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Anxiolytic-Like Effects of Antidepressants After Acute Administration in a Four-Plate Test in Mice

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HASCOËT, M., M. BOURIN, M. C. COLOMBEL, A. FIOCCO AND G. B. BAKER. *Anxiolytic-like effects of antidepressants after acute administration in a four-plate test in mice.* PHARMACOL BIOCHEM BEHAV **65**(1) 339–344, 2000.—The four-plate test (FPT) is an animal model of anxiety based on stress caused by unconditioned fear. An increase of spontaneous punished behavior was used as a measure to determine the anxiolytic effects of various antidepressants (ADs). In the present study, ADs with different mechanisms of action, including tricyclics, selective serotonin reuptake inhibitors (SSRIs), a monoamine oxidase inhibitor (MAOI), and atypicals, were studied in the FPT to evaluate their anxiolytic-like effects following acute administration. The number of punished crossings was dramatically increased by the SSRIs citalopram, fluvoxamine, and paroxetine, but not fluoxetine. The mixed 5-HT/NE reuptake inhibitors, milnacipran and venlafaxine, also demonstrated strong antipunishment effects. The specific NE reuptake inhibitors, desipramine and maprotiline, and the atypical AD trazodone, enhanced freezing behavior, suggesting anxiogenic-like behavior. It was concluded that, in the FPT, a model based on spontaneous response, where animals are exposed to an aversive environment from which they can only escape by being motionless, this kind of behavior might be related to anticipatory anxiety. In this situation, ADs acting preferentially on 5-HT transmission possessed clear anxiolytic like effects. The balance between the two transmitters, 5-HT and NE, seemed to be a crucial factor. © 2000 Elsevier Science Inc.

Antidepressants SSRIs Tricyclics Anxiolytic-like activity Four-plate test Mice Acute administration

WHEN treating anxiety disorders, the use of antidepressants (ADs) may be an effective alternative to benzodiazepines, which are known to have a high potential for dependency and sedative side effects. The selective serotonin reuptake inhibitors (SSRIs) have been reported to be effective treatments for generalized anxiety disorder (GAD) (26) not associated with concomitant phobias, panic, or obsessive–compulsive disorders (OCD). The ability of SSRIs to treat OCD (19) was apparently not solely related to their antidepressant effects because they reduced OCD symptoms in patients who were not depressed (6). Imipramine has also been reported to be active in treating GAD in a double-blind, placebo-controlled study in which it was compared to chlordiazepoxide (22). Although clinical research has revealed promising results concerning the effects of ADs on anxiety, results obtained from animal models of anxiety have remained variable, and thus, controversial. Acute administration of established ADs in animals has been reported to produce anxiogenic-like effects in some studies (23) and no specific effect in others (9,13). However various authors have shown that ADs may even elicit anxiolytic-like responses (8,15).

It must be noted that animal models of anxiety have often been optimized for benzodiazepines and related compounds, and not for ADs. Many paradigms are aimed at studying the anticonflict effect of anxiolytic drugs, which employs the notion of punishment. The four-plate test (FPT) is an animal model of anxiety in which a simple ongoing behavior (exploration of novel surroundings) is suppressed by the delivery of mild electric foot shock contingent to quadrant crossings (2). In this test, benzodiazepines and related compounds induce a

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marked antipunishment effect, which has been proposed as a reflection of their anxiolytic activity (7). The FPT is a widely used animal model of anxiety because the procedure is simple, and there is no need for prior training of animals.

The present study was designed to determine, using the FPT without retest trials, whether AD drugs active on norepinephrine reuptake, serotonin reuptake, or both systems, demonstrate anxiolytic-like activity after acute administration. The effects of atypical ADs and a monoamine oxidase onhibitor (MAOI) were also examined.

METHOD

Ethical rules of the French Ministry of Agriculture for experiments with laboratory animals (No. 87.848) were followed at all times.

