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Chronic Fluoxetine in Tests of Anxiety in Rat Lines Selectively Bred for Differential 5-HT_{1A} Receptor Function

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FILE, S. E., A.-M. OUAGAZZAL, L. E. GONZALEZ AND D. H. OVERSTREET. *Chronic fluoxetine in tests of anxiety in rat lines selectively bred for differential 5-HT_{1A} receptor function*. PHARMACOL BIOCHEM BEHAV **62**(4) 695–701, 1999.—Selective breeding for high and low sensitivity to the hypothermic response induced by the 5-HT_{1A} receptor agonist 8- OH-DPAT has established two lines of rat (HDS and LDS, respectively) whose behavior differs in a model of depression and in the social interaction test of anxiety. The HDS line has a higher level of anxiety and, furthermore, does not display the usual anxiogenic response to intrahippocampal administration of 8-OH-DPAT. It was therefore hypothesized that this line of rat might be a useful model of high trait anxiety with a susceptibility to depression. We thus investigated whether chronic treatment with fluoxetine would result in an anxiolytic effect in the social interaction test in the LDS and HDS lines of rat. In both lines, acute fluoxetine (10 mg/kg) produced an anxiogenic effect in the social interaction test; when rats were tested 24 h after 14 days of fluoxetine treatment there were no anxiolytic effects in either line. In the social interaction test, chronic fluoxetine treatment did not change either the anxiogenic effect of 8-OH-DPAT (100 ng) injected bilaterally into the dorsal hippocampus in the LDS line or the lack of response in the HDS line. In the elevated plus-maze, chronic fluoxetine treatment resulted in a significant anxiogenic effect in the HDS line, but was without effect in the LDS line. Intrahippocampal 8-OH-DPAT was without effect in the plus-maze in either line. These results suggest that chronic treatment with fluoxetine did not modify the hippocampal 5-HT_{1A} receptor in either line. The anxiogenic effects observed in the plus-maze in the HDS line after chronic fluoxetine might relate to line differences in 5-HT_{1A} receptors in other brain regions. © 1999 Elsevier Science Inc.

Social Interaction Plus-maze Anxiety Depression Hippocampus 5-HT_{1A} receptors Fluoxetine

ABNORMALITIES of the 5-HT system have long been implicated in both anxiety and depression, but preclinical investigations have generally been limited to studies of state anxiety. The possibility of assessing the contribution of abnormalities of 5-HT_{1A} receptor function to differences in trait anxiety and depression has been raised by the recent work of Overstreet (18,19). Lines of rat have been selectively bred for high and low sensitivity to the 5-HT_{1A} receptor agonist, 8-OH-DPAT. The selection was based on the hypothermic response to 8-OH-DPAT (18) but, most interestingly, the HDS line was more immobile in the forced swim test (19), which is a test sensitive to antidepressants and chronic stress and was more anxious in the social interaction test of anxiety (9). The low scores of the HDS line in the social interaction test were, at least in part, due to abnormal functioning of the 5-HT_{1A} receptors in the dorsal hippocampus. Unlike other strains of rat and the LDS line, the HDS line failed to show an anxiogenic response to dorsal hippocampal injections of 8-OH-DPAT

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(9). The dorsal hippocampus 5-HT system has proven particularly sensitive to the effects of chronically administered antidepressant drugs (10,17).

The primary purpose of the present experiment was to determine whether chronic administration of fluoxetine would result in anxiolytic effects in the social interaction test, especially in the HDS line, which might be a line with genetic susceptibility to depression. The high light, unfamiliar test condition was selected to test this because it is the most sensitive to anxiolytic effects of benzodiazepines (8) and has detected an anxiolytic effect of chronic paroxetine (16). The dose of fluoxetine (10 mg/kg) and the time of testing (24 h after the last dose) was selected because of its effects in the forced swim test in the LDS and HDS lines (11) and on desensitization of hypothalamic 5-HT_{1A} receptors (22). We also examined whether chronic treatment with fluoxetine would modify in either line the response to 8-OH-DPAT administration into the dorsal hippocampus, and whether such a modification mediated the emergence of an anxiolytic effect of fluoxetine. The dose of 8-OH-DPAT was selected as that giving a robust anxiogenic effect in the LDS line (9), and its effects were assessed in the low light, familiar condition of the social interaction test, which is most sensitive to anxiogenic effects and in the elevated plus-maze test of anxiety.

