THE NEURAL BASIS OF MEMORY AND LEARNING
PHARMACOLOGICAL ASPECTS OF BRAIN RESEARCH

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INTRODUCTION
Generally, the problem of cerebral representation of behavioral patterns is studied by means of classical methods which use electrical stimulation and electrocoagulation of well-defined structures, within the brain. However, it is difficult, when using these methods, to ascertain whether the observed responses are due to the involvement of the target area or adjoining structures, in view of the possible spread of the current or destruction of passing fibers. Recently, several workers have shown that there exists a biochemical topography of putative neurotransmitters within the brain (1-3). It is generally accepted that these compounds released from presynaptic structures initiate or modulate a series of reactions at postsynaptic target cells. In view of these findings, chemical stimulation may be regarded as an additional and more subtle tool for investigating the cerebral representation of behavioral patterns. Chemical stimulation by means of neurotransmitters or functionally related compounds involves selective stimulation of specific structures.

It is currently believed that the basal ganglia regulate the normal muscular activities by means of a complex system of facilitation and inhibition. Disruption of this balance would lead to abnormal motor manifestations such as hyperkinesia and hypertonia (4). The caudate nucleus—a large component of the basal ganglia—is loaded with putative neurotransmitters such as acetylcholine, dopamine and serotonin (5-12). During the last decade considerable information has become available regarding the association of intracaudate dopamine with specific behavioral patterns (13-16).

Recently, it has been shown that dopamine introduced locally into the rostromedial part of the caput caudati in cats induced stereotyped movements of the head and limbs (15-17), reduction of stimulus-induced behavior such as licking and cleaning, as well as reduction of spontaneous behavior such as walking and standing. The nonpatterned limb movements, athetoid and choreiform in nature, are particularly interesting because small lesions restricted to the anteroventral part of the caput caudati also result in choreo-athetosis of the limbs (18). Neither the introduction of dopamine into the anteroventral part of the caudate nucleus nor lesions of the rostromedial part of the caudate nucleus leads to this phenomenon (17). These data suggest a somatotopic organization within the caudate nucleus. Indeed, it has been reported that the head of the caudate nucleus in cats represents two localized functional regions: the inhibitory anteroventral area and the facilitatory rostromedial area.
This increased our interest in the functional role of the so-called inhibitory anteroventral part of this nucleus.

In the present study, the role of this part of the brain was investigated by selective chemical stimulation of structures sensitive to putative neurotransmitters occurring in this part of the brain. For this purpose, dopamine, serotonin and the standard cholinomimetic drug carbachol were tested using intracaudate injections of small amounts. In view of the psychotomimetic action of dexamphetamine (20) and its effect upon catecholamines (dopamine and noradrenaline) and indoleamines (serotonin) (14, 22), a study of this compound was included. In order to determine the specificity of serotonin and dexamphetamine effects, these substances were also given to animals pretreated with a) parachlorophenylalanine, a potent inhibitor of serotonin synthesis (23), b) haloperidol, a competitive antagonist of dopamine (16) and c) D-lysergic acid diethylamide (LSD-25), a possible serotonin receptor agonist (24). Finally, reversible lesions were made by means of the local anesthetic procaine in order to analyze possible inhibitory aspects of the tested compounds.

Results of the experiments reported here show that intracaudate serotonin apparently functions as an important biochemical link in the complex process of eliciting, determining and adjusting the performance of special behavioral patterns, and that the anteroventral part of the caput caudati in cats may function as an important link in the mechanism concerned with the input-output relationships of external stimuli.

METHODS

The subjects were male cats ranging in weight from 2.5 to 3.5 kg. All animals were fed ad lib throughout the experiments. Double barreled, stainless steel cannulas were stereotaxically implanted into the right and left caudate nucleus. Details of the procedure can be found in ref. 15. After adaptation of the cats to the cage during two 1-hr sessions, the experiments were initiated. Small quantities (5.0 µl) of drug solutions were unilaterally injected into conscious cats through the permanently embedded cannulas. Autoradiographic methods, in use in our laboratory, have shown that the distribution of the injected amount was restricted to a well defined area of 2 mm in diameter following the application of 10 µg of serotonin diluted in a volume of 5 µl (unpublished data). All experiments were performed in an air-conditioned room. The animals were placed in a 90 x 90 x 40 cm cage having a clear plexiglass front for observation and photography. The day-night periodicity (8:00 AM to 8:00 PM), temperature (26 C) and light intensity in the room were standardized. The behavior was recorded by means of a closed TV circuit. Tapes provided objective and continuous records which were analyzed with the aid of a standardized list of items (15). Special symbols were used for items 6, 8, 11, 17 and 32. The observation period was divided into time blocks of 5 min each; three blocks preceded the injection and six followed it. At the end of each time block, a noise stimulus was presented.

