*Pharmacology Biochemistry and Behavior*, Vol. 42, pp. 45–47, 1992
Printed in the U.S.A. 

0091-3057/92 $5.00 + .00


# Activity of Litoxetine and Other Serotonin Uptake Inhibitors in the Tail Suspension Test in Mice

GH. PERRAULT,[1] E. MOREL, B. ZIVKOVIC AND D. J. SANGER

*Synthelabo Recherche (L.E.R.S.), 92220 Bagneux, France*

Received 31 July 1991

PERRAULT, GH., E. MOREL, B. ZIVKOVIC AND D. J. SANGER. *Activity of litoxetine and other serotonin uptake inhibitors in the tail suspension test in mice.* PHARMACOL BIOCHEM BEHAV 42(1) 45–47, 1992.—Compounds known to selectively inhibit the neuronal reuptake of serotonin are clinically effective antidepressants. However, in a number of the behavioral models used for detecting and analysing antidepressant action these drugs are inactive. The forced swimming test is not consistently sensitive to these drugs but it has recently been reported that a variation of this procedure, the tail suspension test in mice, is sensitive. The present study showed that five compounds previously shown to be selective serotonin uptake inhibitors—fluoxetine, zimeldine, paroxetine, indalpine, and litoxetine—produced dose-related decreases in immobility in the tail suspension test typical of the effects shown by other antidepressants. In separate experiments, fluoxetine, zimeldine, and indalpine decreased locomotor activity at doses similar to those that decreased immobility. In contrast, paroxetine and litoxetine had no effect on locomotion at the dose ranges active in the tail suspension test. These results confirm the sensitivity of the tail suspension test and indicate that serotonin uptake inhibitors probably decrease immobility and reduce locomotor activity through different mechanisms.

Tail suspension test  Fluoxetine  Zimeldine  Paroxetine  Indalpine  Litoxetine

THERE is considerable evidence of a role for serotonin in the aetiology of depression and in the mechanism of action of antidepressant drugs (21). Several drugs developed for selective inhibition of the neuronal reuptake of serotonin have been shown to be clinically active antidepressants (9). However, in behavioral models in animals used for selecting and evaluating the effects of antidepressants inhibitors of serotonin uptake often show actions different from those associated with tricyclic antidepressants and inhibitors of monoamine oxidase. For example, fluoxetine and zimeldine reverse the passive avoidance deficit produced by olfactory bulbectomy in rats after acute administration, whereas chronic treatment with other antidepressants is necessary to produce a similar effect (4,7). In the learned helplessness procedure, serotonin uptake inhibitors were reported to be active in reversing the escape deficit produced by inescapable shock but only if injected after shuttle box sessions (11).

The forced swimming or "behavioral despair" technique has been widely used for screening antidepressants (13,15). A variety of typical and atypical antidepressants reduce immobility of rats or mice placed in water, and there are also a number of "false positives" in this procedure, particularly when used with mice (2,10). However, most studies have found that inhibitors of serotonin reuptake are inactive or produce very variable effects in the forced swimming test (5,6,8,12) and this has led some workers to conclude that this procedure is not appropriate for investigating the effects of drugs acting through serotonergic mechanisms (2,3).

Steru, Porsolt, and their colleagues recently introduced a test in which the activity of mice hung by their tails is measured during a very short period (14,18,19). The principle of this test is similar to that of the forced swimming test in that antidepressants have been found to reduce the amount of time for which mice remain immobile. However, in contrast to the forced swimming test, it has been reported that the serotonin reuptake inhibitors citalopram, indalpine (18), and fluvoxamine (20) show activity in the tail suspension test. The present study was carried out to investigate the effects of five compounds known to be selective inhibitors of serotonin reuptake on immobility time in the tail suspension test. The compounds used were the antidepressants fluoxetine, zimeldine, indalpine, paroxetine, and litoxetine (SL 81.0385), which has been shown to be a highly selective inhibitor of serotonin reuptake (17). In addition to the tail suspension test, the five compounds were also studied in a test of locomotor activity. A preliminary report of some of these findings has been given elsewhere (1).

[1] Requests for reprints should be addressed to Gh. Perrault, Synthelabo Recherche (L.E.R.S.), 31 ave P.V. Couturier, 92220 Bagneux, France.

## METHOD

### *Animals*

Male NMRI and $OF_1$ mice weighing 18–24 g supplied by Iffa Credo and Charles River, France, were used in tail suspension test and spontaneous locomotor activity measurements, respectively. Mice were housed in groups of 10 under standard laboratory conditions with lights on between 7:00 a.m. and 7:00 p.m. NMRI mice were chosen for the tail suspension experiments because this strain had been found to provide more orderly data in this test. Previous work has reported important strain differences in results obtained in the tail suspension procedure (20).

