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Role of 5-HT in the Action of Some Drugs Affecting Extrapyramidal System

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Abstract. The effects of drugs influencing the function of extrapyramidal system: chlorpromazine (CPZ), haloperidol, amphetamine, and oxotremorine were checked in rats with lesioned MR or DR raphe areas and in animals pretreated with either p-CPA (p-chlorophenylalanine) or LSD, i.e. at impaired functions of the central serotoninergic system. Lesions of the raphe system and pretreatment with either p-CPA or LSD significantly diminished the cataleptogenic effects of both CPZ and haloperidol. The amphetamine-induced stereotyped behaviour was intensified in animals with raphe system lesions, whereas in rats pretreated with p-CPA or LSD the action of amphetamine was diminished. Rats with raphe system lesions showed no change in the tremorogenic action of oxotremorine. In animals pretreated with either p-CPA or LSD the onset of the oxotremorine tremor was even delayed. It is concluded that an intact and functionally unimpaired serotoninergic system is necessary for the cataleptogenic action of neuroleptics.

Key Words
Amphetamine stereotypy
LSD pretreatment
Neuroleptics catalepsy
Oxotremorine tremor
p-CPA pretreatment
Raphe system lesions

Several recent studies have emphasized the hypothesis that interaction between the catecholaminergic and serotoninergic systems may exist within the central nervous system. Amphetamine by strongly releasing both noradrenaline (NA) and dopamine (DA) in CNS (6, 8, 9) stimulates the central catecholaminergic processes (12, 38) and accelerates the turnover rate of serotonin (5-HT) in the brain (32). Amphetamine does not consistently alter the 5-HT content of whole brain (27, 30), but there exists the evidence that it significantly increases the 5-HT levels in certain brain areas, e.g. in both colliculi, corpus striatum, and pons (5). *Lapin et al.* (26) reported that pretreatment with 5-HT antagonists (BOL-48, methysergide, and LSD 25) as well as with the 5-HT depletor *p*-chloro-

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phenylalanine (p-CPA) prevented rearing induced by amphetamine in mice. These data suggest that, at least partially, the central effects of amphetamine are related to the release of 5-HT and/or stimulation of serotoninergic receptors. *Schrold and Squiers* (34) observed in young chicks that p-CPA antagonized the wing droop and the postural changes elicited by amphetamine, and concluded that the action of amphetamine is partially mediated via a serotoninergic mechanism.

DA and 5-HT acted reciprocally within the corpus striatum (19) which receives both DA and 5-HT fibers from substantia nigra and raphe nuclei, respectively (1, 2). L-dopa may accumulate in 5-HT nerve terminals (17, 28) and decrease the 5-HT content in the brain (28, 29). On the other hand, since numerous 5-HT terminals were found in the substantia nigra using the electromicroscopic technique (26) it was postulated that 5-HT may modulate the function of the nigrostriatal system which represents the main portion of central dopaminergic neurones.

In a previous paper (25) we reported a decreased cataleptogenic activity of both chlorpromazine (CPZ) and haloperidol in rats pretreated with p-CPA or animals with lesioned raphe nuclei, i.e. with impaired function of the cerebral serotoninergic system (21, 24). It was, therefore, of interest to test the action of both neuroleptic drugs after pretreatment with LSD which is known to block the 5-HT receptors. We decided also to extend our study on other drugs affecting the extrapyramidal system such as amphetamine and oxotremorine.

Materials and Methods

Experiments were performed in female Wistar rats weighing 180–200 g. The animals were housed 3 per cage at constant room temperature (21–23 °C) and obtained food and water *ad libitum*. Brain lesions were performed stereotaxically under pentobarbitone anaesthesia using 0.1-mm stainless steel monopolar electrodes insulated, except for the tip. The coordinates of the lesions – according to the *König and Klippel* (22) stereotaxic atlas of the rat brain – were as follows:

nucleus raphe medianus (MR) A – 0.4, L – 0.0, D – (–2.6);
nucleus raphe dorsalis (DR) A – 0.4, L – 0.0, D – (–0.8);
lateral midbrain (LM) A – 0.6, L – 1.5, D – (–1.8).

Lesions were made with 2 mA anodal current passing the electrode for 15 sec. After surgery the animals were allowed 10 days for recovery before use in the experiments. After the experiments, the brains were fixed in 4-percent formaline solution and the location of lesion was determined. Results were evaluated only in animals showing an exact position of the lesions. Sham lesions were performed in the same manner but without passing the electrical current.