The following substances were injected: saline (placebo), dopamine (DA)-HCl, dexamphetamine-H3SO4, haloperidol, methylester-HCl of DL-a-methyl-p-tyrosine (H44/68), 5-hydroxytryptamine creatinine-H3SO4 (serotonin: 5-HT), parachlorophenylalanine (p-CPA), D-lysergic acid diethylamide (LSD-25), carbachol and procaine. All drugs were dissolved in saline (pH 4 to 5), apart from haloperidol which was given as sernase (Janssen Pharmaceutica, Belgium) and p-CPA which was given as a suspension. Every drug was tested in at least seven injection loci of different animals; the maximum number of injections per cannula was restricted to eight.

RESULTS

Serotonin (5-HT). A map of the injection loci effective in eliciting the behavioral changes described below is shown in Fig. 1. The behavior evoked by the introduction of 5-HT (10.0 µg) into the anteroventral part of the caput caudati in cats was qualitatively constant. These animals showed many marked symptoms which can be described under five headings: a) propulsive hyperkinesia, b) abortive, compulsive and disjunctive self-
directed activities, c) vacuum activities, d) choreo-a-thetosis and e) "conditioning" effect. However, these symptoms varied from subject to subject with respect to frequency and intensity. The results of Cat no. 5,332 are shown in detail as a representative case in Table 1 which gives a general picture of the syndrome induced by 10.0 μg of 5-HT.

**Propulsive hyperkinesia.** At first there was an increase in ambulatory activities: the animal alternatively sat, stood, walked forward and backward, climbed or moved at random through the cage. Actually, these activities appeared to be a stereotyped hyperkinesia, rather than a hyperreactivity, for the animal did not respond adequately to external stimuli. Characteristic postures and movements, such as the bending down posture and spontaneously occurring leaps, were often displayed. The hyperkinesia had a propulsive nature (obstinate progression). This was best seen when the cat, coming into contact with the wall of the cage, pushed against it, crawled up and displayed back-rolling, trampling or extensive manipulative movements. The cat sniffed, displayed tracing and continuously looked from side to side as if exhibiting normal exploratory behavior; however, the sequence of these events was always interrupted by nonexploratory activities, especially by self-directed patterns. The hyperkinesia gradually decreased, but remained present throughout the observation period.

**Compulsive, abortive and disjunctive self-directed activities.** Within a few minutes after the injection the animal started to spend considerably more time in self-directed activities. These patterns were suddenly initiated.

**FIG. 1.** Loci effective in eliciting behavioral changes following the introduction of 5-HT into the anteroventral part of the caudate nucleus in cats. • = A 18.0, ○ = three test loci.

CC = corpus callosum, VL = ventriculus lateralis, Cd = nucleus caudatus, Ci = capsula interna, Cl = claustrum, Acb = nucleus accumbens, Put = putamen, CA = commissura anterior, TbOf = tuberculum olfactorium.
TABLE I. Frequencies of the behavioral effects induced by saline, serotonin, dopamine and carbachol in the anteroventral part of the caput caudati in Cat no. 5,332

