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ORIGINAL INVESTIGATION

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Active behaviors in the rat forced swimming test differentially produced by serotonergic and noradrenergic antidepressants

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Abstract This study demonstrated that distinct patterns of active behaviors are produced by antidepressants that selectively inhibit norepinephrine (NE) or serotonin (5-HT) uptake in the rat forced swimming test (FST). A behavior sampling technique was developed to score the active behaviors swimming, climbing and diving, as well as immobility. The rat's behavior was recorded at the end of each 5-s period during the test session. The sampling technique was both reliable, as demonstrated by test-retest reliability and inter-rater reliability, and valid, as shown by comparison to the timing of behavior durations. Five different antidepressant drugs which block monoamine uptake and two 5-HT_{1A} receptor agonists were shown to decrease immobility in the FST; however, they produced distinct patterns of active behaviors. The selective NE uptake inhibitors desipramine and maprotiline selectively increased climbing, whereas the selective serotonin reuptake inhibitors (SSRIs) fluoxetine, sertraline and paroxetine selectively increased swimming. The 5-HT_{1A} receptor agonists 8-OH-DPAT and gepirone also selectively increased swimming. These results show that:1) SSRIs are not false negatives in the FST; 2) at least two behaviorally distinct processes occur in the FST; and 3) enhancement of NE neurotransmission may mediate climbing in the FST, whereas enhancement of 5-HT neurotransmission may mediate swimming.

Key words Antidepressants · 5-HT · NE · SSRI · Forced swimming test· Behavioral despair · 5-HT_{1A} receptor· Desipramine· Maprotiline · Fluoxetine · Sertraline · Paroxetine · Gepirone · 8-OH-DPAT

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Introduction

The forced swimming test (FST) is a behavioral test which predicts the efficacy of antidepressant treatments (Porsolt et al. 1977, 1978; Porsolt 1981). The characteristic behavior of the test, termed *immobility*, develops when a rodent has been placed in a tank of water for an extended period of time and "makes only those movements necessary to keep its head above water" (Porsolt et al. 1977, p. 730). The development of immobility is usually facilitated by a pretest for 15 min given 24 h before a 5-min testing period. When administered between the pretest and test periods, antidepressant drugs decrease the duration of immobility in the FST; i.e., they make the rats more active. The FST is an attractive behavioral screen for antidepressant drugs because it is quick and reliable across laboratories (see Borsini and Meli 1988, for an extensive review). It is also sensitive to the effects of all of the major classes of antidepressant drugs, including tricyclic antidepressants (e.g. imipramine and desipramine (DMI)), monoamine oxidase inhibitors (e.g. clorgyline and tranylcypromine) and many atypical antidepressants (e.g. iprindole, mianserin and nomifensine). The test is also relatively selective for antidepressant drugs, because few other psychoactive drugs elicit similar effects in the FST.

One potential weakness of the FST is the method traditionally used for scoring, which generally involves timing only immobility, or the absence of behavior. This method fails to describe any *active behaviors* that are produced by antidepressant drug treatments during the FST. If a class of antidepressant drugs were to produce a characteristic set of *active behaviors* during the FST, the traditional scoring method, which focuses only on

immobility, might fail to detect such a response as an indicator of antidepressant efficacy. Some attempts have been made to describe active behaviors demonstrated in the FST after antidepressant drug treatments. For example, some studies have described the pattern of behaviors produced by DMI, which decreased immobility or floating and increased "struggling" without affecting swimming (Armario et al. 1988; Pare 1992), as different from that produced by the anxiolytic diazepam (Marti and Armario 1993). Other investigators have measured additional behavioral endpoints in the FST, such as head twitching/shaking (Pare 1989a,b; Naitoh et al. 1992), diving and bobbing (Pare 1989a,b), defecation (Armario et al. 1988; Abel 1991; Marti and Armario 1993) and sinking (Nishimura et al. 1988). However, none of these behaviors has been studied systematically across different classes of antidepressant drugs in the FST.

