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Metabolism of N-Alkyl Substituted Aminopropiophenones in Man in Comparison to Amphetamines and Ephedrines [1]

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Abstract—Dimethylaminopropiophenone is reduced (40 %) and excreted (25 %) unchanged in fairly equal amounts and to a small extent demethylated. Diethylaminopropiophenone is mainly reduced (20 %) and dealkylated (25 %). The dealkylated product ethylaminopropiophenone is mainly excreted unchanged (40 %) and also the diethylnorephedrine formed is mainly excreted unchanged and for a small part dealkylated to ethylnorephedrine.

Diethylaminopropiophenone has no big excretion of the unaltered compound (2 %). The reduction of the tertiary amines is much more pronounced than that of the secondary ones. The tertiary aminopropiophenones are rapidly dealkylated to the secondary ones and this behaviour is in accordance with the rate of dealkylation of tertiary amphetamines.

The metabolism of aminopropiophenones shows 4 competitive pathways for eliminating the compound from the body. The metabolic routes that take place are parahydroxylation, reduction, deamination, dealkylation, but also there is excretion of the unchanged compound and the metabolites by the kidneys.

Schreiber (1) produced evidence for all these reactions in the metabolism of diethylaminopropiophenone, but stated also that the parahydroxylation is a minor pathway. Beckett (2, 3) examined the excretion of 4-chloroethylaminopropiophenone and its metabolites and found that the total amount excreted of non-acid compounds was about 50 %. When examining the N-alkylsubstituted aminopropiophenones and their metabolites excreted into the urine, it is observed that all the compounds show a particular metabolic behaviour.

Aminopropiophenone is partly reduced to norephedrine (32 %). Tl ephedrine formed is excreted mainly due to its low lipid solubility (4

N-methylaminopropiophenone is mainly demethylated to aminopro none (60 %). Ethylaminopropiophenone is excreted mainly unchanged i urine (45 %) and there is little dealkylation and reduction.

Isopropylaminopropiophenone is mainly excreted into the urine uncl but the rapid decrease of the compound from the body resembled th elimination of isopropylamphetamine (5).

The compounds N-ethyl, N-propyl, N-isopropyl and N-butylamino phenone all have nearly the same *p*Ka value (Table I) and lipid solubili this may be the most important factor in the metabolism and renal ex competition.

TABLE I

pKa values, apparent and true partition coefficients of some N-alkyl substituted propiophenones

Compound	*p*Ka	TPC_{hept}	TPC_{chl}	APC_{hept}	AP
Aminopropiophenone	8.16				
N-methylamino etc...	7.59			0.22 keto	48
				0.10 enol	20
N-ethyl etc...	8.40	0.500	214	0.05	1
N-propyl etc...	8.46	27.4	2750	2.25	22
N-isopropyl etc...	8.45	28.2	3050	2.25	24
N-butyl etc...	8.47	157	15400	12.2	120
N-dimethyl etc...	8.09	4.60	40.5	0.78	
N-diethyl etc...	8.78	525	15000	21	60

APC_{hept} is the apparent partition coefficient at pH 7.40 in the system heptan (Teorell buffer).

TPC_{chl} is the true partition coefficient in the system chloroform/water.

Dimethylaminopropiophenone is reduced (40 %) and excreted (25 % changed in fairly equal amounts and to a small extent demethylated (F

Dimethylnorephedrine also is slightly demethylated to methylnoreph and mainly excreted unchanged (6).

Diethylaminopropiophenone is mainly reduced (20 %) and dealk (25 %). The dealkylated product ethylaminopropiophenone is mainly ex unchanged (40 %) and also the diethylnorephedrine formed is mainly ex unchanged and for a small part dealkylated to ethylnorephedrine.

Diethylaminopropiophenone has no big excretion of the unaltered com (2 %). This can be explained by its high lipid solubility and the compar