METHOD

Animals

The HDS and LDS lines of rat (14th generation from the breeding colony at UNC Center for Alcohol Studies) were allowed 1 week to recover from shipping before the start of chronic drug treatment. Hooded Lister rats (Harlan, Bicester, UK) were used as uninjected test partners when the effects of central drug injections were assessed. All animals were housed singly after surgery, which took place 7 days prior to behavioral testing. Food and water were freely available, and the room in which they were housed was lit with dim light and maintained at 22°C. Lights were on from 0700–1900 h. In order to keep the cannulae patent, the stylets were replaced daily following surgery.

Drug Treatment

Fluoxetine (Ely Lilly & Co., Indianapolis, IN) was dissolved in saline to a concentration of 5 mg/ml. Rats from the HDS and LDS lines were randomly allocated to chronic (14 days) treatment with vehicle (distilled water) or fluoxetine (10 mg/kg/day IP), with $n = 14$ or 16 in each treatment group. (±)8-OH-DPAT hydrobromide (Research Biochemicals Incorporated, St. Albans, UK) was dissolved in aCSF of the following composition (mM); NaCl 126.6, $NaHCO_3$ 27.4, KCl 2.4, KH_2PO_4 0.5, $CaCl_2$ 0.89, $MgCl_2$ 0.8, Na_2HPO_4 0.48, and glucose 7.1, pH = 7.4. On the central injection test day the rats were held gently by wrapping in a cloth and injected, using needles constructed from 30-gauge steel tubing that extended 2 mm below the tip of the indwelling cannula(e). Injections were 0.5 μl and were made over a period of 30 s using a CMA/102 microdialysis pump (Biotech Instruments, Stockholm, Sweden); the needles were left in position a further 30 s to allow drug diffusion.

Apparatus

The social interaction test arena was a wooden box 60 × 60 cm, with 35-cm high walls and was lit by high or low light (300 or 30 lx, respectively). A camera was mounted vertically above the arena, and the rats were observed on a monitor in an adjacent room by an observer who was blind to the drug treatment. The time spent in social interaction (sniffing, following and grooming the partner, boxing, and wrestling) provides the measure of anxiety. Infrared photocells were mounted in the walls, 4.5 and 12 cm from the floor, and the interruption of these beams provided automated measures of locomotor activity and rearing, respectively [for details, see (3)].

The plus-maze was made of wood and consisted of two opposite open arms 50 × 10 cm, and two opposite arms enclosed by 40-cm high walls. The arms were connected by a central 10 × 10 cm square, and thus the maze formed a "plus" shape. The maze was elevated 50 cm from the floor and lit by dim light. A closed-circuit TV camera was mounted vertically over the maze and the behavior was scored from a monitor in an adjacent room. All scores were entered directly into an IBM computer. The % of time spent on the open arms of the maze and the % of open-arm entries provide the measure of anxiety, and the number of closed-arm entries provides the best measure of locomotor activity in this test (6,7,20).

Surgery

Stereotaxic coordinates were verified histologically prior to each set of cannulations. Rats were anesthetized by inhalation of 3% halothane (May and Baker, Dagenham, UK) in oxygen and positioned in a stereotaxic frame (Kopf Instruments, Tajunga, CA). The skull was exposed and the incisor bar adjusted such that bregma and lambda were at the same height. Three indentations were made in the skull to accommodate screws which, together with the application of dental cement, held the cannulae in place. For bilateral cannulation of the dorsal hippocampus, 7-mm long steel guide cannulae were positioned at 3.3 mm posterior to bregma, lateral ±2.4, and vertical −1.2 mm, thus siting them 2 mm above the target area. Cannulae were kept patent using 7-mm long stainless steel stylets (30 gauge, Cooper's Needle Works Ltd, Birmingham, UK).

Histology

All the brains from operated animals were subjected to histological studies. Injection sites found between 2.8 and 4.16 mm posterior to bregma and ±1.7 and 3.2 mm lateral within hippocampal borders were considered correct. In three animals a unilateral placement fell outside this area, and in one animal both placements were above the target area; the scores from these animals following central injections were excluded from statistical analysis.