Although a strength of the FST is its predictive validity, one class of antidepressants that this test does not reliably detect are selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine (FLX), sertraline (SRT) and paroxetine (PRX). Antidepressant-like effects of SRT in the FST have been reported (Cervo et al. 1991; Overstreet 1993; Singh et al. 1993), although usually only when tested at very high doses (80 mg/kg; Singh et al. 1993) or when given repeatedly for 14 days (Overstreet 1993). FLX was reported to be inactive in the FST (Paul et al. 1990; Maj et al. 1992), active only at high doses (80 mg/kg, Porsolt et al. 1979), or both to increase and to decrease immobility (Gorka et al. 1979). PRX has failed to show any effects in the FST (Gorka et al. 1979). While some SSRIs have been shown to have effects in the FST when mice are employed as the subjects (e.g. Nixon et al. 1994), these effects are often small or measured only when an adjunct compound is added (e.g. lithium). In addition, the FST procedure is thought to be less specific in general when mice are employed (Borsini and Meli 1988). Several reviews of the effects of antidepressant drugs in the FST have concluded that the SSRIs are false negatives in the FST as a whole (Porsolt 1990; Porsolt et al. 1991; Porsolt and Lenegre 1992).

The present study was designed to describe the active behaviors displayed by rats in the FST and to determine whether active behaviors in the FST are differentially altered by selected classes of antidepressant drugs. The study compared the effects of the selective NE uptake inhibitors, DMI and maprotiline (MAP) and the SSRIs FLX, SRT and PRX. The selectivity of these compounds for blocking the uptake of NE and 5-HT are summarized in Table 1. In addition, the 5-HT_{1A} receptor agonists 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT) and gepirone were studied. Based on behavioral observation of pilot studies, we decided to rate the frequency of four behavioral categories which are mutually exclusive and which incorporate the rat's entire body: immobility, swimming, climbing and diving. A time-sampling technique was used, in which the behavior of the animal was recorded every 5 s. Each compound was also tested for its ability to alter locomotor activity, to control for the possibility that any active behaviors in the FST are simply the manifestations of an enhancement of generalized motor activity. The results of this study demonstrate that different classes of antidepressant drugs produce distinctly different active behaviors during the FST without affecting locomotor activity. A preliminary version of some of these data has been presented previously (Detke et al. 1994).

Table 1 Inhibitor constants (K_i values) for blocking uptake of NE and 5-HT into rat brain synaptosomes, and selectivity ratios calculated for the antidepressant drugs used in the present experiments. Data are taken from Richelson and Pfenning (1984) and Bolden-Watson and Richelson (1993)

Drug	K_i values (nM) NE	5-HT	Selectivity ratios NE: 5-HT	5-HT:NE
Desipramine	0.9 ± 0.2	340 ± 60	378	–
Maprotiline	7.4 ± 0.4	3300 ± 300	446	–
Fluoxetine	280 ± 70	12.0 ± 1	–	13
Sertraline	220 ± 40	3.4 ± 0.4	–	64
Paroxetine	33 ± 2	0.73 ± 0.04	–	45

Materials and methods

Animals

Male Sprague-Dawley rats (Charles River, Wilmington, Mass.) weighing 150–175 g upon arrival, were housed in groups of two to four in polycarbonate cages. They were maintained on a 12:12-h light-dark schedule (lights on 0700–1900 hours) in a temperature-controlled (22° C, colony room. Rats received free access to food and water, and were handled for 3–5 days prior to behavioral testing.

Forced swimming test

The procedure used was very similar to that described by Porsolt et al.. (1978), except that the water was deeper. Swim sessions were conducted by placing rats in individual glass cylinders (46 cm tall × 20 cm in diameter) containing 23–25° C water 30 cm deep. Porsolt used cylinders filled with water only to 15 cm, a depth where rats can touch the bottom with their feet. At the 30-cm water depth, the rats could not support themselves by touching the bottom with their feet, and only a few could touch bottom with their tails. One exception to the above is that the data portrayed in Table 3, on non-antidepressants, were collected earlier, using 24-cm deep water (Wieland and Lucki 1990). At this depth, the rats are still unable to support themselves by standing, but some are able to touch the bottom of the jar with their tails. In studying the influence of these water depths on antidepressant effects in the FST (cf. Detke et al. 1995, concerning DMI and 8-OH-DPAT; Detke, Rickels and Lucki, unpublished data), we have found that the difference between these two depths is negligible for the purpose of the measures employed here. Two swim sessions were conducted, always between 1200 and 1800 hours: an initial 15-min pretest followed 24 h later by a 5-min test. Drug treatments were administered during the period between the two sessions. Following both swim sessions, the rats were removed from the cylinders, dried with paper towels and placed in