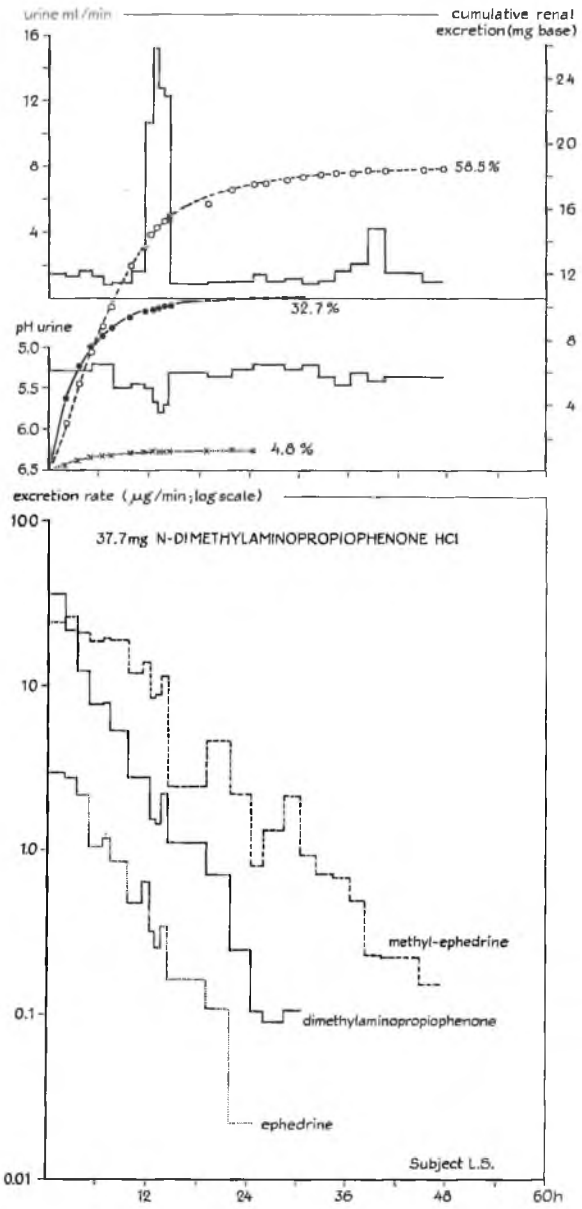

FIG. 1

Renal excretion rate, urine pH, urine production and cumulative renal excretion of

The observed quantitative difference in the way of metabolism of a propiophenones compared to that of amphetamines can be explained as f

For the deamination and dealkylation a H atom is needed (7) and atom is directly involved in the rate limiting step of this oxydative deami When the H atom is not available, as with phentermine, the oxydative r is blocked, and the compound is excreted unchanged in the urine for Aminopropiophenones show a keto-enol tautomerism. This means tha certain fraction of the total amount of aminopropiophenone present liver or metabolic site of the enzyme, the required H atom is present mination occurs to a much smaller amount than with amphetamines. Inc the substituent in N-aminopropiophenone did not show an increase i kylation as observed with the dextro isomers of N-alkylsubstituted am mines. It was observed with the dealkylation of dextro and levo N-alkyl tuted amphetamines that the key for the reaction is the steric configura the hydrogen atom of the amphetamine moiety.

With analogy to this observation it may be understandable that th of the size and nature of the substituents at the nitrogen atom of ami piophenones is less pronounced.

In the keto-enol tautomerism, the enol form of the aminopropiophen excreted unchanged into the urine, or conjugated and then excreted. T form can be deaminated and dealkylated.

With the combined gaschromatograph-mass spectrometer LKB 9000 observed that the KOH of the column 20 % Apiezon-5 % KOH ca dehydrogenation of the secondary aminopropiophenones. The structu be a linear one. The tertiary amines, diethyl- and dimethylaminopropiop were not dehydrogenated, and therefore it must be assumed that the st is more a cyclic one. The reduction of the tertiary amines is much mo nounced than that of the secondary ones. The tertiary aminopropiopl are rapidly dealkylated to the secondary ones and this behaviour is in acc with the rate of dealkylation of tertiary amphetamines.

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Psychopharmacology of Amphetamines

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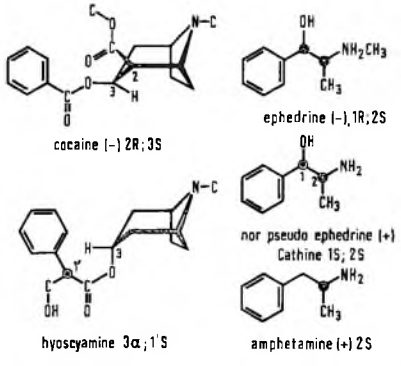
INTRODUCTION

Amphetamine is a prototype of the psychomotor-stimulant drugs or "wekamines". Alertness, stimulation of loco-motoractivity, suppression of fatigue and sleepiness are typical for the central stimulating effects of amphetamine and a number of related compounds.

Ephedrine, the active principle of *Ephedra vulgaris* (*2*) and cathine or nor-pseudo ephedrine from the leaves of *Catha edulis* (*1*) are the oldest known naturally occurring amphetamine derivatives with psychomotor stimulant action. Cocaine from *Erythroxylon coca* (*7*), although structurally not related to amphetamine (Fig. 1) is a psychomotor stimulant drug, very much so like amphetamine and methamphetamine.

Methamphetamine, the *N*-methyl analogue of dextro rotatory amphetamine, has been synthetized long before amphetamine and it is still the most potent psychomotor stimulant drug at present available.



DIFFERENT COMPONENTS IN THE CENTRAL STIMULANT ACTION OF AMPHI

Cocaine and cathine were the first drugs used for the suppression of appetite. Toxic side-effects as the induction of paranoid psychotic stat described for cocaine almost a century ago (*6*). The first clinical applic phetamine was in the treatment of narcolepsy (*8*). Amphetamine-like dru used also in cases of depression, Parkinson's disease, hyperkinesia in ch elderly mentally retarded patients. Its therapeutic success is at the best for the treatment of narcolepsy and adipositas.

