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BRIEF COMMUNICATION

T-Maze Performance in Rats Following Chronic Neuroleptic Treatment

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FERRÉ, S., G. PRAT, T. GUIX, M. GOMÁ, F. JANÉ AND M. CASAS. *T-maze performance in rats following chronic neuroleptic treatment*. PHARMACOL BIOCHEM BEHAV **35**(2) 481–484, 1990.—The effects of chronic haloperidol treatment (0.5 mg/kg/day for 21 days) on maze learning in the rat were studied. There were no differences between haloperidol- and saline-treated groups in percentage of correct responses, but the latency to respond was longer and extinction was faster in the haloperidol-treated group. We speculated that differences between both groups were due to a decrease of appetitive motivation in haloperidol-treated animals, probably caused by a decrease of dopaminergic neurotransmission.

Haloperidol Chronic treatment Food-reinforced behaviour Locomotor activity Rat

MANY experimental data suggest that cerebral dopaminergic systems are mainly involved in locomotor activity and in reinforced behaviour [for review see (1)]. Although many studies about chronic effects of neuroleptics on those systems have been published (3–7, 9–12), studies of reinforced behaviour after chronic neuroleptic treatment are lacking. In the present study we analyze the changes produced by chronic neuroleptic treatment (haloperidol) during the acquisition of a food-reinforced behaviour in the rat.

METHOD

Animals

Male Sprague-Dawley rats, with an initial weight of 495 ± 55 g, were used. They were housed in a colony room and maintained under constant room temperature (21°C) and humidity conditions with a 12-hour light/dark cycle. The rats were maintained on reduced food throughout the experiment in order to keep them at $80 \pm 10\%$ g of the initial weight.

Drugs

Haloperidol (Sintex-Latino, Spain) was diluted with saline from injection ampoules containing haloperidol 5 mg/ml. Apomorphine (Sigma Chemicals, USA) was dissolved in saline and administered immediately following its preparation, avoiding its exposure to the light.

Apparatus

All trials were carried out in a dark (red light) soundproofed temperature-controlled (21°C) experimental chamber, using white masking noise (75 dB). A T-maze was used for the learning process, with the following dimensions: long arm length 80 cm; short arm length 40 cm; height 28.5 cm; width 12 cm. The start box (placed at the beginning of the long arm) and the goal boxes (at the end of each short arm) each had areas of 24 by 32 cm, and were provided with doors which led to the arm in question and which could be opened and closed manually. The boxes were also interchangeable; thus, the animal could remain unhandled throughout a session (see below). Fifty mg food pellets (Letica, Spain) were used as reinforcement, and were introduced through an opening in one of the goal box walls. The pellets were placed in a food dish, which could be removed from outside. Ambulation and emotionality were measured using an open-field apparatus (2) with a diameter of 73 cm, height of 30.5 cm, with 3 concentric circles

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and 19 sections of identical surface area. A 200 W light was placed in the centre of the field at a height of 120 cm. Transparent Plexiglas boxes measuring 25 by 25 cm were used to measure stereotypies and to habituate rats to the food pellets.

Treatment

The animals were randomly assigned to 2 groups: one group was treated with haloperidol 0.5 mg/kg SC injected in a volume of 1 ml/kg body weight and the other with 1 ml/kg SC saline solution. A single daily dose was administered for 21 consecutive days.

Habituation

This stage was initiated one week after completion of the drug treatment. The animals were first placed in the maze for 30 min/day for a period of 10 days, with no food available. Following this ten-day period they were placed in the maze for 5 min/day for 2 days with empty food dishes in the goal boxes, followed by 5 min/day for the next two days with ten pellets in the food dishes in the goal boxes. In the two 5-minute periods in which the rat explored the maze with empty food dishes we measured exploratory activity (total number of entries in the goal boxes in said periods). Animals were always introduced into the maze in the start box, with the doors permanently retracted during the habituation stage. Two days before food habituation in the maze the animals were introduced twice (once/day) into Plexiglas boxes to habituate to pellet consumption (until the rat had eaten 10 pellets). During the second day of habituation to pellet consumption the time of food consumption was recorded.

Open Field

During the second week of habituation, the animals were placed in the open field for 2 minutes once a day over a four-day period. We then measured ambulation (total number of crossed sections in that period), defecation (total number of boli during the four days) and rearings (total number of times the animal got up on its hind legs).