heated cages for 15 min, and then returned to their home cages. Test sessions were videotaped from above (Panasonic color video camera and recorder) for scoring later.

Behavioral scoring

A time-sampling technique was employed to score several behaviors during a single viewing. At the end of each 5-s period during the test session, the scorer would rate the rat's behavior at that time, as one of the following four behaviors: 1) immobility – a rat was judged to be immobile when it remained floating in the water without struggling and was making only those movements necessary to keep its head above water; 2) swimming – a rat was judged to be swimming if it was making active swimming motions, more than necessary to merely maintain its head above water, e.g. moving around in the cylinder; 3) climbing – a rat was judged to be climbing when it was making active movements with its forepaws in and out of the water, usually directed against the walls; 4) diving – a rat was judged to be diving when its entire body was submerged. Because diving occurred rarely in the tests and was not reliably altered by any of the compounds tested, data for diving will not be reported. Grooming behavior (face washing with paws) and head shaking were not considered.

All of the behavior scoring was done by a single rater, who was blind to the treatment condition. Several test sessions ($n = 40$ subjects), chosen at random, were scored a second time by this rater, to determine test-retest reliability. These sessions were then scored by a second rater, who was also blind to treatment condition, to determine inter-rater reliability. Finally, to determine the validity of the sampling method, these sessions were scored again by the first rater, this time using a stopwatch to time the duration of each behavior.

Locomotor activity

The apparatus used to measure locomotor activity has been previously described (Lucki et al. 1989; Wieland and Lucki 1990).Rats were placed individually in eight clear polycarbonate cages ($41 \times 19 \times 19$ cm^3) equipped with fitted sliding tops and wire mesh floors. An aluminum base under each cage held a light source and a photocell detector approximately 13 cm from each end and 4 cm above the photocell amplifiers (Lafayette Instruments, Lafayette, Ind.) which were connected to a solid-state interface (Med Associates, East Fairfield, Vt.) and a Franklin Ace 1000 microcomputer. The computer software differentiated the photocell signals to specifically define sequential disruptions of the two photocell beams in each cage. These sequential beam disruptions corresponded to a necessary ambulation by the rat of approximately 15 cm along the longitudinal axis of the cage, and were called crosses. The number of crosses (locomotor activity) was measured for 30 min. Each antidepressant compound was tested for locomotor effects at the dose which produced the greatest behavioral effect in the FST.

Drug treatment

For subchronic treatment in the forced swimming test and locomotor activity testing, each drug was administered 23.5, 5, and 1 h prior to the start of the given test. All drugs were administered subcutaneously in a volume equivalent to 4 ml/kg, except SRT which was injected intraperitoneally. All drug doses were calculated as mg/kg base, and were dissolved in deionized water, except as follows. SRT and MAP were prepared as suspensions by pulverizing the drug in 1–2 drops Tween 80 and then adding deionized water. All drugs were prepared freshly each morning. Most of the control subjects received 0.9% saline as the vehicle, but some rats ($n = 20$) received deionized water with Tween 80 in concentrations comparable to those used to prepare the SRT and MAP. There were no reliable differences between these groups in the FST, and hereafter all of these controls will be referred to as saline groups.

Drugs

8-Hydroxy-2-(di-*n*-propylamino)tetralin HBr (±8-OH-DPAT) was purchased from Research Biochemicals (Natick,Mass.). Desipramine HCl and maprotiline HCl were purchased from Sigma (St Louis, Mo.). Paroxetine was obtained as a gift from Smith-Kline Beecham Pharmaceuticals (Philadelphia,Pa.), sertraline from Pfizer Central Research (Groton, Conn.), gepirone from Bristol-Myers (Wallingford,Conn.), and fluoxetine from Eli Lilly (Indianapolis, Ind.).

