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Anxiolytic-Like Effect of Paroxetine in a Rat Social Interaction Test

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LIGHTOWLER, S., G. A. KENNETT, I. J. R. WILLIAMSON, T. P. BLACKBURN AND I. F. TULLOCH. *Anxiolytic-like effect of paroxetine in a rat social interaction test.* PHARMACOL BIOCHEM BEHAV **49**(2) 281–285, 1994.– The effects of short- and long-term administration of the selective serotonin reuptake inhibitor paroxetine were investigated in a rat social interaction test. A single administration of paroxetine at oral doses of 0.3, 1, 3 and 10 mg/kg had no effect on social interaction between pairs of male rats under bright light (high anxiety) conditions. After 21 days of daily administration, paroxetine given orally at 3 mg/kg significantly ($p < 0.01$) increased the time spent in social interaction by pairs of rats tested under the same conditions, with no effect on locomotor activity, indicating an anxiolytic-like effect. The magnitude of increase (+97%) was comparable to that seen after a single dose of chlordiazepoxide (4 mg/kg orally). Although there was also an increase in time spent in social interaction after 21 days of repeated oral administration of paroxetine at 0.3, 1, and 10 mg/kg (+44, +56, and +54% increases, respectively), statistical significance was not achieved. These results indicate that in the long term paroxetine has an anxiolytic action, and thus support the clinical evidence for its therapeutic use in the treatment of anxiety disorders in addition to its established role as an antidepressant.

Paroxetine Antidepressant Anxiolytic Social interaction model Rat

PAROXETINE is a highly selective serotonin reuptake inhibitor (SSRI) with antidepressant properties (2,37,39). There is clinical evidence that paroxetine possesses an anxiolytic action in addition to its established antidepressant effect. For example, in controlled clinical trials in patients with mixed anxiety and depression, it has been reported that paroxetine relieves the anxiety component as well as the depressive symptoms (10, 12,13,26). In addition, there is evidence that other members of this class of drug, such as fluoxetine, sertraline, and fluvoxamine, are effective in the treatment of panic and obsessive compulsive anxiety disorders (18,27).

Despite these clinical observations there is little evidence in support of an anxiolytic effect for paroxetine, or indeed other SSRIs, from animal model studies. Paroxetine and the SSRIs sertraline, fluoxetine, fluovoxamine, and citalopram reduce marble-burying behavior in mice (5,34), and paroxetine and citalopram suppress high-frequency vocalization in isolated rat pups (40), effects that may indicate anxiolysis. However, in both tests the activity was seen after a single dose, which contrasts with clinical observations of a delay in anxiolysis. Furthermore, as shown by the effects of other drugs, activity in these tests does not always correlate with an anxiolytic effect clinically. For example, diazepam (a benzodiazepine anxiolytic) reduces mouse marble burying at moderate doses (1–5 mg/kg) but increases it at lower doses (0.1 mg/kg intraperitoneally [IP]) (33), and burying is reduced by 1-(3-chlorophenyl)-piperazine (mCPP) (30), an anxiogenic (25,31). High-frequency vocalization is suppressed by clonidine (an anxiolytic in some populations) (20,28) in isolated rat pups older than 17 days, but is increased by the same drug in younger animals (22). Thus, the relevance of the effects of paroxetine, and the other SSRIs, in these two models to an anxiolytic action is equivocal. Indeed, tested briefly in a rat x-maze model, paroxetine has been reported to be anxiogenic (9), although a very high dose was used (50 mg/kg orally). Short-term paroxetine is inactive in a water lick conflict model of anxiety (35), but an anxiolytic effect was reported after a single dose of fluoxetine in a similar Vogel test (19). However, the fluoxetine-induced increase in punished drinking seen in this model may be due to its reported analgesic properties (30),

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and not a reduction in anxiety. Indeed, in the same study, short-term fluoxetine (1.25–10 mg/kg IP) was found to be anxiogenic in a rat x-maze test.

All of these studies examined the effects of SSRIs only given briefly. We therefore decided to investigate the effects of paroxetine after long-term as well as short-term administration in an attempt to mirror its clinical effects more closely. Recently, an anxiolytic-like effect was reported after repeated paroxetine dosing in a rat x-maze test (7), a result that may reflect clinical observations. We have investigated the short- and long-term effects of paroxetine in another test of anxiety—the social interaction test, which has been validated physiologically and behaviorally, as well as pharmacologically (14). Preliminary findings from this study have been published elsewhere in abstract form (29).

METHODS

Animals

Male Sprague-Dawley rats (Charles River), weighing approximately 300 g, were housed singly for 5 days before behavioral testing and were allowed free access to food and water. The lights were on in the animal house from 0700 to 1900 h.