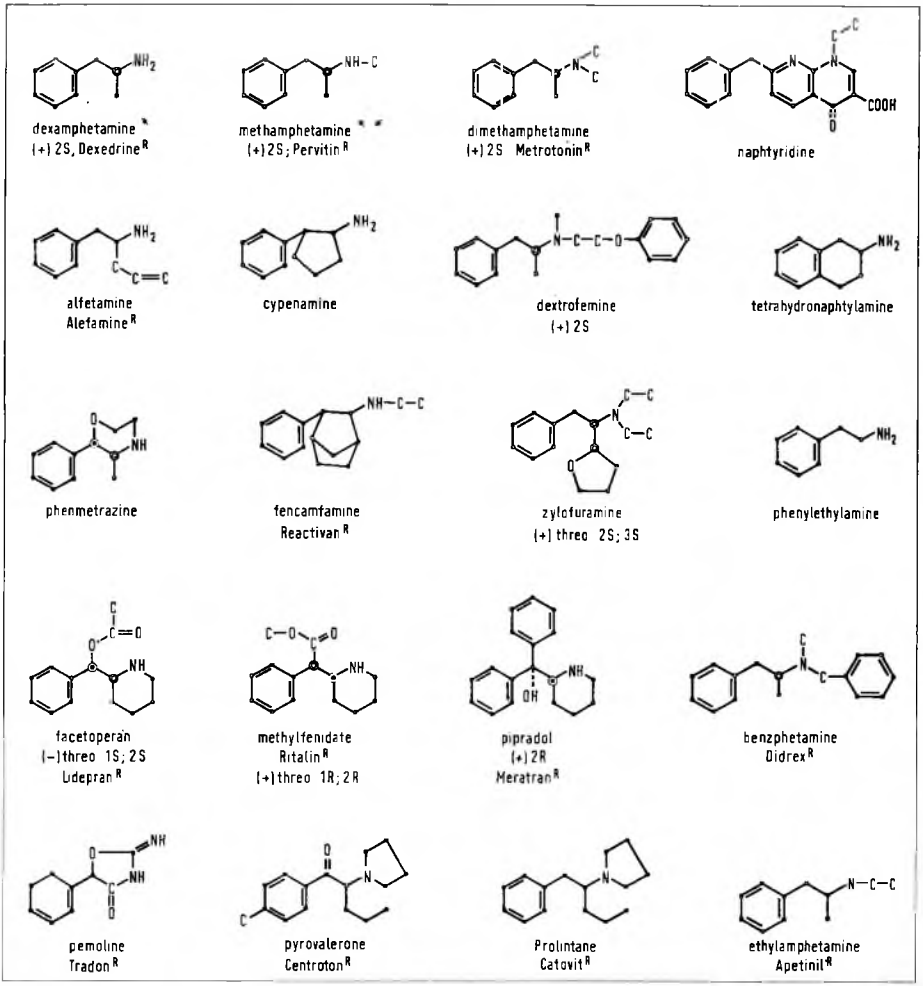
On the other hand, the non-medical use of amphetamine both with resp by athletes, cyclists etc. and drug-abuse by addicts has increased tremend the last decade. In case of doping suppression of fatigue is the desired e addicts the euphoria is aimed at, leading to a perversion of the reward system in the brain. Because of the high doses (especially i.v.) used, a p chosis is often experienced together with an excess of stereotyped behav grinding, ticks etc.

Good evidence is available that the appetite suppression brought abou amine is unrelated to its typical psychomotor stimulant effects. There ar in this group that are purely stimulant (*e.g.* pemoline), mainly stimulant doses appetite reducing (*e.g.* methamphetamine, phenmetrazine), stimu as appetite suppressive in the same doses (*e.g.* amphetamine), mainly su in larger doses stimulating (*e.g.* amfepramon) and finally merely appetit (*e.g.* chlorphentermine and fenfluramine) (*16*).

Also the various other components of the amphetamine action as fati sion, awakening effects, motor-stimulant actions, euphoric effects, psyc and stereotyped behavioural effects are not necessarily connected. In vatives one component may be more pronounced than in another.

In addition the various amphetamines also differ in a pharmacokineti implies that the various amphetamine derivatives may differ with respec of absorption, the rate of elimination and the rate of penetration into in the brain. As a result certain amphetamines may produce strong eup because they reach the brain very rapidly, while for other drugs in t euphoric effects may almost be absent.

Obviously the way of application is very important for the effects that a administration of various amphetamine-like drugs. Following intraven tration, the concentration in the blood is initially very high and if such penetrate into the brain rapidly also a very large concentration in the brai As a consequence such a compound may produce very intensive but



* also in use as anorectic drug
* * to be considered as a dangerous addictive drug

Fig. 2.

STRUCTURE-ACTIVITY RELATIONSHIP

The phenylethylamine moiety seems to be essential for the psychomotor-stimulant action of amphetamine derivatives (*19*). Phenylethylamine as such is a weak psychomotor stimulant because it is rapidly metabolised whereas after blockade of bio-

active (*18*). On the other hand various groups may be attached to the side-chain in the amphetamine derivatives, without losing too much act

As pointed out before, we have, however, to realise that the various in the action of amphetamine are not represented quantitatively to the in the various derivatives. This means that in structure activity relations to consider a particular effect, and not in the one study one effect and case another effect, and still in other cases a mixture of the various actio a number of well-known amphetamine-like compounds have been pres this table it may be seen that these compounds are structurally related. pounds except a few are phenylethylamine derivatives.

As pointed out in the INTRODUCTION cocaine belongs also to the p stimulant drugs, although the chemical structure of cocaine is complet from those of the amphetamines and their derivatives. In addition the synthetic compounds like pemoline and NCA (naphtyridine), which are acidic substances, while the amphetamine-like compounds have basic na It is therefore likely that the mechanism of central stimulant action c compounds may differ from those of amphetamine and methamphetam be remarked here, that the mechanism of action of cocaine also differs f amphetamine. It has long been known that the cocaine action is abolished pretreated with reserpine, while the action of amphetamine is not abo Some investigators find an increase of the effect of amphetamine followi treatment, others find no change while still others note a decrease. Furth change in the action of amphetamine is dose-dependent (*11*, *13*). At c vation, it appears that the so-called "over-all" activity of amphetamine changed by pretreatment with reserpine, but that certain components i are augmented while others are reduced. The reserpine treatment theref the various components in the action of amphetamine. It is therefore certain amphetamine-derivatives may be blocked completely by reserpin compounds particular components in the action are pronounced.

