral NE will be further discussed in section 1.4.6. Recently, fluctuations with more than one peak in the awake period (ultradian rhythms) have been described for NE release in the hypothalamus (Philippu et al. 1979a) and for the NE content of the blood (Levin et al. 1978).

Stress*. Stressors are noxious or hazardous stimuli (A&S 8.5.). Ample evidence is available that stressors increase the activity of the LC as expressed in various biochemical measures (A&S 8.5., Korf 1976, Ritter and Ritter 1977, Ritter and Pelzer 1978, Sauter et al. 1978, Stone 1979a). LC cells are however also activated by stimuli that are not noxious or hazardous (section 1.3.2). In my opinion, the LC is active in both the

* "Stress" is an ambiguous word meaning either noxious/hazardous stimuli (here called "stressors"), the state in the animal induced by stressors, or the effects of stressors (for instance on blood pressure, heart rate, gastric ulceration or behavior).

presence and absence of stressors and its "function" must therefore be formulated for stress and non-stress situations. The functional implications will be discussed in the sections 2.2 and 3.2. With regard to the response to stressors, the central NE cells of the LC react similarly as the peripheral sympathetic NE cells (e.g. Bühler et al. 1978, McCarty and Kopin 1978).

1.3.5. INTERNAL LC CONNECTIONS

Post-stimulus suppression. A stimulus-induced activation of LC cells is generally followed by a long (up to 500 msec or more) period of suppression, here called A-S response (Nakamura 1977, Aghajanian et al. 1977, Cedarbaum and Aghajanian 1978b, Watabe and Satoh 1979, Jones et al. 1979). During the period of decreased firing, the polysynaptic response of the LC cells is diminished (Cedarbaum and Aghajanian 1978b), so that the suppression may possibly be an inhibition (cf. note on page 29). The suppression occurs after activation resulting from ortho- and antidromic stimulation, and it is mediated by NE via α_2-adrenoceptors. Consequently, long-duration suppression must be due to noradrenergic terminals and receptors within the LC.

Models. A number of models can be formulated as explanation of the post-stimulus suppression of the LC cells (fig. 9).

1. Feedback suppression (autosuppression): a LC cell suppresses its own activity.
2. Lateral suppression: LC cells suppress the activity of adjacent LC cells, but not that of their own.

Both types of suppression could be due to 1) release of NE from the dendrites, 2) to a recurrent collateral ending on a NE cells, or 3) to a recurrent collateral ending on a suppressing interneuron (cf. section 1.1 and fig. 9).

Post-stimulus suppression is lateral suppression. Several reasons can be put foreward for supposing that the post-stimulus suppression is lateral suppression.

1. After weak stimulation of LC fibers, antidromic post-stimulus suppression can occur without preceding antidromic stimulus-induced activation (Aghajanian et al. 1977). Depending on the strength and

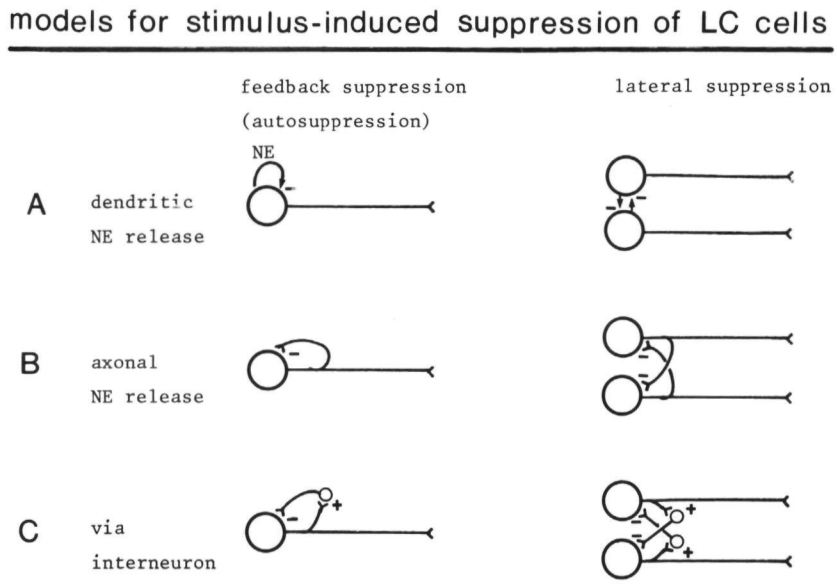


Fig. 9 Models suggested as explanation of the suppression occurring after a stimulus which activates LC cells.

the place of stimulation, a single LC cell can respond with either activation-suppression, or with activation or suppression only (Takigawa and Mogenson 1977, Watabe and Satoh 1979), which is also reflected in the wave form of the antidromic response (Nakamura 1977).

2. The firing pattern of adjacent LC cells is in favour of lateral (or mutual) suppression (Watabe and Satoh 1979).
3. In the case of feedback suppression, a bimodal interspike interval histogram would be expected (cf. Thijssen et al. 1975), but the interspike interval histogram of LC cells is unimodel (Jones et al. 1979).

Consequently, lateral suppression is the most satisfactory explanatory model of the stimulus-induced suppression: activity of LC cell A does not suppress the activity of cell A, but of other LC cells B. This applies to the action of NE released both from the dendrites and from terminals.

1.4. Outputs of the LC.

SECTION 1.4. TABLE OF CONTENTS

1.4.1. EFFERENT FIBERS OF THE LC

General pattern of projection

Introduction. In this section, I will attempt to give both a complete (table 8, p. 193) and comprehensive survey of the LC projections (figs. 10 and 11). Although the LC has fibers ending in parts of the whole of the neuraxis, the projection is not diffuse or uniform: some regions receive a dense LC projection and others none at all. A differential projection of the LCd and the LCv has been proposed (many regions: Tohyama et al. 1978, Mason and Fibiger 1979i; spinal cord: Satoh et al. 1977, Tohyama et al. 1979b; medulla: Abols and Basbaum 1978, Takahashi et al. 1979, Takeuchi et al. 1979, Bystrzycka 1980; hypothalamus and preoptic regions: McBride and Sutin 1976, Sakumoto et al. 1978; hippocampus: Pasquier and Reinozo-Suarez 1978; neocortex: Llamas et al. 1975),

but these differences are not absolute: for instance, although most pontine NE cells projecting to the spinal cord are LCv cells, a small number are LCd cells (Tohyama et al. 1979b). I have simplified and generalized the differential projection of the LCd and LCv in figs. 10 and 11. The LCd and group A4 on the one hand, and the LCv and group A7 on the other hand are regarded as entities in these figures (cf. section 1.1). (The reader is referred to table 9, p. 200, for the references.)

Species differences. Agreement about the general trajectory and terminals of the efferent fibers of the LC in the rat exists, but discussion is continuing on the details of the rat LC projection (cf. A&S 3., Swanson and Hartman 1975, Jones and Moore 1977). The LC projection of carnivores and primates is fairly similar to that of the rat (cf. Maeda et al. 1973, Bowden et al. 1978), so the generalized LC projection of the mammal will be presented below.

Projection of the LCd. The LCd has fibers projecting to the cerebellar cortex and nuclei, colliculi inferior and superior, thalamus (predominantly the specific sensory nuclei, Lindvall et al. 1974b), septum, amygdala, olfactory bulb and all areas of the cerebral cortex (fig. 10, A&S 3., table 8, p. 193). In many of these areas almost all the NE terminals are supplied by the LCd (for instance thalamus and cerebral cortex, table 8).

Projection of the LCv. The LCv has descending and ascending fibers projecting to the spinal cord (predominantly the anterior parts), the area of the nucleus solitarius, the nn. raphes pallidus and obscurus, the cerebellar cortex and the hypothalamus (predominantly the so-called neurosecretory nuclei). In some areas, almost all the NE terminals are supplied by the LCv (for instance the ventral spinal cord); most of the NE in the hypothalamus is supplied by NE cells in the medulla oblongata (Jones et al. 1978, Marchand et al. 1979b).

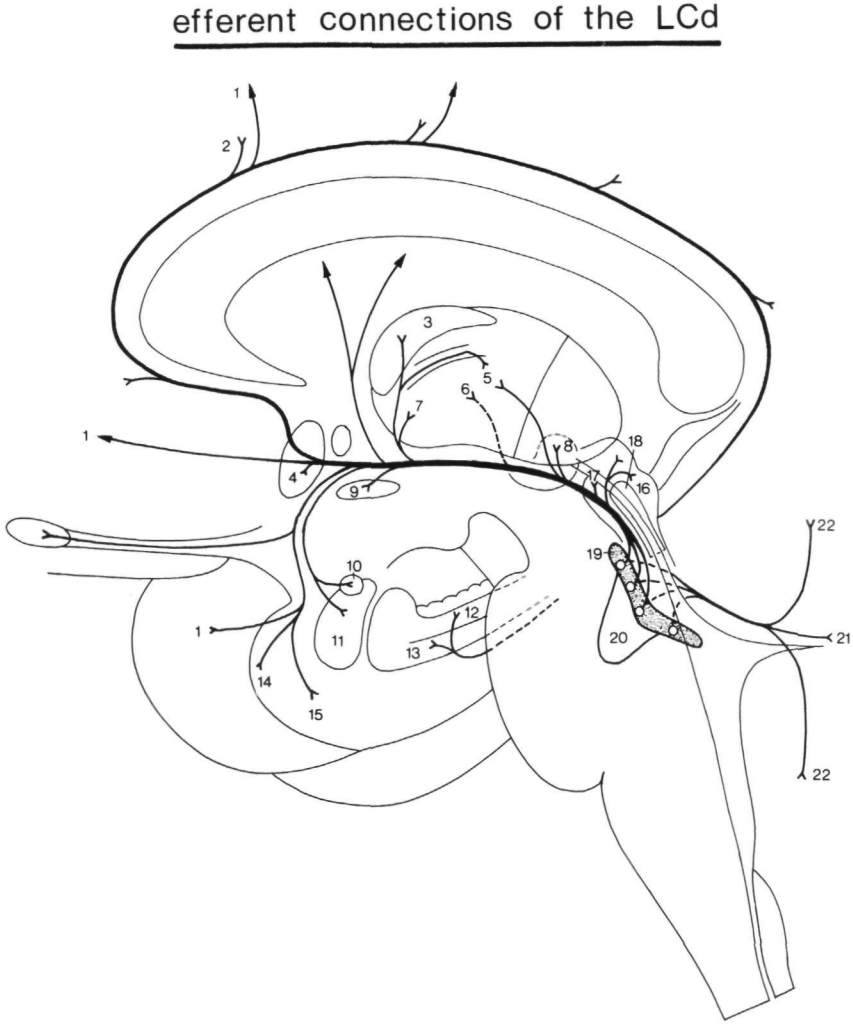


Fig.10 Efferent fibers of the LCd; modified diagram after Nieuwenhuys et al. (1979). 1. cortex cerebri, 2. gyrus cinguli, 2'. bulbus olfactorius, 3. N. anterior thalami, 4. Nn. septi, 5. N. lateralis thalami, 6. N. reticularis thalami, 7. N. ventralis thalami, 8. corpora geniculata, 9. substantia innominata, 10. N. centralis amygdalae, 11. Nn. basalis and lateralis amygdalae, 12. formatio hippocampi, 13. subiculum, 14. cortex piriformis, 15. cortex entorhinalis, 16. corpora quadrigemina, 17. grisea centralis mesencephali, 18. N. raphes dorsalis, 19. LCd, 20. LCv, 21. Nn. cerebelli, 22. cortex cerebelli.

efferent connections of the LCv

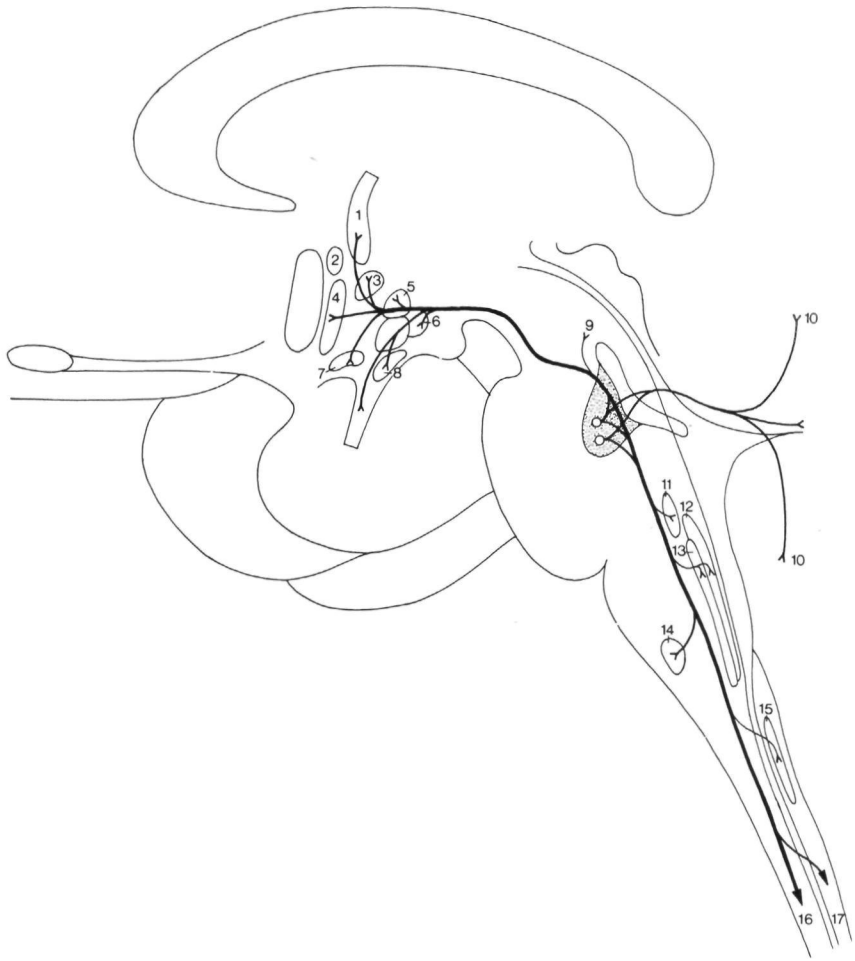


Fig.11 Efferent fibers of the LCv. 1. N. interstitialis striae terminalis, 2. commissura anterior, 3. N. paraventricularis, 4. Nn. preoptici, 5. N. dorsomedialis, 6. N. perifornicalis, 7. N. supraopticus, 8. N. arcuatus, 9. formatio reticularis mesencephali, 10. cortex cerebelli, 11. N. nervi facialis, 12. N. solitarius, 13. N. dorsalis nervi vagi, 14. Nn. raphes pallidus and obscurus, 15. N. spinalis nervi trigemini, 16. spinal cord laminae IV, V, VII, VIII, IX, 17. spinal cord laminae I, II, III.

Major differences between the LCd and LCv projections. My own impression and generalization of the projection of the LCd and LCv is as follows (cf. Silver et al. 1979; fig. 12):

- LCd has ascending fibers to sensory areas in the mes-, di- and telencephalon, and to other areas of the archi-, paleo-, meso- and neocortex.
- LCv projects predominantly into output parts of the CNS: anterior gray matter of the spinal cord and into the so-called neurosecretory hypothalamic nuclei.

Prominent regions not receiving fibers from the LC are the caudate-putamen and the tuberculum olfactorium. Similarities have been mentioned between the projections of the LC cells on the one hand and the projections of the β-LPH/α-MSH cells (Bloom et al. 1978, Jacobowitz and O'Donohue 1978), and the distribution of angiotensin (Printz 1979) on the other hand.

Bilateral projections. Although the LC cells project mainly to the ipsilateral part of the CNS, contralateral projections have consistently been described over the whole of the neuraxis (spinal cord: Satoh et al. 1977; cerebellum: Bhatnagar and Schmidt 1977; thalamus: Kromer 1976; septum: Moore 1978; hippocampus: Koda et al. 1978a,b, Pasquier and Reinozo-Suarez 1978, Finch et al. 1978b, Segal 1977a, Wyss et al. 1979; neocortex: Freedman et al. 1975, Llamas et al. 1975, Divac et al. 1977, Gatter and Powell 1977, Zecevic and Molliver 1978, Arikuni and Ban 1978, Aghajanian et al. 1977). Many LC cells send a small portion of their axonal tree to the contralateral part of the CNS (Freedman et al. 1975). No investigations have been published, as far as I am aware, on whether or not related areas on both sides receive terminals from one single LC cell.

Terminals

Are the varicosities neurosecretory elements? The axons of the NE cells of the LC are beaded fibers consisting of varicosities and thin intervaricose segments (Descarries et al. 1977, Beaudet and Descarries 1979). I have 3 reasons to suppose that NE is released from these varicosities (cf. Beaudet and Descarries 1979).

1. The varicosities contain NE (demonstrated by formaldehyde- and glyoxylic acid-induced fluorescence, Dahlström and Fuxe 1964, Lindvall and Björklund 1974) and vesicles with the appearance of exocytotic (neurosecretory) vesicles (Descarries et al. 1977, Sakumoto et al. 1977, Koda et al. 1978a,b, Zecevic and Molliver 1978, Beaudet and

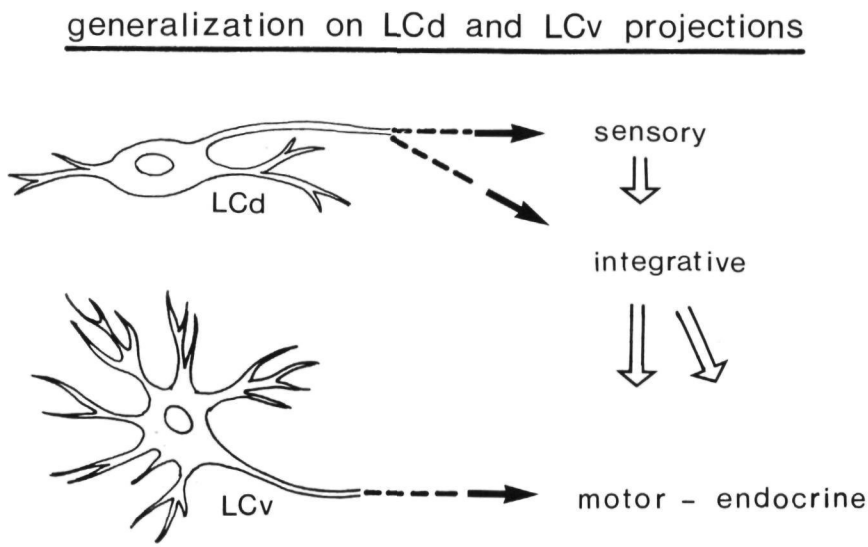


Fig.12 Chief differences between the projections of the LCd and LCv

Descarries 1979).

2. The varicosities contain immunoreactive DBH (Swanson and Hartman 1975, Lundberg et al. 1977, Cimarusti et al. 1979) and therefore probably have a synthetic system for NE.
3. The varicosities accumulate exogenous ^{3}H-NE (Descarries et al. 1977) and other catecholamines (5-OHDA, Zecevic and Molliver 1978) and therefore probably have a specialized re-uptake system for NE.

The varicosities share these 3 properties with classical synaptic boutons; therefore they are probably neurosecretory elements. It is assumed that the varicosities of central NE fibers are terminals further in this book, as has been suggested for peripheral NE fibers (cf. Haefely 1972).

The occurrence of free endings. The frequent occurrence of large numbers of NE terminals without synaptic differentiation has been described by authors using various techniques to identify NE terminals (A&S 3.9., Descarries et al. 1977, Swanson et al. 1977, Sakumoto et al. 1977, Koda et al. 1978a,b, Cimarusti et al. 1979, Ouimet 1979, Beaudet and Descarries 1978, but not by Zecevic and Molliver 1978). The similarities

between the NE terminals of the peripheral sympathetic system and some central NE terminals have been noted and it has been suggested that NE is both a neurotransmitter and a neuromodulator (cf. section 4.3.1, A&S 3.9., Descarries et al 1977, Koda and Bloom 1977, Koda et al. 1978b).

Terminals and receptors on neurons, synapses. In all NE terminal areas investigated some NE terminals are described as being in close contact with neuronal somata and dendrites. In the cerebellum and the hippocampus, these contacts are predominantly on the Purkinje and pyramidal cells respectively (A&S 3.4., Swanson and Hartman 1975), where the β-receptors are also localized (Melamed et al. 1976a, 1977, Atlas and Segal 1977). In the spinal cord and the neocortex on the other hand, the NE terminals are found also near the β-receptors (Melamed et al. 1976b, 1977) on morphologically different neurons (A&S 3.9., Jordan et al. 1977). Some NE terminals have synaptic specializations (Nelson et al 1973, Descarries et al. 1977, Koda et al. 1978a,b, Zecevic and Molliver 1978, Beaudet and Descarries 1978, Cimarusti et al. 1979), these synapses were found to be either symmetrical or asymmetrical synapses on dendrites or somata.

Terminals on cerebral blood vessels The cerebral blood vessels receive NE terminals from the ganglion cervicale superius and from central NE cells. The endings of the ganglion cervicale superius terminate on large vessels and the LC terminals are contiguous for some distance with the small cerebral blood vessels (A&S 3.11., Itakura et al. 1977, De Witt 1978). The proportion of the LC terminals, however, that ends on cerebral capillaries is small (Itakura et al. 1977). The ultrastructure of the LC terminals on small blood vessels indicates that these terminals indeed affect the blood vessels (Swanson et al. 1977, Itakura et al. 1977, but not Edvinsson and MacKenzie 1977). (Note: the large and small cerebral blood vessels also receive a non-noradrenergic input, Edvinsson and MacKenzie 1977, Itakura et al. 1977.)

Terminals on other CNS elements NE terminals have been described in the eminentia mediana, which receives a LC input (Palkovits et al. 1977b, Záborsky et al. 1977), as being in close contact with ependymal cells, neurosecretory fibers and other axons, no classical synapses have been found (Sakumoto et al. 1977). Similar NE terminals have been found in the area postrema (Torack et al. 1973), but it is questionable whether their origin is the LC. It is possible that NE released from these terminals

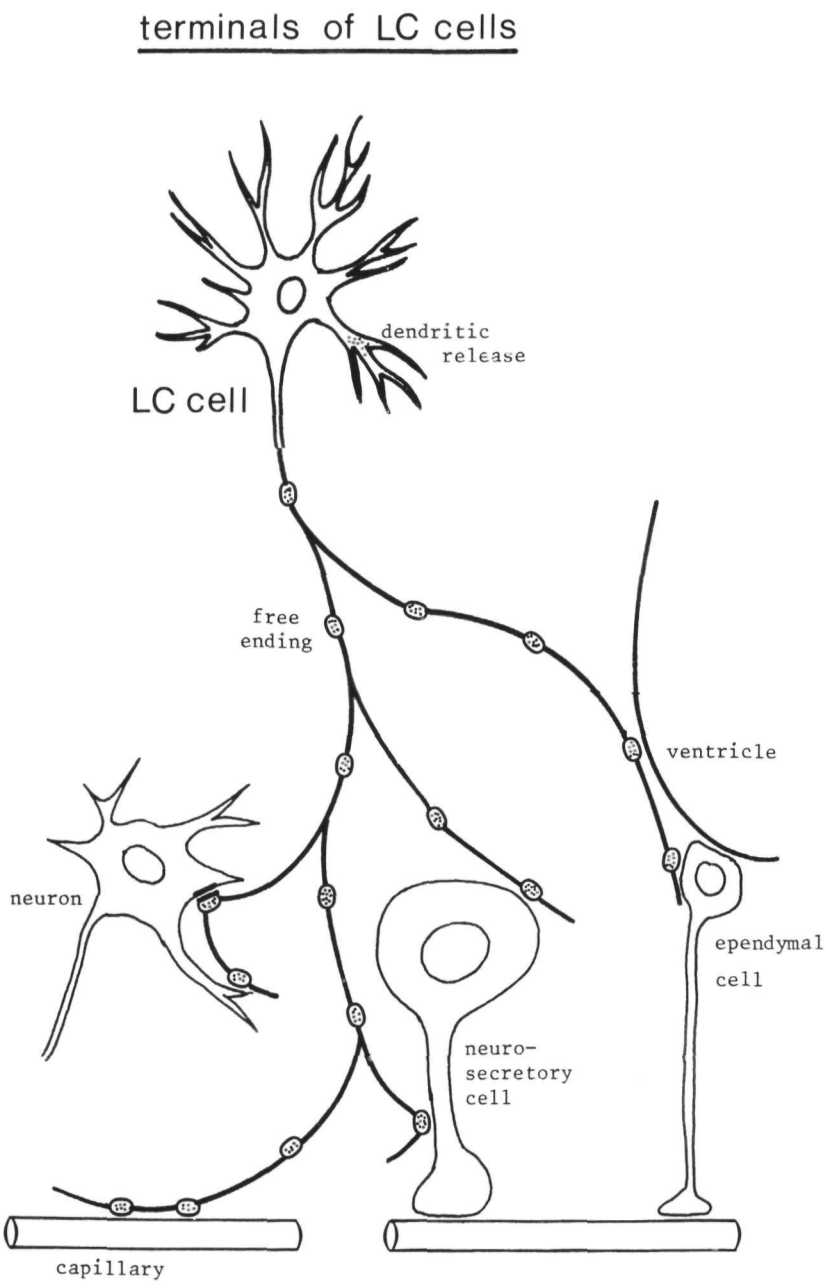


Fig.13 Illustration of the various terminals of the LC NE cells

reaches the ventricle. Fig. 13 gives an illustration of the various LC terminals.

Structure of the LC efferents

LC projection: not diffuse. Divac's (1979) proposed general classification of subcortico-neocortical projections (cf. fig. 14) is used here to describe the overall LC projection. I know no single coherent CNS part with a projection as widely dispersed over the whole CNS as the LC. The LC projection is however not disperse or diffuse, but rather multilocular preferential (cf. table 8). For instance, the LC projection to the cerebral cortex is not disperse, but geometrically ordered over the cortical layers (Morrison et al. 1978, 1979b), with some areas receiving a denser NE innervation than others (Lidov et al 1978, Lindvall et al. 1978, Lewis et al. 1979): the cortical LC projection is preferential.

LC projection: topography. The classification of Divac (1979) has been extended to cover the topography of the projection (fig. 14). After injections of HRP in several restricted CNS regions, the HRP-labelled cells were found to be evenly distributed (or scattered) over the whole extent of the LCd and/or the LCv, suggesting that the LC projection is not topical (cerebellum. Kimoto et al 1978, thalamus: Velayos et al. 1978; septum: Moore 1978; hippocampus Segal and Landis 1974, neocortex Freedman et al. 1975, Kievit and Kuypers 1975, Divac et al. 1977). Besides differential projection of the LCd and the LCv, differences in the projection of the rostal and caudal parts of the LCd and LCv are described in one HRP study (Mason and Fibiger 1979i), but not in the other HRP studies mentioned above. The fibers of the telencephalic part of the ascending NE bundle project topically to the neocortex (Morrison et al. 1979); it is uncertain whether the relationship between the LC cell bodies and the ascending NE fibers is topical.

Collaterals. The axons of the LC NE cells branch to an extensive axonal tree (section 1.1, Kromer 1976, Nygren and Olson 1977b, Moore 1978). Each LC cell projects to many widely dispersed regions, as demonstrated by the retrograde accumulation of NE after transection (histofluorescence, A&S 3.), and by single cell recordings (Takigawa and Mogenson 1977, Faiers and Mogenson 1977, Nakamura 1977). No indications have been published, to my knowledge, of whether or not regions receiving terminals from a single LC

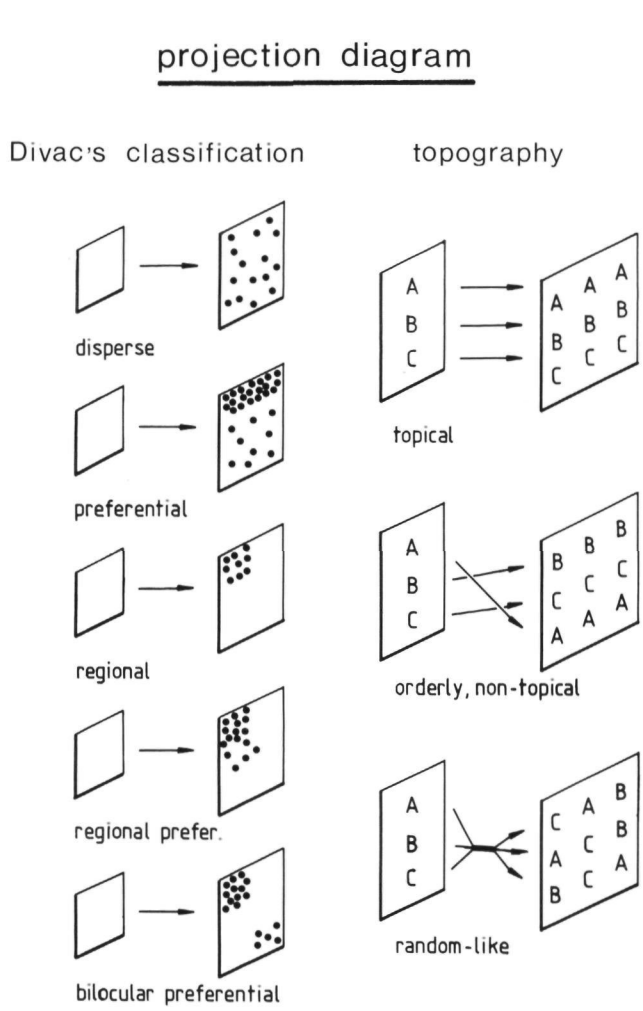


Fig.14 Projection diagram; this is an extension of Divac's (1979) classification; the topography of the projections is also included in this classification.

cell have relationships* other than this common LC input.

* The words "relationships" and "related" are used in the general, abstract sense of section 5; for definitions see the references cited in that section.

LC projection random? Almost all investigations have indicated that the LC projection has random characteristics. Whether the projection of a CNS region is random or ordered, is of course the subject of anatomical investigation. But whether one is inclined at the moment to believe that the projection of this region is random or not, depends also on the implications of random and ordered connections: "*.... the axon of one neuron may innervate formations as widespread as parts of the neocortex, thalamus, brain stem and even spinal cord. Thereby the target neurons in all these areas may become an entity (or system), not through interconnections but through the common input from one cell.*" (reformulated from Divac 1979). Can, or must, the collections of neurons receiving an input from a single LC cell be regarded as an entity* (cf. section 5.2.2)?

Random projections, theoretical implications. If the projection of a single LC cell were random, its target elements would not be related, apart from this common input. In this case, the set of elements receiving input from a single LC cell would be a loose aggregate of otherwise unrelated elements; it would not be a system or an entity. What these elements do (their "function", see section 5.2.4), could not be formulated in a general statement without referring to their common LC input. If, on the other hand, the projection of a single LC cell were not random, its target elements would have other relationships than this common input: they would form an entity or a system, and their "function" could be formulated in a general statement without reference to their common LC input.

Ordered projections, example of implications. It has been shown that single NE fibers innervate a slice of rat cortex from the frontal to the occipital pole (Morrison et al. 1979b). This might, but does not necessarily, imply that such fronto-occipital slices are entities (subsystems) of the cortex: i.e. a completely new subdivision of the cortex.

* This can be visualized by imagining 100 men scattered over a country, all receiving an identical input; these 100 men can be either unrelated (they happen for instance to be watching the same TV program) or related (they are conferencing by telephone and listening to the chairman). Further observation can reveal the presence or absence of relationships.

Structure of the LC afferents and efferents

Reciprocal relationships. Some of the regions projecting to the LC have been reported as receiving fibers from the LC (for instance the A1 and A2 regions, the ventral tegmental area and preoptic and amygdaloid nuclei): the existence of reciprocal (feedback) relations between the LC and these regions has been suggested (Sakai et al. 1977). When such feedback loops exist, however, their action is expected to be evident in the activity of the LC cells, but apart from recurrent lateral suppression (section 1.3.5), no effects have in fact been described that could be attributed to feedback loops. Whether or not direct feedback loops exist and play a definite role in the LC cell's activity, remains to be investigated.

Are input and output random? If the input of the LC cells were random (cf. sections 1.2.1 and 1.3.2), the LC cells would be equal and exchangeable with regard to their input; whether the LC's output is ordered or random would then make no difference as far as the effects of the activity of the LC cells is concerned. Similarly, if the output of the LC cells were random (see above), the LC cells would be equal and exchangeable with regard to their output; it would then again make no difference on the effects of the activity of the LC cells, whether the LC cell's input is random or ordered. Most of the order existing in living organisms is in some way benificial for survival and reproduction (cf. section 5.2.4), so that the questions about the structure of the LC's input and output are related. If input is random then most probably, output is also random; while if input is ordered, then output is most probably ordered also.

Indications for order. There are but a few indirect and relatively weak indications in favour of an ordered structure of the LC's input and output. The projection of the ascending NE fibers on the rat's cortex is topical (Morrison et al. 1979b). In one HRP study, a rostrocaudal specialization of the LC cells with regard to their efferents has been described (Mason and Fibiger 1979i). Moreover, it is most probable that recurrent lateral suppression occurs in the LC (section 1.3.5); such recurrent lateral suppression has been described in regions where regional specialization is evident (the somatotopically ordered parts of the visual, auditive and somatosensory system), and in the case of these regionally specialized regions, one can easily imagine how lateral interaction contribute to the reliable transmission of signals.

Random or ordered, implications for information capacity. If the input or output of the LC cells were topographically random, the LC cells would be equal and interchangeable, and the information they could transport equal to the information capacity of a single neuron. In man, the number of LC cells is some 18,000 (Brody 1976). This is 60% of the number of fibers in the auditory nerve (Larsell 1951); most readerswill have a general idea of the amount of acoustic information reaching them. Consequently, the human LC has an *a priori* information capacity in the order of magnitude of the auditory nerve (cf. Kulikowski 1971), and I simply do not believe that the human LC has an actual information capacity no greater than a single neuron, nor that the CNS is build in such a way and that the LC afferents and efferents are random. But, of course, if future research does not reveal any order in the projections of the individual LC cells, I will have to accept that the chaos in my brain is greater than I think now.

Random or ordered, implications for experimental brain research. If the projection of a CNS region were random, the message of the fibers of this region would not be contained in a spatiotemporal, but simply a temporal pattern of action potentials. Details of this temporal pattern might be relevant for the message, but should the effects of the action potentials be of prolonged duration, the message would simply be contained in the number of action potentials per time period, or in the amount of released transmitter. *"It should be expected that electrical stimulation of such a formation would produce effects opposite from those observed after its destruction. In contrast, stimulation with presently used techniques may be expected to have qualitatively the same effects as ablation when it affects a brain region whose message is coded in the spatio-temporal pattern of its output; either stimulation or lesion interferes with or abolishes this pattern."* (Divac 1979).

Random or ordered, implications for the LC's "function". The structure of a system determines its "function" (section 5.2.4). If the afferents or efferents of the LC were random, the "function" of the LC would be a general one. If the afferents and efferents were orderly, parts of the LC would be functionally specialized. The recent tendency in functional statements about the LC is to emphasize overall ("neuromodulatory") actions (cf. Ramm 1979, Clark 1979, Divac 1979).

Other sources of NE in the CNS

Although the LC contains the largest number of NE cell bodies in the CNS, other sources of NE in the CNS are present:

1. The other central noradrenergic cells (A1, A2, A3, A5), which have projections to the spinal sympathetic column, the hypothalamus and other CNS areas (Silver et al. 1978, Smolen et al. 1979, Moore and Bloom 1979, Jones et al. 1978).
2. The ganglion cervicale superius with projections to the large blood vessels in the CNS, to the epiphysis, the choroid plexus and the hypophysis (cf. Lindvall et al. 1974, Morgan and Hansen 1978, Lindvall and Owman 1978, Møller et al. 1979).
3. NE present in the blood, which cannot however cross the blood-brain barrier (Weil-Malherbe et al. 1961, Ziegler et al. 1977a, Perlow et al. 1978).

NE and DA in the CNS

In some CNS regions, the NE and DA innervation is complementary; the following receive predominantly either NE or DA: parts of the cortex entorhinalis and gyrus cinguli (regionally either NE or DA), the caudate-putamen (DA), the tuberculum olfactorium (DA), parts of the hypothalamus (NE), the thalamus (NE) and the spinal cord (NE) (Brownstein et al. 1974, Moses and Robins 1975, Collier and Routtenberg 1977, Lewis et al. 1979, Reader et al. 1979b). In other CNS regions no complementary innervation seems to be present: the frontal cortex and septal and amygdaloid nuclei receive both catecholamine (Brownstein et al. 1974, Lindvall et al. 1978, Moore 1978).

1.4.2. EFFECTS OF THE LC ON THE CNS: SINGLE CELL ACTIVITY

Suppression of maintained activity. The effects of the LC and NE on single cell activity in the CNS have been reviewed by Woodward et al. (1979) and Szabadi (1979), and are discussed here in section 4.3.1 (table 17, p. 221). In short, when the LC cells are active, NE is released, causing long lasting hyperpolarizations of the LC target neurons. The effects induced by electrical stimulation of the LC are characterized by a long latency (30 msec, nucleus spinalis nervi trigemini, Sasa and Takaori 1973; 40-70 msec, hippocampus, Finch et al. 1978b), and a long duration (typical 120 msec,

Sasa and Takaori 1973, Oishi et al. 1977, Finch et al. 1978b, Daugherty et al. 1977, Igarashi et al. 1979a); after prolonged stimulation (for instance 10 sec at 10 pulses/sec) the LC-induced hyperpolarization and suppression can last as long as 60 sec (Hoffer et al. 1973, Segal and Bloom 1974a, Siggins et al. 1976, Sinnamon et al. 1978, Takemoto et al. 1978). Since in awake animals the firing rate of the LC cells is about 10 spikes/sec (section 1.3.4), the LC causes a permanent tonic suppression of the maintained activity of its target cells during such periods. This is an energy-demanding suppression, and not a usual inhibition (see below and section 4.3.1).

Increase in the signal-to-noise ratio. In the cerebellum and the somatosensory and auditory cortex, the neuronal maintained activity is suppressed by NE from the LC, while responses to electrical or sensory stimulation are either enhanced, or left unaffected, at least in comparison with the maintained activity (Foote et al. 1975, Freedman 1976, Freedman et al. 1977, Woodward et al. 1979, Moises et al. 1979); this can be interpreted as an increase by the LC in the signal-to-noise ratio in cerebellar and somatosensory and auditory cortical cells* (cf. fig. 15). The response of neurons of the corpus geniculate laterale to optic tract stimulation is increased by stimulation of the LC (Nakai and Takaori 1974). Similarly, in the hippocampus, the LC has been reported as selectively enhancing the response to a stimulus associated with the presentation of another significant stimulus (e.g. food) (Segal and Bloom 1976b); this was also regarded as an increase in the signal-to-noise ratio**.

* Serious objections can be raised when the maintained activity of a neuron the input of which is neither fully observable nor fully controllable, is considered as noise, and when only the activity induced by the experimentor is considered as signal. The interpretation that LC cell activity increases the signal-to-noise ratio of LC target cells is however assumed to be right.

** The LC/NE-induced increase in the signal-to-noise ratio of its target neurons is not a unique property of the LC or NE; GABA causes a similar increase in neurons of the cerebellum and the auditory cortex (Foote et al. 1975, Freedman et al. 1977), although by means of different membrane mechanisms.

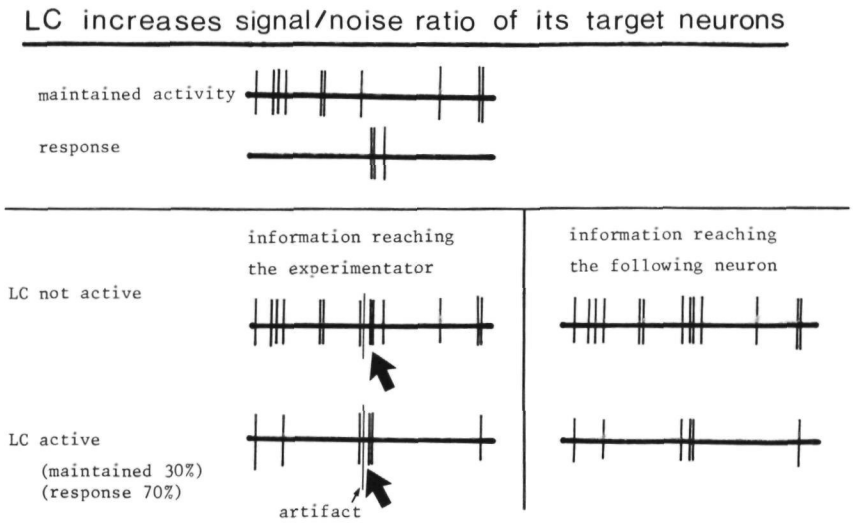


Fig.15 Illustration of the LC-induced increase in the signal-to-noise ratio of LC target cells. Note that the stimulus-induced activity (response) is more prominent, when the LC is active; compare right hand upper column (LC inactive) with right hand lower (LC active).

Selective interactions. Interestingly, it has recently been reported that NE selectively enhances (at least in comparison with the maintained activity) the GABA-induced suppression and the Glu-induced activation of cerebellar Purkinje cells, while at the same time the Gly-induced suppression of these cells is diminished (Moises et al. 1979, Moises and Woodward 1980). The resting transmembrane potential of neurons is not fixed, but shows fluctuations (membrane noise). Consequently, the probability of reaching the threshold for spike generation fluctuates, resulting in stochastic maintained and stimulus-induced activity. NE causes hyperpolarization of its target cells (section 4.3.1), diminishing the probability of firing by chance. Moreover, it is suggested that NE causes such a change in the membrane of its target cell that the effects of some neurotransmitters ("neurotransmitter" is used here loosely speaking) are enhanced and the effects of others diminished. In the future, it is likely that further examples will be described where the combined ac-

tion of 2 neurotransmitters on one target cell is not simply the combination of their separate actions at the cellular level, but a more complicated interaction. If the molecular mechanisms of the different neurotransmitters' actions are known (cf. section 4.3.1, pp. 172; Bonkowski and Dryden 1977), their simultaneous action can be understood.

The LC and nociceptive responses. In the spinal cord (lamina IV and V) and in the nucleus spinalis nervi trigemini, the response to noxious stimuli is reduced by NE and also by electrical stimulation of the LC (Headley et al. 1978, Belcher et al. 1978, Igarashi et al. 1979a, Satoh et al. 1979). In a number of single spinal cells, the response to noxious stimuli has been reported as reduced, while the response to non-noxious stimuli remained unchanged (Headly et al. 1978, Belcher et al. 1978); in another study, however, a decrease in the responsiveness to both noxious and non-noxious stimuli has been reported (Satoh et al. 1979). Since no data are available on the influence of the LC or NE on the maintained activity of the spinal and trigeminal cells, the effects could either be a real decrease in responsiveness, or an increase in the signal-to-noise ratio (cf. Woodward et al. 1979). Both effects could be present, for spinal NE from the LC diminishes spinal nociceptive reflexes (i.e. a decrease in responsiveness of at least some of the neurons involved, cf. section 3.1.1), while part of the nociceptive information ascends to the brain unaffected (section 3.1.2, Andersson and Sjölund 1978).

1.4.3. EFFECTS OF THE LC ON THE CNS: OVERALL ELECTRICAL ACTIVITY

Interpretation of EEG. The overall electrical activity (EEG) of parts of the CNS is related in a complex way to single cell activity (cf. Wolpaw 1979). Since the EEG's effects of the manipulation of the LC or of the central NE transmission are controversial, a discussion about the mechanism would be preliminar.

Evoked potentials. The generally observed effect of NE or of stimulation of the LC on evoked potentials is a decrease in the amplitude (nucleus spinalis nervi trigemini: Sasa et al. 1974a, 1976b; amygdala: Oishi et al. 1979b; hippocampus: Assaf et al. 1979; neocortex: Daugherty et al. 1977, Reader et al. 1979a). This can be related to the frequently found LC/NE-induced suppression of evoked single cell activity (cf. section

4.3.1). A change in the wave form has sometimes been described (Sasa and Takaori 1973, Segal 1977a).

Ongoing EEG activity. Very many investigations have been devoted to the influence of the LC and of cerebral NE on the EEG and on sleep-wakefulness patterns. The ideas concerning the relationships between the activity of the LC and the neocortical and hippocampal EEG activity remain controversial however (cf. A&S 8.6., Jones et al. 1977, Autret et al. 1977, Leppävuori and Putkonen 1978, King 1979, Putkonen et al. 1979, Ramm 1979, Clark 1979). The neocortical low-voltage-high-frequency activity (β-activity) and the hippocampal rhythmical-slow-activity (RSA, θ-rhythm), which were thought to be caused by LC activity (Macadar et al. 1974, Koella 1977), appear in fact to be mainly (or indeed exclusively) due to activity of the reticular formation (Robinson et al. 1977d, Jones et al. 1977, Whishaw et al. 1978, McNaughton and Sedgwick 1978). The activity of the LC cells is highest during active awake periods and lowest during paradoxical sleep (PS), while during both stages neocortical β-activity and hippocampal θ-rhythm predominate (cf. section 1.3.4). After a lesion of the LC, both the neocortical β-activity and the hippocampal θ-rhythm persist (cf. Jones et al. 1977). It is therefore clear, that the activity of the LC cells is neither necessary nor sufficient for either the presence or absence of these patterns. Since immediately before waking the activity of the LC cells is high (cf. section 1.3.4), the LC cells may be involved in the waking process, as is also suggested by some other experiments (cf. Ramm 1979). If however the LC promotes neocortical β-activity and hippocampal θ-rhythm, its influence can only be small (cf. Ramm 1979, Clark 1979). The PGO spikes is another type of EEG activity in which it is probable that the LC is involved (cf. Jones et al. 1977). The involvement of the LC in PS will be discussed further in section 2.1.4.

1.4.4. EFFECTS OF THE LC ON THE CNS: CEREBRAL BLOOD FLOW AND METABOLISM

Introduction. The effects of the LC on cerebral blood flow and metabolism are mentioned here together, since these processes are interconnected (for a review see Kuschinski and Wahl 1978). Conflicting data have been published; I will begin by presenting a survey of the data which fit my general hypothesis, but will also go on to mention contradictory results.

Increase in cerebral blood flow and metabolism. Activation of cerebral adrenoceptors (by NE intracerebroventricular, NE intravenous plus opening of the blood-brain barrier, reserpine or amphetamine) increases the cerebral blood flow, oxygen consumption and glucose uptake (MacKenzie et al. 1976a,b, Hardebo et al. 1977a, McCulloch and Harper 1977, McCulloch et al. 1978, Kuschinsky and Wahl 1978, Edvinsson et al. 1979); this increase is mediated at least partially by β-receptors (MacKenzie et al. 1976b, Savaki et al. 1978), on cerebral microvessels (Herbst et al. 1979, Palmer 1980), which are innervated by the LC (section 1.4.1). Electrical stimulation of the cerebral cortex is accompanied by an increase in the blood volume and cerebral metabolism (Harik et al. 1979, Cummins and Keller 1979). The cerebral metabolism (measured as reduction in NAD(P)) is increased by NE via β-adrenoceptors (Cummins and Keller 1979), and the increase in cerebral blood volume and metabolism (measured as the recovery (re-reduction) of cytochrome a_1a_3) is prevented by a lesion of the LC; the absence of an increase in metabolism after a lesion of the LC is due possibly to the absence of an increase in the blood supply (Harik et al. 1979). An LC-induced increase in the cerebral circulation and metabolism is in agreement with the following data: 1) NE from the LC causes degradation of ATP and therefore probably increases the metabolism (section 4.3.1), 2) the NE-induced effects on the LC target elements are mediated mainly via β-adrenoceptors (section 4.3.1), and 3) activation of β-adrenoceptors on cerebral blood vessels causes vasodilatation (Edvinsson 1975, Edvinsson et al. 1979).

Conflicting data. There is however conflicting evidence. An increase in the activity of the LC cells has been reported as causing a small decrease in the cerebral blood flow, oxygen consumption and glucose uptake (Raichle et al. 1975, De la Torre 1976, Bates et al. 1977a,b, Schwartz et al. 1978, Abraham 1979), but some of these authors raise serious objections to the involvement of the LC NE cells in these effects (Schwartz et al. 1978, Abraham 1979). Moreover, it is possible that the amphetamine-induced effects are not due to interferences with the catecholaminergic transmission (Norberg et al. 1979). The occasionally mentioned NE-induced decreases in the cerebral blood flow (Crawford et al. 1977a,b) may be mediated via α-adrenoceptors, which mediate vasoconstriction (Edvinsson 1975).

Autoregulation not due to the LC. Finally, the regulation of the blood flow and the permeability of the vascular wall in the CNS at changes of

the blood pressure (autoregulation) is due to NE terminals from the ganglion cervicale superius and not of central origin (Kobrine et al. 1977a,b, MacKenzie et al. 1977, Bates et al. 1977a, Hardebo et al. 1977a).

1.4.5. EFFECTS OF THE LC ON THE CNS: POSTNATAL DEVELOPMENT AND PLASTICITY

Postnatal development. Lesions of the LC immediately after birth cause some alterations in the cortical development. The apical dendrites of the pyramidal cells have been reported as remaining in contact with the most superficial cortical layers, just as in the immature cortex (Maeda et al. 1974, but not Wendlandt et al. 1977), with a slight increase in the number of apical dendritic branches (Wendlandt et al. 1977). The LC has a "trophic influence" on the postnatal development of cortical neurons, but this effect is relatively small.

Plasticity. Cells in the visual cortex assume a changed ocular dominance after monocular deprivation: this is a clear demonstration of the plasticity of cortical cells. This cortical plasticity is not present in animals with 6-OHDA-induced lesions of the NE terminals in the visual cortex; perfusion of the visual cortex of these animals with NE has been reported as restoring cortical plasticity (Kasamatsu and Pettigrew 1979, Kasamatsu et al. 1979). Prolonged electrical stimulation (2x2 hours over 2 days) of the LC has been reported as improving learning as much as 28 days after stimulation (Velley and Cardo 1979a), which is considered to be a reflection of plastic changes in the CNS.

1.4.6. EFFECTS OF THE LC OUTSIDE THE CNS, PLASMA NE LEVELS

Indications will be presented that an increase in the activity of LC NE cells causes an increase in the activity of the sympathetic system. 1) Electrical stimulation of the LC causes an increase in the plasma level of the NE metabolite 3-methoxy-4-hydroxyphenylethylene glycol (MHPG), partly due to an increase in the activity of sympathetic neurons (Crawley et al. 1978, 1979b); the electrical stimulation activates the LC cells, as demonstrated by the increase in the brain MHPG levels, but it has not yet been demonstrated whether or not the increase in plasma MHPG is actually due to stimulation of the LC NE cells. 2) A strong positive cor-

relation exists between the CSF NE level and the plasma NE level (of sympathetic origin) (Ziegler et al. 1977), between spinal cord MHPG and plasma MHPG (Crawley et al. 1979a) and between CSF DBH and plasma DBH (Lerner et al. 1978). 3) The plasma NE level is increased by manipulations which also increase the activity of the LC cells (cf. Buhler et al. 1978 and sections I 3.2 and 1.3.4). Plasma NE levels are a measure of sympathetic activity (Axelrod 1974b, Lake et al. 1976b, Buhler et al. 1978, Micalizzi and Pals 1979), I would therefore suggest that the activity of the LC NE cells causes an increase in the activity of the peripheral NE cells. This suggestion is hypothetical, however, a direct projection from the LC to the spinal sympathetic column is small or absent (Smolen et al. 1979), and a partial 6-OHDA-induced lesion of the central NE cells has only a small effect on the plasma MHPG levels (Helmeste et al. 1979).

1.4.7. EFFECTS OF THE LC OUTSIDE THE CNS, CARDIOVASCULAR EFFECTS

Electrical stimulation of the LC. The data on the relationship between the LC and the cardiovascular system are difficult to interpret. Electrical stimulation from electrodes in the region of the LC elicits pressor responses (A&S 8.2., Kawamura et al. 1978a,b, Phillippu et al. 1979b) The relationship between the frequency of the stimulation, and the pressor effect differs from that between the frequency of stimulation and biochemical measures of LC cell activity (MHPG, cyclic-AMP, Korf et al. 1973a, Korf and Sebens 1979); it is therefore uncertain whether the pressor response is due mainly to activation of LC cells or of other elements (cf. Coote et al. 1972). Moreover, electrical stimulation of the LC region, which certainly activated LC cells, as demonstrated by the response of cerebellar Purkinje cells, does not have an effect on the blood pressure (Hoffer et al. 1973), while pressor and depressor responses are elicited by electrical stimulation of regions outside the LC. Adrenoceptor agonists and antagonists injected intracerebrally into the LC region of rats have been reported as eliciting blood pressure responses (Zandberg et al. 1979b), but my view is that these effects are elicited via regions other than the LC just as the effects of electrical stimulation.

Lesions of the LC. Electrolytical and 6-OHDA-induced lesions of the LC region cause hypertension and tachycardia (A&S 8.2., Ogawa et al. 1978, 1979), but on the other hand 6-OHDA-induced lesions of the central CA

cells prevent the development of various experimental hypertensions (renal, denervation, genetical and deoxycorticosterone (DOCA)-salt-induced); once developed, such hypertensions are not reduced by 6-OHDA-induced lesions of central CA cells (Haeusler et al. 1972, Chalmers and Reid 1972, Kubo and Hashimoto 1978, Kubo et al. 1978).

CNS changes concomitant with hypertension. Most authors agree that the most notable change concomitent with the various experimental hypertensions is an increase in the activity of E cells of A2 and possibly also of A1 (determined biochemically, Wijnen et al. 1978, Petty and Reid 1977, 1979, Denoroy et al. 1979, Snyder et al. 1979, Bolme et al. 1979, Renaud et al. 1979, Saavedra 1979). Changes in the LC have been described (Nakamura and Nakamura 1978a,b) but also disputed (Wijnen et al. 1977, Petty and Reid 1977, Versteeg et al. 1976, Denoroy et al. 1979); in any case, if changes in the LC do occur, they are secondary to changes in the E cells (Petty and Reid 1979, Reid and Petty 1979, Saavedra 1979). In DOCA-salt hypertensive rats, a decrease in the central NE turnover has been described, while the peripheral NE turnover was increased (Nakamura et al. 1971, Van Ameringen et al. 1977); evidence has been presented to suggest that the central effects are the cause of the peripheral effects (NE turnover and blood pressure). Adrenoceptor agonists and antagonists applied intracerebroventricularly have a variety of cardiovascular effects via various mechanisms which are not yet understood (Borkowski and Finch 1979, Cohen et al. 1979).

Conclusions on the LC and blood pressure. It is possible that an effect of activity of the LC cells is an increase in blood pressure, mediated by the nucleus solitarius and/or the A2 region; such an increase in blood pressure might be related to an increase in sympathetic activity (cf. section 1.4.6, De Champlain 1978). I tend to consider that the cardiovascular effects are not however the main effect of the LC cells' activity for these reasons: 1) the "functions" of the regions to which the LC projects (section 1.4.1), 2) the absence of correlation between the activity of the LC cells, and the blood pressure and heart rate (Svensson and Thorèn 1979), and 3) the difference between the descending spinal pressor pathway and the descending LC fibers (cf. Chung et al. 1979, Kuypers and Maisky 1977).

2. EXPERIMENTAL RESULTS.

EFFECTS OF INTRA-CEREBRAL INJECTIONS.

EXPERIMENTAL RESULTS: GENERAL INTRODUCTION

Since the discovery that the LC contains the greatest number of NE cell bodies in the CNS, and has by far the most extended target regions in the CNS of all CNS NE cell groups (Dahlström and Fuxe 1964), investigations of this nucleus have become a rage in science. And - like many nuclei, in the current state of neuroscience - the LC has been variously reported as being critically involved in sensory input, in motor output, and in many processes that are, could or should be present between sensors and effectors (for reviews see: Amaral and Sinnamon 1977, Clark 1979, Ramm 1979). All the methods used in functional investigations of the LC have their specific advantages and disadvantages (Routtenberg 1972, Myers 1974, Ranck 1975, Schoenfeld and Hamilton 1977, sections 2.5, p. 107 and 4.2, p. 157). In most studies, lesions, electrical stimulation, or systemic injection of compounds to affect the noradrenergic transmission have been applied, while the intracerebral injection technique has only been used incidentally (Raichle et al. 1975, Broekkamp et al. 1976, Smee et al. 1976, Zandberg et al. 1979b). The intracerebral injection technique has the advantage of providing a more selective influence on cell bodies than on passing fibers, and the opportunity to affect a specified population of receptors in a rather restricted CNS region. A disadvantage is the unpredictable spread of the drug (reviewed in section 4.2), but this can be minimized by applying low dosages in small volumes at a large number of injection sites. In the present section, the behavioral effects of drugs injected intracerebrally into 141 sites in and around the LC of cats are described. The emphasis is laid on the effects of cholinergic (carbachol), (nor)adrenergic (in particular clonidine) and opiate drugs (fentanyl, naloxone); these drugs were selected because the LC cells are activated by cholinergic agonists, and suppressed by α-adrenoceptor and opiate agonists (cf. section 1.2.2). An investigation of the behavioral effects caused by these drugs injected in and near the LC region of freely moving cats was undertaken in order to analyse the behavioral phenomena in which the LC and adjacent regions are involved.

2.1. Carbachol-induced atonia, and paradoxical sleep.

2.1.1. INTRODUCTION

The LC and paradoxical sleep (PS). Although the hypothesis on the function of the LC most often quoted in the text-books is that the LC causes PS or at least the muscular atonia during PS (cf. Jouvet 1972, A&S 8.6., review Ramm 1979), in some more recent studies it has been suggested that the LC actually suppresses PS (cf. Hobson et al. 1975, A&S 8.6., Ramm 1979). The involvement in PS of the LC, other pontine NE-containing cells and the pontine reticular formation is by no means fully understood, and is still a subject for discussion.

Carbachol-induced atonia. Cholinergic receptor agonists (carbachol, oxotremorine, ACh) injected into the pontine tegmentum (i.e. the area in which the LC is situated) are known to induce a state of postural atonia or one resembling PS (Cordeau et al. 1963, George et al. 1964, Baxter 1969, Mitler and Dement 1974, Amatruda et al. 1975). But as a result of 1) insufficient documentation of the position of these injection sites, 2) the scarcety of injection sites in the LC, and 3) the use of relatively high doses of cholinergic agonists, the involvement of the LC and other pontine cells in cholinergic-induced effects is still unresolved.

This study. In this study the effects of low doses of carbachol injected into 141 sites in and around the LC have been investigated. The involvement of pontine NE-cells in the carbachol-induced muscular atonia was investigated. The influence on the carbachol-induced atonia of both 1) α- and β-adrenoceptor blocking agents systemically administered and also of 2) the CA-cell-destroying agent, 6-OHDA, administered intracerebrally was tested. The present data suggest that the carbachol-induced atonia is most probably due to the effects of carbachol on the caudal pontine reticular formation and not on the NE-cells of the LC or the SC. The implications of these results for the role of the pontine NE-cells are discussed.

2.1.2. METHODS

Behavior tests. The methods are described in detail in section 4.1. The following details are relevant only for section 2.1. When the cats adopted a posture indicating muscle relaxation after a intracerebral injection of carbachol (see section 2.1.3), the following additional behavioral tests were carried out to characterize this phenomenon. 1) Tests of the animals' reactions to visual stimuli (objects moving in front of the animals), auditive stimuli (clicks and hissing noises above and behind the animals), and tactile stimuli (touching the animals' limbs, flanks, and ears with the hand); special attention being paid to reactions of the eyes and ears. 2) Motor tests such as lifting a single limb, the head or the whole body from the ground and releasing it; attention being paid to resistance of the legs to passive movements, to active flexion, to the raising of the head, and to the ability to stand, walk, and jump. These tests were carried out after the animals had lain immobile for at least 5 min, but always at least 15 min after the injection. Electromyograms (EMG) were recorded of the neck muscles of 3 of the cats after intracerebral injections of carbachol.

Antagonism. The influence of cholinergic antagonists (intracerebral) and adrenoceptor antagonists (intravenous) on the carbachol-induced atonia was investigated. The carbachol-induced effects were tested 3 times. The second test was carried out after administration of the antagonists; the interval between the initial pair of experimental tests was 2 days, and between the latter 2 tests 2 days after the application of cholinergic antagonists, and 7 days after those of the adrenoceptor antagonists. In addition, in 2 ketamine-anaesthetized (20-30 mg/kg i.m.) cats unilateral lesions were made with 6-OHDA (3 µg in 3 µl, injected at a rate of 1 µl/min).

2.1.3. RESULTS

Description of behavior. In 42 of the 141 injection sites, carbachol (0.5 µg) unilaterally injected caused a state of muscle relaxation. (After a unilateral injection, the cats showed bilateral muscle relaxation; only in 2 cases after a low dose of 50 ng, were the ipsilateral legs more affected than the contralateral ones.) The animals sat down, their heads bent

down and gradually dropping until coming to rest with their noses or cheeks on the ground. Eventually, the animals lay down in an abnormal position; never curled up, but lying on their flanks or bellies with their heads on the floor. The EMG shows that the muscle tone was lost (fig. 16); the animals had become atonic. The criterion used to determine a state of atonia in animals where no EMG was recorded, was that the animal was unable to stand. The latency of the atonia was defined as the moment when the head of an animal with atonia had touched the floor and remained still for at least 5 minutes. The mean latency was 7.3 minutes (range from 20 seconds to 32 minutes in an extreme case). When the animals were left undisturbed, they stayed immobile in this position for 7 to 19 minutes. Then small movements of the head or legs were made for between 10 and 30 seconds. A small tremor was noted in 8 animals superimposed on these movements. A further period of immobility then commenced lasting up to 16 minutes, followed by short periods with movements alternating with longer periods of immobility. The tremor could generalize over the whole body, especially when the animals apparently made attempts to move. After 25 to 95 minutes the animals stood up, made a few staggering steps, sat down, again with their heads gradually sinking to the floor. As long as 140 minutes after an injection the animals remained immobile in the above-mentioned position for several minutes, while even 4 hours after an injection the locomotion had not yet become normal.