Apparatus

The social interaction test arenas were white perspex boxes 54 (width) × 36 (depth) × 29 (height) cm, with a solid floor and a transparent front; the level of light measured on the base of the arena was 240 radiometric lx. The base of the arena was marked by 24 9 × 9 cm squares. An electric fan was switched on in the experimental room to provide constant background noise. A camera was mounted above and to the front of the arena, and the social behavior of the rats was scored by two independent observers from a monitor in an adjacent room. The observers recorded the duration of behavior on a keyboard that fed directly into a microcomputer. All of the experiments were videotaped.

Drugs

Paroxetine (SmithKline Beecham) and chlordiazepoxide (CDP) (Sigma) were administered in 1% methyl cellulose with water to give a constant oral injection volume of 1 ml/kg.

Procedure

The rats were allocated to test pairs on the basis of weight; in all experiments 11–12 pairs were randomly allocated to each drug group. Both members of a pair always received the same drug treatment. Pairs of rats were tested between 0900 and 1700 h. The rats were placed in the test arena under high light and unfamiliar conditions for a 15-min trial, and the following behaviors were scored as active social interaction: sniffing, nipping, following, grooming, kicking, boxing, wrestling, mounting, and jumping on or crawling under or over each other. The number of line crossings made by each animal was also counted for a measure of general motor activity. At the end of each trial the arena was wiped with a damp cloth.

Short-term test. The effects of a single dose of paroxetine were assessed at doses of 0.3, 1, 3, and 10 mg/kg with CDP (4 mg/kg) as a positive control. The animals' behavior was assessed 1 h after dosing. This part of the study was carried out over five experiments, and the results have been combined. Animals from the vehicle, 3 mg/kg paroxetine, and CDP dose groups were tested in each experiment. Animals from the 0.3, 1, and 10 mg/kg paroxetine dose groups were tested in three of five experiments.

Long-term test. Experiments were carried out 1 h after the last of 21 days of once-daily administration of paroxetine at doses of 0.3, 1, 3, and 10 mg/kg. As a positive control, animals were dosed over a long period with vehicle for 20 days and were tested 1 h after receiving CDP (4 mg/kg). This test was carried out over nine experiments. Animals from the vehicle, 1, 3, and 10 mg/kg paroxetine, and CDP dose groups were tested in each experiment. Animals from the 0.3 mg/kg paroxetine dose group were tested in three of nine experiments.

Statistics

The results were analyzed by Dunnett multiple comparison *t*-test after a significant one-way analysis of variance.

RESULTS

Social Interaction

Acute paroxetine test. When tested 1 h after a single dose, there was a significant drug effect on social interaction, as revealed by one-way analysis of variance [$F(5, 138) = 4.02$, $p < 0.01$]. A single dose of paroxetine had no effect on social interaction at any of the doses tested (Fig. 1). In the same experiment the positive control, CDP (4 mg/kg), significantly ($p < 0.01$) increased social interaction, indicating an anxiolytic effect.

Chronic paroxetine test. When tested 1 h after the last of 21 daily doses, there was also a significant drug effect on social interaction, as revealed by one-way analysis of variance [$F(5, 136) = 3.15$, $p < 0.05$]. Paroxetine at 3 mg/kg caused a significant ($p < 0.01$), anxiolytic-like increase in social interaction (Fig. 2). There was also an increase in social interaction in rats that received paroxetine at 0.3, 1, and 10 mg/kg (+44, +56 and +54%, respectively), although it was not

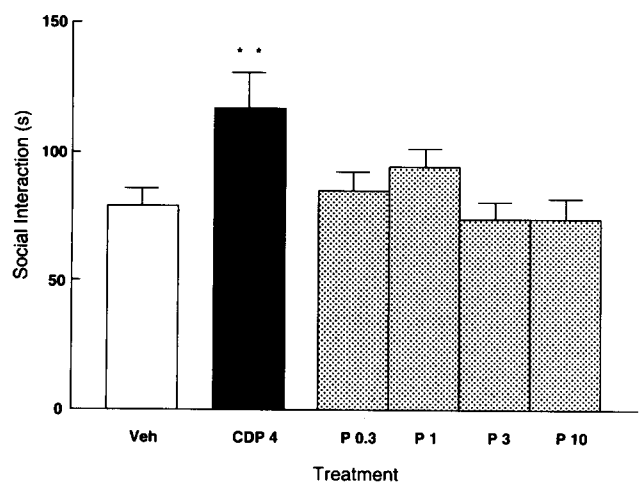

FIG. 1. Mean time spent in active social interaction 1 h after a single dose of paroxetine (0.3, 1, 3, or 10 mg/kg orally) or CDP (4 mg/kg orally): $^{**}p < 0.01$ different from vehicle-dosed animals by Dunnett's test. Veh, vehicle; CDP 4, chlordiazepoxide 4 mg/kg; P 0.3, paroxetine 0.3 mg/kg; P 1, paroxetine 1 mg/kg; P 3, paroxetine 3 mg/kg; P 10, paroxetine 10 mg/kg. Verticle bars represent SEM.