Materials

Animals. Male Swiss mice (4 weeks old) were purchased from R. Janvier (Le Genest, France). Their average body weight on the day of the study was 22 ± 2 g. These animals were housed in groups of 20, at a constant temperature (20°C), with a standard light cycle (lights on between 0700 and 1900 h), and had free access to food and water.

Drugs. The drugs used in this study were: diazepam (Roche), alprazolam (Upjohn Pharmaceuticals), desipramine HCl (RBI), milnacipran (Laboratoire P. Fabre), moclobemide (Roche), trazodone HCl (UPSA), viloxazine HCl (Zeneca Pharma), mianserin HCl (Organon), maprotiline HCl (Ciba Geigy), imipramine HCl (Ciba Geigy), fluoxetine (Lilly), dothiepin (BASF Pharma), paroxetine HCl (Smith-Kline Beecham), citalopram HBr (Lundbeck), fluvoxamine maleate (Duphar), venlafaxine (Wyeth Lederle), and sertraline (Pfizer).

All drugs were ultrasonically dispersed in distilled water. All drugs or vehicle were administered IP in a volume of 0.5 ml/20 g of body weight. Control animals received vehicle only. Drugs were administered 30 min before testing. Mice were used only once.

Psychopharmacological Test

Apparatus: The "four-plate" test. This apparatus consists of a cage (18 × 25 × 16 cm) floored by four identical rectangular metal plates (8 × 11 cm) separated from one another by a gap of 4 mm. The plates are connected to a device that generates electric shocks (0.6 mA, 0.5 seconds). This intensity was chosen so that it evoked a clear flight reaction in the controls.

Testing procedure. Following a 15-s latency period, the animal was subjected to an electric shock when crossing from one plate to another. The experimenter electrified the whole floor, which evoked a clear flight reaction of the animal, who often crossed two or three plates. If the mouse continued running, it received no additional shocks during the following 3 s. The number of crossings was recorded during a 1-min testing period (2,4).

Analysis of data. The mean number of responses for each group, and the final results, were expressed as a percentage of the value observed in control animals. All data were evaluated by nonparametric statistical methods due to a nonnormal distribution. Statistical analysis of the data was performed by application of the Kruskal–Wallis *H*-test for independent groups, followed by an a posteriori Steel test to