Statistical analysis

An experiment consisted of 40–50 subjects assigned randomly to groups of 7–12 animals each. Each experiment included one saline-treated group. In some cases, a given analysis required that subjects be combined from two experiments (to examine a complete dose-effect curve, for example). In all such cases, there were no statistically reliable differences between the saline groups in the experiments which were combined.

The comparisons between different scorers and scoring methods were analyzed using Pearson product-moment correlation. Each behavior (immobility, swimming, climbing, and locomotor activity) was analyzed using a one-way factorial analysis of variance for each compound. For those analyses which were reliable ($\alpha = 0.05$), Dunnett's test was used to compare the saline group to groups treated with drug.

Results

The correlations for reliability and validity for all three behaviors scored using the behavioral sampling technique were very high. The test-retest reliability correlations were: $r = 0.96$ for immobility, $r = 0.93$ for swimming, and $r = 0.98$ for climbing. The inter-rater reliability correlations were: $r = 0.90$ for immobility, $r = 0.81$ for swimming, and $r = 0.97$ for climbing. The validity correlations comparing sampling to the timing of durations were: $r = 0.68$ for immobility, $r = 0.87$ for swimming, and $r = 0.99$ for climbing. All P values were less than 0.0001.

The effects of DMI are illustrated in Fig. 1. DMI produced a dose-dependent reduction in immobility [$F(3,33) = 13.98$, $P < 0.0001$], and increase in climbing [$F(3,33) = 15.07$, $P < 0.0001$], but did not affect the amount of swimming [$F(3,34) = 1.39$, $P > 0.05$]. Immobility was reliably reduced and climbing was reliably increased at all doses tested when compared with values for saline using Dunnett's test.

The effects of MAP are illustrated in Fig. 2. The pattern for MAP was similar to that for DMI; it also dose-dependently decreased immobility [$F(3,38) = 9.05$, $P < 0.0001$] and increased climbing [$F(3,40) = 7.75$, $P < 0.001$]. Dunnett's tests showed that immobility was reliably reduced at all doses, and climbing was reliably

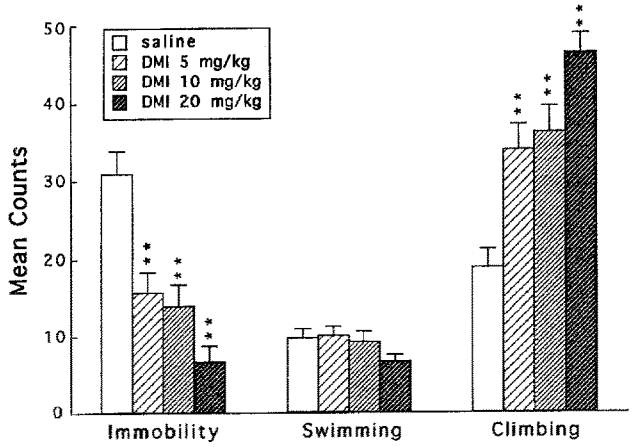

Fig. 1 Mean (± SEM) counts of immobility, swimming and climbing behaviors when sampled every 5 s during the 5-min FST testing period, in response to saline, and to DMI (5, 10 and 20 mg/kg). Group *n*s are 10 each. Differences in comparison to saline: $*P < 0.05$, $**P < 0.01$. Note that the scale of the ordinate of this figure is slightly greater than that of Figs 2–5