Groups of rats treated with p-CPA received the soluble p-CPA methylester HCl, 316 mg/kg i.p. on the first day and 100 mg/kg i.p. on two consecutive days. The experiments were performed 24 h after the last injection of p-CPA. LSD was administered 30 min before injection of the drug under investigation. Control groups received saline.

Evaluation of Catalepsy

Rats were placed on the table and the intensity of catalepsy was scored according to the stages 1–5. In stage 1, both frontal limbs were set on a 6-cm-high block and tested twice. Stage 1 was scored as 1 point. In stages 2 and 3 a frontal or a hind paw was set on a 3-cm-high block with a contralateral paw remaining on the table. Both stages were tested on the left and right side and scored as 1 point for each investigation. In stage 4 both hind paws were set on a 6-cm-high block and tested twice. 2 points were given for each investigation in this stage. In stage 5 a frontal and ipsilateral hind paw were placed on 3-cm-high blocks (contralateral paws remaining on the table) and tested on both left and right sides. 2 points were given for each side. Points were assigned when rats maintained the abnormal position for more than 15 sec. Scoring was made by two independent observers. The maximal sum of scores was 14.

Evaluation of Stereotypy

Stereotypy was scored according to the following system:

(1) high or moderate agitation, vigorous rearing and orienting, only occasionally sniffing (directed upwards);

(2) less active, occasionally rearing and orienting, moderate or intensive sniffing;

(3) head-down posture, permanent sniffing of the floor, occasionally licking and/or biting;

(4) head-down posture, permanent licking and sniffing of the floor, occasionally biting;

(5) head-down posture, permanent biting or gnawing of the floor. Scores were made by two independent observers. For calculation, scores were multiplied by 10 to avoid the particles.

Evaluation of Tremor

Tremor was evaluated visually by two independent investigators in freely moving rats and after slight elevation of hind limbs. The following scoring system was used: 0, no tremor; 1, slight and interrupted tremor of hind limbs; 2, continuous tremor of hind limbs. Scores were multiplied by 10 to avoid particles.

Drugs

The following drugs were used: *p*-chlorophenylalanine methylester HCl (Serva); *d,l*-amphetamine sulphate (Polfa); oxotremorine (Aldrich); chlorpromazine (Largactil®, Specia); haloperidol® (Janssen); LSD (Deliside®, Sandoz). Drugs were freshly dissolved in physiological saline and injected at the volume 0.1 ml/100 g body weight.

The statistical analysis was made according to the Mann and Withney 'U' test.

Results

The effects of p-CPA and LSD (20 μg/kg) pretreatment as well as lesions of MR and DR areas on the catalepsy induced by CPZ (5 mg/kg) and haloperidol (0.2 mg/kg) are summarized in the tables I and II. As it was previously reported (25), lesions of both MR and DR areas markedly reduced the catalepsy induced by both CPZ and haloperidol. On the other hand, lesions involving the lateral midbrain (LM) did not, or only slightly, change the cataleptogenic actions of

Table I. Effect of brain lesions, LSD and p-CPA on catalepsy induced by chlorpromazine (5 mg/kg s.c.)

Experimental group	No. of rats	Intensity of catalepsy (scored) after		
		30 min	1 h	3 h
Sham lesion	10	6.5 ± 1.5	10.0 ± 0.9	10.8 ± 0.6
MR lesion	7	0.4 ± 0.4[1] T = 40.0	0.6 ± 0.5[1] T = 28.5	5.1 ± 2.0[1] T = 41.0
DR lesion	8	0.4 ± 0.3[1] T = 49.5	0.5 ± 0.3[1] T = 36.0	1.5 ± 1.2[1] T = 39.0
LM lesion	6	4.1 ± 2.2 T = 44.0	6.2 ± 2.5 T = 43.5	10.3 ± 0.7 T = 45.0
Control saline	8	10.0 ± 0.6	10.0 ± 0.8	11.6 ± 0.7
LSD, 20 μg/kg	8	2.4 ± 1.2[2] T = 38.0	3.6 ± 1.3[2] T = 42.5	7.6 ± 1.0[2] T = 43.5
p-CPA	8	0.9 ± 0.4[2] T = 36.0	1.7 ± 0.3[2] T = 36.0	3.7 ± 0.4[2] T = 36.5

Figures are means ± SE; T = sum of ranks (according to test 'U' of Mann and Whitney).
1 $p < 0.05$ with respect to sham lesions.
2 $p < 0.05$ with respect to control saline.

either CPZ or haloperidol. No significant differences between sham lesioned and intact animals were noted.