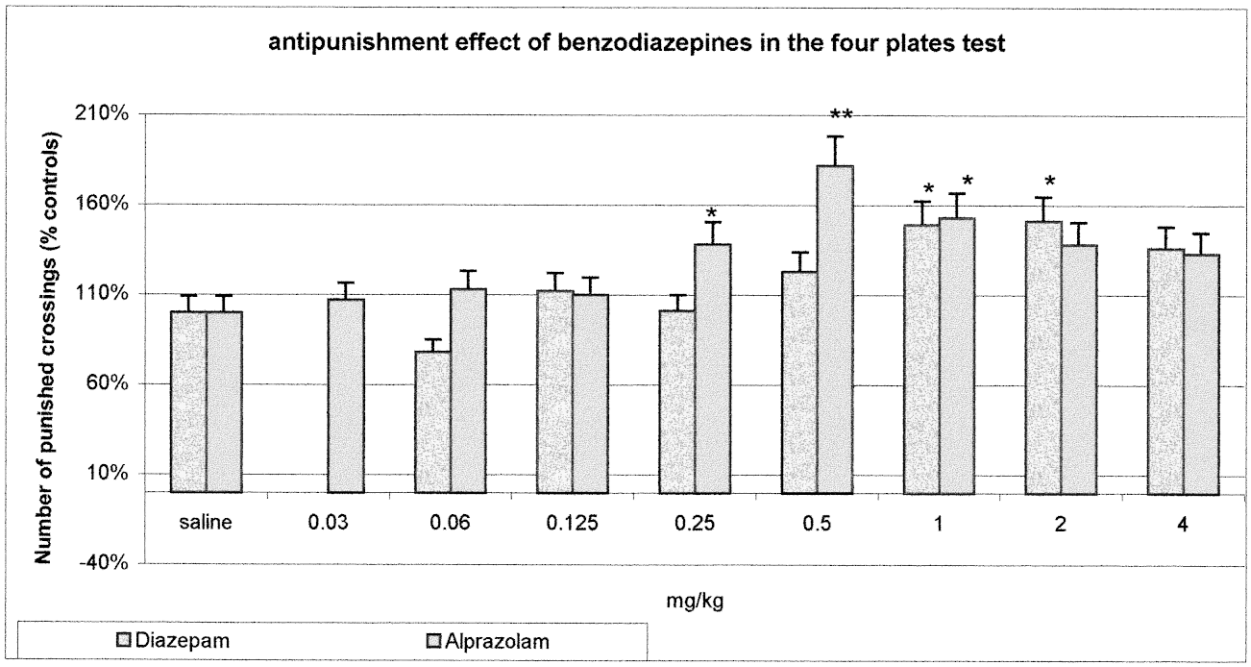

FIG. 1. Effect of diazepam and alprazolam in mice in the four-plate test following acute administration. Results are expressed as the percentage of control values ($n = 12$). Drugs were injected IP 30 min before the test. Statistical analyses were performed using the nonparametric Kruskal–Wallis *H*-test, followed by the "a posteriori" Steel test for comparison with the control group: $^{*}p < 0.05$, $^{**}p < 0.01$. The means of punished crossings for the controls was 7.7 ± 0.7 for diazepam-treated animals and 6 ± 0.5 for alprazolam-treated animals.

detect any significant differences between treated and control groups.

All analyses were conducted using the PCSM program (Deltasoft) for an IBM-compatible computer.

RESULTS

The standard anxiolytic drugs diazepam and alprazolam were found to induce a significant overall effect on punished crossings in the FPT ($H = 35.85$ and $H = 33.73$, respectively). Pairwise comparisons indicated a significant increase of punished crossing in mice given diazepam 1 and 2 mg/kg ($p < 0.05$) and alprazolam 0.5 mg/kg ($p < 0.01$), 0.25 and 1 mg/kg ($p < 0.05$) (see Fig. 1).

The serotonin–norepinephrine reuptake inhibitors milnacipran and venlafaxine both demonstrated strong antipunishment effects, comparable to that of diazepam and alprazolam ($H = 65.41$ and $H = 18.95$, respectively) The doses of 4, 8, 16, and 32 mg/kg were found to be active in comparison with placebo treated mice ($p < 0.01$ for milnacipran for venlafaxine) (see Fig. 2).

Of the five SSRIs tested, sertraline ($H = 35.85$), fluvoxamine ($H = 32.51$), citalopram (H = 23.44), and paroxetine ($H = 103.61$) were all found to be active in this model.

Comparison with the control group indicated a significant increase in the number of punished crossings for the doses of 8 mg/kg ($p < 0.01$) and 32 mg/kg ($p < 0.05$) for sertraline, for the doses of 8, 16, and 32 mg/kg ($p < 0.01$) for fluvoxamine, for the doses of 4, 8, 16, and 32 mg/kg, ($p < 0.01$) for citalopram, and for the doses of 4, 8, and 16 mg/kg $p < 0.01$ for paroxetine (see Fig. 2). Fluoxetine ($H = 4.4$) did not induce any significant changes at any dose (see Table 1).

Of the other antidepressant drugs tested, moclobemide ($H = 4.24$), viloxazine ($H = 5.4$), mianserin ($H = 9.68$), imipramine ($H = 12.98$), and dothiepin ($H = 12.32$) did not induce any significant changes (Table 1).