Not only amphetamine-like drugs may differ considerably in chemic and nevertheless produce a similar central stimulant action (although components in this effect may be quantitatively and qualitatively differen closely related amphetamine-like compounds may have central stimulant others may not. For instance it is known that there is a considerable di tween the central stimulant action of dextro-methamphetamine and levo-m amine. This effect is even more pronounced in isopropylamphetamine. propylamphetamine is a central stimulant while levo-isopropylamphet central stimulant action and rather induces fatigue.

It is not at all certain that a particular amphetamine-like

body into secondary and primary nitrogen containing compounds. So if benzphetamine is dealkylated by removal of the benzyl group, methamphetamine is formed. This process of biotransformation occurs slowly, so that after administration of benzphetamine, a slow continuous production of methamphetamine occurs, whereby long-lasting low levels of methamphetamine are produced in the body. If the biotransformation is further retarded, but not yet completely blocked, the production of methamphetamine is further retarded and the effect produced by benzphetamine is extremely long-lasting. Complete blockade of biotransformation, however, abolishes the central effects of benzphetamine. This is so because benzphetamine itself is hardly at all excreted in the urine, while amphetamine and methamphetamine are reasonable well excreted (*20*). Therefore, benzphetamine itself does leave the body as such but its main route of elimination is dealkylation to methamphetamine and eventually amphetamine. From these data it may be concluded that benzphetamine when injected directly into the blood would not cause a central stimulation but it will take some time until sufficient methamphetamine is formed. So although methamphetamine is a dangerous addictive compound the drug benzphetamine, from which methamphetamine can be formed, may not necessarily or probably not at all be addictive.

BRAIN MONOAMINES AND AMPHETAMINE ACTION

Reserpine blocks certain amphetamine actions and completely blocks t
certain amphetamine-like compounds (Fig. 3) (*7a*). In this figure a rhesu
injected with amphetamine resulting in a staring attitude. Reserpine cau
known inactivation without severe sedation. In the reserpinized monkey a
seems to induce hallucinatory effects which have a "paranoid" character. I
known that reserpine has profound influences on brain monoamines. I
the level of noradrenaline and 5-hydroxytryptamine but also on the le
amine. As pointed out before, the effect of cocaine is blocked by re
reserpinized animals in which cocaine is ineffective, the cocaine effect
stored by giving these animals a low dose of L-Dopa. Administration of D
of dioxyphenyl serine from which directly noradrenaline may be fo
5-hydroxytryptophane from which 5-HT will be formed are not effective
the action of cocaine in reserpinized animals. From such experiments it
likely that dopamine is of predominant importance for the action of co
the effects of amphetamine in reserpinized rats in which especially ster
haviour is pronounced but in which also a typical social interaction occ
pendent on dopamine. In normal rats a low dose of dexamphetamine
causes a substantial increase in locomotor activity. Rats in a group norm
their new environment but soon begin to form clusters in a corner of th
amphetamine treated rats run their own way in a hurry, while disrega
other (Fig. 4A). In higher doses (5–10 mg) dexamphetamine causes ster
haviour as gnawing, spitting and biting, running backwards in their cages
Social interaction is reduced to a minimum (*9*, *10*).

Merely stereotyped behaviour is seen after a low dose of apomorphin
grouped male Wistar rats also bizarre social behaviour is observed (Fig. 4

If the level of brain dopamine is increased by injection of Dopa and a
Dopa decarboxylase inhibitor, this bizarre social interaction together
stereotyped behaviour is seen already after a low dose of dexamphetamin

In reserpinized animals the levels of all monoamines are decreased b
thesis of dopamine which mainly occurs outside the synaptic vesicles is no
This means that the synthesis of dopamine continues under the influence
but that synthesis of noradrenaline is retarded because noradrenaline is
inside the synaptic vesicles and the vesicles are not able to store amines
This implies that under the influence of reserpine the involvement of dopam
tuated, while the involvement of noradrenaline is evidently reduced. As a c
amphetamine may liberate or release dopamine in reserpinized animals
lease may be the cause of the stereotyped behaviour and abnormal s