<table>
<thead>
<tr>
<th>Compound</th>
<th>Saline</th>
<th>Serotonin</th>
<th>Dopamine</th>
<th>Carbachol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time-block</td>
<td>4 5 6 7</td>
<td>4 5 6 7</td>
<td>4 5 6 7</td>
<td>4 5 6 7</td>
</tr>
<tr>
<td>&quot;Dynamic units&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lying</td>
<td>2 2 2 0</td>
<td>0 0 0 0</td>
<td>2 2 1 1</td>
<td>0 1 3 3</td>
</tr>
<tr>
<td>Sitting</td>
<td>2 2 2 3</td>
<td>3 3 3 3</td>
<td>2 2 3 3</td>
<td>3 3 0 0</td>
</tr>
<tr>
<td>Standing</td>
<td>2 2 0 1</td>
<td>3 3 3 3</td>
<td>2 2 0 2</td>
<td>3 0 0 0</td>
</tr>
<tr>
<td>Moving</td>
<td>2 2 2 2</td>
<td>3 3 3 3</td>
<td>2 2 3 2</td>
<td>3 3 0 0</td>
</tr>
<tr>
<td>Exploring</td>
<td>0 0 0 0</td>
<td>0 0 0 0</td>
<td>0 0 0 0</td>
<td>0 0 0 0</td>
</tr>
<tr>
<td>&quot;Static units&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head movement</td>
<td>3A3A3A3A</td>
<td>3C3A3A3A</td>
<td>3A3A3A3A</td>
<td>3C3C2H0</td>
</tr>
<tr>
<td>Neck tension</td>
<td>3 3 3 3</td>
<td>3 3 3 3</td>
<td>3 3 3 3</td>
<td>3 3 2 2</td>
</tr>
<tr>
<td>&quot;Specific units&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cleaning</td>
<td>3 2 0 0</td>
<td>3C3A3C3C</td>
<td>2 0 3 3</td>
<td>3C3 0 0</td>
</tr>
<tr>
<td>Licking</td>
<td>3 2 0 0</td>
<td>3C3A3A3A</td>
<td>2 1 3 3</td>
<td>3C3 0 0</td>
</tr>
<tr>
<td>Sniffing</td>
<td>2 2 0 2</td>
<td>3 3 3 3</td>
<td>2 1 3 3</td>
<td>3 3 0 0</td>
</tr>
<tr>
<td>Gasping</td>
<td>0 0 0 0</td>
<td>1 2 1 0</td>
<td>0 0 0 0</td>
<td>0 0 0 0</td>
</tr>
<tr>
<td>Trampling</td>
<td>0 0 0 0</td>
<td>0 2 2 0</td>
<td>0 0 0 0</td>
<td>0 0 0 0</td>
</tr>
<tr>
<td>Tongue extension</td>
<td>1 0 0 0</td>
<td>2 1 1 2</td>
<td>0 0 2 2</td>
<td>2 0 0 0</td>
</tr>
<tr>
<td>Backward locomotion</td>
<td>0 0 0 0</td>
<td>2 2 2 2</td>
<td>0 0 0 0</td>
<td>2 0 0 0</td>
</tr>
<tr>
<td>&quot;Sense units&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mydriasis</td>
<td>0 0 0 0</td>
<td>0 0 0 0</td>
<td>0 0 0 0</td>
<td>3 2 0 0</td>
</tr>
<tr>
<td>Ear movement</td>
<td>2A2A2A2A</td>
<td>2A2A2A2A</td>
<td>2A2A2A2A</td>
<td>2CIC0 0</td>
</tr>
</tbody>
</table>

The frequencies are indicated as follows: 1 (1/time-block), 2 (2-4/time-block) and 3 (5/time-block). The side of occurrence of the items is shown by A (both sides), H (injection side) and C (the side opposite to the injection side).

but were seldom completed (abortive). Moreover, there was only gradual postural readjustment to the newly initiated patterns. Sometimes, the readjustment was absolutely inappropriate (disjunctive). This was best seen when the cat suddenly switched from cleaning its forelimb on one side to licking its hindlimb on the other side; the animal disregarded its forelimb, although that paw retained its original outstretched position. Sniffing, cleaning, licking and even biting, especially the hair and skin of its genitals, belly and contralateral forelimb, tended to be incessant once started. These manifestations are highly characteristic and might even result in injuries to parts of its own body (compulsive). When the animal was confronted with objects, it violently attempted to push, lift and bite them. These manipulative movements often continued for a long period.

Vacuum activities. When the cat was sitting, it might suddenly stop its rhythmic turning movements or its cleaning activities and start to display the above-mentioned manipulation in the absence of any object. That is, the animal handled "nonexistent" objects as if it were handling real play tools. Similarly, the cat might suddenly go through all the movements of searching for a prey, catching and killing it, although no prey was discernible to the observer. These actions are out of context and are classified as "vacuum activities."