Procedure

In order to allow detection of either anxiolytic or anxiogenic effects of acute administration of fluoxetine rats from both lines were tested in the low light, unfamiliar condition of the social interaction test ($n = 5$/group). These animals were not used in any subsequent tests. To assess the effects of chronic fluoxetine treatment, rats were initially tested in the high light, unfamiliar test condition 24 h after their last chronic injection. They were allocated to test partners of the same chronic treatment and within 10 g in weight ($n = 7$ or 8 pairs/group). In all cases, pairs of rats were given a 4.5-min trial between 0900 and 1200 h, in an order randomized for line and drug treatment, and were scored by an observer with no knowledge of the treatments or lines. The rats in chronic

treatment received their usual vehicle or fluoxetine injection immediately after this social interaction test.

The following day, each rat was given a 10-min familiarization trial in the test arena, lit by low light. The rats received their usual chronic treatments on this familiarization day. Rats from each line and chronic drug treatment were then randomly allocated to be tested the following day after central injections of aCSF or 8-OH-DPAT. The rats were tested in the low light, familiar test condition of the social interaction test, 24 h after their last chronic injection and 3 min after intrahippocampal injections of aCSF or 8-OH-DPAT, with an uninjected hooded Lister rat as a partner. Only the social interaction of the injected rat was scored. Rats were tested between 0900 and 1200 h.

Immediately after the social interaction test, each injected rat was placed in the plus-maze, facing an open arm, and observed for 5 min by an observer without knowledge of drug treatment or rat line. The maze was cleaned between each rat.

Statistics

The data were analyzed by two- or three-way analyses of variance, with genetic line and drug treatment as the independent factors. Following these analyses, Dunnett's tests were used to establish the significance of differences between individual groups.

RESULTS

Social Interaction

It can be seen from Fig. 1 that, whereas acute fluoxetine had a significant anxiogenic effect in both lines of rat, $F(1, 16) = 8.9$, $p < 0.01$, chronic treatment with fluoxetine did not result in a significant effect on the time spent in social interaction in the high light, unfamiliar test condition, $F(1, 27) < 1.0$. The LDS line had a significantly higher level of social interaction than the HDS, $F(1, 27) = 20.5$, $p < 0.0001$. Acute fluoxetine was without effect on locomotor activity or rears, $F(1, 16) = 0.2$ in both cases. Chronic fluoxetine was without significant effect on locomotor activity or rears, $F(1, 27) < 1.2$ in both cases (see Table 1). The lines differed significantly in locomotor activity, $F(1, 27) = 27.4$, $p < 0.0001$, but not in the number of rears made, $F(1, 27) = 2.7$.

TABLE 1

MEAN (±SEM) LOCOMOTOR ACTIVITY (BEAM BREAKS) AND REARS MADE BY LDS AND HDS LINES OF RAT TESTED 24 h AFTER CHRONIC (14 DAYS) TREATMENT WITH VEHICLE OR FLUOXETINE (10 mg/kg/DAY) AND TESTED IN THE HIGH LIGHT, UNFAMILIAR CONDITION OF THE SOCIAL INTERACTION TEST

Rat Line	LDS		HDS	
Drug	Vehicle	Fluoxetine	Vehicle	Fluoxetine
Locomotor Activity	298.4 ± 27.1	262.9 ± 24.2	148.5± 13.0	179.0 ± 23.4
Rears	19.3 ± 2.8	21.6 ± 1.2	22.5 ± 0.7	23.5 ± 1.1

In the low light, familiar test condition there was a significant line × acute drug injection interaction, $F(1, 46) = 4.3$, $p < 0.05$, because 8-OH-DPAT had a significant anxiogenic effect only in the LDS line (see Fig. 2). The chronic fluoxetine was still without significant effect and it did not modify the effects of 8-OH-DPAT (in both cases, $F < 1.0$). In this test condition, there were no significant differences in locomotor activity or rears (see Table 2).