Atonia without sleep. Behaviorally, the animals were not asleep and their eyes remained open all the time. The pupils were normal or slightly miotic in 2 cases. The nictitating membrane remained retracted in almost all cases (see paragraph "Localization" below). The eye movements resembled those of awake animals. Special attention was paid to observing whether phasic behavioural signs of paradoxical sleep occurred such as rapid eye movements and sudden movements of the ears, the whiskers, or the facial muscles, but these movements were not detected.

Sensory and motor tests. The cats reacted in every case to visual, auditive or tactile stimuli, but far less than saline-treated or non-treated animals: most times the reactions were simply the orientation of the eyes and ears, but sometimes the head was also raised and turned towards the stimulus. A nictitating membrane that was initially relaxed was retracted. When the animals were lifted from the ground, they hung limply in the hands of the experimentor. The big postural muscles of the neck,

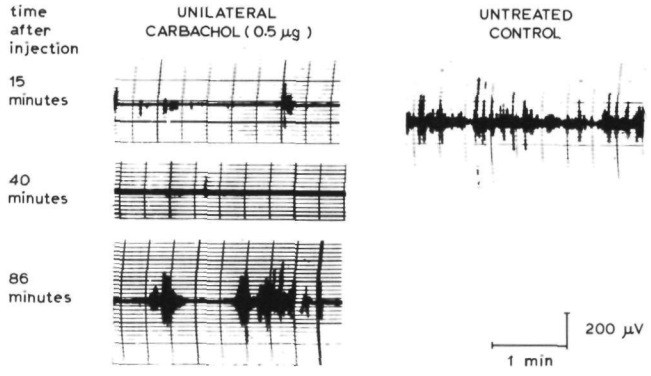


Fig.16 Electromyogram of the neck muscles of a cat after a unilateral intracerebral injection of carbachol; note the absence of muscle tone.

the trunk, and the legs were flacid. The animals could neither stand nor move, but sagged under their own weights. Only small movements of the paws were made.

Effectiveness. The carbachol-induced atonia was reproduced in 79% of the cases (table 10, p. 203); an initially effective site could become ineffective and an initially ineffective site could become effective. In the former cases neither tissue destruction or granulation tissue that could explain the loss of effectiveness could be detected in the Nissl stained material. Two days after an effective injection of 0.5 µg of carbachol, an injection of 50 ng was effective (N = 13). In one cat even lower doses were tested: 20 ng caused atonia, while 10 ng caused some motor disturbances when the animal walked and jumped. No relationship between the occurrence of carbachol-induced atonia and the month or time of injection was detected (respectively $p > 0.05$ and $p > 0.50$, table 13, p. 207).

Antagonism. Atonia induced by carbachol (0.5 µg, unilateral) was completely antagonized by atropine (1.0 µg, intracerebral at the same site

as carbachol, 5 minutes after the beginning of the carbachol-induced atonia, N = 4). The latency of this effect was of the same order of magnitude as the latency of the atonia. On the other hand, mecamylamine in an equivalent dose (0.6 µg) had no or at most a very weak transient effect on the carbachol-induced atonia (N = 4).

Localization. The localization of the injection sites where carbachol (0.5 µg) induced atonia is shown in fig. 17, the correlation between the region of injection and the effectiveness of the sites is shown in fig 18. The occurrence of the carbachol-induced atonia depended on the region of injection ($p < 0.05$, table 13, p 207). The effective sites were mainly situated ventrally to the LC (H -3.0), and caudal to the level of the tegmental nuclei of Gudden (P 1.0). The effective area extended at least from L 1.0 to L 4.0, while its ventral and caudal borderlines could not be determined from the available injection sites. The effective area included the SC, the caudal part of the PCO, the PCC and the NG. Moreover, when an injection into the LC induced atonia, its latency was medium to long, while carbachol into the ventral sites caused atonia with a short latency After injections in ventral parts of the PCC relaxation of the nictitating membrane was observed. Injection sites into the fourth ventricle were not effective. The most effective area was the PCC ($\phi = 0.27$, $p = 0.026$, fig. 18).

Atonia and NE-transmission Large doses of the α-adrenoceptor antagonist phenoxybenzamine (20 mg/kg, i.v.) and the β-adrenoceptor antagonist *dl*-propranolol (2 mg/kg, i.v.) sedated and tranquilized the animals behaviorally (cf. Leszkovszky and Tardos 1965, Nickerson and Collier 1975), after phenoxybenzamine the nictitating membrane was relaxed and the eye-lids were half closed. These cats were sedated, but did not show any effect comparable to that induced by carbachol. The carbachol-induced atonia remained unaffected by these drugs, the animals were sedated, but it was only after an intracerebral injection of carbachol (0.5 µg) that they lay atonically with their heads limply on the ground. A unilateral intracerebral injection of the neurotoxin 6-OHDA caused extensive unspecific brain damage (fig. 19) and not the expected destruction of the NE-cells only, all of the LC-cells were destroyed. Carbachol (0.5 µg) injected at the same site as 6-OHDA was as effective as before in inducing atonia.

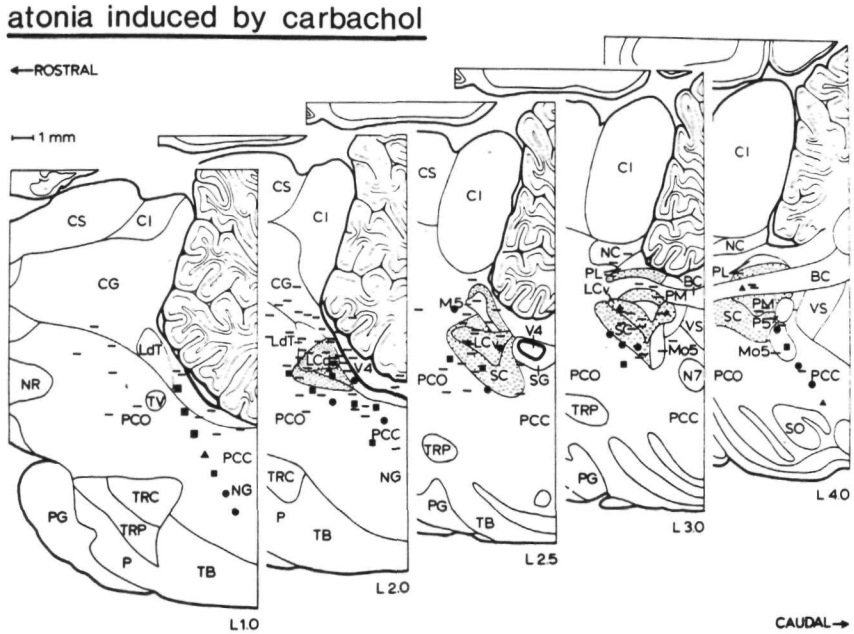


Fig. 17 ▲ = *atonia with a latency longer than 10 minutes*
● = *atonia with a latency between 5 and 10 minutes*
■ = *atonia with a latency shorter than 5 minutes*
– = *no carbachol-induced atonia*

Localization of the injection sites where carbachol (0.5 µg, injected unilaterally) caused muscular atonia.

Other drugs. The carbachol-induced atonia was not mimicked by physostigmine (2 or 20 µg, see discussion), nor by saline, nor by the other drugs mentioned in the " General methods" (section 4.1 for the drugs and dosages, and table 16, p. 210 for the number of carbachol-effective sites tested with each drug).

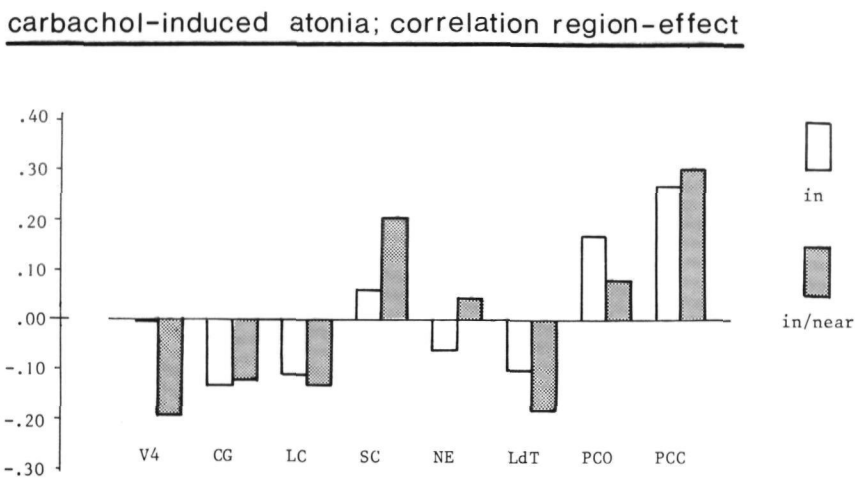


Fig. 18 Correlation (ϕ-coefficient) between the region of injection and the effectiveness of carbachol (0.5 µg) in inducing atonia; the PCC is considered to be the region involved.

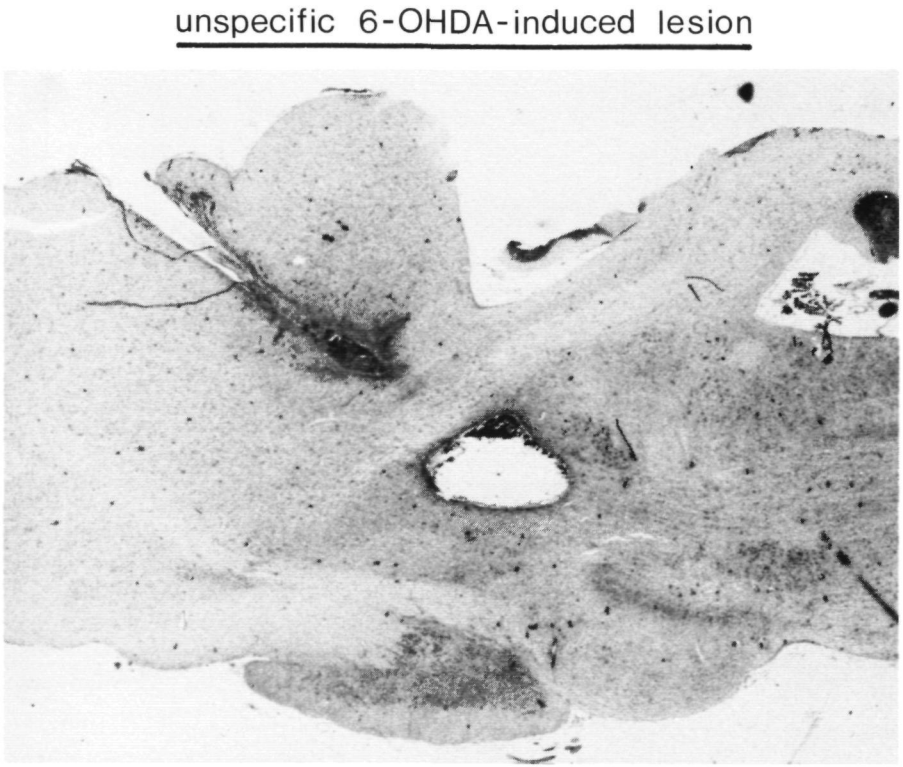


Fig.19 A Nissl-stained parasagittal section showing the effects of 6-OHDA (3 µg) injected intracerebrally into the region of the pontine NE cells; note the extensive unspecific tissue damage (this section is taken from the parasagittal planeL 3.0; cf. the location of NE cells and carbachol-effective sites in fig. 17).

2.1.4. DISCUSSION

Specificity of the receptors. The atonia induced by carbachol injected into the pontine tegmentum appeared to be due to specific interaction between carbachol and muscarinic acetylcholine receptors, since it could be blocked by muscarinic and not by nicotinic acetylcholine receptor blocking agents. This is in agreement with the results of George et al. (1964) and Mitler and Dement (1974). The AChE blocking agent physostigmine was however ineffective, but one has to expect physostigmine to be effective only when there is a sufficient release of endogenous ACh; this is probably not the

case in cats that are awake (cf. Hoshino and Pompeiano 1976, Sitaram et al. 1976, Kuhar et al. 1978).

Effects via the ventricle? The data presented here indicate that the carbachol-induced atonia was not due to diffusion of the drug to the ventricle, and interactions with remote ACh receptors, for the following reasons: 1) carbachol injected into the fourth ventricle or into sites which were in direct connection with the fourth ventricle (cf. section 2.6) did not cause atonia; 2) sites remote from the ventricular wall were effective while most sites near the ventricular wall were not; and 3) the occurrence of carbachol-induced atonia was negatively correlated with the occurrence of clonidine-induced vomiting (table 15, p. 209), most probably due to interactions of clonidine with receptors on the ventricular wall (section 2.6).

Effects via blood vessels? Cholinergic and adrenoceptor agonists influence not only neurons, but also the local cerebral circulation (Edvinsson 1975). Nevertheless, neither α-adrenoceptor agonists (clonidine, oxymetazoline), nor a β-adrenoceptor agonist (isoprenaline), nor *l*-NE mimicked the carbachol-induced atonia, suggesting that it is probably not due to the effect of carbachol on the local cerebral circulation. Carbachol injected in and near the LC has been reported as influencing the general cerebral circulation (Raichle et al. 1975), but the threshold dose for this effect was 100 times as large as a dose eliciting atonia. It follows that the carbachol-induced atonia is probably not an indirect result of influences on the general cerebral circulation.

Changing effectiveness? In a series of repeated injections the effectiveness of carbachol in eliciting atonia has been reported as decreasing (George et al. 1964, Baxter 1969, Mitler and Dement 1974) or increasing (Amatruda et al. 1975). A previous effective site could become ineffective and vice versa (table 10, p. 203), but both cases were rare, and occurred to the same degree: no trend towards an increase or decrease in effectiveness was demonstrated.

Region involved in the carbachol-induced atonia. The occurrence of effective sites was high in the subcoeruleus region (SC) and in the nucleus pontis centralis caudalis (PCC). The following factors suggest to my mind that the carbachol-induced atonia is due to interactions of carbachol with receptors on cells of the PCC.

1. In the cat, the NE cells are situated scattered around the brachium conjunctivum, intermingled with non-catecholaminergic cells, which are regarded as displaced cells of the pontine reticular formation or the central gray (Ramon Moliner 1974). When carbachol injected into the LC (i.e. the dorsal part of the pontine NE area) caused atonia, its latency was medium to long; diffussion of carbachol to more ventral sites probably occurred, where short latency responses could be evoked.
2. Blockade of the α- and β-(nor)adrenergic transmission did not disrupt the carbachol-induced atonia. The α- and β-blocking agents used are nevertheless capable of penetrating the brain (Masuoka and Hansson 1967a,b), and the doses given were large enough to diminish spinal and cortical NE transmission (Andén et al. 1966e, Austin and Takaori 1976).
3. A 6-OHDA-induced lesion which destroyed all NE cells did not affect the carbachol-induced atonia. (In the cat, the 6-OHDA-induced lesion was not specific to CA cells (Ungerstedt, personal communication and this study); in the rat 6-OHDA is often but not always selective for CA cells or fibers (Ungerstedt 1971b,Bloom 1975).)
4. Although both acetylcholine and the α-adrenoceptor antagonist piperoxane increase the firing rate of LC cells (section 1.2), piperoxane did not mimic the carbachol-induced atonia. This is also an indication that cells other than the NE cells are involved.

In conclusion, these results based on a large number of injection sites using low doses of carbachol, and a careful histological determination of the injection sites themselves give firm support to the suggestion of Amatruda et al. (1975) that non-noradrenergic pontine reticular cells contain the cholinergic receptors through which carbachol causes atonia.

Implications: muscular atonia and paradoxical sleep. Carbachol injected into the PCC caused muscular atonia in cats, although the animals remained awake and showed no behavioral signs of sleep or paradoxical sleep. This is in agreement with the results of Mitler and Dement (1974) but not with those of Cordeau et al. (1963), George et al. (1964), Baxter (1969), and Amatruda et al (1975), who reported that the cats were asleep. Electrolytic lesions in this region result either in a normal amount of PS or a complete absence of it depending on the extent of the lesion; when a normal amount of PS is found, it has the phasic and tonic characteristics of PS, except muscular atonia, which is completely absent (with the animals behaving as if they are dreaming, "oneiric" or "hallucinatoir behavior")

(cf. Henley and Morrison 1974, Jones et al. 1977, Ramm 1979, Sastre and Jouvet 1979, Jones 1979). The effects of carbachol injected into this region are the opposite of the effects of lesions; if it is assumed that carbachol activates the cells involved, both lesions and intracerebral injections reflect the effects of activity of the region involved (cf. Zülch 1976). Consequently, I assume that conclusions regarding the brain region containing the receptors through which carbachol causes atonia also apply to the atonia during PS. Therefore it is concluded:

1. Cholinergic effects on non-noradrenergic cells in the PCC generate the atonia during PS (Jones et al. 1977, Jouvet 1962).
2. These cells generate merely the atonia and not the whole pattern of PS (cf. Henley and Morrison 1974, Jones et al. 1977, Mitler and Dement 1974).

The conclusion that the pontine NE cells do not cause the muscular relaxation during PS is in agreement with several recent findings. 1) Electrolytic lesions in the NE area disrupt atonia during PS, but 6-OHDA-induced lesions, which can be more selective for CA cells, do not affect atonia during PS (cf. Jones et al. 1977). 2) The influence of spinal NE terminals, the cell bodies of which are situated in the LC and SC (Nygren and Olson 1977), on spinal reflexes is different from the influence of PS on spinal reflexes (Giaquinto et al. 1964a,b, and section 3.1.1). Spinal NE seems to promote locomotion rather than cause atonia (Grillner 1975). 3) The maintained activity of LC cells is lowest during PS, during PS these cells are silent for a long time (section 1.3.4). 4) Electrolytic lesions of the PCC which leave the pontine NE cells intact completely eliminate PS (Jones 1979). Despite these findings Jouvet continues to suggest that the LC generates atonia (Sastre and Jouvet 1979)

Does the LC suppress PS? The hypothesis that the LC does not generate elements of PS, but on the contrary terminates phases of PS has been proposed by a number of authors (cf. A&S 8.6., Ramm 1979). But even if the LC does suppress PS, this is not a major effect of the activity of the LC cells.

1. After an extensive lesion of the LC region, the amount of PS is reduced during the first week, but its amount and the duration of the PS phases return to normal values in the second week (Jones et al. 1977). The reduction in PS is probably due to a temporary disturbance in the PCC after a lesion of the NE region (after a CNS lesion, the region

temporarily affected is much larger than the region permanently destroyed, cf. Schoenfeld and Hamilton 1977). The pontine NE cells are clearly not necessary for the termination of phases of PS.

2. Electrical stimulation with electrodes in the NE region causes low-voltage-high-frequency activity in the neocortical EEG and theta-rhythm in the hippocampus, which is correlated with active waking (Macadar et al. 1974); this effect has been attributed to the LC, but indications have been presented that it is due to cells or fibers of the PCC rather than to NE cells (Robinson et al. 1978, Whishaw et al. 1978, section 1.4.3).
3. Investigations with drugs affecting LC-induced effects on LC target cells have yielded contradictory results (cf. Jones et al. 1977). The majority of recent studies indicate that stimulation of α-adrenoceptors on LC target cells decreases PS (e.g. Autret et al. 1977, Leppävuori and Putkonen 1978, King 1979), but in some studies an increase in PS has been reported (e.g. Miletich et al. 1979).

In summary, when towards the end of a PS phase, the LC cells become active, this activity might be a cause of the end of the PS phase, but (if this is the case) it is a reflection of the general effect of the LC on CNS signal processing rather than a specific "PS-suppression-function". The "function" of the LC must be related to the effects of the LC cell activity, and thereby related to those periods in which the activity of the LC cells is high, i.e. in active waking rather than PS (cf. section 1.3.4).

The reciprocal interaction hypothesis. Only members of Hobson's group have gone as far as formulating a hypothesis that there is reciprocal interaction in PS between the LC cells and the giant cells of the caudal pontine reticular formation (cf. fig. 20); this hypothetical model is intended to explain alternation in the sleep cycle (McCarley and Hobson 1975, Hobson et al. 1975, Hobson and McCarley 1977, Hobson 1978). I am in agreement with one element of the reciprocal interaction hypothesis: I too think that cells in the PCC, which partly overlaps the region of the giant cells, generate atonia during PS (see above). But it is dubious whether the generation of atonia during PS is the only "function" of these cells; cells in this region are in any case also involved in other activities (cf. Morrison 1978, Siegel and McGinty 1978, Akaike et al. 1978). That part of the reciprocal interaction hypothesis which deals

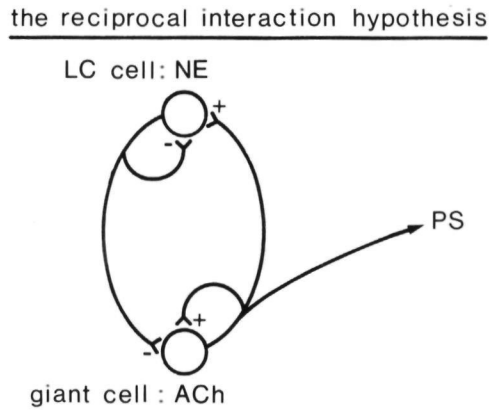


Fig.20 The reciprocal interaction hypothesis (Hobson and McCarley 1977). It is suggested that reciprocal interactions between the pontine giant cells and the LC explain the alternation of sleep phases.

with the LC is questionable and by no means complete.

1. The LC is in any case not the most important part of the CNS that ends PS phases (see above).
2. In the reciprocal interaction hypothesis, reciprocal fiber connections between the LC and the giant cells were postulated, but it is most probable that the LC does not receive any fibers from the giant cells (cf. references in section 1.2.1 and table 6, p. 186), and that the giant cell region receives at most a limited LC projection (cf. table 8, p. 194, and Swanson and Hartman 1975).
3. A necessary element of the reciprocal interaction hypothesis is a feedback loop in the LC which causes the LC cells to fire more slowly after afferent activating pulses from the giant cells, than they would do without these afferent activating pulses (cf. fig. 21). (In the LC lateral suppression rather than feedback suppression occurs (section 1.3.5), but this does not necessarily invalidate the reciprocal interaction hypothesis.) A more serious objection is that a necessary

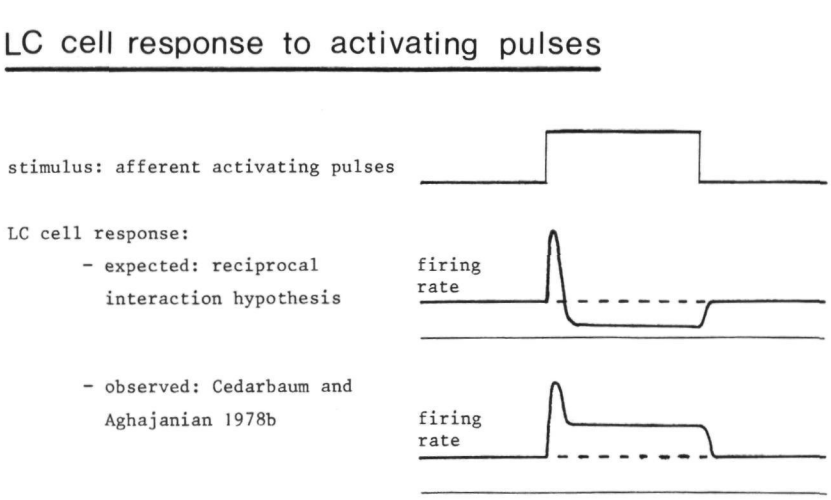


Fig.21 The effects of afferent activating action potentials on the firing rate of LC cells, and their implications for the reciprocal interaction hypothesis. The actual LC cell firing rate differs from the firing rate to be expected on the basis of the reciprocal interaction hypothesis.

assumption of the reciprocal interaction hypothesis (that a reduction of the LC cells' steady firing rate in the presence of afferent activating pulses takes place, cf. fig. 21) seems to be mistaken (Cedarbaum and Aghajanian 1978b, fig. 21).

Taking all these findings together one tends to reject the reciprocal interaction hypothesis.

Pontine NE cells and PS. Two conclusions can be drawn from data presented in the literature and in this study:

1. It are the non-NE PCC cells and not the LC cells that generate atonia during PS.
2. If the LC's "function" is that of a generalized influence on CNS signal processing and metabolism (section 3.2), than an implication of such a generalized "function" may be that the LC cells' activity during PS might result in the termination of PS.

2 2 Carbachol-induced defense, and anxiety

2.2.1. INTRODUCTION

Electrical stimulation of cells in the LC area of the stump-tailed monkey has been reported as causing behavioral responses similar to those shown to threatening stimuli (Redmond et al. 1976). These and related data are taken as support for the suggestion of an "alarm function" for the LC (Redmond 1977), manipulations of the LC or the central NE transmission were taken as models of human anxiety. Electrical stimulation of cells in the LC area of the rat caused however only very rarely flight reactions (Crow 1972, Simon et al. 1975). For years an opposite view was generally accepted: electrical stimulation of LC cells was believed to cause the intracranial self-stimulation elicited with electrodes in the LC region (section 3.1.4, A&S 8.8.). The "anxiety" of rats as measured by various behavioral tests was either not affected by a lesion of the LC or its ascending fibers (Crow et al. 1978, Mason and Fibiger 1979e), or was increased (Mason et al. 1978), which is contrary to what would be expected if the LC is an "alarm system".

The present section deals with defense reactions caused by carbachol injected into the pontine tegmentum of the cat. It is shown that defense reactions are due to effects of carbachol not on the NE cells but on the rostral pontine reticular formation.

2.2.2. METHODS

The methods are described in detail in section 4.1. Response criteria relevant to the present section are described in the section "Results".

2.2.3. RESULTS

Description of behavior. After unilateral injections of carbachol (0.5 µg) growling and/or hissing was noticed in 11 of 141 sites. These sites involved 7 cats (3 males and 4 females). Growling and hissing occurred between 15 and 210 minutes after the injection when the cats were approached by the experimentor. It was accompanied by open mouth threats and attempts to strike with the claws and to bite, followed by quick withdrawal. When handled, these cats bit or hit the experimentor suddenly. Other elements of agonistic behavior occurred small pupils (n=3), wide pupils (n=6), ears turned sidewards (n=3), flattened ears (n=6) and lashing tail movements (n=11). (Lashing tail movements and small or wide pupils were noted after injections into other sites too, but only sites where growling and hissing were elicited were regarded as effective.) Other vocalizations from the agonistic repertoire, for example caterwauling of fighting tom cats, or screams, did not occur. In 2 of these 11 cases spontaneous hissing was observed: without any noticeable change in the observation room these 2 cats suddenly turned their backs to the rearwall, hissed, and raised their forepaws. The latencies of this behavior were 6 min, 15 sec and 14 min, 20 sec.

At 2 of the 3 sites tested the growling and hissing were reproducible. (In one animal 4 repeated injections of carbachol caused growling, hissing and biting, after which the experiments with this animal had to be stopped, since it could not be handled without severe restraint.) During the days before and after the carbachol injections the remaining cats that directed their defense reactions at the experimentor responded with purring and rubbing their heads against objects when the experimentor approached them, just as they normally would. The cats that growled and hissed did not show signs of distress before or during the injection. A dose of 50 ng of carbachol (n=3) was not effective at the sites were 0.5 µg was. A tendency was present for defense reactions to occur more often in the months April and October ($p < 0.10$, table 13, p. 207); this might be due to seasonal hormonal rhythms in the cat. No relationship between the time of injection and the occurrence of carbachol-induced defense reactions was detected ($p > 0.50$, table 13, p. 207).

Other drugs. The carbachol-induced hissing and growling were not mimicked by saline, a local anaesthetic (procaine), or other drugs (see section 4.1

for the drugs and doses, and table 16, p. 210 for the number of carbachol-effective sites tested with each drug).

Localization. The injection sites from which carbachol (0.5 µg) caused growling and hissing are plotted in fig. 22, and enumerated in tables 11 and 12 and fig. 23. The occurrence of carbachol-induced hissing and growling depended on the region of injection ($p < 0.001$, table 13, p. 207). The most effective region was the nucleus pontis centralis oralis (PCO, $\phi = 0.51$, $p < 0.001$, fig. 23), while no effective sites were present in the PCC nor in the fourth ventricle.

2.2.4. DISCUSSION

Defense reactions and the PCO. Carbachol-induced agonistic behavior in the cat (growling, hissing, attempts to strike and bite) is similar to its species-specific defense behavior (Leyhausen 1973). The effective region in this respect was evidently the PCO. This is in agreement with some other studies where carbachol injections or electrical stimulation of this region or the adjacent mesencephalic central gray were carried out (Hernandez-Péon et al. 1963, Baxter 1968, Allikmets 1974).

Interpretation of carbachol-induced defense. The carbachol-induced defense reactions cannot be regarded as an emotional reaction to the carbachol-induced atonia, because the effects were mutually uncorrelated (table 15, p. 209) and were elicited from different regions. It might be speculated that carbachol injected into the PCO caused either sensations of pain (cf. Teschemacher et al. 1973, Lewis and Gebhart 1977) and pain-induced aggression, or a more general change in the cat's perception of its environment, as is suggested by the 2 cats which defended themselves against a non-existant threat.

"Normal" and "pathological" anxiety. Klein et al. (1978) define "anxiety" as a state of being *"uneasy, apprehensive, or worried about what may happen"*. A distinction is made between "normal" (situational) anxiety for which some good reason is present (stressor, peripheral disturbance, justificable anxious expectancy), and pathological anxiety ("anxiety neurosis", "panic" or "panic attack", Feighner et al. 1972, Klein et al. 1978, McNair and Fisher 1978). *"What differentiates (panic attacks) from chronic anxiety is the sudden exacerbation of distress associated with*

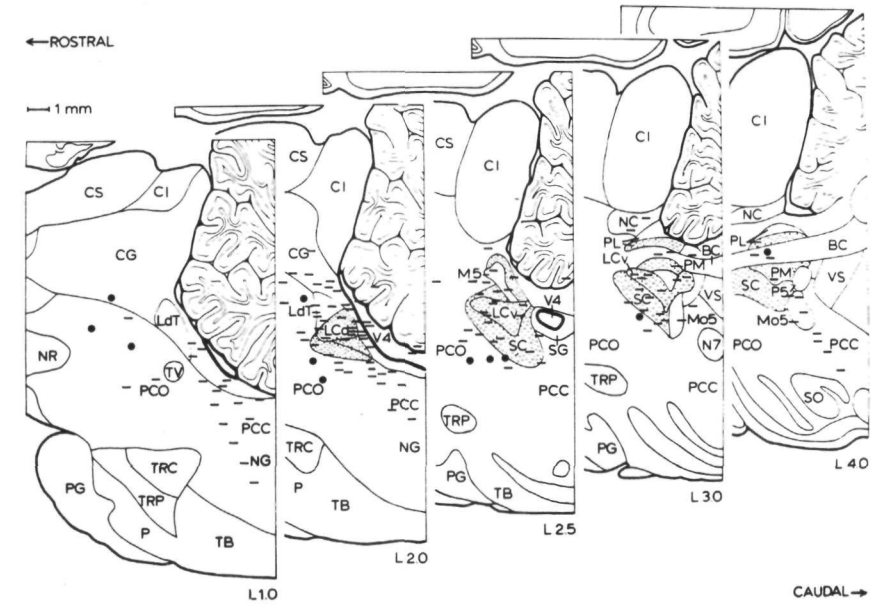


Fig. 22 ● = *carbachol-induced defense reactions*
– = *no carbachol-induced defense reactions*
Localization of the injection sites in which carbachol (0.5 µg, injected unilaterally) caused defense reactions

feelings of impending doom, often erupting in a completely calm person in an unthreatening setting. The idea that panic is simply due to increasing anxiety finally boiling over does not fit the phenomenological facts nor ..... the psychopharmacological facts" (Klein et al. 1978, see also Feighner et al. 1972). These panic attacks (or anxiety attacks) are the symptom best discriminating between "pathological" anxiety and other anxiety-related states (McNair and Fisher 1978).

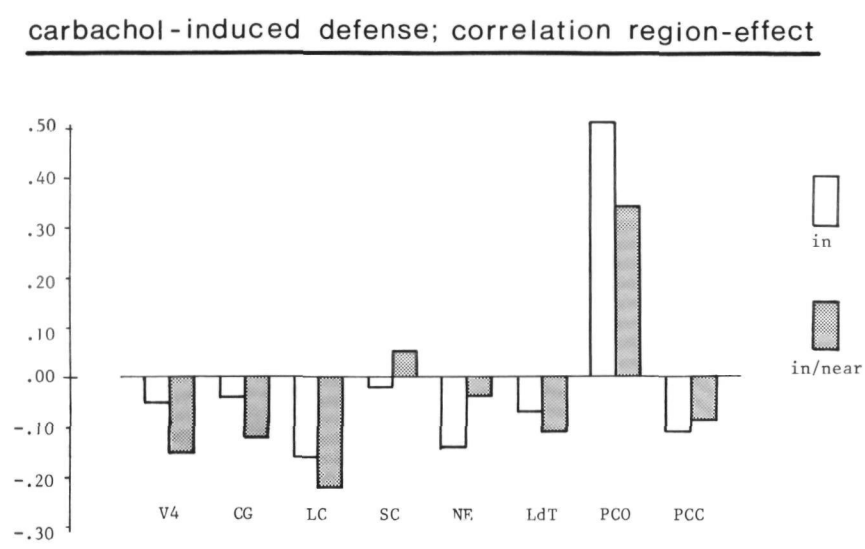


Fig.23 Correlation (ϕ-coefficient) between the region of injection and the occurrence of injection sites from where carbachol (0.5 µg) elicited defense reactions; the PCO is shown to be the most effective region involved.

The "LC anxiety" hypothesis. Redmond has postulated the "LC anxiety" hypothesis: *"brain NE systems, such as the LC, are involved in the production of fear or anxiety"* (Redmond and Huang 1979; Redmond et al. 1976, Redmond 1977, for a critical discussion see Mason and Fibiger 1979L and Redmond and Huang 1979). Judging from other remarks by these authors it appears that the intended meaning of the remark quoted above is (in terms of section 5.4): "activity of central NE neurons, such as the LC neurons, is an effect of threatening stimuli, and is a cause of flight or defense behavior", which would relate the "function" of the LC to situational ("normal") anxiety.

Experiments: flight and defense, and the LC. Experimental manipulations of the LC in the stump-tailed monkey have been reported as eliciting effects in agreement with the "LC anxiety" hypothesis (Redmond et al. 1976, Redmond 1977, Redmond and Huang 1979). Electrical stimulation of this region in man (without precise localization however) causes feelings of

fear (Nashold 1974). In the rat however, flight reactions are found very rarely after electrical stimulation of this region (Crow et al. 1972, Simon et al. 1975). Destruction of the LC or its ascending fibers in the rat has been reported as having either no influence at all, or an influence opposite to that expected on the basis of the "LC anxiety" hypothesis in various anxiety-eliciting situations (noxious stimuli, novel objects, conspecific males) (Mason et al. 1978a, Mason and Fibiger 1979e,L, File et al. 1979, see section 3.1.6). In the present study, carbachol-induced defense in the cat was due to the PCO rather than the LC. With intracerebral injections, cell bodies are affected more selectively, while in electrical stimulation, the threshold stimulation current is generally lower for myelinated fibers than for cell bodies (Ranck 1975). My data in the cat, and the data of Redmond's group in the stump-tailed monkey, are in agreement if one assumes that the changes in flight and defense behavior described by Redmond's group were due actually to stimulation or interruption of the afferent or efferent fibers of the PCO.

Drugs and anxiety Drug-treatment of situational ("normal") and pathological anxiety is different. situational anxiety is generally treated with minor tranquillizers like benzodiazepines (mainly diazepam, valium) or β-adrenoceptor blocking agents (mainly propranolol) (see below), while NE re-uptake blocking tricyclic antidepressants seem to be the drugs chosen to treat pathological anxiety (Klein et al. 1978); in the latter cases propranolol is ineffective (Floru 1977, Greenblatt and Shader 1978).

Benzodiazepines, anxiety and the LC. The drugs most often used in the treatment of situational anxiety are the benzodiazepines (review Haefely 1978). The benzodiazepines enhance the amount of GABA released, thereby enhancing the GABA-induced effects. GABA suppresses the LC cells (section 1.2.2), and benzodiazepines decrease the central NE turnover (see Haefely 1978), these data have been considered as supporting the LC anxiety hypothesis (Redmond 1977, Redmond and Huang 1979). But the benzodiazepine-induced NE effects showed tolerance, while the anti-anxiety action of benzodiazepines showed sensitization and no tolerance (Haefely 1978). Consequently, the anti-anxiety action of benzodiazepines is probably not caused via the LC cells, and the action of benzodiazepines on the LC does not support the LC anxiety hypothesis.

β-Adrenoceptor blocking agents, anxiety and the LC. β-Adrenoceptor blocking agents (mainly propranolol) are used in the treatment of situational anxiety (reviews Floru 1977, Greenblatt and Shader 1978). This anti-anxiety action has been considered as supporting the LC anxiety hypothesis (Redmond 1977, Redmond and Huang 1979). The central and peripheral NE cells are active in the presence of threatening stimuli (or stressors) (sections 1.3.2 and 1.3.4). The peripheral effects (such as tachycardia and tremulousness) of anxiety-eliciting stimuli are mediated via β-adrenoceptors; these effects probably increase the central manifestations of anxiety, which in their turn aggravate the peripheral effects once again (a self-reinforcing action, Greenblatt and Shader 1978). Central and peripheral manifestations of anxiety are difficult to distinguish, but the majority of investigations indicate that β-adrenoceptor blocking agents reduce the somatic rather than the psychic manifestations of anxiety; the anti-anxiety action of propranolol is mainly, but not exclusively, due to blockade of peripheral β-adrenoceptors (Floru 1977, Greenblatt and Shader 1978). Moreover, since *"in general ... diazepam proved superior to ... propranolol"* (Greenblatt and Shader 1978), the anti-anxiety action of propranolol is at most a weak support of the LC anxiety hypothesis.

Conclusions, the LC and fear/anxiety. In terms of the functional concept developed in section 5.4, according to the LC anxiety hypothesis the LC cells are supposed to say: "there is a threatening stimulus; flee or defend". From the data published in the literature it appears that the LC cells are activated not only by threat but also by non-threatening stimuli (section 1.3.2); the behavioral response to these milder, non-threatening stimuli would also be "flee or defend", if the LC anxiety hypothesis were generally valid. The LC anxiety hypothesis could be saved by making extra assumptions, but for the time being I prefer the simpler functional suggestion presented in section 3.2.1. My view is that Redmond and Huang's (1979) remark: *"fear and anxiety is only a part of the function of brain NE systems"* is correct. The implications of these ideas will be elaborated in section 3.2.1.

2.3. Carbachol-induced prolonged vocalizations.

2.3.1. INTRODUCTION

Cells of the dorsal pontine tegmentum are reported as being involved in many activities (sections 1.1 and 3). My findings were that carbachol injected into this area caused disturbed vocalizations; the most effective area appeared to be the PCO.

2.3.2. METHODS

All the relevant details of the methods employed are described in section 4.1.

2.3.3. RESULTS

Description of behavior. Prolonged, hoarse vocalizations were heard after unilateral injections of carbachol (0.5 µg) into 18 of the 141 sites involving 16 cats (10 males and 6 females; none of the females were on heat). The vocalizations were similar in the various cats. Normal "mews" had a duration of 0.2 to 0.6 sec, and occasionally 1.0 sec. The mean duration of the prolonged vocalizations was 4.8 $\pm$ 0.2 sec (mean and s.e.m., the range was 1.2-10.6 sec, based on 265 consecutive vocalizations by 6 cats). The mean latency was 4 min 45 sec (range 2 min 5 sec to 10 min 15 sec) and the mean duration of the period during which prolonged vocalizations were uttered was 9 min 5 sec (range 1 min 15 sec to 18 min 30 sec). The prolonged vocalizations were uttered in bursts of 6-13 per minute, alternating with periods of single vocalizations. Such vocalizations were never uttered by untreated cats and they differed from the prolonged high pitched cries of kittens left alone, from the prolonged caterwauling of fighting tom cats, and from the prolonged cries of female cats on heat. No relationship between the occurrence of carbachol-induced prolonged vocalizations and the date or time of injections was detected (respectively $p > 0.30$, $p > 0.80$, table 13, p. 207).

Drug effects. The sites where carbachol caused prolonged vocalizations were tested with procaine (5 µg); at 4 of these sites, procaine induced vocalizations with a mean latency of 45 sec, and a mean duration of 20 sec. In carbachol-ineffective sites procaine was also ineffective. The effects mentioned in the section on "Methods" (section 2.1) did not modify carbachol-induced prolonged, hoarse vocalizations (see "Methods", p. 70, and table 16, p. 210, for the number of carbachol-effective sites tested). Incidentally, injections of saline or certain drugs (oxytetracycline, piperoxane, morphine) were followed by an increase in the frequency of the vocalizations, but these were of normal pitch and duration, and they were elicited from carbachol-ineffective sites.

Localization. The localization of the injection sites where carbachol (0.5 µg) caused prolonged vocalizations is shown in fig. 24 and indicated in table 11, p. 204, and fig. 25). The most effective sites were found in and near the PCO. Effective sites were not found laterally further than the L 2.0 plane, nor in the fourth ventricle.

2.3.4. DISCUSSION

The carbachol-induced prolonged vocalizations could be due to the actions of carbachol on cell bodies as well as on passing fibers, since procaine injected into this area caused similar vocalizations. The prolonged vocalizations cannot be regarded as an emotional reaction to the carbachol-induced atonia, since the effects were not mutually correlated and elicited from different sites. Electrical stimulation in the PCO and in the adjacent caudal central gray also causes vocalizations, sometimes associated with growling (Kanai and Wang 1962, Jürgens and Ploog 1970). Both defense reactions and prolonged vocalizations were elicited from the PCO, but the cells mediating these two effects are probably different, since 1) procaine never caused defense reactions, and 2) both effects occurred together as well as separately after both injections of carbachol and electrical stimulation (Kanai and Wang 1962).

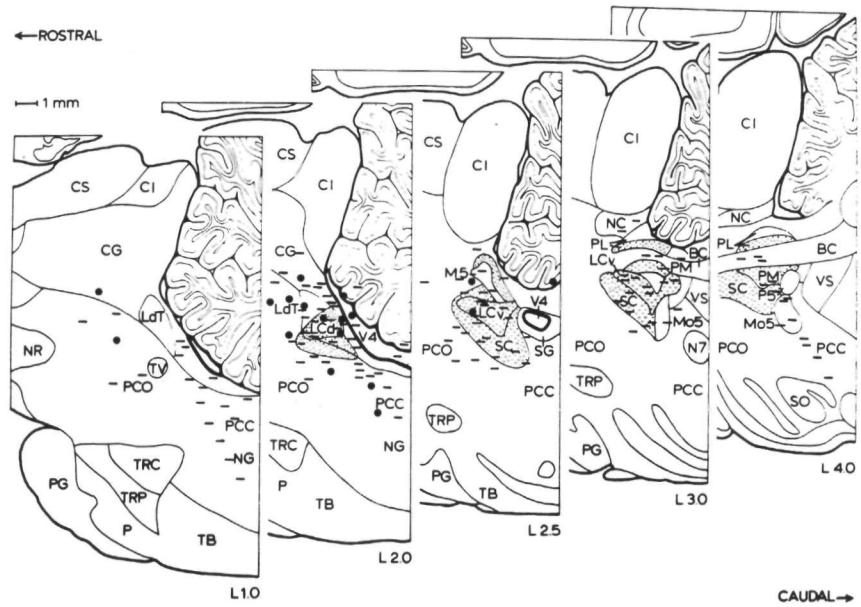


Fig. 24 ● = *prolonged vocalizations*
– = *no carbachol-induced prolonged vocalizations*
Localization of the injection sites where carbachol (0.5 µg, injected unilaterally) caused prolonged vocalizations.

The individual vocalizations were abnormal; this is an indication that carbachol affected a part of the brain close to the executive (motor) mechanism for vocalizations. Direct fibers have been described from the adjacent central gray to those regions in the medulla oblongata which innervate the muscles of the vocal apparatus (Jürgens and Pratt 1979).

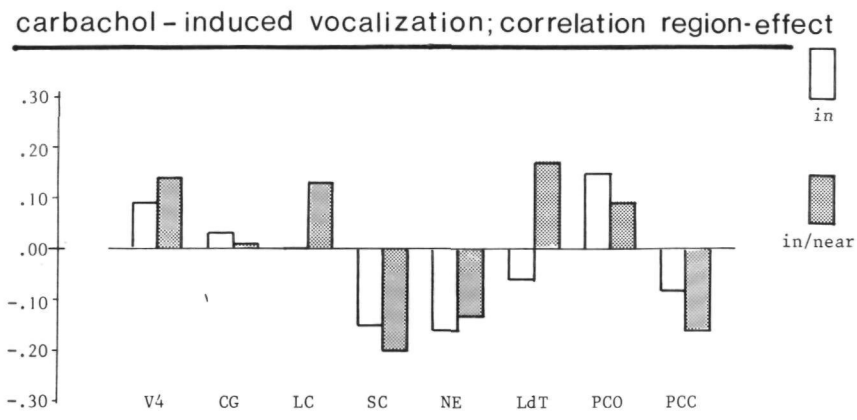


Fig.25 Correlation (ϕ-coefficient) between the region of injection and the occurrence of injection sites where carbachol (0.5 µg) elicited prolonged vocalizations; the PCO is shown to be the most effective region involved.

2.4. Carbachol-induced turning.

2.4.1. INTRODUCTION

Unilateral electrolytic lesions of the LC region or the dorsal or ventral NE bundle of the rat have been reported as causing spontaneous and drug-induced (apomorphine and *d*-amphetamine) turnings (rotations) (Pycock et al. 1975, Donaldson 1976a,b,c,d). The direction of the rotations and other details depended on the region destroyed and the length of time after the lesion (Donaldson et al. 1976a,b,c,d, 1977). These authors suggested that the turnings after lesions of the LC region are due to destruction of the NE cells of the LC, and that this turning is a model of the influence of the LC on behavior; they put forward a speculative hypothesis on the influence of the LC on the dopaminergic nigro-neostriatal system.

In the present section, the effect of unilateral injections into the dorsolateral pontine tegmentum on asymmetric behavior is described. Distinct regions where carbachol elicited either ipsiversive or contraversive rotations are demarcated. It is suggested that manipulations of the pontine NE cell bodies do not cause asymmetric behavior or turning.

2.4.2. METHODS

All the relevant details of the methods employed are described in section 4.1.

2.4.3. RESULTS

Description of behavior. Asymmetric behavior was elicited by unilateral injections of carbachol (0.5 µg). An injection was considered to have elicited asymmetric behavior when the cat held its head sidewards, at an angle of more than 90^{o} with the body-axis, for more than one minute in the first 15 minutes after the injection. This could be accompanied by rotations, but when it was so accompanied by grooming, it was not counted

as asymmetric behavior. On the basis of this criterium, asymmetric behavior occurred after an unilateral injection of carbachol (0.5 µg) in 52 of the 141 cases: 10 ipsiversive and 42 contraversive. Injections of saline into this area caused no cases of asymmetric behavior. The mean latency of the asymmetric behavior was 2 min 25 sec (range 30 sec to 5 min); the duration was more than 45 minutes in all the experiments. Asymmetric behavior was reproducible in 77% of the tests (n=22) (table 10, p. 203). In 24 of the 141 cases the cats made 6 or more rotations during the first 15 minutes, which is the minimum amount required to achieve $p < 0.05$ in a two-tailed binomial test. Of these 24 cases 3 made statistically significant more rotations in the ipsilateral direction and 12 in the contralateral direction. In cases of ipsiversive and contraversive rotation the cats circled around their stationary hindlegs. The turning was compulsive: when the animals were raised from the floor, they still tried to turn in circles. Contraversive turning and a statistically significant number of contralateral rotations occurred after unilateral injections of 50 ng of carbachol (n=3). The asymmetric behavior caused by 0.5 µg of carbachol was antagonized by intracerebral injections of the muscarine receptor antagonist atropine (1 µg, n=3) but not by an equivalent dose of the nicotine receptor antagonist mecamylamine (0.6 µg, n=2). Antagonism of the ipsiversive rotations was not tested. No relationship between the occurrence of carbachol-induced turning and the date or time of injection was detected (respectively $p > 0.50$, $p > 0.50$, table 13, p. 207).

Other drugs. The other drugs mentioned in the section on "Methods" did not mimic the carbachol-induced asymmetric behavior (see section 4.1 for doses, and table 16, p. 210, for the number of carbachol-effective sites tested with each drug).

Localization. The localization of the injection sites where carbachol (0.5 µg) induced asymmetric behavior is shown in fig. 26; the correlation between the region of injection and the effectiveness of the sites is shown in fig. 27. The occurrence of the carbachol-induced turning depended on the region of injection ($p < 0.01$, table 13). Ipsiversive turning was elicited exclusively from injection sites in the rostral pole of the NE region, and in the PCO just rostral to it, i.e. near the nucleus laterodorsalis tegmenti (LdT). The PCC and the fourth ventricle were ineffective. Sites from which contraversive turning was elicited were situated

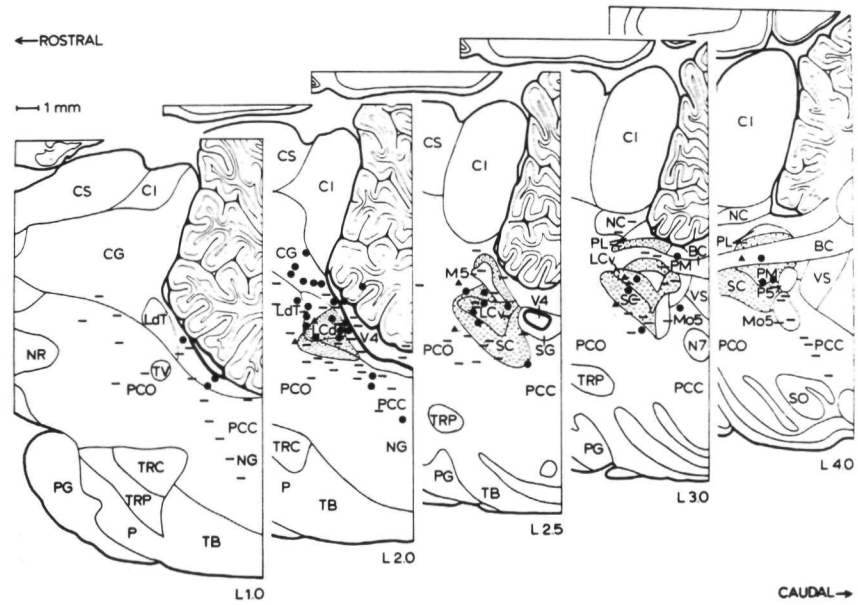


Fig. 26 ▲ = *ipsiversive turning*
● = *contraversive turning*
– = *no carbachol-induced asymmetric behavior*

Localization of the injection sites where carbachol (0.5 µg, injected unilaterally) caused asymmetric behavior.

on a plane at an angle of 45° with the horizontal, from rostrodorsal to ventrocaudal, partly along the ventricular wall (fig. 26). The dorsal and ventral limits of this plane could not be determined from the sites available. Most effective was the caudal central gray (CG) (ϕ = 0.25, p = 0.040, fig. 27); ineffective were the sites in the fourth ventricle and in the PCO.

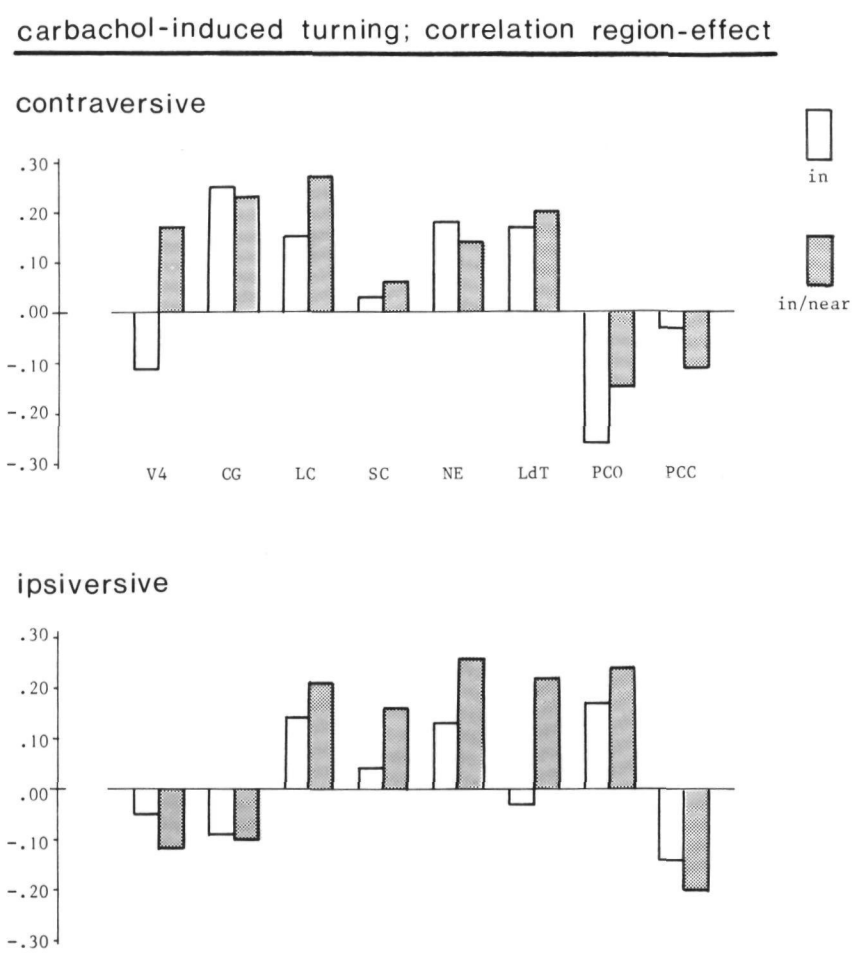


Fig. 27 Correlation (ϕ-coefficient) between the region of injection and the occurrence of injection sites where carbachol (0.5 µg) elicited asymmetric behavior; the CG is shown to be the most effective region involved in contraversive turning, and the part of the PCO just rostral to the NE region in ipsiversive turning.

2.4.4. DISCUSSION

Asymmetric behavior is elicited by carbachol, probably via muscarinic receptors, because atropine (but not mecamylamine) blocks these carbachol-induced effects. From many sites in and near the NE region ipsiversive as well as contraversive turnings could be elicited (cf. fig. 26). Experiments with electrical stimulation (Crow et al. 1972) and lesions of the NE region (Donaldson 1976a,b,c,d) yield either ipsiversive, or contraversive or no rotations. My suggestion is that the NE cells do not significantly contribute to turning behavior, because 1) clonidine, which suppresses the LC cells (section 1.2.2), did not induce rotations, 2) the NE cells of the LC project bilaterally (section 1.4.1), and 3) electrolytical lesions produce stronger rotations than the more specific 6-hydroxydopamine-induced lesions (Donaldson et al. 1976c). Manipulations in the dorsolateral pontine tegmentum cause ipsiversive and contraversive rotations. Circling behavior has been used for many years as a model of nigro-neostriatal dopaminergic activity (cf. Andén et al. 1966g), but asymmetries and rotations are also caused by manipulations in other cortical and subcortical regions (cf. Hassler 1975, Glick et al. 1976), and after damage to various CNS regions (McGrath 1956). Whether or not the last mentioned effects are due to interactions with the nigro-neostriatal cells is a subject of discussion (Cools et al. 1975, 1976, Cobbin and Atrens 1976, Glick et al. 1976, Donaldson 1976a,b,c,d). Rotations are most probably not a specific model of the activity of the dopaminergic nigro-neostriatal fibers (cf. Cools 1973).

Carbachol-induced micturation and defecation.

INTRODUCTION

One-stage bilateral lesions of the LC region of the rat or cat can debilitate the animals severely: urogenital disorders (haematuria) occur, and up to half the animals have been reported as dying (Amaral and Foss 1975, Roberts et al. 1976a, Roussel et al. 1976, Jones et al. 1977, Kolb and Whishaw 1977, Bodnar et al. 1978). Electrical stimulation in this region also affects the bladder and the bowels (Russel 1955, George et al. 1962). A region in the dorsolateral pons is primarily involved in micturation and the existence of a pontine "micturation centre" or "detrusor nucleus" has been postulated (A&S 8.4.); its localization and cell form is identical to the localization and cell form of the LC and LdT. In the present section, the influence of drugs injected into the dorsolateral pontine tegmentum on micturation and defecation is described. My findings corroborate the conclusions from anatomical and functional studies that it is the LdT rather than the NE cells which are primarily involved in micturation and defecation (Satoh et al. 1978a,b)

METHODS

All the relevant details of the methods employed are described in section 4.1.

RESULTS

Description of behavior. Micturation and defecation were observed after unilateral intracerebral injections of carbachol (0.5 µg) in 11 of the 141 sites. The way the cats micturated or defecated was species-specific; sniffing of the feces or urine and digging movements occurred. Some animals adopted only the posture for defecation (flexion of the hip and knee, and extension of the heel) and made movements with the flanks without actual defecation. Cats left for 2 hours in a familiar observation box, without a cat's box, did not exhibit micturation or defecation. Micturation and

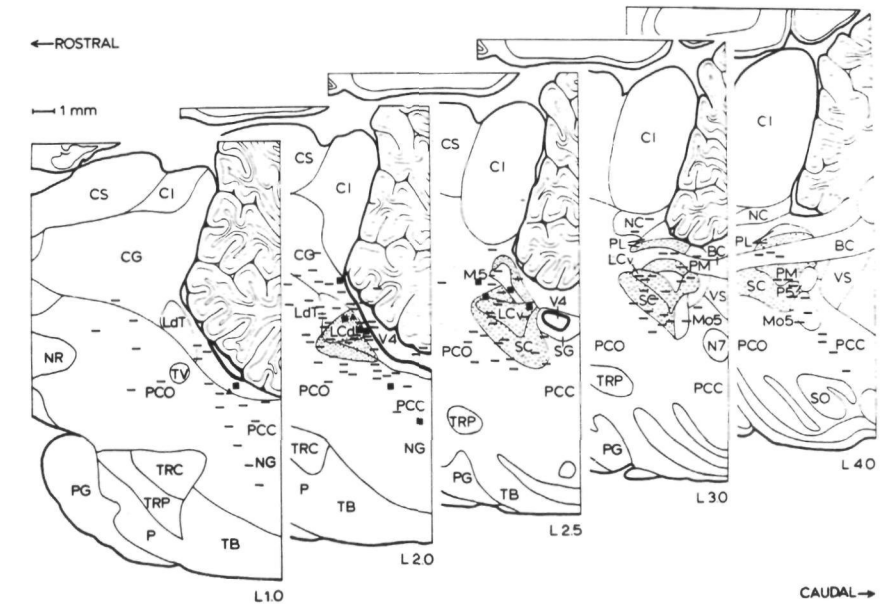


Fig. 28 ▲ = *micturation*
■ = *defecation*
– = *no carbachol-induced elimination*

Localization of the injection sites where carbachol (0.5 µg, injected unilaterally) caused elimination.

defecation are indicated separately in fig. 28, but in the further analysis combined and treated as a single effect, "elimination", since both effects are caused by an identical spinal region. The mean latency of elimination was 4 min 45 sec (range 1 min 15 sec to 8 min 55 sec). Elimination was reproducible (n=3) and brought about by as little as 50 ng of carbachol (n=2). No relationship between the occurrence of carbachol-induced elimination and the date or time of injections was detected (respectively $p > 0.10$ and $p > 0.50$, table 13, p. 207).

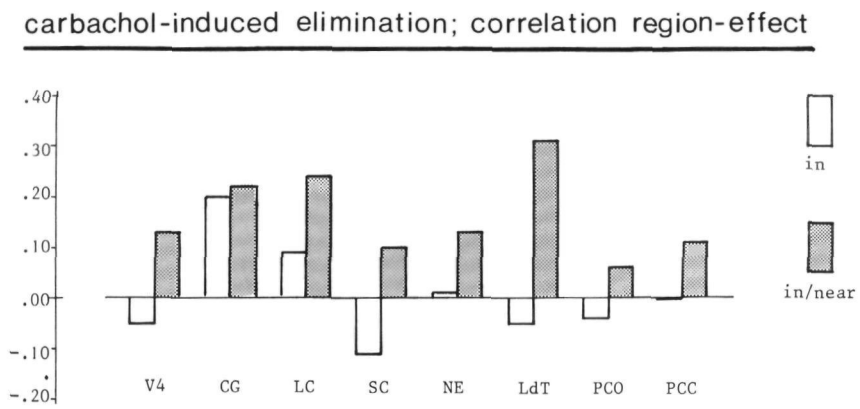


Fig. 29 Correlation (ϕ-coefficient) between the region of injection and the occurrence of injection sites where carbachol (0.5 µg) elicited elimination; the LdT is considered as being the most effective region.

Other drugs. At sites where carbachol did not cause elimination, fentanyl injected bilaterally (2 x 5 µg) caused defecation in 3 of 23 cases, but unilaterally injected fentanyl (5 µg) at one of these sites was ineffective. At 3 carbachol-ineffective sites, clonidine (5 µg) caused micturation; at these sites, situated in and near the fourth ventricle, clonidine also caused vomiting (see below). The other drugs mentioned in the "Methods" section did not mimic the carbachol-induced elimination (see section 4.1 for the drugs and doses, and table 16, p. 210, for the number of carbachol-effective sites tested with each drug).

Localization. The localization of the injection sites from which carbachol (0.5 µg) induced elimination is shown in fig. 28; the correlation between the region of injection and the effectiveness of the sites is shown in fig. 29 (cf. table 12, p. 205). The effective region was situated on a plane at an angle of 45° with the horizontal, along the ventricular wall from at least L 1.0 to L 2.5 (fig. 28); it partly overlapped the region from which contraversive turning was elicited. Most effective were the LdT and the CG (fig. 29), while sites in the fourth ventricle were not effective.

2.5.4. DISCUSSION

LdT and micturation/defecation. Carbachol injected into the dorsolateral pontine tegmentum caused defecation and micturation; most effective was the region near the LdT, which is in agreement with the figure of Hernández-Péon et al. (1963). Electrical stimulation and lesions of the NE region have also been reported as having urogenital effects (George et al. 1962, Amaral and Foss 1975, Roberts et al. 1976, Roussel et al. 1976, Jones et al. 1977, Kolb and Whishaw 1977), but these effects are most probably due to manipulations of the LdT rather than of the NE cells (Sessions et al. 1976, Satoh et al. 1978a,b). The effects on defecation caused by lesions or electrical stimulation (Russel 1955, Jones et al. 1977) are also most probably due to effects on the LdT or its afferent or efferent fibers rather than on the NE cells.