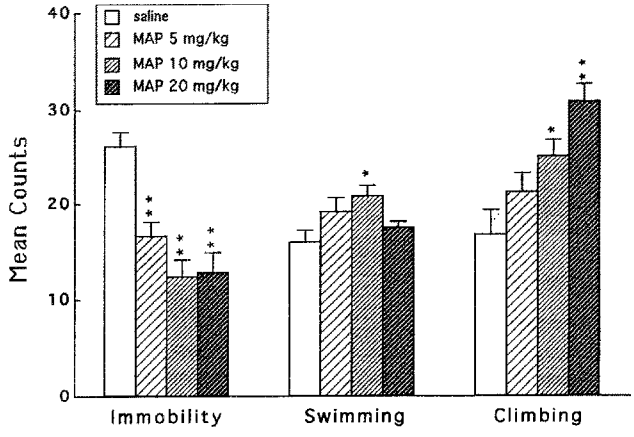

Fig. 2 Mean (± SEM) counts of immobility, swimming and climbing behaviors when sampled every 5 s during the 5-min FST testing period, in response to saline, and to MAP (5, 10 and 20 mg/kg). Group *n*s are 10–12 each. Differences in comparison to saline: $*P < 0.05$, $**P < 0.01$

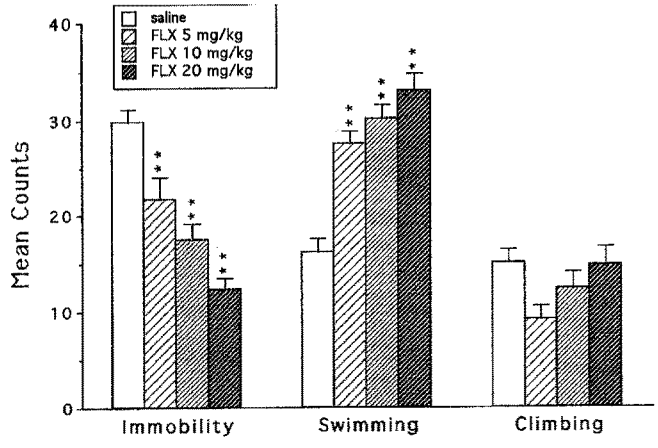

Fig. 3 Mean (± SEM) counts of immobility, swimming and climbing behaviors when sampled every 5 s during the 5-min FST testing period, in response to saline, and to FLX (5, 10 and 20 mg/kg). Group *n*s are 10 each. Differences in comparison to saline: $*P < 0.05$, $**P < 0.01$

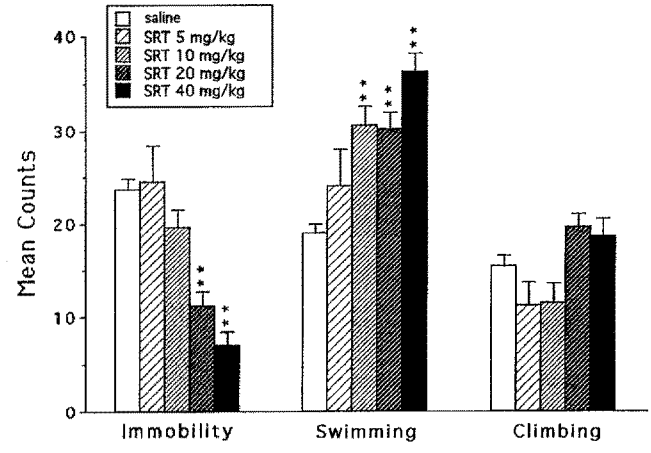

Fig. 4 Mean (± SEM) counts of immobility, swimming and climbing behaviors when sampled every 5 s during the 5-min FST testing period, in response to saline, and to SRT (5, 10 and 20 mg/kg). Group *n*s are 9–17 each. Differences in comparison to saline: $*P < 0.05$, $**P < 0.01$

increased at 10–20 mg/kg when compared with values for saline. The ANOVA for swimming was also reliable [$F(3,38) = 2.90$, $P = 0.048$]. Swimming was increased reliably only at 10 mg/kg, and the pattern was not dose-dependent.

The SSRIs also reduced immobility dose-dependently, but in contrast to DMI and MAP, they increased swimming without affecting climbing. This pattern is illustrated for FLX in Fig. 3. FLX dose-dependently reduced immobility [$F(3,35) = 18.82$, $P < 0.0001$] and increased swimming [$F(3,36) = 23.04$, $P < 0.0001$] while climbing was unaffected [$F(3,35) = 2.55$, $P > 0.05$]. Immobility was reliably reduced and swimming reliably increased at all doses tested when compared with values for saline using Dunnett's test.