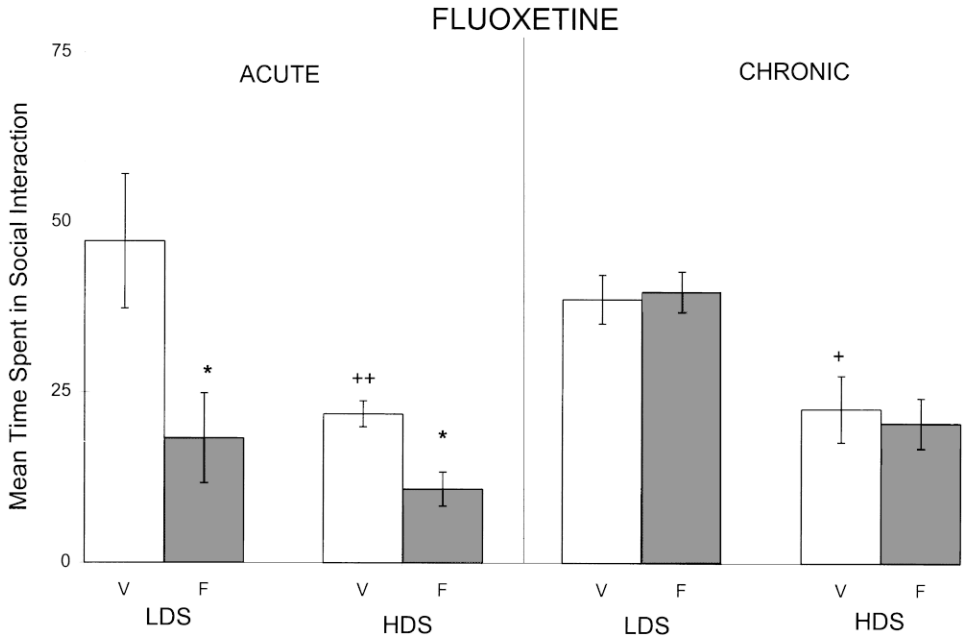

FIG. 1. Mean (±SEM) time (s) spent in social interaction by LDS and HDS lines of rat tested in the low light unfamiliar (LU) condition after acute treatment with vehicle (V) or fluoxetine (F,10 mg/kg) or tested in the high light unfamilair condition (HU) 24 h after the last of 14 days of treatment with vehicle (V) or fluoxetine (F, 10 mg/kg/day) $*p < 0.05$, compared with vehicle (V) group, $++p < 0.01$, $+p < 0.05$ compared with LDS line.

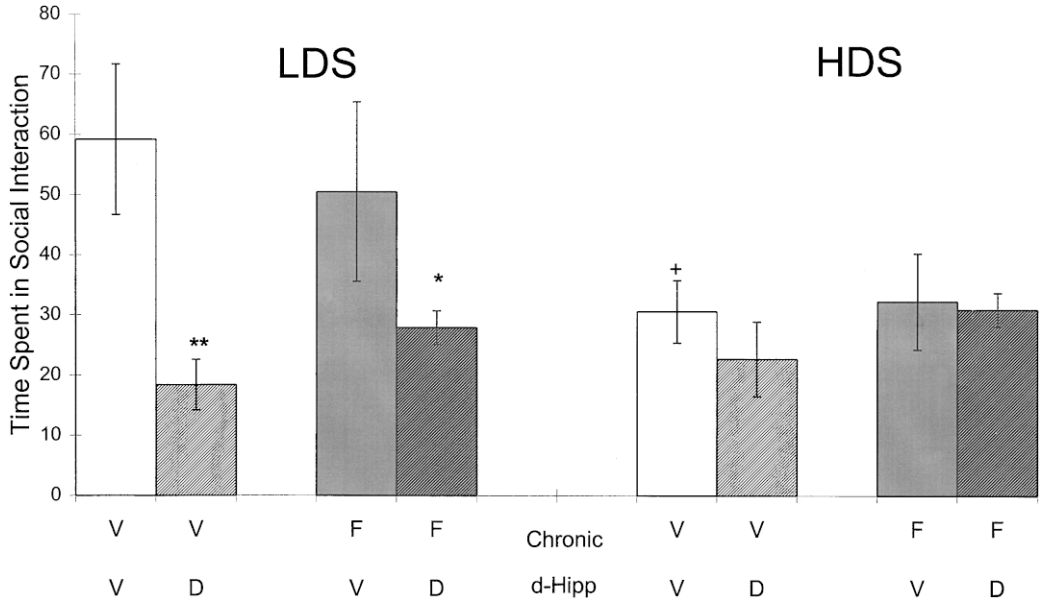

FIG. 2. Mean (±SEM) time (s) spent in social interaction by LDS and HDS lines of rat tested in the low light familiar (LF) condition 24 h after 14 days of treatment with vehicle (V) or fluoxetine (F, 10 mg/kg/day) and 5 min after acute dorsal hippocampal injection of aCSF (V) or 8-OH-DPAT (D,100 ng). *$p < 0.05$, compared with vehicle (V) group, +$p < 0.05$ compared with LDS line.