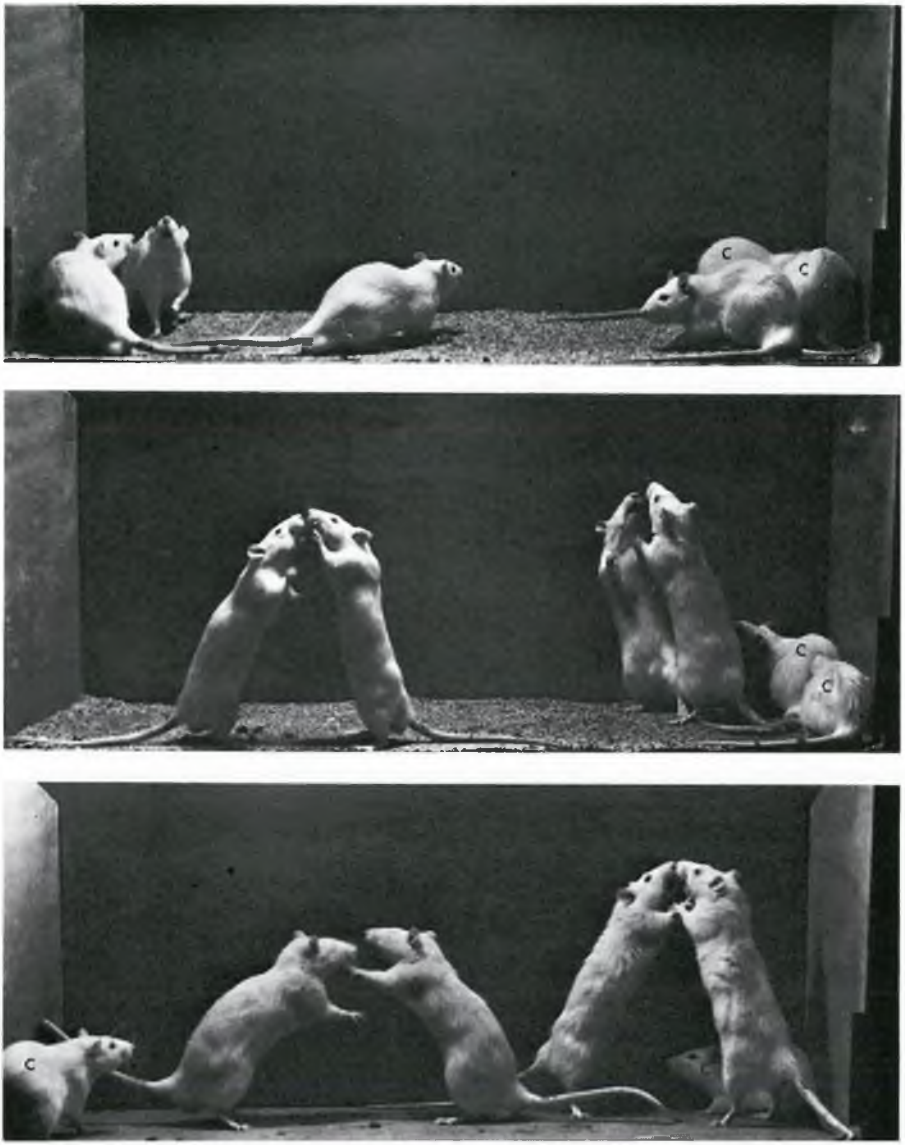


Fig. 4. Effects of amphetamine on behaviour in rats. In each case 4 rats were treated, while 2 served as controls (c). *A*: dexamphetamine (5,62 μmol/kg = 1 mg/kg of sulphate) 30 min. after i.p. injection. The injected rats are very active and run around on their own. The controls cluster together in the corner of the cage; *B*: the same rats after apomorphine (3.16 μmol/kg = 1 mg/kg of the HCl salt). 10 min after i.p. injection. Stereotyped movements as gnawing and biting is observed. Following introduction of noise the rats run around and stand against each other, when they meet. The rats

