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Selectively Bred Lines of Rats Differ in Social Interaction and Hippocampal 5-HT_{1A} Receptor Function: A Link Between Anxiety and Depression?

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GONZALEZ, L. E., S. E. FILE AND D. H. OVERSTREET. *Selectively bred lines of rats differ in social interaction and hippocampal 5-HT_{1A} receptor function: A link between anxiety and depression?* PHARMACOL BIOCHEM BEHAV **59**(4) 787–792, 1998.—Selective breeding for high and low sensitivity to the hypothermic response of the 5-HT_{1A} receptor agonist 8-OH-DPAT has established two lines (HDS and LDS, respectively) whose behavior differs in a model of depression, but not in the elevated plus-maze test of anxiety. The lines also differed in postsynaptic, but not presynaptic, 5-HT_{1A} receptors. Based on previous evidence that postsynaptic 5-HT_{1A} receptors mediate anxiogenic effects in the social interaction test of anxiety, but not the elevated plus-maze, we investigated possible differences between the lines in these two tests. The HDS line had a consistently lower level of social interaction compared with the LDS line, but no differences were found on any of the measures of the anxiety on trials 1 or 2 in the elevated plus-maze. To determine whether the line differences in anxiety were mediated by different hippocampal 5-HT_{1A} receptor function, 8-OH-DPAT (50 and 100 ng) was applied bilaterally to the dorsal hippocampus. This elicited anxiogenic effects in the LDS line, as has been previously reported in other rat strains, but there was no response in the HDS line, thus demonstrating an abnormal 5-HT_{1A} receptor function in the hippocampus. The 5-HT_{1A} receptor antagonist WAY100635 (200 ng) was administered to the dorsal hippocampus to test for possible differences between the lines in 5-HT tone. There were no significant changes in social interaction in either the HDS or LDS rats, indicating that the different level of anxiety between lines is not due to differences in hippocampal 5-HT tone. It is proposed that the HDS line may prove a useful model of a type of high trait anxiety linked to a susceptibility to depression. © 1998 Elsevier Science Inc.

Social interaction Anxiety Depression Hippocampus 5-HT_{1A} receptors

ABNORMALITIES in the 5-HT system have long been implicated in anxiety and depression, and although considerable progress has been made in the development of animal tests of anxiety and depression, research has been limited by the use of normal animals to study these psychiatric disorders. Existing animal tests of anxiety can successfully generate different states of anxiety by exposing animals to anxiogenic stimuli such as bright light, unfamiliar arenas, elevated platforms, and shocked probes (19), but there is as yet no convincing candidate that models differences in trait anxiety. Recently, Overstreet et al. (22,23) have selectively bred lines of rats with high and low sensitivities (HDS and LDS) to the hypothermic effects of the 5-HT_{1A} receptor agonist, 8-OH-DPAT. Interestingly, the HDS rats showed greater immobility in an animal test of depression, the forced swimming test, than either the LDS line or the randomly bred control group, leading to the suggestion that these rats may provide a useful model of genetic predisposition to depression (23). There were no differ-

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ences between the HDS and LDS lines in the elevated plus-maze test of anxiety or in 5-HT_{1A} binding in the dorsal or median raphe nuclei, but the HDS line had a higher density of postsynaptic 5-HT_{1A} receptors in the frontal cortex.

Administration of 8-OH-DPAT to the median raphé nucleus has anxiolytic effects in both the social interaction and the elevated plus-maze tests of anxiety, but the tests differ in their sensitivity to administration of 8-OH-DPAT to postsynaptic areas, such as the dorsal hippocampus (10) or basolateral nucleus of the amygdala (11), and anxiogenic effects were detected in the social interaction test, but not in the plus-maze. Because these two tests measure independent types of anxiety (6), we therefore hypothesized that it was possible that the HDS and LDS lines would show baseline differences in anxiety, as measured in the social interaction test. Experiment 1 explored this possibility by testing the two lines in three different test conditions—low light, familiar arena; high light, familiar arena; high light, unfamiliar arena. The social interaction test uses high light and an unfamiliar test arena as the two stimuli that generate anxiety, and decreases in anxiety are reflected in decreased social interaction [see (5) for details]. To confirm that there were no differences in the plus-maze, the two lines were tested for two 5-min trials, separated by 3 days. Factor analysis has shown that the measures of anxiety on trial 1 in the plus-maze load on a factor that is independent of that measuring trial 2 anxiety, thus suggesting that the nature of the anxiety experienced in the plus-maze is totally changed by plus-maze experience (7). It seems that the main anxiogenic factor on trial 1 is the open nature of the arms (26), whereas on trial 2 it is the elevation of the arms.