Pretreatment with p-CPA or LSD significantly reduced the cataleptogenic actions of both CPZ and haloperidol.

Stereotypy

Table III summarizes the effects of brain lesions, p-CPA, and LSD on the stereotyped behaviour induced by amphetamine. It can be seen that the amphetamine stereotypy developed more rapidly in DR-lesioned animals than in the control group. In MR-lesioned rats the action of amphetamine was markedly prolonged: 300 min after drug administration the stereotypy was significantly higher than in control animals. In contrast to the raphe-system lesioned rats the group treated with p-CPA showed a faster disappearance of amphetamine action which was, after 120–240 min, significantly less than in control animals. After LSD treatment the amphetamine-induced stereotypy developed slower, being 30 min after amphetamine significantly less than in the controls.

Table II. Effect of brain lesions, LSD and p-CPA on catalepsy induced by haloperidol (0.2 mg/kg s.c.)

Experimental group	No. of rats	Intensity of catalepsy (scored) after		
		30 min	1 h	3 h
Sham lesion	5	10.4 ± 1.0	11.0 ± 0.4	9.4 ± 1.0
VR lesion	5	2.5 ± 1.2[1] T = 18.5	2.0 ± 0.8[1] T = 18.0	2.5 ± 0.8[1] T = 18.0
DR lesion	5	1.0 ± 0.8[1] T = 15.0	0.8 ± 0.8[1] T = 15.0	1.0 ± 1.0[1] T = 15.0
LM lesion	5	8.5 ± 1.7 T = 24.0	8.1 ± 2.4 T = 23.0	8.9 ± 1.4 T = 24.5
Control saline	8	8.6 ± 1.2	10.0 ± 0.6	8.1 ± 0.6
LSD, 20 μg/kg	8	2.4 ± 0.9[2] T = 40.5	4.0 ± 0.8[2] T = 37.5	4.7 ± 1.4[2] T = 50.0
p-CPA	8	1.2 ± 0.7[2] T = 38.0	2.9 ± 1.0[2] T = 38.0	4.1 ± 0.6[2] T = 36.5

Figures are means ± SE; T = sum of ranks (according to test 'U' of Mann and Whitney).
1 $p < 0.05$ with respect to sham lesions.
2 $p < 0.05$ with respect to control saline.

Tremor

No statistically significant changes in the tremorogenic action of oxotremorine were observed in either MR- or DR-lesioned groups of animals (table IV). In both p-CPA- and LSD-pretreated groups of rats the onset of tremorogenic effect of oxotremorine was delayed. 15 min after oxotremorine, tremor in both p-CPA- and LSD-pretreated groups was significantly less as compared with control animals.

Discussion

Dopaminergic mechanisms are commonly believed to be involved in cataleptogenic effects of neuroleptics (36). The results presented in this paper, however, confirmed our previous observations (25) and indicated that an intact and functionally unimpaired serotoninergic system is necessary for the development of cataleptogenic actions of neuroleptics. Both CPZ and haloperidol are known to

Table III. Effects of brain lesions, LSD and p-CPA on stereotypy induced by amphetamine (5 mg/kg s.c.)

Experimental group	No. of rats	Intensity of stereotypy (scored) after					
		30 min	1 h	2 h	3 h	4 h	5 h
Sham lesion	12	15.0 ± 1.2	29.6 ± 1.4	30.8 ± 1.3	28.3 ± 1.6	25.4 ± 2.7	16.1 ± 2.7
MR lesion	8	17.5 ± 1.3 T = 92.0	28.7 ± 1.2 T = 79.5	31.8 ± 0.9 T = 87.0	32.5 ± 1.3 T = 101.5	30.6 ± 1.1 T = 96.5	28.3 ± 1.6[1] T = 28.5
DR lesion	5	24.0 ± 4.0[1] T = 62.5	36.0 ± 1.8[1] T = 67.0	32.0 ± 2.0 T = 45.0	28.0 ± 2.0 T = 42.5	20.0 ± 1.6 T = 32.5	17.5 ± 1.2 T = 28.5 (n = 4)
Control saline	8	16.2 ± 2.6	21.8 ± 1.3	29.4 ± 2.4	28.1 ± 1.8	17.5 ± 2.7	12.5 ± 2.5
LSD, 100 μg/kg	8	8.7 ± 2.6[2] T = 51.0	27.5 ± 2.7 T = 83.5	36.9 ± 2.6 T = 84.5	26.9 ± 1.6 T = 62.5	15.9 ± 2.6 T = 61.0	12.5 ± 0.9 T = 24.0
p-CPA	8	14.3 ± 1.5 T = 65.5	25.0 ± 0.0 T = 84.0	25.0 ± 0.0[2] T = 52.0	25.0 ± 0.0[2] T = 52.0	12.5 ± 1.3[2] T = 48.0	

Figures are means ± SE; T = sum of ranks (according to 'U' test of Mann and Whitney); n = number of rats.
1 $p < 0.05$ with respect to sham lesions.
2 $p < 0.05$ with respect to control saline.