Implications for functional theories on the LC. Taking account of all these findings, my suggestion is 1) urogenital disorders are the cause of illness and perhaps even death in these animals, and that 2) these disorders are due to destruction or malfunction of the LdT or its afferent or efferent fibers and not of the NE cells. An alternative view (Amaral and Sinnamon 1977) is that the cases of death after a bilateral lesion in this region indicate that 1) the animals were no longer stress-tolerant and 2) this was caused by destruction of the NE cells: the "stress-dampening function of the LC". No conclusive evidence can however yet be presented in favour of one or other of these interpretations (see section 3.2.1).

2.6. Clonidine-induced vomiting.

2.6.1. INTRODUCTION

Vomiting and the CNS. Centrally acting α-adrenoceptor stimulating agents cause vomiting (Holman et al. 1971, Florio et al. 1975, Putkonen et al. 1977), but the localization of the central α-adrenoceptors involved is still uncertain. In the present section, evidence is provided that the α-adrenergic vomiting-inducing receptors are located close to the wall of the fourth ventricle. A localization in the area postrema, a presumed "vomiting center" (Borison 1977) adjacent to the ventricle, is suggested.

The ventricular hypothesis. Some authors have suggested that many of the effects of drugs injected intracerebrally arise after transport of the drug via the ventricular fluid, the so-called "ventricular hypothesis" (Baxter 1968, 1969, Routtenberg 1972). This ventricular hypothesis can be conclusively tested, when a drug-induced effect, due unequivocally to the amount of the drug reaching the ventricular fluid, can be demonstrated. The α-adrenergic-induced vomiting depends most probably on the amount of α-adrenoceptor agonists in the fourth ventricle. It can be concluded that 1), as a rule, a pharmacologically insignificant amount of clonidine reaches the ventricle when injected into brain tissue, and that 2) most of the effects described in this study are not mediated via the ventricular fluid. This is in agreement with the conclusions of Myers et al. (1971), Pert and Yaksh (1974), and Myers and Hoch (1978).

2.6.2. METHODS

All the relevant details of the methods employed are described in section 4.1.

2.6.3. RESULTS

Description of behavior. After a unilateral injection of clonidine (5 µg), which is, among others, a α-adrenoceptor agonist, vomiting was observed in 10 of the 60 clonidine-treated cases. This vomiting was similar to normal vomiting. Initially, the cats stuck out their tongues rhythmically, and opened and closed their mouths with a swallowing motion for 1 to 2 minutes. Then they vomited with rhythmical movements of their flanks and heads, taking some steps backwards. Sniffing of the vomit occurred regularly, while licking and eating the vomit were observed occasionally. A single injection caused this pattern 2 to 5 times, but after the second or third occasion the animals only retched. The clonidine-induced vomiting was reproducible in 83% of the cases (table 10, p. 203). The mean latency of the first vomiting was 6 min 20 sec (range 4 min to 9 min 25 sec). Clonidine at an amount of 1 µg did not induce vomiting when injected at sites where 5 µg was effective (n=5). No relationship was detected between the occurrence of clonidine-induced vomiting and the date or time of injection (respectively $p > 0.80$ and $p > 0.70$, table 13, p. 207).

Characterization of the receptors. At clonidine-effective sites the α-noradrenergic receptor agonist oxymetazoline (5 µg, n=5) was also effective, while the β-noradrenergic receptor agonist isoprenaline (5 µg, n=5) was ineffective. The clonidine-induced vomiting was antagonized by α-noradrenergic receptor antagonists; yohimbine (0.5 mg/kg, i.p., 30 min before clonidine) (n=3) prevented the vomiting, and piperoxane (10 µg, intracerebrally, at the same site as clonidine and administered just before clonidine) (n=2) attenuated the vomiting.

Other drugs. At clonidine-effective sites the clonidine-induced vomiting was not mimicked by *d*-amphetamine (5 µg, n=4), desipramine (5 µg, n=4), morphine (5 µg, n=5), fentanyl (5 µg, n=5) or apomorphine (5 µg, n=3), although the last three drugs caused vomiting when administered systemically. At 2 of the 10 clonidine-effective sites carbachol (0.5 µg) caused retching, being ineffective at the remaining 8 clonidine-effective sites. The other drugs mentioned in the "Methods" section did not mimic the clonidine-induced vomiting (see section 4.1 for the drugs and doses, and table 16, p. 210, for the number of clonidine-effective sites tested with each drug). At 3 of the 10 sites where clonidine caused vomiting, it also caused micturation, while at other sites clonidine never caused mictura-

tion. The association between the clonidine-induced vomiting and the clonidine-induced micturation was statistically significant ($\phi = 0.52$, $p = 0.006$).

Localization. The localization of the injection sites where clonidine (5 µg) caused vomiting, is shown in fig. 30; the correlation between the region of injection and the effectiveness of the sites is shown in fig. 31. The occurrence of clonidine-induced vomiting depended on the region of injection ($p < 0.05$, table 13, p. 207). Injection sites in and near the fourth ventricle were clearly the most effective. Many effective sites were also found in the CG, but these were in connection with the fourth ventricle: either the shaft of the cannula had opened the ventricular wall or granulation tissue had been formed between the cannula track and the ventricular wall (fig. 32). Clonidine elicited vomiting in only one site remote from the ventricle. There were no effective sites in the NE region.

2.6.4. DISCUSSION

Central α-adrenoceptors involved in vomiting. α-Adrenoceptor agonists (clonidine, oxymetazoline) injected into the fourth ventricle caused vomiting or retching. Similar effects occur after systemic injection of clonidine or other centrally acting sympathomimetic drugs (Holman et al. 1971, Florio et al. 1975, Putkonen et al. 1977). Comparison of the threshold doses for systemic injection with those for intracerebral administration (20 µg/kg and 5 µg respectively) makes it unlikely that the vomiting after intracerebral injections is due to diffusion of the drug outside the CNS. Yohimbine antagonized the vomiting induced by clonidine administered systemically (Florio et al. 1975) or intracerebrally, suggesting that the receptors involved are α-adrenoceptors.

Region involved. Injections in and near the fourth ventricle were most effective. Since only sites in the central gray which were in connection with the fourth ventricle were effective, it can be safely assumed that the vomiting-inducing α-adrenoceptors are not located in the central gray, but elsewhere in or near the ventricular wall. The more remote area postrema in the ventricular wall is reported as being involved in vomiting (Borison 1977), and in this region (nor)adrenergic (dopamine-β-hydroxylase-containing) terminals are found in close proximity to the ependymal

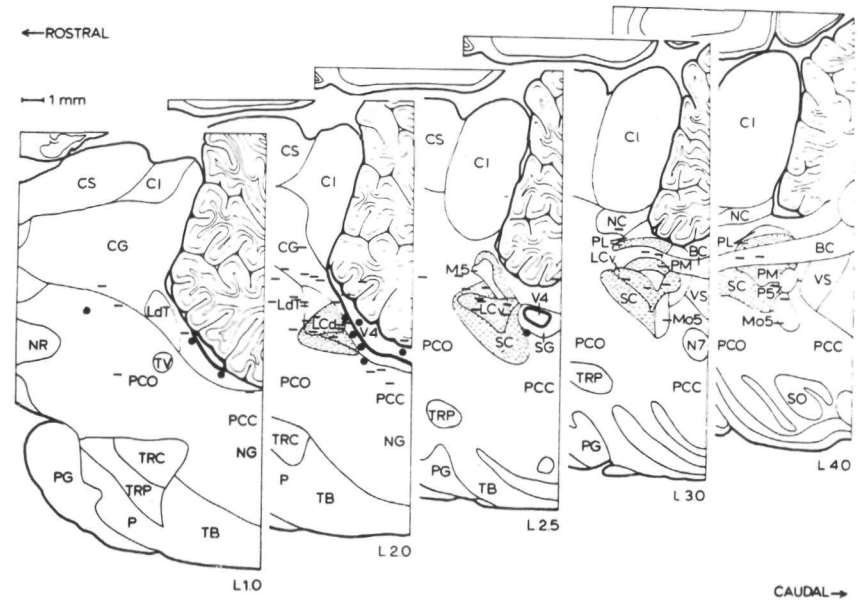


Fig.30 ● = *clonidine-induced vomiting*
– = *no clonidine-induced vomiting*

Localization of the injection sites where clonidine (5 µg, injected unilaterally) caused vomiting.

cells of the ventricular wall (Torack et al. 1973); the activity of these terminals is probably mimicked by injections of α-adrenoceptor agonists into the fourth ventricle.

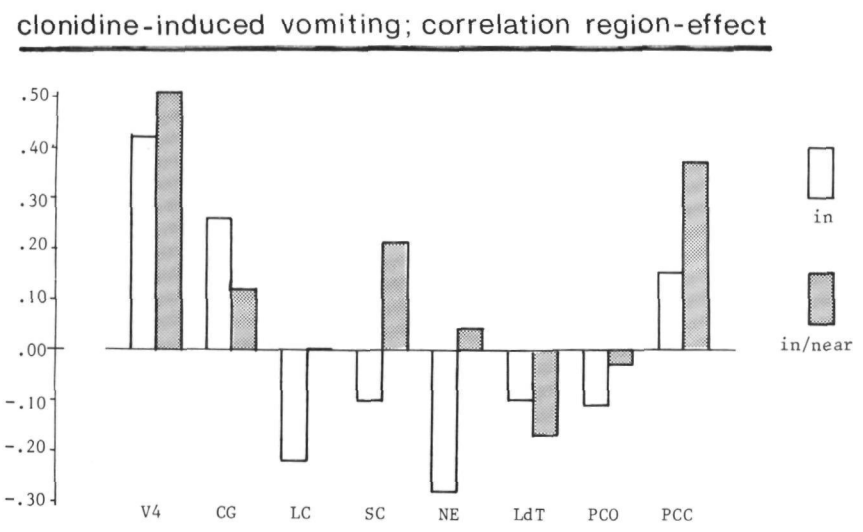


fig.31 Correlation (ϕ-coefficient) between the region of injection and the occurrence of injection sites where clonidine (5 µg) elicited vomiting; the fourth ventricle is shown to be the most effective region involved.

Spread to the ventricle? Clonidine caused vomiting in only one site remote from the ventricle; this indicates that, as a rule, only a pharmacologically insignificant amount of clonidine reaches the ventricle. The negative association between the occurrence of clonidine-induced vomiting and the other effects mentioned in this study (section 2.9) indicates that none of the other effects were mediated via the ventricle.

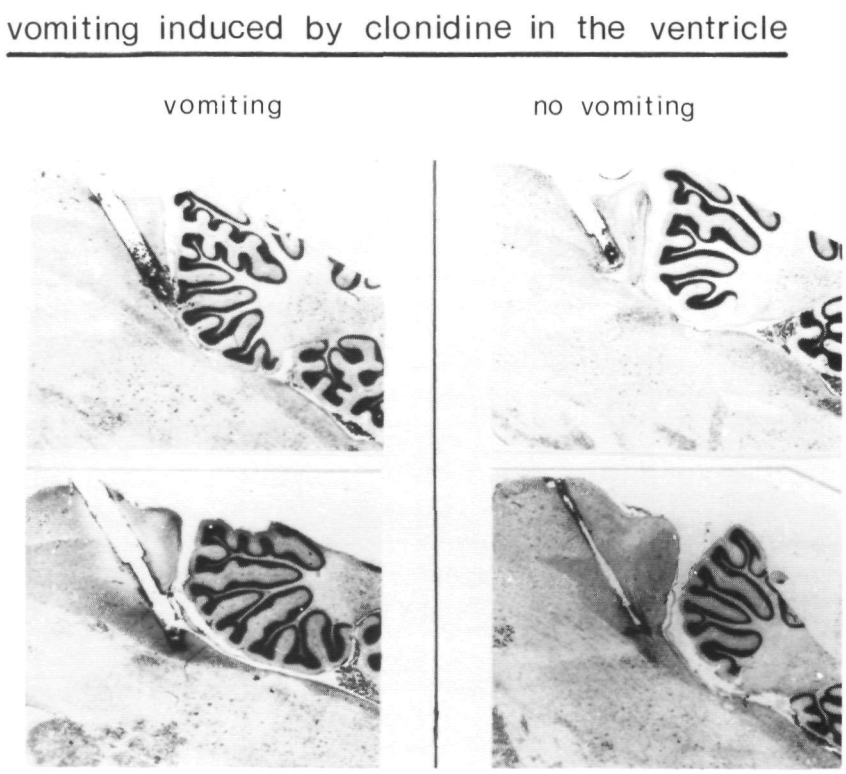


Fig.32 Nissl-stained parasagittal sections showing the tracks of the cannulae near the fourth ventricle where clonidine did or did not cause vomiting; in effective sites, the ventricular wall was opened or affected.

2.7. Drug-induced behavioral inactivation.

2.7.1. INTRODUCTION

The behavioral activity of rats has been reported as being reduced by a lesion of the LC (Amaral and Foss 1975, Kostowoski et al. 1978c), but these findings are contested by a number of authors (Roberts et al. 1976a, Sessions et al. 1976, Crow and Wendlandt 1976, Crow et al. 1977, 1978, Mason and Fibiger 1977, 1979a,b,c, Mason and Iversen 1977a). Other manipulations which reduce the LC cells' activity (intracerebral morphine) have also been reported as deminishing behavioral activity (Broekkamp et al. 1976). After a systemic injection of clonidine suppressing the activity of the LC cells via α_2-receptors (section 1.2.2), a behavioral inactivation ("sedation") has been described which was also a result of α_2-adrenoceptor activation (Putkonen et al. 1977, Drew et al. 1979). Similarly, morphine applied systemically causes an initial behavioral inactivation (depression phase, Cools et al. 1974b), and suppression of the LC cells' activity (section 1.2.2). In the present study the cats became behaviorally inactivated after an intracerebral injection of clonidine or opiate agonists. The clonidine-induced behavioral inactivation was due to clonidine injected into the nucleus pontis centralis oralis (PCO) just rostral to the LC rather than into the LC itself.

2.7.2. METHODS

Most of the details of the methods employed are mentioned in section 4.1. Exploratory tests were carried out with 21 cats. Two days before they were placed in the observation box for the first time, a needle was inserted into the sites where the injections were to be made while the animals remained in their home cages. Before being placed in the observation box for the first time, they received either saline (bilaterally 2 x 0.5 µl, n=11) or fentanyl (bilaterally 2 x 5 µg, n=10). They were placed in the observation box immediately afterwards and their behavior observed. They were kept for one hour in the box, and the following day they also stayed for one hour in the box. A series of 8 to 11 experiments was carried out;

afterwards they received a further bilateral injection of either saline or fentanyl (at the same dose, cats previously treated with saline received fentanyl and vice versa), and were placed in another observation box of identical dimensions, but constructed from other materials and with a different smell. During both exploratory experiments, the number of seconds spent walking or sniffing during each minute was measured. The values for the fentanyl-treated animals were tested against the values for the saline-treated animals 6 minutes after the injections (Mann-Whitney U), because in all cases the animals were inactive 7 minutes after the injection at effective sites.

2.7.3. RESULTS

Description of behavior. The cats were behaviorally sedated, sitting down with their eyes closed and hardly moving, after unilateral intracerebral injections of the α-adrenoceptor agonist clonidine (5 µg; in 14 of 60 cases), and after bilateral injections of morphine (2 x 5 µg; in 6 of 12 cats). A trained observer of cat behavior judged it to be abnormal, drug-induced inactivation, but no statistically significant difference with saline-treated or untreated cats could be demonstrated; the cat's basic level of activity was already very low. To demonstrate drug-induced behavioral inactivation, the effects of the opiate receptor agonist fentanyl (2 x 5 µg) was tested in a situation where the animals were spontaneously active: being placed in an unfamiliar observation box. All the saline-treated and untreated cats showed a similar behavior pattern when placed in an unfamiliar observation box. walking with their bellies close to the ground and sniffing to the ground, followed by rearing and sniffing the walls, with the activity gradually decreasing over time (fig. 33). Nine of the 21 fentanyl-treated cats interrupted their exploration behavior and also showed abnormal drug-induced inactivation for some minutes (with a mean latency 4 min 15 sec, range 2 min 15 sec to 6 min; mean duration 7 min 15 sec, range 3 min to 18 min), after which they recommenced exploration. Seven minutes after the injection the proportion of time spent walking and sniffing had decreased to 48% and 36% respectively, which was a statistically significant reduction ($p < 0.01$, two-tailed Mann-Whitney U for the whole group ($n=21$), compared with the saline-treated controls). In the cats where fentanyl bilaterally had caused an interruption of the

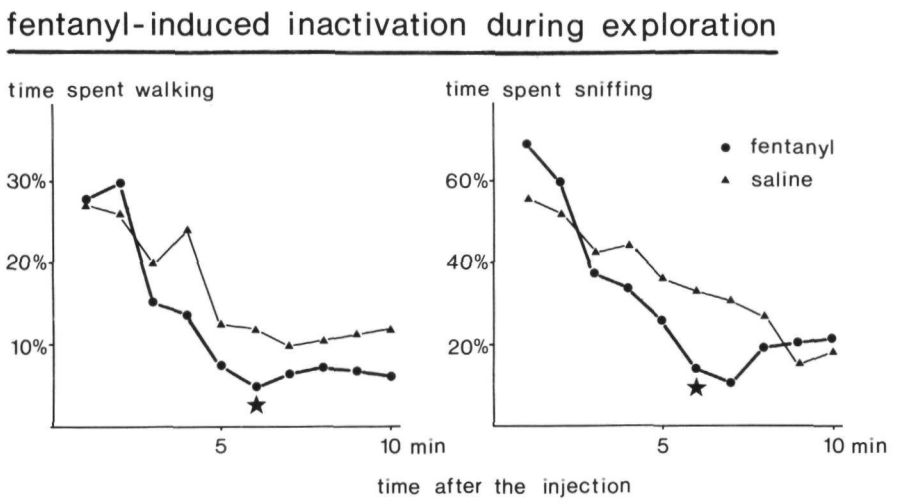


Fig.33 Exploration behavior of cats in an unfamiliar observation box; the fraction of time spent walking and sniffing is given for each whole minute; note that only the values at 6 minutes were statistically tested (two-tailed Mann-Whitney U, ★ = $p < 0.01$).

exploratory behavior, clonidine injected unilaterally either on the right or left side caused inactivation. No relationship between the occurrence of clonidine-induced inactivation and the date or time of injection was detected (respectively $p > 0.10$ and $p > 0.50$, table 13, p. 207).

Other drugs. After an unilateral injection of carbachol (0.5 µg) into only 2 of the 141 sites tested a similar inactivation was observed; clonidine was ineffective at both of these sites. The cats showing carbachol-induced atonia were of course inactive, but the clonidine-/morphine-/fentanyl-treated cats were not atonic, and the occurrence of clonidine-induced inactivation was negatively correlated with the occurrence of carbachol-induced atonia (table 15, p. 209). The clonidine-/morphine-/fentanyl-induced behavioral inactivation was not mimicked by the other drugs mentioned in the "Methods" section, except oxymetazoline (n=1) (see section 4.1 for the drugs and doses, and table 16, p. 210, for the number of clonidine-effective sites tested with each drug).

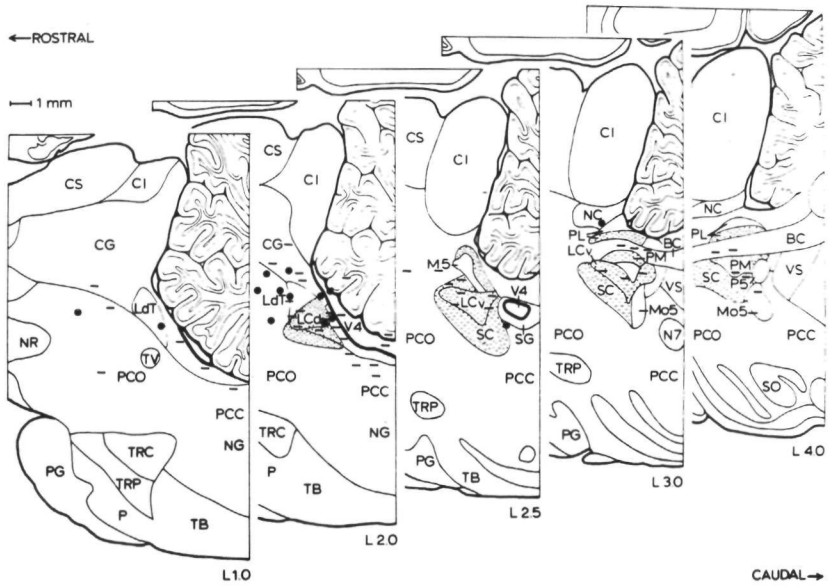


Fig.34 ● = *clonidine-induced behavioral inactivation*
– = *no clonidine-induced behavioral inactivation*

Localization of the injection sites where clonidine (5 µg, injected unilaterally) caused behavioral inactivation.

Localization. The localization of the injection sites where clonidine (5 µg) caused behavioral inactivation is shown in fig. 34; the correlation between the region of injection and the effectiveness of the sites is shown in fig. 35. The effective sites were clustered rostrodorsally to the LC pars dorsalis and the LdT; the PCO and the LdT were the most effective regions, while sites in the fourth ventricle were not effective. It turned out in practice to be impossible to implant bilateral cannulae at exactly the same site, with the result that no relationship between the effects and the localization of the injection sites could be determined for the effects of morphine and fentanyl bilaterally injected.

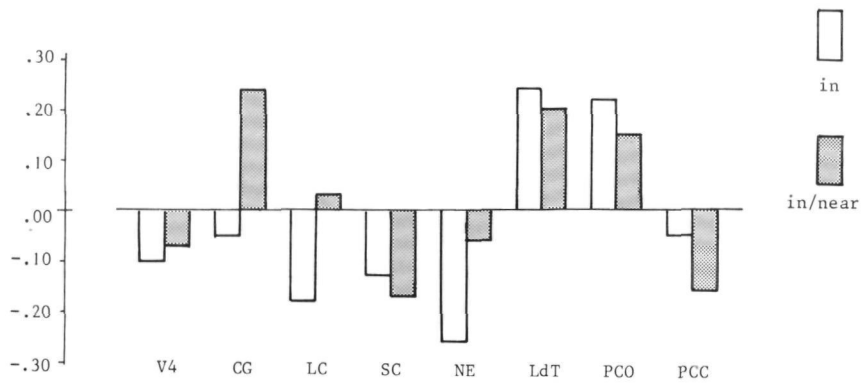


Fig.35 Correlation (ϕ-coefficient) between the region of injection and the occurrence of injection sites where clonidine (5 µg) elicited behavioral inactivation; sites in the LdT and the adjacent part of the PCO were most effective.

2.7.4. DISCUSSION

Region involved in behavioral inactivation. Both α-adrenoceptor agonists (especially clonidine) and opiate agonists (morphine and enkephalins) suppress the LC cells (section 1.2.2) and opiate receptor binding sites and opiate sensitive cells are reported as being abundant in the LC, as of an intermediate density in the central gray, and as almost absent in the pontine reticular formation (Pert et al. 1976, Bird and Kuhar 1977, see also section 1.2.2). An attractive interpretation might therefore be that of imputing behavioral effects elicited in an area close to the LC by both NE and opiate agonists to diffusion of the drugs into the LC (cf. section 4.2). I do not however share this interpretation of the clonidine-induced behavioral inactivation, because the effective sites were not clustered around, but rostral to, the LC. Moreover, the majority of the researchers have not found any change in the open field activity of the rat after destruction of the LC or its ascending fibers (Roberts et al. 1976, Sessions et al. 1976, Crow et al. 1976, 1977, 1978, Mason and Fibiger 1977, 1979a,b,c, Mason and Iversen 1977), and only a few have

described a decrease in activity (Amaral and Foss 1975, Kostowski et al. 1978c). Fentanyl injected into the dorsolateral pontine tegmentum interrupted the exploratory activity of cats (this study), while selective 6-OHDA-induced lesions of the ascending LC fibers on the other hand increased the exploratory activity (Mason and Fibiger 1977). The present results for the cat lead to the suggestion that a decrease in behavioral activity can be attributed to the part of the PCO just rostral to the LC. The majority of the above mentioned results for the rat support the suggestion that the LC cells are not involved in this effect.

Drug-induced behavioral inactivation. Clonidine injected systemically into the cat and rat (at threshold doses of 5-50 µg/kg) causes behavioral inactivation ("sedation") (Putkonen et al. 1977, Drew et al. 1979). At the present time it is not clear whether the inactivation subsequent to systemic applications of clonidine can be attributed to the same brain regions as the inactivation subsequent to intracerebral clonidine. The mechanism of the behavioral inactivation following systemical and intracerebral injection of clonidine is unclear, but is would not be surprizing to find a disturbance in some vegetative parameters (cf. Drew et al. 1979, Zandberg et al. 1979b). Morphine injected systemically into the cat and rat causes initial behavioral inactivation (cat, depression phase, Cools et al. 1974b; rat, Broekkamp et al. 1976). The inactivation caused by morphine applied systemically in the rat has been ascribed to action of morphine on the LC cells (Broekkamp et al. 1976), but in the latter study, the involvement of adjacent regions could not be discounted. The behavioral inactivation caused by morphine injected systemically in the cat was in any case not antagonized by intracerebral injections of the morphine antagonist naloxone (2 µg) injected in and near the LC (section 2.8.3).

2.8. Locus coeruleus and Substantia nigra: Involvement in morphine-induced behavior.

2.8.1. INTRODUCTION

Numerous investigations have dealt with the interaction between morphine, enkephalins, endorphins and the central catecholaminergic transmission. In rats, for instance, morphine-induced analgesia and behavioral activation and abstinence after morphine-withdrawal are influenced by drugs which affect the central catecholaminergic transmission (Carroll and Sharp 1972, Cicero et al. 1974, Scheel-Krüger 1976, Schulz and Herz 1977), or by destruction of catecholaminergic regions (Price and Fibiger 1975, Sasa et al. 1977a). In cats, manipulation of the dopaminergic (DA) or noradrenergic (NE) transmission influences morphine-induced behavioral symptoms (Dhasmana et al. 1972, Cools et al. 1974b, 1977, 1978a). The behavioral effects of morphine injected intracerebrally into the pontine NE region and the mesencephalic DA region (substantia nigra, SN, and ventral tegmental area, VTA) of rats have been investigated (Broekkamp et al. 1976, Broekkamp 1976). In the present study, the role of morphine receptors in the regions of the LC and the SN in the behavior elicited by morphine administered systemically is investigated. The effects on morphine-induced behavior of the morphine antagonist naloxone injected intracerebrally into the LC or the SN are investigated. Blockade of the morphine receptors in the LC was found to interrupt the morphine-induced stereotyped behavior and the morphine-induced disturbance of the senso-motor co-ordination, while blockade of the morphine receptors in the SN and VTA interrupted the morphine-induced hyperactivity.

2.8.2. METHODS

For details of the methods employed see section 4.1. The cats received an intraperitoneal injection of morphine (5 mg/kg) and their behavior was observed. Forty minutes after the injection of morphine the animals received an intracerebral injection either of naloxone (0.8, 2, 5 or 10 µg

in 0.5 µl saline) or saline into the LC or SN region. (In 11 experiments, the animals received naloxone into the dorsolateral pontine tegmentum 7 minutes after the injection of morphine.) The most conspicuous changes after the injection of naloxone were quantified by counting the behavioral categories affected: head movements, leg movements and stereotyped turning, i.e. turning (cf. section 2.4.2) repeated in a fixed way. The number of movements and stereotyped turnings per minute were counted. For each experiment, the relative number per minute after the intracerebral injection was calculated, i.e. the number after the intracerebral injection ("post-injection value") divided by the mean found in the 10 minutes before the intracerebral injection ("pre-injection value"). The absolute 10 minutes post-injection values in each experiment were tested against the absolute 10 minutes pre-injection values. Per experimental group, the values 7 minutes after the intracerebral injection were tested: the absolute pre-injection versus post-injection, and relative experimental post-injection versus relative saline-control post-injection. In all cases the two-tailed Mann-Whitney U test was used. When a cat received more than one injection of morphine, the inter-trial intervals were 2 days (for SN experiments) or 7 days (for LC experiments). After repeated injections of morphine an increase in salivation and a decrease in defecation were noted; except from these changes, no signs of tolerance or abstinence could be demonstrated for this dose and schedule of injections (cf. Cools et al. 1977, French et al. 1979).

2.8.3. RESULTS

Morphine-induced behavior

The behavior observed after intraperitoneal injections of morphine (5 mg/kg) in 40 cats was similar to the morphine-induced behavior described by Cools et al. (1974) and comparable to the morphine-induced behavior described by other authors in other situations, both with identical or different doses of morphine, and a different route of administration (cf. Wikler 1944, Dhasmana et al. 1972, French et al. 1979). In 38 of the 40 cats, characteristic morphine-induced behavior was found: 30 to 60 minutes after the injection of morphine, the cats showed morphine-induced repetitive movements (Cools et al. 1974, 1977). These movements were poorly co-

ordinated and consisted of repeated sequences of disintegrated behavior: a great inter-individual variation in the morphine-induced stereotyped patterns was found, but the intra-individual variation between different experiments was small (cf. Cools et al. 1974). Morphine-treated cats were hyperactive, as indicated by the high frequency of head and body movements. (One of the 2 remaining cats showed the so-called morphine-induced "mania" and could not be handled, while the other remained quiet and did not even show an increase in the number of head movements (cf. Cools et al. 1977); the data on these 2 cats were discarded.) Between 30 and 40 minutes after the morphine injection, the number of head and leg movements had reached a stable level (cf. also Cools et al. 1977): a neglectable, not statistically significant (see fig. 36, in all cases $p > 0.50$, Friedman two-way analysis of variance), increase in the number of stereotyped turnings was found, so that the numbers found between 30 and 40 minutes could be used as a stable baseline level. The reaction to various sensory stimuli was impaired: the cats often seemed to be tracking non-existant "objects" visually ("staring", French et al. 1979), or bumped into the walls; they either failed to react to auditory stimuli, or they showed an exaggerated startle response instead of an orientation reaction. Moreover, the cats often dirtied their fur with feces or vomit in cases when morphine-induced defecation or vomiting had occurred earlier in the experiment.

Saline-treated controls

Injections of saline (0.5 µl; control experiments) into the dorsolateral pontine tegmentum (n=9), or near the SN (n=5), resulted in an increase in the number of head and leg movements, and of stereotyped turnings (for stereotyped turnings, increase $p < 0.05$, 7 minutes after saline in and near the LC, cf. fig. 36). A comparison of pre- and post-injection levels per animal yielded a statistically significant increase in 4 of 14 cases: these animals showed intensified morphine-induced behavior. It is uncertain whether this increase was due to handling, the injections, saline or another unknown cause.

Naloxone in and near the LC

Description of behavior. Within a few minutes after a unilateral or a bilateral intracerebral injection of naloxone into the dorsolateral pontine tegmentum (40 minutes after a morphine injection), the morphine-induced

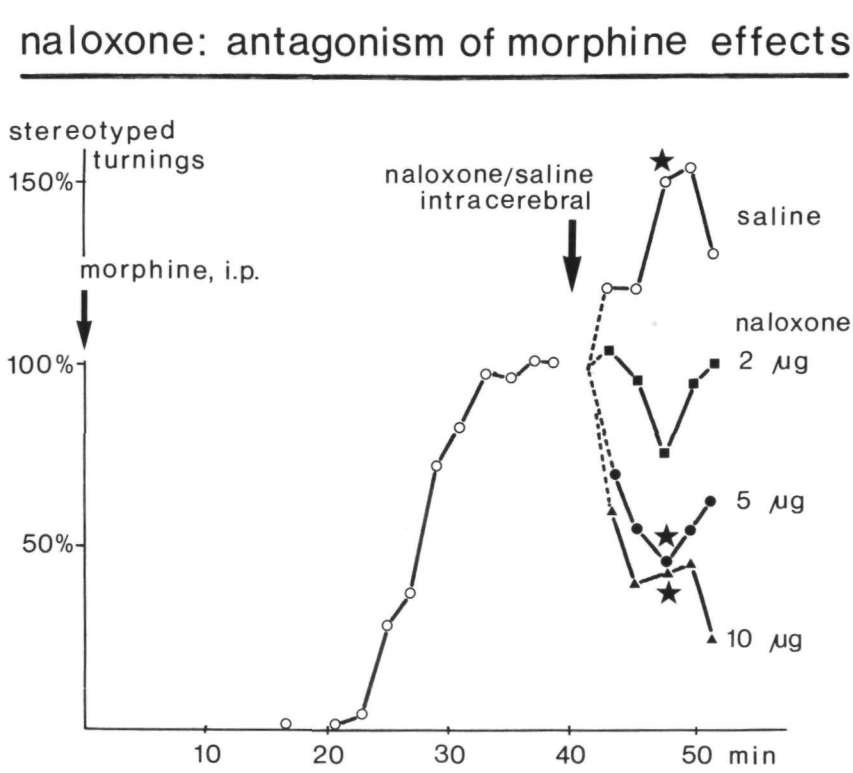


Fig.36 Number of stereotyped turnings made by morphine-treated cats; naloxone caused a dose-dependent decrease in the number of stereotyped turnings. Note that only the values at 47 minutes were statistically tested (two-tailed Mann-Whitney U, ★ = $p < 0.05$).

behavior was disrupted in a number of cats. These cats stopped the morphine-induced repetitive movements, and instead, began to walk, sniff, explore, roll, sharpen their nails, groom themselves (which otherwise never occurred in morphine-treated cats, cf. also French et al. 1979), scratch their heads, stretch, and made smoother and oriented head movements; in addition they no longer showed the exaggerated startle response, nor dirtied their fur with feces or vomit any more. Naloxone induced a statistically significant decrease in the number of stereotyped turnings (fig. 36). The cats remained hyperactive however; no change in the number of head and leg movements was observed, and inactive behavior such as

lying down or sleeping was absent throughout the observation period. After an effective injection, the decrease in morphine-induced behavior in individual cats was greater than suggested by the mean values (fig. 36), because with every dose of naloxone ineffective injections occurred (table 2). In practice, the stereotyped movements of the individual animals disappeared completely, or almost completely, for between 2 and 20 minutes. Morphine-induced behavioral patterns which remained unaffected after an otherwise effective injection of naloxone near the LC were mydriasis, restless movements of the forelegs, salivation, the crouched back, and the posture of the hindlegs characteristic for defecation (flexion of the hip and knee and extension of the heel). The naloxone-induced effect lasted several minutes, and then faded gradually away (fig. 36, table 2), and the previously exhibited stereotyped patterns reappeared. The intensity of the naloxone-induced partial antagonism of the morphine-induced behavior varied between individual cats ranging from smoother, more oriented head movements (intensity 1), to a decrease in the frequency of more complex stereotyped patterns (called intensity 2 when a statistically significant decrease in the number of stereotyped turning is found), and to a normalized active behavior (intensity 3). These measures of intensity are ordinal measures, because intensity 1 was always present, when intensity 2 was present, and intensities 1 and 2 were always present, when intensity 3 was present. Table 2 indicates the number of experiments at each dosage level when a given intensity was found. In conclusion, naloxone injected into the dorsolateral pontine tegmentum of morphine-treated cats partially antagonized the morphine-induced disturbance of behavior. No relationship between the occurrence of naloxone-induced partial antagonism of morphine-induced behavior and the date or time of injection was detected (respectively $p > .50$ and $p > 0.10$, table 13, p. 207). Naloxone (2 µg, n=11) injected into the dorsolateral pontine tegmentum 7 minutes after injection of morphine ("depression phase", Cools et al. 1974) did not cause a change in the morphine-induced behavior.

Dose-response relationship. The naloxone-induced effect was reproducible per cat: a second injection into a previously effective site was always effective (n=5), while one into a previously ineffective site never was (n=10, cf. table 10, p. 203). The naloxone-induced effect was dose-dependent: at higher doses of naloxone, the proportion of sites which were

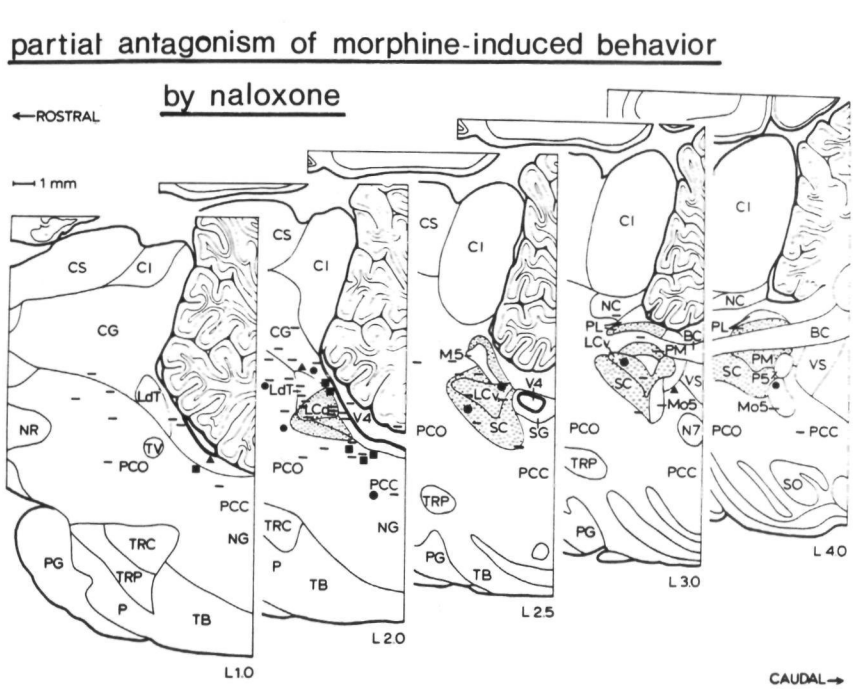


Fig.37 ● = *limited antagonism (intensity 1)*
■ = *moderate antagonism (intensity 2)*
▲ = *strong antagonism (intensity 3)*
– = *no antagonism*

Localization of the injection sites where naloxone (2 µg, injected unilaterally) caused partial antagonism of morphine-induced behavior.

effective, and the intensity and duration of the naloxone-induced effect increased (fig. 36, table 2). Bilateral injections of naloxone were more effective: 2 x 0.8 µg of naloxone caused a decrease in the number of stereotyped turnings to 33% of the saline control value ($p < 0.01$ versus saline-treated controls, Mann-Whitney U), while a unilateral injection of 2 µg only caused a decrease to 71%. No effect on behavior was caused by naloxone (2 µg) injected into the dorsolateral pontine tegmentum of non-morphinized cats (n=18).

Localization. The localization of the injection sites where naloxone (2 µg) caused partial antagonism of morphine-induced behavior is shown in fig. 37; the correlation between the region of injection and the effec-

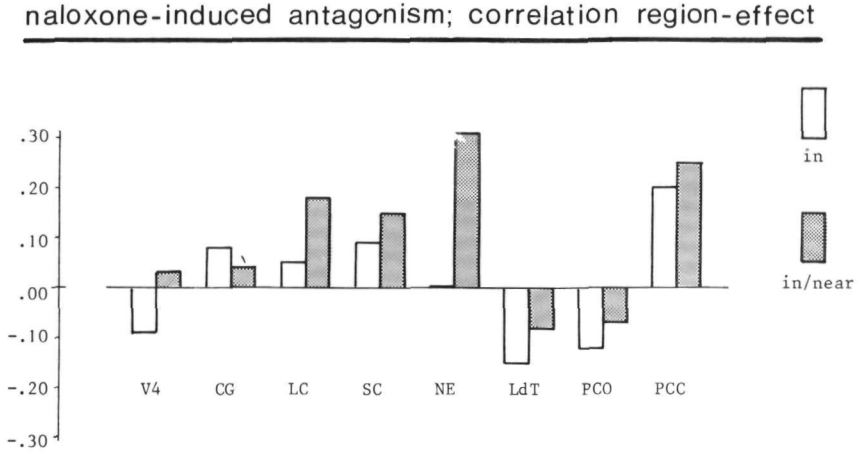


Fig.38 Correlation (ϕ-coefficient) between the region of injection and the number of injection sites where naloxone (2 µg) elicited partial antagonism of morphine-induced behavior; the NE region is shown to be the most effective region involved.

Table 2

Effectiveness of naloxone injected into the dorsolateral pontine tegmentum as antagonist of morphine-induced behavior

	bilateral		unilateral			
	2 x 0.8 µg		2 µg		5 µg		10 µg	
number of sites total tested	15		58		11		12	
intensity: 0	7	(47%)	41	(71%)	6	(54%)	5	(42%)
1	8	(53%)	17	(29%)	5	(46%)	7	(58%)
2	6	(40%)	9	(16%)	3	(27%)	6	(50%)
3	4	(27%)	4	(7%)	1	(9%)	2	(17%)
latency (min)	1.1 (0-2)		1.1 (0-7)		0 (0)		1.6 (0-4.2)	
duration (min)	8.4 (4-12)		5.0 (2.6-8)		6.3 (2.5-8.8)		21.2† (14.3-31.3)	

† = $p < 0.001$, *Mann-Whitney U, compared to the effect of 2 µg of naloxone*

tiveness of the sites is shown in fig. 38. The most effective regions were the NE region (LC and SC) and the PCC, while sites in the fourth ventricle were not effective.

Naloxone in and near the SN

Description of behavior. Naloxone injected bilaterally (2 x 2 μg) at effective sites in the region of the SN of morphine-treated cats (n=13) 40 minutes after injection of morphine, caused these animals to become hypoactive. The decrease in the number of stereotyped movements, head movements and leg movements compared with saline-treated controls was statistically significant (7 minutes after naloxone, $p < 0.05$, Mann-Whitney U): and in 4 individual cats this decrease was also statistically significant in comparison with their pre-injection values. After effective injections of naloxone the cats sat with the upper part of their bodies upright and their forelegs extended. Otherwise effective injections of naloxone did not affect the morphine-induced crouched back, the hindlegs in the posture characteristic of defecation, mydriasis and salivation. These effects were dose-dependent: with a higher dose the proportion of effective sites was higher (table 3), and the mean intensity of the effects per group was greater. In contrast to the injections in the LC, injections in the SN made the cats hypoactive, so that, although the number of stereotyped movements decreased in both cases after effective injections, the effects associated with injections in the 2 regions differed.

Localization. The effective injection sites were located in the ventromedial part of the SN, pars compacta, in the ventral tegmental area (VTA) and slightly ventral to the SN. In the 5 cats where the injections were ineffective, the injection sites were located in the SN, pars compacta (in one cat in both sites, and in the other in one site) and rostrodorsally in the tegmental fields of Forel in the remaining 3 cats.

Table 3

Effectiveness of different doses of naloxone injected into the SN region as antagonist of morphine-induced behavior

	bilateral		
	2 µg	5 µg	10 µg
number of sites total tested	16	6	7
effective	7 (44%)	5 (83%)	5 (71%)
latency (min)	1.5 (0-5)	1.2 (0-5)	2.1 (0-15)
duration (min)	15	15	15

Combined injections, naloxone in the LC and SN

In a group of 10 cats, 2 pairs of cannulae were implanted directed both to the LC and SN; in these cats the effects of combined LC and SN injections were investigated. The effects of such double injections were of course most interesting in cats where the separate LC and SN injections were effective at a low dose of naloxone. After injections of a dose of 2 µg of naloxone, unilaterally, in the LC the cats showed a clear effect in 4 cases. intensity 2 (n=3), and intensity 3 (n=1). After injections in the SN (2 x 5 µg), 4 of the 10 cats showed a statistically significant decrease in the number of head and leg movements. In 2 of the 10 cats both the SN sites and at least one LC site were effective; in the 2 cats, the effects of combined injections into the LC (2 µg) and the SN (2 x 5 µg) could not be distinguished from the effects of SN injections only the animals became inactive, the number of head and leg movements decreased, and the cats sat in the posture described above as resulting from SN injections.

2.8.4. DISCUSSION

Injections into the dorsolateral pontine tegmentum. Naloxone injected into the dorsolateral pontine tegmentum of morphine-treated cats partially antagonized morphine-induced behavioral disturbance in a number of cats. The effect was repeatable per site and a cluster of effective sites was found. The most effective regions were the NE region and the PCC; the present study does not permit of a definite conclusion regarding the cells involved, but the following factors favour the involvement of NE cells.

1. 15 of the 17 effective sites were located in and near the NE region (table 11, p. 204), and the correlation between effectiveness and localization was highest for the NE region ($\phi = 0.31$, fig. 38).
2. Opiate receptor binding is very high in the LC, and much lower in the more ventral PCC (Pert et al. 1976, Atweh and Kuhar 1977b, Kuhar 1978a, Beaudet et al. 1979), where also in this study many naloxone-effective sites were found.
3. In the dorsolateral pontine tegmentum, the morphine-sensitive cells are mainly confined to the LC (Bird and Kuhar 1977, Young et al. 1977).

For these reasons, I have made the assumption that the naloxone-induced effects described above really are due to the action of naloxone on the NE cells. The technique used however does not allow one to distinguish whether these naloxone-induced effects are due to the actions of naloxone on the SC, the LCd or the LCv. In rats, morphine causes a decrease in the maintained activity of the LC cells, which can be antagonized by naloxone (Bird and Kuhar 1977, Young et al. 1977, Guyenet and Aghajanian 1977, 1979, Aghajanian 1978, cf. also section 1.2.2). Accordingly, the naloxone-induced effects described here can be attributed to restoration of the activity of the LC cells in morphine-treated cats, and consequently to restoration of the activity of the NE terminals over many extended parts of the CNS. This is in agreement with the observation that NE injected into a single LC terminal region of a morphine-treated cat also interrupts morphine-induced stereotyped movements (Cools et al. 1974). Since in the present study all LC terminal regions are involved, it is not surprizing that naloxone in the NE region causes a more generalized behavioral effect: partial normalization of behavior. The effects involved can be generalized to the statements: 1) that the morphine-induced decrease in the activity of the pontine NE cells is a necessary condition for the occurrence of morphine-induced sensory motor disturbances, and 2) that

naloxone restores the activity of the NE cells, thereby restoring the sensory motor and integrative actions of those parts of the CNS which receive terminals from the pontine NE region.

Injections into the mesencephalic DA region. Naloxone injected into the region of the mesencephalic DA cells of morphine-treated cats brought the morphine-induced hyperactivity of these cats to an end, and made them hypoactive instead. The activity of the SN-DA cells is increased by morphine; this effect can be antagonized by naloxone (Iwatsubo 1976, Nowycky et al. 1978). It is therefore reasonable to assume that naloxone injected into the region of the mesencephalic DA cells diminishes the release of DA in the caudate nucleus and other DA terminal regions. Indeed, the activity of morphine-treated cats is also modified by DA agents injected into particular parts of the caudate nucleus. The present study indicates the involvement of the mesencephalic DA cells, but these data do not permit conclusions on the involvement of a particular group of DA cells: the SN pars compacta (A9) or the VTA (A10). The results on a morphine antagonist injected into the DA region of morphine-treated cats described in the present study are partly the opposite of the effects of morphine injected into this region of the cat and the rat. Naloxone injected into the mesencephalic DA region of morphine-treated cats made them hypoactive and decreased the number of abnormal, morphine-induced leg movements; conversely, morphine injected into the mesencephalic DA region of rats and cats made them hyperactive, and increased the frequency of dyskinetic leg movements in the self-stimulation and open field test situations respectively (Broekkamp et al. 1976, Broekkamp 1976).

NE and DA cells in morphine-induced behavior. The present results indicate that the morphine-induced stereotyped behavior can be interrupted either by restoration of the activity of the NE cells, or by reducing the stimulation of DA receptors in the caudate nucleus. This can be brought about either by DA antagonists injected into parts of the caudate nucleus (Cools et al. 1978), or by morphine antagonists injected into the region of the mesencephalic DA cells. Nevertheless, neither morphine injected in the region of the pontine NE cells (Broekkamp et al. 1976, section 2.7) nor in the region of the mesencephalic DA cells (Broekkamp et al. 1976, Broekkamp 1976) alone induced stereotyped behavior. Consequently, it becomes an attractive suggestion that a necessary condition for morphine-induced behavior is simultaneous action

on morphine receptors in the regions of the pontine NE cells and the mesencephalic DA cells.

2.9. The combined occurrence of effects.

Figure 39 is a summary of the various regions to which the drug-induced effects are attributed. A correlation matrix of the various drug-induced effects elicited from any given injection site has been made (tables 14 and 15, pp. 208, 209). These tables should be interpreted with caution, since the effects elicited by one drug (in one experiment) may be *a priori* dependent. For instance, a combination of carbachol-induced atonia and carbachol-induced turning may be impossible; for ipsiversive turning and atonia, however, a positive correlation was found (ϕ = 0.26, p = 0.021), suggesting that the strong negative correlation between carbachol-induced atonia and carbachol-induced contraversive turning (ϕ = -0.39, p < 0.001) was not an *a priori* result.

summary: effects attributed to the various regions

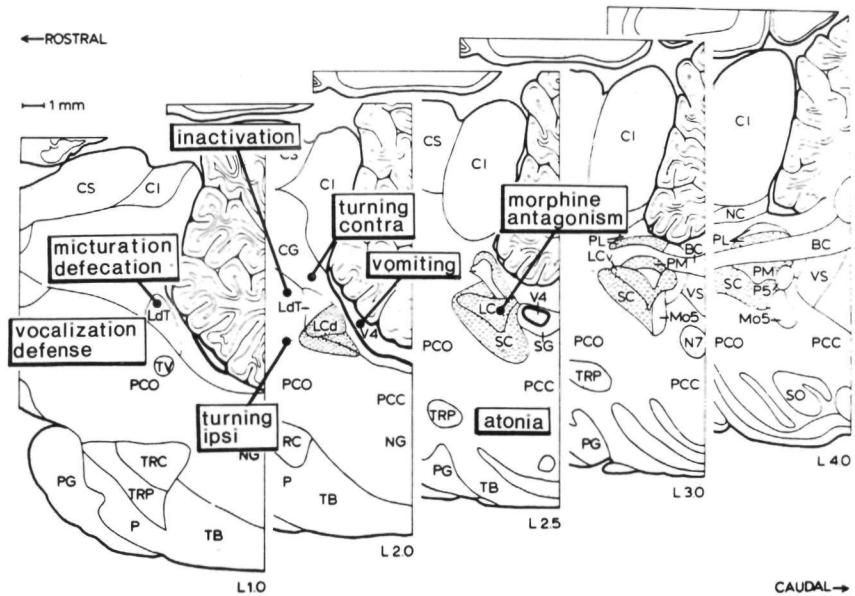


Fig.39 Summary of the effects caused by the intracerebral injection of drugs described in the sections 2.1 to 2.8, and of the regions to which these effects are ascribed.

The effects elicited from approximately the same region were positively associated in every case:

- PCO: carbachol-induced defense reactions, carbachol-induced prolonged vocalizations and clonidine-induced inactivation.
- in/near the CG: carbachol-induced contraversive turning and carbachol-induced elimination.
- in/near the NE region: clonidine-induced inactivation and naloxone-induced partial antagonism of morphine-induced behavior.

A positive association was found between clonidine-induced vomiting and clonidine-induced micturation ($\phi = 0.52$, $p = 0.006$, not included in the tables 14 and 15). A test was carried out for the combined occurrence of clonidine-induced vomiting and all the other effects listed in table 14: the expected number of combined occurrence (under the assumption of independence) was tested against the observed number of combined occurrences, and a negative association was found ($p < 0.05$). This would suggest that the other effects of table 14 are probably not the result of a proportion of the drug reaching the ventricle.

3. GENERAL DISCUSSION.

THE "FUNCTION" OF THE LOCUS COERULEUS.

3.1. "Functions" attributed to the LC.

"Über die Bedeutung der Zellen des Locus caeruleus ist noch nichts Sicheres bekannt" (Merkel 1917).

SECTION 3.1. TABLE OF CONTENTS

Introduction

In section 3.1 some "functions"* attributed to the LC in the literature and not mentioned in section 2 will be briefly discussed. In section 3.2 I will present my own ideas on the "function" of the LC.

* In the present section (3) "function" is used in the meaning "I/O-function" (see section 5.2.4).

THE LC AND SPINAL PROCESSES

The LC, NE and spinal reflexes. *l*-Dopa (a precursor of the catecholamines DA, NE and E) and clonidine (an α-adrenoceptor agonist) affect mono- and polysynaptic spinal reflexes at least partially via α-adrenoceptors (for a review see Grillner 1975, and see below). In the spinal cord, almost all CA terminals in the ventral motor nuclei are NE terminals from the LC, and in the dorsal parts, half of the NE terminals come from the LC (Nygren and Olson 1977b); it is the LCv and SC rather than the LCd that give off fibers to the spinal cord, so that the effects of *l*-dopa and clonidine on spinal reflexes reflect the effects of the LCv and SC on spinal transmission, although DA terminals also may play a role (Commissiong and Sedgwick 1979, Langer et al. 1979). The effects of the LC cells on spinal transmission are also evident after decapitation: the post-decapitation convulsions are reduced or absent after a lesion of the LC or its descending fibers (Pappas et al. 1978, Suenaga et al. 1979, Roberts et al. 1979).

The "mesencephalic locomotor region". In the decerebrated cat, electrical stimulation of the rostral dorsolateral pontine tegmentum elicits locomotor movements; the most effective region, the "mesencephalic (!) locomotor region", is identical to the NE region (Steeves et al. 1975). *"The CA cells ... in close proximity to the mesencephalic locomotor region are situated in the LC, and it is likely that a portion of these CA cells are activated during stimulation of the mesencephalic locomotor region. Further, these cells may be the source of the NA terminals in the spinal cord which release the intrinsic spinal mechanism for locomotion."* (Steeves et al. 1975). The spinal locomotor patterns are generated in the absence of afferent (sensory) spinal input (Jordan et al. 1979): *"the message supplied to the spinal cord from the mesencephalic locomotor region is sufficient for activation of the spinal locomotor generator."*

The LC, NE and locomotion. The effects of *l*-dopa and clonidine (in spinal "animals") on the one hand, and electrical stimulation of the mesencephalic locomotor region on the other hand are similar (cf. Grillner 1975, Jordan et al. 1979, Grillner and Zangger 1979). To summarize the relevant findings: 1) spinal adrenoceptor activation plus afferent spinal input are sufficient for locomotion, and 2) electrical stimulation of the mesencephalic locomotor region, in the absence of afferent spinal input, is sufficient for locomotion, so that it is most probable that elements other

than the LC cells are also activated. *"NE ... (is) responsible for setting the spinal cord circuitry so that it can generate locomotor movements."* (Grillner 1975). It should be noted, however, that 1) LC terminals in the spinal cord are not necessary for locomotion in intact animals, and 2) activating the spinal locomotor generator is one effect, but not the only effect of the LC's activity.

The LC, NE and spinal nociceptive reflexes. *l*-Dopa, clonidine in spinal "animals", and electrical stimulation of the mesencephalic locomotor region in decerebrated "animals" reduce nociceptive reflexes (for a review see Grillner 1975). The following 2 nociceptive reflexes are reduced: the short latency flexor reflex (Grillner and Rossignol 1978, Andersson and Sjölund 1978, Zemlan et al. 1978) and the tail-flick reflex (Kawasaki et al. 1978). Only in one recent study, has a NE-induced increase in spinal C-fiber reflexes been described (Matsumiya and Bell 1978). Grillner and Zangger (1978) have suggested that one effect of the LC cells' activity is the incorporation of nociceptive reflexes in locomotion. Although the LC cells' activity reduces spinal nociceptive reflexes, part of the neural message reflecting the presence of a noxious stimulus still ascends to the brain unaffected (Andersson and Sjölund 1978).

3.1.2. THE LC AND BEHAVIORAL RESPONSES TO NOXIOUS STIMULI

The findings on the effects of the LC cells' activity on the response to noxious stimuli are inconsistent (Cicero et al. 1974, Akil and Liebeskind 1975, Price and Fibiger 1975, Hammond and Proudfit 1977, Sasa et al. 1977a, Bodnar et al. 1977, Sandberg and Segal 1978, Kostowski et al. 1978a, Margalit and Segal 1979, Yaksh 1979, Kuraishi et al. 1979b, Wendlandt and File 1979, Mason and Fibiger 1979a). These discrepancies do not apparently depend either on the type of manipulation of the LC activity or on the type of pain response measured (hot plate, tail flick, jumping, hindlimb flexor response, and stimulation- or morphine-induced analgesia). In any case, although a LC/NE-induced reduction of nociceptive reflexes in spinal and decerebrated "animals" is well documented (section 3.1.1), it seems that pain-induced effects in intact animals are scarcely affected by the LC cells: 1) no consistent relationship has been described between adrenoceptor activation of LC target cells and responses to noxious stimuli (see

above), and 2) the acquisition of passive and active avoidance tasks with a footshock as a reinforcer is not affected by a lesion of the LC or its ascending fibers (reviews A&S 8.9., Clark 1979, Mason 1979c; Mason and Fibiger 1979a,e,i, see also section 3.1.5).

THE LC, NE AND INGESTION

Transient hypophagia and hypodipsia followed by normal food intake or hyperphagia and hyperdipsia have been found after destruction of the LC (A&S 8.7.). Various findings indicate however that the LC is not primarily involved in ingestion.

1. The hyperdipsia is only weakly correlated with the loss of forebrain NE (Sessions et al. 1976a).
2. The changes in food and water intake are most probably due to destruction of other parts of the dorsolateral pontine tegmentum. The ascending taste fibers relay in the parabrachial nuclei (cf. section 1.1.2), so that destruction of these fibers deprives the animal of sensory taste information. The hyperdipsia may also be related to the reno-urogenital disturbances, which are probably due to destruction of the nucleus laterodorsalis tegmenti (cf. section 2.5).
3. NE terminals in the hypothalamic nuclei paraventricularis and/or ventromedialis are involved in eating (Leibowitz 1978, Van der Gugten et al. 1977, Maes and Callens 1979), but these NE terminals originate from the medullary NE cells of the A1 and A2 group rather than the LC (Jones et al. 1978, O'Donohue et al. 1978, Suenaga et al. 1979, Marchand et al. 1979b).
4. Stimulation-induced eating and drinking is not affected by a 6-OHDA-induced lesion of the ascending LC fibers (Van der Kooy 1979).
5. Neither baseline food and water intake, nor the acquisition of tasks reinforced by food or water is affected by a 6-OHDA-induced lesion of the LC or its ascending fibers (Mason 1979d, Mason and Fibiger 1979d,g, Mason et al. 1979b, File et al. 1979).
6. Predation by the rat (mouse killing) is reported as being either enhanced (Oishi and Ueki 1978) or not affected by a lesion of the LC (Kostowski et al. 1979d).

3.1.4. INTRACRANIAL SELF-STIMULATION (ICSS)

ICSS can be elicited from electrodes in the dorsolateral pontine tegmentum (reviews A&S 8.8., Clark 1979). It has been suggested that electrical stimulation of the LC cells or fibers causes ICSS, but convincing evidence has been presented that the cells through which the ICSS is mediated are not the LC cells (Amaral and Routtenberg 1975, Simon et al. 1975, Clavier et al. 1976a, Clavier and Routtenberg 1976a, Corbett et al. 1977, Cooper et al. 1978, Wise 1978b (review), Van der Kooy 1979, Maxim and Storrie 1979, Corbett and Wise 1979, Sinnamon et al. 1978, Edwards et al. 1979). It is uncertain which cells or fibers in the dorsolateral pontine tegmentum are the substrate of the ICSS; trigeminal fibers (Van der Kooy 1979) and gustatory-visceral fibers (Corbett and Wise 1979) have been suggested, but many other fibers run also through this region.

3.1.5. THE LC, NE AND LEARNING

Acquisition and retention. The effects of destruction of the LC or its ascending fibers on a great variety of learning tasks have been investigated (reviews A&S 8.9., Clark 1979, Mason 1979c). The acquisition and retention of simple learning tasks are not affected by lesions of the LC or its ascending fibers, independent of whether food, water, ICSS, or footshocks were used as reinforcer: the LC is not important for food or water motivation, reward or punishment, and the LC is not necessary for learning *per se* (e.g. Mason 1979d). The acquisition of a more difficult task (visual discrimination by rats) was somewhat retarded (Mason and Iversen 1978a,c), and LC-lesioned rats are easier distracted during the performance of a learning task (Roberts et al. 1976, Koob et al. 1978b, Mason and Fibiger 1978c).

Extinction. Extinction of various tasks learned is retarded by a lesion of the ascending LC fibers (review Mason 1979c); this retardation of extinction only occurs, when the dorsal NE bundle is destroyed before the acquisition (Mason 1979d, Mason and Fibiger 1979d). Mason and his colleagues have carried out many experiments to analyse the retardation of extinction, which has led to various explanatory hypotheses being rejected. The only hypothesis not rejected is the (selective) attention hypothesis:

"(The LC) seems to be telling ... the forebrain when to attend incoming stimuli and when to ignore them." (Mason 1979a). It is not that the LC can be regarded as something akin to an "extinction center", but rather the animal is said to be able to sample relevant stimuli thanks to its LC (Mason 1979a,c). In the absence of an LC, more stimuli are sampled, relevant or irrelevant to the task involved but characteristic of the learning situation; more stimulus-response connections are said to be made, so that in extinction more stimulus-response connections have to be broken down.

The LC, the adrenals and learning. The acquisition and retention of avoidance tasks is severely impaired by the combined destruction of the ascending LC fibers and the adrenals, while destruction of only one of these parts causes no or only minor impairment (Ögren and Fuxe 1977, Roberts and Fibiger 1977b, Mason et al. 1979b, Wendlandt and File 1979). The effects of adrenalectomy were countered by corticosterone (Ögren and Fuxe 1974). An impairment of passive or active one-way avoidance was found by all these authors, while the effects on two-way avoidance are still a matter of discussion. No impairment of food-rewarded lever pressing has been found after destruction of the dorsal bundle plus adrenalectomy: it has been suggested that this combined destruction affects fear motivation rather than learning *per se* (Mason et al. 1979b).

