Pharmacology Biochemistry and Behavior, Vol. 43, pp. 631–633, 1992
Printed in the U.S.A.

0091-3057/92 $5.00 + .00

BRIEF COMMUNICATION

Anxiogenic Properties of Cocaine in the Rat Evaluated with the Elevated Plus-Maze

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Received 3 October 1991

ROGERIO, R. AND R. N. TAKAHASHI. *Anxiogenic properties of cocaine in the rat evaluated with the elevated plus-maze.* PHARMACOL BIOCHEM BEHAV **43**(2) 631–633, 1992. – In previous work, we reported that cocaine (5, 10, and 20 mg/kg) failed to induce significant responses in naive rats in the elevated plus-maze test of anxiety. This study investigates the putative anxiogenic properties of cocaine in rats selected as "anxious" or "nonanxious" on the basis of their behavior in the plus-maze prior to drug treatment. In nonanxious rats, cocaine (10 mg/kg) increased the latency to the first entry into the open arms and reduced the number of entries into and time spent on the open arms. All these measures are indicative of an anxiogenic action of cocaine. In contrast, cocaine failed to modify the behavior of anxious rats. These findings demonstrate that rats with high exploratory activity in the plus-maze and regarded as nonanxious are more sensitive to cocaine's anxiogenic effects. Further, the present manipulation provides a useful procedure for investigating the anxiogenic effects of cocaine in rats.

Cocaine Anxiety High and low activity Elevated plus-maze Rat

COCAINE effects in humans are reported to include both euphoric and anxiogenic properties (4). Although it is well documented that the chronicity of cocaine abuse is associated with the development of anxiogenic states (1,12), a recent report suggests that even occasional cocaine experimentation can induce panic attacks (5). On the other hand, studies examining the anxiogenic properties of cocaine in experimental models are limited and conflicting. Thus, cocaine has been reported to have anxiogenic effects in the pentylenetetrazol discrimination test in rats (10) and increase the incidence of retreat behaviors of rats in a straight alley (3), whereas our recent study failed to show a significant anxiogenic response of naive rats treated with cocaine and tested in the elevated plus-maze (11).

The elevated plus-maze test has been used as a simple and reliable animal model of anxiety and to assess anxiogenic and anxiolytic drugs (8). This model exploits the aversion generated in the rat by placing the animal on an elevated open arm. Anxiogenic drugs reduce the time spent on and the number of entries into the open arms, while the opposite effect is induced by anxiolytics (8). Nevertheless, it has been recognized recently that there is a fairly high variability between control animals in the parameters measured in this test (2,7). Indeed, in our experience the total number of entries into the plus-maze presented by some rats was quite low (11). Therefore, it is possible that low baseline levels of the open/total arm entries prevented the finding of a clear-cut anxiogenic effect of cocaine (10 mg/kg) in our previous study (11).

Recently, Harro et al. (6) demonstrated that it is possible to differentiate rats according to their behavioral response in an elevated plus-maze test into "anxious" and "nonanxious" animals. Anxious rats had a considerably lower exploratory activity and a significantly lower number of benzodiazepine receptors in frontal cortex compared to nonanxious animals (6). The present study was conducted to evaluate the putative anxiogenic properties of cocaine in rats selected as anxious and nonanxious in the elevated plus-maze under drug-free conditions.

METHOD

Animals

Male Wistar rats (300–350 g body weight) from our own colony were housed in groups of five per cage, under a 12 L : 12 D cycle in a room with temperature kept at 23 ± 1°C.

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Food and tapwater were available ad lib, except during elevated plus-maze sessions.

Apparatus

The plus-maze was made of wood and consisted of two opposite open arms 50 × 10 cm (length and width) and two enclosed arms 50 × 10 × 40 cm (length, width, and height) and the whole apparatus was elevated 50 cm from the floor. To determine the exploratory activity of rats, white tapes (about 2-mm wide) were used to divide the floor of each open arm into three equal sectors.

Drugs

Cocaine HCl (Merck) was dissolved in distilled water. The selected dose of 10 mg/kg was based upon our previous behavioral studies (9,11). All injections were administered IP.

Procedure

Rats were separated into subgroups with high or low exploratory activity in the elevated plus-maze using a procedure similar to that described by Harro et al. (6). Each rat was placed in the center of the maze and the number of entries into and time spent on open and closed arms were recorded over a 5-min test period by an observer sitting at a distance approximately 1 m from the apparatus. The values obtained were converted into percentages of time spent on the open arms relative to the total time spent on open and closed arms (8). In addition, the following parameters were registered: the latency period of the first entry into one of the open arms of the maze and the number of sectors crossed on the open arms.

For the selection procedure, the number of sectors crossed and the total time spent on the open arms by each undrugged rat were considered (6). Twenty-four hours after the selection, rats with high and low exploratory activity received control solution or cocaine (10 mg/kg) 15 min prior to testing in the plus-maze. It is known, that rats do not show a lesser avoidance of elevated plus-maze after repeated exposure (8). Testing was performed as in the preceding experiment. The maze was cleaned after each test with a cloth dampened with 10% ethanol. Rats were tested between 1300 and 1700 h in a dimly lit room.

Statistics

All results are expressed as the mean ± SEM and were analyzed by the two-tailed Mann–Whitney *U*-test. Differences were considered significant when $p < 0.05$.