Table IV. Effects of brain lesion, LSD and p-CPA on tremor induced by oxotremorine (0.04 mg/kg i.p.)

Experimental group	No. of rats	Intensity of tremor (scored) after		
		15 min	30 min	1 h
Sham lesion	8	6.9 ± 1.3	6.2 ± 0.8	1.2 ± 0.8
MR lesion	6	5.0 ± 0.0 T = 36.0	3.3 ± 1.0 T = 34.0	0.0 ± 0.0 T = 39.0
DR lesion	4	6.2 ± 1.3 T = 23.5	3.8 ± 2.4 T = 20.5	2.5 ± 1.4 T = 30.0
LM lesion	4	6.2 ± 1.2 T = 23.5	8.8 ± 2.4 T = 30.5	3.7 ± 1.2 T = 34.0
Control saline	8	8.1 ± 0.9	4.4 ± 0.6	0.6 ± 0.6
LSD, 100 µg/kg	8	5.0 ± 0.0[1] T = 48.0	3.1 ± 0.9 T = 60.0	0.6 ± 0.6 T = 68.0
p-CPA	8	5.0 ± 1.3[1] T = 51.0	4.4 ± 0.6 T = 68.0	0.0 ± 0.0 T = 64.0

Figures are means ± SE; T = sum of ranks (according to 'U' test of Mann and Whitney).
1 $p < 0.05$ with respect to control saline.

increase the synthesis rate of brain 5-HT (7, 14, 15). CPZ inhibited the reserpine-induced release of 5-HT (15) as well as the release of this amine in the forebrain of rats due to electrical stimulation of the midbrain raphe area (23). It is also known that in some patients paradoxical responses to CPZ such as increased motor restlessness, extreme anxiety and visual hallucinations have been observed after previous administration of LSD (35). These data seem to indicate that 5-HT could play an important role in the action of neuroleptics belonging to the phenothiazine and butyrophenone groups.

Amphetamine markedly increased the turnover rate of brain 5-HT (32). This effect was considered to be a secondary one depending upon the hyperthermia produced by amphetamine. On the other hand, *Beauvallet et al.* (5) found amphetamine to increase the 5-HT concentration in certain areas of the rat brain. Furthermore, at least some of the central effects of this drug were considered to be mediated via serotoninergic mechanisms (26, 34). Because of these findings and the possible interaction of dopaminergic and serotoninergic systems within the corpus striatum (13, 19, 29) it is of interest that we found now an increased

action of amphetamine in both MR- and DR-lesioned rats whereas LSD or p-CPA decreased it. This difference is at present rather difficult to interpret. It was suggested that the stereotyped behaviour due to amphetamine is mediated via a dopaminergic mechanism in the striatum (37). Furthermore, it was recently postulated (10) that the cholinergic-dopaminergic balance strongly influences the stereotyped behaviour. Therefore, possibly at least two different mechanisms are involved in the central action of amphetamine, which may explain the differences described here. However, unknown interactions between p-CPA or LSD and amphetamine are also possible. Thus, we agree with other authors (11) that disturbances induced by brain lesions should provide a better test than drug-induced changes which could mask drug interactions.

Some experimental findings seemed to indicate that parkinsonian tremor depends upon central decrease of 5-HT rather than dopamine (16, 31). Rats with lesioned MR area showed a marked decrease of striatal 5-HT (18) and often a fine tremor (18, 24). Furthermore, 5-HTP diminished or even abolished the harmaline and tremorine tremor (16, 33). Quipazine, a compound with serotonine-like properties, also markedly diminished the tremorine and oxotremorine tremor (33). Quipazine and 5-HTP potentiated the antitremorine effect of L-dopa (33). On the basis of these findings one may expect a marked augmentation of the oxotremorine tremor when the function of the central serotoninergic system is impaired. However, no changes of oxotremorine action were observed in raphe-system lesioned animals, and in p-CPA- or LSD-pretreated groups oxotremorine effects were even decreased. This problem requires further study.

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