Choreo-athetosis. Throughout the observation period, especially during the fifth time block, the cat displayed nonpatterned movements involving either the distal part of the forelimb or the entire forelimb. When the cat was sitting or standing, the first type of rather slow movements, athetoid in nature, involved lifting the forelimb from the floor, alternating hyperextension and flexion of the paw and toes, often associated with piloerection and curling of the tail. The whole purposeless, nonadaptive and compulsive pattern occurred independently of this ongoing activi-
**Table 2.** Quantitative aspects of the athetoid and choreiform episodes in Cat no. 3,345 after microinjection of 10.0 µg of serotonin into the anteroventral part of the caput caudati.

<table>
<thead>
<tr>
<th>Postinjection time intervals (min)</th>
<th>Choreiform</th>
<th>Athetoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4 to 6</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>7 to 9</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>10 to 12</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>13 to 15</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>16 to 18</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>19 to 21</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Limb movements varied from 1 to 10 per episode. Number of episodes are average rates: 0 = none, 1 = 1 to 3, 2 = 4 to 6 and 3 ≥ 7.

The cat had no visual interest in the induced patterning of its limb. This second type of limb movement was a rapid, jerky, shaking-off movement, violent and choreiform in nature, involving the entire limb. Usually, these movements followed up or interrupted the first type of movements. The animal, apparently forced to execute an irrelevant movement, immediately performed a normal motor pattern of which the elicited movements form the initial phase. These initially involuntary acts were often followed by very active cleaning movements. An example of the high frequency of these choreo-athetoid episodes is given in Table 2.

*Conditioning* effect. In general, all these symptoms persisted unchanged in successive sessions. However, one important feature was of particular interest. Apparently a close association developed between the syndrome and the experimental environment in which the syndrome was induced. When the animal was returned to the experimental cage within one week, it immediately started to display not only the intensive self-directed activities, but also the so-called vacuum activities. This “conditioning” effect disappeared after a saline injection. Saline injections, per se, elicited a short-term increase of cleaning and licking activities; however, these symptoms disappeared within about 4 min.

**DA and dexamphetamine** (Table 1). When the animal was injected with 10.0 µg of DA, no effects were observed apart from an increase in self-cleaning and licking activity after a latency of about 10 min. Conversely, unilateral injections of 10.0 µg of dexamphetamine induced intensive cleaning and licking movements, especially of the contralateral forelimb, the genitals and the middle of the lower back during the fourth period of 5 min. Gradually, the whole 5-HT syndrome developed. After about 10 to 12 min the animal stopped these activities, showed increasing paucity of movements and displayed profound hypokinesia, characterized by continuous retention of the lying posture. In short, the dexamphetamine effects may be described as a short-term “serotonin-like” syndrome and a long-term hypokinetic syndrome.

**Carbachol** (Table 1). Unilateral injections of 2.0 µg of carbachol resulted in an extensive and consistent syndrome. Apart from continuous cleaning, licking (especially of the contralateral side of the body), hyperkinesia and choreo-athetosis similar to the 5-HT effects, it evoked rhythmic contralateral turnings of the head, twitchings of the facial muscles, fluttering of the contralateral ear, mydriasis and piloerection of the tail during the first postinjection period of about 7 min. The above symptoms gradually disappeared and hypokinesia became a significant feature, although the animal still displayed rhythmic turning movements of the head.

**p-CPA and LSD-25** (Table 3). Unilateral injections of 25.0 µg of p-CPA resulted in rhythmic self-cleaning and licking patterns during the first postinjection period of about 6 min; these patterns, performed in the sitting posture, were accompanied by tongue protrusion, gasping and choreo-athetoid movements of the forelimb and did not differ from those evoked by 5-HT. These activities were
interrupted more and more by the arrest position at the end of this period. Then, the movements became slow and dull in nature. A long-term hypokinesia started at about 8 to 10 min after the injection, and lasted for at least 20 min. The cat lay on its belly or its side with flexed limbs and showed a disinclination to move. Even when external stimuli were offered, only the eyelids moved and in some cases the facial muscles twitched. If the animal lay in the middle of the cage, it sometimes dragged itself with nonadjusted limbs toward a corner, where it remained throughout the observation period. All these effects persisted unchanged when the experiments were performed between 9:00 AM and 11:00 AM or between 4:00 PM and 7:00 PM. If performed at other times, however, the time spent in cleaning activities etc. was much more variable and in most cases considerably prolonged. The effects of unilaterally applied LSD-25 (1.0 μg) were similar to those evoked by p-CPA apart from the fact that the first phase went on for at least 10 to 12 min. In short, p-CPA and LSD-25 induce a short-term “serotonin-like” effect followed by a long-term hypokinetic effect.