The pattern of effects for SRT, another SSRI, is similar to that seen for FLX, and is depicted in Fig. 4. Again, immobility was dose-dependently decreased [$F(4,59) = 16.16$, $P < 0.0001$] and swimming was dose-dependently increased [$F(4,57) = 10.82$, $P < 0.0001$]. Dunnett's tests showed that immobility was reliably reduced at 20–40 mg/kg, and that swimming was reliably increased at 10–40 mg/kg, compared with values for saline. While the overall ANOVA for climbing was reliable [$F(4,59) = 4.65$, $P < 0.01$], post-hoc tests showed that none of the doses was reliably different from saline.

The pattern of effects for PRX, a third SSRI, is similar to that of the other SSRIs, and is illustrated in Fig. 5. Again, immobility was dose-dependently decreased [$F(4,76) = 8.09$, $P < 0.0001$] and swimming was dose-dependently increased [$F(4,73) = 11.34$, $P < 0.0001$], while climbing was not affected [$F(4,77) = 0.33$, $P > 0.05$]. Immobility was reliably reduced at

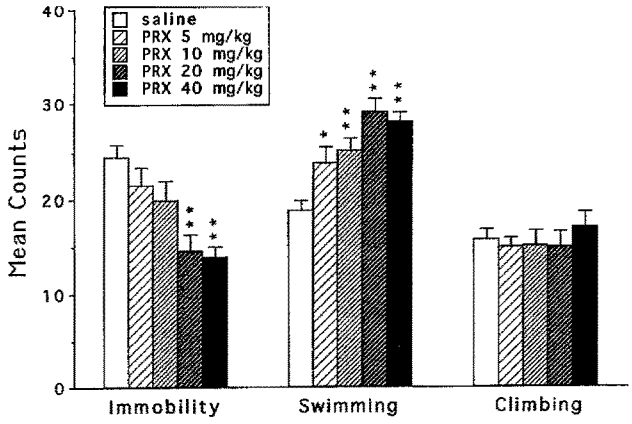

Fig. 5 Mean (± SEM) counts of immobility, swimming and climbing behaviors when sampled every 5 s during the 5-min FST testing period, in response to saline, and to PRX (5, 10 and 20 mg/kg). Group *n*s are 12–21 each. Differences in comparison to saline: $^{*}P < 0.05$, $^{**}P < 0.01$

20–40 mg/kg, and swimming was reliably increased at 5–40 mg/kg when compared with values for saline using Dunnett's test.

The effects of two 5-HT_{1A} receptor agonists on behaviors in the FST are depicted in Table 2. The selective 5-HT_{1A} receptor agonist 8-OH-DPAT dose-dependently reduced immobility [$F(3,48) = 6.49$, $P < 0.001$] and increased swimming [$F(3,49) = 11.83$, $P < 0.0001$], without affecting climbing [$F(3,49) = 2.54$, $P > 0.05$]. Dunnett's tests showed that immobility was reliably reduced at 0.50 mg/kg, and swimming was reliably increased at 0.125–0.50 mg/kg compared with values for saline. The 5-HT_{1A} receptor agonist gepirone administered at 20 mg/kg reduced immobility [$F(1,8) = 7.02$, $P < 0.03$] and increased swimming [$F(1,8) = 16.71$, $P < 0.005$], without affecting climbing [$F(1,8) = 5.21$, $P > 0.05$].

The effects of several non-antidepressants on active behaviors in the FST are depicted in Table 3. The 5-HT_{1A} postsynaptic receptor antagonist and presynaptic partial agonist NAN-190 had no effect on any of the behaviors. The clinically effective anxiolytic diazepam was also without effect. The psychostimulant amphetamine reduced immobility [$F(1,17) = 76.38$, $P < 0.0001$] and increased climbing [$F(1,17) = 72.27$, $P < 0.0001$], without affecting swimming [$F(1,17) = 2.60$, $P > 0.05$].