Because Experiment 1 revealed clear differences between the lines in the time spent in social interaction in all three of the test conditions investigated, Experiment 2 explored whether these baseline differences were due to differences in the 5-HT_{1A} receptor function in the dorsal hippocampus. This was assessed by testing the animals after direct hippocampal administration of 8-OH-DPAT. To assess whether there were differences between the lines in the endogenous 5-HT tone in the dorsal hippocampus, the lines were tested after hippocampal administration of the 5-HT_{1A} receptor antagonist, WAY 100,635.

METHOD

Animals

The HDS and LDS lines of rat (12th and 13th generations came from the breeding colony at UNC Center for Alcohol Studies) were allowed 1 week to recover from shipping before behavioral testing or surgery. Both HDS and LDS lines comprise pigmented and albino rats; because of the restricted numbers available of the selected lines hooded Lister rats (Harlan, Bicester, UK) were used as test partners, where specified. All animals were housed singly for 7 days prior to testing in the social interaction test. 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 Experiment 2, rats were singly housed following surgery and were allowed to recover for 7 days prior to behavioral testing. To accustom the animals to handling and to keep the cannulae patent, each day following surgery the rats were gently wrapped in a cloth and the stylets were replaced.

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 (5)].

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 perecent of time spent on the open arms of the maze provides the measure of anxiety and the number of closed-arm entries provides the best measure of locomotor activity in this test (6,24).

Drugs and Chemicals

(±) 8-OH-DPAT hydrobromide (Research Biochemicals Incorporated, St. Albans, UK) and WAY 100635 (Wyeth, UK) were 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. 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.

Procedure

Experiment 1: social interaction test. Rats from the HDS and LDS lines were randomly allocated to the three social interaction test conditions: high light, unfamiliar arena (HU); high light, familiar arena (HF); and low light, familiar arena (LF). The usual methodology in the social interaction test is to test pairs of rats from the same experimental treatment and to treat the pair score as the unit of analysis (5,7,8), and this is the most sensitive to treatment differences. However, where numbers are limited, for example, in studies of central drug administration, it is common to test the experimental animal with an unoperated stooge partner, and in this case only interaction initiated by the treated rat is scored [e.g., (10)]. Because of limited numbers of the HDS and LDS lines these rats were tested with hooded Lister partners in the HU and LF test conditions (n = 8–10 of each line tested in each condition). In the HF test condition, the lines were tested with a partner from the same line (four pairs from the HDS line, seven pairs from the LDS line); this allowed us to check that any differences found in the other test conditions were not due to the use of the hooded Lister rats as test partners. The rats allocated to the familiar test conditions were placed singly in the test arena for two 5-min trials, under the appropriate light condition, on the days preceding the social interaction test. On the test day, rats were tested in a randomized order between 0800 and 1200 h, each test lasted 4.5 min. The time spent in active social interaction by the target rat was scored by an observer blind to the rat line, and locomotor activity and rears were automatically recorded from infrared beam breaks. The apparatus was wiped between each pair of rats.

Elevated Plus-Maze

The HDS (n = 7) and LDS (n = 10) rats allocated to the plus-maze tests were placed on the central platform, facing an open arm, and observed for 5 min. The maze was cleaned between each rat. Three days later the rats were given a second trial in the plus-maze.

Experiment 2: 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, Tujunga, 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 (23 gauge, Cooper's Needle Works, Birmingham, UK) 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).