**Haloperidol** (Table 3). Unilateral injections of 25.0 μg of haloperidol evoked no abnormal symptoms during the first postinjection period of about 9 min. At the end of this period, the cat displayed a short-term increase of self-cleaning, self-licking and self-rubbing activities (for about 5 min). This increased activity gradually gave way to so-called hypokinesia, marked by the absence of any movement.

**Procaine.** Local application of 10.0 μg of procaine immediately resulted in the long-term hypokinesia, described under the heading of p-CPA.

**p-CPA, LSD-25 and haloperidol, in combination with serotonin.** When p-CPA (25.0 μg) was administered 15 min prior to 5-HT, the following effects were observed. A normal effective dose of 10.0 μg of 5-HT resulted in a short-term activation of self-cleaning, self-licking and ground-sniiffing patterns; however,
the animal resumed its characteristic lying posture very rapidly (after a disruption of about 2 to 4 min). High doses of 5-HT (30.0 μg) definitely disrupted this posture and elicited the 5-HT symptoms excepting the vacuum activities. When LSD-25 (1.0 μg) was administered 15 min prior to 5-HT, the normal effective dose of 10.0 μg did not induce any change in the LSD-25-evoked hypokinesia. When the LSD-25 pretreatment was combined with higher doses of 5-HT (30.0 μg), the previously mentioned 5-HT syndrome was superimposed on the LSD-25-evoked hypokinesia. Immediately after the injection, the cat started to move about and displayed intensive cleaning, licking and biting activities. Suddenly, the animal blinked and lay down. It retained this prone posture without any movement; the LSD-25-evoked hypokinesia apparently returned. However, the animal suddenly struggled to its feet and exhibited one of the 5-HT symptoms. The display of these intermittent patterns continued for at least 10 min, though the duration of the hypokinetic phase increased. During the active phase the cat might show ambulatory, propulsive hyperkinesia, choreo-athetosis and intensive manipulative movements; during the passive phase choreiform movements might also occur. When haloperidol (25.0 μg) was administered 20 min prior to 10.0 μg of 5-HT, the hypokinesia elicited by haloperidol was immediately disrupted and the 5-HT symptoms were normally displayed; however, the hypokinesia returned very swiftly (within 6 to 8 min after the 5-HT injection). In brief, both p-CPA and LSD-25 appeared to inhibit the 5-HT effect in a competitive way, while haloperidol appeared to be ineffective in this respect.

**DISCUSSION**

The present study shows that 5-HT introduced into the anteroventral part of the caput caudati in cats evokes an extensive syndrome, marked by hyperkinesia, compulsive, abortive and disjunctive self-directed activities, choreo-athetosis and "vacuum activities." Apart from quantitative fluctuations, this syndrome is highly reproducible and qualitatively constant from subject to subject. The quantitative variability of these symptoms may reflect the influence of genetic and constitutional characteristics (the cats are not derived from a standard stock) and of internal variables such as circadian and ultradian rhythms (25). The induced effects appear to be 5-HT-specific because 1) the inhibitor of tryptophan hydroxylase and selective depletor of 5-HT, p-CPA, completely prevents the 5-HT-induced syndrome when normally effec-
tive doses are used. High doses of 5-HT disrupt the hypokinesia evoked by p-CPA, indicating that the receptive sites are still sensitive to 5-HT. 2) It is impossible to ascribe the syndrome to activation of DA-sensitive sites, for DA does not induce any effect comparable with that of 5-HT. Furthermore, the 5-HT syndrome is not prevented by a pretreatment with the competitive DA antagonist haloperidol. Apparently, the number of DA-receptive sites in this part of the brain is either too small or too diffuse to be triggered by small amounts of DA.

