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Effect of Haloperidol and Chlorpromazine on Reversal Learning of Normal and Striatectomized Rats in a Y-Maze

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ARUSHANIAN, E. B. AND V. A. BATURIN. *Effect of haloperidol and chlorpromazine on reversal learning of normal and striatectomized rats in a Y-maze.* PHARMAC. BIOCHEM. BEHAV. **16**(4) 541–545, 1982.—Haloperidol (0.05–0.1 mg/kg) and chlorpromazine (0.5–1.0 mg/kg) improved reversal learning avoidance responses in a Y-maze, decreased intersessional fluctuations of errors and decreased the number of spontaneous exits from a correctly selected chamber. After bilateral lesions of the striatum this effect disappeared. Brain lesions also attenuated the ability of neuroleptics to suppress amphetamine-induced stereotypy and accompanying defects in avoidance responses. The improvement of avoidance behavior by neuroleptics may be related to the reduction of spatial preference caused by functional asymmetry between the bilateral nigro-striatal systems.

Neuroleptics Striatum Avoidance response Spatial preference

NUMEROUS investigations suggest that neuroleptics disturb different parameters of avoidance behavior in animals. This is sometime accepted as a criterion of their specific activity ([8, 20, 21] among others). Haloperidol and chlorpromazine are known to improve some avoidance responses in Y-mazes, particularly when animals are trained to perform complex reversal tasks [7]. The present work investigated the role the striatum plays in this effect of neuroleptic drugs, both in normal rats and in animals whose performance was disrupted by high doses of amphetamine.

METHOD

Animals

The experimental subjects were 91 male and female albino rats weighing from 200 to 250 g. They were housed four to a cage with food and water freely available.

Procedures

The experiments were carried out in a Y-maze. The procedure was identical to that described in a previous paper [2]. Each trial began with a conditioned stimulus (a buzzer tone 10 sec long) followed by the unconditioned stimulus (electrical shock 1, 6 mA, 1 Hz, up to 60 sec long) delivered through the electrical grid floor, if the animal failed to perform any running (see Fig. 1).

The experiment consisted of 4 consecutive sessions 10 trials each. They were carried out over a day and lasted 3–4 hours with no intersession interval. Animals were trained to learn and relearn avoidance responses by running to the safe chamber. In the first session the safe chamber was to the right and the animals easily learned to run there. In the second session they were required to change avoidance response direction to the left. Further reversal learning was required during the 3rd and 4th session (safe to the right and safe to the left). The following parameters were recorded: latency, defined as the time interval between the start of the sound signal and the animal's avoidance response, the number of errors and exits from a correctly selected chamber (within 45 sec following the buzzing tone). Our previous observation [2] show that the mean number of errors (incorrect avoidance responses) do not reflect the rats' reversal learning ability, since in some sessions their mistakes as to the choice of the safe chamber are rare, while in others much more frequent. This may be due to an inborn spatial perference. Therefore, in order to properly evaluate reversal learning the number of intersessional fluctuation of errors (IFE) was taken into account—the mean difference in the number of incorrect responses between the first and the second, the second and the third, the third and the fourth training session.

Lesions

Surgery was carried out under nembutal (40 mg/kg) anesthesia injected IP. Bilateral striatal lesions were produced by intracerebral insertion of an electrode insulated except for 0.5 mm at the tip. The stereotaxic coordinates for striatal lesions were as follows: A=8.6 mm, H=5–6 mm,

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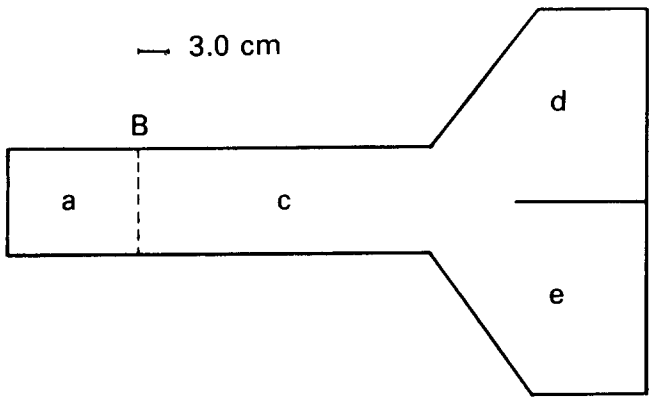

FIG. 1. Apparatus. a—start box, b—automatic door, c—central alley, d,e—terminal chamber.