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 ±2.1 and 3.2 mm lateral within hippocampal borders were considered correct. In only one animal a needle tip mark did not reach the dorsal hippocampus area on the right side and the data from this animal were, therefore, excluded from statistical analysis.

Behavioral Testing

On each 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). Three minutes after central injection the rat was placed together with an unoperated hooded Lister partner in the social interaction test arena, and its behavior observed for 4.5 min by an observer blind to the drug treatment. On each test day the animals were tested between 0800 and 1200 h in an order randomized for drug treatment, and the test arena thoroughly wiped after each trial. Rats from the two lines were randomly allocated (n = 10/group) to the following groups: LF test condition, aCSF and 8-OH-DPAT (50 ng); LU test condition, aCSF and 8-OH-DPAT (100 ng); HF test condition, aCSF and WAY 100635 (200 ng).

Statistics

The data were analyzed by one- or two-way analyses of variance with genetic line and drug treatment as the independent factors. Where measures of anxiety and activity both changed, analyses of covariance were conducted to determine the independence of each change.

RESULTS

Social Interaction Test

It can be seen from Fig. 1 that, in all three of the test conditions, the LDS line had significantly higher social interaction levels than the HDS line [HU: $F(1, 16) = 14.2$, $p < 0.005$; HF: $F(1, 9) = 45.1$, $p < 0.0001$; LF: $F(1, 17) = 13.8$ $p < 0.005$]. The higher social interaction scores in the LDS line were not due to a nonspecific stimulant effect, because the lines did not differ in locomotor activity and the trend was for the LDS line to make fewer, rather than more, rears (see Table 1).

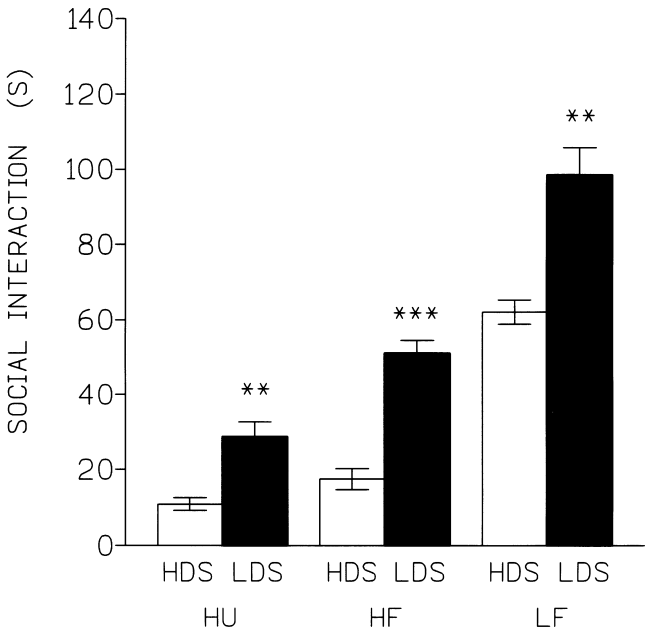

FIG. 1. Mean (± SEM) time (s) spent in social interaction by the HDS (clear bars) and LDS (black bars) lines of rat in the high-light unfamiliar (HU), high-light familiar (HF), and low-light familiar (LF) test conditions. *$p < 0.005$, **$p < 0.0001$ compared with HDS line in the same test condition.

In the HF test condition there was a significant difference between the lines in locomotor activity with the LDS line having higher scores, $F(1, 9) = 7.8$, $p < 0.05$, but analysis of covariance showed that this was secondary to the increased social interaction in the LDS line, and after ANCOVA the difference in locomotor activity was no longer significant, $F(1, 8) < 1.0$; it is the adjusted scores after ANCOVA that are shown in Table 1. The increased social interaction shown by the LDS line remained significant after ANCOVA, $F(1, 8) = 21.0$, $p < 0.005$, indicating that this was the primary change.