It is well known that 5-HT terminals are present within the corpus striatum of rats and other mammals (2, 3). Although it has been argued that these terminals in the rat belong to neurons arising from 5-HT-containing cell bodies in the raphe nuclei (2), other workers have argued that these terminals in the cat and monkey belong to neurons arising from the nucleus linearis, nucleus paranigralis and other minor cell groups located in the ventromedial tegmental area below the level of the third root fibers (26, 27). It is quite possible that at least a part of the above 5-HT symptoms are due to the activation of the postsynaptic structures of these axons. The possibility that other 5-HT postsynaptic structures are involved should, however, not be ruled out in view of the lack of histochemical studies of a 5-HT topography within the forebrain of the cat. A reconstruction of the effective area leads to the conclusion that it is identical to the so-called inhibitory anteroventral area described by Liles and Davis (19). With respect to the area effective in evoking the 5-HT syndrome, the injections into the rostromedial part of the caput caudati are ineffective (unpublished data).

Dexamphetamine evokes symptoms similar to those evoked by 5-HT although the duration is somewhat shortened. It is well known that dexamphetamine interferes mainly with DA in the corpus striatum (28). However, Fuxe et al. (14) have recently shown that dexamphetamine may also induce a release of extragranular 5-HT. It is quite likely that the dexamphetamine symptoms elicited from the anteroventral area are caused mainly by this effect. It is seen that a) the dexamphetamine effect mimics the 5-HT effect, although DA appears to be ineffective; b) the effects of normally effective dexamphetamine doses are completely blocked by a p-CPA pretreatment; c) high doses of dexamphetamine disrupt the p-CPA hypokinesia only partially and d) haloperidol does not inhibit the dexamphetamine syndrome. In conclusion, dexamphetamine appears to activate 5-HT sensitive sites, either directly or indirectly. Although indirect evidence has been presented that the stereotyped behavior induced by i.p. injections of dexamphetamine is mainly dependent on the cerebral DA (28), our data indicate that activation of 5-HT stores in specific parts of the brain may also be involved in the appearance of these stereotyped behavioral patterns. In view of these considerations it is important to note that chronic methamphetamine intoxication in cats induces a number of symptoms which show a remarkable resemblance to the 5-HT syndrome, especially the self-directed activities and the so-called “conditioning” effect (29–31).

Apparently, LSD-25 introduced locally into the 5-HT-sensitive area induces two kinds of effects: a 5-HT-like syndrome and a hypokinetic syndrome. Although LSD-25 was regarded as a 5-HT antagonist on the basis of studies in peripheral tissues (12), it has recently been argued that LSD-25 may have a 5-HT-like effect at the postsynaptic receptors, on the one hand, and may specifically inhibit 5-HT neurons, on the other hand (24, 32, 33). In our study, the 5-HT-like syndrome evoked by LSD-25 seems to support the hypothesis of a short-term activation of postsynaptic 5-HT receptors. Conversely, the
competitive inhibition of the 5-HT effects following LSD-25 pretreatment appears to emphasize the antagonistic action of LSD-25 (34). As LSD-25 evokes a powerful inhibition of the rate of firing of single 5-HT raphe neurons, it is possible that the LSD-25-induced hypokinesia is produced by some sort of neuronal feedback mechanism in which postsynaptic neurons may regulate the firing activity of the 5-HT-containing neurons (24, 32, 33). On the other hand, the LSD-25-induced hypokinesia may be produced by a local anesthetic effect, because LSD-25 appears to depress neurons directly by local anesthesia (35); the resemblance to the procaine-induced hypokinesia would support this latter hypothesis.

The standard cholinomimetic drug carbachol also evokes a short-term, 5-HT-like syndrome followed by a hypokinetic syndrome. On the basis of studies in guinea pig ileum, fundus of the rat stomach etc., it is known that the 5-HT effect mimics the acetylcholine effect and is blocked by atropine. Accordingly, it has been suggested that 5-HT acts through an acetylcholine release. However, some results strongly contradict this hypothesis; for instance, 5-HT still remains effective in tissues such as rat duodenum and rat colon in the presence of atropine (12). Our results cannot give any indication of the mechanism involved at this level of the brain. A study of the actions of p-CPA and atropine-like substances on the 5-HT and carbachol response might provide more information about this mechanism. The interpretation of our results is further complicated by the fact that some symptoms such as the strong contralateral tendency of the movements show similarities with the DA syndrome induced by the introduction into the rostromedial area of the caput caudati (15–17).