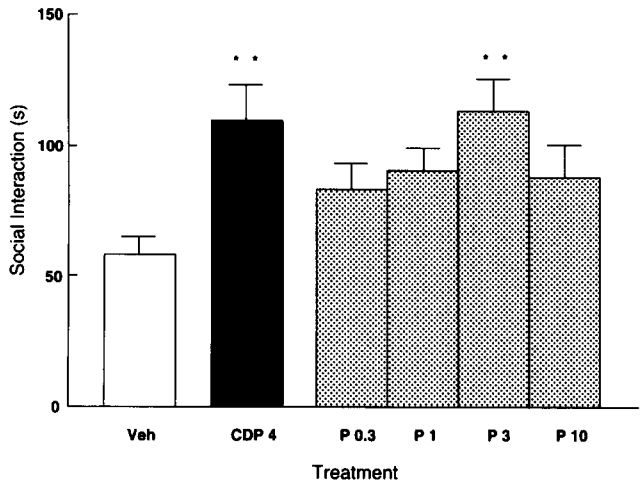

FIG. 2. Mean time spent in active social interaction 1 h after the last of 21 daily doses of paroxetine (0.3, 1, 3, or 10 mg/kg orally) or 20 daily doses of vehicle and a single dose of chlordiazepoxide (CDP; 4 mg/kg orally) on the test day: $^{**}p < 0.01$ different from vehicle-dosed animals by Dunnett's test. Veh, vehicle; CDP 4, chlordiazepoxide 4 mg/kg; P 0.3, paroxetine 0.3 mg/kg; P 1, paroxetine 1 mg/kg; P 3, paroxetine 3 mg/kg; P 10, paroxetine 10 mg/kg. Vertical bars represent SEM.

significant. The +97% increase in social interaction produced by paroxetine at 3 mg/kg was similar to that seen for the positive control (+89%), acute CDP (4 mg/kg).

Locomotion

No effects on locomotion were detected in either the short- or long-term tests after any drug treatment, when compared with vehicle-dosed animals (Table 1). However, the number of line crossings made after long-term dosing tended to be lower than after short-term administration. This is true for the vehicle-treated as well as the paroxetine-dosed animals, with the reduction ranging from 6–30%.

DISCUSSION

Given for a short period, paroxetine lacks anxiolytic activity in the rat social interaction test of anxiety. Given repeatedly for 21 days, paroxetine had no effect on locomotion and caused an anxiolytic-like increase in social interaction at each dose tested (0.3, 1, 3, and 10 mg/kg orally), with a significant effect seen only after the 3 mg/kg dose.

As an illustration of pharmacologic activity for paroxetine over the dose range used in this study, it has previously been shown that the 5-HT synthesis rate is not significantly affected by short-term paroxetine orally at 0.3 and 1 mg/kg in specific rat brain regions, but is significantly and dose-dependently reduced by oral doses of 3, 10, and 30 mg/kg. (4). This indicates a dose-dependent inhibition of 5-HT reuptake, with a submaximal inhibition occurring at 3 mg/kg.

It is possible that the increases in social interaction produced by long-term paroxetine and short-term chlordiazepoxide in this study were due to effects on predominantly different behaviors. Because the behaviors measured have not been scored individually it is not possible to say whether this is the case. Whichever interacting behaviors are increased by each treatment, it is likely that they were ones that would otherwise have been suppressed by the induction of anxiety by the novel, aversive environment. Thus, the observed increases in overall activity are most probably indicative of drug-induced anxiolysis.

This is the first report of an SSRI possessing anxiolytic activity in the social interaction model of anxiety. A previous investigation of the effects of short- and long-term uses of clomipramine (a tricyclic antidepressant selective for the inhibition of serotonin reuptake) in a similar social interaction test failed to demonstrate any effect (15). However, in the former study the duration of dosing was not as long (14 days) and clomipramine was tested over a limited dose range (3 and 10 mg/kg IP). Furthermore, the animals were observed for only 7.5 min under familiar and unfamiliar low-light conditions. Under unfamiliar conditions, rats are less anxious in dim than in bright light (14), and the effect of drug-induced anxiolysis is smaller (16). Rats are less anxious under familiar than unfamiliar conditions with little difference between dim and bright light (16). Of numerous anxiolytics tested under familiar conditions, whether brightly or dimly lit, only phenobarbitone has been shown to increase social interaction (17). Thus, it is less likely for an anxiolytic effect to have been detected under the conditions used in the investigation of clomipramine than under those used in our study.