RESULTS

Table 1 summarizes the results of the selection procedure of rats with high and low exploratory activity in the elevated plus-maze. As can be seen, rats separated into the high-activity subgroup exhibited shorter latencies to entry on open arms, crossed more sectors, and spent more time on the open arms of the maze compared to the total pooled data. All these measures are suggestive of a reduced aversiveness in the high-activity subgroup. The opposite was true in the case of rats selected into the low-activity subgroup.

The percentage of open-arm entries and the percentage of time spent on the open arms were not significantly altered following control or cocaine injection in rats with low activity. The data were 13.6 ± 6.2 vs. 3.6 ± 3.3% and 3.1 ± 1.6 vs. 2.3 ± 2.1%, respectively ($p > 0.05$).

There is no clear explanation for the differences between the latencies of open-arm entries of the high-activity group (Table 1) and the control subgroup in Table 2. However, some familiarity of these nonanxious rats with the plus-maze may have occurred upon second exposure to the apparatus. Moreover, in this high exploratory activity subgroup cocaine (10 mg/kg) significantly increased the latency of first open-arm entry and reduced the number of crossed sectors, the percentage number of entries, and the time spent on the open arms of the maze (Table 2). An important additional finding in this subgroup is that the total mean number of arm entries was not affected by cocaine (10.7 ± 2.8 vs. 10.3 ± 1.2 for the controls ($p > 0.05$). These data suggest that the decreased behavioral measures of anxiety following cocaine are dissociated from a nonspecific depressant effect of the drug and that rats with high exploratory behavior are more sensitive to the anxiogenic actions of cocaine.

DISCUSSION

Harro et al. (6) have recently shown that animals displaying different exploratory activity in the elevated plus-maze reflect differences in their anxiety state. So, according to these authors, rats with high exploratory activity can be termed nonanxious whereas rats with low activity are regarded as anxious. The results of the present study demonstrate that acute administration of cocaine to nonanxious rats induces an anxiogenic-like effect in the elevated plus-maze because these animals showed an increased latency to the first open-arm entry and a reduced number of crossings, number of entries into, and duration of time spent on the open arms of the maze. In marked contrast, anxious rats treated with cocaine failed to show anxiogenic properties as measured in the plus-maze. As

TABLE 1

SELECTION EXPERIMENT ACCORDING TO THE EXPLORATORY ACTIVITY OF NAIVE UNDRUGGED RATS IN AN ELEVATED PLUS-MAZE

Group	Number of Rats	Latency of First Open-Arm Entry (seconds)	Number of Crossed Sectors in Open Arms	Total Time Spent in Open Arms (seconds)
Total	29	96.2 ± 22.9	16.9 ± 2.9	75.3 ± 13.1
High activity	16	21.8 ± 5.2	28.7 ± 2.6*	127.5 ± 12.8*
Low activity	13	187.9 ± 38.0*†	2.3 ± 1.1*†	11.2 ± 3.1*†

Data are presented as the mean ± SEM.
*Significantly different from total group, $p < 0.05$, Mann–Whitney *U*-test, two tailed.
†Significantly different from high activity group, $p < 0.05$.

TABLE 2

ACUTE-EFFECTS OF COCAINE (10 mg/kg) IN PERFORMANCE OF RATS WITH HIGH EXPLORATORY ACTIVITY IN AN ELEVATED PLUS-MAZE

Group	Number of Rats	Latency to First Open-Arm Entry (seconds)	Number of Crossed Sectors On Open Arms	% Entries into Open Arms	% Time Spent on Open Arms
Control	8	7.1 ± 1.5	21.8 ± 1.9	55.3 ± 4.9	42.7 ± 4.9
Cocaine 10 mg/kg	8	50.8 ± 31.8*	15.0 ± 5.1	38.2 ± 6.0*	14.5 ± 5.0*

Animals were injected IP 15 min before 5-min test. Data are presented as the mean ± SEM.
*Significantly different from control group, $p < 0.05$, Mann-Whitney U-test.

mentioned in the introductory section, it is likely that a "floor effect" precluded the observation of an anxiogenic action of cocaine in anxious rats in the elevated plus-maze.

In any event, it is clear that the ability of cocaine to induce anxiogenic properties in rats may depend upon the emotional state of the animal. Thus, the current findings that only nonanxious rats treated with cocaine presented a significant anxiogenic response are congruent with the limited evidence showing similar responses to this drug in this and other animal models of anxiety (3,10,11). Furthermore, they emphasize the importance of subject selection in evaluating the anxiogenic effects of cocaine in rats.

The present results showing that the anxiogenic properties of cocaine can only be detected in animals displaying low basal levels of anxiety may help explain the inconclusive clinical reports concerning the relationship between cocaine abuse and anxiety in humans (1,5,12).

In conclusion, our results indicate that acute administration of cocaine induces anxiogenic-like effects in rats with nonanxious type of exploratory behavior in the elevated plus-maze but not in anxious animals.

ACKNOWLEDGEMENTS

R.R. was supported by a graduate studentship from Conselho Nacional de Desenvolvimento Cientifico e Tecnologico (CNPq). R.N.T. is the recipient of a research fellowship from CNPq. The authors thank Jose Iaczinski for technical assistance and Drs. Gina S. Morato and Giles A. Rae for their helpful comments on the manuscript.

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