Although the role of 5-HT and its relation to behavioral changes has been extensively studied in animals, its functional role is far from clear (12, 36). Using indirect manipulation techniques such as changing the content of the whole cerebral 5-HT by means of the 5-HT precursor 5-hydroxytryptophan or the 5-HT depleter p-CPA, many authors have established a relationship between cerebral 5-HT and sleep, sexual, aggressive and learned behavior (36–39). However, the 5-HT syndrome induced locally in the caudate nucleus of cats appears to be absolutely unrelated to the effects induced by systemic injections. These differences emphasize that the indirect manipulations with the whole cerebral 5-HT content do not inform us about the mechanisms involved in the relationship of 5-HT at specific levels of the brain and behavior. Nevertheless, they may provide useful information if these studies are combined with specific brain lesions of 5-HT-containing cells or fiber systems in well-defined areas (40, 41).

The existence of hyperkinesia, abortive and disjunctive self-directed activities, and choreo-athetosis supports the generally accepted hypothesis that the caudate nucleus regulates the normal muscular activities by means of a complex system of facilitation and suppression (4). The observed abnormalities may reflect a disruption of this balance system. The presence of “vacuum activities” such as playing with “nonexistent” objects indicates that the mechanism concerned with the integration of stimuli is strongly affected; the animal displays goal-directed behavior, although no goal-stimuli are presented. In 1962, it was suggested that the caudate nucleus, inter alia, functions as a part of a high-level integratory system modifying novel stimuli according to sensory information previously received and stored in the cerebral cortex (42). Several findings support this hypothesis. 1) The caudate nucleus can be anatomically regarded as a relay station between the sensory input (thalamus), the
tentatively suggested that 5-HT has a primarily inhibitory function at this level of the brain. Similar nonpatterned movements of the limbs are evoked by the introduction of DA into the rostromedial area of the caput caudati in cats (17). The different regional specificity of DA and 5-HT with respect to choreo-athetosis indicates that these two areas are functionally related to each other.

From the clinicopathological point of view, it is important to note that patients with Huntington's chorea have a loss of small ganglia cells of the caudate nucleus (52). Recently, it has been reported that 5-hydroxytryptophan, the precursor of 5-HT, given orally, increases chorea in these patients (53). In view of these and other considerations, it has been suggested that increased responsiveness to 5-HT, inter alia, may underlie the initiation of chorea in man (52). Our results strongly support this hypothesis.

In short, these experiments have shown that selective chemical stimulation is a useful tool for investigating the behavioral function of a specific part of the brain. Undoubtedly, the main discovery is that intracaudate 5-HT is indispensable for the complex process of eliciting, determining and adjusting the performance of specific behavioral patterns.

SUMMARY

In order to investigate the functional role of the anteroventral part of the caput caudati in cats, a behavioral study of locally applied 5-hydroxytryptamine (5-HT), dopamine (DA), dexamphetamine, carbachol, parachlorophenylalanine (p-CPA), D-lysergic acid diethylamide (LSD-25) and procaine has been undertaken. Behavioral parameters have been applied to measure the action of drugs unilaterally injected through permanently implanted cannulas.

Small doses of 5-HT produce a consistent syndrome, marked by hyperkinesia, abortive, compulsive and disjunctive self-directed activ-
ities, choreo-athetosis, "vacuum activities" and a "conditioning" effect. It is shown that this syndrome is 5-HT specific; pretreatment of the animals with p-CPA or LSD-25 blocks these effects in a competitive way. Unlike DA, dexamphetamine produces a 5-HT-like syndrome which is blocked by p-CPA. Pretreatment of the animals with haloperidol does not prevent the dexamphetamine syndrome. It is suggested that dexamphetamine also interferes with 5-HT in this part of the brain. The effects of LSD-25 and carbachol are discussed. The behavioral symptoms are considered in view of the function of the caudate nucleus. The hypothesis is put forward that the anteroventral part of the caudate nucleus in cats functions as a high level interlocking mechanism concerned with the integration of external stimuli.

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REFERENCES