3.1.6. THE LC AND BEHAVIOR

Female rats, sexual and maternal behavior. Lesion of the ascending LC fibers has been reported as making female rats less sexually receptive (Wright and Everitt 1977), and causing impairment of the maternal behavior (Steele et al. 1979). In my experiments, no changes in the sexual behavior of female cats arising from acute intracerebral injections were observed. Whether or not the above mentioned effects really are due to the LC remains to be investigated; such effects might reflect the hormonal input to the LC (section 1.2.3). The LC should not however be considered as a "sexual center" or a "maternal center": it is rather that effects on sexual or maternal behavior reflect merely one aspect of the generalized action of the LC.

Male rats, agonistic behavior. Lesion of the LC has been reported as increasing the occurrence of aggressive behavior of individually housed male

rats (Kostowski et al. 1978d, File et al. 1979). An increase was found under different agonistic situations (water-competition, home-cage intruder, shock-induced fighting) in the occurrence of boxing, pushing and wrestling, but not of more severe attacks. On the other hand, a radiofrequency lesion of the LC or 6-OHDA injected intraventricularly into certain male rats of an all-male colony has been reported as decreasing the occurrence of aggression and increasing positive social behavior (Ellison 1976, Eison et al. 1977a). the lesioned males fought less, lost more fights, and became lower in rank. In these animals motor disturbances were also found; it is unclear whether the changes in agonistic behavior were secondary to the motor impairments or independent of them. A decrease in aggression after a lesion of the LC is in line with the finding that in a more aggressive strain of mice the NE level and turnover in some LC target regions is higher (Tizabi et al. 1979). In the present study, however, defense reactions caused by carbachol injected in and near the LC of cats were not due to the LC but rather to the more rostral nucleus pontis centralis oralis (section 2.2), so that the changes in agonistic behavior mentioned above might be (at least partly) due to effects on the nucleus pontis centralis oralis rather than the LC. Apart from the findings mentioned above, further contradictory findings have been presented on central NE and aggression (for references see Kostowski et al. 1978d, File et al. 1979). In any case, the LC is not an "aggression center": specific manipulations of the LC affect aggressive behavior, but such effects reflect aspects of the general influence of the LC on the CNS and behavior.

3.2. The "function" of the LC.

"The locus coeruleus is the brain's multinervous centre" (Bloom 1976)

SECTION 3.2. TABLE OF CONTENTS

Introduction

In this section, I attempt to formulate general functional statements about the LC, based on my own results and on findings from the literature. The theoretical basis for these statements is presented in section 5, the empirical basis is presented more extensively in the sections to which is referred below. Two meanings of the question "What is the function of the LC?" are relevant (cf. section 5.2.4):

1. "What does the LC do?" Tentative answers to this question at different levels (section 5.3) will be given in section 3.2.1.
2. "Why did the LC evolve?" A tentative answer to this question will be given in section 3.2.2.

3 2.1. "WHAT DOES THE LC DO?"

Introduction. The question "What does the LC do?" is identical to "What is the relationship between the inputs and the outputs of the LC?" (section 5.2.4). The inputs and outputs can however be formulated at different levels (section 5.3), for instance molecular or cellular. A survey of the inputs and outputs of the LC at different levels is given in fig. 40 When neuroscientists ask the question "What does the LC do?" (or equivalent questions), they have an answer in mind at the behavioral (or organ) level. The question "What does the LC do at the organ or behavioral level?" is identical to "What is represented by the activity of the LC cells outside the CNS, and what are the effects of the activity of the LC cells outside the CNS?" (section 5 4). (A functional statement at the organ or behavioral level consists of a cause and an effect outside the CNS.)

Input. what is represented by the LC cells' activity? From the available data from the literature, no generally accepted conclusion has yet been drawn on what is represented by the LC cells' activity. The LC cells are active in the presence of novel stimuli (Cedarbaum and Aghajanian 1977b), stressors (section 1.3.4), noxious stimuli (sections 1.3.2 and 3.1.3), alarming (anxiety eliciting) stimuli (section 2.2), but also in less threatening situations (sections 1.3 and 2.2) The LC cells are activated by peripheral sympathetic signals, and suppressed by peripheral parasympathetic signals (section 1.3.2). My suggestion based on the LC literature is that the activity of the LC cells represents the notion that "Something important may be going on". ("Something important" is not more specified, because extensive sensory convergence on the LC cells has been described (section 1.3.2), so that the LC cells cannot tell what is going on, and "may be", because the response to sensory stimuli can be of a short latency (section 1.3.2), such that the signal processing required to make certain that something important really is going on, cannot yet be completed in time.)

Output. what are the effects of the LC cells' activity on behavior? If the LC cells' activity is a representation of "something important may be going on", what then are the effects of this message? My suggestion is that the LC cells' activity prepares the CNS (and the animal) for an adequate reaction when something important is going on. Several findings provide

circumstantial evidence for this suggestion.

1. Restoration of the activity of the LC cells in morphine-treated cats can restore the animal's reaction to its environment (section 2.9).
2. Spinal NE coming from the LC and SC promotes locomotion in spinal cats and suppresses spinal nociceptive reflexes (section 3.1.1).
3. The LC may be involved in filtering away irrelevant stimuli (selective attention, section 3.1.5): *"(The LC) seems to be telling ... the forebrain when to attend incoming stimuli and when to ignore them"* (Mason 1979a).
4. Co-operation between the LC and the adrenals has been suggested (section 3.1.5).
5. Morphological resemblance exists between the LC cells and the peripheral sympathetic NE cells (A&S 9., Hartman and Udenfriend 1972, Iijima 1978); a functional resemblance has also been suggested: *"the central NE cells prepare the CNS to cope with a crisis situation"* (Hartman and Udenfriend 1972), and central NE *"modulates the central component of sympathetic tone"* (Brown and Van Huss 1973).
6. The symptoms concomitant with LC cell loss in man or with change in the cerebral NE metabolism (intellectual impairment, dementia, depression, paranoid schizophrenia; section 6) are in line with the suggestion mentioned above.

All these suggestions taken together are generalized into the following metaphorical statement about the effects of the LC cells' activity: "observe what is going on (LCd), and stand by to react (LCv)".

Conclusion: "relevance? / stand-by function". The "function" (I/O-function) of the LC consists of what is represented and what is generated by the LC cells' activity and can be expressed in full as follows:

Metaphorically, the LC cells say:
'Something important may be going on;
- LCd: observe what is going on,
- LCv: stand-by to react.'

This hypothetical "function" of the LC is called the "relevance? / stand-by function".

All the "functions" of the LC at all levels

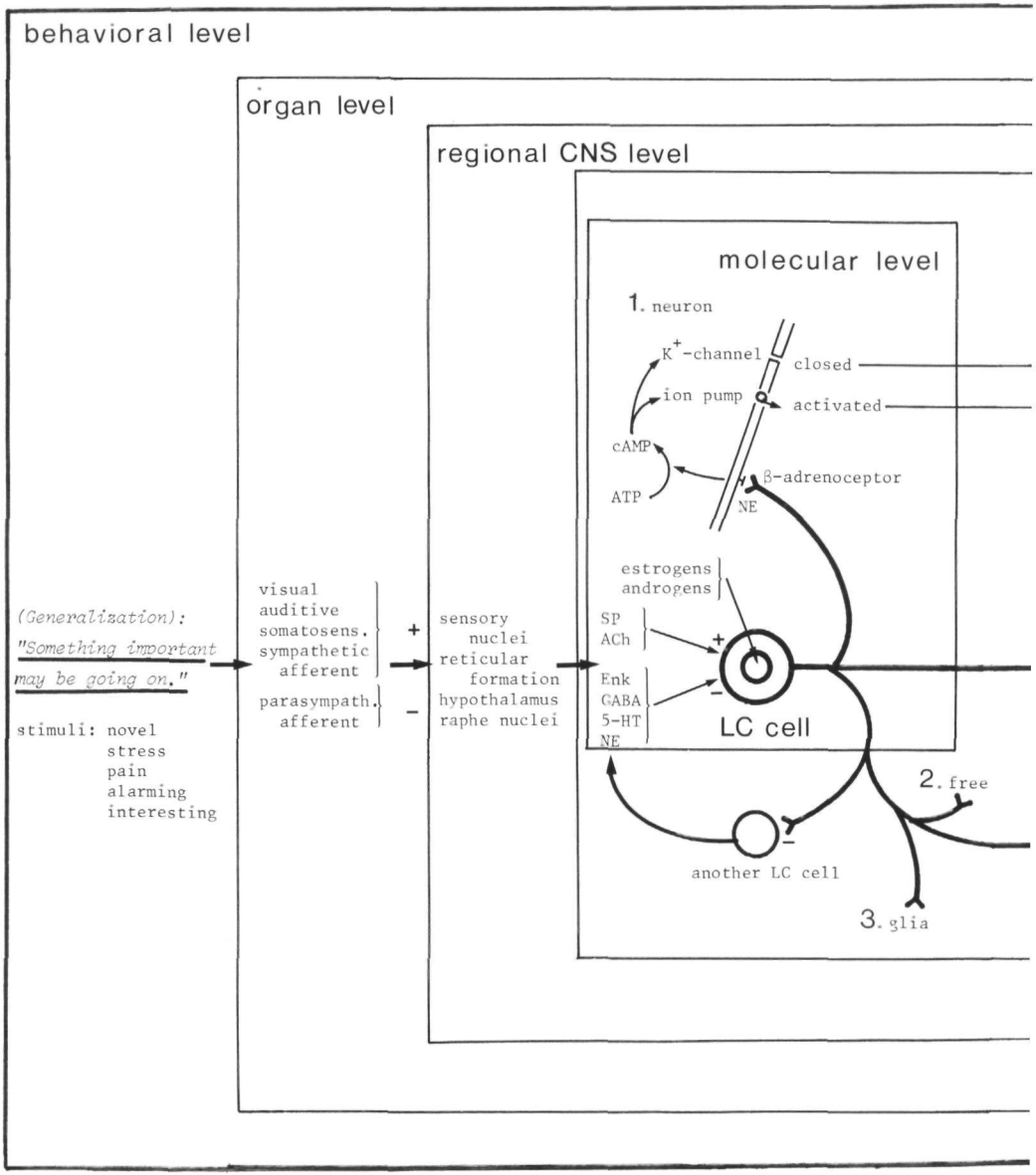
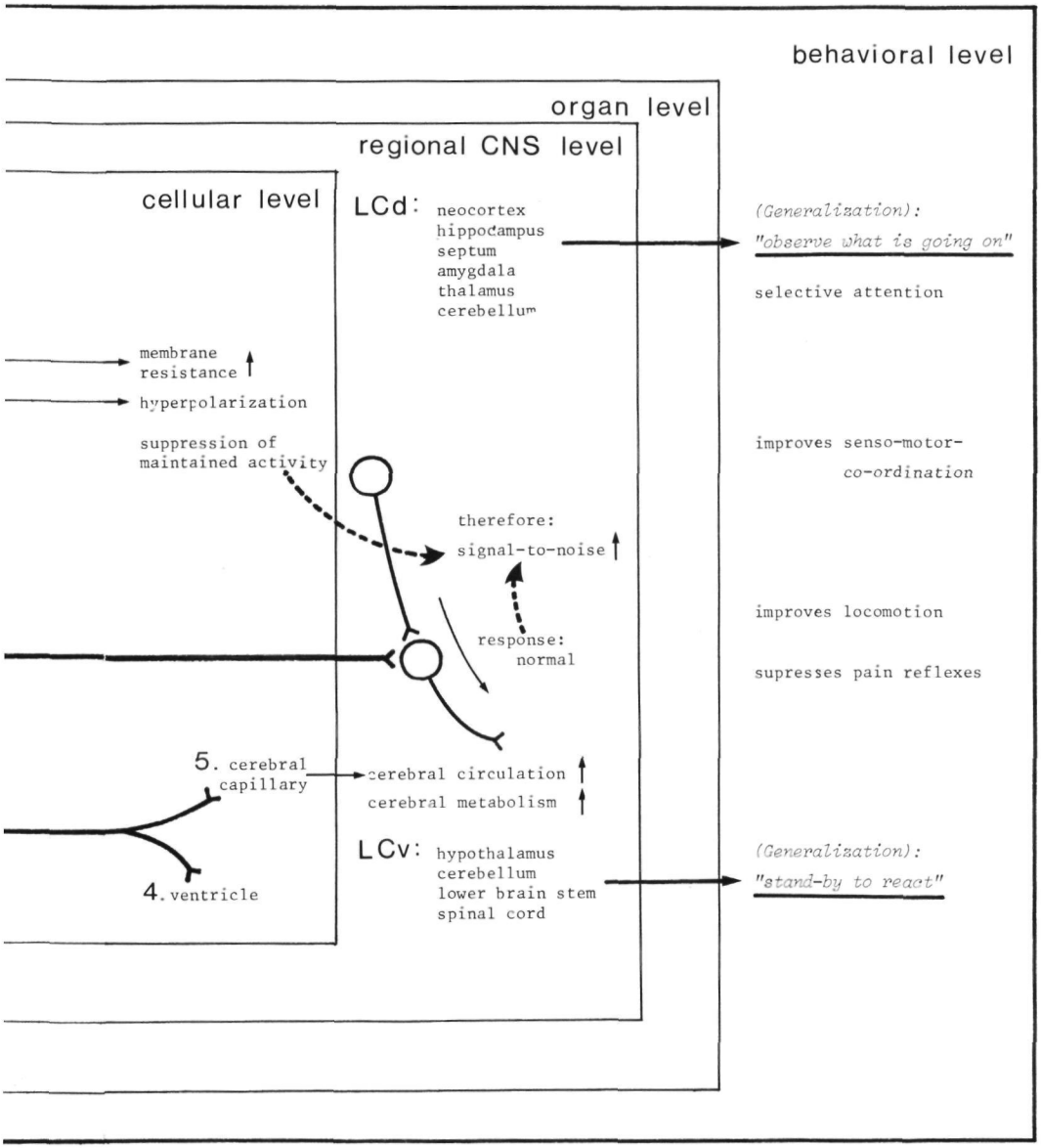


Fig.40 Survey of the experimentally demonstrated inputs and outputs of the LC at the various levels; thereby indicating all I/O-functions of the LC at all levels.


behavioral level
organ level
regional CNS level
cellular level
LCd: neocortex
hippocampus
septum
amygdala
thalamus
cerebellum
(Generalization):
"observe what is going on"
selective attention
membrane resistance ↑
hyperpolarization
suppression of maintained activity
improves senso-motor-co-ordination
therefore:
signal-to-noise ↑
response: normal
improves locomotion
supresses pain reflexes
5. cerebral capillary
cerebral circulation ↑
cerebral metabolism ↑
4. ventricle
LCv: hypothalamus
cerebellum
lower brain stem
spinal cord
(Generalization):
"stand-by to react"

Mechanism of the LC's effects. The LC cells are thought to improve the CNS signal processing. The mechanism of this effect at the regional level is an increase in the signal-to-noise ratio of a number of neurons, as has been suggested for the cerebellum, the corpus geniculate laterale, the hippocampus and the somatosensory and auditive cortex (section 1.4.2), and an increase in the cerebral circulation. At the cellular level, the mechanism of this process is the NE-induced hyperpolarization and increase in membrane resistance, the mechanism of which at the molecular level is an increase in the activity of a transmembrane ion pump, and a closure of K^+-channels (section 4.3.1) (for a survey see fig. 40).

The LC and the ARAS. Is the "relevance? / stand-by function" of the LC identical to the "function" of the ascending reticular activating system (ARAS)? The ARAS has been defined originally by its effects on behavior and on the neocortical EEG; these effects are not (primarily) mediated via the LC. It should be recalled that the LC receives afferents from the reticular formation (section 1.2.1). An attractive hypothesis is that part of the effects of the ARAS are effectuated via the LC: the LC increases the cerebral circulation and the signal-to-noise ratio of its target neurons. The proposed suggestion for the "relevance? / stand-by function" of the LC greatly resembles the "attention function" of the LC (cf. the 20 papers published by Mason in 1979). Under the present suggestion, the meaning of "attention" and "function", and the mechanism of the LC's effects are more specified.

The "stress-dampening function" of the LC. In their extensive review of the LC, Amaral and Sinnamon (1977) suggested that the LC's function is to dampen an animal's response to stressors. Translated into the terms of the functional concept proposed, Amaral and Sinnamon suggest that the LC cells say "A stressor is present, but keep quiet". Apart from the indications in favour of the "relevance? / stand-by function" of the LC presented above, I will put forward 3 reasons which make the "stress-dampening function" of the LC less attractive.

1. Stimuli much milder than stressors also activate the LC cells (section 1.3.2); the behavioral response to these stimuli would also be dampened, if the stress-dampening hypothesis would be generally valid. The stress-dampening hypothesis could be maintained by making extra assumptions, which make it more complicated, but for the time being, I prefer the simpler suggestion mentioned above.

2. "The LC inhibits [illegible] ... [illegible] the animal's perception of stimuli" (Amaral and Sinnamon 1977). Evidence has however been presented that the LC-induced suppression is not inhibition, but rather improved information processing requiring energy (sections 1.4.2 and 4.3.1).
3. Urogenital disorders after destruction of the LC region are regarded as indications that the animals were no longer stress-tolerant (A&S 9.); such urogenital disorders, however, are probably due to the destruction of the nucleus laterodorsalis tegmenti or its fibers, rather than of the LC or its fibers (section 2.5.4).

The data on the influence of the LC on the cerebral circulation and metabolism are conflicting (section 1.4.4). An LC-induced decrease in the cerebral circulation and metabolism (as reported by some authors) would be in agreement with a "stress-dampening function" of the LC, while an LC-induced increase (as found by others) would be in agreement with the "relevance? / stand-by function".

The "relevance? / stand-by function" and other effects attributed to the LC. According to the "relevance? / stand-by function" of the LC, the activity of the LC cells improves the CNS signal processing. Such an improvement of the CNS signal processing during PS might end PS phases (section 1.2), and it might improve the reactions to alarming stimuli (section 2.2), stimulus sampling (section 3.1.5) and sexual, maternal and agonistic behavior (section 3.1.6). At the moment, it is uncertain whether the influences of the LC on CNS ontogenesis and plasticity (section 1.4.5) are direct (specific) LC-induced influences on cell growth, or indirect influences due to an LC-induced change in CNS signal processing. It is no less uncertain whether or not the message "stand-by" of the LC cells also causes an increase in peripheral sympathetic activity (section 1.4.6) and blood pressure (section 1.4.7).

Limitations of the present functional suggestion. There are a number of limitations to the suggestion of a "relevance? / stand-by function" for the LC which for the time being cannot be overcome.

1. The "relevance? / stand-by function" of the LC is a suggestion based on circumstantial evidence, but scarcely a hypothesis, since I cannot think of a practicable experiment to critically test this suggestion.

In all honesty, this is characteristic at the present time of functional statements on many parts of the CNS.

2. At present it is unclear whether we have to distinguish only 2 LCs (the LCd and LCv), or as many as 5 systems within the LC (section 1.1).
3. In the "relevance? / stand-by function" of the LC it is assumed that the activities of the LCd and LCv cells represent identical messages. The afferents of the LCd and LCv seem however to be different (sections 1.2.1 and 1.2.2), so that the activities of their cells most probably represent different messages. At the very least it will be necessary in the future for certain refinements to be made to take account of what is represented by the LCd's and LCv's activity, but up to the present no indications of further details on differences in the inputs of the LCd and LCv have been published.
4. It is probable that the generalization in its present from on the effects of the LC cells' activity ("observe what is going on, and stand-by to react") is too general. In its present form the suggested effects of the LC cells' activity would apply to the whole CNS, but the LC does not project to the whole CNS: some CNS regions receive a dense LC innervation, and others none at all (section 1.4.1). I am not at the moment able to formulate any functional generalization which covers those regions of the CNS which receive either a dense innervation of the LC or none at all. Any generalization of the effects of the LC cells' activity must however be restricted to the functional generalization of the LC's target regions.
5. It is uncertain whether the LC's inputs and outputs are random or ordered (pp. 52-56). If the structure of the inputs or outputs is random, the "functions" of the various LC cells are identical, and can be formulated in one general statement: the proposed "relevance? / stand-by function" would not only apply to the whole LC, but also to each individual cell of the LC. If on the other hand the structure is to some degree ordered, the individual LC cells would be specialized: a general statement such as the "relevance? / stand-by function" might be valid for the whole LC, but would be too general for the individual LC cells. Unfortunately, at the present time, we simply do not know whether the LC cells are specialized or not. Furthermore, we do not even know on which dimensions the LC cells would be specialized.

ON THE ORIGIN OF THE LC

When one knows what the LC does at the behavioral level, one can determine the evolutionary value of the LC (section 5.2.4). If the "relevance? / stand-by function" of the LC is correct, the evolutionary value of the LC is the answer to the question "Why does a part of the CNS which improves the observations and reactions of the CNS (and the animal) exist?", or in other words "Why is the CNS (and the animal) not always ready to observe and react?". One should keep in mind that the effects of the LC on the CNS require energy: ATP is degraded to form cyclic-AMP and to activate Na, K-ATPase (section 4.3.1). An economical use of energy resources improves the animal's chance of survival, so that the evolutionary value of the LC is suggested to be that of preparing the CNS for reacting to a demanding situation at the expense of energy, but only when certain stimuli indicate that the situation may be demanding.

4. APPENDICES.

4.1. Methods.

Animals. In this study 64 adult and young adult cats of both sexes were used; 27 males and 37 females. Healthy cats which approached the experimentor purring or rubbing their heads against his hand or against other objects when their boxes were opened ("gentle cats") were selected from a large stock. Of the cats that withdrew at the experimentor's approach ("anxious cats") only 3 were used in the study. Since black cats are difficult to observe, I avoided using them; only 2 black cats were used. The cats were housed individually in stainless steel cages (60 x 40 x 40 cm), with 20 to 30 cats in one room. Daylight did not reach the room, which was illuminated by a pair of 40 W fluorescent lamps, on a fixed light-dark schedule (the light period was 5.00 to 19.00 hour). Food was supplied twice a day, milk at 9.30 h and tinned food at 17.00 h. The light-dark alternations and feeding times were standard clock-times, involving a change twice a year (summertime).

Surgery. Food was withheld for at least 15 hours before an operation. The cats received atropine-H_2SO_4 (0.5 mg, i.p.) 15 minutes before injection of anaesthetics. Pentobarbital (Nembutal^R, 30-40 mg/kg, i.p.) anaesthesia was used in 35 cats. Where necessary additional injections of pentobarbital or thiopental (Nesdonal^R) were given (5-10 mg/kg, i.p.). Barbiturate anaesthesia was however considered to be less satisfactory for the following reasons. 1) The therapeutic range of barbiturates for anaesthesia is small in cats (Clifford and Soma 1969). In a number of cats the reaction to noxious stimuli could not be eliminated by a sublethal dose of barbiturates (i.p.); this was also the case after intravenous injections (earlier observations). In attempts to eliminate nociceptive reflexes 3 cats died. 2) Recovery from barbiturate anaesthesia takes 12 to 36 hours; during recovery one cat died. For these reasons the subsequent 29 cats received the more elaborate, but more reliable halothane (Fluothane^R) anaesthesia. Initially, 15 minutes after the injection of atropine, these cats received ketamine (Vetalar^R, 20 mg/kg, i.m.) and, if necessary, a supplementary injection of 10 mg/kg i.m. They were intubated and received artificial respiration with N_2O/O_2 (a 2/1 mixture) (intermittent positive pressure respiration, inspiration pressure always less than 8 gr/cm^2).

Anaesthesia was taken over by halothane, initially at 4-8%, until palpebral, cornea and hindlimb flexor reflexes were fully absent. At this stage halothane was reduced and titrated to the smallest amount consistent with the hindlimb flexor reflex being fully absent after a single pinch of the skin between the toes: this was 0.4-0.8% for all cats; at this dose the animal's respiratory movements were also fully absent. (In some cats the hindlimb flexor reflex could be evoked by repeated pinching, the cats slowly withdrewing their legs. In combination with local anaesthesia (see below) this state was however considered to be sufficient anaesthesia for surgery.) The CO_2-percentage of the exhaled air was monitored continuously and artificial respiration was set to an amount that resulted in a CO_2-percentage between 3.6 and 4.0%. All pressure points were infiltrated with lignocaine unguent (Xylocaine^R, 5%) and the cats were placed in a stereotaxic apparatus (Lohman and Peters 1975), and the skin of the heads shaved and iodized. The skull was exposed, and all wound edges were injected with lignocaine-adrenaline (Lidocaine^R, 2%). The eyes were kept wet with chloramphenicol ophthalmic unguent (Globenicol^R) and the cats kept warm with a heating blanket. The stainless steel cannulae used were double barrelled; the diameter of the outer cannula was 0.8 mm and that of the inner (dummy) cannula 0.5 mm, with its tip extending 1 mm beyond the outer cannula (Cools 1971). Cannulae aimed 2 mm above the locus coeruleus (LC) (Horsley-Clarke co-ordinates P 1.5 to 2.5, L 2.0 to 2.5, H -0.3 to -2.0) were implanted bilaterally. They were placed in a parasagittal plane at an angle of 30^o (fig. 41) piercing the visual cortex, superior or inferior colliculus, and the lateral periaqueductal gray. This orientation was preferred because cannulae to the LC piercing through the cerebellum would have opened the ventricular wall near the LC, promoting the spread of the drug to the ventricle (cf. section 4.2, Levin and Stolk 1977). In addition, 2 cannulae were directed vertically to the substantia nigra (Horseley-Clarke co-ordinates A 5.5, L 3.0, H -3.0). These pierced the visual cortex, hippocampal formation, pretectal region and the mesencephalic reticular formation. The cannulae were fixed with dental cement (Paladur^R) and a pair of screws in the skull. Chloramphenicol powder (Gloveticol^R) was sprinkled on the wound and the wound sutured. Acryle-resin (Nobetucane^R) was sprayed over the sutured wound. The halothane was now discontinued, and the cats regained consciousness, allowing the artificial respiration to be terminated. The animals received phenylbutazon (Butazolidin-alka^R, 50 mg, orally) immediately, and 24 hours after the operation for post-operative

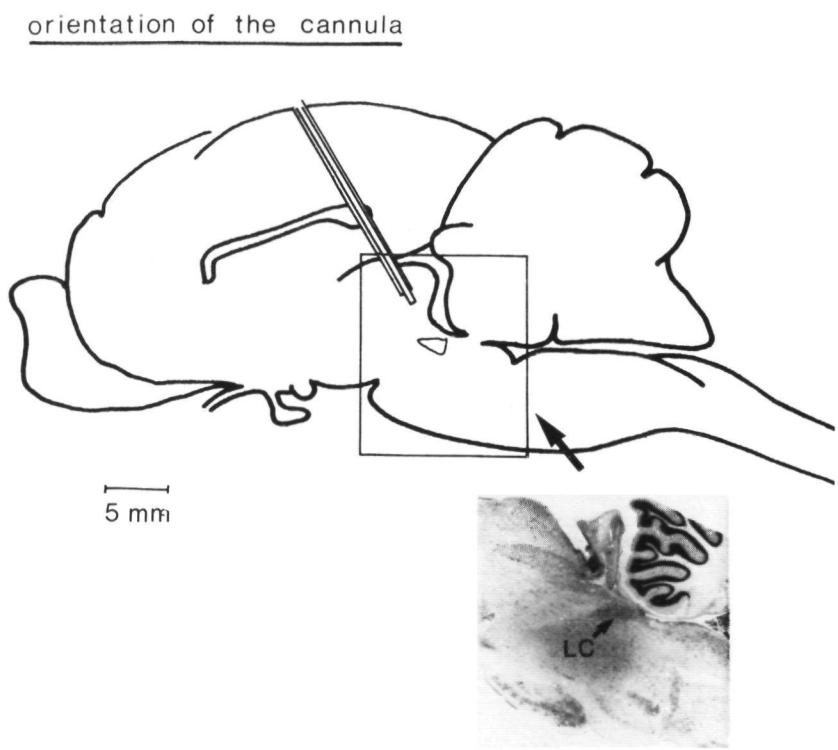


Fig.41 Orientation of the cannula to the LC, and a Nissl-stained parasagittal section showing the LC and a cannula track belonging to an injection site exactly in the LC. This injection site was used in 7 experiments; note the integrity of the LC.

analgesia and anti-inflammation. The day after the operation the general state of the cats was examined and a number of reflexes tested: cornea, extensor postural thrust, righting reactions, visual and tactile placing reactions, hopping, and jumping (McGrath 1956). The day after halothane-anaesthesia, all the cats had recovered well and showed normal reflexes. Compared with pentobarbital, halothane was the better drug: it was safer, better to dose, and quicker acting, and it had in combination with N_2O a superior anaesthetic and analgesic action. (Four cats died, however, before the experiments could be started; one 4 days after the operation from an unknown cause, and 3 others at 9, 12 and 17 days after the operation through an Salmonella infection.)

Equipment. The observation box was placed in a sound-attenuated room; food, water, and a cat's box were absent. The cats' behavior was observed via closed circuit TV and recorded on tape. The camera was 2.5 m away from the observation box; its direction and its zoom lens (11.5 - 90 mm) were remotely controlled. The room was illuminated by 4 40 W fluorescent lamps.

Procedure. The details of the procedure that are relevant for the interpretation of the individual behavioral effects are mentioned in the short sections on "Methods" in chapter 2; general aspects of the procedure are covered in this section. The animals were allowed to recover from their operations for at least a fortnight. Two days before experiments began the cats were placed for one hour per day in the observation box. The 21 cats used in exploration tests received an intracerebral injection before they were placed in the observation box for the first time (see section 2.7.2). The following day a needle was inserted through the cannula into the site where the injections were to be given. When after a touch of their backs before the experiments female cats were rolling over and adopting the posture for copulation, note was made in the protocols that they were in heat. Before the intracerebral injections of the drugs the cats were placed in the observation box, the dummy cannula removed, and the cats were left undisturbed for 30 minutes; during the last 15 minutes their behavior was observed to provide pre-injection controls of each cat's behavior. An ethogram (see below) was used to describe the behavior. The cats then received the intracerebral injections manually using a Hamilton 5 µl syringe, the needle of which extended 2 mm beyond the site of the tip of the dummy cannula. In most experiments, the injection was unilateral (see below for the number of experiments), but in a number of cases the effects of bilateral injections were also tested (carbachol n=17; clonidine n=10, oxymetazoline n=5, naloxone in morphine-treated cats n=14). The volume injected was 0.5 µl in every case. The duration of the injections was about one second; after which the dummy cannula was replaced. The cats' behavior after the injections was observed for at least 45 minutes, during the first 15 minutes of which the animals were left undisturbed. Only effects which began in the first 15 minutes have been considered. Experiments with intracerebral injections were carried out in naive cats and in cats previously treated with morphine (i.p., section 2.8). Given the dose and schedule of morphine injections used no

signs of morphine-dependence were noted; all the effects mentioned in this study were observed in naive cats and in cats treated 2 days to 4 weeks earlier with morphine. After a series of experiments another dummy cannula, 1-2 mm longer, replaced the original one in 19 cases, and another series of experiments carried out at a more ventrocaudal site. This was repeated 6 times along 2 cannula tracks.

Localization. At the end of the experiments the animals were anaesthetized with pentobarbital and perfused transcardially with saline followed by a Susa-solution. Their brains were sectioned in a parasagittal plane and stained with Nissl's stain. Of the 141 injection sites covered in this study 129 were histologically localized, since 4 brains were lost. The actual size of the cannula was known, so that the amount of tissue shrinkage could be determined with a calibrated ocular micrometer. Since the exact distance between the tip of the dummy cannula and the tip of the injection needle was known, the localization of the needle tip could be determined using the calibrated ocular micrometer (cf. fig. 40). (The site of the needle tip has been designated the "injection site".) The localization of the injection sites is indicated in the composite drawings in chapter 2.

Data analysis. The relationship between the drug-induced effects and the region of injection has been investigated. For each effect, the number of effective and ineffective sites in each anatomically demarcated region was counted, and the number of sites in and near each region, i.e. sites at a distance of less than 1 mm from the region, to allow for the spread of the drug (cf. section 4.2). (Sites located on the boundary of 2 regions were counted in both regions.) The occurrence of sites in 4 distinct regions, the NE region, the central gray and the nuclei pontis centrales oralis and caudalis, was analyzed statistically; these regions contained more than 10 injection sites. For each effect a 2x4 contingency table (number of effective and ineffective sites in the 4 regions) was drawn up, and a χ^2-test was used to test whether or not the effective sites were distributed randomly over the 4 regions (table 13, p. 207). Secondly, a 2x2 contingency table (number of effective and ineffective sites, in and outside each region; sites on the boundary were counted in a region and not outside) was drawn up for each of the 4 regions, and the correlation between the region of injection and the effectiveness of the sites calculated (ϕ-coefficient, Ferguson 1966, pp. 236-239). The probability

(p) to find the observed number of effective sites by chance was then calculated: p = 4p', where p' is the two-tailed accurate binomial approximation of the exact probability of finding the actual or more extreme set of frequencies according to Molenaar (1970). (The factor 4 corrects for the number of tests done; the p was calculated only for the 4 regions mentioned above). Contraversive turning was initially tested against the combination of "no turning" and "ipsiversive turning", thereafter "ipsiversive turning" was tested against "no turning". A correlation matrix was made for the combined occurrence of each pair of effects, and the χ^2 and the p calculated, the latter according to the two-tailed accurate binomial approximation after Molenaar (1970). A satisfactory correction for the number of tests carried out was not available in this case. The relationship between the occurrence of all the drug-induced effects and the date and the time of injection was tested. The year was divided into 6 periods of 2 months, and the day into 4 blocks of 2 hours (only light period), a contingency table drawn up, and the (χ^2, table 13, p. 207) relationship tested. (The data obtained during the week after the change to summer time are not included in the analysis of the dependence of the effectiveness and the time of injection.)

Drugs. The following drugs were used (the numbers between brackets indicate the dosage and the number of injection sites tested with the drug): carbamylcholine-HCl (Carbachol^R, Sigma, 0.01-0.5 µg, n=141), physostigmine-H_2SO_4 ("De Onderlinge Pharmaceutische Groothandel" OPG, 2-20 µg, n=6), atropine-H_2SO_4 (Ned. Farm., 1 µg, n=8), mecamylamine-HCl (Merck, Sharp and Dohme, 0.6 µg, n=6), *l*-norepinephrine-HCl (Fluka, 10 µg, n=13), clonidine-HCl (Boehringer, Ingelheim, 1-5 µg, n=60), oxymetazoline-HCl (Ciba Geigy, Arnhem, 5 µg, n=9), isoprenaline-bitartrate (Sigma, 5 µg, n=9), piperoxane-HCl (Brocades, 5 µg, n=9), yohimbine-HCl (Nogepha, 0.5 mg/kg, n=3), *l*-propranolol-HCl (ICI, 10 µg, n=10), *dl*-propranolol-HCl (Sigma, 2 mg/kg, n=2), phenoxybenzamine-HCl (Dibeniline^R, Smith, Kline and French, 20 mg/kg, n=2), 6-hydroxydopamine-HBr (6-OHDA, Sigma, 3 µg, n=2), *d*-amphetamine-H_2SO_4 (Brocades, 5 µg, n=4), desipramine-HCl (Pertofran^R, Ciba Geigy, 5 µg, n=4), apomorphine-HCl (OPG, 5 µg, n=3), morphine-HCl (OPG, intracerebral, 5 µg, n=12; intraperitoneal 5 mg/kg, n=91), fentanyl-citrate (Janssen Pharmaceutica, 5 µg, n=23), naloxone-HCl (Endo Laboratories, 0.8-10 µg, in morphine-treated cats n=81, in naive cats n=18), procaine-HCl (OPG, 5 µg, n=23), L-glutamic acid (Boom Meppel, 5 µg,

n=11). All the drugs were dissolved in saline, except yohimbine (distilled water), morphine (saline or distilled water for intracerebral injections), and 6-OHDA (nitrogen-bubbled/oxygen-free saline with ascorbic acid, 0.3 mg/ml). All dosages refer to the salts.

Ethogram. The following ethogram was used to describe the cats' behavior (see also: Norton and De Beer 1956, Cools and Van Rossum 1970, Leyhansen 1973).

General postures

1. lying. the head resting on the ground or on the paws
2. sitting relaxed: forepaws folded under the body
3. sitting: forelegs extended forwards
4. lying actively: the head upright and the hindlimbs beside (not under) the body
5. sitting alert the body low, the heel resting on the floor, only the paws of the forelegs resting on the ground, the elbows flexed
6. upright alert. sitting with the heels resting on the ground and the forelegs extended
7. stalking. crouching with flexion in the should, elbow, hip and knee
8. standing. all legs extended
9. rearing. standing upright with only the hindlegs on the ground
10. hanging. with the forepaws from an object

General movements

11. walking (forwards)
12. withdrawal. moving backwards
13. turning a single turn being an uninterrupted movement of the cat in which the body axis changes between 180° and 360° (the direction of the turning was also coded)
14. staggering. poorly co-ordinated walking
15. falling
16. jumping
17. rolling
18. digging
19. sharpening the claws
20. stretching
21. sniffing the object which was sniffed at (the ground, wall, air, or another object) was coded
22. licking
23. eating: since food and water were absent in the observation box, licking and eating occurred only after vomiting
24. grooming. 2 behaviors: 1) rubbing the head with the forelegs followed by licking them, and 2) licking the fur
25. scratching the head with the hindlegs
26. scratching the flanks with the hindlegs
27. defecation
28. posture for defecation: sitting with the forelegs extended, flexion in the hip and knee and extension of the heel
29. micturation
30. posture for micturation. sitting with the forelegs extended, and flexion in the hip, knee and heel
31. vomiting

32. retching: opening the mouth with rhythmical movements of the head and flanks, often with some steps backwards
33. sneezing
34. tremor

Head

35. moving the head: every movement of the head
36. shaking the head: quickly, often to shake something off the head
37. holding the head sidewards: with an angle between the head and body axis of at least 90°
38. holding the head prone
39. staring

Mouth

40. opening the mouth
41. open-mouth threat (cf. Leyhausen 1973, p. 137, often with hissing)
42. biting
43. extrusion of the tongue
44. licking the lips
45. salivation
46. swallowing
47. yawning

Eyes

48. eyes open
49. eyes half-closed
50. eyes closed
51. winking (usually both eyes)
52. pupil in miosis
53. pupil in mydriasis
54. nictitating membrane relaxed
55. retraction of the nictitating membrane

Ears

56. turning the ear
57. shaking the ear quickly (often to shake something off the ear)
58. flattened ear
59. ear turned sidewards

Legs

60. leg movement: every movement of the legs
61. limb flick: sudden movement of the legs (often to shake something off the legs)
62. raising a paw
63. striking with the paws

Skin

64. moving the skin of the back

Tail

65. lashing tail movements
66. movements of the tip of the tail only
67. piloerection of the tail

Vocalizations

68. miaowing: duration and pitch being estimated

61. hissing (with open-mouth threat)
62. growling

The behavior was observed and scored continuously; the general posture was always noted, and when movements occurred they were described with an accuracy of 5 seconds.

4.2. The intra-cerebral injection technique.

"Everything in experimental research depends upon the methods, for it is the method which gives the results."
(Flourens 1842, translated by Webster 1973)

SECTION 4.2. TABLE OF CONTENTS

4.2.1. INTRODUCTION

The credibility of studies relating effects to demarcated regions of the CNS rests heavily on the reliability of the technique used: which CNS region is affected by the manipulations, and how reproducible the results obtained are. The various techniques for manipulating CNS regions have their specific advantages and disadvantages (cf. Myers et al. 1971, Routtenberg 1972, Ranck 1975, Schoenfeld and Hamilton 1977, Myers and Hoch 1978). The advantage of the intracerebral technique is the possibility of studying acute effects, of affecting specific receptors, and of excluding effects due to interactions with passing fibers, where local anaesthetic effects are excluded. The major disadvantage of the intracerebral injection technique is the unpredictable spread of the drug, which can be limited or extensive (section 4.2.2).

4.2.2. THE SPREAD OF DRUGS INJECTED INTRACEREBRALLY

Introduction. The spread of drugs injected into the brain has been the subject of a number of investigations (reviews Routtenberg 1972, Myers 1974). Drug solutions at a volume of 0.05 µl have been reported as yielding unreproducible results (Routtenberg 1972), while drug injected at a volume larger than 1 µl often either leaked along the entire path of the cannula (MacLean 1957), caused lesions (Rech and Domino 1959, Routtenberg 1972), or spread over unexpectedly large regions (Myers 1966, Myers and Hoch 1978). Data presented in the literature regarding the spread of drugs at injected volumes ranging between 0.25 and 1.0 µl will be reviewed here, because in most recent studies (including this one) volumes within these ranges have been used. Two processes are involved in the spread of drugs injected into brain tissue: 1) primary spread: how is the amount of aqueous solution injected distributed over the brain tissue?, 2) secondary spread: how does the drug diffuse into the brain tissue?

Primary spread, theoretical. The primary spread of the aqueous solution over the brain tissue depends on 1) the hydrodynamical properties of the brain tissue, 2) the presence of blood vessels, 3) the integrity of the walls of the blood vessels and ventricular wall, and 4) the velocity of injection. The primary spread is independent of the compound used. The amount of primary spread must of course be at least as large as the droplet that is injected into the brain (Lomax 1966, Routtenberg 1972, Myers 1974). A volume of 0.5 µl of fluid represents a spherical droplet with a radius of 0.5 mm. The solution is not injected, however, into an empty space, but into brain tissue containing many cells in mutual contact, which, it is hoped, will remain largely intact after an intracerebral injection; fortunately, they generally do (Routtenberg 1972, this study). The most obvious assumption is that the fluid injected forces out the extracellular fluid, which is reported to occupy 20-28% of the volume of rat and cat brain respectively (Bourke et al. 1965, Bondareff and Pysh 1966). Under this assumption, 0.5 µl of fluid injected into the brain would spread in the first instance into a volume of between 1.8 and 2.5 mm^3. The actual pattern of distribution depends on the hydrodynamical properties of the brain tissue and the velocity of injection; if the fluid is distributed in a spherical shape, it has a radius of between 0.75 and 0.85 mm. This is within the range of primary spread often reported.

Primary spread, experimental. The primary spread of drugs injected into the brain depends on the orientation of the cannula. A primary spread of the drug along or in the direction of the cannula shaft has often been described (Myers 1966, Herz et al. 1970, Bondareff et al. 1970, Myers et al. 1971, Iwamoto et al. 1978, Leibowitz 1978a, Myers and Hoch 1978). The concentration of a drug at a distance of 1 mm from the needle tip, but at right angles to the direction of the cannula shaft, is generally less than 20% of that measured around the needle tip, measured between 3 and 60 minutes after the injection (dyes: MacLean 1957, Myers 1966; morphine: Lomax 1966, Herz et al. 1970, Pert and Yaksh 1974, Iwamoto et al. 1978, Costall et al. 1978; NE: Booth 1968, Myers et al. 1971, Leibowitz 1978a; ACh and 5-HT: Myers et al. 1971; DA: Myers and Hoch 1978). After an intracerebral injection of a small dose at a volume between 0.25 and 1.0 µl, the greatest amount of the drug is generally restricted either to a spherically shaped region with a radius of about 1 mm, or to a pear-shaped one with a long axis of 3 mm and a short axis of 1.5 mm. Incidentally almost all the drug is found in the cerebrospinal fluid (CSF) or in the blood (Myers et al. 1971).

Secondary spread, theoretical. Once injected into the brain, drugs will penetrate further; this process depends on physicochemical properties of both the brain and the drugs, and on the presence of transport systems.

1) As far as the physicochemical properties of the brain and the drugs are concerned the following remarks will be made. The diffusion of drugs into brain tissue depends on their solubility in polar and non-polar solvents, and on the partition coefficient of their distribution between these solvents. In general, it can be expected that compounds with a high fat solubility will penetrate more quickly into the brain tissue, but the compound used must also be sufficiently soluble in water, otherwise the appropriate amount cannot be dissolved in a small enough volume water.
2) Many transport systems for compounds are present in the brain, as exampled for instance by the high affinity uptake systems for many putative neurotransmitters, acting on both endogenous and exogenous compounds.

Secondary spread (diffusion), experimental. The secondary spread of intracerebrally injected drugs can be estimated by a comparison either of the spread of drugs applicated in solution with those as crystals, or of the

spread of various drugs with different physicochemical properties. The distribution pattern of drugs applicated as crystals closely resembles the pattern of drugs injected in solution (cf. Grossman and Stumpf 1969). The pattern of distribution of a series of drugs has not yet been tested, but some relatively small differences in the spread of various dyes and putative neurotransmitters and their metabolites have been described (see above). Indirect evidence can be obtained from a comparison of the effects of different drugs: the opiate agonists fentanyl and etorphine, which have a high fat solubility, have actions with a much shorter latency and duration than morphine (Pert and Yaksh 1974, Sharp et al. 1974, Yaksh et al. 1976a).

Overall pattern of distribution. One group of investigators has described a significant spread of compounds along fiber bundles (Routtenberg et al. 1968, Bondareff et al. 1970), but this has not been confirmed by other investigators. In general, small amounts of the compounds are found in the ventricle (Myers et al. 1971, Costall et al. 1978); the ventricular hypothesis that effects of drugs injected intracerebrally are generally evoked after spread to, and transport by, the CSF can be rejected for the majority of effects found after intracerebral injections (Myers et al. 1971, sections 2.6 and 2.9 of this study). After an injection of a large dose, considerable amounts of the drug can be detected in regions more than 4 mm from the injection site (Grossman and Stumpf 1969, Javoy et al. 1970, Myers et al. 1971, Hedreen and McGrath 1977).

How much of the drug actually reaches the target region? The variation in the amount of intracerebrally injected drug found back in the tissue around the injection site is very great indeed between different individuals: variations by more than a factor of 100 have been described (cf. the tables of Myers et al. 1971, Myers and Hoch 1978). Such fluctuations probably form a serious limitation in this and in other studies to the reliability of the results obtained with intracerebral injections of compounds in doses 10 to 100 times the "real" threshold.

Summary, the spread of intracerebrally injected drugs. The remarks below apply to intracerebral injections of aqueous solutions at volumes of 0.25 to 1.0 µl, into brain tissue.

1. The highest concentration of drug is generally present in a spherical or pear-shaped region, within 1 mm from the injection site.

2. The amount of drug present in the target region may vary by a factor of 100, intracerebral injections of amounts less than 100 times the threshold dosage will be less reliable.
3. Almost all the drug finds its way into the ventricle or the blood incidentally.
4. After injection of a large dose, an amount of the drug which is probably effective can be detected more than 4 mm from the injection site.
5. The optimum dose for experimentation using intracerebral injections is a compromise between the necessity of obtaining repeatable experiments and that of reliable localization of the effective sites.

WHICH ELEMENTS ARE AFFECTED BY DRUGS?

In the CNS, neurons as well as glia cells and blood vessels are influenced by putative neurosecretes. Generally, one wants to have some evidence that drug-induced effects are not primarily due to the action of the drugs on the local cerebral circulation: one can compare the effects of drugs with those of drugs which are known to affect the cerebral circulation. β-Adrenoceptor agonists and low doses of cholinergic agonists cause dilatation, while α-adrenoceptor agonists and high doses of cholinergic agonists cause constriction of the cerebral blood vessels (Edvinsson 1975). Nevertheless, in this study, neither α- nor β-adrenoceptor agonists (clonidine, oxymetazoline, isoprenaline) nor l-NE, mimicked the effects of the cholinergic agonist carbachol. The effects were therefore probably not due to influences on the local cerebral circulation.

THE PROBLEM OF INEFFECTIVE SITES

When a large number of injection sites and relatively low doses of injected compounds are used, drug-induced effects can be reliably ascribed to a limited region of the CNS (Pert and Yaksh 1974, Leibowitz 1978a, this study). Yet even in the effective region, ineffective sites are often found, sometimes as many as 50% of the sites used (Pert and Yaksh 1974, Akaike et al. 1978, this study). Three possible explanations of the occurrence of ineffective sites in an effective region can be rejected.

1. The experiments might be not repeatable; but actually they were reproducible in 81% of the cases (table 10, p. 203).
2 The dose used might be close to the ED_{50}; in the regions where carbachol (0.5 µg) caused atonia, turning and micturation however many ineffective sites were found, while these effects were also caused by 50 ng of carbachol, indicating that 0.5 µg is well above the ED_{50}.
3 The effective region might be destroyed by the cannula or the injections. No signs of tissue destruction or granulation tissue could however be detected in our Nissl-stained material which could explain a loss of effectiveness (except in one animal, the data of which were discarded).

The occurrence of ineffective sites in an effective region, and the occurrence of a few effective sites remote from the effective region can be tentatively ascribed to differences in the spread of the drugs in this and other studies (cf. Leibowitz 1978, cf. section 4.2.2). My own view is that the spread of a drug at a given injection site is fairly reproducible, but that a greater variation between sites probably occurs.

4.2.5. ELIMINATION OF THE DRUGS

The action of intracerebrally injected drugs can be terminated by removal of the drug or by metabolic conversion. A significant amount of the drug can be removed by the blood (Lomax 1966, Grossman and Stumpf 1969, Myers et al. 1971); when the effect of a drug administered intracerebrally is similar to that of one administered systemically, evidence has to be presented on whether or not the effect is mediated via peripheral receptors.

4 3. The putative neurosecretes of the LC

SECTION 4.3. TABLE OF CONTENTS

INTRODUCTION

Many lists of criteria for neurotransmitters and neuromodulators have been published (cf Florey 1967, Scharrer 1969, Davidson 1976, Torda 1977a, Barchas et al. 1978, Orrego 1979, Iversen 1979). In this section, I will in general follow the definitions of Barchas, Iversen and Orrego. The collective term "neuroregulator" is often used for neurotransmitters and neuromodulators, but this unsatisfactory collective term will be avoided and the term "neurosecrete"* will be used instead

*The word "neurosecrete" was originally used for compounds secreted by some hypothalamic neurons (so-called "neurosecretory nuclei"), but these compounds now seem to be also neurotransmitters (see references at table 7, p. 188); therefore the etymologically neutral term "neurosecrete" is used as the general collective term in this book.

Definition of "neurosecrete". Compound C is a "neurosecrete" of neuron N (or group of neurons N), when the following statements are confirmed experimentally:

1. C is present in neuron N.
2. C is synthetized by neuron N.
3. C is secreted by neuron N. This secretion is not necessarily related to the activity of neuron N.
4. C interacts with specific sites of action (receptors).
5. One or more mechanisms exist which terminate the action of C after the secretion of C.
6. Direct application of C mimics the effect of increasing its endogenous concentration. This effect is identical in all respects, also pharmacologically.

Definition of "neurotransmitter". Compound C is a "neurotransmitter" of neuron N, when the following statements are confirmed experimentally:

1. C is a neurosecrete.
2. C is present in the presynaptic part of a morphologically identified, specialized synapse (cf. Cobb and Pentreach 1978, fig. 5a to g). C acts transsynaptically, i.e. the postsynaptic membrane is the target site of C.
3. Electrical stimulation of N causes secretion (release) of C.

Definition of "neuromodulator". Compound C is a "neuromodulator" of neuron N, when the following statements are confirmed experimentally:

1. C is a neurosecrete.
2. C is present in non-synaptic terminals, i.e. terminals without synaptic specializations (Cobb and Pentreach 1978, fig. 5h).

Other criteria. Some additional criteria can be found in the literature, which are in my opinion unnecessary and unelegant.

1. Differential distribution
   A differential distribution (Orrego 1979) as well as a ubiquitous distribution (Myers 1974) have been used as a criterion for neurotransmitters; this represents a good reason to avoid distribution as a criterion.
2. Chemical structure
   Torda (1977a) included as a criterion for a neuromodulator that the compound is a protein, peptide or glycoprotein; I prefer to define

neurotransmitters and neuromodulators on the basis of the presence or absence of synaptic specializations rather than their chemical structure.

3. Temporal characteristics of action
   Some authors (cf Meyers 1974, Torda 1977a) include in their criteria for a neurotransmitter that the compound must act rapidly, and for a neuromodulator that the compound must act slowly; no convincing reason has been presented for this distinction criterion.

LC's neurosecretes. It will be discussed below whether 3 putative neurosecretes of the LC (NE, dopamine-β-hydroxylase (DBH) and acetylcholine (ACh)) fulfil the criteria for neurosecrete, neurotransmitter, or neuromodulator on the basis of different criteria.

4.3 1. NOREPINEPHRINE (NE)

Presence

Abundant evidence has been presented that NE is present in the cell bodies, axons and terminals of the LC cells of the rat (A&S 2.2.1.). In all mammals investigated a catecholamine-containing presumed homologue of the rat's LC has been found, and this CA has been demonstrated to be NE both in the cat and in man (Jones et al. 1977a, Farley and Hornykiewitz 1977, Marchand et al. 1979a,b). NE is transported somatofugally from the LC cell bodies (Levin et al. 1976, Levin and Stolk 1977). At the moment, nobody doubts the presence of NE in the cell bodies, axons and terminals of the LC in the rat. The presence of NE (as revealed by formaldehyde- or glyoxylic acid-induced fluorescence) has been used in mapping studies of the efferent fibers of the LC (Ungerstedt 1971a, Lindvall and Bjorklund 1974), and the decrease in telencephalic NE after a lesion of the LC has been used to check the completeness of the lesion (for references see columns biochemistry and CA/NE histochemistry, table 9, p. 200) NE is present in LC terminals in small exocytotic ("synaptic") vesicles (Hokfelt et al. 1968, Descarries et al. 1977, Swanson et al. 1977, Koda et al. 1977, 1978a).

Synthesis

The enzymes necessary for the synthesis of NE are present in the LC TH is demonstrated enzymatically in the LC region (Saito et al. 1977a, Bullard et al. 1978) and immunohistochemically in the LC cell bodies (Hokfelt et al. 1976, Nagatsu et al. 1979a). Immunoreactive DBH is present in the LC cell bodies, axons and terminals (Hartman and Udenfriend 1972, Swanson and Hartman 1975, Grzanna et al. 1977, 1978, Cimarusti et al. 1979, Nagatsu et al. 1979a), the presences of immunoreactive or enzymatically active DBH has been used in mapping studies of the LC efferents (Ross and Reis 1974, Swanson and Hartman 1975). The subcellular distribution of DBH is mentioned in section 4.3.2. Other compounds probably related to the synthesis of NE are also present in the LC: copper (Yoshinaga and Shimizu 1968, cf Friedman and Kaufman 1965, Molinoff et al. 1971, Lander and Austin 1976), vitamin A (Iijima 1977, 1978) and reduced pterins (Bullard et al. 1978). Moreover, ^{3}H-DA injected into the LC is converted into ^{3}H-NE, and transported orthogradely (Levin et al 1976, Levin and Stolk 1977).

Stimulation-induced release

Only in one *in vivo* study (Tanaka et al. 1976b) has a direct measurement of the NE release after electrical stimulation of the LC been described; NE release was measurable only in the presence of the NE uptake inhibitor desipramine. The *in vivo* release of NE by electrical stimulation of the LC has been measured indirectly on the basis of the levels of the main metabolite of central NE, 3-methoxy-4-hydroxyphenylethylene glycol (MHPG) (Korf et al. 1973a, Crawley et al. 1978, 1979a, cf. Rutledge and Johanson 1967, Schanberg et al 1978). This is in line with observations of the highest CSF NE level during waking hours (Ziegler et al. 1976, Perlow et al. 1978), when the LC cells' activity is at its highest (cf. section 1.3). Release of central NE can be increased *in vitro* by depolarizing manipulations (electrical stimulation or K^{+}-ions) or by amphetamine (Dismukes and Mulder 1976, Dismukes et al. 1977, Lane and Aprison 1977, Kant and Meyerhoff 1977a, 1978, Rutledge 1978).

Inactivation after release

Re-uptake. The action of a neurosecrete must after a while come to an end; this termination of the action can be accomplished in 3 different ways.

1. Uptake of the compound by cells, thereby removing it from the site of action; the neurosecretory terminal generally takes up its own neuro-

secrete (re-uptake), and this re-uptake is the main cause of inactivation of released central NE (cf. Iversen 1971). Central NE is most probably taken up quickly, because release of NE after electrical stimulation of the LC is only measurable in the presence of the uptake inhibitor desipramine (Tanaka et al. 1976). Moreover, central NE terminals appear to accumulate exogenous ^{3}H-NE (Descarries et al. 1977).

2. Metabolic conversion of the compound into metabolites which are inactive, or at least have a different action.
3. Diffusion of the compound away from the site of action.

Enzymatical inactivation. Released central NE is enzymatically inactivated by MAO, COMT and aldehyde reductase; these conversions are rapid, and the resulting metabolite is MHPG or its SO_4-conjugated form (Rutledge and Johanson 1967, Schanberg et al. 1968). Enzymatically active MAO and COMT are present in all the CNS regions investigated (Saavedra et al. 1976b, Hirano et al. 1978). In the brain, immunoreactive COMT is demonstrated only on non-neuronal elements, such as ependymal and other glia cells and the choroid plexus, but the presence of small quantities on neurons cannot be excluded (Kaplan et al. 1979); COMT is regarded as preventing the free diffusion of active NE through the CNS. NE released after electrical stimulation of the LC is rapidly converted into MHPG (Korf et al. 1973a, Crawley et al. 1978, 1979a).

Specific receptors

In the CNS, several different catecholamine receptors are present; it is therefore difficult to characterize the adrenoceptors, which are a subpopulation of these catecholamine receptors. The available data however indicate that the central adrenoceptors are similar to the peripheral ones: α_1 and α_2 (U'Prichard and Snyder 1979, Young and Kuhar 1979), β_1 and β_2 (Nahorski 1978, Bylund 1978, Minneman et al. 1979a,b, Dolphin et al. 1979). In a number of LC terminal regions, β-adrenoceptors (or rather "binding sites") are shown up with fluorescent β-adrenoceptor antagonists: these β-adrenoceptors are present in the parts of the CNS and on the neurons which receive NE terminals as demonstrated with other techniques (Melamed et al. 1976a,b, 1977, Atlas et al. 1977, Atlas and Melamed 1978, but cf. Barnes et al. 1980). These β-adrenoceptors are close to the NE terminals (Atlas and Segal 1977). Central α-adrenoceptors have been much less investigated directly; α_1- and α_2-adrenoceptors have been recently

shown up in the CNS (Young and Kuhar 1979). α_2-Adrenoceptors are found on NE terminals (Berthelsen and Pettinger 1977) and on NE target cells (Cedarbaum and Aghajanian 1977, section 1.2 2).

Identical actions (also pharmacologically identical)

Introduction. The effects of the LC or NE on the LC target neurons will be discussed in more detail, because some of the conclusions of this subheading are relevant to the general discussion on the action of the LC and NE (cf. sections 1.4.2 and 3.2.1). The action of NE on CNS neurons has recently been reviewed (Szabadi 1979).

LC- and NE-induced effects. If NE is a neurosecrete of the LC, then electrical stimulation of the LC must have effects on the target cells identical to iontophoretical application of NE. This is clearly the case (table 5). Strict electrophysiological tests have never been used to make certain that the target cell is directly influenced by the LC.

Table

Effects of electrical stimulation of the LC and iontophoretical application of NE on the same cells (for references see table 17, p. 214)

	effects	references
membrane potential	hyperpolarization	39
this hyperpolarization is:		
increased by	papaverine	39
reduced by	prostaglandines (E)	39
membrane resistance	increase	39
maintained activity	suppression	39,48,49,58,91, 100,144,147
this suppresion is:		
antagonized by	sotalol (MJ-1999)	30,48,49,100,144
	fluphenazine	58
increased by	papaverine	39,48,49
	desipramine	48,49
reduced by	prostaglandines (E)	39,48,49
	glycoprotein	91
	lithium ions	147
response to stimuli	suppression	144

These effects are however assumed to be evoked directly (i.e. via adrenoceptors on the neuron from which the recording is made), because: 1) the regions investigated are LC target regions (section 1.4.1), 2) NE synapses and terminals have been identified (section 1.4.1), and 3) the various authors agree remarkably well on the effects of the LC. The response type described below and in figures 42 and 43 is considered to be the typical LC/NE response.

Hyperpolarization and suppression. NE hyperpolarizes its target neurons, depolarizations have never been described (cf. tables 5 and 17, p. 211). Concomitant with these NE-induced hyperpolarizations, the maintained activity of the target cells is generally suppressed. Electrical stimulation of the LC causes suppression with a long latency (30-70 msec) and a long duration (cf. section 1.4.2). During the LC/NE-induced hyperpolarization the resistance of the membrane to transmembrane ion currents is increased.

LC/NE-induced activations? A relatively small number of authors report the occurrence of NE-induced activations (cf. table 17, p. 211; Szabadi 1979) These may either be evoked via an interneuron, be due to NE-induced vasoconstriction of the cerebral blood vessels (Stone 1971, section 1.4.4), or be the effect of interaction of NE with dopamine, octopamine, or other receptors (cf. Hicks and McLennan 1978, Bevan et al. 1978a,b). NE-induced activations could also be due to physiological NE-induced activations via NE receptors (possibly α-adrenoceptors, Bevan et al. 1977, Szabadi 1979).

Receptors involved. In studies where the effects of the LC and of NE on the same neuron have been investigated, the LC/NE-induced effects came about via β-adrenoceptors, blocked by sotalol, propranolol and fluphenazine (tables 5 and 17, p. 211, both β_1- and β_2-adrenoceptors, Dolphin et al. 1979). The only well-documented electrophysiological example of LC/NE-induced suppression via α-adrenoceptors (α_2) is the lateral NE-induced suppression of the LC cells (cf. sections 1.2.2 and 1.3.5). In a number of studies, effects of central NE via α-adrenoceptors on other organs or on behavior have been reported (sleep: Putkonen et al. 1977, eating: Leibowitz et al. 1978; endocrine: Weiner and Canong 1978; spinal reflexes: Kuraishi et al. 1979; startle response: Davis et al. 1979, conditioned avoidance: Hawkins and Monti 1979; vomiting: section 2.6). At the moment, it is not at all clear whether these effects are due to receptors for which NE is the endogenous ligand (and not for instance DA, octopamine or

F), and, where NE is the endogenous ligand, whether these receptors are located either on target neurons, on terminals, or on other CNS target elements (such as blood vessels, cf. section 1.4.1).

