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Behavioural Effects in Mice of Subchronic Chlordiazepoxide, Maprotiline, and Fluvoxamine. I. Social Interactions

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CUTLER, M. G., R. J. RODGERS AND J. E. JACKSON. *Behavioral effects in mice of subchronic chlordiazepoxide, maprotlinine and fluvoxamine I: Social interactions.* PHARMACOL BIOCHEM BEHAV **57**(1/2) 119–125, 1997.—The present study compares the effects of subchronic administration (daily, 21 days) of chlordiazepoxide (CD), maprotiline and fluvoamine on the behavior of male mice during dyadic social interactions. Maprotiline, like chlordiazepoxide, stimulated aggression at 4 mg/kg and 2 mg/kg respectively (intermediate dose levels), whereas effects of fluvoxamine (3–8 mg/kg) were mainly sedative. Non-social activity was reduced by CD at 4 and 8 mg/kg and by maprotiline at 0.5 mg/kg. At the highest dose tested (10 mg/kg), maprotiline increased immobility, resembling the effects of fluovoxamine, while at 2 mg/kg, it reduced social investigation. Thus, despite some commonalities, there were several differences in behavioral profile of the compounds tested. Data are discussed in relation to the efficacy of each of these compounds in treating anxiety and depressive disorders. © 1997 Elsevier Science Inc.

Social Behavior Anxiolytics Antidepressants Chlordiazepoxide/Maprotiline Fluvoxamine Mice

ANXIETY and depression are the most frequent of the stress-related disorders in modern society (41) and generally are treated by pharmacological intervention. Reports from clinical studies that antidepressant agents can be effective in treating anxiety and that a range of anxiolytic agents possess antidepressant efficacy (9,27,37,42,48) suggests that there may be a potential underlying commonality between these conditions. Indeed, the interrelationship between anxiety and depression has engendered much debate throughout the past century (27), relating in part to the high degree of symptom overlap and in part to the absence of a clear therapeutic demarcation. For example, panic disorder can be successfully treated with monoamine oxidase inhibitors and tricyclic antidepressants (3,38,46).

If there is such a commonality in the mechanisms underlying anxiety and depression, this would pose distinct problems for basic research. At present, very different and highly specific animal models have been developed for the detection of anxiolytic and antidepressant efficacy (44,47). Thus, if these disorders lack the full specificity often ascribed to them, there is a clear need for more extensive laboratory studies to examine more fully the effects of these agents on the spontaneous behavior of animals. Furthermore, in view of clinical patterns, it is of obvious importance to examine the effects of treatment following chronic, rather than acute, administration.

Earlier experiments have shown that ethopharmacological methods of behavioral analysis are highly sensitive, giving detailed information on all behaviors displayed in a given test, thus providing reproducible, dose-related, and comprehensive drug profiles (6,11,12,13,15,22,23). These experiments included assessment of effects of the antidepressants, imipramine, mianserin, and phenelzine, which induced diverse effects on behavior of the CD-1 mice used. In contrast, the anxiolytics tested in a similar test environment showed many similarities in their behavioral actions (12). The ethopharmacological method draws on powerful techniques with which to measure drug effects on the whole range of spontaneously occurring acts and postures in an animal's behavioral repertoire (15).

These experiments thus provide more detail than the simple tests measuring drug effects on anxiety and depression. Indeed, in several rodent models of anxiety, antidepressant drugs have been found to be devoid of anxiolytic efficacy.