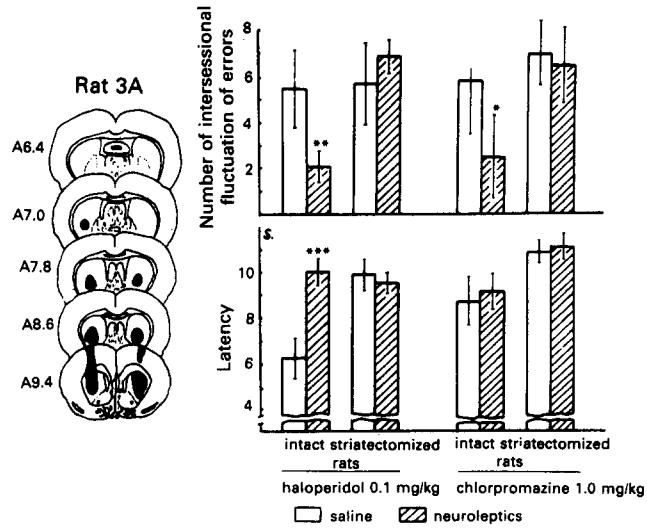

FIG. 2. Effect of neuroleptics on avoidance response parameters in intact and striatectomized rats. On the left—standard histological sections show typical striatal lesions of one of the animals. Brain damage eliminates the effect of neuroleptics (striped columns) on the intersessional fluctuation of errors and latency of response as compared with that of the saline control (light columns). $*p<0.05$, $**p<0.01$, $***p<0.001$.

L=2.5 mm according to the atlas of König and Klippel [16]. A direct current of 2 mA was passed through the electrode for 25 sec. The parameters of avoidance responses were estimated at two periods after striatectomy: early—on the 7th–14th days, and later—on the 28th–35th days. Upon completion of the experiment, the surviving rats were anesthetized and intracardially perfused with isotonic saline followed by 10% Formalin. Frozen 50 micron thick sections of tissue through lesions were used for microscopic examination. The histological data indicated that the destruction of the striatum had a limited volume (up to 12%) and was found at the A=6.4 and A=9.7 levels of the atlas.

Drug Treatments

The experimental animals were subdivided into 6 groups, each treated with one dose of a drug or their combination (group 6). The dosages were as follows (the figures in parentheses indicate the number of animals tested before and after surgery, respectively): haloperidol 0.05 mg/kg (10;6) and 0.1 mg/kg (9;6), chlorpromazine 0.5 mg/kg (7;4) and 1.0 mg/kg (6;6), amphetamine 5.0 mg/kg (18;16), amphetamine 5.0 mg/kg combined with haloperidol 0.1 mg/kg (10;6). The drugs were injected IP 30 min before placing the rats in the maze. Haloperidol was administered 15 min after amphetamine.

The animals underwent testing 6 times. Each preoperative and postoperative (early and later) test was followed by a control saline test separated by a one week interval. The results were then compared and verified by Student's t-test ($p<0.05$). Two control groups of animals were used where reversal learning was tested twice with saline administration before and after lesions of the striatum (20 and 16 rats) and after similarly sized lesions of the parieto-occipital cortex (11 and 9 rats).

RESULTS

Effect of Neuroleptics on Reversal Learning of Intact Rats

In the first control sessions with saline rats easily learned to run to the right safe chamber of the Y-maze. Reversal avoidance to the left chamber was more complicated. Some animals continued running to the right despite the adversive stimuli. Their intersessional fluctuation of errors (IFE) over 4 training sessions increased considerably. This indicated deficits in reforming the trajectory of runnings. The control saline group displayed no distinct tendency in the change of avoidance response parameters. This provides evidence that behavioral shifts in drug-treated animals is not due to improved performance after repeated testing.

Neuroleptics did not influence performance in the first training session. However, even low doses of haloperidol (0.05 mg/kg) improved reversal learning. This was apparent in a reduced IFE and lower mean incorrect responses. Other parameters of avoidance remained unchanged. Higher doses of neuroleptic gradually increased the effect (Fig. 2).

The analysis of individual reversal learning showed that neuroleptics in some animals actually impaired the reforming of motor patterns. Such results were obtained in rats, that demonstrated good performance in the control tests and had a low IFE. On the contrary, in animals with retarded learning the drugs considerably improved the performance of the task.