Table 2 Mean (± SEM) behavior counts in the FST in response to treatment with 5-HT_{1A} receptor agonists

Durg	Dose (mg/kg)	*n*	Immobility	Swimming	Climbing
Saline		13	25.4 ± 2.2	14.1 ± 1.4	18.8 ± 1.7
8-OH-DPAT	0.125	10	23.1 ± 1.3	19.9 ± 1.6*	16.8 ± 1.9
	0.25	15	22.0 ± 1.4	23.2 ± 10**	12.9 ± 1.2
	0.50	16	15.7 ± 1.6**	25.8 ± 1.8**	16.8 ± 1.5
Saline		5	35.6 ± 1.9	12.8 ± 1.5	11.6 ± 1.5
Gepirone	20	5	28.2 ± 2.1*	25.4 ± 2.7**	6.2 ± 1.8

$^{*}P < 0.05$ in comparison to saline
$^{**}P < 0.01$ in comparison to saline

Table 3 Mean (± SEM) behavior counts in the FST in response to treatment with various non-antidepressants

Drug	Dose (mg/kg)	*n*	Immobility	Swimming	Climbing
Saline		10	26.4 ± 3.3	16.8 ± 1.6	14.1 ± 2.0
NAN-190	3.2	10	29.6 ± 4.3	20.2 ± 1.0	10.1 ± 1.2
Diazepam	5	10	24.0 ± 2.2	20.2 ± 2.9	15.7 ± 3.0
Amphetamine	2	9	2.2 ± 0.7**	13.2 ± 3.3	44.6 ± 3.9**

$^{**}P < 0.01$ in comparison to saline

Table 4 Mean (± SEM) number of crosses of the locomotor activity chamber in response to treatment with several antidepressants and their appropriate vehicles

Drug	*n*	Crosses
Saline	23	65.7 ± 5.4
Fluoxetine (20 mg/kg)	8	20.3 ± 2.9**
Paroxetine (40 mg/kg)	8	26.3 ± 3.8**
Tween 80	23	54.6 ± 3.6
Maprotiline (20 mg/kg)	8	19.4 ± 3.0**
Sertraline (40 mg/kg)	8	54.3 ± 8.0

$^{**}P < 0.01$ in comparison to appropriate control

The effects of the antidepressant drugs on locomotor activity are shown in Table 4. None of the antidepressant drugs tested increased general locomotor activity, and many of them substantially decreased activity. In comparison to saline-treated controls [$F(2,36) = 19.25$, $P < 0.0001$], FLX and PRX both reliably decreased locomotor activity ($P < 0.01$). In comparison to Tween 80 vehicle [$F(2,36) = 13.16$, $P < 0.0001$], MAP reliably decreased locomotor activity ($P < 0.01$), while SRT had no effect. DMI, 8-OH-DPAT and gepirone have previously been shown, employing the same apparatus and methodology, to reduce locomotor activity, whereas amphetamine increases it (Wieland and Lucki 1990).

Discussion

The present study showed that two active behaviors demonstrated by rats in the FST, swimming and climbing, are selectively altered by two different groups of antidepressant drugs. All five of the antidepressants tested reduced immobility, the characteristic behavior measured in the FST. However, the NE-selective uptake inhibitors DMI and MAP robustly enhanced only climbing behavior. In contrast, the SSRIs FLX, SRT and PRX enhanced swimming but did not alter climbing behavior. The active behaviors in the FST did not reflect increased general motor activity, because treatment with these antidepressant drugs reduced (FLX, PRX, MAP and DMI) or failed to alter (SRT)

locomotor activity. The pattern of behaviors seen with DMI closely parallel that described by Armario et al. (1988), who showed that DMI decreased immobility and increased "struggling", but did not affect "light swimming". The similar findings seen with MAP in the present study suggest that this pattern may be common to other antidepressant drugs which enhance NE neurotransmission. The finding that the SSRIs FLX, SRT and PRX increase swimming and decrease immobility in the rat FST are novel and suggest that the SSRIs are active in this test, not false negatives as previously thought.