Desipramine, the specific norepinephrine reuptake inhibitor, significantly decreased the number of punished crossings ($H = 18.93$). The doses of 4 to 32 mg/kg ($p < 0.05$) were significantly different from the control group (Table 1). Similarly, trazodone, and maprotiline were found to decrease antipunishment activity ($H = 27.83$ and $H = 15.32$ respectively), with a significant reduction in the number of punished crossings when compared to controls ($p < 0.01$ for a dose of 32 mg/kg for trazodone and for a dose of 16 mg/kg, $p < 0.05$, for maprotiline) (Table 1).

DISCUSSION

Using a simple model, the FPT, a punished procedure in mice, the present study compared several ADs with different mechanisms of action (tricyclics, atypical ADs, MAOIs, and SSRIs) following acute administration. The results obtained with the ADs were unexpected and not readily explicable.

As was expected (7), diazepam and alprazolam demonstrated a strong antipunishment effect in the FPT when administered 30 min before testing. The decrease of punished crossings observed for the higher doses was due to the sedative properties of benzodiazepines, but the number of punished crossings was still higher than for saline control animals. This test, based on unconditioned, punished responses, has been clearly validated for classical anxiolytic compounds (7,21).

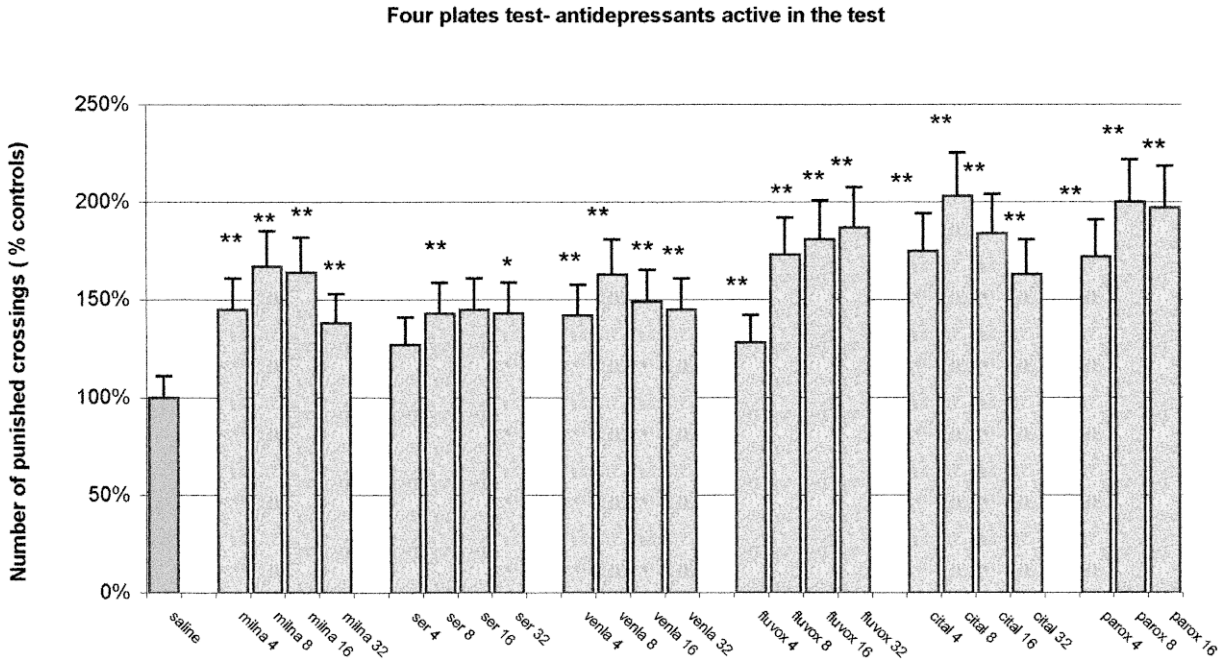

FIG. 2. Effect of various ADs in mice on the number of punished crossings in the four-plate test in mice. Results are expressed as the percentage of control values ($n = 12$). Drugs were injected IP 30 min before the test. Statistical analyses were performed using the nonparametric Kruskal–Wallis H-test, followed by the "a posteriori" Steel test for comparison with saline control group: $^{*}p < 0.05$, $^{**}p < 0.01$. The mean of punished crossings for the controls was 5.6 ± 0.5 (100% ± 8%) for the six antidepressants tested.