NE and cyclic AMP. It is now generally accepted that NE causes its suppression through an increase in the adenylate cyclase activity, the enzyme that produces cyclic AMP (cyclic 3',5'-adenosinemonophosphate) (Korf and Sebens 1979, reviews Iversen 1977a, Nathanson 1977; but not: Godfraind and Pumain 1971, 1972, Lake and Jordan 1974). Cyclic AMP is similar to NE in causing hyperpolarization with an increase in membrane resistance (Siggins et al. 1971a, Nathanson 1977); adenylate cyclase inhibitors (Pb^{2+}, La^{3+}, Li^{+}) decrease LC- and NE-induced responses (Segal 1974, Nathanson et al. 1977, Taylor et al. 1978, Nathanson et al. 1976, Reches 1978, Siggins et al. 1979). On the other hand, inhibitors of phosphodiesterase (the enzyme that inactivates cyclic AMP, its inhibitors are papaverine, aminophylline, theophylline and caffeine) increase the NE- and cyclic AMP-induced responses (Hoffer et al. 1973, Segal and Bloom 1974a,b, Siggins et al. 1971b, Hoffer et al. 1971c, Gahwiler 1976a). Since the response of cerebellar Purkinje cells to NE applied iontophoretically is much slower than to GABA or cyclic AMP ejected from the same electrode (Siggins et al. 1971b, Hoffer et al. 1971c, Gahwiler 1976), a slow process must be present between the release of NE and the synthesis of cyclic AMP. The activation of adenylate cyclase is not a unique property of NE; DA and other neurosecretes also activate adenylate cyclase. Biochemically too, electrical stimulation of the LC and application of exogenous NE have identical effects on cyclic AMP production (Korf and Sebens 1979, Korf et al. 1979).

NE and prostaglandines. The prostaglandines of the E series (PGE_1, PGE_2) reduce the effects of the LC's activity or of NE on the IC target cells (Hoffer et al. 1973, Segal and Bloom 1974a,b), but not the effects of cyclic AMP (Siggins et al. 1971b, Hoffer et al. 1971c). It has been suggested that the PGEs counter the NE-induced increase in adenylate cyclase activity (Hoffer et al. 1971c, Nathanson 1977). It is remarkable that the effect of prostaglandines on NE-induced effects is opposite to their action on DA-induced effects (Nathanson 1977).

NE and Na,K-ATPase. Ample evidence has been presented that NE increases the activity of the ouabain-sensitive ATPase (the so-called Na,K-ATPase, adenosinetriphosphatase) and the ouabain-insensitive ATPase (Ca,Mg-ATPase).

The Na,K-ATPase in particular has attracked special interest, since *"Na,K-ATPase is thought the enzymatic representation of the transmembrane Na-K pump, which could have electrogenic properties under some conditions"* (Ewart and Logan 1978b). NE causes suppression of its target cells through an increase in the Na,K-ATPase activity (as demonstrated in cerebellar Purkinje cells and somatosensory cortical cells), since the NE-induced suppression is countered by inhibitors of Na,K-ATPase (ouabain, Na-azide; Phillis et al. 1974, Yarbrough 1976, review Phillis 1976). It is remarkable that no increase in the activity of Na,K-ATPase by cyclic AMP has been found (Phillis 1976, Akagawa and Tsukada 1979). The activity of the Na,K-ATPase is increased not only by NE, but also by DA, but not by ACh, Glu or GABA (Yarbrough 1976, Desaiah and Ho 1977, Akagawa and Tsukada 1979, Schaefer et al. 1979).

NE and calcium-ions. The NE-induced suppression of somatosensory cortical cells is reduced by compounds interfering with Ca^{2+} transport and binding (Phillis et al. 1974, reviews Phillis 1974, 1976). The action of Ca^{2+} could be due to interactions of Ca^{2+} with adenylate cyclase and/or phosphodiesterase (Ahn et al. 1976, Nathanson et al. 1976, review Rasmussen and Goodman 1977), or to a change in membrane properties either due to binding of Ca^{2+} to the membrane, or to fluxes of Ca^{2+} through it (Phillis 1974, 1976).

The mechanism of the NE-induced suppression. The data on the mechanism of the action of NE are summarized in fig. 42. NE causes a two-fold action: 1) an increase in the activity of an electrogenic ion pump which causes an outward current of Na^+ or K^+ (or perhaps even Ca^{2+}) and consequently a hyperpolarization, and 2) a closure of K^+ and perhaps also Na^+ channels which is reflected as an increase in the membrane resistance (cf. Phillis 1976, Marshall and Engberg 1979). In this process, cyclic AMP, prostaglandines, Na,K-ATPase and Ca^{2+} are involved. It has to be admitted that no interpretation of the mechanism of NE action on the target cell membrane has ever been presented in the literature that was consistent with all the findings mentioned above, and this drawback applies to my interpretation too (fig. 42). (Points of agreement are that NE and cyclic AMP cause hyperpolarization with an increase in membrane resistance, and that NE causes ouabain-sensitive suppression while an inconsistent point is that cyclic AMP has been reported as not influencing the Na,K-ATPase activity in the CNS. I cannot however conceive of a simple interpretation

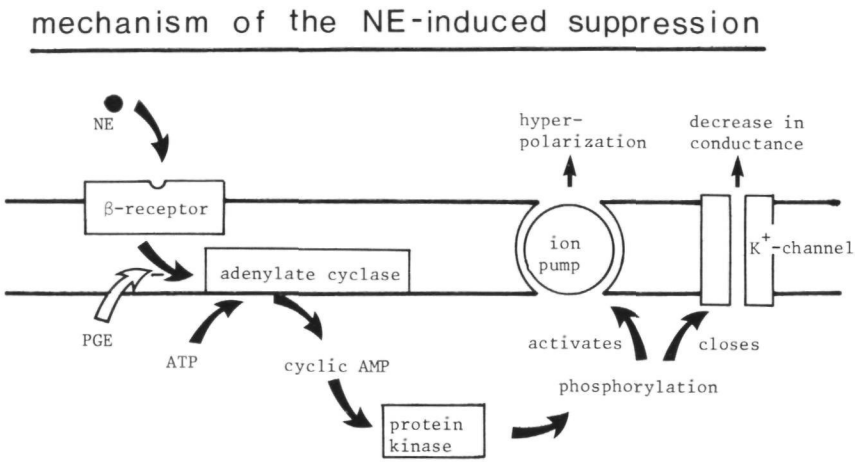


Fig.42 Hypothetical mechanism of NE-induced suppression, hyperpolarization and decrease in membrane conductance; this mechanism seems to be the most plausible explanation of the NE effects on neurons as presented in the literature.

that is in agreement with all data).

LC/NE-induced suppression is not inhibition. The prototype of "classical inhibition" is the inhibition of α-motoneurons by Renshaw cells; the transmitter involved is Gly, and the mechanism is opening of K^+ channels (cf. fig. 43 and Curtis and Johnson 1976, Davidson 1976). The NE-induced suppression involves a different mechanism (cf. fig. 42). The most striking difference between Gly-induced inhibition and NE-induced suppression is that the Gly-induced hyperpolarization is a passive process, the opening of K^+ channels, while the NE-induced hyperpolarization is an active, energy requiring process, which involves the degradation of ATP for the synthesis of cyclic AMP and (probably) for actively pumping ions across the membrane (for further differences between NE-induced suppression and inhibition see section 1.4.2).

Theoretical implications. NE appears to have unique effects on its target cells, and it is probable that the other putative neurosecretes each have differing unique effects on their target cells (cf. Bonkowski and Dryden

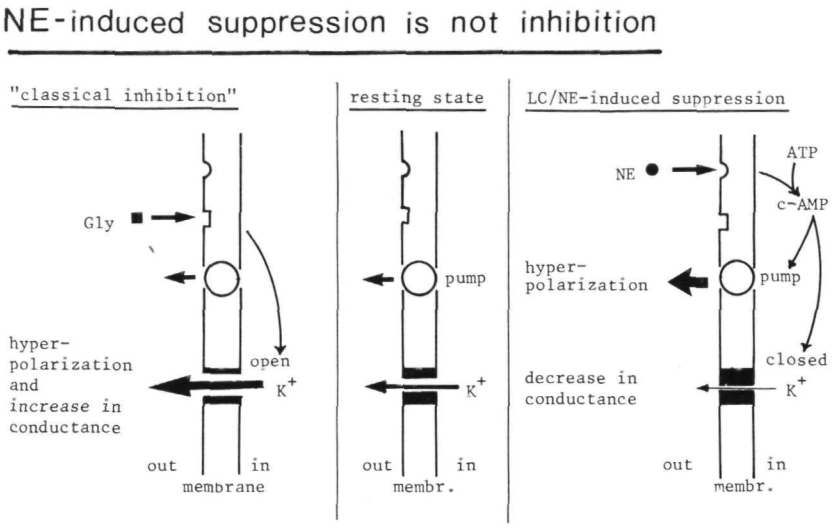


Fig.43 Diagram illustrating the differences between "classical inhibition" (as induced by glycine) and the LC/NE-induced suppression.

1977). Therefore, *"the important and universally accepted point: different presynaptic fibers can exert one of two fundamentally opposite effects on postsynaptic neurons, either facilitation or inhibition"* (Patton 1965, p. 168) is not valid any more: various terminals can exert one of more than 2 different effects, which makes the dichotomy excitation and inhibition an inadequate and a too simple description of the various neurosecrete effects. The action of a putative neurosecrete should be described in detail at the molecular level; interactions between the effects of different neurosecretes can then be explained (cf. section 1.4.2, subheading "Selective interactions?").

Conclusion

NE is a neurotransmitter and a neuromodulator of the LC cells.

Implications. What are the similarities and differences between the neurotransmitter and the neuromodulator effects of the LC/NE terminals? The above mentioned actions of the LC/NE terminals probably come about through synaptic and non-synaptic terminals, and thus reflect the similarities be-

tween the neurotransmitter and the neuromodulator effects. Some speculative remarks can be made on the differences. The synaptic release of a neurotransmitter assures strictly local action, while a freely released neuromodulator may exert more distant actions. But distant actions of freely released NE are probably still restricted, because 1) in the NE target regions the adrenoceptors are abundant and they are present on neurons near NE terminals, while they are virtually absent in non-NE target regions (cf. figures of Melamed et al. 1976b, 1977, Atlas and Segal 1977, Atlas et al. 1977, Atlas and Melamed 1978), and 2) NE degrading enzymes (MAO and COMT) are present throughout the CNS, and rapidly inactivate diffused NE (see above, subheading "Inactivation after release"). It is only NE released into the ventricle (cf. Adër et al. 1979b) or reaching the ventricle by diffusion (cf. Ziegler et al. 1976, Perlow et al. 1978) that may have distant actions, but at the moment it is unclear whether endogenous NE released into the ventricle generates specific actions.

4.3.2. DOPAMINE-β-HYDROXYLASE (DBH)

Presence. DBH is present in the LC cell bodies, axons and terminals (cf. section 4.3.1., subheading "Synthesis"). Immunoreactive DBH is present in small vesicles with the appearance of exocytotic ("synaptic") vesicles, and in large ones (Lundberg et al. 1977, Cimarusti et al. 1979); DBH has been reported as being present in all vesicles of a DBH-positive terminal, thus also in vesicles identical to NE-containing vesicles, so that single vesicles would contain both NE and DBH (Lundberg et al. 1977); this is however still the subject of discussion (Cimarusti et al. 1979). Enzymatically active DBH is present in the synaptic vesicle fraction (Lau and Slotkin 1976, Lander and Austin 1976).

Synthesis. The LC cells synthesize immunoreactive ^{3}H-DBH from ^{3}H-amino acids (Ross et al. 1978a, 1979b).

Stimulation-induced release. A combined release of DBH and NE from the peripheral sympathetic terminals and from the adrenals is well-documented (cf. Algate and Leach 1978, Sorimachi and Yoshida 1979, review Weinshilboum 1978). Direct evidence for DBH release from LC terminals has not yet been presented, but circumstantial evidence is growing: the CSF contains

enzymatically and immunoreactive DBH (Goldstein and Cubbedu 1976, Lerner et al. 1978, 1979, Major et al. 1979), and the CSF DBH content has a strong positive correlation with the CSF NE content, which indicates a co-release (Lerner et al. 1979).

Action. DBH may be present in NE vesicles to synthetize NE, and it may possibly be released together with NE, but the action of released DBH may be neglectable, or without "evolutionary value" (section 5.2.4). On the other hand, one can speculate that released DBH converts either extracellular DA into NE, or extracellular tyramine into octopamine (cf. Cooper et al. 1974, p. 107-108), thereby inactivating the first mentioned compounds' speculations on biochemical interaction between DA released from DA terminals, and DBH and NE from NE terminals are obvious In any case, the effects of electrical stimulation of the LC mentioned in section 4.3.1 were mimicked by NE, indicating that these effects are not due to DBH, and it is questionable whether DBH has any influence on these LC/NE effects.

Inactivation. As long as we do not know the action of released DBH, we cannot tell when released DBH must be regarded as inactivated. In any case, the half-life of DBH released into rat plasma is extremely long (4 days, Weinshilboum 1978).

Conclusion. Circumstantial evidence has been presented that DBH is released together with NE from central NE terminals. Whether or not the action of released DBH is neglectable however is unclear.

ACETYLCHOLINE (ACh)

Introduction. Of the different putative neurosecretes, only ACh will be discussed more extensively, because 1) it has been suggested that the LC is cholinergic* (Lewis and Shute 1967, Shute and Lewis 1966), and 2) the hypothesis that there is only one neurotransmitter, ACh, and that all other neurosecretes modify the action of ACh (cf. references in Myers 1974), is still heard.

* At that time, the names "locus coeruleus" and "nucleus laterodorsalis tegmenti" were synonymous.

Presence. A measurable amount of ACh is present in the LC (cf. Cheney et al. 1975), but its presence in terminals or cell bodies is uncertain, because no technique is available to make ACh directly visible.

Synthesis. A small amount of choline-acetyltransferase (ChAT), the enzyme that synthetizes ACh, is present in the LC (Cheney et al. 1975). In studies where cell bodies containing immunoreactive ChAT were localized, ChAT positive LC cells have never been mentioned (cf. McGeer et al. 1974, McGeer and McGeer 1979).

Degradation. Enzymatically active acetylcholine-esterase (AChE, or rather acetylthiocholine-esterase, AThChE, Ramon-Moliner 1972) is present in the LC as determined histochemically (Lewis and Shute 1967, Ramon-Moliner and Dansereau 1974b, Lewis and Schon 1975, Butcher et al. 1977); the so-called "specific AChE" has been reported as being present in the LC. The presence of both AChE and NE in the same LC cell has been directly demonstrated (Palkovits and Jacobowitz 1974, Albanese and Butcher 1979). One might expect that AChE would be present in cholinoceptive rather than cholinergic cells (Ramon-Moliner 1972), suggesting that the LC cells might be cholinoceptive, but AChE has been found in the endoplasmatic reticulum of the LC cells and not in pre- or postsynaptic processes (Lewis and Schon 1975); the implications of these findings are unclear (see below).

Stimulation-induced release. Electrical stimulation of the LC has been reported as reducing the cortical ACh outflow via α-adrenoceptors (Bianchi et al. 1979). This is contrary to what would be expected if ACh were a neurosecrete of the LC.

Identical actions. In one study, the effects of both electrical stimulation of the LC, and application of NE and ACh to the same cells (hippocampal pyramidal cells) have been described (Segal 1974): ACh caused activation, and both NE and electrical stimulation of the LC caused suppression. In the latter and in other studies, NE has been reported as reducing the response to ACh (Segal 1974, Reader 1978, 1979). This is once again in contradiction with the hypothesis that ACh is a neurosecrete of the LC. Moreover, since the effects of electrical stimulation of the LC mentioned in section 4.3.1 were mimicked by NE, these effects are not due to ACh.

Conclusion. ACh is not a neurosecrete of the LC*.

Is the LC cholinoceptive? "Specific AChE" has been demonstrated in the LC cells (see above), but it is unclear what conclusions can be drawn from the presence of "specific AChE" (cf. Silver 1974, Ramon-Moliner 1972, Lehrmann and Fibiger 1979). It has been demonstrated electrophysiologically that LC cells are activated by ACh through muscarinic receptors (Bird and Kuhar 1977, Kuhar et al. 1978, Guyenet and Aghajanian 1977, 1979, cf. Kobayashi et al. 1978), and the ratio between ChAT and ACh also indicates that the LC is cholinoceptive (Cheney et al. 1975), but no AChE has been found in pre- or postsynaptic processes in the LC (Lewis and Schon 1975). The majority, but not all, of the evidence indicates that the LC is cholinoceptive.

4.3.4. OTHER PUTATIVE NEUROSECRETES

For reasons mentioned in section 1.1, the LC is defined as the collection of aggregated NE cells in the dorsolateral pontine tegmentum; these NE-containing cells are in fact most probably noradrenergic (cf. section 4.3.1). Neurotensin- and substance P-containing cells have been described in the region of the LC, but it is uncertain whether these cells also contain NE, or in other words, whether these cells are LC cells (cf. section 1.1). Although many putative neurosecretes have been found in other regions (cf. section 1.1), they have not been found in the LC cell bodies. In cases where other putative neurosecretes co-exist with NE in the LC cells, these compounds would be candidate LC neurosecretes but as yet, no indications of such co-existence (apart from DBH) have been presented. It is possible that some non-NE interneurons in the LC region might appear to form an entity (a single system) with the LC NE cells. Some evidence for the existence of such interneurons is available (section 1.1), and

* Sufficient evidence has also been accumulated for other compounds to regard them as neurotransmitters in the CNS: DA, 5-HT, Glu, Gly and GABA (cf. Curtis and Johnston 1974, Davidson 1976), so that the hypothesis that there is only one neurotransmitter, ACh, can be rejected.

these interneurons could well be GABAergic, because 1) interneurons often are GABAergic (cf. Curtis and Johnston 1974, Davidson 1976), and 2) GABA-ergic terminals are quantitatively the most numerous in the LC (section 1.2.2).

4.4. Biochemical measures of the activity of the LC

Introduction. A number of biochemical parameters from the animal or human brain are used as measures of LC or NE activity. NE content, MHPG content (or MHPG in the plasma or urine), NE synthesis from ^{3}H-tyrosine or ^{3}H-dopa, ^{3}H-NE degradation, DBH activity, adrenoceptor sensitivity or the activity of the NE uptake system. The majority of authors want to develop a measure for the so-called "functional NE activity". In my opinion, a conceptual problem coupled with the use of the word "functional" has to be solved first (cf. section 5.2.4).

Vagueness of "functional". The vagueness of the concept "functional" is evident in statements such as "... *there may be a functional deficit of ... NE or DA at the neuronal synaptic cleft in brain ... individuals experiencing severe depression ... (and) an increase in functional brain NE or DA in manic individuals*" (Bunney 1975). The following questions arise. Is a "functional deficit of NE" identical to "a deficit of functional NE"? Is "functional NE at the synaptic cleft" identical to "NE at the synaptic cleft"? The (presumed) intended meaning of Bunney's remark will however be understood by most readers: the meaning of "functional" is intended to be analogous to "effective", including some measure of "effectiveness" (see below for a more precise description of the intended meaning). For instance, a decrease in the amount of NE released per action potential of a NE neuron would be called a "functional decrease", unless the nervous system had undergone compensatory changes (e.g. a greater sensitivity of adrenoceptors, a greater number of adrenoceptors, an executing system activated by adrenoceptors having a stronger effect, or an increase in the firing rate of NE cells); in the presence of compensatory actions, however, a decrease in NE released per action potential would not necessarily be a "functional decrease", and it might even be a "functional increase" - where overcompensation is present -.

Intended meaning of "functional". The intended meaning of "functional NE activity" is "the NE-induced effects at the cellular (or higher) level" (cf. section 5.3). Consequently, the intended meaning of either "a functional deficit of NE", or "a deficit of functional NE" in X, is "the NE-induced effects at the cellular (or higher) level in X are smaller than

in control (reference) X'. ("X" stands here for "individual S in situation Y", and "X'" for either "individual S' in situation Y" or "individual S in situation Y'".)

Biochemical measures of the activity of central NE neurons The biochemical measures used for the activity of central NE neurons (especially the LC) depend not only on the parameter they are intended to represent (i.e. the activity of these neurons), but also on synthesis, storage, re-uptake and metabolic routes of degradation of NE, and on the routes of removal of these degradation products. The situation is still further complicated, because all these processes are dynamic ones often including compensations for high and low activity. Some of the above mentioned measures are however more directly coupled to NE release (and thereby to the activity of the NE cells) than others: NE found in the CSF, brain MHPG, and measures of NE turnover (NE sythesis from ^{3}H-tyrosine or ^{3}H-dopa, or ^{3}H-NE degradation) may give information on the activity of the NE cells. At the moment, it is unclear whether an increase in the activity of the NE cells, be it "spontaneous" or induced by the experimentor, is reflected by an increase or decrease in brain NE content (cf. Korf et al. 1973a, Crawley et al. 1979a).

Biochemical measures of netto NE effectiveness. It has to be admitted that no unequivocal measure has been presented of the net effectiveness of NE (using other researchers' words: of the amount of "functional NE"). As a consequence of this uncertainty, a single phenomenon may be explained either by a decrease in the netto NE effectiveness by some authors, or an increase by others, while these hypotheses are partly based on similar data (cf. Maas 1979). I fully agree with Maas (1979) that a solution to this discrepancy might be found by measuring the NE-induced effects "downstream", or in my words, to investigate the effects (and effectiveness) of the activity of central NE neurons on their target elements at the cellular level, or at some higher level.

4.5. Causal statements in brain research.

Introduction. The statement "a specified change in the brain (A) in disease (P) is a cause of symptom (E) (for instance dementia or paranoid schizophrenia)" might cause resistance in some readers for 2 reasons related to the meaning of "a cause" (cf. Hospers 1967, p. 279-307). (The remarks in this section apply to all causal statements in this book.)

Other causes. One might object by saying "E (= dementia) can be caused by other factors than A (= subcortical brain damage)". This is a true statement (cf. section 6.3.1). *"According to Mill, this is the correct scientific definition of "cause". The cause (the whole cause) is the (complete) set of conditions sufficient to produce the event."* (Hospers 1967, p. 293). "A in P causes E" means "A in P is a cause of E", or in other words, "if A in P occurs, and all other things being equal, E will occur". This is illustrated in fig. 44: A, B and C are the (whole) cause of E (i.e. A, B and C represent a complete set of sufficient conditions for E, as do either C + D + F, or G alone). In this example A, B and C are called "simultaneous" causes, because only their simultaneous occurrence is a sufficient condition for E. The sets of causes "A, B and C", "C, D and F" or "G" are called "unrelated causes". It is a scientific challenge to detect the different sets of unrelated causes, and all the simultaneous causes of each set.

"More fundamental" causes. On the other hand, one might object by saying "It is misleading to regard brain change D as a cause of E, because D is only an effect of the "real" (primary, fundamental, underlying) cause d". This may be true, but it does not invalidate the statement "D in P causes E". In fact, each process has both direct and remote effects (section 5.4), and the processes and effects can be described at different levels (section 5.3). Particularly in systems as complicated as the nervous system or a human being, the relationship between processes and their remote causes and effects cannot be taken in at a glance. In a perhaps somewhat extreme example, the statements "d (= his mother not caressing him on his 3rd birthday) caused E (= paranoid schizophrenia)" and "D (= a 10% decrease in brain compound X) caused E (= paranoid schizophrenia)" may both be true: d may either be a cause of D, and D a cause of E, or d may be

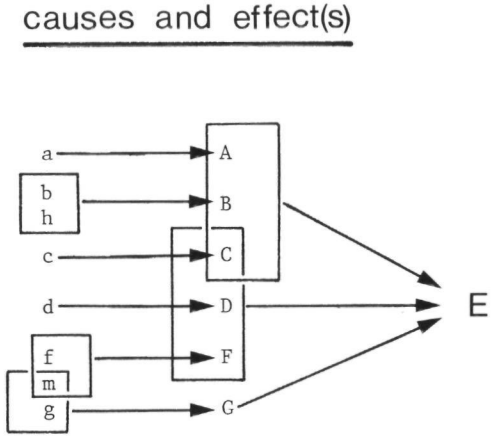


Fig.44 Diagram of simultaneous, successive, related and unrelated causes. a → A means "a is the (whole) cause of A". (For further comment see the text.)

independent of D. When d is a cause of D, and D is a cause of E, d and D are called "successive causes" of E. Whether one wants to consider either d or D as a cause of E, depends only on the level at which one wants to investigate the causes of E. A scientific challenge is the detection of the whole set of successive causes.

Complication: compensating action. It becomes (apparently) more confusing, when d and D are successive causes of E, and D is an overcompensation to d. Take for instance, d to be a loss of NE cells, and D to be an overcompensating supersensitivity of adrenoceptors (cf. references p. 307). d (= loss of NE cells) may be generalized to "a decrease in the NE-induced effects at the cellular level at time t_1" (= $\delta(t_1)$) (cf. section 4.4), and D (= overcompensating supersensitivity) may be generalized to "an increase in the NE-induced effects at the cellular level at time t_2" (= $-\delta(t_2)$). At first sight, it seems that 2 opposite causes have an identical effect, but that is not the case, because $\delta(t_1)$ is the opposite of $-\delta(t_1)$, and not of $-\delta(t_2)$. This example might seem far-fetched, but in practice 2 apparently opposite theories on the involvement of NE in depression do exist (Maas 1979, section 6.6). It cannot be denied that the theories are

different, but if $\delta(t_1)$ is a cause of $-\delta(t_2)$, it is pointless to argue whether $\delta(t_1)$ or $-\delta(t_2)$ is the "real" cause.

Criteria for causal statements. A specified change in the brain (C) is said to be a cause of symptom (E), when the following statements are confirmed experimentally:

- C is positively correlated with E
- C precedes E
- manipulations increasing C, increase E, while manipulations reducing C, reduce E

4 6 Tables

SECTION 4.6. TABLE OF CONTENTS.

	retrograde transport of HRP		autoradiography		degeneration	references (key to the references to be found after table 7)
		LCd/LCv		LCd/LCv		
SPINAL CORD						
dorsal horn, [illegible]	++					30
MEDULLA OBLONGATA						
formatio reticularis	+					14,30,72
dorsal to oliva inferior	+	LCv				13
around n. reticularis lateralis (AL)	++	LCv	++	LCd		13,14,30,33,49,72,73
around n. tractus solitarii	+++	LCv	++	LCv		13,14,28,30,32,72,73
n. dorsalis motorius vagi	+	LCv				13,30,72
n. parasolitarius	++					30
n. commissuralis	+					30
oliva inferior	+					14
medullar raphe nuclei (pallidus, obscurus, magnus)	±					13,73
n. nervi trigemini spinalis	+					30
PONS						
formatio reticularis	+					14,30,72
dorsolateral to oliva superior	++	LCv				13,73
other pontine reticular regions	–					13
nuclei vestibulares	++					14,30,72,73
n. prepositus	+					30
contralateral parabrachial region:						
LC	++	LCv				13,72,73
parabrachial nuclei	+					13,30,72,73
n. principalis sensorius nervi trigemini	+					30
raphe nuclei:						
n. raphe pontis	+++		+++			10,13,73
n. centralis superior	±		+		+++	6,10,13,16,48
CEREBELLUM						
cortex cerebelli	–				+	7,13
cerebellar nuclei:	+					72
n. fastigii	++		+		+	7,9,13,14,30,73
n. interpositus	±					14,30
n. dentatus	±					14,30

	tetropride transport of HRP		autoradio-graphy		degene-ration	references
	LCd/LCv		LCd/LCv			
MESENCEPHALON						
tegmentum mesencephali	+	LCv			±	4,13,30
area ventralis tegmenti (VTA)	±		+		++ LCd	16,46,70,74
substantia nigra	+++	LCv	–			13,77
	–					30,73
grisea centralis, p. ventrolateralis	++	LCv			±	4,13,30,72,73
raphe nuclei						
n. raphe dorsalis	++	LCd,v	+			6,10,13,30,72,73
n. centralis linearis intermedius	+	LCv				13
n. Edinger-Westphall	+	LCv				13
DIENCEPHALON						
hypothalamus					+	4
n. posterior hypo. (dorsalis)	++	LCv				13
area dorsalis hypothalami	++	LCv				13
n. periformicalis	+++	LCv				13,30
n. lateralis hypothalami	++	LCv	+			13,30,67,72
n. supraopticus	±					13
n. dorsomedialis	++		+			30,34
n. ventromedialis	±		+			8,13,30
n. paraventricularis	++					30
n. arcuatus	++	LCv				13,30
n. suprachiasmaticus	±					13,30
thalamus*	–					13
n. parafascicularis	+					30,72
n. lateralis habenulae					+	71
TELENCEPHALON						
n. preopticus medialis	±		–			11,13,30
n. preopticus lateralis	+	LCv	+			11,13,73
n. preopticus magnocellularis	+	LCv	+			11,13,30
amygdala	++		±			14,29,30,72
n. interstitialis striae terminalis	++	LCd	+			11,23,30,34,69,72
septum					++	35
cortex cerebri						
hippocampus	+					14
insula (areas 13 and 14)	+					30
sulcal prefrontal cortex	+					72
other cortical areas	–					30

Table 7

Regions of the mouse brain containing neurons that project to the LC

Regions possibly projecting to the LC (cf table 6)	ACh	DA	NE	F	5-HT	GABA	Glu	TRH	LHRH	ANG II	β-LPH	α-MSH	β-end	ACTH	enk	SP	neurotensin	Vaso/Oxy
SPINAL CORD																		
dorsal horn, lamina I																		
MEDULLA OBLONGATA																		
formatio reticularis:																		
dorsal to oliva inferior			+	+												+		
around n. reticularis lateralis (A1)			+	+												+		
around n. tractus solitarii			+	+											+	+	+	
n. dorsalis motorius vagus	+		+	+														
n. parasolitarius																		
n. commissuralis																+		
oliva inferior																		
medullar raphe nuclei																		
(pallidus, obscurus, magnus)					+										+	+		
n. nervi trigemini spinalis															+	+	+	
PONS																		
formatio reticularis																		
dorsolateral to oliva superior																		
nuclei vestibulares															+	+		
n. prepositus																		
contralateral parabrachial region																		
LC	+		+													+	+	
parabrachial nuclei																		
n. principalis nervi trigemini																		
raphe nuclei:																		
n. raphe pontis	+				+											+		
n. centralis superior	+				+													
CEREBELLUM																		
cortex cerebelli						+												
cerebellar nuclei:																		
n. fastigii																		
n. interpositus																		
n. dentatus																		

	ACh	DA	NE	E	5-HT	GABA	Glu	TRH	LHRH	VNC II	α-LPH	α-MSH	β-end	ACTH	enk	SP	neurotensin	Vaso/Oxy
MESENCEPHALON																		
tegmentum mesencephali	+																	
area ventralis tegmenti (VTA)	+	+															+	
substantia nigra	+	+																
grisea centralis, p. ventrolateralis		+													+	+	+	
raphe nuclei																		
n. raphe dorsalis	+				+											+	+	
n. centralis linearis intermedius	+				+													
n. Edinger-Westphall																+		
DIENCEPHALON																		
hypothalamus																		
n. posterior hypo. (dorsalis)																+		
area dorsalis hypothalami																		
n. periformicalis	+	+						+		+					+	+		+
n. lateralis hypothalami	+															+		+
n. supraopticus	+																	+
n. dorsomedialis								+								+		
n. ventromedialis		+													+	+		
n. paraventricularis	+	+								+						+		+
n. arcuatus	+	+							+		+	+	+	+	+	+		
n. suprachiasmaticus																+		+
thalamus																+		
n. parafascicularis																		
n. lateralis habenulae																		
TELENCEPHALON																		
n. preopticus medialis	+								+							+		
n. preopticus lateralis	+														+	+		
n. preopticus magnocellularis																		
amygdala																+		
n. interstitialis striae terminalis															+	+		
septum									+							+		
cortex cerebri																		
hippocampus							+											
insula (areas 13 and 14)							+											
sulcal prefrontal cortex							+											

	ACh	DA	NE	E	5-HT	GABA	Glu	TRH	LHRH	ANG II	β-LPH	α-MSH	met-end	ACTH	enk	SP	neurotensin	Vaso/Oxy
TERMINALS																		
terminals on identified IC cells					+										+	+		
terminals in the LC region				+	+	+		+		+	+	−	+	+			+	+
terminals in or near the IC region									+			+						
RESPONSE TO IONTOPHORETIC APPLICATION (+ activation; − suppression)	+	(−)	−	−	−	−	+								−	+	−	

REFERENCES: PUTATIVE NEUROSECRETIS

ACh	20,21,22	Glu	78,79	met-end	37,43
DA	24,25,26	TRH	57	ACTH	38,43,59,60
NE	12,23,24	LHRH	57,62,63	enk	18,19,44,56,58,66
E	5	ANG II	39,57,64	SP	40,41
5-HT	17,24,27,36	β-LPH	38,61	neurotensin	45
GABA	65	α-MSH	42,67	Vaso/Oxy	15,50,51,52,53,54,55,68

KEY TO THE REFERENCES IN TABLES 6. AND 7.

1. Russel 1955, 2. Shute and Lewis 1967, 3. Lewis and Shute 1967, 4. Mizuno and Nakamura 1972, 5. Hokfelt et al. 1974, 6. Conrad et al. 1974, 7. Snider 1975, 8. Saper et al. 1975, 9 Moolenaar and Rucker 1976, 10. Bobillier et al 1976, 11. Swanson 1976a, 12. Lewis et al. 1976b, 13. Sakai et al. 1977, 14. Gupta et al. 1977, 15. Swanson 1977, 16. Simon and LeMoal 1977, 17 Pickel et al. 1977, 18.Hokfelt et al. 1977b, 19, Simantov et al. 1977, 20. Pirent et al. 1977, 21. Poirier et al. 1977, 22. Butcher et al. 1977, 23. Swanson and Hartman 1975, 24. Dahlström and Fuxe 1964, 25. Hökfelt et al. 1976, 26 Lindvall and Bjorklund 1974, 27 Chan-Palay 1977, 28. Loewy and Burton 1977, 29. Krettek and Price 1978, 31. McDonald 1978, 32. Loewy and Burton 1978, 33. Ricaldo and Koh 1978, 34 Swanson and Sper 1975, 35 Heath and Harper 1976, 36 Leger and Descarrier 1978, 37. Bloom et al. 1978, 38. Watson et al. 1978, 39. Chaugaris et al. 1978, 40. Ljungdanl et al. 1978a, 41. Ljungdahl et al. 1978b, 42. Jacobowitz and O'Donohue 1979, 43. Sofroniew 1979, 44. Uhl et al. 1979a, 45. Uhl et al 1979b, 46. Simon et al 1979a, 47. Saper et al. 1979, 48. Bobillier et al. 1979, 49. Rose 1979, 50. Choy and Watkins 1977, 51. Watkins and Choy 1977, 52 Brownfield et al 1978, 53. Buijs et al. 1978, 54. Buijs 1978, 55. Reaves and Hayward 1979, 56. Elde et al. 1976, 57 Hokfelt et al. 1978a, 58. Glazer and Basbaum 1979, 59 Hostetter et al. 1979, 60. Pelletier and Désy 1979, 61. Zimmerman 1978, 62. Silverman and Krey1978, 63. Ajika 1979 64. Fuxe et al. 1976b, 65. Iversen and Schon 1973, 66. Sar et al. 1978, 67. Swaab and Fisser 1978 68. Van Leeuwen et al. 1978, 69. Swanson and Cowan 1979, 70. Beckstead et al. 1979, 71. Herkenham and Nauta 1979, 72. Clavier 1979, 73. Morgane and Jacobs 1979,74. Simon et al. 1979b, 75.

Flindt-Egebak 1979, 76. Swanson and Hartman 1980, 77. Hedreen 1978a, 78. Stone 1976, 79. Storm-Mathisen and Opsahl 1978.

Technical comments on Table 6. "Afferent fibers".

- HRP-studies have been carried out on the rat (Pasquier et al. 1977, Cedarbaum and Aghajanian 1978a, Clavier 1979, Morgane and Jacobs 1979) and on the cat (Sakai et al. 1977, Gupta et al. 1977). Since the LC of the rat is small (0.8 mm^3, A&S 2.2.1.), it is virtually impossible to inject a compound (or HRP) exclusively into it (cf. section 4.3.). The cat's LC is larger (it is estimated to be 20 mm^3), but since NE cells are intermingled with many non-NE cells (section 1.1.), extra evidence is required to determine whether the HRP-labeled cells after a HRP injection into the cat's LC region really make contact with the LC NE cells.
- Sakai et al. (1977) tried to distinguish the afferent connections to the LCd and LCv from the results of retrograde HRP transport. Although the HRP technique alone does not seem to be suitable for distinguishing the afferent connections of small adjacent regions, the differential projection of the nucleus solitarius, as proposed on the basis of HRP material, has been confirmed by autoradiographic studies (Loewy and Burton 1978, Ricardo and Koh 1978). In contrast with the findings in HRP studies, the nucleus interstitialis striae terminalis seems to project mainly to the LCd (see the figures in Swanson and Cowan 1979).

Technical comments on Table 7. "Afferent putative neurosecretes".

- In table 7, a putative neurosecrete is indicated as present in some regions, in cases where evidence is available of the presence of this compound in the cell bodies in these regions, and when the compound is at least a putative neurosecrete (see section 4.3.). ACh is indicated when acetylcholine-esterase (AChE) is found in the cell bodies in the region; not all AChE-containing cells are however cholinergic (cf. Silver 1974, Ramon-Moliner 1972, section 1.2.2.). For many regions, more than one putative neurosecrete is indicated, but in most cases it is uncertain whether more than one putative neurosecrete is present in one neuron; where there is evidence in the literature that more than one

putative neurosecrete is present in one neuron, it was indicated in the text of section 1.2.2.

- The shape of HRP labeled cells found after HRP injections into the LC region is mentioned only by Cedarbaum and Aghajanian (1978a). The shape of the cell bodies containing the various putative neurosecretes is mentioned only occasionally and contradictory descriptions are to be found (LHRH: cf. Silverman and Krey 1978 and Ajika 1979; ß-end: cf. Bloom et al. 1978 and Sofroniew 1979; ACTH: cf. Sofroniew 1979 and Pelletier and Désy 1979). Consequently, the available data on the shapes of the HRP labeled cells and of cells containing putative neurosecretes do not at the moment permit conclusions on the putative neurosecretes of the HRP labeled cells to be drawn.
- Where immunocytochemical indications of the presence of a putative neurosecrete, for instance ACTH, are presented, the term "ACTH cells", instead of "cells containing ACTH-like immunoreactivity" will be used for simplicity (cf. Hökfelt et al. 1978a).
- The criteria for neurotransmitter or neuromodulator (section 4.3.) are fulfilled for none of these putative neurosecretes in the LC.
- Phrases in table 7 have the following meanings:
  "Terminals on identified LC cells": synapses (i.e. pre- and/or postsynaptic specializations) on dendrites or cell bodies that are identified as NE cells in the LC region have been observed through the electron microscope.
  "Terminals in the LC region": either light-microscopiscally visible terminal-like boutons, or electron-microscopiscally identified boutons containing vesicles with the appearance of exocytotic vesicles but without synaptic specializations have been observed.
  "Terminals in or near the LC region": terminals have been described in the dorsolateral pontine tegmentum , but without mention of whether or not they occur in the LC.

Table 1.

Efferent connections of the LC, part 1.
Spinal cord and Medulla oblongata.

	NE[†]	LC[¶]	LCd/LCv[‾]
SPINAL CORD (CERVICAL TO SACRAL)			
trajectory:			LCv
funiculus anterior	2	4	
funiculus lateralis, pars anterior	2	4	
pars posterior	2	0	
funiculus posterior	0	0	
terminals:			LCv
laminae I - III	2	?	
laminae IV and V	2	4	
sympathetic column (lamina VI)	4	0	
retrodorsal motor group (lamina VII)	1-2	4	
medial motor group (lamina VIII)	1-2	4	
ventral motor groups (lamina IX)	3	4	
central (lamina X)	1-2	+[Φ]	
MEDULLA OBLONGATA			
trajectory.			
through lateral tegmental field	2	3	
terminals:			
cranial nerve nuclei:			
n. ambiguus	1-2	1	LCv
n. nervi trigemini spinalis	2	1	
pars substantia gelatinosa	2	4	
n. nervi vagus dorsalis motorius	3	3	
n. solitarius	3	?	LCv
n. parasolitarius	2	0-1	
n. commissuralis	3-4	0-1	
n. intercalatus	2	0-1	
n. salivatorius	0	0	
n. hypoglossus	2	0-1	
n. prepositus hypoglossi	3	0-1	
n. parahypoglossus	2	0-1	
n. retrofacialis	2	0-1	
reticular formation:			
lateral tegmental field	3	1-2	
gigantocellular tegmental field	1	2	
magnocellular tegmental field	2	2	
medial tegmental field	2	0-1	
n. lateralis reticularis	3	0-1	
raphe nuclei:			
n. raphes pallidus	3	0-1	
n. raphes obscurus	3	0-1	
n. raphes magnus	3	0-1	
oliva inferior:			
n. olivaris princ. inf. p. dorsalis	3-4	0-1	
p. ventralis	2-3	0-1	
n. olivaris accessorius dorsalis	1	0-1	
ventralis	2	0-1	
sensory nuclei:			
n. gracilis	2	0	
n. cuneatus	1	0	
area postrema	1	0-1	

Table (continued).
Efferent connections of the [illegible], part 1.
Pons and cerebellum.

	NF	IC	ICd/LCv
PONS			
[illegible]			
[illegible] tract	3	2	
commissural tract [illegible]	2	4	
terminals:			
cranial nerve nuclei:			
nn. vestibulares	0-1	3	
nn. cochleares	2	3	ICd+LCv
n. nervi facialis	3	1	LCv
n. abducens	1	0-1	
n. trochlearis	0-1	0-1	
n. sensorius principalis n. trigemini	1	1/3[f]	
n. motorius nervi trigemini	3	0-1	
reticular formation.			
lateral tegmental field	2	1-2	
gigantocellular tegmental field	1	2	
magnocellular tegmental field	2	1-2	
n. reticularis tegmenti (Bechterew)	2	1-2	
raphe nuclei.			
n. raphes pontis	0-1	0-1	
n. centralis superior	1-2	0-1	
n. tegmentalis dorsalis (Gudden)	1	3-4	
n. tegmentalis ventralis (Gudden)	3	0-1	
griseum centrale pontis, pars lateralis	3	3	
remaining parts	1	0	

	NE	IC	LCd/LCv
contralateral parabrachial region			LCd+ICv
LC	4	1	
SC	3	1	
n. parabrachialis medialis	2	1	
n. parabrachialis lateralis	2	1	
n. of Kolliker and Fuse	2	1	
sensory nuclei			
oliva superior	0-1	0	
n. trapezoideus	0-1	0	
n. lemniscus medialis	1	2	
pontine nuclei:			
n. pontis principalis	2-3	3-4	
lateralis	2	3-4	
dorsalis	1-2	3-4	
medialis	3-4	0-1	
CEREBELLUM			
[illegible]			LCd+LCv
[illegible]	3	4	
[illegible]	0/2	0	
[illegible]	0/2	0	
terminals			LCd+LCv
cerebellar nuclei	+	+	
cerebellar cortex	2-3	4	

	NF	LC	LCd/LCv
MESENCEPHALON			
[illegible]:			
[illegible]	4	4	LCd
[illegible]	3	2-3	LCv
[illegible]	2	3	
[illegible]	2	3	
[illegible]	2	3	
terminals:			
cranial nerve nuclei:			
n. mesencephalicus nervi trigemini	2	2	
n. nervi oculomotorii	0	0	
n. Edinger-Westphal, pars rostralis	0-1	0	
pars caudalis	3	1	
formatio reticularis	2	2	
raphe nuclei:			
n. raphes dorsalis	2	0/3	
n. centralis linearis intermedius	2	1-2	
rostralis	2	0-1	
griseum centrale mesencephali:			
pars ventrolateralis	3	1/3	
remaining parts	0-1	0/2	
sensory nuclei:			
colliculus superior:			
superficial layers	3	3	
deep layers	0-1	0	
colliculus inferior	2	2-3	
n. parabigeminalis	0-1	0	
n. tractus optici accessorii medialis	0	0	
"extrapyramidal nuclei":			
n. ruber	1	2	
substantia nigra pars compacta	0-1	0-1	
pars reticulata	0-1	0-1	
pars lateralis	1	1	
remainder:			
area ventralis tegmenti	1	2	
n. cuneiformis	0	0	
n. interpeduncularis	2	1/4	
n. sagulum	0-1	0	
n. Darkschewitz	1	0	
n. interstitialis colliculorum infer.	1	0	
DIENCEPHALON			
[illegible]			
[illegible]	3	3	
[illegible]	3	3	

Table 8 (continued)

Efferent connections of the ventral, dorsal, anterior, subthalamic, epithalamic and midline nuclei

	NE	LC	LCd/LCv
DIENCEPHALON (CONTINUED)			
terminals			
pretectum			
area pretectalis medialis	0-1	0	
n tractus optici, pars medialis	2	?	
pars lateralis	2	4	
n pretectalis principalis	1	4	
subthalamus			
n subthalamicus	0	0	
zona incerta	2	+	
n areae tegmentalis (Forel)	1	+	
epithalamus			
habenula	3	0	
epifyse	3	0	
thalamus			
anterior nuclei			
n anteroventralis	4	4	
n anterodorsalis	2	4	
n anteromedialis	3	4	
midline nuclei			
n parataenialis	1	4	
n paraventricularis	4	0-1	
n reuniens	1	4	
n rhomboidalis	1	4	
n gelatinosus	3	3	
medial nuclei			
n dorsomedialis	1	+	
intralaminar nuclei			
n centromedian	2	0/2	
n parafascicularis	2	0/2	
n paracentralis	1	2	
n centralis lateralis	1	4	
n centralis medialis	1	4	
lateral nuclei			
n lateralis dorsalis	2	4	
n lateralis posterior	2	+	LCd
n pulvinaris	1	+	
ventral nuclei			
n ventralis anterior	3	4	
n ventralis medialis	2	4	
n ventralis lateralis	2	4	
n ventralis basalis	3	4	
n posterior	1	4	
metathalamus			
corpus geniculate mediale	?	4	
corpus geniculate laterale p dorsalis	3	4	LCd
p ventralis	1	+	
n suprageniculatus	0	0	
n reticularis thalami	3	4	

	NE	LC	LCd/LCv
DIENCEPHALON (CONTINUED)			
hypothalamus:			
"neuro-endocrine nuclei"			
n. periformicalis	3	2	
n. dorsomedialis	4	2	
n. paraventricularis	4	2	
n. arcuatus	2	2	
n. supraopticus	4	2	
n. suprachiasmaticus	0-1	0-1	
posterior nuclei:			
nn. mamillares	1	3	
nn. premamillares	1	3	
n. posterior hypothalami	2	0	
lateral nuclei:			
n. lateralis hypothalami	1	2	LCv
area retrochiasmatica	3	2	
medial nuclei:			
n. ventromedialis	1	0	
n. periventricularis	4	2	
anterior nuclei:			
n. anterior hypothalami	1	0	
eminentia mediana	1	2	
hypophysis	3	0	

	NE	LC	LCd/LCv
TELENCEPHALON			
[illegible]:			
[illegible]	3	4	
[illegible]	2	4	
[illegible]	3	4	
[illegible]	3	4	
[illegible]	0/2	(4)	
[illegible]	0-1	(4)	
[illegible]	2	4	
rhinencephalon olfactorius anterior	2	4	
terminals:			
telencephalic nuclei:			
area preoptica			
n. preopticus medialis	3	0-1	
lateralis	2	0/3	LCv
magnocellularis	1	0	
suprachiasmaticus	3	0	
periventricularis	3	0	
amygdala			
n. tractus olfactorii lateralis	2	2	
n. amygdaloideus medialis	1	0-1	
lateralis	2	2	
centralis	3	0/3	
remaining amygdaloid nuclei	0	0	

	NP	IC	LCd/ICv
septum			LCd
n septalis medialis	2	3	
dorsalis	0	0	
intermedius	2	?	
lateralis	?	2	
fimbrialis	?	3	
triangularis	2	2	
n septohippocampalis	1	3	
n tractus diagonalis	2	2	
n interstitialis striae terminalis			
pars dorsalis	?	0/2	
pars ventralis	4	1-2	
n commissurae anterioris	2	?	
striatum			
n caudatus and putamen	0	0	
globus pallidus	0-1	0/2	
substantia innominata	0	0	
n accumbens	0-1	(?)	
olfactory areas			
tuberculum olfactorium	0	0	
bulbus olfactorius principalis			
lamina interna granularis	?	+	
remaining parts	0	0	
bulbus olfactorius accessorius			
lam int granularis and plexiform	?	+	
remaining parts	0	0	
nucleus olfactorius anterior	1	4	

	NP	IC	LCd/ICv
cerebral cortex			
hippocampus interior	?	+	
formatio hippocampi			LCd
hippocampus			
regio inferior (CA1)			
stratum oriens	3	4	
stratum pyramidale and lucidum	2	4	
stratum radiatum	3	+	
regio superior (CA3)			
stratum moleculare and lacunosum	?	+	
remaining parts	0-1	+	
gyrus dentatus			
hilus	3	+	
lamina granularis	2	+	
lamina molecularis	1	+	
subiculum			
dorsal and deep parts	2	+	
remaining parts	0	0	
presubiculum	0-1	+	
parasubiculum	0-1	+	
cortex entorhinalis			
medial	2	+	
lateral, pars anterior	0	0	
pars posterior	-	+	

	NE	LC	LCd/LCv
Cerebral cortex (continued)			
paleocortex			
cortex piriformis	[illegible]	+	
cortex amygdaloideus	[illegible]	+	
mesocortex			
cortex cinguli			
lamina I	4		
remaining parts	3	+	
cortex retrosplenialis	2	+	
neocortex total			Cd
lamina I	3	+	
laminae II to V	[illegible]	+	
frontal cortex	3	+	
remaining neocortex	[illegible]	+	

Legends at Table 8

NE column: ranking scale 0 – 4. 0 = no or almost no NE detected with the different techniques used, 4 = very high levels of NE have been detected

Column LC

0 = LC not the origin of NE terminals in this region
[illegible] up to 25% of the NE terminals are derived from the LC
2 = 25 to 50% of the NE terminals are derived from the LC
3 = 50 to 75% of the NE terminals are derived from the LC
4 = 75 to 100% of the NE terminals are derived from the LC

Only indicated when HRP injected into the region indicated labeled cells only either in the LCd or the LCv.

Two numbers separated by a / : contradictory results are to be found in the literature

+ NE terminals derived from the LC are present, but their proportion [illegible] uncertain

? [illegible] uncertain whether or not any NE terminals are derived from the LC

Table 3.

Key to possible locations of LC projections in the rat *.

	retrograde tracing	radio-graphy	CA/NE histochemistry	degene-ration	bio-chemistry	adreno-ceptors
spinal cord	13,17,18,20,24,55,62, 72,73,90,100,101,102, 106	33,73,83, 92	10,36,50,52,89		36,40,72	1
medulla oblongata	15,82,90,95,113	83	95,96			
pons	16,91,107,110	83	96,110			
cerebellum	37,49,76,90	33	22			25
mesencephalon	11,14,63,65,69,70,88, 99,104	33,104	96			
diencephalon					many †	
thalamus	32,64,67,78,79,90,112	33	2		77	
hypothalamus	27,74,90,109		6,8	8,74	77	
telencephalon		33	46		many †	
preoptic nuclei	27,90					
amygdala	30,58,66,89,98		98	61		
septum	28,42,103		28,42		28	
basal ganglia	26,71,108					
bulbus olfactorius	4,51					
formatio hippocampi	3,5,48,56,84		9,17,31		60,77	12
neocortex	7,34,35,54,81,85,90, 111		39,45,94,97		many	47,87

* see the following page for the authors to which these numbers refer.

† a loss of NE in these regions has been used in many studies to be shure that the LC has been effectively and completely lesioned.

Recent publications on efferent connections of the LC (tables 8 and 9).

1. Melamed et al. 1976, 2. Kromer 1976, 3. Pasquier 1976, 4. Broadwell and Jacobowitz 1976, 5. Pasquier and Reinozo-Suarez 1977, 6. Hoffman et al. 1976, 7. Divac et al. 1977, 8. Palkovits et al.1977a,b, 9. Collier and Routtenberg 1977, 10. Nygren and Olson 1977b, 11. Anderson et al. 1977b, 12. Atlas and Segal 1977, 13. Kuypers and Maisky 1977, 14. Palkovits et al. 1977c, 15. Brown et al. 1977, 16. Sakai et al. 1977, 17. Satoh et al. 1977, 18. Castiglioni et al. 1977, 19. Morgane et al. 1977, 20. Schoenen and Domesick 1977, 21. Royce 1977, 22. Bhatnagar and Schmidt 1977, 23. Wyss 1977, 24. Humbertson et al. 1977, 25. Atlas et al. 1977,26. Cough and Goldstein 1977, 27. Sakumoto et al. 1978, 28. Moore 1978, 29. Silver et al. 1979, 30. Mehler et al. 1978, 31. Koda et al. 1978a,b, 32. Sapawi and Divac 1978, 33. Bowden et al. 1978, 34. Bentivoglio et al. 1978, 35. Arikuni and Ban 1978, 36. Commissiong et al. 1978a, 37. Kimoto et al. 1978, 38. Kneisley et al. 1978, 39. Zecevic and Molliver 1978, 40. Commissiong et al. 1978b, 41. Hefti and Lichtensteiner 1978, 42. Lindvall and Stenevi 1978, 43. Oke et al. 1978b, 44. Nowaczyk et al. 1978, 45. Morrison et al. 1978, 46. Danner and Pfister 1978, 47. Bylund 1978, 48. Beckstead 1978, 49. Batini et al. 1978, 50. Martin et al. 1978b, 51. De Olmos et al. 1978, 52. Crutcher and Bingham 1978, 53. Lidov et al. 1978, 54. Divac et al. 1978, 55. Ten Donkelaar and De Boer-Van Huizen 1978, 56. Pasquier and REinozo-Suarez 1978, 57. Didov et al. 1978, 58. Veening 1978, 59. Somana and Walberg 1978, 60. Gage et al. 1978, 61. Kaelber 1978, 62. Smolen et al. 1978, 63. Phillipson 1978, 64. Spreaficio et al. 1978, 65. Simon et al. 1978, 66. Ottersen and Ben-Ari 1978, 67. Hoogland and Lohman 1978, 68. Grofova et al. 1978, 69. Simon et al. 1979, 70. Baleydier and Magnin 1979, 71. Vandermaelen et al. 1979, 72. Adèr et al. 1979, 73, Martin et al. 1979, 74. Záborsky et al. 1977, 75. Finger 1978, 76. Eller and Chan-Palay 1976, 77. Jones et al. 1978, 78. Lewis et al. 1979, 79. Velayos et al. 1979, 80. Pretorius et al. 1979, 81. Leinetz and Astruc 1979, 82. Abols and Basbaum 1979, 83. Westlund and Coulter 1979, 84. Wyss et al. 1979, 85. Divac 1979, 86. Artieda and Ullán 1979, 87. Melamed et al. 1977, 88. Pasquier et al. 1977, 89. Jordan et al. 1977, 90. Tohyama et al. 1978, 91. Cedarbaum and Aghajanian 1978a, 92. Holstege et al. 1979, 93. Collingridge et al. 1979, 94. Berger et al. 1979, 95. Takahashi et al. 1979, 96. Levitt and Moore 97. Morrison et al. 1979b, 98. Emson 1979, 99. Phillipson 1979, 100. Sakai et al. 1979, 101. Tohyama et al. 1979, 102. Basbaum and Fields 1979, 103. Mason and Fibiger 1979i, 104. Simon et al. 1979b, 105. Reader et al. 1979, 106. Satoh 1979, 107. Takeuchi et al. 1979, 108. DeVito et al. 1980, 109. Swanson and Hartman 1980, 110. Kromer and Moore 1980, 111. Krist and Silverman 1980, 112. McGuines and Krauthamer 1980, 113. Bystrzycka 1980.

	+ +	+ −	− +	− −	Reproducible effective (%)
carbachol-induced ataxia	15	4	3	22	79
carbachol-induced turning	17	5	2	20	77
clonidine induced vomiting	10	2	0	10	83
naloxone-induced antagonism	5	0	0	6	100
Total	47	11	5	58	81

+ + both injections effective

+ − first injection effective, second injection ineffective

− + first injection ineffective, second injection effective

− − both injections ineffective

Table 11.
Distribution of effective injection sites over anatomically demarcated regions.

		V4		CG		LC		SC		NE		LdT		PCO		PCC		total
			+1*		+1		+1		+1		+1		+1		+1		+1	
carbachol-induced:																		
atonia	+	0	2	2	9	3	8	5	21	8	21	0	3	10	17	12	17	33
	−	3	23	16	39	18	37	10	39	30	57	4	25	20	41	12	20	96
turning	ipsi	0	0	0	1	2	4	1	5	3	7	0	3	4	6	0	0	7
	no	3	13	7	25	9	19	9	34	18	42	1	11	23	38	17	28	81
	contra	0	12	11	22	10	22	5	21	17	29	3	14	3	14	7	9	41
defense reactions	+	0	0	1	2	0	0	1	6	1	6	0	1	9	10	0	2	11
	−	3	25	17	46	21	45	14	54	37	72	4	27	21	48	24	35	118
vocalizations	+	1	6	3	7	3	9	0	4	2	8	1	7	7	10	2	2	18
	−	2	19	15	41	18	36	15	56	36	70	3	21	23	48	22	35	111
elimination	+	0	4	4	8	3	8	0	7	4	9	0	7	2	6	2	5	11
	−	3	21	14	40	18	37	15	53	34	69	4	21	28	52	22	32	118
total carbachol		3	25	18	48	21	45	15	60	38	78	4	28	30	58	24	37	129
clonidine-induced:																		
vomiting	+	2	9	5	7	0	4	0	6	0	6	0	1	1	4	2	5	10
	−	0	12	10	27	12	20	3	16	17	27	3	15	11	22	4	6	50
inactivation	+	0	4	3	11	1	6	0	3	1	7	2	6	5	8	1	1	14
	−	2	17	12	23	11	18	3	19	16	26	1	10	7	18	5	10	46
total clonidine		2	21	15	34	12	24	3	22	17	33	3	16	12	26	6	11	60
naloxone-induced:																		
morphine-antagonism	+	0	5	5	10	4	10	1	11	5	15	0	4	2	7	6	8	17
	−	1	11	9	22	8	16	1	20	12	23	3	13	9	20	7	9	41
total naloxone		1	16	14	32	12	26	2	31	17	38	3	17	11	27	13	17	58

* sum of the sites in the region indicated and at a distance of less than 1mm from this region.

Table 11.

Correlation between the various brain-induced effects and anatomically emphasized [illegible]

	V4		CG		LC		SC		NE		IdT		PCO		PCC	
	-1	+1	-1	+1	-1	+1	-1	+1	-1	+1	-1	+1	-1	+1	-1	+1
carbachol-induced (N = 129):																
atonia	-.00	-.19	-.13	-.12	-.11	-.13	.07	.20	-.06	.04	-.10	-.18	.17	.08	.27	.30
turning, contra	-.11	.17	.25	.23	.15	.27	.03	.06	.18	.14	.17	.20	-.26	-.15	-.03	-.11
turning, ipsi	-.05	-.12	-.09	-.10	.14	.21	.04	.16	.13	.26	-.03	.22	17	.24	-.14	-.20
defense reactions	-.05	-.15	-.04	-.12	-.16	-.22	-.02	.05	-.14	-.04	-.07	-.11	.51	.34	-.11	-.09
vocalizations	.09	.14	.03	.01	.00	13	-.15	.20	-.16	-.13	.06	.17	.15	.09	-.08	-.16
elimination	-.05	.13	.20	.22	.09	24	-.11	.10	.01	13	-.05	.31	-.04	.06	-.00	.11
clonidine-induced (N = 60):																
vomiting	.42	.51	.26	.12	-.22	.00	-.10	.21	-.28	.04	-.10	-.17	-.11	.03	.15	.37
inactivation	-.10	-.07	-.05	.24	-.18	.03	-.13	-.17	-.26	-.06	24	.20	.22	.15	-.05	-.16
naloxone-induced (N = 58):																
morphine-antagonism	-.09	.03	.08	.04	.05	.18	.09	.15	00	.31	-.15	-.08	-.12	-.07	.20	.25

These [illegible] are plotted in the [illegible]

	Region-effectiveness					Site-effectiveness					Time-effectiveness				
carbachol-induced:															
stomia	9														
asymmetry	19	8	6	00	p										
defense reactions	18	7			p	00									
vocalizations		7		10	p	20			30		30				
elimination		0		30					10	p	20				
clonidine-induced															
vomiting															
inactivation															
naloxone-induced															
morphine-antagonism					p	70			50	p	70				

Table 14.
Combined occurrence of various drug-induced effects at individual injection sites.

carbachol-induced:										
atonia	+	8	33	1						
	−	2	56	41						
defense	+	0	9	2	3	8				
	−	10	80	40	39	91				
vocalizations	+	0	7	10	1	16	3	14		
	−	10	82	32	41	83	8	116		
elimination	+	0	2	9	1	10	0	11	2	9
	−	10	87	33	41	89	11	119	15	115
clonidine-induced:										
vomiting	+	0	8	2	1	9	1	9	0	10	1	9		
	−	3	23	24	6	44	2	48	10	40	5	45		
inactivation	+	0	6	8	0	14	2	12	6	8	0	14	1	13		
	−	3	25	18	7	39	1	45	4	42	6	40	9	37		
naloxone-induced:																
morphine-antagonism	+	0	8	9	2	15	1	16	4	13	4	13	1	16	3	14
	−	2	23	17	3	39	4	38	11	31	5	37	4	27	11	20
		i	−	c	+	−	+	−	+	−	+	−	+	−	+	−
		turning			atonia		defense		vocalizations		elimination		vomiting		inactivation	
							carbachol-induced						clonidine-induced			

Table 15.
Correlation matrix (φ-coefficients) of the combined occurrence of the various drug-induced effects at individual injection sites (data from Table 14).

carbachol-induced:								(N=141)
atonia	-.39¶	.26†						
defense	-.07	-.13	-.02					
vocalizations	.23†	-.09	-.19†	.14				
elimination	.33¶	-.05	-.13	-.08	.05			
clonidine-induced:								(N=60)
vomiting	-.22	-.17	-.02	.10	-.20	.00		
inactivation	.15	-.14	-.20	.23	.39†	-.18	-.14	
naloxone-induced:						(N=59)		(N=48)
morphine-antagonism	.13	-.14	.07	-.06	-.03	.15	-.11	-.19
	contra ipsi turning		atonia	defense	vocalizations	elimination	vomiting	inactivation
				carbachol-induced			clonidine-induced	

† $p < .05$, two-tailed test, exact method.