Elevated Plus-Maze

There was a significant line difference in the % time spent on the open arms, $F(1, 47) = 29.5$, $p < 0.0001$, and the % number of open-arm entries, $F(1, 47) = 24.1$, $p < 0.0001$, but no differences in the number of closed-arm entries or time spent in the central square (in both cases $F < 1.0$) (see Fig. 3 and Table 3). Chronic fluoxetine had a significant anxiogenic effect in the HDS line that was not reversed by intrahippocampal administration of 8-OH-DPAT (see Fig. 3).

DISCUSSION

These experiments have once again revealed clear line differences in the social interaction test, as previously reported (9). Previous studies (9,19) have not found significant differences in the plus-maze, but our present experiment found clear line differences in this test; one possible explanation for this could be that in the present study all rats received extensive handling over 3 weeks. Handling has previously been reported to increase the % time spent on the open arms and the % of open-arm entries (1), and although comparisons across different experiments must be made with great caution, it does look as if the scores from the LDS line increased as a result of handling, whereas those from the HDS did not. We have not previously found that handling modifies the scores in the social interaction test, but because the acute and chronic treatments were assessed in different test conditions we cannot say whether the more extensive handling involved in the present experiment would change scores. However, Lightowler et al. (16) found no change in social interaction after 21 days of daily handiling and injections.

Acute fluoxetine was anxiogenic in the social interaction test in both lines of rat, thus demonstrating that it is possible to see an anxiogenic drug effect in the HDS rat. This line did not show an anxiogenic response to intrahippocampal 8-OH-

TABLE 2

MEAN (±SEM) LOCOMOTOR ACTIVITY (BEAM BREAKS) OR REARS MADE BY LDS AND HDS LINES OF RAT TESTED IN THE LOW LIGHT, FAMILIAR CONDITION OF THE SOCIAL INTERACTION TEST 24 h AFTER CHRONIC (14 DAYS) TREATMENT WITH VEHICLE OR FLUOXETINE (10 mg/kg/DAY) AND AFTER ACUTE DORSAL HIPPOCAMPAL ADMINISTRATION OF ACSF OR 8-OH-DPAT (DPAT 100 ng)

Rat Line	LDS				HDS			
Chronic Treatment	Vehicle		Fluoxetine		Vehicle		Fluoxetine	
Hippocampal Injection	aCSF	DPAT	aCSF	DPAT	aCSF	DPAT	aCSF	DPAT
Locomotor activity	328.0 ± 19.7	316.8 ± 28.4	316.6 ± 22.6	338.3 ± 39.4	305.6 ± 29.5	309.0 ± 21.8	281.5 ± 18.8	339.8 ± 26.9
Rears	19.3 ± 2.5	20.5 ± 2.7	22.9 ± 1.3	21.3 ± 2.0	22.1 ± 1.5	19.8 ± 1.6	21.0 ± 1.0	19.5 ± 1.8