TABLE 1
EFFECTS OF VARIOUS ANTIDEPRESSANTS IN THE FOUR PLATES TEST FOLLOWING ACUTE ADMINISTRATION

	Vehicle	1 mg/kg	2 mg/kg	4 mg/kg	8 mg/kg	16 mg/kg	32 mg/kg	*H*-Value
Nonactive drugs								
Moclobemide	6.0 ± 0.26	5.7 ± 0.47	5.8 ± 0.61	6.2 ± 0.61	5.2 ± 0.32	6.4 ± 0.45	5.7 ± 0.54	$H = 4.24$
	100%	95%	97%	103%	67%	107%	95%	
Viloxazine	7.8 ± 0.42	—	7.4 ± 0.37	7.6 ± 0.63	7.5 ± 0.67	6.4 ± 0.37	—	$H = 5.4$
	100%	—	95%	97%	96%	82%	—	
Mianserin	6.6 ± 0.40	—	5.9 ± 0.76	6.6 ± 0.67	6.2 ± 0.62	6.2 ± 0.46	4.3 ± 0.45	$H = 9.68$
	100%	—	89%	100%	94%	94%	65%	
Imipramine	6.7 ± 0.37	6.8 ± 0.42	6.8 ± 0.57	7.7 ± 0.59	7.4 ± 0.45	6.4 ± 0.52	4.8 ± 0.39	$H = 12.98$
	100%	101%	102%	115%	110%	96%	72%	
Fluoxetine	6.0 ± 0.40	6.4 ± 0.65	6.2 ± 0.59	6.8 ± 0.44	6.4 ± 0.60	7.0 ± 0.75	5.0 ± 0.4	$H = 4.4$
	100%	105%	102%	111%	105%	115%	82%	
Dothiepin	5.1 ± 0.48	5.0 ± 0.44	6.7 ± 0.51	5 ± 0.60	6.6 ± 0.52	6.3 ± 0.45	7.2 ± 0.74	$H = 12.32$
	100%	100%	131%	100%	129%	124%	141%	
Anxiogenic drugs								
Desipramine	5.3 ± 0.22	—	4.3 ± 0.41	3.7 ± 0.26*	3.8 ± 0.25*	3.8 ± 0.35*	4.0 ± 0.30*	$H = 18.93$
	100%	—	81%	69%	70%	70%	75%	
Trazodone	7.4 ± 0.42	7.5 ± 0.54	7.5 ± 0.70	7.4 ± 0.40	6.7 ± 0.73	8.4 ± 0.45	3.7 ± 0.36†	$H = 27.83$
	100%	101%	101%	100%	91%	73%	50%	
Maprotiline	7.2 ± 0.92	—	8.3 ± 0.68	5.8 ± 0.70	6.1 ± 0.43	4.6 ± 0.47*	—	$H = 15.32$
	100%	—	115%	81%	85%	64%	—	

Effects of various ADs on the number of punished crossings in the four plates test in mice following acute administration, IP, 30 min before the test ($n = 12$). Results are expressed as the mean value and the percentage of the control group value. ($n = 12$). Statistical analyses were performed using the nonparametric Kruskal–Wallis *H*-test, followed by the "a posteriori" Steel test for comparison with the control group: *$p < 0.05$, †$p < 0.01$.

Until now, the FPT has been essentially used for studies implicating benzodiazepines or related compounds (i.e., acting on the GABAergic system) (3,27). Few data on drugs acting on other transmitter systems are available in the literature.