¶ $p < .01$, exact

[illegible]

	atonia	running, rapid	turning, circling	defense	vocalizations	elimination	vomiting	inactivation
carbachol (141)†	42	10	42	11	17	11	10	14
l-NE (13)	6	4	3	0	1	0	0	0
clonidine (60)	7	3	26	3	10	6	10	14
oxymetazoline (9)	1	0	4	0	0	0	5	1
isoprenaline (9)	3	1	4	0	0	0	5	1
piperoxane (B¶,9)	3	1	4	0	0	0	5	1
l-propranolol (10)	4	3	3	0	1	0	0	0
d-amphetamine (4)	1	0	2	0	0	0	4	1
desipramine (4)	2	0	1	0	0	0	4	0
apomorphine (3)	2	0	1	0	0	0	3	0
morphine (B,12)	9	4	7	0	1	0	5	1
fentanyl (B,23)	2	2	22	3	12	5	5	12
naloxone (18)	2	0	11	0	4	2	0	3
procaine (23)	2	0	15	2	8	1	1	7
L-glutamic acid (11)	2	0	2	2	3	0	1	6

† between brackets the number of cats tested.

¶ [illegible]

	whole brain	spinal cord	brain stem
TECHNIQUES			
[illegible] stimul[illegible]			3 ,87,11(,15
- [illegible]			43 [illegible] 63
- [illegible]	55	1 ? 7,1[illegible] ,36 61,86, 106 1 1 14[illegible]	5, 1 [illegible]
[illegible] NE + [illegible]		4 11	8 1[illegible] 3 [illegible] 33 38,6 ,143
[illegible]		1 [illegible],7,11,1(,[illegible],3(, 61,8[illegible] 1[illegible]	1[illegible] [illegible],57,43,44,[illegible],57, 63 87,15[illegible]
RESULTS			
m[illegible] level			
- receptors [illegible] and [illegible] receptors			
mainly [illegible]-adrenoceptors			
mainly [illegible]-adrenoceptors			5, [illegible]
- [illegible] AMP involved	13[illegible]		[illegible]
not involved			
[illegible] induces [illegible]			38
- [illegible] K-[illegible] involved	51		
- [illegible] involved	51,1 1		
cellular level			
- m[illegible]			
• transmembrane potential [illegible]			
- depolarization			
- hyperpolarization	5[illegible] 13	11,11 [illegible] 36 61 1 [illegible]	
• increase in membrane resistance	5[illegible] 13[illegible]	11,[illegible] ,36,1	
maintained [illegible] (extra[illegible])			
• activation and suppression			6[illegible]
• mainly activation			8, 1,
• mainly suppression	13[illegible]	1, [illegible],7,8[illegible],141	[illegible] 3, [illegible] 38,143
regional level			
re[illegible]			
• increase [illegible]			
• decrease [illegible]		1 4,7,	
[illegible]			
increase [illegible] response			
• decrease [illegible] response	13[illegible]	1,106,1 1	37,43, [illegible],57 63,87, 11[illegible],14[illegible],15
increase [illegible] ratio	13[illegible]		
depending [illegible] location			

	cerebellum	telencephalic nuclei
TECHNIQUES:		
- electrical stimulation of the LC (esLC)	108	95
- esLC + pharmacology		
- iontophoresis of NE (iont.NE)	8,64	113
- iont.NE + pharmacology	26,27,28,30,31,34,46,66, 82,83,89,90,109,146	
- esLC + iont.NE + pharmacology	39,58,65,91,139,147	
- cells physiologically identified	26,27,28,30,39,46,64,65, 66,88,89,90,91,108,109, 139,146,147	95
RESULTS:		
molecular level:		
- receptors: α- and β-adrenoceptors		
mainly α-adrenoceptors		
mainly β-adrenoceptors	146	
- cyclic AMP: involved	26,27,30,32,39,65,66,83 90,109,147	
not involved	31,34,46	
- prostaglandine involved	27,30,39	
- Na,K-ATPase involved	82	
- calcium ions involved	30	
cellular level:		
- membrane mechanism (intracellular)		
• transmembrane potential change:		
- depolarization		
- hyperpolarization	26,39	
• increase in membrane resistance	26,39	
- maintained activity (extracellular):		
• activation and suppression	8†	
• mainly activation		
• mainly suppression	27,28,29,30,31,34,39,46, 64,65,66,82,83,89,90,108 109,139,147,91	113
regional level:		
- response to compounds·	146§,162§	
• increase in response		
• decrease in response		
- electr.(synaptic) and sensory stimuli:	64¶,88¶,139¶,146¶	
• increase in response		
• decrease in response		95
- increase in signal-to-noise ratio	64,88,139,146,162,163	

† depending on location

¶ depending on the elements stimulated

§ depending on the compound

	hippocampus, g pyriformis and cinguli	neocortex
TECHNIQUES:		
- electrical stimulation of the LC (esLC)	115	
- esLC + pharmacology	71,72	
- iontophoresis of NE (iont.NE)		32b,35a,125,150
- iont.NE + pharmacology	6,48,73,75,116	10,11,15,16,17,18,35,40,42,52,53,54,55,56,60,75,97,99,117,118,119,120,121,124,126,127
- esLC + iont.NE + pharmacology	49,50	100
- cells physiologically identified		40,100,124
RESULTS:		
molecular level:		
- receptors: α- and β-adrenoceptors		17,35,97[r],126[r],127[r]
mainly α-adrenoceptors		127
mainly β-adrenoceptors	48,116	40,54,55,100,124
- cyclic AMP: involved	48,50	
not involved		
- prostaglandines involved	48,50	
- Na,k-ATPase involved		52
- calcium ions involved		52,53,56
cellular level:		
- membrane mechanism (intracellular)		
• transmembrane potential change:		
- depolarization		
- hyperpolarization		
• increase in membrane resistance		
- maintained activity (extracellular):		
• activation and suppression		35a,54,97[r],126[¶],127[r],15
• mainly activation		16,17,18,55,99
• mainly suppression	6,48,49,50,71,72,73,75,115,116	10,32b,35,40,42,52,53,56,60,75,100,117,118,119,120,121,124,150
regional level:		
- response to compounds:		
• increase in response		
• decrease in response	6,50	32b,35,42,52,53,121,125,150
- electr (synaptic) and sensory stimuli		
• increase in response		
• decrease in response	6	32b,60,125
- increase in signal-to-noise ratio	72	60,139

[r] depending on cell type: [a] activation, [s] suppression

R[illegible] [illegible] [illegible] in table 17, effects of the IC and M[illegible] on single unit activity*

1. Engberg and [illegible] 1966, [illegible] 1966a, 3. [illegible] and Salmoiraghi 1966b, 4. [illegible] et al. 1966, 5. [illegible] et al. 1966, 6. [illegible] et al. 1966, 7. Weight and Salmoiraghi 1967, 8. Yamamoto 1967, 9. Phillis and [illegible] 1967, 10. Phillis and York 1967, 11. Phillis et al. 1968a, 12. Boakes et al. 1968a, 13. Boakes et al. 1968b, 14. [illegible] 1968, 15. Phillis et al. 1968b, 16. [illegible] and Straughan 1968, 17. Johnson et al. 1969a, 18. Johnson et al. 1969b, 19. [illegible] and [illegible] 1970, 20. [illegible] and [illegible] 1971, 21. [illegible] et al. 1971, 22. Boakes et al. 1971, 23. Gonzalez-Vegas 1971, [illegible] Gonzalez-Vegas and [illegible] 1971a, 25. Gonzalez-Vegas and [illegible] 1971, 26. Siggins et al. 1971a, 27. Siggins et al. 1971b, 28. Hoffer et al. 1971a, 29. Hoffer et al. 1971b, 30. Hoffer et al. 1971c, 31. Godfraind and Pumain 1971, 32. Siggins et al. 1971, 32a. Stone 1971, 32b. Frederickson et al. 1971, 33. Boakes et al. 1972, 34. Godfraind and Pumain 1972, 35. Fredericks[illegible] et al. 1972, 35a. Stone 1972, 36. Engberg and Marshall 1973, 37. Sasa and Takaori 1973, 38. Anderson et al. 1973, 39. Hoffer et al. 1973, 40. Stone 1973, 41. Bradshaw 1973, 42. Nelson et al. 1973, 43. Sasa et al. 1974a, 44. Sasa et al. 1974b, 45. Boakes et al. 1974, 46. [illegible] and Jordan 1974, 47. Sasa and Takaori 1974, 48. Segal and Bloom 1974a, 49. Segal and Bloom 1974b, 50. Segal 1974, 51. Phillis 1974, 52. Phillis et al. 197[illegible], 53. Yarbrough 1974, 54. Bevan et al. 1974a, 55. Bevan et al. 1974b, 56. Phillis and Limacher 1974, 57. Sasa et al. 1975, 58. [illegible] and Hoffer 1975, 59. Phillis 1975, 60. Foote et al. 1975, 60a. Colbert et al. 1975, 61. Jordan and [illegible] 1976, 62. Kirsten and Sharma 1976, 63. Sasa et al. 1976, 64. Freedman 1976, 65. Siggins et al. 1976, 66. Nathanson et al. 1976, 67. Gallager and Aghajanian 1976, 68. [illegible] et al. 1976, 69. [illegible] et al. 1976, 70. Bunney and Aghajanian 1976, 71. Segal and Bloom 1976a, 72. Segal and Bloom 1976b, 73. Segal 1976b, 74. Ohta 1976, 76. Dismukes and Mulder 1976, 77. Dismukes et al. 1976, 78. Vetulani et al. 1976a, 79. Vetulani et al. 1976b, 80. Skolnick and Daly 1976a, 81. Skolnick and Daly 1976b, 82. Yarbrough 1976, 83. [illegible] 1976, 83a. [illegible] 1976, 84. Bockaert et al. 1977, 85. Bonkowski and Dryden 1977, 86. Jordan et al. 1977, 87. Sasa et al. 1977, 88. Freedman et al. 1977, 89. Wise and Hoffer 1977, 90. Nathanson et al. 1977, 91. Jordan 1977a, 92. Harden et al. 1977b, 93. Vetulani et al. 1977, 94. Anderson et al. 1977b, [illegible] Sasa et al. 1977, 96. Oishi et al. 1977, 97. Bevan et al. 1977, 98. [illegible] 1977, 99. Sharma 1977, 100. Phillis and Kostopoulos 1977, 101. Iversen 1977, 102. Nathanson 1977, 103. Ahn and [illegible] 1977, 104. Rasmussen and Goodman 1977, 105. [illegible] and Ho 1977, 105a. Nishino and [illegible] 1977, 106. [illegible] et al. 1978, 107. [illegible] et al. 1978, [illegible] [illegible] et al. 1978, 109. [illegible] et al. 1978, 110. Takemoto et al. 1978, 112. Jordan 1978, 113. Winokur and Beckman 1978, 114. Perkins and Whitehead 1978, 115. [illegible] et al. 1978, 116. [illegible] et al. 1978, 117. Stone and Taylor 1978a, 118. Stone and Taylor 1978b, 119. Stone and Taylor 1978c, 120. Stone and Taylor 1978d, 121. Ewart and Logan 1978a, 122. Ewart and Logan 1978b, 123. Ewart and Logan 1978c, 124. Hicks and McLennan 1978, 125. Reader 1978, 126. Bevan et al. 1978a, 127. Bevan et al. 1978b, 128. Harris 1978, 129. Jones 1978, 130. Hauser 1978, 131. Robinson 1978, 132. Skolnick et al. 1978a, 133. Skolnick et al. 1978b, 134. [illegible] 1978, 135. Nimit[illegible] and Skolnick 1978, 136. Tsang and Lal 1978, 137. Tsang et al. 1978, 138. Wu and Phillis 1978, 138a. Schmeter et al. 1978, 139. Woodward et al. 1979, 140. Horn and McAfee 1979, 141. Satoh et al. 1979, 142. Marshall and Engberg 1979, 143. [illegible] et al. 1979, 144. Sasa and Takaori 1979, 145. Latham and Paul 1979, 146. Moises et al. 1979, 147. Siggins et al. 1979, 148. Oishi et al. 1979b, 149. Assaf et al. 1979, 150. Reader 1979, 151. Stone and Taylor 1979, 152. Korf and Sebens 1979, 153. Herbst et al. 1979, 154. Nathanson and Glaser 1979, 155. Parsche and Stefanovich 1979, 156. Wu and Phillis 1979, 157. Akagawa and Tsukada 1979, 158. Schmeter et al. 1979, 159. Igarashi et al. 1979, 160. Phillis and Wu 1979, 161. Colbert et al. 1979, 162. Moises and Woodward 1980

* See the review of Salmoiraghi (1966) for earlier articles

5. STRUCTURE AND FUNCTION IN THE CNS.

5. Structure and function in the CNS.

SECTION 5. TABLE OF CONTENTS

Summary of the main conclusions

"Our brains are as complicated as we are."

A framework consisting of strictly defined concepts on structure and function of the nervous system is presented.

Function The word "function" as generally used has several different meanings. Two meanings of the question "What is the function of S?" are particularly relevant for this book: 1) "What does S do?" and 2) "Why did S evolve?". Of course, question 1 must be answered, before question 2 can be.

Function of brain region S. The question "What does brain region S do?" is identical to "What effects do inputs of S (incoming signals, afferents) have on outputs of S (outgoing signals, afferents)?". This question can however be answered at different levels, for instance at the molecular or cellular level. When neuroscientists ask "What is the function of brain region S?", the intended meaning is either the question "What does S do on the organ or behavioral level?", or the question "Why did S evolve?". "What does S do on the organ or behavioral level?" is identical to "What is represented by the inputs of S outside the CNS, and what are the effects of the outputs of S outside the CNS and outside the organism?."*

Localization of function. "Localization of function F" means "demarcation of the CNS subsystem S doing F". Subsystem S can only be demarcated when F is sufficiently specified, i.e. when the inputs of the CNS (stimuli), the conditions of the organism, and the outputs of the CNS ("response" or "behavior") are specified.

* Johannesma has formulated this idea earlier, albeit in other words, the original idea was his, for which he deserves recognition here.

5.0. Foreword.

This chapter* attempts to present clear concepts on structure and function of the nervous system. Unfortunately, the meaning, implications and limitations of these ideas cannot be fully clarified in a chapter smaller than this one. However, the "Summary of the main conclusions" provides sufficient information for an understanding of the application of these ideas in the general discussion of this book (section 3.2). For readers who are primarily interested in the implications and applications of these concepts to the nervous system, a reading of the following sections may be sufficient: 5.2.4 ("Function"), 5.4 ("The I/O-function of CNS regions") and 5.5 ("The "localization of functions" once again"). The ideas and concepts presented can however only be fully understood by reading the whole chapter.

* This chapter is the main body of a paper in preparation on structure and function of the nervous system, in which the concepts "redundancy", "functional recovery", "take-over of functions" etc. will also be mentioned.

5.1. Introduction.

"Science is built up with facts, as a house is with stones. But a collection of facts is no more a science than a heap of stones is a house."
(Poincaré 1952)

5.1.1. OBJECTIVES AND MY POINT OF VIEW

Ambiguities. A great deal of research has been devoted to functional analyses of regions of the CNS and to the "localization of functions". The discussion what it is that parts of the CNS do is confused because (as will be shown below) the key concepts, such as "function", "localization of function", "functional", "structure", "redundancy" and "functional recovery" are ambiguous or unnecessarily circularly defined; and even the more fundamental concepts such as "meaning" and "explanation" appeared to be used ambiguously (cf. Hospers 1967, Pattee 1979, Walter 1979). The need to define the former concepts has been felt by many authors: experimental neuroscientists (e.g. Von Holst and Van Saint-Paul 1963, Stein 1976, Stein et al. 1974a, Zülch 1975, 1976), "neuro-engineers" (Gregory 1961), neuropathologists (Luria 1966, 1973, Denny-Brown in Rasmussen 1975), system analysts (e.g. Sagasti 1970, Ackhoff 1972), psychologists (Weiskrantz 1968, 1973, Webster 1973), ethologists (Hinde 1975) and philosophers (e.g. Hospers 1967, White 1968, Woodfield 1976). An attempt to precisely define the concepts relevant to investigations of the CNS is therefore undertaken here.

Objectives. This chapter is intended to be a contribution to the discussion on the working of (parts of) the CNS. I have aimed to create clarity and to formulate those kinds of questions on the working of (parts of) the CNS that are unambiguous, that can be answered by experiment, and that even get close to answering the fascinating questions on the brain we always wanted to solve. My objective is the development of a conceptual framework derived from system analysis, and the application of this to

investigations of the CNS. The reason for this choice is that the concepts of system analysis are concise and clear, and system analysis is pre-eminently suited for my purpose, since it is designed to analyze the working of objects consisting of complexely arranged elements (e g. systems such as the nervous system).

Pure causality? In this book, I will restrict myself to a purely causal description of the working of the CNS, because the causal principle is a rule of the game in science (cf. Hospers 1967, p. 317). Whether or not a complete description of the working of the CNS can logically be purely causal depends on whether the CNS actually works purely causally (this is related to the brain-mind discussion, cf. Hospers 1967, pp. 378-404). In a future age, neuroscientists may agree either that their causal descriptions can even explain purposive behavior, or that their failure to find such explanations is so monumental, that it is better to abandon the causal principle altogether neuroscience may contribute to the maintenance or abandonment of the causal principle. A necessary condition, however, for deciding to what degree causal explanations are appropriate in neuroscience, is a consistent and unambiguous use of the relevant causal and teleological concepts.

Caution or imagination? Teuber (cited by Passingham 1979) divided neuroscientists into "all-at-oncers" and "creeping-uppers", depending on the weight they attribute to the scientific virtues of imagination and caution. I am a "creeping-upper". Imaginative neuroscientists have already "localized many functions", and attributed many "functions" to CNS nuclei or areas. Yet many seemingly unrelated hypotheses regarding a single subject often persist, while nobody can formulate practicable critical experiments. This is *"characteristic of a science that has not yet developed mature theoretical structures and paradigms"* (Swazey and Worden 1975, cf. section 3.2.1, pp. 143-144).

5.1.2. THE PREDICAMENT OF THE NEUROSCIENCES

The "localization of functions". One can localize parts of the CNS the activity of which (and therefore the existence of which) is a necessary condition for instance for respiration or aggression (or more appropriately for intermale aggression or offspring defense). Is this however actually

localization of respiration or intermale aggression? The system that regulates the blood CO_2-level, the input of which is the initial level of blood CO_2, and the output of which the state of respiration muscles, can be localized. So too can the system that makes a patient exhale when the doctor requests it,be logically demarcated. But can the system that mediates the "function" of respiration logically be localized? When one examines which regions of the CNS are involved in respiration, such regions are found along the whole of the neuraxis, *"so that nobody knows its precise limits"* (Pavlov, cited by Luria 1966). Partsof these regions are also involved in other "functions" (this example is further elaborated in section 5.5.1). To take another example, let us suppose that one is interested in intermale aggression (cf. Moyer 1968). It is known that all the sensory systems, the endocrine, the motor system and most of the remainder of the CNS are involved in intermale aggression. If "localization of intermale aggression" means "demarcation of those parts of the CNS that are involved in intermale aggression", almost all the CNS must be included. But does a group of neurons exist that are exclusively (or even mainly) involved in intermale aggression, and consequently not in other activities? If "localization of intermale aggression" means "demarcation of a part of the CNS that is specifically (or extensively) involved in intermale aggression", it is doubtful whether such parts exist, and therefore whether intermale aggression is localizable (this is further elaborated in section 5.5.1).

My own opinion is that concepts such as respiration and intermale aggression are too vague to localize, and have to be specified (this will be further elaborated in section 5.5.1).

The "functional systems" in the CNS. At the moment, it is often unclear which parts of the CNS can rightly be regarded as entities. Histochemically identified parts of the CNS (nuclei, laminae and cortical areas) sometimes do not appear to be entities. An example is the nucleus solitarius, which appears to consist of respiratory and gustatory parts Inverse cases also occur some parts of histochemically different regions may appear to form together an entity, as is suggested for some thalamic nuclei, at least as far as their frontal cortical projections are concerned (Kievit and Kuypers 1977). This problem is especially urgent for the set of neurons having the same neurosecrete. If one is interested in the cerebral metabolism of GABA for instance, one might regard all CNS GABAergic neurons together as an entity; but it is questionable whether the GABAergic neurons (cf. Roberts

et al. 1976b) have any generalizable effect on behavior. At the biochemical level, the GABAergic neurons are an entity, a system, but this need not imply that they are a system at the behavioral level.

My own opinion is that if one wants to know what a part of the CNS does, one must have *a priori* knowledge* that this part really is an entity as far as the aspect investigated is concerned. (Note: what is here called "entity", is often called "functional system", but the latter term will be avoided for reasons to be mentioned in section 5.2.4.)

The function of parts of the CNS. Even when parts of the CNS that seem to be entities have been demarcated, no general agreement need exist about their function. For instance, the hippocampus and the cerebellum do seem to be entities, and a relatively great deal of knowledge is available about the internal connections in these regions, and how their signals are processed. Yet no generally accepted** ideas exist on their "function", or what these regions "actually do". Less satisfactory still, the meaning of "their function" or "what these regions actually do" is unclear; it might be something akin to: "their role in behavior", "their role in higher functions", "how these regions contribute to survival" or "their integrative functions in the cerebral circuitry".

My own opinion: 1) It must be made clear what is meant by "what CNS parts do". 2) The most important and vaguest point in the investigation of what systems do, is the amount of *a priori* knowledge available. I think that the amount of generally accepted *a priori* knowledge for many CNS regions is as yet too small to gain generally acceptable *a posteriori* knowledge experimentally on what these parts do, at least at the level at which most investigators are seeking knowledge.

* "*A priori* knowledge" is used in the meaning "knowledge available before the investigation was started"; this is usually identical to "knowledge settled experimentally in earlier experiments"; consequently, "*a posteriori* knowledge" is "knowledge gained from the current experiments".

** "Generally accepted" and "generally acceptable" mean "accepted by" and "acceptable to" the forum of scientists (cf. Swazey and Worden 1975) considered to be the most qualified to judge the relevant statement.

Treatments and inferences. Knowledge of what kind of system one is dealing with is a necessary but not sufficient condition for the understanding of the effects of treatments such as lesions or electrical stimulation (cf. Gregory 1961, Weiskrantz 1978, Divac 1979). One is however often confronted with the vicious circle of infering what a part of the CNS does from the effects of treatments. In general it is difficult to infer what the normal function of a part of the CNS is from mal-functioning after its stimulation or destruction (cf. Gregory 1961, Teuber 1968, Weiskrantz 1968, Zülch 1975, 1976, Schoenfeld and Hamilton 1977). In any case, the function of a part of the CNS is not simply all the activities that are disturbed after it has been manipulated; in a system as complicated as the CNS, a complex relationship has to be expected between the function of an element and the effects of its manipulations.

My own opinion is that manipulations of the CNS such as electrical stimulation, lesions and chemical manipulations may give a global impression of which activities the part of the CNS under investigation is involved in. Conclusions about its "function" require a more refined analysis however (see below).

Assumptions considered as *a priori* knowledge. In neuroscience, it is possible to detect many implicit assumptions on how the brain handles information and generates behavior; such assumptions underlie investigations of the function of a CNS part in which specific experimental situations are used to test the effect of manipulations. These underlying assumptions are however not tested and, even worse, often not generally accepted, although the value of the experimental results and of the hypotheses and theories based on these results depends critically on the truth of them. *"Understanding ... (of the cerebral cortex) is still woefully deficient. This is partly because it is very complex, not only structurally but also in its functions, and partly because neurobiologists' intuitions about the functions have so often been wrong ... To speculate broadly on how the brain may work is fortunately not the only course open to investigators. To explore the brain is more fun and seems to be more profitable."* (Hubel and Wiesel 1979). Some cell types found already in the retina (Cleland and Levick 1974a,b, Stone and Fukuda 1974) were not foreseen by the extremest brain model builders, which is a warning against other speculations on how the brain should work.

My own opinion is that the chance to do generally acceptable statements on the CNS's working increases when such statements are based only on a few underlying assumptions which must be generally accepted.

Brain and behavior. Many investigators are interested in the question of how behavior is generated by the brain, and in "complex behavior" as studied by the ethologist or psychologist. It must however be admitted that how the brain generates "complex behavior" is unknown: the limit of our present knowledge is that a number of brain regions are involved in single behaviors, but in most cases not exclusively. Very little attention will be devoted here to learning: a good deal has already been said implicitly above under the subheading "Assumptions considered as *a priori* knowledge". Many models of learning have been proposed, but as yet no CNS region has been found which does identical things as a subsystem of one of these models, and there are no compelling reasons that such regions exist (see section 5.2.4, subheading "Model").

My own opinion is that the present knowledge on the representation of sensory and motor patterns is indeed growing, but the generally accepted *a priori* knowledge on how the CNS works and deals with information is as yet too limited to be a basis for generally acceptable *a posteriori* knowledge on the cerebral representations of behavior, and on cerebral mechanisms of learning.

The predicament of the neurosciences. In the course of time, neuroscientists have expressed doubts on whether the knowledge they wanted to gain is logically possible, and if so, have wondered how they could gain this knowledge. They were either impressed by the problem of understanding the brain with their brains, or they felt cheated by the tricks of the brain. In experimental brain research, the brain seems capable of being kind to its investigators (*"Thanks to its manifold capacities, moreover, (the central nervous system) is able to answer the most diverse 'leading questions' with a conciliatory 'yes' - even to postulates which are mutually exclusive."*, Von Holst and Von Saint-Paul 1963), or of being able to elude any critical test (*"... it is sometimes depressing to brain researchers to find how many ways the brain can solve a problem."*, Gazzaniga 1975). The effects of brain injuries in man *"are often subtle, elusive, require special tasks for their discovery, and even then might go undiscovered"* (Teuber 1959), while *"the neurological literature is full*

of bizarre effects that may be of clinical or diagnostic interest, but that remain entirely incomprehensible." (Weiskrantz 1968). Despite the doubts on whether the goal can indeed be reached *("What I suspect is difficult, indeed impossible, is to locate functional regions of the (central nervous) system."*, Gregory 1961), neuroscientists have been busy in tackling the brain in all possible ways. As a consequence of these investigations, it has been suggested that certain brain regions (such as the frontal cortex, hippocampus, septum, amygdala, the reticular formation or the central gray) are involved in many apparently incoherent activities: while the present generally accepted knowledge about them is limited, many unrelated hypotheses persist, and as yet no conclusive critical experiments can be envisaged, let alone carried out. In a theoretical paper on neuroscientific research, Swazey and Worden (1975) have suggested *"that the multidisciplinary nature of neuroscience introduces complications with regard to whether neuroscience is potentially an entity, or whether it is intrinsically a collection of sciences identifiable only on the basis of a common interest in research on the nervous system."*.

My own opinion is that for reasons of esthetics, neuroscience should be (or become) an entity; it is not so apparently at the moment. Although the opinions tend to converge as far as brain regions up to the first cortical relay area, and some motor systems are concerned, the current "theories" about other brain regions are a series of rather speculative guesses.

Final introductory remarks. Neuroscience is confronted with conceptual and experimental problems. In the remainder of this chapter, I will suggest certain solutions to some of the conceptual problems; some of these solutions are not original but have been suggested previously by others.

5.2. Conceptual framework.

"Defining concepts is frequently treated by scientists as an annoying necessity to be completed as quickly and thoughtlesly as possible, ... (but) systems thinking, if anything, should be carried out systematically."

(Ackhoff 1972)

5.2.1. "MEANING", "REPRESENTATION" AND "EXPLANATION"

Introduction. The fundamental concepts "meaning" and "explanation" are used ambiguously in discussions about structure and function in biology (cf. Hospers 1967, Pattee 1979, Walter 1979). In this book however, these concepts are used only in the meanings mentioned below.

Meaning. In this book, the use of the word "meaning" will be restricted to "what signals, symbols and words and sentences stand for" (cf. Tavolga 1970, Cullen 1972, Hinde 1972), i.e. things that convey information, and the transmission of this information has either "evolutionary value" (see p.240), or is the "purpose" (see p.242) of the sender and/or receiver. Other meanings of "meaning" will be denoted by the corresponding terms (cf. Hospers 1967, pp. 11-12).

Meaning of words/sentences. Even the concept "the meaning of man-made signs such as words or sentences" is ambiguous, as will be illustrated by the following example. If an ancient manuscript is found, but nobody knows what the signs stand for, does it have a meaning?* This problem can be solved, if one is clear about the "meaning of meaning". If you say: "these are man-made signs standing for words, and they therefore have a meaning

* This question is comparable to the question whether the sound of a falling tree exists, if nobody hears it (cf. Hospers 1967, p. 37).

of some sort" (cf. Hospers 1967, p. 20), the ancient manuscript has by definition a meaning. On the other hand, if you say: "nobody knows what these signs stand for, and they are therefore meaningless, do not have a meaning", the manuscript does not by definition have a meaning. Clearly, even in the case of man-made signs, one has to distinguish between meaning as an intrinsic property of signs, and meaning as a property attributed to signs by cognitive being (cf. MacKay 1969). This distinction is necessary when we deal with the question of what is represented by neural messages (section 5.4, p. 260).

Representation. The element (or set of elements) A is said to be a representation of another element (or set of elements) B, when A stands for B.
Notes:

1. This definition is in line with the definition of MacKay (1969).
2. The set of elements B (and consequently A) are not necessarily an entity, or system (p. 230).
3. A is a representation of an aspect of B. For instance, a blackbird's image can be represented in the optic tract, and the blackbird's song in the auditory nerve.
4. B can be represented in various ways: for instance the image of the blackbird can be represented chemically (on a photograph or film), magnetically (on a video-tape), electromagnetically (as light), or by a spatio-temporal pattern of action potentials (which is again different in the optic nerve in the CGL, and in cortical area 17). These various representations can have an identical (or similar) information content, and they can be transformed ("translated") into one another.
5. "Representation" and "meaning" (see above) are related concepts, but "representation" has a broader meaning:
   1) The meaning of the word "blackbird" (A) is the thing blackbird (B): A means B, and A is a representation of B.
   2) Light waves reflected from a blackbird (B) form the light-image (A) of the blackbird: A is a representation of B, but one will not be inclined to say "the meaning of this reflected light is the thing blackbird", and this is in any case not the meaning of "meaning" as used in this book (cf. section 5.4, alinea "The meaning of neural messages").

Explanation. "Explanation" is used here in the meaning of "law-covering explanation", which is considered to include every "scientific explanation" (Hempel 1965). Explanation is the answer to a particular class of "why-questions" (Nagel 1961, Hospers 1967, p. 240). Consequently, I deal only with "explanation of biological complexity" and "explanation of beauty" (Pattee 1979), if this is rephrased into a "why-question".

5.2.2. CONCEPTS IN SYSTEM ANALYSIS

System = a collection of two or more elements with a non-empty set of relationships between the elements such that the investigator can regard the collection as an entity as far as the aspect investigated is concerned.

Notes:

1. This definition is in line with most definitions of "system" (cf. DiStefano et al. 1967, Klaus 1969, Ackhoff 1972), this concept "system" is identical to "object" of Sagasti (1970).*
2. The elements and therefore the system can be abstract or physical.
3. "Entity" is a elementary concept, which cannot be defined without circularity.
4. Element E_1 has a relationship with element E_2, when the state of E_1 influences that of E_2 (and/or vice-versa); such influences can for instance be a flow of material, energy or information, or E_1 and E_2 can be parameters in coupled equations (cf. Klaus 1969, Sagasti 1970).
5. "System" is a concept set up by an investigator: he can freely choose an object and a level of investigation, but having made his choice, he is no longer free to set the boundaries of the system under investigation. For instance, (see fig. 45), he is allowed to choose either S_1, or S_2, or S_3 etc. as the systems he wants to investigate because these can be considered as entities. But he may not regard either S_1 and S_3 (omitting S_2), or S_4 and S_7 as systems.

* This and other definitions of this chapter are derived from these authors, and Gilbertson 1968 and Woodfield 1976.

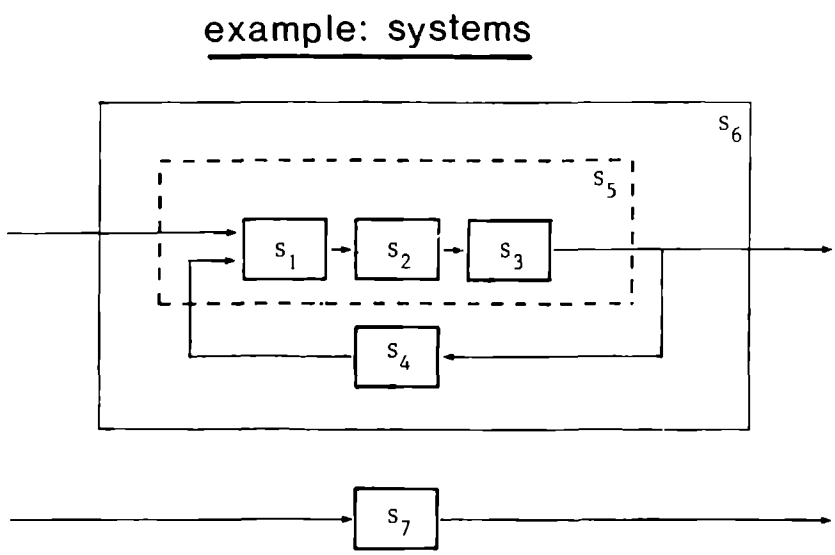


Fig.15 Diagram indicating which elements (subsystems) may or may not be considered as a system (entity) (see the text under "system", note 5).

6. In the CNS, no sharp demarcation lines exist between parts that are still sensory, integrative, or yet motor; so strictly speaking, the demarcation of a sensory system is arbitrary. Taking the visual system as an example: are all the regions receiving input from the cortical areas 17 and 18 still visual? The "visual system" is therefore not demarcated. The unambiguous use of systems concepts requires the demarcation of the systems investigated: in "visual system" the word "system" is used loosely speaking; in this book, the word "system" will only be used in the above mentioned narrowly defined meaning.
7. "Elements" and "subsystems" are interchangeable concepts.

Environment = the collection of elements, not belonging to the system, which have relationships with elements of the system.

Surroundings of an organism = the environment of that organism.

Notes:

1. When a part of the CNS is the system under investigation, other

parts of the CNS, other organs, or the surroundings of the organism are the environment of the system depending on the level of investigation (cf. section 5.3). On the other hand, when an organism and part of its surroundings are the system under investigation, the remaining parts of the surroundings are the environment.

Structure of a system = the collection of relationships between the elements of the system

Notes:

1. This definition is identical to those of Gilbertson (1968), Klaus (1969) and Sagasti (1970).
2. Structure is an abstract concept in abstract as well as in physical systems.
3. In everyday use, the word "structure" is ambiguous, meaning either the above mentioned concepts "system" (for instance building or part of the CNS) or "structure"; in this book, the word "structure" will only be used in the above mentioned meaning.
4. "Structure" is identical to "organization" (Klaus 1969), but only the word "structure" will be used here.
5. By definition, "structure of subsystem S" (of the nervous system) has a broader meaning than "anatomical connections of subsystem S": "structure of S" means "the anatomical connections between the elements of S, and the influences between the elements of S".
6. In the CNS, the relations between the elements are not fixed, but continuously changing (adaptation, habituation, learning, extinction, compensatory action); this is called a "dynamic structure".

Input of the system = the state of one or more elements of the environment which causes a change in the state of at least one element of the system

Output of the system = the state of one or more elements of the system which causes a change in the state of at least one element of the environment of the system

TYPES OF SYSTEMS

Closed system = a system where all the relationships under investigation are relationships between elements of the system

Notes:

1. The environment of a closed system is empty.
2. Strictly speaking, a closed system cannot be known to an investigator outside it, because information about the state of elements of the system is output, and a closed system has no output.
3. The concept "closed system" is usually used less strictly; for instance, a thermostat-controlled room heating system is called a closed system (and could be described as a closed system), even though the state of (at least) one element of the system affects elements outside the system: i.e. the room temperature felt by the occupants of the room.
4. A closed system is sometimes called a "circuit", but the word "circuit" will not be used here.
5. The various subsystems of a closed system must be open systems, otherwise they would not by definition be parts of the complete system.
6. Forrester's world model (1971) is probably the best known example of a closed system.

Open system = a system with a non-empty set of relationships between the elements of the system and its environment

Notes:

1. Open and closed systems should not be confused with open-loop and closed-loop control systems (see below).

Oriented system = an open system with fixed input and output elements

Non-oriented system = an open system with elements that can be both input and output elements, depending on the state of the environment

Notes:

1. See Lewis (1970) for a more extensive description of oriented versus non-oriented systems; a non-oriented system was called "circuit" by Lewis (1970), but the word "circuit" will not be used here.
2. An example of an oriented system is a radio-receiver: the aerial is the input element, and the speaker or headphones the output element.

A radio that can be used both as a receiver and as a transmitter is partially non-oriented: the aerial can be an input or an output element; whether the aerial is an input or output element depends on the user of the radio, who is part of the environment of the radio-system.

Feedback system = a system consisting of 2 or more subsystems such that a single element E is both input and output element of subsystem S'

Notes:

1. Fig. 46 gives the general diagramatic representation of a feedback system S, where the elements E (or subsystems E) feed the output of S' back to the input of S'. In some definitions of a feedback system, the elements E are included in the feedback system (Gilbertson 1978), while in other definitions they are not (Klaus 1969), and in yet others they may or may not be included (DiStefano et al. 1967). In the definition presented here, the elements E are included, because the relationships between E and S' are of direct concern to the investigator, and they are therefore both included in the feedback system by definition. A comparable question is dealt with "Control systems" (pp. 243-246), where a distinction between control system and controlling system is proposed.
2. Feedback systems are "closed-loop systems", but the latter term will be avoided.

Control system = system to keep the value of a parameter of an element within preset limits in the presence of changes in the environment

Notes:

1. The only satisfactory definitions of control systems are teleological ones (cf. DiStefano et al. 1967, Gilbertson 1968, see below).
2. The solar system, for instance, maintains a number of the parameters of its elements constant (earth-day length, earth-year length). Yet this is generally not what investigators mean, when they refer to "control systems"; they have systems in mind that were designed (or evolved) to maintain stable values of parameters, such as thermostat systems be it man-made, or in homoiothermic animals.
3. The relevant teleological (or apparently teleological) concepts "evolutionary value" and "purpose" must initially be mentioned (section

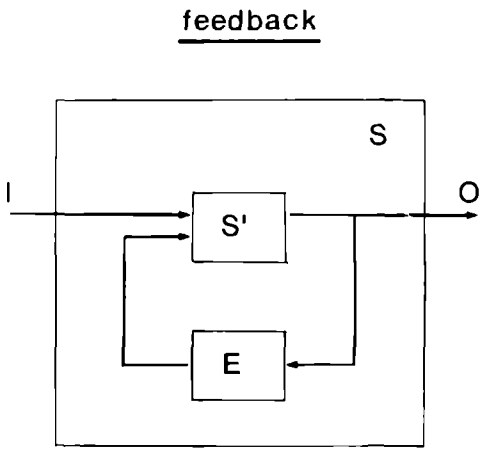


Fig.46 General schematic diagram of a feedback system; the feedback element E feeds the output of S' back into the input of S'; the system S is called a "feedback system".

5.2.4), to be followed by some remarks on control systems.

Network = a system with many input and/or output channels such that all (or many) of the input channels are connected (directly or indirectly) with all (or many) of the output channels

Hierarchical system = a system consisting of more than one subsystem; the structure of the system is such that one "higher" subsystem, S_H, controls one or more "lower" subsystems, S_L

Notes:

1. Large systems consisting of many subsystems tend to be unwieldy and difficult to control; a hierarchical structure however can allow such systems to be efficiently controlled (for example an army, or the animal's body, cf. Arbib 1975).
2. Hierarchical systems are especially less vulnerable, when each S_H controls more than one S_L (called "multiple control", cf. Dawson 1973).
3. A hierarchical structure is appropriate when S_H receives input of more relevance for the whole system than S_L does.

5.2.4. FUNCTION

1. Introduction

Introduction. The words "function" and "functional" are key concepts in the whole of this book and particularly in the present chapter. The need to define "function" has been felt by many authors, but only rarely has an explicit definition been proposed (cf. Von Holst and Von Saint-Paul 1963, Gregory 1961, Dawson 1973, Denny-Brown in Rasmussen 1975, Zülch 1975, 1976, Stein 1976, Schoenfeld and Hamilton 1977). The dictionary definition (Hornby 1976) of "function" is: *"the special activity or purpose of a person or a thing"*, leaving the word "function" ambiguous. I think that this ambiguity has confused the discussion on "localization of functions" in the brain. One thing is plain enough: in every meaning of the word "function", it is a characteristic of something or somebody.

Meanings of "function". Analysis reveals that the word "function" has at least 4 different meanings (cf. Luria 1966, 1973, Hospers 1967, White 1968, Klaus 1969, Sagasti 1970, Ackhoff 1972, Woodfield 1976):

1. Function$_1$ is the answer to the question "What does system S do?"
2. Function$_2$ is the answer to the question "Why did system S evolve?"; in this question, S is a part, property or activity of an organism, and in some cases S is the entire organism.
3. Function$_3$ is the answer to the question "What is the purpose of (animal) P in doing A?". Some authors consider that P must be human; this is identical to the teleological answer to the question "Why does (animal) P perform action A?".
4. Function$_4$ is the answer to the question "What is the purpose of object O, or of action A?"; this is identical to the teleological answer to the questions "Why did P make/use object O?" or "Why does P do A?" (function$_3$ and function$_4$ are clearly related).

The word "function" is used in yet other meanings. These are, however, less relevant for this book:

5. Mathematical function: "F is a function of x, or F(x)" means "a systematical relationship between x and F exists".
6. "Job" or the "activities and competences of a job"; for instance in the sentences "his function is minister" and "the functions of a minister".
7. The answer to the question "What is S good for?" (in a broader meaning than evolutionary value and purpose) e.g. "the function of war is that people start praying again".

Comments. Function$_1$ is a concept of a different order than functions$_{2-4}$: function$_1$ is a description of what S does, while functions$_{2-4}$ are explanations (cf. Hempel 1965; the corresponding questions are why-questions, or can be restated as why-questions). Function$_1$ (what system S does) can be an explanandum (Why does S do what it does?) for which the "mechanism" (see below) is the explanation. The functions$_{2-4}$ are, or seem to be, teleological explanations; function$_2$ may be of a different order than the functions$_{3,4}$, since function$_2$ can be reduced to purely causal statements, while, according to a number of philosophers, this is not possible for functions$_{3,4}$. These 4 meanings of "function" will be discussed to some extent below. To avoid ambiguity, the various meanings of "function" will be denoted by different words, and the word "function" will not be used again, except between quotation marks in certain special sentences.

2. "What does system S do?"

Types of system. The description of what system S does depends on what kind of system S is. The "function" of system S is generally related to what system S generates, that is to say to the output of S (cf. Sagasti 1970, Ackhoff 1972), but a problem arises in the treatment of closed systems.

1. Closed system. The answer to the question "What does closed system S do?" depends entirely on what one wants to know. This will be illustrated by Forrester's (1971) world model. In this model, one can calculate the values of a number of parameters over time (for example population or pollution) under unchanged policy, or after changes in population or pollution policy; the observed values over time are considered as output, and the change in policy as input. But the choice of input and output is however arbitrary: a closed system does what it does. No *a priori* reasons are available to determine which elements are inputs or outputs.

2. Open, oriented systems. If system S is an open, oriented system, the question "What does S do?" is answered by the relationships between inputs and outputs under specified conditions. Fortunately, subsystems of the CNS are indeed open, oriented systems (cf. section 5.3); since this is so, the description what oriented systems do will be elaborated below (under "I/O-function").

3. Open, non-oriented systems. What an open, non-oriented system does, depends on its environment: such a system is more difficult to investigate than an oriented one (cf. Lewis 1970). A method of dealing with such

such systems will be mentioned below (under "I/O-function").

I/O-function (= function$_1$) of system S = the set of outputs of S given specified inputs and conditions

Notes:

1. This definition is in line with definitions of "function" of Klaus (1969), Sagasti (1970) and Ackhoff (1972).
2. "Conditions" are the states of elements of S; these conditions are also called "state variables".
3. The I/O-function can easy be expressed as a "mathematical function": the output of S is a "function" of its inputs and conditions: O = F(I,C).
4. For an open, oriented system, this definition of I/O-function can be directly applied; for a linear oriented system, the I/O-function is the transfer function (Klaus 1969).
5. For an open, non-oriented system, the inputs and outputs can be defined for each state of the environment, thereby defining an I/O-function for each state of the environment.
6. For a closed system, an I/O-function as mentioned above, is not defined. If one chooses to consider the values of certain parameters as outputs (and others eventually as inputs), an open system has effectively been formed, so that the I/O-function is defined in that case.
7. The I/O-function of S is completely determined by the structure of S, and by the I/O-functions of the elements of S.
8. The I/O-function is the relationship between all the (relevant) inputs and all the (relevant) outputs; an I/O-function is the effects of some of the inputs on some or all of the outputs, or of all the inputs on some of the outputs.
9. Where S is an animal, the I/O-function is the set of all stimulus-response (S-R) relationships, and an I/O-function is an S-R relationship.
10. The I/O-function is comparable with the "function of a tissue" (Luria 1966).
11. Where S is an animal, investigation of the I/O-function (S-R relationships) is what ethologists call "causal analysis" (cf. Hinde 1970, 1974).
12. The "sum of mechanistic operations" of system S (Dawson 1973) is identical to the I/O-function of system S; I prefer the term I/O-function,

because "mechanistic operations" sound mechanical, and because my intention is to propose a general description of the working of systems that can also be applied to abstract, mathematical systems, and to information processing systems (such as the CNS), whose workings are primarily understood to be information processing, independent of the physical representation* of the information.

13. A part of the CNS has a changing (dynamic) structure, and therefore a changing (dynamic) I/O-function.

Mechanism of a system's action = the way the system generates its output

Notes:

1. The mechanism of a system's action is the answer to the question "Why does the system do what it does?"; it is the causal explanation of the system's I/O-function.
2. The I/O-function of a system is explained (and determined) by the I/O-function of its elements, its structure and the laws describing the processes in the system; the mechanism consists of these 3 parts (cf. Hempel 1965).
3. In everyday usage, the word "mechanism" is ambiguous, meaning either "working parts of a system" (here called "elements" or "subsystems"), "structure", or "the way in which the system works" (the latter is the sole meaning of "mechanism" used in this book).

Model of a system S = another system, S', which is considered by the investigator to perform identically to S as far as the processes under investigation are concerned

Notes:

1. Given a system S with a known I/O-function (see above for the I/O-function of non-oriented and closed systems), many different models S' can be made with identical I/O-functions (cf. Klaus 1969, Lewis 1970). There are no *a priori* reasons (apart perhaps from simplicity) for prefering one model to another.

* See section 5.2.1 for "representation".

2. It follows from 1. that, if an investigator tries to localize a part of the CNS which has an identical I/O-function to that of a subsystem of his model, he is not able, *a priori*, to be sure that he is searching for something that actually exists.

3. "Why did system S evolve?"

Introduction. Investigators are continually amazed at the high degree of adaptation of organisms to their particular surroundings (habitats): it seems as if every part of an organism "serves the purposes of survival and reproduction". An early definition of "function" was: " «*A function of subsystem S' in organism S is to do (make) effect E* » *means: S' does (makes) E, and E is useful, in the sense, that if,* ceteris paribus, *E was not present (was not done) in S, then the probability that S would survive and produce offspring would be smaller than the probability that another S in which E is present (done), would survive and produce offspring.*" (formulation modified from Canfield 1963). More recently, however, arguments have been presented that natural selection works through the genes rather than through individuals (Hamilton 1964, Dawkins 1976); the following definition is therefore proposed.

Evolutionary value (= function$_2$) of subsystem S' in organism S = the mechanism by which S' caused or still causes an increase in the frequency of G+ genes which generate S' at the expense of G- genes which generate non-S'

Comments. A system S" is here defined in which the organism S is only a subsystem: S" consists of the breeding system of the organism and the biotic and abiotic elements influencing it. The system S" is a closed or a non-oriented system, but the frequency of G+ genes which generate S' can be regarded as the output of S" (see above). Given complete knowledge of the stochastic system S", the expected frequency of the G+ genes at any moment can be calculated. If the frequency of G+ genes has increased or is still increasing, the mechanism of this increase is called "evolutionary value".

Notes:

1. It is clear that the question "What is the evolutionary value of S?" only is meaningful if S is generated, at least partially, by genes. A rat's innate preference for dark places has evolutionary value, while a rat's learned preference to keep to the righthand side in a

maze has no evolutionary value.

2. A part, property or activity of an organism, and in some cases an organism itself can have evolutionary value. Individuals that are either sterile (male ants), or which are in other ways excluded from reproduction (for instance certain male baboons) can have evolutionary value, because their presence and activities increase the probability that other individuals in their breeding system which have a high probability of sharing "selfish genes" with the "unselfish" non-reproducing individuals will survive and reproduce.
3. The I/O-function of S is an intrinsic property of S: it is determined by the elements and the structure of S. The evolutionary value of S is an extrinsic property of S: it is determined by a larger system S" of which S is a subsystem.
4. The evolutionary value of S is the answer to the question "Why did S evolve?", and it is thereby also the answer to the question "Why does S exist?": the evolutionary value of S is the genetic (statistical) explanation of S (cf. Nagel 1961, Hempel 1965).
5. One must of course know what S does (I/O-function) before one can determine its evolutionary value.
6. In biology, the question "What is the function of S?" often means "What is the evolutionary value of S?" (cf. Nagel 1961, p. 19, Hinde 1975, Woodfield 1976). The answer to this question is however often expressed in the form of a "shorthand" in which a great deal is left implicit. In the statement "The function of the heart is to circulate blood" for instance, the reader/listener is assumed already to know why it is good for an animal's survival and reproduction that its blood circulates.
7. In this definition, a strictly causal formulation is used for evolutionary value; all teleology is removed from the concept (cf. Woodfield 1976).
8. Not all parts of an organism have to have evolutionary value: some parts may evolve and persist by chance.
9. In some cases, the emergence and existence of S cannot be explained by the properties of S, but by the properties of another system S'; this applies to the case where both S and S' are generated by the G+ genes.
10. The concept of "evolutionary value" presented here is in line with Luria's (1966) first concept of "function"; in his concept, a biological task and the organisms' requirements were key concepts.

11. The concept "evolutionary value" is identical to the concept "function" (in both its strong and weak meaning, Hinde 1975) as used by ethologists (cf. also Hinde 1970, 1974).

4. "What is the purpose of animal P in doing A?"

The word "purpose" is ambiguous (Hospers 1967, p. 245), but in the heading above it means "conscious intent". A discussion on mind, consciousness, purpose, reason, and goal goes beyond the scope of this book; the reader is referred to the writings of the following authors: philosophers (Sommerhof 1950, Nagel 1961, Canfield 1966, White 1968, Woodfield 1976), the systems and information analysts (Sagasti 1970, Ackhoff 1972, MacKay 1972), ethologists (Hinde 1975) and neuropathologists (von Cramon 1978, LeDoux et al. 1979). Some comments on the relationships between "purpose" and "goal" will be made below under the subheading "Control systems once again".

5. "What is the purpose of object O, or of action A?"

The purpose of object O or action A depends on their designer, maker, user or performer, and therefore on their purpose; remarks about the purpose of individuals apply therefore to the purpose of objects and actions.

"Purpose" in this book. Relatively little attention has been paid to "purpose". This is intentional: my purpose was to develop a conceptual framework for the description of the CNS's working limiting myself to causal descriptions. Whether or not a complete description of the CNS's working can be made with purely causal (albeit stochastical) interactions depends on whether the CNS actually works purely causally (cf. section 5.1).

6. Structural and functional

It is not only the noun "function", but also the adjective "functional" which are ambiguous. For obscure reasons, "function" is often used as the opposite of "structure" (cf. Rosen 1972, Lahiri 1977); both "structural" and "functional" must therefore be defined.

Structural = of the structure
Functional = of the I/O-function

Notes:

1. In some papers, "structural" and "functional analysis" mean something similar to "analytic" and "holistic investigation" (cf. Rosen 1970, Lahiri 1977). In this book, the words "structural" and "functional"

are only used according to the above mentioned definitions, and "analytic", "holistic" and "levels" will be used in the definitions of Bunge (1977, cf. sections 5.3, 5.4 and 5.5).

2. Localizationistic brain theories are called "structural and functional" or "mechanistic" by Dawson (1973), but there are no compelling *a priori* reasons that a structural and functional analysis of the CNS must result in a localizationistic theory.
3. In ethology, "functional analysis" means "analysis of the evolutionary value" (Hinde 1975); in this book however "functional" is not used in that meaning.
4. "Functional" is often used in the meaning "teleological"; in this book, however, it is not used in that meaning (cf. Nagel 1961, Hempel 1965, Hospers 1967, pp. 244-246).
5. In this book, "functional" is only used when it can be replaced by "of the I/O-function".
6. In the present conceptual framework, the concept "functional system" is meaningless; when it is used by others, its meaning is unclear.
7. A nice example of the abuse of the word "functional" is given in section 4.4.

7. Control systems once again

Introduction. "Control system" has earlier (section 5.2.3) been defined teleologically: "a system to keep the value of a parameter stable". Now that "evolutionary value" and "purpose" have been discussed, some further remarks on control systems can be made. Such systems are either designed by organisms (as a rule man-made, for instance a thermostat controlled heating system), a part of an organism (for instance the blood pressure control system), or a system consisting of an organism and part of its surroundings (for instance a man-machine system).

Controlled element = the element to control which the control system has evolved or been designed

Controlling system = the control system apart from the controlled element

Goal of a control system = the state of the controlled element when between preset limits (setpoint)

Notes:

1. Strictly speaking we have a controlled parameter rather than a controlled element. A stable value of this parameter either has evolutionary value

or is the purpose of the designer of the control system.

2. A control system has evolved, or is designed, to keep the value of a parameter of an element stable. The controlled element can be defined only by reference to the genetic explanation of the system's existence.
3. Control systems can be either open-loop or closed-loop control systems (DiStefano et al. 1967, Milhorn 1966, Gilbertson 1968); closed-loop control systems are feedback systems, which can exercise better control. Control is called "better" when the state of the controlled element comes closer to a state that either has evolutionary value or is the purpose of the designer (cf. Lener 1972, p. 75).
4. In some definitions of "control system", the controlled element is included in the control system (as here) and in others not (cf. DiStefano et al. 1967, Gilbertson 1968, Klaus 1969). The concept of "controlling system" employed here is identical to some author's concept of "control system".
5. A control system (including closed-loop (feedback) control systems) is an open oriented system (cf. fig. 47 and see below).
6. The input of a control system is, in all cases, the effect of the environment on the controlled element (often called "disturbance"). In some cases the setpoint is influenced from outside the control system, while in other cases the setpoint is intrinsic to the control system.
7. The output of a control system is the effect of the state of the controlled element on the environment; such output exists for all control systems. When the control system is a part of an organism (e.g. the blood pressure regulator), the output of the system is the effect on tissues other than the sensors (i.e. the effect of the blood pressure on the body apart from on the barosensors). When the control system is an artificial system (e.g. a thermostat-controlled room heating system), the output of the system affects its user directly or indirectly (i.e. the occupant of the room feels the temperature).
8. Control systems have also been called "goal-directed systems", "goal-seeking systems" or "state-maintaining systems" (cf. Sagasti 1970, Ackhoff 1972).
9. The I/O-function of a control system is the relationship between the state of the environment and the state of the controlled element.

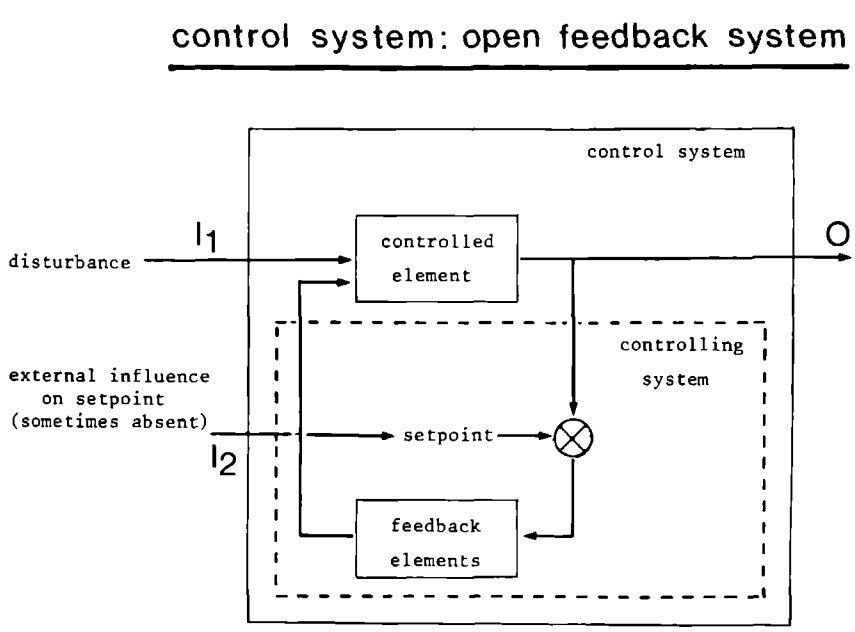


Fig.47 Schematic diagram of a control system, controlled element and controlling system; this representation differs from the conventional one, but the input and output are more clearly illustrated here (cf. Powers 1978).

Goal and purpose. The discussion on whether every purpose can be reduced to goals (as defined above), is related to the discussion on the universal validity of the causal principle. Apart from this discussion, attempts have been made to formulate behavioral criteria to distinguish purposive activities of conscious individuals from goal-directed activities of systems for which there are no compelling reasons for the attribution of consciousness (cf. Sagasti 1970, Ackhoff 1972, Woodfield 1976). The presence of various ways which a system can take to generate its output (i.e. to reach its goal) is sometimes taken as a criterium of a purposive (or purposeful) system; the later concept of "function" by Luria (1973) is in line with this concept.

What is controlled? By definition a control system controls a controlled element. To exercise this control, the controlling system must have at least one element whose state is a representation of the state of the

controlled element; such an element is called a "sensor", "feedback element" or "sensory system", and its state is called "representation", "neural representation" or "perception" of the state of the controlled element. As long as the sensors reflect the state of the controlled element accurately (and the control system works properly), the control system maintains the state of the controlled element and of the sensors within preset limits. If one does not know what the control system has been evolved or made for (evolutionary value or purpose), one cannot distinguish the controlled element from the sensors. Strictly speaking, the only thing that matters for the controlling system is the state of the sensors: the controlling system itself cannot know whether the state of the sensors is an accurate representation of the state of the controlled element or not (for instance, goal-directed human behavior is performed until the achievement of the goal is perceived, whether or not the goal is actually reached). The control system exists however to control the controlled element, or in other words the effects of the controlled element on elements other than the sensors (i.e. the output of the control system) are part of the genetic explanation of the control system. Consequently, the statement "behavior controls perception" (Powers 1973, 1978) is as true - but also as irrelevant and as misleading - as the statements "a thermostat-controlled room heating system controls the state of the room sensor" and "the blood pressure controlling system controls the barosensors".

5.3. System analysis, the CNS and behaving animals.

"The nervous system is a system, so it has to be investigated as a system."

"Systems" in neuroscience. A system analysis of the CNS implies a subdivision of the CNS into subsystems (unless one wants to consider the whole CNS as a black box). A number of subdivisions have been proposed in the various disciplines in the neurosciences (see below); these "subsystems"* will be mentioned more extensively, because the assumptions and limitations of each experimental approach are closely connected with the "systems" distinguished in each approach.

1. So-called "functional systems" (physiology)
   - . sensory systems: visual, auditory, somatosensory, olfactory, etc.
   - . motor systems: locomotor, oculomotor, etc.
   - . endocrine CNS systems
   - . regulatory systems: respiration, blood pressure, thermoregulation
   - . integrative systems: the remainder of the CNS

   Note: these so-called "functional systems" cannot be demarcated in the CNS except arbitrarily (cf. sections 5.1.2, 5.5.5 and 5.5.).
2. Cell groups and their connections (anatomy)
   - . nuclei, brain regions and cortical areas
   - . groups of nuclei, regions or areas, for instance "limbic system", "extrapyramidal system", hypothalamus, thalamus, amygdala, reticular formation

* - A number of the "systems" mentioned here are not in fact "systems" according to the definition given in section 5.2.2.
- In some cases, a "system" mentioned for one discipline is also used in other disciplines.

Note: anatomical and histological methods (in particular experimental methods) have been successfully used to demarcate entities of the CNS (subsystems); it is sometimes questionable, indeed unlikely, whether some anatomically defined "systems" are in fact entities (cf. "limbic system", thalamus, reticular formation, section 5.1.2).

3. Cells containing a specified compound (neurochemistry)
   . GABAergic, cholinergic, enkephalinergic systems
   . interactions between neurotransmitter systems
   Note: techniques are available for the demarcation of the set of neurons containing certain specified compounds, but it remains dubious whether these neurons together are an entity (cf. section 5.1.2).
4. Systems of behavior (ethology)
   . aggression, reproduction, feeding systems
   . relationships between these systems
   Note: systems of behaviors and stimuli can be demarcated; behaviorally defined systems of stimulus-response relations (or more extensive behavior systems) must exist within the CNS, but these systems are not necessarily localizable (sections 5.1.2 and 5.5).
5. Systems (models) of mental activities or of interfering variables in behavior (psychology, psychophysics)
   . perception, learning, motivation, emotion, reward, punishment
   . short-time memory
   Note: Since it is uncertain whether the CNS in practice works in the same way as these theoretical models, it is uncertain whether the subsystems of these CNS models actually exist in the CNS (cf. sections 5.1.2 and 5.2.4).