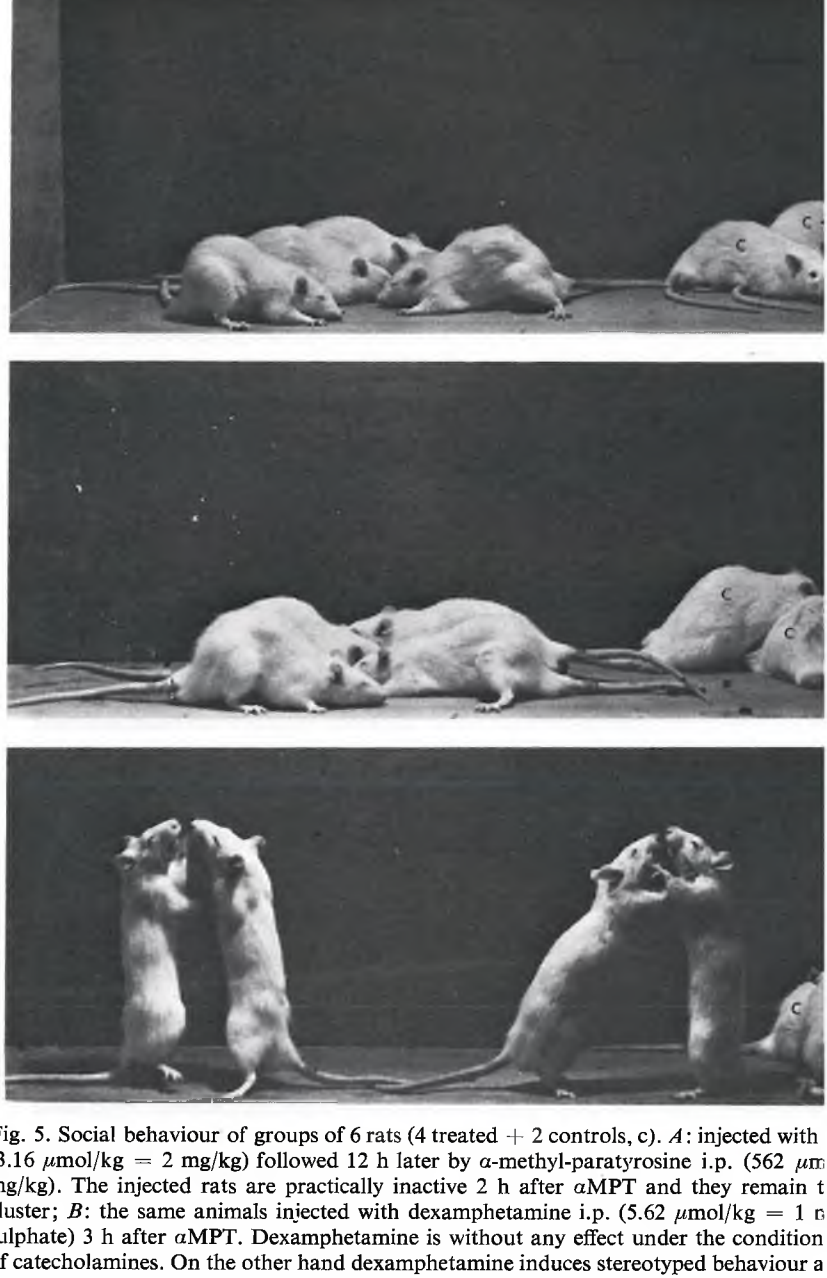


Fig. 5. Social behaviour of groups of 6 rats (4 treated + 2 controls, c). *A*: injected with (3.16 μmol/kg = 2 mg/kg) followed 12 h later by α-methyl-paratyrosine i.p. (562 μm mg/kg). The injected rats are practically inactive 2 h after αMPT and they remain t cluster; *B*: the same animals injected with dexamphetamine i.p. (5.62 μmol/kg = 1 n sulphate) 3 h after αMPT. Dexamphetamine is without any effect under the condition of catecholamines. On the other hand dexamphetamine induces stereotyped behaviour a

This implies that amphetamine with respect to the components of action that are still predominant after reserpine treatment (as stereotyped behaviour) are due mainly to the involvement of dopamine. Since amphetamine may also release other monoamines in the brain under normal circumstances the central effects may be a combination of the results of the release of all three monoamines. Reserpine does not have the same quantitative effect on the various monoamines in the brain with respect to their levels and turnover rate. It is therefore understandable that the various components in the action of amphetamine in reserpinized animals are changed to a different extent. If animals are pretreated with α-methyl-paratyrosine and thereafter injected with reserpine, brain levels of noradrenaline and dopamine are reduced to a very large extent. In this condition the action of all components of amphetamine are blocked.

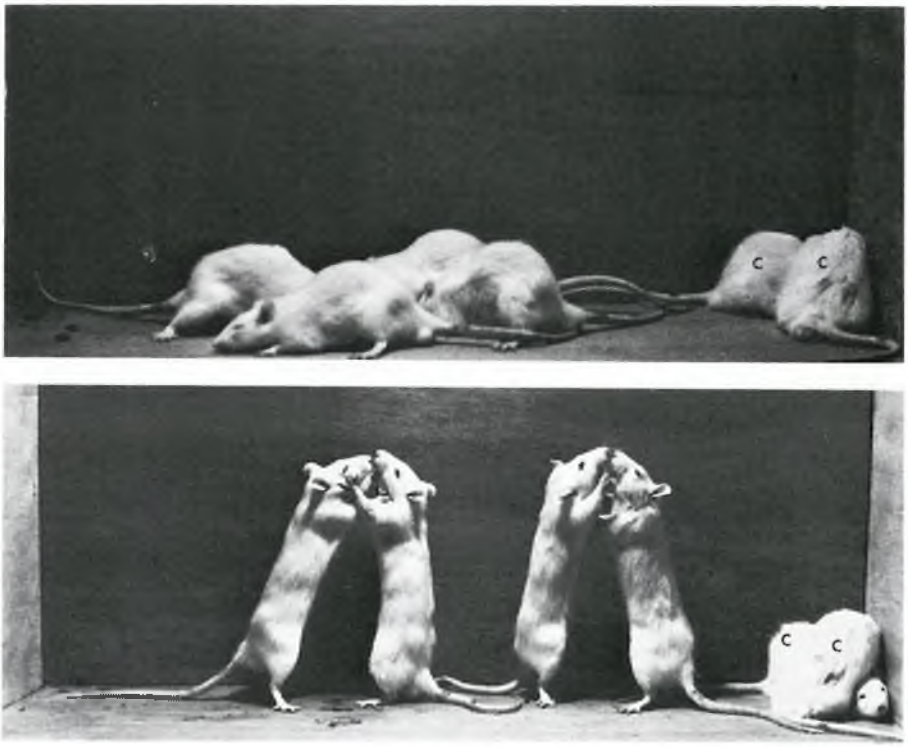
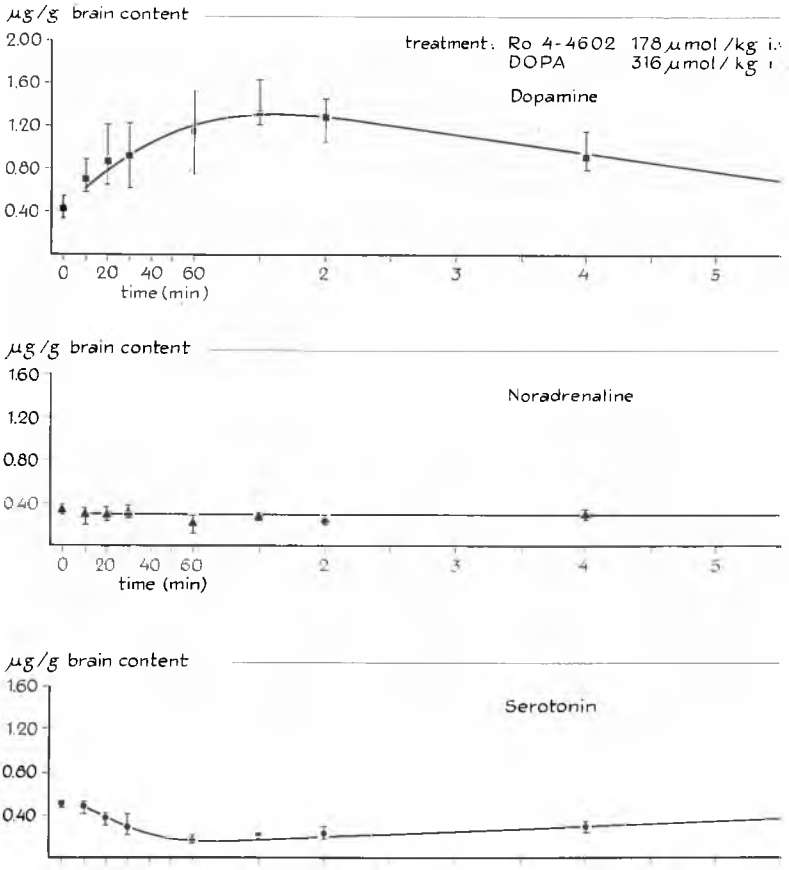