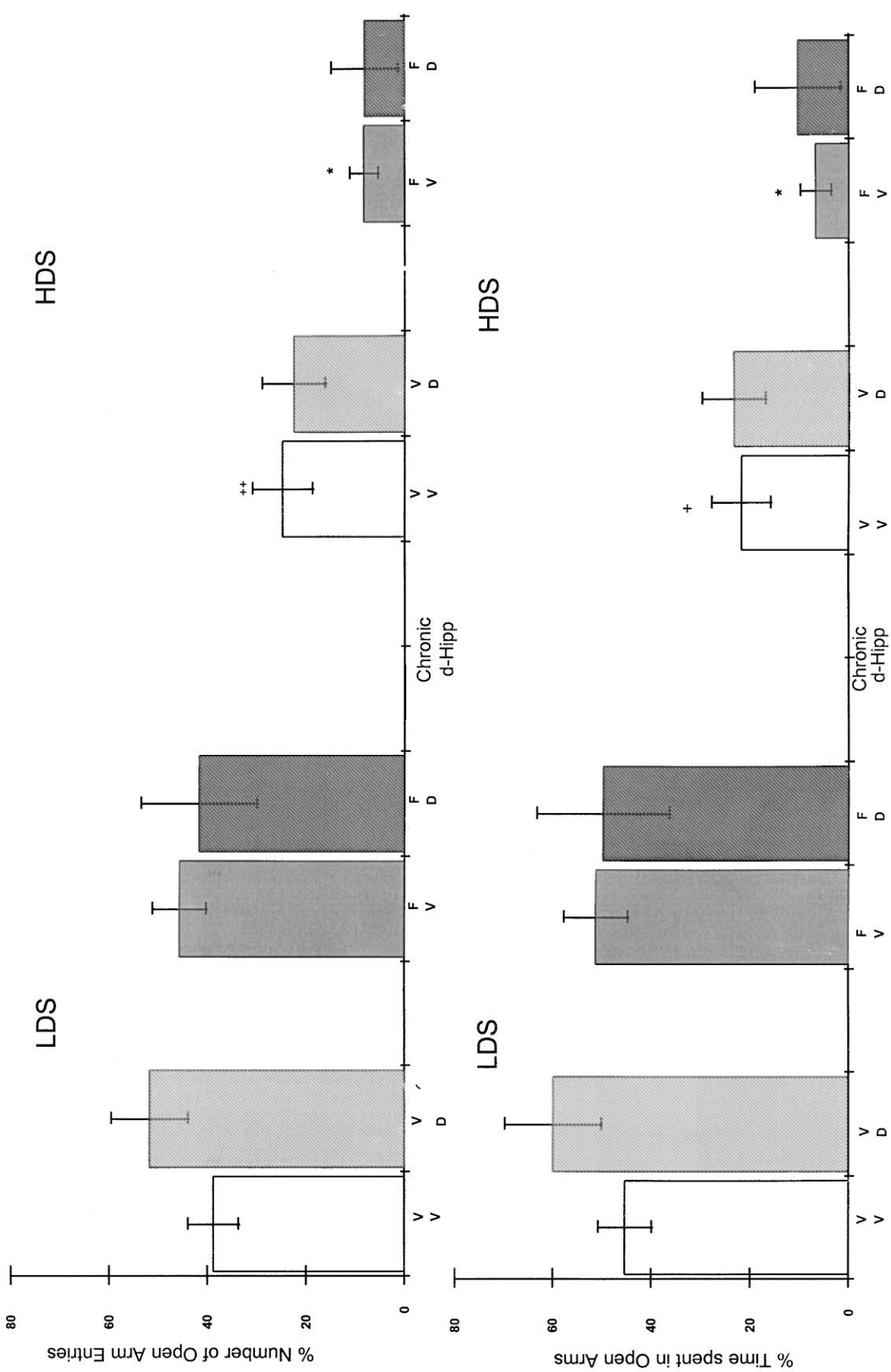

FIG. 3. Mean (±SEM) % number of open-arm entries and % of time spent on open arms by LDS and HDS lines of rat tested in the elevated plus-maze 24 h after 14 days of treatment with vehicle (V) or fluoxetine (F, 10 mg/kg/day) and 5 min after acute dorsal hippocampal injection of aCSF (V) or 8-OH-DPAT (D,100 ng). $^{*}p < 0.05$, compared with vehicle (V) group, $^{++}p < 0.01$, $^{+}p < 0.05$ compared with LDS line.

TABLE 3

MEAN (±SEM) NUMBER OF CLOSED ARM ENTRIES AND TIME (S) SPENT IN CENTRAL SQUARE OF THE PLUS-MAZE BY LDS AND HDS LINES OF RAT TESTED IN THE PLUS-MAZE 24 h AFTER CHRONIC (14 DAYS) TREATMENT WITH VEHICLE OR FLUOXETINE (10 mg/kg/DAY) AND AFTER ACUTE DORSAL HIPPOCAMPAL ADMINISTRATION OF ACSF OR 8-OH-DPAT (DPAT, 100 ng)

Rat Line	LDS				HDS			
Chronic Treatment	Vehicle		Fluoxetine		Vehicle		Fluoxetine	
Hippocampal injection	aCSF	DPAT	aCSF	DPAT	aCSF	DPAT	aCSF	DPAT
Closed-arm entries	11.6 ± 1.0	11.0 ± 2.0	12.0 ± 1.4	9.5 ± 1.4	11.4 ± 1.5	11.8 ± 1.8	11.0 ± 1.6	12.0 ± 3.0
Time in centre	115.9 ± 9.1	102.3 ± 5.9	94.5 ± 6.9	124.9 ± 23.2	110.2 ± 9.9	110.3 ± 11.3	116.1 ± 16.5	124.9 ± 23.2

DPAT, which suggests that the anxiogenic effect of fluoxetine is not primarily mediated by stimulation of hippocampal 5-HT_{1A} receptors. Because the rats were not tested in the presence of fluoxetine after chronic treatment, our experimental design did not permit us to determine whether tolerance had developed to this effect.