Influence of Striatectomy on the Effects of Neuroleptics

Bilateral damage to the caudate-putamen complex produced impaired avoidance behavior by increasing the IFE (the mean number of incorrect responses and exits from the safe chamber). In later sessions following brain lesions impairment decreased but performance remained below normal. In short, the different behavioral parameters of striatectomized animals resembled those of low performance intact rats. Therefore, there were reasons to expect improvement of their behavior after treatement with neuroleptics.

To the contrary, striatectomy significantly attenuated the improving action of haloperidol and chlorpromazine. Shifts in IFE produced by low doses of the drugs after brain lesions

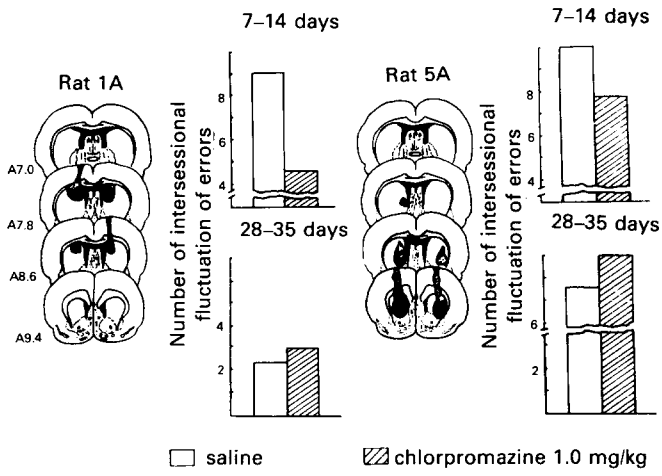

FIG. 3. Data from representative animals demonstrating the effect of chlorpromazine on IFE in individual rats as conditioned by localization and size of striatal lesions. Dorsal striatum lesions (rat 1A) cause less significant shifts in neuroleptic effect than destruction of central and ventral parts of structure (rat 5A).

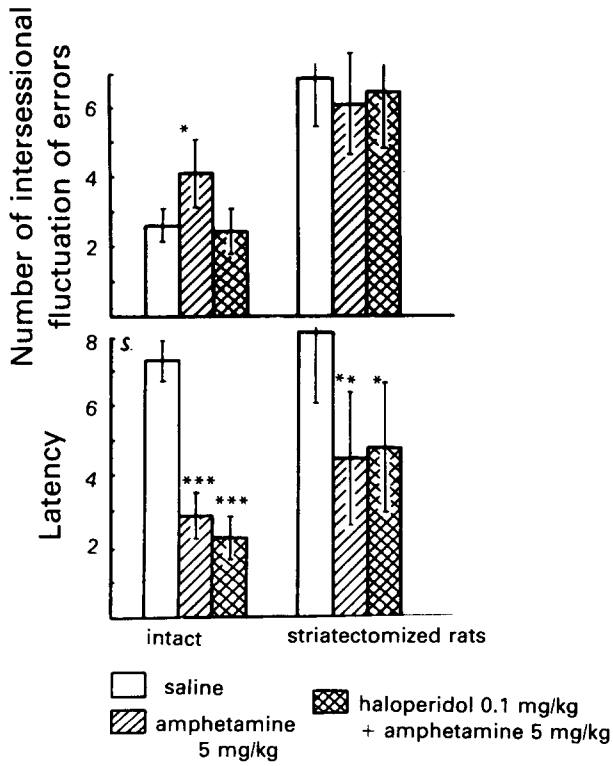

FIG. 4. Effect of amphetamine and its combination with haloperidol on IFE and latency of avoidance in intact and striatectomized rats. In intact animals haloperidol attenuates the effect of amphetamine on IFE, while after striatectomy this shift disappears but the latency instead of usual lengthening has a tendency to further shortening. $*p<0.05$, $**p<0.01$, $***p<0.001$, as compared with saline control.

disappeared entirely. Improved reversal learning after large doses was preserved in the early postoperative period and eliminated in the period later (Fig. 2). Thus, striatectomized animals were unable to improve their performance of a complex behavioral task while under the influence of neuroleptics. In addition, one month after surgery, the drugs weakly decreased the number of exits from the safe chamber and did not prolong the latency of avoidance responses.

In control rats the parieto-occipital neocortex overlying the striatum was damaged to a comparative extent. Such lesions did not change the parameters of avoidance and the effect of haloperidol (0.1 mg/kg) on reversal learning. A week after surgery the rats fully recovered to their preoperative level.