TABLE 1

MEAN (±SEM) LOCOMOTOR ACTIVITY (BEAM BREAKS) AND REARS MADE BY LDS AND HDS LINES OF RAT TESTED IN THE HIGH LIGHT UNFAMILIAR (HU), HIGH LIGHT FAMILIAR (HF), OR LOW LIGHT FAMILIAR (LF) TEST ARENAS

	Locomotor Activity	Rears
HU		
LDS	249.9 ± 14.9	20.9 ± 1.2
HDS	204.4 ± 23.6	24.4* ± 0.42
HF		
LDS	117.4 ± 17.4	21.9 ± 0.94
HDS	162.4 ± 7.1	22.3 ± 2.0
LF		
LDS	216.6 ± 19.2	20.4 ± 1.5
HDS	242.2 ± 20.4	22.9 ± 1.6

*$p < 0.05$ compared with LDS line.

TABLE 2

MEAN (±SEM) SCORES BY LDS AND HDS LINES OF RAT ON TRIALS 1 AND 2 IN THE ELEVATED PLUS-MAZE

		Trial 1	Trial 2
% time in open arms	LDS	25.5 ± 5.5	16.4 ± 6.0
	HDS	25.3 ± 6.8	7.4 ± 3.8
% number of open arm entries	LDS	30.8 ± 4.3	17.2 ± 5.7
	HDS	29.0 ± 6.5	20.1 ± 7.6
Time (s) in central square	LDS	126.8 ± 7.0	107.8 ± 15.7
	HDS	145.5 ± 8.5	104.3 ± 38.9
Number of closed arm entries	LDS	7.2 ± 0.32	6.1 ± 0.66
	HDS	6.7 ± 0.18	2.6** ± 0.68

**$p < 0.005$ compared with LDS line.

Elevated Plus-Maze

There were no significant differences between the lines in any of the measures from trial 1 in the plus-maze, $F(1, 15) < 1.0$ for percent time on the open arms and percent number of open arm entries; $F(1, 15) = 1.3$ for number of closed arm entries; $F(1, 15) = 2.9$, $p = 0.11$ for time in the central square (see Table 2).

On trial 2 in the plus-maze, although the LDS spent a higher percentage of time on the open arms, this did not reach significance, $F(1, 15) = 1.3$, and there were no line differences in the percent number of entries onto the open arms or the time spent in the central square, $F(1, 15) < 1.0$. However, the HDS line did make significantly fewer entries into the closed arms, $F(1, 15) = 12.7$, $p < 0.005$ (see Table 2).

Effects of 5-HT$_{1A}$ Receptor Ligands in the Social Interaction Test

In the LU test condition there was once again a significant difference between the lines in the time spent in social interaction, $F(1, 36) = 24.6$, $p < 0.0001$, with the LDS line having higher scores. 8-OH-DPAT (100 ng) significantly reduced the time spent in social interaction, $F(1, 36) = 6.7$, $p < 0.01$, but it can be seen from Fig. 2 that it was only the LDS line that showed a significant decrease. The LF test condition is the most sensitive to anxiogenic effects, shown by a decrease in social interaction, and it can be seen from Fig. 2 that there was a significant decrease in social interaction in the LDS line following 8-0H-DPAT (50 ng), but no decrease in the HDS line [drug × line interaction $F(1, 36) = 4.9$, $p < 0.05$]. There were no significant differences in locomotor activity (all F-values < 1.0); or in rears [LU: $F(1, 36) < 1.0$; LF: line $F(1, 36) = 2.9$; drug $F(1, 36) = 1.2$] (see Table 3).

The effects of the 5-HT$_{1A}$ receptor antagonist, WAY 100635 (200 ng) were examined in the HF test condition, in which it is possible to detect both anxiolytic and anxiogenic effects. Once again, there was a significant difference between the lines in the time spent in social interaction, $F(1, 36) = 15.8$, $p < 0.0005$, but WAY 100635 was without significant effect, $F(1, 36) = 1.1$ (see Table 4). There were no significant effects on locomotor activity or rears (F ratios < 1.0) (see Table 4).