Dooley and Klamt (10) found that the CCK_B antagonist CI-988 attenuated avoidance behavior in the FPT, suggesting an anxiolytic potential. The increase in the number of punished crossings induced by the CCK_B receptor antagonist was not antagonized by flumazenil (a benzodiazepine receptor antagonist), suggesting an anxiolytic potential involving a distinct neuronal system other than the GABAergic one. Furthermore, an antagonist of the NMDA subtype of the glutamate receptor was effective in antagonizing the suppressive effects of punishment on locomotor activity in the FPT in mice (28).

Results obtained with serotonergic drugs have been less revealing. The $5\text{-}HT_3$ receptor antagonist DAU 6215 was found to have no effect on the FPT (5), and findings with odensetron, also a $5\text{-}HT_3$ antagonist, suggested a weak anxiolytic-like effect in the FPT (10). Taking these data together, the FPT is able to detect anxiolytic-like behavior induced by drugs acting on distinct neuronal systems, and not only by benzodiazepine-related compounds.

Following acute administration, three of the ADs tested demonstrated anxiogenic-like effects: these included the two specific inhibitors of norepinephrine reuptake, desipramine, and maprotiline, and the atypical antidepressant trazodone. These results are in accordance with data generally found in the literature. It has been reported that acute administration of established antidepressants often results in anxiogenic-like effects (23) and no specific effects in others studies (9,13).

Doses of trazodone and maprotiline that induced a decrease in punished crossing were close to sedative doses [(16 mg/kg for antipunishment effect of maprotiline and 32 mg/kg for sedative effect) (8), 16 and 32 mg/kg for antipunishment and sedative effects for trazodone (unpublished data)]. Nevertheless, it must be noticed that benzodiazepines still demonstrated antipunishment effects for the first sedative doses [e.g., 1 and 2 mg/kg for diazepam; this study, (7)]. In addition, spontaneous locomotor activity of moclobemide-treated mice was strongly decreased from the dose of 32 mg/kg ($p < 0.01$), but at the same dose, mice still demonstrated 105% of activity in the FPT. Finally, desipramine did not reduce spontaneous locomotor activity for the doses that induced anxiogenic-like effects; thus, it may be concluded that the decrease in number of punished crossings was not due to sedation, but was indeed an anxiogenic-like effect.

For the doses chosen in this study, spontaneous locomotor activity did not seem to influence results obtained in the FPT. Milnacipran did not significantly modify locomotor activity in the range of doses studied in a spontaneous behavioral procedure using an actimeter test (unpublished data), but demonstrated strong antipunishment in this study. Sertraline, a typical SSRI, and venlafaxine, a serotonin/norepinephrine reuptake inhibitor (SNRI) increased spontaneous locomotor activity, but at higher doses than those active in the FPT. Furthermore, adrafinil, a psychostimulant with noradrenergic activity (11), increased dramatically spontaneous locomotor activity (16), but did not show any effect in the FPT. Paroxetine did not significantly modify locomotor activity in the range of doses studied (24).

One major problem in interpreting these results concerns the analgesic effect of AD drugs (they have been widely used

in the treatment of chronic pain). However, in animal experiments, systemic administration of ADs has yielded confusing results in tests of nociception. Theoretically, a possible analgesic action could account for the effects observed in this procedure. However, at doses active in alleviating pain in various tests, morphine did not increase the number of shocks received in the FPT (4). Concerning AD drugs, serotonin reuptake inhibitors produce analgesic effects in the hot-plate test (1,12), but the effect was not stronger than those of norepinephrine reuptake inhibitors, like desipramine (12). Furthermore, antinociceptive activity was not observed in the hot-plate reaction test with citalopram (18) except at high doses (12).

Although most SSRIs and SNRIs have both been found to have analgesic properties, they were not all found to be active in the present study. For example fluoxetine did not induce any antipunishment effects in the current investigation. Thus, one may conclude that the effects found for the active ADs in the FPT were indeed anxiolytic-like, and not analgesic effects.