A surprising finding from our study is that the locomotor activity of the animals dosed over a long period was somewhat lower than those briefly dosed (Table 1). This is the case for the vehicle- as well as the paroxetine-dosed animals, indicating that it is due to a nonspecific effect of long-term dosing and/or the increased handling involved with dosing. Also, the animals that were dosed for a long time with vehicle interacted slightly less than those dosed briefly. A recent report demon-

TABLE 1

MEAN ± SEM OF LINE CROSSINGS MADE 1 H AFTER 1 OR 21 DAILY DOSES OF PAROXETINE (0.3, 1, 3, 10 MG/KG ORALLY) OR A SINGLE DOSE OF CDP (4 MG/KG ORALLY) IN NAIVE OR 20-DAY VEHICLE-DOSED RATS

Duration of Paroxetine Dosing	Vehicle	CDP (4 mg/kg)	Paroxetine			
			0.3 mg/kg	1 mg/kg	3 mg/kg	10 mg/kg
1 day	338 ± 21	343 ± 20	332 ± 14	311 ± 18	317 ± 19	292 ± 21
21 days	269 ± 19	269 ± 22*	231 ± 21	279 ± 23	298 ± 24	246 ± 17

No significant differences were found. *Animals were dosed for 20 days with vehicle and received a single dose of CDP on the test day.

strated that the handling history of rats modifies their behavioral effects and consequently drug-induced behavioral effects in a rat x-maze model of anxiety (1). The authors of the former study reported that handling habituation had an anxiolytic effect and allowed the detection of drug-induced anxiogenesis, whereas a reduced control baseline in unhandled animals allowed the detection of drug-induced anxiolysis. In our study a slight reduction in social interaction was observed after repeated dosing, and hence more handled animals, which is opposite to the anxiolytic effect seen in the former study, and which may have helped in revealing the long-term paroxetine-induced anxiolysis. Therefore, it is possible that anxiolysis did occur in animals briefly dosed with paroxetine, but was not detected because unhandled animals were used. However, this is unlikely because the conditions used still allowed detection of the anxiolytic positive control.

The anxiolysis induced over a long period observed in this study substantiates findings from a rat x-maze test (7) and clinical observations (10,12,13,26), and is presumably due to adaptive changes. The mechanism of action of the psychological effects of repeated SSRI administration is unknown. Repeated paroxetine administration is known to cause a downregulation of postsynaptic cortical 5-HT_{2A} receptors (32). In contrast, more recently, it has been demonstrated that long-term administration of paroxetine enhances 5-HT_{2A} receptor function in the cerebral cortex of the guinea pig (6), although the relevance of these findings to effects on anxiety is questionable because drugs that selectively antagonize 5-HT_{2A} receptors have no effect in animal models of anxiety (23,24). Long-term use of paroxetine also downregulates the function of presynaptic 5-HT_{1B} autoreceptors on pyramidal neurones of the hippocampus in rats (8). Whether this change contributes in any way to the anxiolytic effect of paroxetine remains to be determined. Postsynaptic 5-HT receptors that may show adaptive changes and that have been implicated in anxiety include 5-HT_{2C} (25) and 5-HT_3 (11,21,36). If downregulation of a postsynaptic "anxiogenic" 5-HT receptor subtype(s) is required for a delayed anxiolytic effect, SSRIs might be expected to increase anxiety upon brief administration. However, in this study the animals were tested under conditions in which basal anxiety levels were high and a further increase in anxiety was difficult to detect. On the other hand, it might be that short-term SSRI administration causes a preferential activation of inhibitory somatodendritic autoreceptors (38), leading to no significant enhancement of neurotransmission at low, but pharmacologically active, doses, and hence no anxiogenesis. A desensitization of autoreceptor function with long-term administration (3) leading to a net increase in 5-HT release and a downregulation of postsynaptic "anxiogenic" receptors may then occur, leading to anxiolysis. Clearly, the development of more selective pharmacologic tools should help in determining which of the adaptive changes, proven and possible, produced by SSRIs are important in producing their long-term effects.

The results from this study indicate that long-term use of paroxetine has an anxiolytic action, and thus support the clinical evidence for its therapeutic use in the treatment of anxiety disorders in addition to its established role as an antidepressant.

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