Fig. 6. Social behaviour in groups of 6 male rats (4 treated + 2 controls, c). *A*: rats pretreated with reserpine and αMPT as in Fig. 3A were given a low dose of the peripheral Dopa decarboxylase inhibitor RO-4-4602 i.p. (100 μmol/kg = 29 mg/kg) and Dopa i.p. (31.6 μmol/kg = 6.4 mg/kg),

The stereotyped behaviour and abnormal social interaction of dexamphe be restored, however, if these animals are injected with a low dose of Dopa of Dopa does not change the behaviour of animals. They appear to b reserpinized state (Fig. 6A). If, however, now amphetamine is injected the behaviour and social interaction is observed again (Fig. 6B). These experi point to the strong involvement of dopamine in the action of amphetami pect to these two components in its action. It must, however, be realized condition serotonin levels are decreased substantially as well as noradren So the effects seen under these circumstances after injection of amphetam due not only to the involvement of dopamine alone, but also of a lack c neurotransmitters. A further indication of the importance of a balance b various monoamines of the other neurotransmitters is the finding that I



injected in rats pretreated with a Dopa-decarboxylase inhibitor exhibits a strong abnormal social interaction and stereotyped behaviour (*5*). In these rats, brain dopamine levels are increased and this increase is paralleled by a decrease in brain serotonin levels, whereas noradrenaline levels remain constant (Fig. 7). On the other hand, if Dopa is combined with a monoamine oxydase inhibitor quite different effects are observed. Under these circumstances stereotyped behaviour is practically absent but the rats are excited. Following Dopa and a MAO-inhibitor, dopamine levels are increased also, but at the same time serotonin levels are increased considerably (Fig. 8).

It has been shown that amphetamine facilitates self-stimulation in rats with electrodes in the reward areas in the hypothalamus and mid-brain areas (*12*). This facilitary effect of amphetamine can be suppressed by disulfiram, a drug that inhibits the conversion of dopamine into noradrenaline. Reversal of this suppression occurred with intraventricular injection of noradrenaline, but not if dopamine was given instead (*21*). So also noradrenaline certainly fulfills a role in certain components of the action of amphetamine. Whether under normal circumstances also the release of serotonin is of importance for the overall action of amphetamine is probable but not yet certain. It must again be stressed that changes in the relative role of the monoamines both in the various levels and turnover rates of the free monoamines to a large extent determine the various components in the action of amphetamine. For instance increase of dopamine and decrease of noradrenaline may result in stereotyped behaviour, while an increase of dopamine and an increase in serotonin and noradrenaline may cause for example locomotor activity, while an increase of both noradrenaline and dopamine may change motivation. The use of selective amphetamine-like compounds which have one or only a few of the various components of the amphetamine action present, as well as the use of selective depletors of brain monoamines and drugs that selectively increase either the level and or turnover rate of these amines may be of great help in elucidating the action of amphetamine and its derivatives. Also the use of selective antagonists of neurotransmitters may be of great advantage. There is reasonable evidence that neuroleptic drugs block certain effects of amphetamine by inhibiting dopamine at the level of its receptors (*14*).