The analysis of individual behavior of striatectomized rats shows that the initial ability for reversal learning ceased to play an important role after the brain lesion. This is well illustrated by experiments on two animals (Fig. 3). Both rats had high levels of IFE on the eight postoperative day. In this case chlorpromazine definitely improved performance. One of the animals (1A) recovered whereas the second (5A) displayed a small improvement. However, in both cases the 28th–35th postoperative days showed the reverse effect of chlorpromazine on IFE.

The results demonstrated in Fig. 3 emphasize another important fact: the significance of the volume and localization of the striatal lesions. Limited lesions (less than 5% of each nucleus) of the dorsal regions of the striatum (e.g., rat 1A) produced weak behavioral disturbances and changed the neuroleptic effect to a small extent. If damages were more extensive (6–12% volume of the nucleus) or were localized in the central and ventral regions of the structure (rat 5A), shifts in behavior and pharmacological effect were more significant.

Influence of Striatectomy on the Effects of Amphetamine and Its Interaction with Haloperidol

In non-operated rats amphetamine (5 mg/kg) produced stereotyped behavior and changed various parameters of avoidance response. The IFE and the total number of errors and exits from the safe chamber increased, whereas latency shortened. In general the pattern of avoidance response of amphetamine-treated rats resembled that of striatectomized animals (Fig. 4).

In striatectomized rats amphetamine administration increased the nonreversal tendency of avoidance in spite of the changes in the pattern of stereotyped behavior. At early postoperative testing some rats displayed less stereotypy. Some of the typical turnings of the head, gnawing and sniffing were gone. In other cases the pattern of stereotyped movements remained at the high levels, but the experimental subjects displayed marked signs of hyperactivity. All of the cases recorded chaotic and unceasing runnings usually of the same trajectory. As a result the IFE remained high (Fig. 4) and retention in the safe chamber was disturbed in spite of the shortened latency of responses. Hence, our data showed that striatectomy did not eliminate amphetamine stereotypy. Behavioral disturbances in the maze were preserved at the previous level or even intensified.

The doses of haloperidol used altered the amphetamine-induced stereotypy in intact animals but did not suppress it fully. Locomotion increased, gnawing disappeared, but sniffing remained. On the other hand, the neuroleptic entirely blocked amphetamine-induced defects in reversal learning,

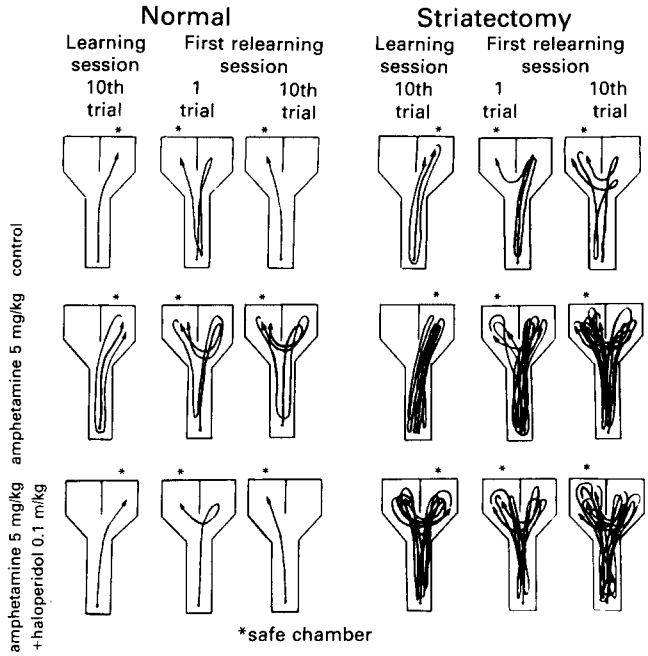

FIG. 5. Peculiarities of reversal learning of intact and striatectomized rats treated by amphetamine and its combination with haloperidol. Trajectory of runnings as applied to the scheme of Y-maze in the last trial of the first session and the 1st and last trials of the reversal learning session.

significantly decreasing the IFE and the number of exits from the safe chamber. We also noted a paradoxical change in latency: it became shorter instead of increasing as expected.