DISCUSSION

There was a clear and reliable difference in the levels of social interaction between the LDS and HDS lines of rat in all four of the test conditions. The greatest sensitivity was found when pairs of rats from the same line were tested together, but the difference was robust enough to be significant even

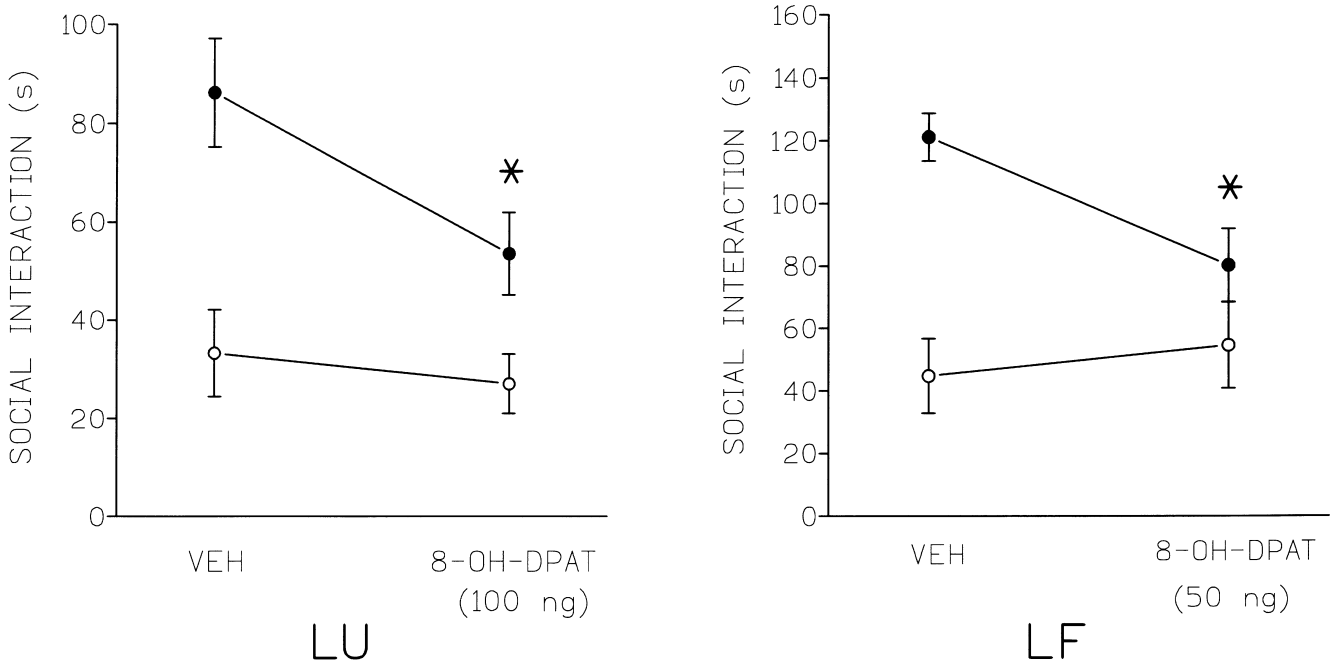

FIG. 2. Mean (± SEM) time (s) spent in social interaction by HDS (○) and LDS (●) lines of rat after dorsal hippocampal injection of vehicle (aCSF) or 8-OH-DPAT (100 ng in LU test condition, 50 ng in LF test condition). In both test conditions there was a significant difference between the lines ($p < 0.0001$); *$p < 0.05$, 8-OH-DPAT compared with vehicle control.