Application of the conceptual framework to the CNS: entities in the CNS. A conceptual framework, as presented in section 5.2, can be either circular (or in other words "analytic", "consistent" or "necessarily true", cf. Hospers 1967, pp. 160-208) or non-circular (in which case it is inconsistent and false). Since I have tried to develop a consistent (necessarily true) conceptual framework; I hope that the concepts "entity", "system", "relation", "structure" and "I/O-function" are circular When these concepts are used as concepts describing physical objects, however, the conclusions about the physical objects are no longer necessarily true, and they cannot be necessarily true, at best they are generally accepted. For instance, objects that are today considered to be entities,

might tomorrow be considered as sets of unrelated elements. When we want to apply this framework to the CNS, the basic question is "Which parts of the CNS are entities (or systems)?" or "On what grounds do we consider parts of the CNS to be entities?". Elements that have relationships can be a system (definition section 5.2.2), and these relationships are the structure; in the CNS, "structure" means "anatomical connections and influences between the elements" (p. 232, note 5). Anatomically identified connections between A and B are a necessary condition for regarding A and B as a single system. In the CNS, one should be cautious in regarding A and B as an entity, in cases where manipulations in A affect B; for in a network as complex as the CNS, a manipulation somewhere in the system might be reflected throughout the system, and it is therefore premature to regard A and B as a system on the basis of the effects of A on B, or of similar effects (so-called "functional" relationships). For neurons have relationships in but one way: by having connections, so the presence of anatomically identified connections is the most important criterium for considering CNS regions as a system.

Levels in neuroscience. In this book, "levels" (cf. Bunge 1977) in neuroscience as mentioned below have been distinguished. I have chosen these levels which are related to the anatomy of organisms, because the distinction of these levels is based on fewer assumptions than levels related to a model of behavior or brain activity (cf. Powers 1973).

- molecular level: interactions between compounds in the nervous system
- cellular level: interactions between neurons
- regional level: interactions between nuclei or cortical areas
- organ level: interactions between the nervous system and other organs
- behavioral level: interactions between the organism and its surroundings (including other organisms)

Comments on "levels". A simplified diagram of these levels is given in fig. 48. If one chooses to investigate a CNS nucleus (S_2) for instance, the various levels are as indicated in fig. 48. Even also the largest system S_5 (the "surroundings" or the "whole world") can however be completely described at the molecular level; and the systems S_3 (CNS) and S_4 (animal) can be completely described at the molecular, cellular and regional levels. But if a system S (other than S_5) is chosen as the system for investigation, investigation of S at a higher level implies taking account of a physically more extended part of the environment of S. The

simplified diagram: levels in brain and behavior

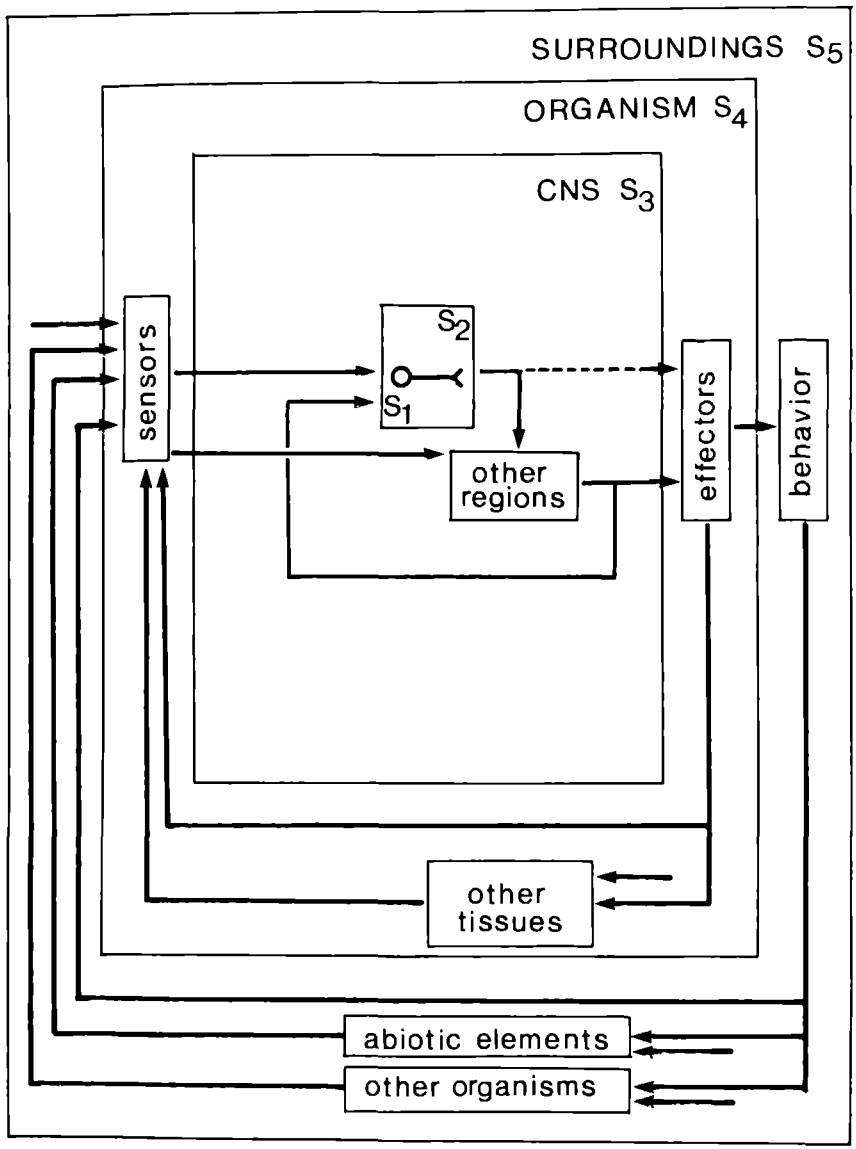


Fig.48 Diagram to illustrate the various levels in the application of system analysis to the CNS and to behavior

different levels will be discussed more extensively below, and their application is indicated in section 3.2.1 (fig. 40, pp. 140-141).

Cellular level: the neuron as a system. A neuron can be regarded as an open oriented system, whose input elements are the receptors on the membrane, and whose output elements are the vesicles from which the neurosecrete is released. The concept of the dendrites and the cell body as the input part (receptive part), and the terminals as the output part had to be revised. The input elements, the receptors, are located on the dendrites, the cell body and the terminals; the compounds which normally react with these receptors are neurotransmitters or hormones. The output elements, the exocytotic ("synaptic") vesicles, are located in synaptic and non-synaptic terminals, and possibly in some neurons in the dendrites. The concept of a neuron as an oriented system should perhaps be refined on some points: 1) the neurotransmitter affects both the terminals from which it is released, and its own release, and 2) although in the normally working CNS the axons transmit action potentials in one direction only, they also transport information-carrying molecules in the opposite direction. In general, however, the concept of the neuron as an open, oriented system seems to be valid.

Regional level: a CNS region as a system. A set of neurons can be regarded as a system, when they are related in such a way that they can be considered as an entity. These relationships concern input and output; such input-output relationships can be defined and determined either anatomically or physiologically; the generally accepted subsystems of the CNS are entities on both anatomical and physiological criteria. For instance, it is generally accepted that the retina, the CGL and the cortical area 17 are systems, and similarly it is possible to consider either the retinal ganglion cells or a subgroup of them as a system; the X- and Y-cells are regarded as systems, but the W-cells probably are a set of unrelated systems (Cleland and Levick 1974a,b, Fukuda and Stone 1974). When a CNS region is accepted as a system, it is an open, oriented one with distinct afferent and efferent fibers (or other types of input and output). Examples of CNS subsystems whose outputs are much more relevant than their inputs are the circadian pacemakers, which can operate freely in the absence of external circadian signals; there is however an input to these pacemakers, since a reversal of the light-dark period reverses the circadian rhythm.

The nervous system as a system (supraregional level). The nervous system is a single system, consisting of many subsystems, none of which is completely independent of the others: the nervous system is an entity. It is an open, oriented system, with sensory and hormonal inputs, and with motor and hormonal outputs. The nervous system is a network: every input channel can, in principle, affect every output channel. Some parts of the nervous system are however relatively independent such that they can be treated on a first approximation as being independent; examples of such subsystems are those parts of the nervous system involved in the initial stages of processing sensory information, and certain controlling systems involved in the regulation of the body temperature, blood pressure, pupil diameter etc. The nervous system is often considered as a hierarchical system, consisting of a further number of hierarchical subsystems. Hierarchical signal processing is particularly evident in the output parts of the nervous system: in the spinal and supraspinal control of movements; in this case, it is clear which system is the controlling system and which the controlled one. Whether a "highest level", a "definitive leader", exists is uncertain. The nervous system is probably a *heterarchy* at a high level (Arbib 1975): at one moment A controls B, and at another moment B controls A. Heterarchical signal processing is particularly appropriate, when no *a priori* information is available on which input and output channel is the most relevant for the system's goals.

Organ level: the animal as a system. In many cases, one does not want to study the CNS in isolation, but the whole animal. When the animal's boundaries are chosen as the system's boundaries, the system is open and oriented: its input is sensory information (often called "stimulus"), and its output movements ("response" or "behavior") and other effector-mediated processes (e.g. emission of olfactory signals, blushing and so on). When the system under investigation is the entire animal, the effects of the CNS on the body, and the effects of the various organs on the CNS must be considered. The subsystems of the animal, its organs, are open and often oriented. Some parts of the body together with parts of the CNS form control systems which regulate parameters such as the blood pressure, muscle length and body temperature.

Behavioral level: the animal and its surroundings as a system. Many of the activities of an animal can only be understood, when the effects of these activities on the animal's sensory input are also taken into account.

The animal is, in this respect, a controlling system (goal-directed, or purposive), and the controlled element is an element outside the animal (e.g. a teritory of a certain extent, or the absence of conspecific males there). In other words, such behaviors can only be understood when external goals are attributed to the animal; these behaviors can resemble the goal-directed activity of an artificial feedback system (cf. MacKay 1972, Powers 1978). For example, "... *signalling would be considered goal-directed, if the effect of the sender's behavior on the receiver was monitored by the sender in such a way as to promote corrective action by the sender to maximize the signal's effectiveness*" (Hinde 1974, cf. MacKay 1972). Some authors would like to consider all behavior as goal-directed behavior (cf. Powers 1973, 1978), but it is questionable whether a feedback model can explain all behavior (cf. Hinde and Stevenson 1970). In any case, the description of an animal and a part of its surroundings as a closed control system, is only an appropriate model when no account is taken of a number of effects both of the animal on its surroundings, and of the surroundings on the animal. Any observation of a behavior which is not in line with the action of a control system might be explained away by assuming a "higher control system". Such assumption might be correct, but it can "explain" everything, or rather nothing until we can observe the goals of the "higher control system" independent from the effects it is intended to explain: such assumption is undesired in science.

5.4. The I/O-function of a CNS region.*

"Since a neural message makes sense,
we can therefore make sense of it."

I/O-functions and levels. At a low level, the I/O-function of system S can be formulated independently of the larger system S' of which S is a part. For instance, the I/O-function of a transistor S can be formulated independent of whether S is part of an electronic clock, a computer, an audio-amplifier, or is not built into any system at all. At a higher level (i.e. taking a physically more extended part of the environment of S into account), an identical transistor S has different I/O-functions, when built into different systems, or located at different places in the same system; a transistor in a computer may for instance be involved in memory, in addition, stabilizing the energy supply. In the nervous system, the I/O-functions of all cholinergic neurons at the molecular level are identical: excitatory input causes release of ACh at their terminals; this is the case for the motorneurons of flexors and extensors, the preganglionic cells of sympathetic and parasympathetic neurons and the septal neurons which project to the hippocampus. The I/O-functions of these neurons differ at a higher level: for instance, no general statement can be made about the effects of cholinergic neurons on behavior which is valid for all the above mentioned cholinergic neurons.

* The ideas of this section have been previously formulated by Johannesma, albeit in other words and with other emphasis; he stressed that neural messages can be interpreted by what they represent and generate outside the nervous system, or outside the organism.

The I/O-function of CNS subsystems. The I/O-function of a CNS subsystem *at the cellular level* is completely known, when all the afferent neurons, all the efferent fibers, and all the effects of the inputs on the outputs are known. There is a relatively great deal of generally accepted knowledge on the anatomy of the hippocampus and the cerebellum, and on how signals are processed in these regions (i.e. knowledge about the structure and the I/O-function of their elements). Yet despite this knowledge at the cellular level, there continue to be many apparently incoherent ideas on what these regions "actually do" (cf. Watson 1977, Ciba Symposium 1978). It is clear that a wealth of knowledge at the cellular level about a CNS subsystem does not necessarily solve the problem of what its "function" is.

The I/O-function of CNS subsystems at the behavioral level. When neuroscientists ask "What is the function of a CNS region?", they generally* want to know how this region is involved in the actions and reactions of the animal in its environment: they want to know the effects of this region on the animal or its behavior, i.e. to know the I/O-function of this region at the *behavioral level*, or in some cases at the *organ level*. The meaning of a description of "the I/O-function at the behavioral level" is as follows. The input of a CNS region is a neural message; a description of "the input at the behavioral level" is a description of "the content of the message, or in other words, what is represented by the message" (this is sometimes called the "meaning of a neural message" (Chung 1970), but see page 260). The output of a CNS region is a neural message; a "description of the output at the behavioral level" is a description of "the effects of the message outside the organism". Consequently, the meaning of "the I/O-function at the behavioral level" is "what is represented by the neural activity outside the animal, and what are the effects of the neural

* When neuroscientists ask the question "What is the 'function' of S?" they often also mean "What is the evolutionary value of the activity of S?"; "functional" questions and statements are frequently (quasi-) teleological too (cf. Luria 1966, 1973, Ruse 1973, Pattee 1979).

activity outside the animal?"*

Input: what is represented by neural activity? The first stages of information processing in the CNS are obviously related to sensory input. The relationship between properties of the stimulus and the activity of the neuron is described in terms such as "receptive field", "dynamic properties", "trigger features" or "this-or-that detector". The most rigorous steps to identify what it is that neural activity (action potentials) exactly represents, have been taken, to the best of my knowledge, by Johannesma's group (cf. Johannesma et al. 1973, Grashuis 1974): they determined the stimulus properties preceding an action potential of cochlear nucleus neurons, and often made successful predictions of the response to a complex new stimulus. Neural messages of some sets of neurons are nothing more than a representation of sensory stimuli, for instance the neurons forming the optic and acustic nerve. Other messages contain mixed information: they represent a combination of an external and an internal state; for instance, the action potentials of the Ia afferents from the muscle spindles represent a signal indicating a discrepancy between the actual and the set-point value of the muscle length (cf. also Andersson and Sjölund 1978). Fig. 49 is a theoretical diagram of representations of sensory stimuli. Note that in the real CNS, we find stochastic representations: an action potential represents a chance that a specified stimulus is present (Johannesma et al. 1973, Grashuis 1974). Moreover, since the CNS has a changing ("dynamic") structure, it will often change in time what is represented by the activity of a neuron.

* It is assumed that an I/O-function at the behavioral level can be formulated for all CNS regions, i.e. that each CNS region (often indirectly) has effects outside the animal, and that its activity is in some way related to the animal's surroundings. The reason for this assumption is that only a system S which is part of animal S' can have evolutionary value, if S has effects outside S' (cf. p. 240); so if CNS region S has evolutionary value, it must have effects outside the animal, and an I/O-function at the behavioral level.

diagram of representations of sensory stimuli

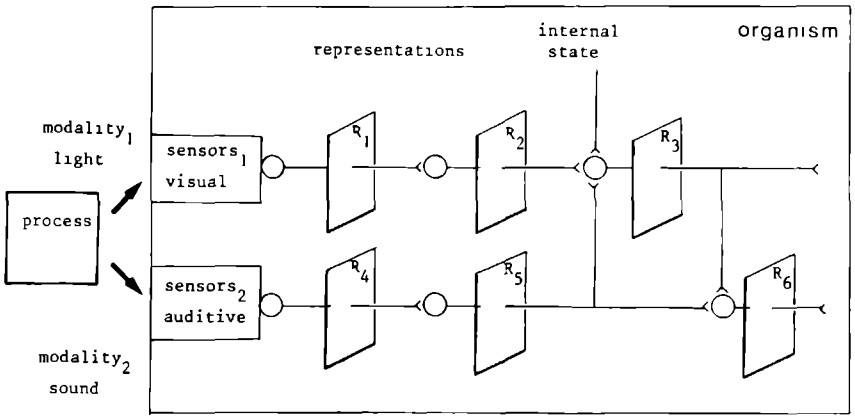


Fig.49 Diagram illustrating the transformation of representations: R_2 represents R_1; R_3 represents a combination of R_2, R_5 and an "internal state"; and R_6 represents a combination of R_3 and R_5

Output: what are the effects of neural activity? At the molecular level, the effects of neural activity are release of the neurotransmitter, and modifications in membrane molecules in the target cell; at the cellular level, the effects are excitation or inhibition (but see section 4.3, p. 173). At the organ level, the effects are contraction of the muscles, excretion of hormones, and changes in the activity of other organs. At the behavioral level, the effects are movements, other behavioral manifestations and the contribution of other organs to behavior. (At a low level, the effects are direct; at a high level, they are often indirect.) An example is illustrated in fig. 50. Visual stimuli have many effects, including for instance the regulation of the pupil diameter, eye movements, and verbal reports on what is seen. The effects of the message of the total optic tract are simply all visual influences on behavior. Parts of the CNS are identified the activities of which are primarily involved in the regulation of the pupil diameter or in eye movements.

diagram of the effects of neural messages

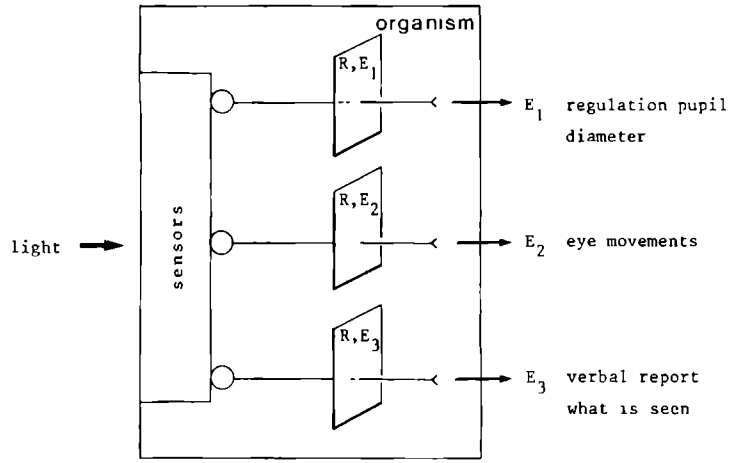


Fig.50 Diagram illustrating the various effects of neural messages, depending on the effector cells to which the message is sent

A theoretical example. Every neural message is a representation of something else, and has a certain (often indirect) effect on behavior. Investigating such a representation implies looking-back to what the cause of the activity is; investigating the effects implies looking-ahead to what is caused by the activity. This is illustrated in fig. 51: a neuron (for a CNS subsystem), N_4, receives 3 inputs and generates 3 outputs. The receptors on the membrane of N_4, and the cell body including the spike generating system, are considered as the system under investigation; the action potentials of N_4 are its output. It is possible to fully deduce what this output, R_4, represents from what its inputs (R_1, R_2 and R_3) represent, and from the effects of these inputs on N_4 (i.e. R_1E_2, R_2E and R_3E_1 at the cellular level). The effects at a level L of the activity of N_4 (R_4E) are fully deducible from the effects of the inputs at level L (where L is a higher level than the cellular level). The differential effects of N_4 (R_4E_1, R_4E_2 and R_4E_3) depend on the different regions to which the output is sent and on the effects of this output on these regions. This was a very

transformation of representations and effects

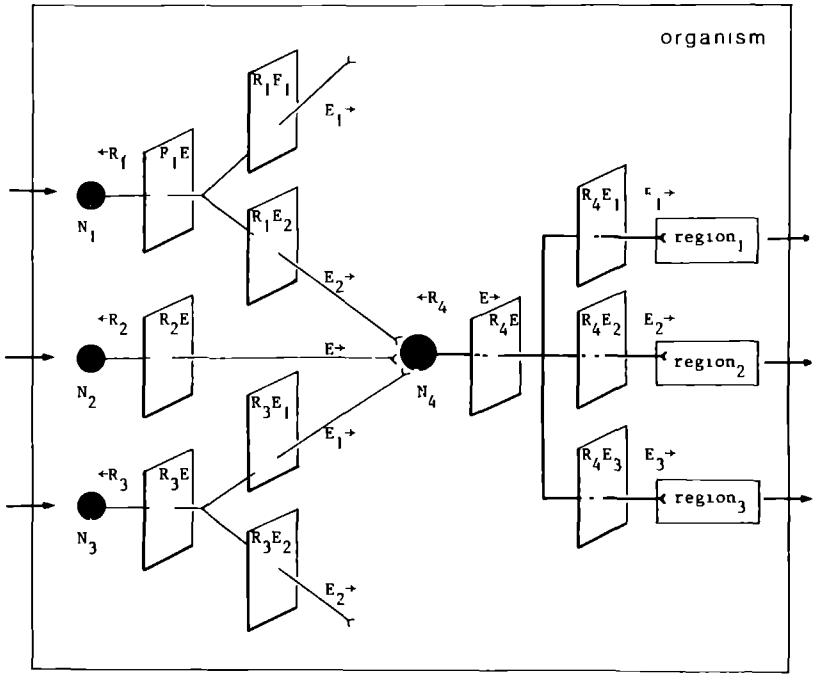


Fig 51 Diagram illustrating the I/O-function of CNS subsystems at the behavioral level the I/O-function at the behavioral level consists of a representation (being what the neural activity outside the CNS represents, or what causes the neural activity outside the CNS) and of an effect (outside the CNS).

simple example to illustrate the idea. I realize of course that the actual nervous system is much more complex, with many feedback loops occurring for instance, but in the case of feedback systems in the CNS as well as in artificial ones, one can unambiguously formulate what the signals represent. Having done single cell recording in the optic tract and in the primary auditory cortex, I know how difficult it can be to conclude what is represented by neural messages.

Examples of I/O-functions at the organ and behavioral level. Some examples of I/O-functions at the behavioral level, as interpreted from the literature, will be presented. These are primarily intended as illustrations; some examples may well be illustrative but incorrect. Attempts were already being made some 20 years ago to describe what is represented and generated at the behavioral level by neural messages in the frog's tectum (Lettvin et al. 1959); metaphorically, the "fly-detectors" say "there is a prey at that place; catch it". More recently, in view of the receptive field properties of cells which have been identified in the retina, the following hypotheses on what the effects of the activity of these cells could be, seem plausible. For instance, the "on-center sluggish sustained cells" (Cleland and Levick 1974a, Fukuda and Stone 1974) say "the retinal illumination, integrated over a certain area and over a certain time, is high; contract the pupil"; and some "direction-selective cells" (Oyster et al. 1972) say "the retinal foveal image is moving; make eye movements such that the foveal image becomes stationary". The Ia afferents are a more generally known example; since they are active when the muscle is longer than its set-point length, and cause muscle contraction, they effectively say "the muscle is too long; contract it". These are but a few of the examples that could be given. It should be noted once again that these I/O-functions are stochastical. In this book, I have made an attempt to describe the I/O-function of the locus coeruleus at the behavioral level (section 3.2.1).

The meaning of neural messages. I prefer to speak about "what neural messages represent" rather than "what neural messages mean". The reason for this distinction has already been indicated in section 5.2.1, and will be elaborated somewhat below. For instance, the word "table" stands for the thing table, and so the spoken word (sound) "table" therefore means the thing table (meaning is here used as "intrinsic property of signs"). Children however have to learn what the sound "table" means (meaning is used here as "a property attributed to signs by a cognitive being"). Based on my knowledge of the auditory nerve, I think the sound "table" is invariably represented in that nerve, whether or not the listener knows its meaning (intrinsic). The reaction to the sound "table", however, will be different when its meaning (intrinsic) is understood (cognition, cf. MacKay 1969); consequently, the process of learning the meaning of a word will be reflected as a change in the neural activity evoked by the sound "table"

somewhere in the CNS. It is a huge scientific challenge to detect these changes, i.e. to differentiate neural activity to which the organism (and therefore its CNS) does and does not attribute a meaning.

Complete knowledge? We have complete knowledge of the I/O-function of a CNS subsystem at the behavioral level, when we know what is represented and generated by its activity. All the inputs and outputs of the subsystem, and what is represented by all the inputs and generated by all the outputs, have to be taken into account. The nervous system is a network, where all the inputs can in principle affect all the outputs, and moreover, all the outputs can, directly or indirectly, influence all the input channels. Consequently, our knowledge at the organ or behavioral level of the I/O-function of a part of the CNS can only be complete when our knowledge of the whole CNS is complete. For the next decades at least, we have to be content with incomplete knowledge.

Analytic and holistic. My suggestion that neuroscientists want to know the I/O-function of parts of the CNS at the behavioral level combines elements from both analytic and holistic approaches. It is analytic, because an attempt has been made to explain the working of the whole system by its structure and the working of its parts, and also because I have implicitely recommended to limiting ourselves to those subsystems of which there is sufficient generally accepted *a priori* knowledge. The approach is also holistic, because the I/O-function of a part of the CNS is described in terms of the highest relevant level, i.e. the behavioral level. (In the present conceptual framework the I/O-function of a CNS subsystem is defined, completely independently of the results of experiments with lesions, electrical stimulation or chemical manipulation: this paves the way for future comments on "functional recovery", "functional take-over", "redundancy" etc. without circular argumentation.)

5.5. «The localization of functions» once again.

> *"What is ment by saying that some feature of behaviour is localized in a part of the brain? It cannot mean that the behaviour itself is to be found in the brain, or that a region of the brain can be sufficient for any behaviour. The intended meaning is that some necessary, though not sufficient, condition for this behaviour is localized in a specific region of the brain."*
>
> (Gregory 1961)

Introduction. "Function" is an abstract concept, being a property of a system. "Function" is not localized and logically not localizable: only physical systems are. My intention is to restrict myself to the cerebral representation of those "functions" which can be established experimentally. Consequently, the effects of the activity of a CNS subsystem must be observable, and the observed effect must be directly and unambiguously related to the "function" investigated; an output of the CNS must be observed, and in general an input and/or the actual conditions too. After a discussion of some examples, 2 conclusions will be drawn:

1. "Localization of function F" means "localization of CNS subsystem S having I/O-function F".
2. A necessary condition for the localization of system S is the specification of F in terms of inputs and outputs (and often conditions).

When there are lesions in the CNS, a CNS subsystem can do things that it would not have done without that lesion; for instance in deaf people, understanding of spoken language can be achieved through the visual system (i.e. lip-reading). To avoid such unnecessary complications, I will restrict myself here to "normal functions"* (cf. Luria 1966, 1973, Rasmussen 1975). Three examples with different degrees of complexity will be given (section 5.5.1).

* A paper dealing with "functional recovery" and "functional take-over" is under preparation.

EXAMPLES OF CEREBRAL LOCALIZATION

Example 1: respiration. *"Pavlov, when discussing the question of a «respiratory centre» was compelled to recognize that «whereas at the beginning we thought that this was something of the size of a pinhead in the medulla, ... now it has proved to be extremely elusive, climbing up into the brain and down into the spinal chord, and at present nobody can draw its boundaries at all accurately»."* (cited by Luria 1973). This must be expected for a network as complex as the CNS: if "localization of respiration" means "localization of all the CNS regions involved in, or influenced by, respiration", a great deal of the CNS would have to be included, much more than the original intention of the investigator. "Respiration" is too less specified for one to be able unambiguously to state what it is one wants to localize; but it is possible to localize, for instance, the system that is primarily involved in the regulation of the blood CO_2-level through respiration movements; and indeed a great deal is already known about its localization. Analoguously, the system that controls respiration during speech, or makes a patient exhale when requested to do so by the doctor, can be unambiguously demarcated. To conclude, system S with I/O-function F can be localized, if F is specified in terms of input and output (and often conditions too).

Example 2: vision. Let us suppose that we want to localize "vision", and that we agree that "localization of vision" means "localization of those CNS subsystems whose presence/activity is necessary for vision"; even in that case it is not clear what we want to localize, because the meaning of "vision" is unclear. For instance, after major damage to the occipital cortex, a patient can report seeing nothing, but his eyes can still make movements oriented to visual stimuli, which he denies "seeing" (Pöppel et al. 1973). It is most probable, that he can make correct eye movements thanks to intact connections from his eyes to the colliculus superior; the answer to the question "must the colliculus superior be included in the set of CNS regions necessary for vision?" depends on the meaning attributed to "vision". More puzzling still are experiments with split-brain subjects (Sperry 1974). The left hand of a human split-brain subject can successfully retrieve objects the written names of which were shown in such a way that they were only represented in the right hemisphere; yet the subject will deny having seen the stimulus and recognizing the objects.

"Is the right occipital cortex necessary then for vision?" The question "Is CNS part S necessary for vision?" is unclear, because "vision" is not sufficiently specific, unless specified in terms of input and output Examples are given below:

1. "Which CNS regions are necessary for reactions to visual stimuli?" The answer is simply all regions receiving a projection from the eye (and in many animals the pineal gland too).
2. "Which CNS regions are necessary for a differential reaction to complex visual stimuli?" The answer is the corpus geniculate laterale and the cortical areas 17, 18, and 19.
3. "Which CNS regions are necessary for naming visual stimuli?" The answer is probably the angular gyrus (Geschwind 1979).
4. "Which CNS regions are necessary for naming persons from photos of their faces?" The answer is probably the medial underside of the occipital and temporal lobes (Geschwind 1979).

Such question can now be answered, because the "function" to be localized has been specified in terms of an input (stimulus) and an output (response, reaction).

Example 3. intermale aggression. "Aggression" is restricted to intermale aggression here, because "aggression" is a group of heterogeneous behaviors, of which intermale aggression for instance is a homogeneous subgroup (Moyer 1968). This implies that a group of stimuli and movements can be demarcated that are related and can be regarded as an entity. the behaviorally defined intermale aggression system. In the CNS, there must be a unique group of spatio-temporal patterns of neural activity representing the intermale aggressive stimuli, and generating intermale aggressive movements. a unique CNS intermale aggression system must therefore exist. This is in any case a set of neural activities, but it is not necessarily a physical, localizable system such as a neuron, a group of neurons, a nucleus or a circumscribed region. A spatio-temporal pattern of neural activity must of course be activity of localized neurons, but these neurons may be involved in other activities too, which would make the concept "intermale aggression system" an incomplete and inappropriate describing term of the set of these neurons. Behaviorally, the input, output and part of their relationships are known, but the structure and the mechanism of the underlying CNS system is not known. Since there is no generally accepted knowledge of how intermale aggressive stimuli are represented in the CNS, and of how complex intermale

aggressive behavior is generated by the CNS, we do not know what we are looking for in search of the CNS intermale aggression system.

CONCLUSIONS ON CEREBRAL LOCALIZATION

The "localization of functions". "Localization of function F" means "localization of that CNS subsystem S which does F"; S can be localized when F is specified as I/O-function F. The questions to be answered experimentally become "Which CNS regions are involved in I/O-function F?" and "Which CNS regions are necessary for I/O-function F?"*. When S has been localized, the conclusion "F is the I/O-function of S" is not justified, but only the conclusion "F is an I/O-function of S".

Assumptions in cerebral localization. The story of attempts to localize behaviorally defined subsystems in the CNS is a history of failures to formulate generally acceptable theories identifying behaviorally identified subsystems to known CNS subsystems (i.e. the I/O-function F of model subsystem S is equivalent to the I/O-function F' of CNS subsystem S'), at best, CNS subsystems have been found to be involved in behaviorally defined I/O-functions F. This failure to formulate generally acceptable theories may be due to the choice of the wrong assumptions. the currently identified behavioral subsystems which are generally accepted may not be equivalents of the generally accepted currently identified CNS subsystems. (A theory that is not-generally accepted at present may however become the generally accepted theory in a few decades time.)

* Note that these are different questions: in a redundant nervous system, CNS region S can be involved in I/O-function F, while being not necessary for F.

The growth of knowledge in neuroscience. It is clear that the I/O-function of a CNS region S is related to the localization of the CNS subsystem with I/O-function F. They are related not only logically, but also as far as the growth of knowledge in neuroscience is concerned: the following phases can be distinguished in the practice of neuroscientific research:

1. As a first step, one tries to localize CNS system S necessary for I/O-function F (lesions, electrical stimulation and chemical manipulations being appropriate techniques).
2. As a result of such investigations CNS subsystem S appears as a rule to be involved in many I/O-functions F.
3. One tries to infer the I/O-function F' from these I/O-functions F.
4. In other words, one tries to formulate and investigate what is represented by the activity of the neurons of S, and what the effects of this activity are (single cell electrophysiology may be the appropriate technique, but it could be that simultaneous recordings of many single cells is necessary for this purpose).

5.5.3. *A PRIORI* KNOWLEDGE AND FUNCTIONAL STATEMENTS

In my view Gregory (1961) was correct with his remark *"To deduce the function of a part from the effect upon the output of removing or stimulating this part we must know at least in general terms how the machine works."* This idea has been formulated in more general terms: to conclude what a system does, the most important and vaguest point is the amount of *a priori* knowledge on the system (cf. Graupe 1972). In my opinion, the current *a priori* knowledge on the clearly sensory, motor and hormonal parts of the CNS can be a firm basis for functional investigations of directly related parts of the CNS. Current generally accepted knowledge on many other parts of the CNS is so limited, however, that functional investigations cannot at the moment lead to generally acceptable conclusions.

THE HUMAN LOCUS COERULEUS IN NEUROLOGY AND PSYCHIATRY.

6. Pathology (review of the literature).

SECTION 6. TABLE OF CONTENTS

SECTION 6. TABLE OF CONTENTS (continuation)

6.0. Introduction.

Introduction. Neuropathologists have been interested for many years already in the LC, which appears to be depigmented in idiopathic Parkinson's disease (Redlich 1930, Hassler 1938). Changes in the human LC and in the central NE transmission correlated with neurological and psychiatric symptoms will be reviewed in this chapter. The social relevance of LC research is closely connected with knowledge of diseases in which the LC is involved, and with knowledge of the treatment of these diseases; the findings in pathology will therefore be reviewed fairly extensively together with the treatment of the diseases.

Limitations in pathology. Attempts to draw generally acceptable conclusions from findings in pathology are limited for the following reasons.

1. Nosology. If one wants to identify the brain changes in a specified disease, one has to provide evidence that the disease really is a single disease, i.e. a nosological entity, or in other words, that the group of patients is homogeneous. A well-developed and generally accepted nosology of the diseases in which Parkinsonian motor symptoms are frequent, is available (section 6.2), while it is still rather weak for instance in the cases of the schizophrenias and dementias.
2. Diagnostic reliability. In the past decade, research criteria have been developed and used for the diagnosis in psychiatry (e.g. Feighner et al. 1972, Spitzer et al. 1975a, 1978). The use of such standarized criteria has undoubtedly increased the symptomatological homogeneity within a given group of patients of which the disease is given the same name, but this by no means guarantees that we deal with an etiologically homogeneous group: *"high (diagnostic) reliability is no guarantee of validity and there is no independent "test" of most of the diagnostic conditions"* (Spitzer et al. 1978). Many of the findings mentioned in this chapter are derived from patients, which were subjected to routine diagnosis, the reliability of which is often small (Spitzer et al. 1978).
3. The findings are often based on a small number of cases.
4. Names of diseases and symptoms are used inconsistently by various authors, and the meaning of these names changes in time. When an

author uses a word for which no currently used synonym is present (such as for instance "organic psychosis"), the word used by that author is also used in this book.

6.1. The LC and NE in development and aging.

Introduction. Knowledge of the state of the brain in developing and aging of individuals without neurological or psychiatric symptoms is a necessary condition for evaluating brain changes in various diseases. For a survey of the biochemistry, morphology and physiology of the brains of elderly people see Alvord et al. (1973), Domino et al. (1978) and Carlsson (1979). Prominent findings are that although the weight, cell count and content of various compounds decrease with age in a number of brain regions, other regions show minimal changes.

6.6.1. MORPHOLOGY OF THE LC IN THE DEVELOPING AND AGING BRAIN

Neuromelanin. The neuromelanin content of the LC increases linearly with time between birth and middle age (Mann and Yates 1974, 1979, Graham 1979); this neuromelanin is contained in granules within the LC cell bodies. Neuromelanin is also found in other pigmented nuclei (for instance the SN and the nucleus dorsalis motorius nervi vagi, actually these nuclei are pigmented by neuromelanin, section 1.1.1). In the LC of individuals aged 60 or more, clumping of neuromelanin and extracellular neuromelanin have been found, together with atrophy and death of the LC cells; in this respect the other neuromelanin-containing nuclei are similar to the LC (Mann and Yates 1974, 1979, Graham 1979). Because the increase in the neuromelanin content precedes the cell death, it has been suggested that cell death is caused by neurmelanin at high (toxic) levels in individuals more than 60 years old (Mann and Yates 1974, 1979, Graham 1979).

Neurofibrillary tangles. From the age of 30 years, an increase in the occurrence of "Alzheimer's neurofibrillary tangles" in the LC has been found (Alvord et al. 1973). These "Alzheimer's neurofibrillary tangles" appear to consist of paired helical filaments (PHFs), related to neurofilament proteins (Kidd 1962, Wisniewski et al. 1970, 1976, 1978). They are predominantly found in regions with monoamine (MA) cell bodies, and in the hippocampus and neocortex (Hirano and Zimmerman 1962, Ishii 1966, Tomonaga 1977a, Wisniewski et al. 1978). The LC is especially vulnerable

to pathological changes leading to PHF formation (Hirano and Zimmerman 1962, Tomonaga 1977a): no brain region has been described where the onset of PHF is as early as in the LC (Alvord et al. 1973). The PHFs are abundant in the brains of patients with presenile and senile dementia, but less frequent in arteriosclerotic brains (arteriosclerosis was considered to be a feature of "normal aging"; Ishii 1966, cf. section 6.3); PHFs have also been described however in the brains of asymptomatic individuals (Hirano and Zimmerman 1962).

Lewy bodies. In the LC of individuals aged more than 60 peculiar concentric hyaline inclusion bodies have been found, "Lewy bodies". Lewy bodies are predominantly found in regions with MA cell bodies (Ohama and Ikuta 1976); the implications of this finding will be reviewed more extensively in section 6.2.

Cell loss. Cell loss in individuals over 60 years has been noted in the LC and SN, the LC being the more severely affected (Alvord et al. 1973, Mann and Yates 1976, 1979). After age 60, the number of LC cells gradually decreases from 18,000 to 11,000, while cell loss in other brainstem nuclei was denied (although quantitative data were lacking; Brody 1976, Vijayashankar and Brody 1979).

BIOCHEMISTRY OF THE CENTRAL NE TRANSMISSION IN AGING

Not only a LC cell loss with age has been described, but also reductions in biochemical parameters related to the central NE transmission: NE levels (brainstem and hippocampus, Robinson 1975, Carlsson 1979), TH activity (amygdala, McGeer and McGeer 1976a) and ß-adrenoceptor binding (cerebellum, Maggi et al. 1979). The MHPG content and MAO activity (Robinson 1975, Carlsson 1979), and, unexpectedly, the CSF DBH content (Lerner et al. 1978) have been reported as increasing with age.

6.2. The LC and NE; diseases with frequent occurrence of Parkinsonian symptoms.

Introduction. The classical motor symptoms of patients with Parkinson's disease are 1) akinesia, 2) rigidity and 3) tremor at rest (reviews Hornykiewicz 1975a, Barbeau 1978). It was however recognized long ago that:

1. Parkinsonian symptoms can have various causes: they are symptoms of different diseases,
2. all of these diseases can be accompanied by other symptoms,
3. and all of these diseases (especially the early phases) can occur without Parkinsonian motor symptoms.

Classification scheme. The classification scheme* presented here is based on the nosological considerations of Beheim-Schwarzbach (1952), Stadlan et al. (1966), Bannister and Oppenheimer (1972), Alvord et al. (1974), Sung et al. (1979) and others.

1. Lewy body "disease"**: at autopsies of these cases, Lewy bodies are found in the LC, SN or nucleus dorsalis motorius nervi vagi (MotX) (Woodard 1962, Forno 1969, Forno et al. 1978, Hakim and Mathieson 1979); in 26-56% of these cases, Parkinsonian motor symptoms have been found.
2. Postencephalitic Parkinsonism: the criteria are: the presence of Parkinsonian motor symptoms, and a history of encephalitis lethargica. PHFs (paired helical filaments, "Alzheimer's neurofibrillary tangles") are present in the brains, but not Lewy bodies.
3. Degenerative diseases without Lewy bodies: the extension of the brain atrophy, and the regions involved vary: "striato-nigral atrophy" and/or "olivo-ponto-cerebellar atrophy", or "multiple system atrophy" (section 6.2.4).

* This classification is incomplete; for a more extensive classification, which would be beyond the scope of this section, the reader is referred to Korten (1969).

** It is somewhat erroneous to call this state a "disease", since many people with Lewy bodies in their brains are asymptomatical.

4. "Vascular Parkinsonism" Parkinsonian symptoms that can be ascribed to arteriosclerosis or infarction of the brain (Pollock and Hornabrook 1966, Bannister and Oppenheimer 1972).
5. Drug-induced "Parkinsonism". symptoms resembling those of Parkinson's disease can be induced by various drugs such as phenothiazines, reserpine or butyrophenones (Pollock and Hornabrook 1966, Robinson et al. 1979)

Parkinson's disease concomitant with Lewy body disease is called "idiopathic Parkinson's disease" ("paralysis agitans"), the types 3 to 5 are sometimes called "symptomatical Parkinsonism". It should be noted that these diagnoses can be settled with certainty only post-mortem, for this reason the disease with characteristic akinesia and rigidity (and often tremor) is called "Parkinson's disease" (and the patients are "Parkinsonian patients"), and only in autopsied cases the restrictive adjectives "idiopathic", "postencephalitic" and so on will be added

THE LC AND LEWY BODY "DISLASE"

Lewy bodies. morphology and composition. Lewy (1912) was the first one to describe spherical hyaline inclusion bodies in brain nerve cells in Parkinsonian patients. These bodies are now generally called "Lewy bodies" and they vary in size from 5 to 25 µm Lewy bodies have a eosinophilic core and a pale outer zone or halo (Greenfield and Bosanquet 1953, Duffy and Tennyson 1965). (For a survey of staining reactions and histochemical criteria to identify Lewy bodies see Greenfield and Bosanquet (1953) and Den Hartog Jager (1969).) Various forms of Lewy bodies with intermediate forms have been described, different forms have been found in a single patient (Forno and Norville 1976, Forno et al. 1978) None of these Lewy bodies is separated by a limiting membrane from its surrounding. The most frequent type of Lewy body in the CNS is the "filamentous Lewy body" (Duffy and Tennyson 1965, Roy and Wolman 1969, Forno 1969, Forno and Norville 1976, Forno et al 1978). The filamentous Lewy body consists of filaments of a diameter from 7.5 to 20 nm, which are closely packed in the core, and radiate outwards in the periphery. Filamentous Lewy bodies are surrounded by neuromelanin granules, and the filaments extend into the zone of these granules. (In Parkinsonian patients these neuromelanin granules have often lost part of their neuromelanin leaving a lipofuscin matrix behind (Forno and Alvord 1974).) The chemical composition of Lewy

bodies is still uncertain: on the basis of histochemistry either proteins (Lipkin 1959, Issidorides et al. 1978) or sphingomyelin (Den Hartog Jager 1969) has been proposed. It is also uncertain whether neuromelanin (see above), dense core vesicles (Watanabe et al. 1977) or protein vesicles (Issidorides et al. 1978) contribute to the formation of Lewy bodies.

Lewy bodies, occurrence and distribution. The findings of some authors (Greenfield and Bosanquet 1953, Bethlem and Den Hartog Jager 1960) seemed to indicate that Lewy bodies occurred only in the brains of idiopathic Parkinsonian patients. But now it has clearly been shown in studies in which hundreds of brains were investigated that Lewy bodies also occur in non-Parkinsonian individuals (Woodard 1962, Forno 1969, Alvord et al. 1973, Hakim and Mathieson 1979): in about 10% of the brains of individuals aged more than 60 Lewy bodies have been found, while only about 30% of these Lewy body-containing cases were Parkinsonian patients. When Lewy bodies were found in a brain, they were always present in the LC, and in only 66% of the cases in the SN or MotX (Forno 1969). Lewy bodies have only been found in the brains of individuals aged more than 60, except in cases with Hallervorden-Spatz disease (section 6.2.3). Lewy bodies were mainly found in central and peripheral CA cell bodies: the pigmented brain nuclei, sympathetic ganglia and adrenal medulla. They have also been found in regions without CA cell bodies (for instance the neocortex), but only in cases where Lewy bodies also occurred in the pigmented brainstem nuclei (Forno 1969).

6.2.2. THE LC AND NE; IDIOPATHIC PARKINSON'S DISEASE

1. Brain changes

Lewy bodies in Parkinson's disease. Lewy bodies have been found in (almost) all the brains and sympathetic ganglia investigated of (untreated and drug-treated) patients diagnosed as suffering "idiopathic Parkinson's disease" (Beheim-Schwarzbach 1952, Greenfield and Bosanquet 1953, Bethlem and Den Hartog Jager 1960, Duffy and Tennyson 1965, Stadlan et al. 1966, Den Hartog Jager 1969, Bannister and Oppenheimer 1972, Alvord et al. 1973, Ohama and Ikuta 1976). The association between Lewy bodies and idiopathic Parkinson's disease is so strong, that the presence of Lewy bodies is now considered to be the conclusive defining characteristic of idiopathic Parkinson's disease (Bannister and Oppenheimer 1972, Alvord et al. 1973, Sung et al. 1979).

Morphology of the Parkinsonian brain. A prominent characteristic of the brains of idiopathic Parkinsonian patients is depigmentation of the SN and the LC. Cortical changes characteristic for presenile dementia have also been described in association with idiopathic Parkinson's disease (Selby 1968, Alvord et al. 1973, Hakim and Mathieson 1979). Lewy bodies are most frequent in the SN, LC, MotX, the intermediolateral column, the sympathetic ganglia and in the adrenal medulla in idiopathic Parkinsonian patients; cell loss is also prominent in these regions. In the LC of idiopathic Parkinsonian patients a loss of small spherical protein-rich bodies has also been described (Issidorides et al. 1978), this may be a cause of idiopathic Parkinson's disease.

Neurochemistry in idiopathic Parkinson's disease. Apart from the cell loss in the SN and LC, a number of biochemical changes has been found in the brains of idiopathic Parkinsonian patients A considerable decrease in the content of DA in the SN and basal ganglia is well documented (cf. Ehringer and Hornykiewicz 1960, Birkmayer et al. 1977, Carlsson 1979), but a number of studies mention a decrease in the NE content* too (Ehringer and Hornykiewicz 1960, Sano 1960a,b (cited by Ohama and Ikuta 1976), Fahn et al. 1971, Teychenne et al. 1977). The largest loss of NE was found in the n. paranigralis and n. pigmentosus and their projection regions, while in the LC and its projection regions the decrease in NE content was moderate (Farley and Hornykiewicz 1976, cf. Birkmayer et al. 1974, 1977, amygdala, raphe and gyrus cinguli). Moreover, in cases with idiopathic Parkinson's disease, the tyrosine hydroxylase (TH) activity is reported as being decreased in the LC and its terminal regions (hippocampus, McGeer and McGeer 1976a, Riederer et al. 1979), the DBH activity in the LC is also reported as being decreased (Nagatsu et al. 1979c).

* Circumstantial evidence has been presented for a species-difference between man and rodents the homologue of the dopaminergic area ventralis tegmenti in rodents (with its projections to the n. accumbens and other regions, the so-called "mesolimbic DA system"), is probably noradrenergic in man, the n. paranigralis and the n. pigmentosus (cf. Farley and Hornykiewicz 1976, 1977).

2. Symptoms of Parkinson's disease

Introduction. My intention here is to relate the symptoms of a disease to the accompanying brain changes. For this purpose, attention has to be paid to the occurrence of the various symptoms. By definition, idiopathic Parkinsonian patients have the Parkinsonian symptoms akinesia, rigidity and tremor at rest. Idiopathic Parkinson's disease is a progressive disorder: the severity and the occurrence of the various symptoms increase with the duration of the illness, just as the brain changes correlated with them.

Intelligence (WAIS/IQ-tests) of Parkinsonian patients. WAIS-tests have been used on Parkinsonian patients (Asso 1969, Meier and Martin 1970, Loranger et al. 1972a). In the most extensive of these studies (Loranger et al. 1972a), Parkinsonian patients with symptoms of affective disorders, dementia or psychosis were excluded, although such symptoms are not uncommon in Parkinsonian patients (Mindham 1970, Celestia and Wanamaker 1972). Despite the exclusion of the most severely mentally impaired patients, severe intellectual impairment was detected in the remaining group of Parkinsonian patients (Loranger et al. 1972a). It is noteworthy that the intra-individual variation in the various WAIS scores was larger than that of the controls: the various intellectual activities seem to be affected to a differing degree. The most severely affected WAIS score was that on "perceptual organization" (Meier and Martin 1970, Loranger et al. 1972a). The intellectual impairment could not be attributed to the age of the patients, and only a part could be attributed to motor impairment. *"It seems that the Parkinsonians greatest difficulty is in comprehending and analysing novel or unfamiliar stimuli. His immediate memory span is also impaired, but to a less extend."* (Loranger et al. 1972a). In the same patients the scores "verbal" and "verbal comprehension" were normal. *"I would willingly say that a slight degree of intellectual disturbance is almost the rule in this disease"* (Ball, translated by Loranger et al. 1972a).

Dementia and depression in Parkinsonian patients. As Parkinson's disease progresses, the intellectual impairments become more severe, and the diagnosis "dementia" is made. The dementia in Parkinson's disease will be mentioned more extensively in section 6.3.2. A high incidence of depression (37-90%) has been reported in Parkinsonian patients (Mindham 1970, Celestia and Wanamaker 1972, Lieberman 1979); these depressions will be mentioned more extensively in section 6.6.5.

Vegetative disorders in Parkinson's disease. Vegetative disorders of which idiopathic orthostatic hypotension (Shy-Drager syndrome) is the most noteworthy, are often encountered in Parkinsonian patients (cf. Vanderhaegen et al. 1970, Appenzeller and Goss 1971, Bannister and Oppenheimer 1972, Rajput and Rozdilsky 1976, Sung et al. 1979). These disorders occur in patients with the pathological image both of Lewy body disease and of multiple system atrophy; in either case, they can occur together with Parkinsonian symptoms or separately. Such vegetative disorders have been related to Lewy bodies and cell loss in the spinal intermediolateral column, the sympathetic ganglia and in the adrenal medulla (Den Hartog Jager 1970, Thapedi et al. 1971, Schober et al. 1975, Rajput and Rozdilsky 1976, Vuia 1976, Castaigne et al. 1977, Sung et al. 1979).

3. *l*-Dopa-therapy* of Parkinson's disease

l-Dopa: DA, NE and Parkinsonian symptoms. *l*-Dopa is a precursor of the CAs DA, NE and E: *l*-dopa increases the turnover (or levels) of DA and NE (Bartholini and Pletscher 1968, Andén and Fuxe 1971, Fahn et al. 1971, Chalmers et al. 1971, Keller et al. 1974). Being a precursor of the active substances DA, NE and E, *l*-dopa can be therapeutically effective only when sufficient CA cells are present to synthetize DA, NE or E. Moreover, *l*-dopa has a direct (i.e. not via CAs) action on 5-HT neurons, causing a decrease in 5-HT levels (Pradhan and Bose 1978). *l*-Dopa appears to be very effective in the treatment of idiopathic Parkinson's disease: in most patients, the "extrapyramidal symptoms" (mainly akinesia and rigidity) declined, the survival time increased, and the quality of life of most of the sufferers greatly improved (Barbeau 1969, 1978, Yahr 1969, Cotzias et al. 1969, Birkmayer 1976). *l*-Dopa therapy *"can be regarded as a specific, though probably symptomatic, treatment of the main extrapyramidal symptoms in Parkinson's disease"* (Bernheimer et al. 1973); *"l-dopa's principal therapeutic effects ... are consistent with its transformation to DA in the striatum"* (Lloyd et al. 1975). The effects of *l*-dopa on intellectual performance in Par-

* Although about 1967, *l*-dopa has often been administered together with an inhibitor of peripheral (dopa-)decarboxylase (cf. Birkmayer 1976, Barbeau 1978), I will only mention *l*-dopa for simplicity.

kinsonian patients will be described in section 6.3.3, and the influence of *l*-dopa on depression will be mentioned in section 6.6.5. The idiopathic orthostatic hypotension in Parkinsonian patients has been reported as being reduced by *l*-dopa (Schober 1975, Vuia 1976).

6.2.3. THE LC AND HALLERVORDEN-SPATZ DISEASE

Hallervorden-Spatz disease seems to be a type of Lewy body disease with an early onset (about 10 years of age): the patients have Lewy bodies in the LC and SN, cell loss, depigmentation and extracellular neuromelanin (Bornstein et al. 1966, Rozdilsky et al. 1968, 1971, Defendini et al. 1973, Dooling et al. 1974). The symptoms of Hallervorden-Spatz disease are rigidity, dementia and psychotic manifestations (see the above mentioned references). The similarities and differences in the etiology of Hallervorden-Spatz disease and idiopathic Parkinson's disease are still unclear.

6.2.4. THE LC AND PARKINSON'S DISEASE WITHOUT LEWY BODIES

Brain changes in non-idiopathic parkinsonism. In the brains of postencephalitic Parkinsonian patients, PHFs, depigmentation, and cell loss are found in brain regions, including the SN and LC, similar to those where brain changes have been found in the brains of idiopathic Parkinsonian patients (Ishii 1966, Beheim-Schwarzbach 1952, Greenfield and Bosanquet 1953, Duffy and Tennyson 1965, Ohama and Ikuta 1976). Another form of "symptomatical Parkinsonism", striato-nigral degeneration, is often accompanied by other degenerations in the CNS: ponto-olivo-cerebellar degeneration, or "multiple system atrophy" (Adams et al. 1964, Stadlan et al. 1966, Izumi et al. 1971, Bannister and Oppenheimer 1972, Sharpe et al. 1973, Schober 1975, Sung et al. 1979); but in pure cases of it, brain regions other than the SN and the basal ganglia are relatively spared (Adams et al. 1964).

Symptoms of postencephalitic and arteriosclerotic Parkinsonism. Apart from the Parkinsonian symptoms of akinesia, rigidity and tremor, the symptoms intellectual impairment, dementia, depression and psychotic disturbances are often found in postencephalitic and arteriosclerotic Parkinsonian

patients, and in these patients the latter symptoms are more severe than in idiopathic Parkinsonian patients (Celestia and Wanamaker 1972, Brown and Wilson 1972, Martilla and Rinne 1976).

Symptoms of striato-nigral and related degenerations. Since patients with striato-nigral degeneration have akinesia and rigidity, but much less or no tremor than idiopathic, postencephalitic and arteriosclerotic Parkinsonian patients, the former disease is called "akinetic Parkinsonism" (Stadlan et al. 1966, Jellinger and Danielczyk 1968, Gray and Rewcastle 1967, Izumi et al. 1971). Vegetative disturbance occur, of which the idiopathic orthostatic hypotension (Shy-Drager syndrome) is most remarkable; these vegetative disorders are an expression of "multiple system atrophy" and they are ascribed to cell loss in the intermediolateral column and/or sympathetic ganglia (Sung et al. 1979). Unfortunately, the data available on symptoms and brain changes are too limited to ascribe reliably other particular symptoms to a circumscribed brain deficit (see sections 6.2.5 and 6.3.3).

THE SN AND THE BASAL GANGLIA; PARKINSONIAN SYMPTOMS

A number of reasons will be presented below that each of the following states in the CNS is a sufficient condition of Parkinson-like akinesia and rigidity: 1) cell loss or lesions of the SN, 2) lesions of the basal ganglia, and 3) a decrease in the DA-induced effects in the basal ganglia (cf. section 4.4). In other words: these states are a cause of akinesia and rigidity*.

1. A correlation is present between morphologically demonstrated changes in the dopaminergic SN and its main terminal region the basal ganglia on the one hand, and akinesia and rigidity on the other hand. 1) In cases of idiopathic Parkinson's disease a simple relationship between SN cell loss and the severity of Parkinsonian motor symptoms has been described (Alvord et al. 1973). Parkinsonian motor symptoms have been

* For an analysis of the statement "a specified brain change (C) is a cause of a specified symptom/syndrome (E)" see section 4.5.

reported as being absent in cases of Lewy body disease in which the LC, the intermediolateral column and the sympathetic ganglia were affected but the SN was spared (Black and Petito 1976). 2) In a number of cases of non-idiopathic Parkinsonism, the degree of SN cell loss correlated with the degree of Parkinsonian symptoms (Alvord et al. 1973). 3) Cases of striato-nigral degeneration show Parkinsonian motor symptoms, whether or not other regions of the brain (including the LC) are affected (Adams et al. 1964). 4) The Parkinsonian motor symptoms in cases of brain infarct could be explained by destruction of the SN and/or the basal ganglia (Oppenheimer 1967, cf. Fahn et al. 1971).

2. Circumstantial evidence is present that changes in the SN and basal ganglia precede the Parkinsonian motor symptoms. 1) In a number of cases of Lewy body disease, relatively minor changes (cell loss, Lewy bodies, extracellular neuromelanin) in the SN have been described, while the Parkinsonian motor symptoms were (still) absent (Forno 1969, Alvord et al. 1973)· Lewy body disease precedes Parkinson's disease (see also Stadlan et al. 1966). 2) In cases of Parkinsonian symptoms concomitant with infarcts of the SN or basal ganglia, one will be inclined to accept that the infarct preceded the motor symptoms.
3. Manipulations of the DA transmission have effects on Parkinsonian motor symptoms, which are in line with the hypothesis that a decrease in the DA-induced effects in the basal ganglia is a cause of Parkinsonian motor symptoms. 1) The L-dopa therapy of Parkinsonian motor symptoms can be explained by an L-dopa-induced restoration of striatal DA (Lloyd et al 1975, Birkmayer 1976). 2) Drug-induced "extrapyramidal symptoms" ("Parkinsonian side-effects" of neuroleptics) are related to the action of these drugs as DA receptor antagonist (Van Rossum 1967, Robinson et al. 1979); a subgroup of DA receptors might be involved (Cools and Van Rossum 1976, Kebabian and Calne 1979).

The conclusion of many of the above mentioned authors is that disfunction or cell loss in the SN is a cause of akinesia and rigidity. Reasons have also been presented above that other regions than the SN and the basal ganglia that are affected in these diseases are not, or to a much less extent, a cause of these symptoms. An implication of this conclusion is relevant for this whole chapter· cell loss (or cell changes) in the LC is not a cause of akinesia or rigidity.

6.3. The LC and NE; the dementias.

Introduction. "Dementia" is a name of a family of etiologically unrelated diseases. Up to now relatively few attention has been paid to the dementias (Lishman 1978). Consequently, the nosology of the dementias is poorly developed; for instance, the features for distinguishing (parenchymatous) senile dementia from Alzheimer's disease (the common form of presenile dementia) are subject to dispute (Spillane et al. 1977, Lishman 1978). The diagnostic criteria for distinguishing psychiatric disorders and presenile dementia are vague (Lishman 1978), and it is even unclear whether a sharp, non-arbitrary distinction can be made between dementia and "normal aging", and what the meaning of "normal aging" is. The following statements about the dementias are therefore inevitably tentative.

Various dementias. Different forms of dementia have been distinguished based both on the brain regions affected and on the concomitant symptoms (cf. Albert et al. 1974, Martilla and Rinne 1976):

1. "Cortical dementia": dementia with extensive cortical atrophy (presenile forms: Alzheimer's and Pick's disease; some forms of senile dementia; these forms can be distinguish only post-mortem). The most conspicious symptoms are impairments of language-dependent activities and perceptual or perceptual-motor skills.
2. "Subcortical dementia": dementia without extensive cortical atrophy. The most conspicious symptoms are forgetfulness, slowing of thought processes, emotional or personal changes (apathy, depression), impaired ability to manipulate acquired knowledge, while verbal and perceptual-motor capacities are often intact. In this section are especially relevant the subcortical dementia in Lewy body disease, in Parkinson's disease and in progressive supranuclear palsy.

6.3.1. "CORTICAL DEMENTIA"

The cortex is by definition considerably affected in "cortical dementia": cortical atrophy, cell loss, "senile plaques" and neurofibril degeneration ("neurofibrillary tangles" = Alzheimer's tangles = paired helical filaments = PHFs) take place. In cases with cortical dementia, the severity of the dementia are reported as being correlated with the cortical changes (Blessed et al. 1968, Farmer et al. 1976, cf. Alvord et al. 1973). In cases of "senile dementia", the brain changes are not limited to the cortex: some brain regions are often affected, and others not (Wisniewsky et al. 1978). The regions affected are the neocortex, hippocampus, hypothalamus, SN, LC, reticular formation and other regions; particularly vulnerable are the monoaminergic neurons (cf. Hirano and Zimmerman 1962, Ishii 1966, Wisniewsky et al. 1978). In cases of Alzheimer's disease, the hippocampal NE content is decreased, and other neurochemical parameters are also affected (Spillane et al. 1977, Carlsson 1979). It is far too early to ascribe some symptoms of cortical dementia to the loss of specific subcortical regions.

6.3.2. "SUBCORTICAL DEMENTIA"

Subcortical dementia in Lewy body disease. A strong relationship has been described between Lewy body disease (and idiopathic Parkinsonism) and dementia: in Lewy body disease both the cortical signs of Alzheimer's disease, and the symptoms of "subcortical dementia" have been found (Hakim and Mathieson 1979, Lieberman et al. 1979). The occurrence of the cortical signs and the symptoms of dementia is independent of *l*-dopa treatment. In Lewy body disease, Lewy bodies are found predominantly in the LC and in some other CA nuclei, probably concomitant with a decrease in brain DA and NE levels (cf. sections 6.2.1 and 6.2.2).