A drug that has certain components of the action of amphetamine but lacks others, is apomorphine. Apomorphine mainly increases stereotyped and abnormal social behaviour, but hardly increases locomotor activity in rats and other animals. It must be realized that apomorphine in humans causes vomiting probably by involvement of dopamine receptors in the area postrema. The interesting aspect in this regard is the finding that neuroleptic drugs which very effectively block dopamine and so completely antagonize the stereotyped behaviour and abnormal social behaviour of

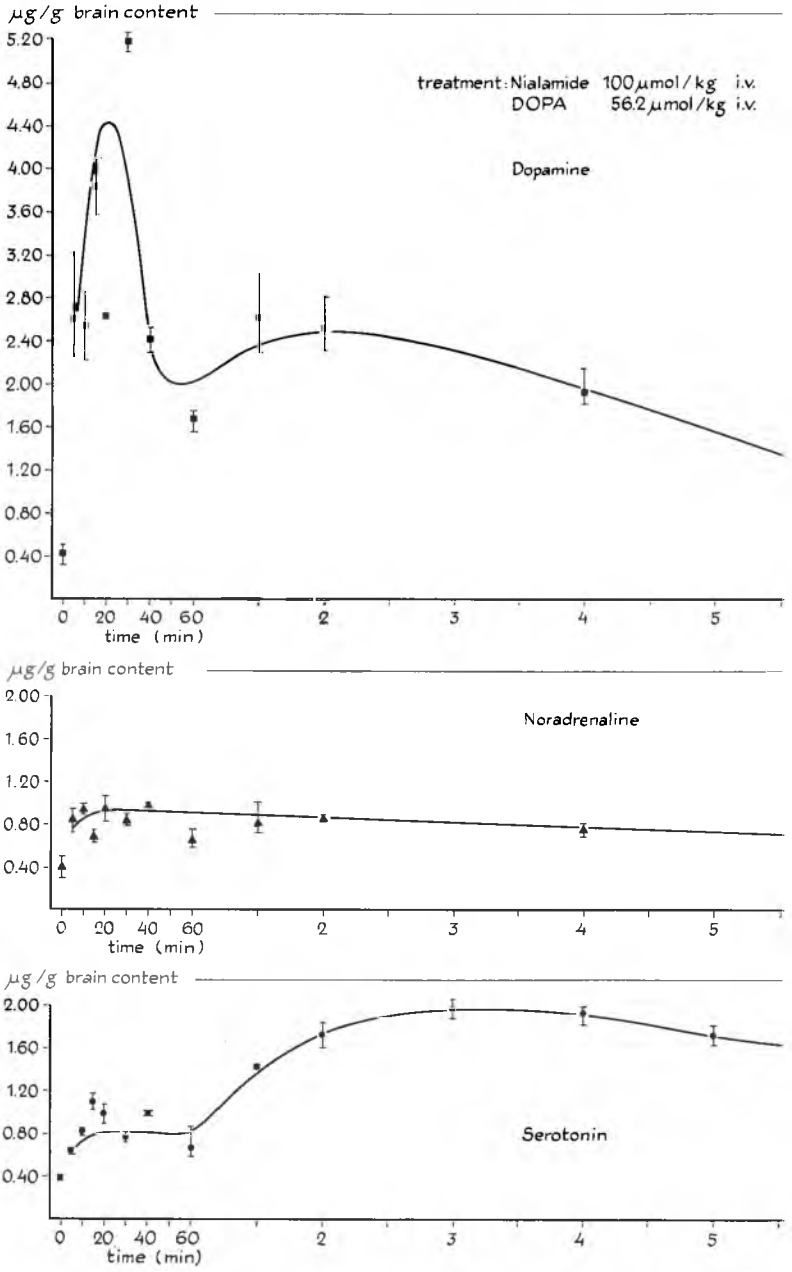


Fig. 8. Levels of brain monoamines in male Wistar rats at various times after i.p. inje

is mainly found in the nigro–striatal system, noradrenaline especially in the hypothalamus and serotonin in the midbrain raphe nuclei. It is not at all certain that amines found in the largest amounts in certain areas would fulfill their most important role in that area. It may therefore be true that monoamines which are found only to a small extent in a particular area may be of great importance for the action of for instance amphetamine. In the light of the foregoing discussion it is likely that amphetamine has a multiple action, therefore may act in different parts of the brain and in the various parts in different ways.

Since dopamine is found in the caudate nucleus and other areas mainly, it is interesting to note that with injection of dopamine directly into the caudate nucleus, the same effects can be induced as with the injection of amphetamine in those areas. The effects in this case are mainly stereotyped behaviour but of a restricted type, because of the fact that while injection of such a substance in minute amounts in the caudate nucleus only a small part of that area is reached (*3*).

Studies of the locus of action of amphetamine derivatives which are more restricted in their components of action in combination with drugs that directly interfere with brain monoamines metabolism may be used for a further elucidation of the mechanism of action and the locus of action of amphetamine and other psychomotor stimulant drugs in the central nervous system. As practical consequence from such studies, selective compounds may be found that preferentially may be used in the treatment of narcolepsia or for hyperkinetic children without producing euphoria and addiction. As pointed out in the beginning of this paper not only the mechanism of action, but also the locus of action has to be taken into account in designing better drugs of this class. In addition the pharmacokinetics or rate processes governing absorption distribution and elimination, should be studied in order to design an optimal amphetamine-like drug which can be used for the correct medical indication.

SUMMARY

A review of the psychopharmacology of amphetamine-like compounds has been given with emphasis on:

(1) Different components in the central stimulant action of amphetamine and derivatives.

(2) Structure–activity relationships taking into account differences in the relative contribution of the various components of the central stimulant action as well as differences in pharmacokinetic parameters.

(3) The significance of the various brain monoamines in the various components of central stimulant action.

(4) The locus of action of amphetamines in the brain.

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