TABLE 3

MEAN (±SEM) LOCOMOTOR ACTIVITY (BEAM BREAKS) AND NUMBER OF REARS MADE BY LDS AND HDS LINES OF RAT TESTED IN THE LOW UNFAMILIAR (LU) TEST CONDITION AFTER DORSAL HIPPOCAMPAL INJECTIONS OF VEHICLE (aCSF) OR 8-OH-DPAT(100 ng) OR IN THE LOW LIGHT FAMILIAR (LF) TEST CONDITION AFTER DORSAL HIPPOCAMPAL INJECTIONS OF VEHICLE OR 8-OH-DPAT (50 ng)

	Locomotor Activity		Rears	
	Vehicle	DPAT	Vehicle	DPAT
LU				
LDS	340.9 ± 9.3	325.8 ± 16.8	18.3 ± 1.7	19.6 ± 1.7
HDS	310.9 ± 29.2	323.5 ± 19.7	19.8 ± 1.5	19.7 ± 1.0
LF				
LDS	391.2 ± 19.4	380.4 ± 22.5	11.7 ± 1.1	16.1 ± 1.7
HDS	372.6 ± 30.3	360.9 ± 19.3	17.2 ± 2.1	16.7 ± 2.0

when the lines were tested with hooded Lister rats as partners. However, the lines did not differ in the measures of anxiety on either trial 1 or trial 2 in the elevated plus-maze. One possible explanation for this result is that the differences in social interaction reflect differences between the lines in sociability rather than anxiety. This possibility arises because the line differences were found even in the least anxiogenic of the test condition (LF). Benzodiazepines do not increase the time spent in social interaction in the LF test condition and have increasing effects as the conditions become more anxiogenic. However, barbiturates increase social interaction equally in all the test conditions (8), which is the pattern of differences found between the LDS and HDS lines. Because factor analysis has shown that the measures of anxiety derived from the social interaction test load on an independent factor from those derived in the plus-maze (6), the alternative explanation for our results is that the LDS and HDS rats differ in one type of anxiety.

Support for this latter interpretation comes from the effects of 8-OH-DPAT. We have previously shown, using hooded Lister rats, that administration of 8-OH-DPAT to the dorsal hippocampus has an anxiogenic effect in the social interaction test (10), and this is precisely the pattern observed in the LDS rats. Furthermore, the effects of 8-OH-DPAT suggest that the differences in social interaction between the lines are due to differences in hippocampal 5-HT_{1A} receptor function. Thus, the LDS line responds with an anxiogenic response to the 5-HT_{1A} receptor agonist, 8-OH-DPAT, whereas there is no change in the behavior of the HDS line. In fact, 8-OH-DPAT administration to the dorsal hippocampus removes the difference between the lines (most strikingly seen in the LF test condition). It is unlikely that the lack of response to 8-OH-DPAT in the HDS line is due to a "floor" effect, because a decrease below 40 s would be possible. Our previous studies demonstrated that the anxiogenic effect of 8-OH-DPAT was due to an action on 5-HT_{1A} receptors because it was reversed by a silent dose (200 ng) of the highly specific 5-HT_{1A} receptor antagonist, WAY 100635 (10). Unfortunately, the short supply of the LDS and HDS lines meant that we were unable to conduct a reversal experiment, but in both lines WAY 100635 (200 ng) was silent. This suggests that the lines did not differ in their levels of 5-HT release in the dorsal hippocampus and therefore, presumably in presynaptic 5-HT_{1A} autoreceptor function, which control the rate of cell firing and, hence, 5-HT release. If the lower social interaction in the HDS rats had been due to a higher level of 5-HT release in this area, then it would be expected that the postsynaptic receptor antagonist would have had an anxiolytic effect in the HDS line.

Our results, therefore, suggest that the HDS line differs from the LDS line in the type of anxiety generated in the social interaction test and that the difference is mediated by a changed function of the postsynaptic 5-HT_{1A} receptors in the dorsal hippocampus. This suggestion would be supported by the pattern of results previously found after dorsal hippocampal administration of 8-OH-DPAT, with an anxiogenic effect in the social interaction test, but no effect on trial 1 in the plus-maze. The difference between trials 1 and 2 in the plus-maze were emphasized by the anxiogenic effects of 8-OH-DPAT on trial 2 (10). We did not find a significant difference between the lines in the measures of anxiety on trial 2, although the percentage of time spent on the open arms was twice as high in the LDS line. Clearly, possible differences between the lines on trial 2 and in the response to 5-HT_{1A} receptor ligands deserves further investigation.