After striatectomy the neuroleptic did not suppress the outer features of amphetamine stereotypy and accompanying defects of avoidance behavior. The pattern of runnings changed somewhat but it did not decrease the IFE (Figs. 4 and 5). Weakening of haloperidol action was obvious when lesions occupied the ventral regions of the striatum.

DISCUSSION

Following striatectomy neuroleptics failed to improve the reversal avoidance response of rats in a Y-maze. Brain lesions also attenuated the ability of haloperidol to improve avoidance in amphetamine-treated animals.

The effect of the neuroleptics could be explained in several ways: changes in the arousal and reactivity of the rats, prolonged latency of responses, or shifts in spatial orientation. Although the first suggestion is important it does not give an exhaustive explanation for our results. No doubt, high arousal of some rats could produce behavioral disturbances in the Y-maze such as a high number of incorrect responses and signficant IFE. By reducing arousal, neuroleptics would naturally improve reversal learning. However, in some cases especially in the later postoperative period, haloperidol and chlorpromazine normalized reactivity in striatectomized animals without restoring their ability for reversal learning.

Another reason for the improving effect of the neuroleptics on reversal avoidance responses may be a prolongation of latency. When rats slowly ran along the main alley and stopped at the fork of the Y-maze, they had another opportunity to make the correct choice of the safe chamber. However, this explanation is not satisfactory either. The analysis of individual behaviour of experimental subjects showed that they sometimes had few errors and low IFE accompanied with short latency responses. Also according to our previous observations [4], some psychostimulant drugs that shorten the latency of avoidance responses do not disrupt reversal learning in the maze.

In our opinion, the described effect of the neuroleptics is best explained by shifts in spatial orientation. This process is closely connected with the functions of striatum which is part of egocentric system providing regulation of the body position in space [19]. Electrostimulation of the main component of the striatum, the caudate nucleus, provokes turning and circling in cats, while unilateral caudatectomy causes postural asymmetry [6, 11, 17]. It is of importance that bilateral electrolytic lesions in the striatum results in a tendency of rats to perform avoidance in one (left or right) direction. As a result reversal learning in a Y-maze is sharply impaired and the IFE is high. According to histological data the direction of avoidance may be related to the degree of striatal damage on each side. Avoidance responses as a rule, are directed toward the more lesioned striatum [2,3].

The functions of the striatum are controlled by the nigro-striatal system. Under normal conditions a slight asymmetry of the dopaminergic nigro-striatal systems would produce unequal functional activity of both striata; hence, inborn spatial preference [13,15]. By releasing dopamine, amphetamine may increase the disbalance and induce spatial preference or make it more prominent [12,14]. We believe this to be a plausible explanation for unidirectional runnings and difficulties in reversal learning.

By blocking nigro-striatal transmission neuroleptics may reduce interstriatal functional asymmetry. As a result spatial preference would decrease and the reconstruction of a running trajectory would become easier. According to previous reports the effect of neuroleptics on the caudate related turning and circling is contrary to that of amphetamine and DOPA [6]. By evoking sharp disturbances in spatial preference striatectomy limits the effect of haloperidol and chlorpromazine on reversal learning of a spatial task. When striatectomy is combined with the administration of high doses of amphetamine orientation defects are more prominent and runnings acquire an obvious unidirectional appearance (Fig. 5), while with neuroleptics their reorganization is much weaker.

Considerable changes in reversal learning and neuroleptic action were noted after ventral striatal lesions. These results agree with earlier observations [18,23] and confirm our suggestion that the ventral striatum contains a mechanism that keeps animals from inadequate actions [5].

According to the present data, striatectomy did not block behavioral disturbances induced by high doses of amphetamine. According to Fog *et al.* [10], striatal lesions in rats considerably impaired amphetamine stereotypy. When studying spontaneous behavior and a simple model of avoidance response, we came to the same conclusion [2]. However the present investigation of a complex behavioral task provides evidence that amphetamine-induced defects in avoidance reactions do not disappear after striatectomy. This confirms observations of Divak [9] and our own view that amphetamine-induced stereotypy is a functional deficit of the striatum [1].

The improving action of high doses of haloperidol and

chlorpromazine on reversal learning disappears in the later postoperative period. In all probability the improving effect of neuroleptics in the early post lesion period depends on the activation of still intact parts of the nucleus. Later, the field of degeneration of intranuclear cells and fibers of passage around the site of destruction expands [22] with subsequent decreases in striatal function. At this point the improving effect of neuroleptics is attenuated.

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