### *Apparatus and Procedure*

*Tail suspension test.* Mice were individually suspended by the tail from a thread attached to a force displacement transducer in a sound-attenuating box. The force of displacement produced by alternative periods of agitation and immobility was amplified, converted to a digital signal, and automatically recorded. Results are expressed as the time mice spent immobile during a 6-min test period.

*Spontaneous locomotor activity.* Locomotor activity was recorded immediately after placing mice individually in circular activity cages (diameter 20 cm) equipped with photocells for 10 min.

*Statistical analysis.* Dose-response curves were obtained from groups of 10–20 animals per dose with mice being randomly allocated to different groups before experiments. The effect of drug treatment was compared with the effect of vehicle treatment using Dunnett's test.

*Drugs.* Drugs were injected IP 30 min before the test as solutions in saline or as fine suspensions in saline containing 0.1% Tween-80 for indalpine and litoxetine.

## RESULTS AND DISCUSSION

Effects of the five serotonin uptake inhibitors on immobility time and on locomotor activity are shown in Fig. 1. All five compounds produced dose-related decreases in immobility time. The figure also shows that fluoxetine, zimeldine, and indalpine produced dose-related decreases in locomotor activity in dose ranges similar to those active in the tail suspension test. In marked contrast, paroxetine and litoxetine did not affect locomotor activity at doses that decreased immobility.

These results confirm previous findings that the tail suspension test is sensitive to the effects of antidepressant drugs that selectively inhibit the uptake of serotonin (18,20). As the forced swimming test is generally insensitive to these compounds (3), these results suggest that the two procedures may not be evaluating the same effects. Further work will be necessary to identify the essential differences between the two methods.

It was particularly interesting to note that fluoxetine, zimeldine, and indalpine decreased locomotor activity at the same doses as those reducing immobility. Although it is not surprising that these drugs should decrease locomotion, an effect observed with many antidepressants, it seems paradoxical that doses decreasing immobility (i.e., increasing the duration of motor activity) should also decrease locomotion. There are, of course, many differences between the two experimental procedures that may explain these results.

Paroxetine and litoxetine, however, did not decrease locomotor activity at doses that reduced immobility. This indicates it is possible to dissociate these two behavioral actions of serotonin uptake inhibitors, suggesting different mechanisms are involved in the two effects. It is known that serotonin uptake inhibitors produce less sedative activity in the clinic than do some other antidepressant drugs (16). However, information

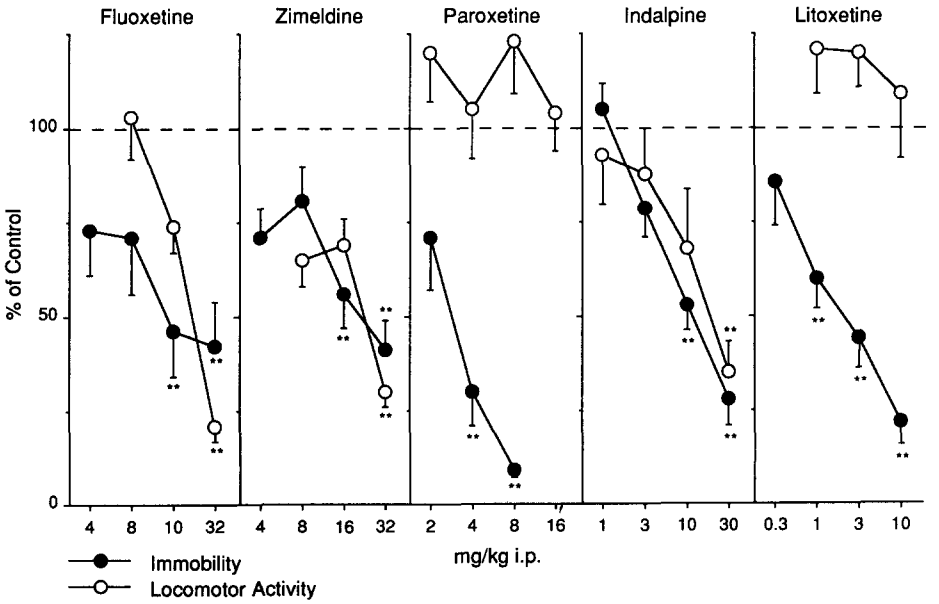


FIG. 1. Effects of five serotonin uptake inhibitors on immobility time in the tail suspension test and locomotor activity in mice. Immobility time was measured during a 6-min period and locomotor activity during a 10-min period in photocell activity cages. Results are expressed as percentages of values observed in vehicle-treated mice. $*p < 0.05$, $**p < 0.01$ difference from control values, Dunnett's test.

is not available indicating major differences between individual members of this group of drugs in this respect. Similarly, there are few studies in the laboratory comparing the behavioral profiles of different compounds. In one study, however, it was found that zimeldine depressed active avoidance responding whereas alaproclate did not (5). Whether such differences would indicate different clinical profiles is not, at present, clear.