Because the postsynaptic 5-HT_{1A} receptor has been heavily implicated in theories of depression (3,4,17), and because the HDS and LDS lines have been found to differ in an animal test of depression (23), the interesting possibility arises that the lines differ in the type of anxiety associated with depression. With the exception of the effects of paroxetine (18), the social interaction test has not been sensitive to the anxiolytic effects of chronically administered antidepressants in normal rats (9,14,25). It is possible that an anxiolytic action of antidepressant drugs could be detected in the HDS line and, if so, it would be possible to determine whether the anxiolytic effect

TABLE 4

MEAN (±SEM) TIME (s) SPENT IN SOCIAL INTERACTION, LOCOMOTOR ACTIVITY (BEAM BREAKS), AND NUMBER OF REARS MADE BY THE LDS AND HDS LINES OF RAT TESTED IN THE HIGH LIGHT FAMILIAR TEST CONDITION AFTER DORSAL HIPPOCAMPAL INJECTIONS OF VEHICLE (aCSF) OR WAY 100635 (200 ng)

	LDS		HDS	
	Vehicle	WAY 100635	Vehicle	WAY 100635
Social interaction	88.4 ± 12.7	72.1 ± 16.7	35.3 ± 9.7	25.5 ± 9.5
Locomotor activity	355.0 ± 19.2	349.8 ± 28.2	368.5 ± 27.4	349.4 ± 20.4
Rears	18.6 ± 1.5	19.4 ± 2.1	20.5 ± 1.7	20.7 ± 1.5

There was a significant difference ($p < 0.0001$) between the lines in the time spent in social interaction.

was due to a change in 5-HT_{1A} receptor function in the dorsal hippocampus. If the chronic antidepressant treatment restored the HDS line to normal functioning, this line should then show an anxiogenic response to 8-OH-DPAT, similar to that found in the present study in the LDS line.

On the other hand, chronic antidepressant treatment downregulates 5-HT_{1A} receptor function, as indexed by 8-OH-DPAT–induced hypothermia (12,15). Recently Janowsky and Overstreet (13) reported that chronic treatment of the HDS line with fluoxetine both blunted the hypothermic response to 8-OH-DPAT and reduced immobility in the forced swim test. Thus, this line of evidence suggests that the anxiogenic effect of hippocampally administered 8-OH-DPAT may be reduced in rats chronically treated with antidepressants.

Chaouloff et al. (2) found that the Roman low- and high-avoidance lines of the rat differ in the elevated plus-maze and black and white crossing tests, but not in the social interaction test. Subsequent assessment with several indices of serotonergic neurotransmission revealed that the Roman lines differed in central 5-HT_{2A} but not in 5-HT_{1A} receptor function (16). The inverse pattern found with the HDS and LDS lines in this study compared with the Roman lines suggests that the elevated plus-maze (in particular, trial 1) and the social interaction test selectively detect abnormalities in 5-HT_{2A} and 5-HT_{1A} receptors, respectively. The results of the present study also suggest a linkage between a particular type of anxiety and depression traits. Clinical and epidemiological analysis have yielded convincing evidence for a high proportion of patients with simultaneous manifestations of both anxiety and depression [for review, see (20)]. One explanation for this association is a longitudinal relationship in which subjects start with a relative "pure" anxiety and later tend to develop additional depressive disorders (1). A second model of this association proposes that the two disorders (anxiety and depression) are manifestations of the same underlying aetiological factor. This is supported by family and twin studies where anxiety and depression comorbidity has been found to have a substantial degree of transmissibility, which can be attributed to genetic factors (21). Because the HDS line exhibits a significantly higher trait anxiety and increased susceptibility for depression than the LDS line, the lines may represent an animal model that offers the possibility of studying the genetic bases and neurological mechanisms underlying the cooccurrence of anxiety and depression, as well as the actions of potential therapeutic agents.

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