Training

The animal was placed in the start box with the door closed, this door and the goal box doors being opened five seconds later. When the rat left the start box or entered one of the goal boxes the corresponding door was then closed. A correct entry into a goal box was reinforced by 10 pellets and counted as a correct response; an entry into the wrong box counted as a failed response and the rat received no reinforcement. Once the rat had eaten the pellets or had entered the wrong box, the food dish was removed and the start box was interchanged with the box in which the rat was found, and the food dish once again placed in the goal box. This experiment was carried out at 1 session/day, each session comprising 10 trials, for a 14-day period. For the initial 7 days, the pellets were placed in the left-hand goal box, and subsequently placed in the right-hand goal box for the last 7 days. The number of correct responses and latency (in minutes) was recorded. On completion of the 14-day training period, the extinction period began, during which the reinforcement was not present. For three days, the number of trials performed by the rat before it stopped entering either goal box (with a maximum trial length of 10 min) were counted. The order with which the animals were introduced to the different apparatus was randomized.

Stereotypies

Dopaminergic supersensitivity was measured by determining the amount of stereotypy produced by a 2 mg/kg body weight SC injection of apomorphine, once the extinction period was over (6 weeks after completing treatment). Stereotypy level was measured using the method of Haveman *et al.* (8).

Statistics

SPSS PC/+ software was used. The statistical tests used were: Kolmogorov-Smirnov's test of normality (K-S test), Bartlett's test of homogeneity of variances (B-test), Student's *t*-test (*t*-test), Mann-Whitney's U-test (U-test) and repeated measures ANOVA test.

RESULTS

Of the initial 24 rats, 3 from the group treated with haloperidol (final n = 9) and 2 from the saline-treated group (final n = 10) were eliminated (because they took more than 30 minutes per session).

Habituation

No significant differences were found in the two groups, neither in maze exploratory activity (means ± S.E.M. from serum- and haloperidol-treated groups were, respectively, 11.7 ± 1.3 and 8.7 ± 2.3; K-S-test: $p = 0.998$; B-test: $p = 0.126$; *t*-test: $p = 0.273$), nor in defecation (rank means from serum- and haloperidol-treated groups were, respectively, 9.3 and 10.7; K-S-test: $p < 0.001$; B-test: $p < 0.001$; U-test: $p = 0.403$). There were no significant differences in food consumption time between the groups (rank means from serum- and haloperidol-treated groups were, respectively, 9.2 and 10.9; K-S-test: $p = 0.002$; B-test $p < 0.001$; U-test: $p = 0.422$).

Open-Field Activity

No significant differences were found in ambulation (means ± S.E.M. from serum- and haloperidol-treated groups were, respectively, 158.8 ± 10.3 and 145.3 ± 18.3; K-S-test: $p = 0.982$; B-test: $p = 0.143$; *r*-test: $p = 0.519$), rearing (means ± S.E.M. from serum- and haloperidol-treated groups were, respectively, 28.8 ± 4.9 and 22.1 ± 4.5; K-S-test: $p = 0.949$; B-test: $p = 0.730$; *t*-test: $p = 0.335$) or defecation (rank means from serum- and haloperidol-treated groups were, respectively, 8.6 and 11.5; K-S-test: $p = 0.027$; B-test: $p = 0.250$; U-test: $p = 0.219$).

Training

No significant differences in the percentage of correct responses in both the saline- and haloperidol-treated groups, in the initial learning of one arm and its reversal (Fig. 1A). There was, however, a significant difference in latency with the haloperidol-treated group exhibiting longer performance latencies during the entire training period (Fig. 1B) (ANOVA test; $p < 0.001$). On elimination of reinforcement, the group administered haloperidol reached the goal box a smaller number of times than the control group (Fig. 2) (ANOVA test; $p < 0.001$).

Stereotypies

The stereotypy level was markedly higher in the group treated with haloperidol (rank means from serum- and haloperidol-treated groups were, respectively, 6.9 and 13.3; K-S-test: $p = 0.113$; B-test: $p = 0.029$; U-test: $p = 0.008$).