## REFERENCES


1. Ali-Kodja, F.; Bougard, M.; Perrault, G.; Zivkovic, B. Effect of serotonin uptake inhibitors on the immobility of mice in the tail suspension test. Br. J. Pharmacol. 87:130P; 1986.
2. Borsini, F.; Bendotti, C.; Velkov, V.; Rech, R.; Samanin, R. Immobility test: Effects of 5-hydroxytryptaminergic drugs and role of catecholamines in the activity of some antidepressants. J. Pharm. Pharmacol. 33:33–37; 1981.
3. Borsini, F.; Meli, A. Is the forced swimming test a suitable model for revealing antidepressant activity. Psychopharmacology (Berl.) 94:147–160; 1988.
4. Cairncross, K. D.; Cox, B.; Forster, C.; Wren, A. F. A new model for the detection of antidepressant drugs: Olfactory bulbectomy in the rat compared with existing models. J. Pharmacol. Meth. 1:131–143; 1978.
5. Danysz, W.; Plaznik, A.; Kostowki, W.; Malatynska, E.; Jarbe, T. U. C.; Hiltunen, A. J.; Archer, T. Comparison of desipramine, amitriptyline, zimeldine and alaproclate in six animal models used to investigate antidepressant drugs. Pharmacol. Toxicol. 62:42–50; 1988.
6. Gorka, Z.; Wojtasik, E.; Kwiatek, H.; Maj, J. Action of serotonin mimetics in the behavioral despair test in rats. Commun. Psychopharmacol. 3:133–136; 1979.
7. Joly, D.; Sanger, D. J. The effects of fluoxetine and zimeldine on the behavior of olfactory bulbectomized rats. Pharmacol. Biochem. Behav. 24:199–204; 1986.
8. Koe, B. K.; Weissman, A.; Welch, W. M.; Browne, R. G. Sertraline, 1*S*,4*S*-*N*-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphtylamine, a new uptake inhibitor with selectivity for serotonin. J. Pharmacol. Exp. Ther. 226:686–692; 1983.
9. Lemberger, L.; Fuller, R. W.; Zerbe, R. L. Use of specific serotonin uptake inhibitors as antidepressants. Clin. Neuropharmacol. 8:299–317; 1985.
10. Luttinger, D.; Freedman, M.; Hamel, L.; Ward, S. J.; Perrone, M. The effects of serotonin antagonists in a behavioral despair procedure in mice. Eur. J. Pharmacol. 107:53–58; 1985.
11. Martin, P.; Soubrie, P.; Puech, A. J. Reversal of helpless behavior by serotonin uptake blockers in rats. Psychopharmacology (Berl.) 101:403–407; 1990.
12. Porsolt, R. D.; Bertin, A.; Blavet, N.; Jalfre, M. Immobility induced by forced swimming in rats: Effects of agents which modify central catecholamine and serotonin activity. Eur. J. Pharmacol. 57:201–210; 1979.
13. Porsolt, R. D.; Bertin, A.; Jalfre, M. Behavioral despair in mice: A primary screening test for antidepressants. Arch. Int. Pharmacodyn. Ther. 229:327–336; 1977.
14. Porsolt, R. D.; Chermat, A.; Lenegre, A.; Avril, I.; Janvier, S.; Steru, L. Use of the automated tail suspension test for the primary screening of psychotropic agents. Arch. Int. Pharmacodyn. 288:11–30; 1987.
15. Porsolt, R. D.; LePichon, M.; Jalfre, M. Depression: A new animal model sensitive to antidepressant treatments. Nature 266: 730–732; 1977.
16. Rickels, K.; Schweizer, E. Clinical overview of serotonin reuptake inhibitors. J. Clin. Psychiatry. 51(12)(suppl. B.):9–12; 1990.
17. Scatton, B.; Claustre, Y.; Graham, D.; Dennis, T.; Serrano, A.; Arbilla, A.; Pimoule, C.; Schoemaker, H.; Bigg, D.; Langer, S. Z. SL 81.0385: A novel selective and potent serotonin uptake inhibitor. Drug Dev. Res. 12:29–40; 1988.
18. Steru, L.; Chermat, R.; Thierry, B.; Mico, J. A.; Lenegre, A.; Steru, M.; Simon, P.; Porsolt, R. D. The automated tail suspension test: A computerized device which differentiates psychotropic drugs. Prog. Neuropsychopharmacol. Biol. Psychiatry 11: 659–671; 1987.
19. Steru, L.; Chermat, R.; Thierry, B.; Simon, P. The tail suspension test: A new method for screening antidepressants in mice. Psychopharmacology (Berl.) 85:367–370; 1985.
20. Van der Heyden, J. A. M.; Molewijk, E.; Olivier, B. Strain differences in response to drugs in the tail suspension test for antidepressant activity. Psychopharmacology (Berl.) 92:127–130; 1987.
21. Willner, P. Antidepressants and serotonergic neurotransmission: An integrative review. Psychopharmacology (Berl.) 85:387–404; 1985.