Subcortical dementia in Parkinson's disease. In patients with Parkinson's disease, intellectual impairments and dementia(with the following symptoms: memory impairment, confusion, disorientation, personality change, auditory hallucinations and delusions) have been described (Pollock and Hornabrook 1966, Mindham 1970, Brown and Wilson 1972, Hakim and Mathieson 1979, cf. also section 6.2.2). These symptoms are similar in the various forms of Parkinson's disease, but they are more severe in the postencephalitic and

arteriosclerotic forms (Loranger et al. 1972a, Brown and Wilson 1972).

l-Dopa and dementia in Parkinson's disease. The intellectual capacities of Parkinsonian patients are improved by l-dopa, which improvement cannot simply be accounted for by its relief of akinesia and rigidity (Cotzias et al. 1969, Meier and Martin 1970, Loranger et al. 1972a,b). l-Dopa does not relieve dementia in either Parkinsonian patients (Markham 1974, cf. Martilla and Rinne, 1976) or in non-Parkinsonians (Kristensen et al. 1977); this may be related either to l-dopa-induced psychotic symptoms (section 6.5.2), or to a CA cell loss in demented Parkinsonian patients which is progressed too far for benificial action of l-dopa. On the other hand, both the cortical signs and the symptoms of dementia were frequently found in cases of Parkinson's disease (and Lewy body disease) which were not l-dopa-treated (Mindham 1970, Loranger et al. 1972a, Brown and Wilson 1972, Hakim and Mathieson 1979, Rosenblum and Ghatak 1979): dementia is part of the natural history of Parkinson's disease (Pollock and Hornabrook 1966), and the dementia after l-dopa treatment is probably not exclusively due to l-dopa's "psychotic side-effects" (confusions, hallucinations, delusions; section 6.5.2).

Subcortical dementia in other diseases. Patients with other neurological diseases such as progressive supranuclear palsy have symptoms characteristic for "subcortical dementia" (see Steele et al. 1964, Albert et al. 1974). In these cases cell loss and neurofibrillary tangles are found mainly in the pallidum, n. subthalamicus, n. ruber, SN, LC and other regions, while the cerebral cortex is relatively spared (Steele et al. 1964, Albert et al. 1974, Ishino and Otsuki 1975, Tomonaga 1977b, Bugiani et al. 1979). (Note that the "neurofibrillary tangles" in progressive supranuclear palsy are not PHFs, but straight 15 nm filaments, Tomonaga 1977, Bugiani et al. 1979.) The distribution of affected brain regions, and the kind of brain changes in progressive supranuclear palsy resemble those in postencephalitic Parkinsonism, although some differences are present (Steele et al. 1964, Ishino and Otsuki 1975). Pathological resemblance with other diseases has been noted: Parkinson-dementia complex of Guam, and amyotrophic lateral sclerosis of the Guam or Kaukasian type (Hirano and Zimmerman 1962, Hirano et al. 1967, Meyers 1974, Queiroz et al. 1977). The intellectual impairment and dementia is similar in progressive supranuclear palsy and in Parkinson's disease, including the intact verbal capacities (Albert et al. 1974).

6.3.3. CENTRAL CA NUCLEI; INTELLECTUAL IMPAIRMENTS AND DEMENTIA

A number of reasons will be presented below that atrophy (or malfunction) of central CA nuclei (such as the dopaminergic SN, and the (presumed) noradrenergic n. paranigralis, n. parabrachialis pigmentosus and LC) is a cause of intellectual impairments and "subcortical" dementia.

1. Intellectual impairments and dementia are present in diseases in which the central CA nuclei are affected. 1) Intellectual impairments, and both the symptoms and the cortical changes of dementia are more severe in cases with Parkinson's and Lewy body disease than in a age-matched control group (Pollock and Hornabrook 1966, Mindham 1970, Loranger et al. 1972a, Alvord et al. 1973, Hakim and Mathieson 1979, Lieberman et al. 1979). 2) In Parkinsonian patients a more severe dementia has been found than in a coupled group of non-Parkinsonians with comparable cortical degeneration (Alvord et al. 1973): subcortical brain atrophy in Parkinson's disease contributes to the dementia.
2. Circumstantial evidence is present that cell changes and cell loss in central CA nuclei precede the dementia: cell loss and cell inclusions have been found in not (yet) demented cases of Lewy body disease (Forno 1969, Hakim and Mathieson 1979, Alvord et al. 1973).
3. Manipulations of the central CA transmission have effects on intellectual capacities and dementia which are in line with the hypothesis that a decrease in the central CA-induced effects is a cause of intellectual impairments and dementia. 1) The *l*-dopa therapy of intellectual impairments of (not demented) Parkinsonian patients (Cotzias et al. 1969, Meier and Martin 1970, Loranger et al. 1972a,b) can be explained by a *l*-dopa-induced restoration of the central CA transmission. 2) The confusional states induced by DBH-inhibitors (fusaric acid, disulfiram; Liddon and Sartran 1967, Hotson and Langston 1976, Cross et al. 1978, Hartman and Keller-Teschke 1979) can be explained by a reduction of the central NE transmission. 3) Drug-induced manipulations of the central DA and NE transmission cause psychotic manifestations (see section 6.5.2).

The LC and dementia. A number of reasons will be presented that cell loss in the LC contributes to (or even is a main cause of) some forms of "subcortical dementia":

1. Cell loss in the LC deprives vast cortical areas from their NE innervation: the involvement of the LC in (forms of) dementia is obvious.

2. The temporal pattern of PHF inclusions in the LC and the development of dementia is similar, while this was not the case for other regions including the SN, hippocampus and cortex (Alvord et al. 1973).
3. Patients with striato-nigral degeneration in which the LC was only mildly affected were "in full possession of mental faculties" and showed "no obvious fault in memory or other cognitive functions", while in a case with severe LC cell loss, a memory defect and mental disorientation was found (Adams et al. 1964).

It should however be noted that the symptoms have to be correlated with brain changes in a "symptom-oriented approach" (section 6.7) to conclude which CA and which CA region is primarily involved in "subcortical dementia".

6.4. The LC and NE; epilepsy, convulsions and electroconvulsive treatment.

NE, epilepsy and convulsions. In animal studies, the generally confirmed conclusion is that central NE reduces susceptibility to seizure (review Maynert et al. 1975; Browning and Maynert 1978, Libet et al. 1977, Jobe et al. 1978, London and Buterbaugh 1978, Quatrone et al. 1978b, McNamara 1978, Mason and Corcoran 1979b,c,d; apart from post-decapitation convulsions). (Other putative neurosecretes are also involved: GABA, ACh, Glu; Maynert et al. 1975.) The above mentioned agreement contrasts with the results in epileptic patients. Manipulations thought to increase the NE concentration at NE target cells both increased (tricyclic antidepressiva) and decreased (amphetamines) susceptibility to seizure, while manipulations designed to diminish the NE-induced effects increased the susceptibility (cf. Maynert et al. 1975). Moreover, the CSF MHPG remained unchanged in epileptic patients (Peters 1979, Laxer et al. 1979). Some authors maintain that clinically effective anticonvulsants (diphenylhydantoin, carbamazepine, barbiturates) act through the central NE transmission, but there are many contradictory results (for references see Quatrone et al. 1978). In any case, these anticonvulsants do not act selectively, let alone exclusively, via the central NE transmission.

Electroconvulsive treatment: therapeutical action and central NE. The view that epilepsy and a variety of psychotic manifestations ("dementia praecox") are mutually exclusive, or antagonistic, the so-called "antagonism theory", has been popular for some time (reviews Flor-Henry 1969a, 1972). *"The antagonism theory in its original and general formulation was clearly shown to be incorrect"* (Flor-Henry 1969a), although in a number of individual patients an alternation of convulsive and psychotic manifestations occurred (Flor-Henry 1969a). The antagonism theory was a theoretical basis for electroconvulsive treatment (ECT) of psychotic manifestations. Whatever the value of the antagonism theory may be, ECT is reported as being rather effective in the treatment of psychosis in endogeneous depression (Kalinowsky 1975). In animal studies, acute as well as chronic ECT increased the NE turnover leaving DA and 5-HT unaffected (Kety et al. 1967, Schildkraut 1975,

Modigh 1976). In man, however, ECT diminishes lumbal CSF MHPG (Härnryd et al. 1979), which may indicate a decrease in NE turnover and activity (cf. section 4.4). Evidently, the relationship in man between epilepsy and ECT on the one hand, and central NE transmission on the other hand is unclear.

6.5. The LC and NE; schizophrenia and psychoses.

6.5.1. SCHIZOPHRENIA

1. Introduction

Definition. "Schizophrenia" is the name of a family of complex disorders *"characterized by a withdrawal in a private fantasy world, which is maintained through the use of personal beliefs, idiosyncratic thought patterns, and percepts that are not culturally shared"* (Bemprat and Pinsker 1974). *"An especially important aspect is the splitting, or desintegration, of the so-called basic psychological functions: thought, affect, impulses, and so forth are disassociated from one another and within their own constitutive elements"* (Arana 1978). (For an extensive description of schizophrenic symptoms, and the meaning of the words to describe them see Arana 1978.)

Classification of schizophrenic syndromes. Although a generally accepted classification of the schizophrenias does not yet exist, the following classical syndromes are often distinguished (cf. Bemporat and Pinsker 1974, Arana 1978; these authors review also further classifications); these syndromes can be distinguished however only in the early stages of the disease:

1. Hebephrenia: characterized by affect and thought disorders, while bizarre disorganized hallucinations and delusions occur.
2. Catatonia: characterized by a dissociation from volition and emotion, leading to either stupor or excitement.
3. "Simple schizophrenia": mainly characterized by apathy and impoverishment of interpersonal relations; the validity of this subtype is however questionable.
4. Paranoid schizophrenia: characterized by a systematized disruption of logical thinking and a disturbance of relationships with others; prominent hallucinations occur, which are frequently persecutory. Paranoid schizophrenia is the most homogeneous subtype. On the basis of biochemical measures too (platelet MAO), paranoid schizophrenia is considered to be a separate disorder from the other forms of schizophrenia: paranoid schizophrenics have a lower platelet MAO activity (Schildkraut et al. 1976b, Potkin et al. 1978, Wyatt et al. 1978).

The chronic manifestations of schizophrenia are similar in patients who began as hebephrenic, catatonic or paranoid; this state is called "chronic undifferentiated schizophrenia". Apart from these syndromes, a number of syndromes have been described, some of which are called "pseudoschizophrenia" and might be related to affective disorders (such as "schizoaffective disorder"; Arana 1978).

Diagnosis. A discussion of the different diagnostic criteria of schizophrenia goes beyond the scope of this section; for the most often used diagnostic criteria the reader is referred to Feighner et al. (1972) and Spitzer et al. (1975), and for a survey of diagnostic systems to Spitzer et al. (1978). The nosological distinction between schizophrenia and affective disorders is not always clear, and consequently diagnostic confusion exists between these diseases (Taylor et al. 1974, Abrams et al. 1974).

Hypotheses on etiology. *"Various areas of neuroscience, and not at least the realms of schizophrenia research, appear to follow swings of fashion. After much emphasis on the role of dopamine supersensitivity in the development of schizophrenia, noradrenaline is now considered by some as being a more crucial neurotransmitter in this disorder"* (Ter Haar 1979a). Apart from DA and NE, other compounds and processes have also been suggested as a cause of forms of schizophrenia: endorphins/enkephalins, prostaglandins, melatonin, gluten, immunological disorders and virus infections (see Ter Haar 1979b). It is at the moment far from clear whether these presumed causes are related or unrelated, and whether they act simultaneously or in succession (cf. fig. 44). I will restrict myself here to the involvement of NE and DA in schizophrenia.

2. Central NE transmission in schizophrenia

Paranoid schizophrenia. All the recent studies about the NE content of brain nuclei in paranoid schizophrenic patients are in agreement that the NE content may be up to 3 times as large (Farley et al. 1978, 1979, Carlsson 1979, Hornykiewicz 1979 (cited by Ter Haar 1979), Kleinman et al. 1979, Lake et al. 1980), both in LC terminal regions (mesencephalon, n. interstitialis striae terminalis, ventral septum, corpora mammilaria) and in presumed non-LC terminal regions (n. accumbens, footnote on p. 279), and in the CSF. A normal brain DBH activity and CSF MHPG content is described in paranoid schizophrenics (Wise and Stein 1975, Peters 1979). These bio-

chemical measures cannot alone indicate whether the central NE transmission is disturbed in paranoid schizophrenia, and if so, what sort of disturbance there is (cf. section 4.4). Parameters related to the DA transmission (levels of DA, DOPAC, HVA) are not changed in paranoid schizophrenia (Kleinman et al. 1979).

Non-paranoid schizophrenia. No abnormalities in the NE content of brain regions in non-paranoid schizophrenics have been described (Farley et al. 1979); this might explain why no, or smaller, NE changes are found (Bird et al. 1979) in brain regions of a larger group of schizophrenics (without further subclassification). The activities of enzymes related to NE transmission (TH, Dopa-decarboxylase, DBH, COMT) in schizophrenia are reduced according to a number of studies (Wise and Stein 1973, 1975, Wyatt et al. 1975, 1978), but unchanged according to others (Cross et al. 1978, Lerner et al. 1978). The mean urinary MHPG content of chronic schizophrenic patients (without schizoaffective or paranoid features) did not differ from that of controls, but the variation was much larger, which might indicate a heterogeneous composition of this group of schizophrenics (Taube et al. 1978). An increase in the content of free MHPG, and a decrease in conjugated MHPG has been described in the hypothalamus of psychotic patients (including paranoid and undifferentiated schizophrenics; Kleinman et al. 1979).

6.5.2. DRUG-INDUCED PSYCHOTIC MANIFESTATIONS

Introduction. Psychotic manifestations (confusions, delusions, hallucinations) are induced by some drugs administered to man. Some of these drugs are directly involved in the NE neurotransmission, and will be mentioned below.

Amphetamine-induced psychosis. Amphetamines cause mental disturbance resembling acute paranoid schizophrenia (references see Carlsson 1977, Crow 1979a). They increase the release of both DA and NE, but from a comparison of the effectiveness of the *d*- and *l*-isomers a number of authors concluded that NE rather than DA is involved in amphetamine-induced psychosis (Sulser and Robinson 1978, Mason 1979a, Hornykiewicz 1979, cited by Ter Haar 1979).

l-Dopa-induced psychosis. l-Dopa alone in a high dose, or l-dopa plus a MAO-inhibitor administered to Parkinsonian patients has been reported as causing psychotic manifestations (confusions, delusions, hallucinations; for references see Birkmayer 1976). These psychoses are probably really l-dopa-induced, since they disappeared after discontinuation of l-dopa administration (Birkmayer 1976). The NE content of several brain regions (SN, n. ruber, and the LC terminal regions raphe, amygdala, and gyrus cinguli) is increased in psychotic Parkinsonian patients compared to Parkinsonian patients without l-dopa-induced psychosis (Birkmayer et al. 1974, 1976, 1977); in the gyrus cinguli and raphe the NE content was far above that of asymptomatic controls. The DA content of the brain regions in l-dopa-induced psychotic Parkinsonian patients was similar to that of l-dopa-treated non-psychotic Parkinsonian patients, except in the SN and in the predominantly LC terminal regions gyrus cinguli and raphe nuclei (Birkmayer et al. 1974, 1977): *"the trend to higher NE-levels in L-dopa psychosis seems to be remarkable"* (Birkmayer et al. 1974). The l-dopa-induced psychotic manifestations were probably related to the l-dopa-induced changes in NE rather than in DA*.

6.5.3. PSYCHOTIC MANIFESTATIONS IN LEWY BODY DISEASE

The frequency of Lewy bodies (cf. section 6.2.1) in the brains of "patients with psychosis or mental deficiency" is similar to that in a large sample of individuals without predominance of psychiatric symptoms (Woodard 1962, cf. Forno 1969). No Lewy bodies were found in 77 cases of "organic psychosis other than Alzheimer's disease", they have been found in 10% of the cases of Alzheimer's disease, and in 28% of the cases of "mental disturbance without established morphological basis" (Woodard 1962). The clinical features associated with these cases with Lewy body disease are paranoia, violence,

* It should be noted however that the increases in NE levels mentioned do not necessarily imply that the NE-induced effects at the cellular (or higher) level must be increased.

confusion, affective disorders and relatively minor and often late intellectual deterioration (Woodard 1962). (But quantitative investigations (WAIS) indicate a clear intellectual impairment in idiopathic Parkinson's (Lewy body) disease (see sections 6.2.1 and 6.2.2.).)

6.5.4. DRUG-TREATMENT OF PSYCHOTIC MANIFESTATIONS

Antipsychotics. For many years (Van Rossum 1967) it has been a broadly accepted opinion that neuroleptics exert their antipsychotic action through a blockade of DA receptors. Although it is well established that neuroleptics are DA receptor antagonists, discussion continues on whether their antipsychotic action (and the antipsychotic action of non-neuroleptic antipsychotics) is predominantly due to blockade of DA receptors or α-adrenoceptors (see the reviews of Sulser and Robinson (1978) and Carlsson (1978) in the same book), at least *"the α-NE blockade may play a contributory role in the antipsychotic action"* (Carlsson 1978). In any case, *"Large drug studies have shown that at most only 30% (of schizophrenic patients) derive some benifit from pharmacotherapy"* (Sulser and Robinson 1978). This is not unexpected: only if schizophrenia is in some respect a neurochemical entity, attempts to develop a specific antipsychotic drug, and to formulate a single theory on the origin and termination of psychoses, can be successful. At the moment there are no grounds to assume that the schizophrenias are a neurochemical entity; the available data just indicate the neurochemical heterogeneity of the group of schizophrenics (Taube et al. 1978).

Propranolol. Although as yet *"no well-designed trial which demonstrates the superiority of propranolol over placebo, uncomplicated by other neuroleptic medication"* (Crow 1979b) has been published, a number of investigations indicate improvements in certain scores in schizophrenic patients by propranolol in high doses (book Roberts and Amacher 1978); in particular, a substantial improvement has been reported in paranoid schizophrenics (Yorkston et al. 1977, Bigelow et al. 1979). At the moment it is uncertain whether the (presumed) antipsychotic action of propranolol is due to its central β-adrenoceptor blockade, or to other actions (peripheral actions or membrane stabilization, antiserotonergic action).

Antipsychotic action and adrenoceptor blockade. The adrenoceptors on the LC target cells are mainly of the β-type (section 4.3.1), while the adrenoceptors on NE terminals are mainly of the α-type (Berthelsen and Pettinger 1977). The simplest interpretation of the antipsychotic action of propranolol is that propranolol blocks the β-adrenoceptors on the NE target cells, thereby reducing the NE-induced effects on the NE target cells at the cellular (or higher) level (cf. section 4.4). On the other hand, the simplest interpretation of the action of other antipsychotics via α-adrenoceptors is that they block the α-adrenoceptors on the NE terminals, thereby reducing the NE-induced decline in NE release, and consequently increasing the NE-induced effects on the NE target cells at the cellular (or higher) level (cf. section 4.4). One can also incorporate into the theory the indirect effects of these drugs (for instance on NE synthesis and on adrenoceptor number and sensitivity, section 4.4); but then the theory begins to include so many uncertain factors that it can explain everything, or rather nothing. Conclusions about the involvement of central NE in schizophrenia and psychoses on the basis of antipsychotic drug action remain therefore highly speculative at the moment.

6.5.5. NE AND DA IN SCHIZOPHRENIA

Only circumstantial and rather weak evidence can be presented that a change in the central NE and/or DA transmission is a cause of some forms of schizophrenia.

1. Some correlations between changes in central NE transmission and schizophrenia have been described: an increase in the brain NE content in paranoid schizophrenia, and a decrease in brain DBH activity in schizophrenic patients; in cases of Lewy body disease paranoid features were frequent. It has to be investigated which NE region is primarily involved in schizophrenia.
2. No indications have been published thus far that changes in the central NE or DA transmission precede schizophrenia or psychoses.
3. Some manipulations of the central NE or DA transmission are not conflicting with the hypothesis that a change in the central NE or DA transmission is a cause of schizophrenia: 1) the antipsychotic action of neuroleptics and (possibly) propranolol, and 2) the induction of psychotic manifestations by amphetamines and *l*-dopa.

It should be noted that the DA hypothesis of schizophrenia is based mainly on pharmacological evidence, which is (at least partly) also in agreement with the involvement of NE in schizophrenia (Carlsson 1979, Bunney et al. 1979b).

6.6. The LC and NE; affective disorders.

6.6.1. INTRODUCTION, AFFECTIVE DISORDERS

Nosology and classification. Patients with affective disorders are characterized by (periods of) a depressed mood: they are depressed, sad, fearful and so on (Feighner et al. 1972). Patients with affective disorders are further distinguished symptomatically on a number of dimensions (Katz and Hirschfeld 1978):

1. unipolars and bipolars: the former have only depressed periods, while in the latter depressed and manic periods occur.
2. endogenous versus non-endogenous: "endogenous depression" refers to a complex involving early morning awaking, anorexia and weight loss, psychomotor disturbance, diurnal mood variation, severe depressed mood and lack of reactivity.
3. schizophrenia-related-depressed and schizoaffective patients (cf. Spitzer et al. 1978, Arana 1978); patients of this group also are called "psychotic depressed patients".
4. primary versus secondary: primary depressed patients did not have a psychiatric disturbance before the affective illness.

These symptomatological differentiation of depressed patients appears to correlate with biochemical measures (Schildkraut et al. 1979). Moreover, the group of endogenous unipolar depressed patients is reported as being biochemically heterogeneous: "NE-depression" and "5-HT-depression" have been distinguished (see below). *"We note a major gap between the nature of the "biological" depressives (endogenous and bipolar) on the one hand, and that of the "psychogenic" depressives (primarily neurotic, some secondary, some unipolar) on the other"* (Katz and Hirschfeld 1978). This section will be limited principally to bipolar and endogenous unipolar affective disorders, i.e. to the groups about which a relatively great deal of biochemical and pharmacotherapeutic knowledge is available.

Symptoms in depression. A depressed mood is not the only characteristic of depressed patients. Actually these patients are affected on more dimensions: affect, thinking, behavior and somatic activities: 12 groups of symptoms (factors) have been distinguished in depression; these include:

(of course) a depressed mood, feelings of guilt and worthlessness, hostility, anxiety-tension, cognitive loss, loss of interest, somatic complaints, motor retardation and bizarre thoughts (Katz and Hirschfeld 1978). A quantitative analysis of the intellectual capacities of depressed patients revealed that these patients have exactly similar, but less severe, intellectual impairments as Parkinsonian patients (Loranger et al. 1972a).

6.6.2. BRAIN CHANGES IN AFFECTIVE DISORDERS

Bipolar patients. Plasma and urinary MHPG content show differences associated with the alterations in mood of bipolar patients (Bond et al. 1972, Jones et al. 1973, Schildkraut 1978, Garver and Davis 1979, Halaris and DeMet 1979b). The MHPG levels of bipolars in the depressed phase are lower than those of controls, and in the manic phase equal to the controls' levels. The changes in the MHPG levels are reported as preceding the clinical changes; the MHPG levels are related to mood rather than to agitation or retardation (Schildkraut 1978, Taube et al. 1978). Contrary to what might be expected the CSF DBH activity in bipolar patients is lower during the manic phase (Lerner et al. 1978).

Unipolar endogenous depression. The brain NE content in depressed patients is lower in only a few regions (amygdala, n. ruber, Birkmayer et al. 1976), while the CSF DBH activity seems to be normal (Lerner et al. 1978). The group of unipolar endogenous depressed patients is heterogeneous in respect of urinary MHPG content: both high and low values occur, while an inverse relationship exists between urinary MHPG and CSF 5-HIAA (the main 5-HT metabolite; Goodwin et al. 1978, Schildkraut 1978, Schildkraut et al. 1979, Halaris and DeMet 1979b, Taube et al. 1978, Garver and Davis 1979). After recovery from depressive illness, urinary MHPG appears to have increased to normal values (Shaw et al. 1973, Sweeney et al. 1979). The urinary MHPG content was related to mood rather than to retardation or agitation (Schildkraut 1978, Taube et al. 1978). While the data on urinary MHPG content in affective disorders agree fairly well, contradictory data have been published on CSF MHPG in depressed patients (Schildkraut 1978).

6.6.3. PHARMACOTHERAPY OF DEPRESSION, TRICYCLIC ANTIDEPRESSIVA

NE- and 5-HT-depression. *"There is a subgroup of depressed patients who may be more likely to respond to tricyclic antidepressiva as a class. This subgroup is characterized by the presence of «endogenous symptoms»"* (Goodwin et al. 1978, cf. Katz and Hirschfeld 1978). The group of unipolar endogenous depressed patients is however heterogeneous (Fawcett and Siomopoulos 1971, Beckman and Goodwin 1975, Goodwin et al. 1978, Garver and Davis 1979, Halaris and DeMet 1979b):

1. "NE-depression": patients with low urinary MHPG, high CSF 5-HIAA, better response to treatment with the secondary tricyclic antidepressiva (imipramine, desimipramine) and less good to treatment with the tertiary tricyclic antidepressiva (amitriptyline, chlorimipramine), temporary improvement brought about by *d*-amphetamine, and urinary MHPG levels increased by imipramine or desimipramine.
2. "5-HT-depression": patients with high urinary MHPG, low CSF 5-HIAA, better response to treatment with amitriptyline or chlorimipramine, and less good to treatment with imipramine or desimipramine, no improvement with *d*-amphetamine, and no urinary MHPG response to treatment with tricyclic antidepressiva.

Tricyclics, blockade of NE- and 5-HT re-uptake. The tricyclic antidepressiva block the re-uptake of NE and/or 5-HT, and also have certain other effects (cf. Lewi and Colpaert 1976, Maggi et al. 1980)*. The secondary tricyclic antidepressiva (imipramine, desimipramine) predominantly block the NE re-uptake, while the tertiary tricyclic antidepressiva (amitryptiline, chlorimipramine) predominantly block the 5-HT re-uptake (Carlsson and Lindquist 1978b, U'Prichard et al. 1978, Goodwin et al. 1978, Garver and Davis 1979).

* A DA hypothesis of affective disorders (for instance Randrup et al. 1975) has been impopular for a number of years, because the clinically effective antidepressants imipramine, desimipramine, chlorimipramine and amitryptiline are devoid of action on DA re-uptake (Goodwin et al. 1978), but clinically effective antidepressiva have been described with a direct effect on the DA re-uptake and metabolism (Carlsson and Lindquist 1978b).

Tricyclics, NE and depression. A close correlation has been described between the therapeutic effects of tricyclic antidepressiva and their affinity to α-adrenoceptors (U'Prichard et al. 1978), but the further mechanism of the therapeutic effects of the tricyclic antidepressiva is the subject of discussion (Maas 1979):

1. Some authors ascribe the therapeutic effects (in "NE-depression") directly to the blockade of NE uptake: it is thought that the NE-induced effects at the cellular (or higher) level (section 4.4) are smaller in unipolar endogenous depressed patients than in controls (due for instance to NE cell loss, to a decrease in NE release, or to a decrease in the number or sensitivity of adrenoceptors on the NE target cells). It is thought that the presumed decrease in NE-induced effects is a cause of depression, and is compensated by a tricyclic-induced blockade of the NE re-uptake.
2. Some authors (Sulser et al. 1978, Maggi et al. 1980) ascribe the therapeutic effects of tricyclic antidepressiva to brain changes secondary to the blockade of NE re-uptake, for instance subsensitivity of β-adrenoceptors (section 4.4). It is thought that the NE-induced effects at the cellular (or higher) level are greater in unipolar endogenous depressed patients than in controls. The presumed increase in NE-induced effects is regarded as a cause of depression, and these effects are thought to be reduced to normal values by a tricyclic-induced secondary subsensitivity of β-adrenoceptors on NE target cells.

6.6.4. PHARMACOTHERAPY OF MANIA

Experimental results indicating that in bipolar patients, the NE-induced effects on the cellular (or higher) level (section 4.4) are greater in the manic than in the depressed phase, and that this increase is a cause of mania, can be summarized as follows. During the manic phase, plasma and urinary MHPG are increased compared with the depressive phase (section 6.6.2), and manic symptoms are alleviated by propranolol (at least partly by blockade of β-adrenoceptors, Emrich et al. 1979), by DBH inhibitors (fusaric acid in mild hypomania, Sack and Goodwin 1974) and by Li^+ (Gerbino et al. 1978; Li^+ antagonizes the CA-induced activation of adenylate cyclase, section 4.3.1).

6.6.5. AFFECTIVE DISORDERS IN PARKINSON'S DISEASE

Occurrence of depression in Parkinson's disease. A high incidence of depression (37-90%) has been described in Parkinson's disease (the idiopathic as well as the postencephalitic and arteriosclerotic forms) (Warburton 1967, Mindham 1970, Celestia and Wanamaker 1972, Brown and Wilson 1972). The symptoms of depression are relatively independent from the Parkinsonian motor symptoms: 1) depression can precede the Parkinsonian motor symptoms, 2) depression can be successfully treated without improvement in the motor symptoms, and 3) the correlation between the severity of the motor symptoms and of depression is small. Unfortunately, the depression in Parkinson's disease is rarely further described; only Brown and Wilson (1972) report the presence of the "biological concomitants" of depression, which might indicate a similarity with endogenous depression. Further similarities and differences between endogenous depression and depression in Parkinson's disease are unclear.

Depression in Parkinson's disease, *l*-dopa. The depression of certain depressive Parkinsonian patients could be treated effectively by *l*-dopa (Bunney et al. 1969a, Damasio et al. 1970, Celestia and Wanamaker 1972, Birkmayer 1976). Some authors have however described *l*-dopa-induced depression symptoms in Parkinson's disease (Birkmayer 1976), but these findings should be regarded with caution, since depression is part of the natural course of Parkinson's disease (Celestia and Wanamaker 1972). On the other hand a subpopulation of Parkinsonian patients with a family history of depression may represent a higher risk group for *l*-dopa-induced depression (Mendlewicz et al. 1976).

No mania in Parkinson's disease. While depression is part of the natural course of Parkinson's disease, mania is almost completely absent (Mindham 1970); the low (1%) incidence of bipolar affective diseases in *l*-dopa-treated Parkinsonian patients (Mendlewicz et al. 1976) may be attributed either to misdiagnosis of Parkinson's disease (Pollock and Hornabrook 1966) or to *l*-dopa treatment. It is inviting to conclude that the etiology of depression in Parkinson's disease differs from that of depression in bipolar affective disorder.

6.6.6. CONCLUSIONS ON AFFECTIVE DISORDERS

Etiology. The hypothetical somatic causes of affective disorders are disturbances in brain NE and/or 5-HT, in the cell membranes, in hormone action or in amino acid transport across the blood-brain barrier (Goodwin et al. 1978, Carlsson 1979, Garver and Davis 1979). It remains to be settled whether these presumed causes are related or not, and whether they act simultaneously or successively (section 4.5).

Central NE and endogenous "NE-depression" and bipolar depression. A number of reasons will be presented that a change in the central NE transmission is a cause of "NE-depression"* and of bipolar affective illness:

1. Measures of central NE transmission are correlated with mood: 1) during depression in endogenous NE-depressive and bipolar patients the urinary MHPG content is low (see above), and 2) after recovery from depressive illness, urinary MHPG appeared to be increased (Shaw et al. 1973, Sweeney et al. 1979). It has to be investigated which NE region is primarily involved in "NE-depression".
2. The changes in urinary MHPG in bipolar patients seem to precede the changes in mood (Schildkraut 1978, Taube et al. 1978).
3. The effects of manipulations of the central NE transmission by the NE re-uptake blocking agents imipramine and desimipramine, and by *d*-amphetamine in endogenous NE-depressive patients are in line with the hypothesis that a change in the central NE transmission is a cause of a change in the mood.

What kind of a change in the central NE transmission would be a cause of endogenous NE-depression is uncertain: at the present time, one can present good evidence for either too much NE or too little NE in endogenous NE-depression (Maas 1979).

* Some, but not all, of the following statements regarding "NE-depression" are more or less circular: if "NE-depression" is defined by a low urinary MHPG content, the statement "in NE-depression central NE metabolism is reduced" is less informative (but not completely circular), but the statement "in NE depression, imipramine is an effective drug" is highly informative.

Central CA and depression in Parkinson's disease. There are some indications that loss of central CA cells or a decrease in the central CA-induced effects is a cause of depression in Parkinson's disease:

1. The loss of central CA cells in Parkinson's disease and the depression in Parkinson's disease may be correlated; at the moment it is uncertain which CA, and which CA region would be primarily involved in depression in Parkinson's disease.
2. Asymptomatical individuals of Lewy body disease have been found; the loss (or dysfunction) of CA cell bodies seems therefore to precede the depression in Parkinson's disease.
3. Manipulations of the central CA transmission are in agreement with the hypothesis that a decrease in the central CA-induced effects is a cause of depression in Parkinson's disease: the depression in some Parkinsonian patients could be treated effectively by *l*-dopa.

Since the involvement of NE rather than other CAs has been suggested in endogenous unipolar and bipolar depression (see above), a loss of NE may be a cause of depression in Parkinson's disease too.

6.7. Suggestions for future research.

Symptoms and syndromes. It is current medical practice to diagnose a disease on the basis of a number of symptoms and other diagnostic criteria (for instance age of onset), and thereupon to investigate the brains of patients with a specified disease (syndrome); this will be called here the "syndrome-oriented approach". Such syndrome-oriented approach is necessary for medical action: classification of the uniques individual patients into larger groups is necessary to get a general idea about the type of treatment. If one has however not the main intention to cure patients, but to explain diseases, correlating symptoms rather than syndromes with other factors (such as brain lesions or biochemical parameters) will be more successful.

A symptom-oriented approach in the explanation of diseases. One can have the purpose of getting to know either the causes and effects of diseases, or the "function" of brain regions. For both purposes, the syndrome-oriented approach has 3 disadvantages all of which can however easily be overcome with a "symptom-oriented approach".

1. Age of onset is a diagnostic criterium in a number of diseases (for instance in the often used diagnostic scheme of Feighner et al. (1972), an age of onset prior to age 40 is a diagnostic criterium of "schizophrenia" and "anxiety neurosis" and "phobic neurosis"). Identical symptoms which manifest themselves at different age, may be diagnosed as different diseases, although the underlying brain changes may be identical. A consequence of this practice is moreover that a very heterogeneous category of symptoms is simply called "dementia" (cf. Lishman 1978).
2. A previous history of neurological and psychiatric diseases is a diagnostic criterium. In my opinion however, no convincing arguments have been presented for giving different names, for instance, to depressions diagnosed before and after a diagnosis of Parkinson's disease (cf. sections 6.2 and 6.6).
3. The presence and severity of the symptoms in a given syndrome differ between individual patients, and this difference is probably related to different brain changes. Combining the symptoms may obscure a brain-defect/symptom relationship.

In my opinion, a syndrome-oriented approach is unnecessary and inelegant for research purposes. If the combined occurrence of a set of symptoms (which might previously have been assumed to be a single disease) correlates with a change in a brain parameter (as is assumed in the syndrome-oriented approach), the finding is not dependent on an assumption, but rather the assumption is validated. If, on the other hand, only one or a few symptoms correlate with a brain change, a discovery has been made which would have been missed under the syndrome-oriented approach.

Neurochemistry and histology. One of the recent swings of fashion is to measure various biochemical rather than histological parameters in the brains in various diseases. The value of such purely biochemical investigations depends heavily on the assumption that the set of neurons using the same neurotransmitter is also a single system in other respects (see section 5.1.2) such as etiology and symptomatology.

Compensation for compensatory actions. The compensatory actions of the NE cells and the NE target cells in the presence of too much or too little NE, especially the "sub-" and "supersensitivity" of the central adrenoceptors are well demonstrated (Atlas and Segal 1977, U'Prichard and Snyder 1978, Crews and Smith 1978, Schwarz et al. 1978, Greenberg and Weiss 1979). If one accepts the possibility of overcompensation, each effect might be justifiably "explained" by both an increase and a decrease in the NE-induced effects (unless one of these possibilities is explicitely excluded) (sections 4.4 and 4.5). Such a situation is scientifically unacceptable. An unequivocal measure of the NE-induced effects is badly missed.

6.8. The effects of disturbances in the human LC.

Vulnerability. Certain brain regions appear to be particularly vulnerable to disturbances: if brain changes take place, the chance is high that these regions will be the ones affected. One of the most vulnerable brain regions is in fact the LC (Alvord et al. 1973, sections 6.1, 6.2.1 and 6.3.1). The changes found in the LC are PHFs (Alzheimer's neurofibril tangles), tangles consisting of straight filaments, extracellular neuromelanin, atrophy, cell death and/or Lewy inclusion bodies.

The LC, intellectual performance and depression. What are the effects of changes in the LC in man?* Cell loss in the LC is probably a cause of intellectual impairments and, at a later stage, of dementia (section 6.3.3). *"The parkinsonian's greatest difficulty is in comprehending and analyzing novel or unfamiliar stimuli"* (Loranger et al. 1972a). Arguments have been presented (section 6.3.3) that this impairment is due to cell loss in the LC, and this is in agreement with the suggested "function" of the LC, based on animal studies (section 3.2.1): the LC cells have been proposed to say "maybe something important is going on; observe what is going on, and stand-by to react". Arguments have been presented that a decrease in the NE-induced effects is a cause of some depressions (section 6.6.6, p. 304); this might be due to a loss of LC cells in combination with other, still unknown, factors, or to a loss of central NE cells other than the LC.

* In a symptom-oriented approach (section 6.7) the data could be provided to answer this question more directly. I will nevertheless attempt to draw some general conclusions from the data on pathology already available.

The LC, dementia and schizophrenia. Arguments have been presented that a severe LC cell loss is a cause of "subcortical dementia", accompanied by the following symptoms: memory impairment, confusion, disorientation, personality change, hallucinations and delusions (section 6.3.2). These symptoms are found in the later stages of Parkinson's disease, Lewy body disease, Hallervorden-Spatz syndrome, progressive supranuclear palsy, endogenous depression, and part of them in schizophrenia. Paranoid symptoms have been found in cases with an increase in brain NE and with Lewy body disease (sections 6.5.1 and 6.5.3), and it has been suggested that a disturbance of central NE transmission is a cause of schizophrenic symptoms (section 6.5.5, and Mason 1979a).

A dream on dreams and hallucations. I will end with a (rather wild) speculation. I have proposed that the LC is active when something important may be going on, and that it improves CNS information processing (section 3.2.1). During paradoxical sleep (and dreaming), the LC is inactive. Let us now make the speculation that NE from the LC is a cue for the CNS on which neural activities are representations of the real outside world, and which merely dreams. If the LC is disturbed (with either increased or decreased NE-induced effects), and the CNS has compensated for this, the distinction between waking and dreaming is reduced or non-existant· waking and dreaming become indistinguishable for the CNS, and the resulting symptoms manifest themselves as confusion, delusions or hallucinations.

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Subject index.

Curriculum vitae.

Paul A.M. van Dongen werd geboren op 18 augustus 1949. Hij bezocht van 1961-1968 het St. Oelbert Gymnasium te Oosterhout (N.B.), waar hij in 1968 het diploma gymnasium-β behaalde.
Van 1968-1974 studeerde hij biologie aan de Katholieke Universiteit van Nijmegen; het kandidaatsexamen biologie met fysica legde hij af in 1972, en het doctoraalexamen, cum laude, in november 1974 met als hoofdvak biofysica en als bijvakken chemische cytologie en vergelijkende en fysiologische psychologie.
Van november 1974 tot november 1975 was hij in dienst van de Nederlandse Organisatie voor Zuiver Wetenschappelijk Onderzoek (Z.W.O.) te Den Haag en heeft hij onderzoek gedaan op de afdeling Medische Fysica en Biofysica van de Katholieke Universiteit van Nijmegen aan de representatie van natuurlijke geluiden in het auditieve systeem van de kat.
Van november 1975 tot juli 1979 was hij in dienst van de Katholieke Universiteit van Nijmegen en werkzaam aan een gezamenlijk projekt van de afdelingen Farmacologie en Anatomie en Embryologie. Hij heeft onder leiding van Dr. A.R. Cools, Prof.Dr. J.M. van Rossum en Prof.Dr. R. Nieuwenhuys onderzoek verricht naar de rol van de noradrenerge locus coeruleus in gedrag; de resultaten van dit onderzoek staan beschreven in dit proefschrift.
Hem is recent een baan aangeboden aan de afdeling Vergelijkende en Fysiologische Psychologie van de Katholieke Universiteit te Nijmegen.

Uit gezamenlijk onderzoek zijn de volgende publicaties voortgekomen:

Van Dongen, P.A.M., H.J. ter Laak, J.M. Thijssen and J.H. Vendrik, Functional classification of cells in the optic tract of a tree shrew (Tupaia chinensis), Exp. Brain Res. 24, 441-446 (1976).

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De ideeën die ten grondslag liggen aan dit proefschrift, zijn in de loop der jaren gerijpt in contacten met de medewerkers van de volgende afdelingen van de Katholieke Universiteit te Nijmegen: Anatomie en Embryologie, Farmacologie, Medische Fysica en Biofysica, en Vergelijkende en Fysiologische Psychologie; de bijdragen van de afzonderlijke mensen tot deze ideeën zijn veelal niet meer te ontrafelen. Inspirerende discussies met John van den Bercken, Rik Broekkamp en Peter Johannesma hebben de grondslag gelegd voor hoofdstuk 5; Peter Johannesma dank ik nog voor zijn suggesties na het lezen van een eerdere versie van hoofdstuk 5. Ton Coenen heeft een aantal suggesties gegeven, die ik graag overgenomen heb, voor de tekst van de secties 1.3.4, 1.4.3 en 2.1.

Het Centraal Dierenlaboratorium heeft op uitstekende wijze zorg gedragen voor de huisvesting en verzorging van de proefdieren, in het bijzonder Albert Peters, Piet Spaan, Jan Koedam en hun medewerkers.

De fotografische opnamen werden gemaakt door de afdeling Fotografie van de Medische Faculteit. Het histologische werk werd zeer deskundig verricht door mensen van de afdeling Anatomie en Embryologie, waarvan ik vooral mevr. Roelie de Boer-van Huizen wil bedanken. Verschillende bibliotheken hebben op prettige wijze medewerking verleend; vooral wil ik vermelden het personeel van de bibliotheek van de Prekliniek te Nijmegen.

Donald Hatch nam de Engelse tekst door en heeft vele verbeteringen voorgesteld, waarvan ik graag gebruik heb gemaakt. Jeanette Peters was een inspirerende, geïnteresseerde leek. Margot Janssen ben ik heel erkentelijk voor het typewerk, de lay-out en de lay-out adviezen voor dit proefschrift; ze heeft dit niet alleen heel mooi gemaakt, maar bovendien in een uiterst

prettige samenwerking.

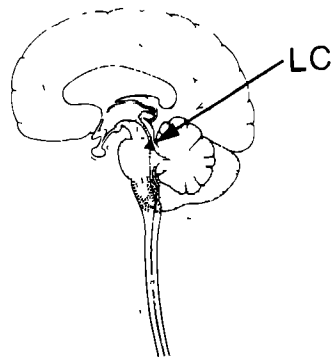
Ik dank Mieke Bögemann voor de jarenlange steun, die ze me verleend heeft, en voor de prettige samenwerking en haar inzet om de tekst van dit proefschrift na te kijken - ook toen we niet meer bij elkaar woonden -.

Samenvatting voor de geïnteresseerde leek.

Wat is de locus coeruleus? Ieder mens heeft links en rechts in zijn hersenen een klein blauw gebiedje: het ligt achter in de hersenen, zoals in de figuur is aangegeven. Dit blauw gebiedje heet de locus coeruleus, in het vervolg afgekort als LC. Zoals gezegd, de LC is maar een klein gebiedje - ongeveer 20 mm^3 - en heeft zo'n 18.000 cellen. Dat is niet veel als je bedenkt dat de hele hersenen zo'n 1.500.000 mm^3 zijn en 10.000.000.000 cellen bevatten. De LC is blauw, omdat daar noradrenaline gemaakt wordt, en daarbij ontstaan blauwe afvalprodukten. De LC is wel klein, maar dat wil niet zeggen, dat hij onbelangrijk is: allerlei delen van de hersenen worden direct door de LC beïnvloed: de grote hersenen, de kleine hersenen en het ruggemerg. Ik ken zelfs niet één ander hersengebiedje, dat zoveel andere delen van de hersenen direct beïnvloedt.

De LC bij proefdieren en bij de mens. Wij zijn, wie we zijn, door onze hersenen: dat maakt hersenonderzoek zo intrigerend, hersenonderzoek gaat niet alleen zomaar over een orgaan zoals de longen of de nieren, maar het gaat ook over onszelf. Om iets over de werking van een lichaamsdeel te weten te komen, is onderzoek met proefdieren vaak de aangewezen methode, want (in mijn ogen) zijn een aantal ingrepen in dieren (en zeker in de hersenen van dieren) wèl geoorloofd, terwijl je die ingrepen bij mensen niet mag doen. Bij zulke dierexperimenten moeten we ons wel steeds afvragen in hoeverre de conclusies nog geldig zijn voor de mens. Gelukkig

De ligging van de LC



Figuur met toestemming overgenomen uit Nieuwenhuys e.a. "The human central nervous system", Springer Verlag, Berlin, 1979.

voor de hersenonderzoeker, lijken de LC's van mensen, apen, katten en ratten veel op elkaar: bij al deze dieren bevat de LC dezelfde stofjes en heeft hij contacten met dezelfde hersendelen. Daarom ga ik er voorlopig van uit, dat conclusies over de LC van deze proefdieren ook van toepassing zijn voor de LC van de mens. Voor veel mensen is het verrassend te horen dat nog maar van ongeveer 1/10 van de hersendelen bekend is, waar ze voor dienen. Maar eigenlijk is dat niet zo vreemd, wanneer we bedenken, dat onze hersenen zo gecompliceerd zijn als wijzelf. Ook van de LC was niet bekend, waar hij voor dient. Wij zijn de LC gaan onderzoeken, vooral om meer van de hersenen te weten te komen. We mogen verwachten, dat zulke kennis in de toekomst de genezing van ziektes aan de hersenen ten goede komt.

Communicatie tussen hersencellen. Hersencellen geven voortdurend boodschappen af door kleine hoeveelheden van bepaalde stofjes bij elkaar uit te scheiden: zoals de communicatie per telefoon via stroompjes gaat, zo gaat deze tussen zenuwcellen via stofjes. We willen nu de betekenis te weten komen van de boodschappen van de LC cellen; het was al bekend dat de LC cellen het stofje noradrenaline uitscheiden. De betekenis van de boodschappen van de LC cellen en van noradrenaline onderzochten we nu door stofjes in de hersenen van katten in te spuiten. Daardoor konden we boodschappen, die normaal ook in de hersenen voorkomen, min of meer nabootsen. (Eigenlijk is dit wat veel stofjes doen, die de hersenen beïnvloeden, zoals koffie, LSD of heroïne, maar door stofjes in de hersenen in te spuiten, werd alleen een klein gebiedje van de hersenen beïnvloed.)

Methode van onderzoek. Ik heb het effect van stofjes in en bij de LC van katten onderzocht. Er was gekozen voor de kat als proefdier om 2 redenen. De hersenen van de kat zijn groter dan van de rat en dat heeft voordelen bij deze experimenten. Bovendien was er in de werkgroep grote ervaring aanwezig in het werken met katten en veel kennis over het gedrag van katten. Ik heb holle naaldjes geïmplanteerd in de hersenen van katten, onder volledige narcose, gericht op van te voren nauwkeurig bepaalde plaatsen. Na een ruim herstel van de operatie, begon ik met de experimenten. Met een nog dunner naaldje heb ik, door het geïmplanteerde naaldje, stofjes ingespoten in zeer kleine hoeveelheden (10 miljardste tot 2 miljoenste gram in ½ miljoenste liter). De hersenen zijn zelf gevoelloos, dus dit kon zonder verdoving gebeuren, maar ik heb wel lieve, handzame katten geselecteerd voor deze experimenten. Ik heb een paar maanden geëxperimenteerd

met een groep katten, en daarna heb ik die opgeofferd met een overdosis narcosemiddel, want ik moest in de hersenen kunnen kijken, waar ik precies ingespoten had. Dat was nodig, want ik kon de holle naaldjes wel 0.05 mm precies implanteren, maar de ene kat is de andere niet, en de LC kan wel een paar mm verschillend zitten. Dus bij nogal wat katten spoot ik niet in, maar naast de LC. dat was heel nuttig, want daardoor kon ik precies onderscheiden welk effect door de LC kwam en welke effecten door hersengebieden vlak bij de LC.

De LC en spierverslapping tijdens dromen. Als we liggen te dromen, kunnen we wel de ervaring hebben, dat we allerlei bewegingen maken, of zelfs hollen, terwijl we toch (als regel) rustig in bed blijven liggen, en dat is maar goed ook. We blijven liggen omdat tijdens dromen de grote spieren van de romp en de benen verslapt zijn. Het is lange tijd de algemene opvatting geweest, dat de LC ervoor zorgde, dat die spieren tijdens dromen verslapt zijn· de betekenis van de boodschappen van de LC cellen zou dan zijn: "Je bent aan het dromen, blijf dus rustig liggen". Na het inspuiten van een stofje (carbachol) heb ik bij katten eenzelfde spierverslapping gevonden als tijdens het dromen, maar ik heb kunnen aantonen dat dit niet kwam door de LC, maar door het hersengebied dat aan de LC grenst.

De LC en angst. Een andere groep onderzoekers meent, dat de LC een "angst kern" is. een hersengebied, dat actief is in een bedreigende situatie en dat zorgt, dat de dieren vluchten of zich verdedigen. Volgens deze theorie zouden de LC cellen zeggen: "Gevaar! Vlucht of verdedig je". Na het inspuiten van een stofje (ook weer carbachol) reageerden een aantal katten alsof ze bedreigd werden ze gromden, bliezen, sloegen met hun nagels uit en trokken zich dan snel terug. Ik heb aan kunnen tonen, dat deze reacties niet door de LC kwamen, maar door het hersengebied dat daar precies vóór ligt. De LC is geen "angst-kern".

De invloed van morfine op de LC en op gedrag. Het was al lang bekend, dat morfine (en dus ook heroïne) de LC cellen helemaal inactief maakt; maar daarnaast heeft morfine op veel andere hersengebieden invloed. Het was ook al lang bekend, dat morfine een heel ingrijpende invloed op de werking van de hersenen heeft. Als katten morfine ingespoten krijgen, waren ze een tijd lang zwaar gestoord: ze reageerden overdreven of niet op geluid, botsten tegen voorwerpen, en bleven een beperkt aantal bewegingen alsmaar herhalen, welke bewegingen alsmaar herhaald werden, verschilde van kat tot kat. Als katten, die met morfine behandeld waren, een remstof

van morfine (naloxon) in de LC ingespoten kregen, dan was korte tijd de werking van de LC hersteld, en de katten hielden enkele minuten op met het steeds herhalen van de bewegingen die ze maakten, en ze reageerden tijdelijk normaal op hun omgeving. Dit duurde maar kort, want na enige minuten was die remstof weggespoeld. Door het tijdelijk herstel van de LC activiteit, was de reactie op de omgeving tijdelijk hersteld.

Mijn theorie. de functie van de LC. Heel recent hebben andere onderzoekers gegevens gepubliceerd, dat de LC cellen actief zijn, als er "iets belangwekkends" in de omgeving van het dier aanwezig is. Ik heb aannemelijk kunnen maken, dat het gevolg van de activiteit van de LC cellen is, dat er beter op de omgeving wordt gereageerd. In mijn theorie is de betekenis van de boodschappen van de LC cellen. "Misschien is er iets bijzonders aan de hand, observeer wat er aan de hand is en sta klaar om te reageren". Dit doen de LC cellen door andere hersencellen als het ware "op scherp te stellen" en door te zorgen dat hersengebieden meer bloed toegevoerd krijgen. Nou moet ik wel toegeven, dat deze theorie nog te algemeen is, en dat deze in de toekomst nog precieser gemaakt zal moeten worden. Het is nog veel te vroeg om nu te kunnen zeggen, wat dit soort verbeteringen in zullen houden.

Waarom zijn we niet altijd op ons qui-vive? Het is natuurlijk gevaarlijk, als de hersenen pas "op scherp gesteld" worden (en als we dus pas op ons qui-vive zijn) als er al iets bijzonders is waargenomen, want dat kan net te laat zijn .... Je zou dus denken, dat het veel veiliger is, als de hersenen altijd op scherp staan. Maar dat is zo vermoeiend de LC zet de hersenen op scherp, en dat kost veel energie, en daarom staan de hersenen niet altijd "op scherp". De hersenen, die bij de mens 1/50 van het lichaam wegen, gebruiken gemiddeld 1/5 van alle energie; en als de hersenen werkelijk actief zijn, nog veel meer. Er moet dus een soort compromis gevonden worden, dat de hersenen nog goed genoeg werken, maar niet al te veel energie gebruiken; en dat gebeurt nu door de LC, die de hersenen pas oppept, als er "misschien iets bijzonders aan de hand is". In deze tijden van energie-schaarste is het dus maar goed, dat we een LC hebben.

Mensen, waarbij de LC kapot is. Bij het ouder worden, en bij sommige ziektes gaan de cellen van de LC dood: wel één derde of meer van de LC cellen kunnen dood gaan. Als ik de gegevens, die gepubliceerd zijn over patienten, zo goed mogelijk combineer, krijg ik de indruk, dat mensen met een kapotte LC de volgende gebreken gaan vertonen: vergeetachtigheid,

trager denken, onverschilligheid, lusteloosheid, depressiviteit en slechter reageren op nieuwe situaties. Tegelijkertijd is hun taalvaardigheid, hun waarnemingsvermogen en hun handelen nog behoorlijk intact. Als nog meer LC cellen dood gaan, en de hersenen proberen zich daaraan aan te passen, dan kunnen de volgende verschijnselen optreden: verwardheid, hallucinaties en waandenkbeelden. Het is sinds kort bekend, dat de LC tijdens dromen helemaal inactief is, en het meest actief als we zelf ook actief wakker zijn. Als we dromen, weten we in de regel ook, dat we dromen: er moet dus "iets" zijn in de hersenen, dat voor de hersenen informatie is, dat we dromen. Ik heb de wilde gedachte geuit, dat het noradrenaline, uitgescheiden door de LC cellen voor de hersenen een signaal is, dat we niet dromen, maar dat wat we beleven, ook werkelijk zo is. Als nu de LC cellen dood zijn gegaan, en de hersenen hebben zich daar zo goed en zo kwaad als het ging aan aangepast, dan is het verschil tussen droom en werkelijkheid voor de hersenen (en dus voor ons) kleiner geworden: verwarring, hallucinaties en waandenkbeelden zijn het gevolg.

Wat koop je nu voor dit onderzoek? Voorlopig nog niets. Laat ik dit maar onomwonden toegeven: het eerste doel van dit onderzoek was meer van de hersenen te weten te komen, en het was niet primair gericht op de toepasbaarheid. Toch mogen we verwachten, dat een betere kennis van de LC heel nuttig zal zijn, want er is een heel scala van geneesmiddelen, die de LC beïnvloeden. Een grotere kennis van de LC zal ertoe leiden dat betere geneesmiddelen ontwikkeld en gebruikt kunnen worden: geneesmiddelen, die meer speciaal gericht zijn tegen wat er mis is, en die - zo goed als het nog kan - de natuurlijke toestand herstellen.

STELLINGEN

Activiteit van locus coeruleus cellen is niet een oorzaak van spierverslapping tijdens paradoxale slaap.

dit proefschrift

Activiteit van locus coeruleus cellen is niet een oorzaak van vlucht- of verdedigingsgedrag.

dit proefschrift

Urogenitale stoornissen na een letsel in het locus coeruleus gebied worden niet veroorzaakt door destructie van de noradrenerge cellen van de locus coeruleus.

De "ventricular hypothesis" (Routtenberg 1972*), volgens welke vele effecten verkregen na injecties van stoffen in hersenweefsel tot stand komen na transport van de stof door de ventrikel vloeistof, is niet houdbaar.

dit proefschrift

Veel onderdelen van het hersenonderzoek en van het hersenen-en-gedragsonderzoek verkeren in een vóórwetenschappelijk (of pre-paradigma) stadium (vergelijk Kuhn 1970, en Swazey en Worden 1975).

De vraag "Wat is de functie van de locus coeruleus ?" heeft meerdere betekenissen; voor veel hersenonderzoekers zijn twee van die betekenissen van bijzonder belang: "Wat doet de locus coeruleus op gedragsniveau ?" en "Waarom is de locus coeruleus ontstaan in de evolutie ?"

dit proefschrift

Bij de huidige kennis is de beste generalisatie over een sensorische stimulus die een oorzaak is van de activiteit van de locus coeruleus cellen, dat dit een stimulus is die aangeeft, dat er "wellicht iets bijzonders aan de hand is".

dit proefschrift

Bij de huidige kennis is de beste generalisatie over de effecten van de activiteit van de locus coeruleus cellen op gedragsniveau, dat deze activiteit de waarneming en reactiebereidheid bevordert.

dit proefschrift

* Referenties zijn te vinden in de algemene lijst met referenties.

Bij de huidige kennis is de "relevance?/stand-by function" van de locus coeruleus de beste functionele generalisatie over de locus coeruleus.

dit proefschrift

Norepinephrine is een efferente neurotransmitter èn een efferente neuromodulator van de locus coeruleus.

dit proefschrift

Om de invloed van een hersenkern op de celactiviteit van een andere hersenkern te onderzoeken dient men te letten op de invloed op de spontane zowel als op de opgewekte (evoked) single cell activiteit.

dit proefschrift

Voor neurotransmitters die een invloed hebben op electrogene ionenpompen bestaat geen ionenconcentratie waarbij een omkeerpotentiaal optreedt.

Aangezien de term "neuromodulator" in minstens 7 verschillende betekenissen gebruikt wordt (Hamberger et al. 1976, Oka en Hosoya 1977, Woodward et al. 1979, Torda 1977a, Renaud 1978, Barchas et al. 1978, Orrego 1979), dient bij het gebruik van deze term expliciet de bedoelde betekenis vermeld te worden.

Vanuit een energetisch oogpunt is voor een zenuwcel de rustpotentiaal de actieve toestand, en de actiepotentiaal de passieve toestand.

De tweedeling "excitatie" versus "inhibitie" geeft een te beperkte beschrijving van de gevarieerde effecten, die een zenuwcel op zijn doel-zenuwcel kan hebben.

Een hersenonderzoeker wordt geconfronteerd zowel met de kennis dat de hersenen complex zijn, en dat dus simpele hersentheorieën onjuist zullen zijn, als met het mes van Ockham, dat steeds de simpelste theorie dient te worden aangehouden.

Veel woorden en zinnen in geschriften over neurobiologische onderwerpen en over hersenen-en-gedrag hebben zoveel betekenissen dat ze geen betekenis hebben.

Een functie is niet localiseerbaar in het centrale zenuwstelsel.

dit proefschrift

De hersenen van de mens bepalen de grenzen van de kennis van de mens, maar de kennis van de kennis van de mens (kenleer) beschrijft de grenzen van de kennis over de hersenen (neurobiologie). De neurobiologie kan dus nooit de basis van de kenleer zijn (vergelijk Wilson 1978).

Het neerschrijven of uitspreken van "Ik ben me bewust van..." is een fysische gebeurtenis waarvan een mentale gebeurtenis een oorzaak is; het filosofische standpunt dat mentale processen geen oorzaak zijn van fysische processen lijkt onjuist (vergelijk Hospers 1967, pp. 394 - 398).

In de teleologische discussie hebben de Engelse woorden "goal" en 'purpose" verschillende betekenissen; het is verwarrend, wanneer beide woorden worden vertaald door het Nederlandse woord "doel".

Omdat albinisme en daarmee verwante erfelijke afwijkingen gepaard gaan met afwijkende verbindingen in het centrale zenuwstelsel (Nattan 1974, Guillery 1974, Lund et al. 1974, Mustari en Lund 1976, Shatz 1977, Creel et al. 1978, Shatz en LeVail 1979), mogen conclusies uit hersenonderzoek verricht aan albino's niet zonder meer gegeneraliseerd worden naar niet-albino's; daarom is het te betreuren, dat zeer veel hersenonderzoek aan albino proefdieren verricht wordt.

Woestijnratten *(Meriones unguiculatus)* gehuisvest in een semi-natuurlijke omgeving vertonen veel gewelddadiger intraspecifiek aggressief gedrag (eigen observatie) dan vermoed werd op grond van waarnemingen van deze dieren gehuisvest onder laboratorium omstandigheden (vergelijk Schwentker 1968).

V. Schwentker, 1968, "Care and maintenance of the mongolian gerbil. A basic manual for laboratory animal technicians", Tumblebrook Farm, Brant Lake, N.Y.

In de praktijk van het experimentele onderzoek worden vaak slechts die verbanden statistisch getest "waar iets in lijkt te zitten", worden niet-statistisch significante uitkomsten weggelaten, en wordt vaak niet gecorrigeerd voor het aantal tests dat uitgevoerd is: de feitelijke kans dat de beschreven resultaten slechts toeval zijn, is vaak groter dan de vermelde p-waarde.

In het rooster van iedere opleiding dienen de hoofdspecialisaties van alle vervolgopleidingen voor te komen.

In het Nederlandse belasingsysteem is de kans op "winst" erg groot bij belastingontduiking; als "rationeel gedrag" gedefinieerd wordt als "gedrag met de grootste winstverwachting", dan is belastingontduiking rationeel gedrag; dit ondermijnt het belastingstelsel.

Uit de pupilreacties op verschillende stimuli (Hess 1975) kan men verklaren, waarom dichters licht met geluk associeren.

E.H. Hess, 1975, Sci. Amer. 233, 5, 110 - 119.

De logica van de hersenen is ver te zoeken.

Als "abnormaal" betekent "afwijkend van wat in de regel wordt waargenomen", dan is voor hogere primaten het uitsluitend heterosexuele gedrag abnormaal.

Nijmegen, 25 september 1980

Paul A.M. van Dongen