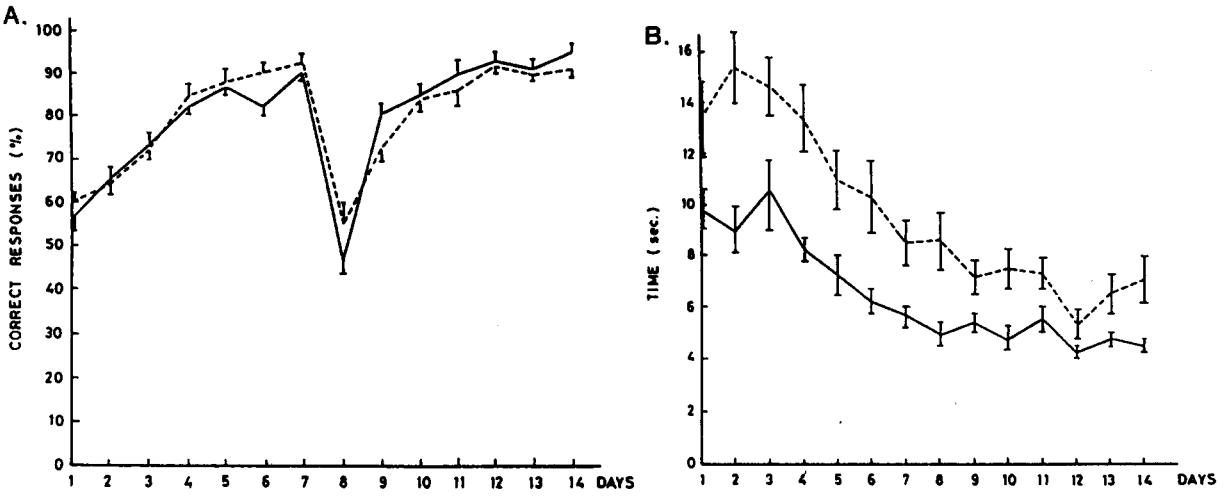

FIG. 1. (A) Means ± S.E.M. of correct responses/session (10 trials/session and 1 session/day) from both haloperidol- (broken line) and saline-treated (continuous line) groups. (B) Means ± S.E.M. of each session duration (latency) from both haloperidol- (broken line) and saline-treated (continuous line) groups. For the initial 7 days, reinforcement (10 pellets/correct response) was placed in the left-hand goal box, and subsequently placed in the right-hand goal box for the last 7 days.

DISCUSSION

In open-field experiments, defecation is widely accepted as a measure of emotion and ambulation as a measure of locomotor activity (2). The absence of significant differences between the haloperidol- and saline-treated groups in both parameters in the open field, and in defecation and exploratory behavior in the maze, suggests that the rats differed neither in emotion nor in locomotor activity at the beginning of maze training. Additionally, the absence of differences in exploratory behaviour in the maze suggests that both haloperidol- and saline-pretreated groups had the same opportunity for latent learning. It can be suggested that the qualitative changes found in haloperidol-pretreated animals (i.e., a longer latency to respond and a faster extinction) reflect a decrease of appetitive motivation during the training period. This decrement appears to be specific to training since immediately before such training food motivation, as measured by food consumption time, did not seem to be altered.

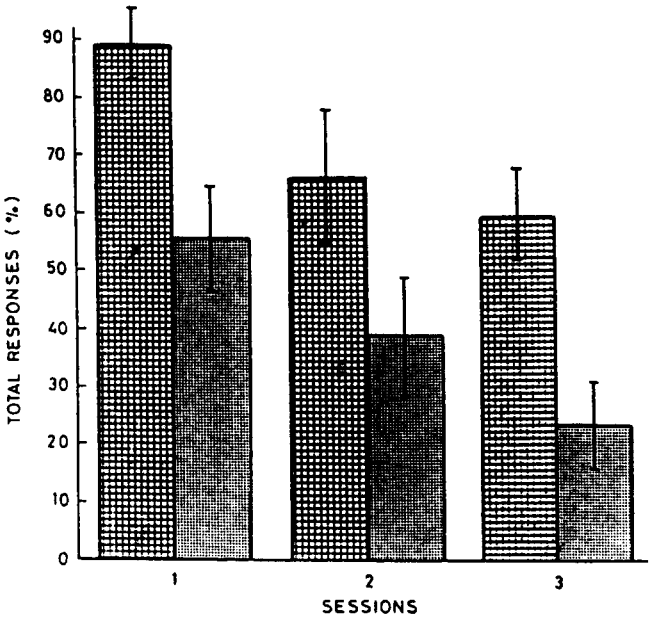

FIG. 2. Means ± S.E.M. of total responses/session during extinction (1 session/day) from both haloperidol- (dotted bars) and saline-treated (squared bars) groups.

It could be argued that the acute effects of neuroleptics, which include the attenuation of the reinforcing consequences of food presentation in hungry animals (13), could explain our results. However, all behavioural studies were started one week after the last administration of haloperidol or saline, to assure that the acute effects of neuroleptics, such as decreased locomotor activity, would not influence the results (10). In fact, no significant alterations in locomotor activity were found between the two groups. On the other hand, the greater stereotyped behaviour induced by apomorphine, that was observed after the extinction period in animals pretreated with haloperidol, indicates that chronic effects of neuroleptics, e.g., supersensitive dopamine receptors, were indeed present at the end of the experiment (9,10). In addition to the development of supersensitive dopamine receptors (4, 6, 10, 11), chronic neuroleptic treatment produces a decrease of the activity of cerebral dopaminergic neurons (3, 5, 12). This phenomenon is probably due to the induction of a tonic state of depolarization inactivation (7) and to the development of supersensitive dopamine autoreceptors (3,5). Consequently, a decrease of dopaminergic neurotransmission could cause the decrease of appetitive motivation induced by chronic neuroleptic treatment.

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