The mixed SNRIs milnacipran and venlafaxine, together with the SSRIs, paroxetine, fluvoxamine, sertraline, citalopram, but not fluoxetine, dramatically increased the number of punished crossings. One conclusion could be that the ADs that induce antipunishment effects seem to act preferentially on the serotoninergic system. More precisely, the selectivity on the uptake of the biogenic amines serotonin (5-HT) and norepinephrine (NE) seems to play a role in the activity of the ADs. The selectivity ratio (r) of the SSRIs as calculated by the IC_{50} NE/IC_{50} 5-HT (the higher the values, the more selective for 5-HT uptake) decreased from citalopram (r = 3400) through sertraline (r = 840), paroxetine (r = 280), fluvoxamine (r = 160) (all active in the FPT) to fluoxetine (r = 54) inactive in the FPT [data from (18)]. This is corroborated by the fact that at low doses (4, 8, and 16 mg/kg) venlafaxine acts preferentially on the 5-HT system, while at higher doses it inhibits both 5-HT and NE reuptake (25). Milnacipran displays the same mechanism of action. This also explains the bell-shaped curve with venlafaxine and milnacipran induced by an increased activity of the drugs on NE system. On the other hand, the decrease of activity observed with citalopram at a dose of 32 mg/kg was probably due to the serotonin syndrome. The two drugs that decreased the antipunishment effects in the FPT had the lowest IC_{50} NE/IC_{50} 5-HT ratio; these were 0.0015 and 0.004, respectively, for maprotiline and desipramine (18). The lack of activity in the FPT obtained with fluoxetine and imipramine was surprising. But an effect of active metabolites cannot be ruled out. Norfluoxetine is a potent inhibitor of 5-HT, but not NE, reuptake. Desipramine, a major metabolite of imipramine, is a very potent inhibitor of the NE reuptake. In addition, imipramine and desipramine have anticholinergic effects. It is of interest that imipramine gave the same result as an earlier study with FPT by Boissier et al. (4), with the same number of punished crossings with 4 and 8 mg/kg (3.9 crossings vs. 4 for the controls).

These results are similar to those of Hashimoto et al. (17), who reported that, using conditioned fear stress (CFS)-induced freezing behavior in rats, SSRIs reduced the duration of freezing behavior. This reduction in freezing behavior was utilized as an index of anxiolytic-like behavior. Milnacipran was also found to reduce CFS-induced freezing after acute administration, whereas maprotiline and a dopamine reuptake inhibitor, GBR12909, were without effect. The exact mechanism remains unclear. The authors concluded that in the CFS-induced freezing behavior, facilitation of serotonin neurotransmission decreases anxiety. An interaction with any of the serotonin pre- and postsynaptic receptors following the increase of synaptic serotonin cannot be ruled out.

The classical hypothesis of anxiolysis is related to decreased activity in central serotonin neurones (20), but paradoxical drug effects have often been found. The reasons for this variability of effect include species differences, stress differences, and the environment in which a test is conducted. In a recent review, Griebel (14) reported that acute administration of reuptake inhibitors in animal models of anxiety results in variable effects ranging from anxious responses in 46% of the studies to anxiolytic like responses in 31% of the studies. Tests based on spontaneous responses more often demonstrated modifications of the behavior in comparison with control animals.

In conclusion, in the FPT, a model based on spontaneous response, animals are exposed to an aversive environment from which they can only escape by being motionless (passive avoidance). This kind of behavior might be related to anticipatory anxiety with controllable aversive events (14), opposite to depressive anxiety linked with uncontrollable stress. In this situation, ADs acting preferentially on serotonin transmission, possessed clear anxiolytic like effects. The exception was the SSRI fluoxetine. On the other hand, the balance between the two transmitters, serotonin and norepinephrine, seemed to be a crucial factor to obtain anxiolytic-like activity in the FPT. Thus, to detect false positive effects, the study should be complete by adding results obtained in other animal models.

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