The present study validated the use of a behavior sampling procedure in the FST which allows one to score more than one behavior at a time. Such techniques have been employed in ethological field work (e.g. Leger 1977; Rhine and Flanigon 1978) and animal learning (e.g. Holland 1977, 1986) for decades. These empirical data, along with mathematical analyses (Altmann 1974; Dunbar 1976; Tyler 1979) have shown that the "instantaneous sampling" or "point sampling" method used here approximates actual durations well if the sampling interval is short relative to the average duration of the behavior(s) being recorded (for an overview, see Martin and Bateson 1993, pp. 90–91). The correlations between actual timing and sampling of behaviors in the FST in the present study provide further support for this position.

The results of the present study support the importance of distinguishing the active behaviors shown by rats in the FST. The wide differences between laboratories in the immobility times reported for rats receiving vehicle (140–280 s out of 300; Gorka et al. 1979; Armario et al. 1988), may be due to the failure to score swimming as a separate behavior. Unlike climbing, which is a very distinct behavior (inter-rater reliability correlation = 0.97), swimming involves less vigorous movement and is more likely to be confused with immobility (inter-rater reliability correlations = 0.81 and 0.90, respectively). When immobility and swimming are not distinguished, but are collapsed, a decrease in immobility and an increase in swimming would be likely to cancel each other out. This may be why the effects of the SSRIs were not detected using the traditional scoring method. It is also possible that the use of deeper water in the present study enhanced the rats' tendencies to swim, as it makes them unable to stand on the bottom of the jar. Thus it may increase the likelihood of observing swimming behavior when it is elicited by the appropriate compounds. Most of the previous studies which showed no effects of SSRIs in the rat FST used water that was 15–17 cm deep.

Scoring active behaviors as well as immobility in the FST enhanced the sensitivity of the test as a screen for antidepressant compounds by detecting SSRIs as active. Although such an increase in sensitivity might be thought to reduce the specificity of the test (i.e. its ability to screen out compounds which are without antidepressant efficacy), the preliminary data presented here suggest that this is not the case. Diazepam, an anxiolytic without antidepressant efficacy, which is inactive in the traditional FST (e.g. Wieland and Lucki 1990), had no effects when scored using the system presented here. NAN-190, another compound inactive in the traditional FST (Detke et al. 1995) which is a postsynaptic 5-HT_{1A} receptor antagonist and a partial agonist at presynaptic 5-HT_{1A} receptors (Hjorth and Sharp 1990), was also without effects in the present study. In addition, amphetamine, a psychostimulant without antidepressant efficacy, is a false positive in the traditional FST (e.g., Wieland and Lucki 1990) and was shown to enhance climbing without altering swimming. Thus, there is so far little reason to suspect that either scoring active behaviors in general or attention to swimming specifically will worsen the specificity of the test. However, many more non-antidepressant compounds will need to be screened with the scoring method presented here before this can be concluded with certainty.

The pattern of behavioral effects produced by the antidepressant drugs employed here suggests that enhancement of NE neurotransmission is related to climbing in the FST, and that enhancement of 5-HT neurotransmission is related to swimming in the test. These results appear to parallel recent studies of depressed patients where the NE and 5-HT neurotransmitter systems have been suggested to produce distinguishable contributions to therapeutic efficacy. Delgado et al. (1991, 1993) have shown that dietary depletion of 5-HT precursors leads to clinical relapse in depressed patients who have been successfully treated with SSRIs, but not in those treated with NE selective uptake inhibitors, and that blockade of NE synthesis has the complementary set of effects. While certain aspects of the pharmacology of the effects of DMI and related compounds in the rat have been discerned (e.g. Kitada et al. 1983; Cervo et al. 1990), relatively little is known about the pharmacological and anatomical substrates for the antidepressant effects of SSRIs. Having identified a behavioral assay for SSRI antidepressants using the FST, it will be possible to study further what specific components of the 5-HT system mediate these effects. For example, the demonstration that the 5-HT_{1A} receptor agonists 8-OH-DPAT and gepirone produced a pattern of behavioral effects resembling that of the SSRIs supports the significance of postsynaptic 5-HT_{1A} receptors in mediating the antidepressant effects of 5-HT receptor agonists (Lucki et al. 1994). The role played by other subtypes of 5-HT receptors in mediating this pattern of behaviors remains to be examined.

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