Chronic fluoxetine treatment did not cause lasting changes that resulted in an anxiolytic effect in either the social interaction or plus-maze tests when the rats were tested 24 h after the last dose, a time at which an antidepressant effect has been observed in both the HDS and LDS lines (11). An anxiolytic effect of chronically administered paroxetine has been reported in the social interaction test, but in rats that were tested 1 h after the last dose (16). Our results suggest that either the presence of fluoxetine is necessary to stimulate the anxiolytic, but not the antidepressant, effect, or the 5-HT receptors that adapt during chronic fluoxetine treatment are not involved in the behaviors reflecting anxiety in this test. The latter possibility is strengthened by the observation that the chronic treatment with fluoxetine did not modify the anxiogenic effect in the LDS line of 8-OH-DPAT administered into the dorsal hippocampus, nor did it change the lack of response in the HDS line. Chronic fluoxetine has been found to have a weaker anxiolytic effect in the ultrasonic vocalization test than paroxetine and, furthermore, the anxiolytic effect of paroxetine was antagonized by 5-HT_{2A} receptor antagonists (5), suggesting that the anxiolytic actions of SSRIs might be mediated by 5-HT_{2A} receptors.

Our data provide evidence that the function of the dorsal hippocampal 5-HT_{1A} receptors, at least as regards to anxiety, were not altered by the chronic fluoxetine treatment, a conclusion that is in complete agreement with the electrophysiological studies of chronic SSRI treatment by de Montigny and colleagues (2,3). Even so, these negative findings are at odds with a number of other studies demonstrating that there is a desensitization of 5-HT_{1A} receptor function following chronic SSRI treatment; both hypothermic and neuroendocrine responses to 5-HT_{1A} agonists have been reported to be blunted following chronic SSRI treatment (12,15). These disparate findings raise the possibility that the 5-HT_{1A} receptors located in different brain regions may differentially adapt during chronic SSRI treatment. It should also be emphasized that those investigators reporting a functional desensitization of 5-HT_{1A} receptors during chronic SSRI treatment have never detected a downregulation in the number or density of 5-HT_{1A} receptors. Neither are there differences in the numbers of hippocampal 5-HT_{1A} receptors in the HDS and LDS rats (13,19). Rather, the changes during chronic SSRI treatment seem to be associated with a change in G proteins, which are coupled to the receptor (15) At present, we do not know whether the same G proteins are coupled to the hippocampal 5-HT_{1A} receptors as those in other areas (e.g., hypothalamus), but it is reasonable to suggest that they may be different and that this difference accounts for the failure of the 5-HT_{1A} receptor to adapt to chronic fluoxetine treatment, as demonstrated in the present experiment.

Although there was no adaptation that was apparent in the social interaction test resulting from chronic treatment with fluoxetine, a difference in the adaptation of the two lines emerged in the elevated plus-maze. In the LDS line chronic fluoxetine treatment was without effect, whereas in the HDS line it resulted in an anxiogenic effect, which occurred even though this line had baseline scores indicating higher anxiety than the LDS line (see Fig. 3). This line difference clearly indicates that the HDS and LDS lines are differentially adapting to the effects of chronic fluoxetine to the point where now the HDS rats exhibit evidence of higher anxiety in both the social interaction and plus-maze tests.

The postsynaptic 5-HT_{1A} receptor has been heavily implicated in theories of depression (4,14), but its role in theories of anxiety is much less clear (21). Because HDS and LDS lines have been found to differ in an animal test of depression (19) as well as the social interaction test of anxiety (9), the possibility that the lines would show a differential response to antidepressants was explored in this study. There was no differential response in the social interaction test because neither line exhibited any changes after chronic fluoxetine. The LDS line did not exhibit a response to fluoxetine in the plus-maze either, while the HDS rats, somewhat surprisingly, exhibited an anxiogenic response. On the other hand, both HDS and LDS rats exhibited reduced immobility in the forced swim test following chronic treatment with fluoxetine (11). These different patterns of adaptation in the different behavioral tasks following chronic fluoxetine treatment might be related to the possibility that the tasks are subserved by 5-HT_{1A} receptors located in different brain regions, and that these 5-HT_{1A} receptors differentially adapt to chronic fluoxetine treatment, as suggested above.

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