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TABLE 1

EFFECTS OF SUBCHRONIC TREATMENT (21 DAYS) WITH CHLORDIAZEPOXIDE (CD) ON THE FREQUENCY AND DURATION OF MAJOR CATEGORIES OF BEHAVIOUR SHOWN BY MICE DURING SOCIAL ENCOUNTERS

Group dose (*n*)	Injected controls (35)	CD-treated (mg/kg daily) 1.0 (15)	4.0 (18)	8.0 (15)
	Mean frequency (± S.E.)			
Non-social activity	128.3 ± 6.9	120.3 ± 7.4	102.5 ± 8.5*	103.2 ± 8.1*
Social investigation	50.6 ± 4.7	49.1 ± 3.9	48.2 ± 5.4	52.4 ± 4.0
Aggression	18.2 ± 7.1	25.0 ± 10.1	53.5 ± 15.9*	4.2 ± 0.5
Flight	0.1 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.1
Immobility	0.1 ± 0.1	0.1 ± 0.1	0.2 ± 0.2	0.8 ± 0.4
	Mean duration (s) (± S.E.)			
Non-social activity	228.7 ± 6.2	222.2 ± 8.5	175.0 ± 13.1**	212.1 ± 11.2
Social investigation	62.5 ± 5.8	64.5 ± 6.1	69.3 ± 8.4	76.8 ± 6.0
Aggression	11.8 ± 4.2	17.7 ± 6.8	46.3 ± 12.5**	5.2 ± 2.9
Flight	0.1 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	0.2 ± 0.2
Immobility	0.1 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	0.2 ± 0.2

*$p < 0.05$, **$p < 0.01$, between drug-treated and control mice by the Kruskal–Wallis and Mann–Whitney *U*-tests.

Negative findings have been reported for antidepressants tested in the potentiated startle paradigm (26), the light/dark exploration model (10,53), conflict/conditioned suppression tasks (20,30), and in separation-induced ultrasonic vocalization (49). In contrast, anxiolytic-like effects have been observed in a range of animal models when antidepressants have been given by chronic administration rather than as a single dosage (4,5,20,21,24,35).

The present study uses ethopharmacological procedures to compare the effects upon behavior induced by subchronic treatment with a standard anxiolytic agent (chlordiazepoxide) (18) with those of two antidepressants, maprotiline (a noradrenaline selective reuptake inhibitor) (40), and fluvoxamine (a 5-HT selective reuptake inhibitor) (28,51). A companion article presents data from a parallel study using the elevated plus-maze (45). The behavioral responsiveness of rodents to drugs is known to be strain-dependent (17,31,44), and mice of the CD-1 strain are used in the current study because of their demonstrated sensitivity to the effects of anxiolytic and antidepressant drugs (12,22,23).

METHODS

Animals

Adult male CD-1 mice (Charles River), weighing 23–45 g, were used in these studies. Animals were housed in groups of 10 or 11 (cage size: 45 × 28 × 13 cm) for 3 weeks and then were pair-housed (cage size: 30 × 13 × 10 cm) for 10–14 days prior to the experiments. All animals were maintained in a temperature and humidity controlled environment (21 ± 2°C, 52 ± 2% respectively) under a 12 h reversed light cycle (lights off at 0600 h). Testing was conducted under dim white light (60 W) during the dark phase. All mice received an ad libitum supply of water and pelleted stock cubes (SDS, Weltham, Essex), except during the brief test sessions.

Drugs

Drugs used were chlordiazepoxide hydrochloride (Sigma, UK), fluvoxamine maleate (SmithKline Beecham, UK) and maprotiline hydrochloride (Sigma UK). Drugs were dissolved in physiological saline, which served for control injections in these studies. Compounds were administered by intraperitoneal injection in a volume of 1 ml/300 g once a day for a period of 21 days, and on the last dosing day (day 21) were given at 30 min prior to testing.

Experimental Procedures

Animals were randomly assigned to 1 of 11 treatment conditions; uninjected control ($n = 16$), saline injected control ($n = 35$), chlordiazepoxide injected (1.0, 4.0, or 8.0 mg/kg daily, $n = 15$–18), maprotiline injected (0.5, 2.0, or 10.0 mg/kg daily, $n = 16$), or fluvoxamine injected (2.0, 4.0, or 8.0 mg/kg daily, $n = 16$).

Ethopharmacological procedures used in previous studies (22) were used to assess the behavioral responsiveness of experimental mice when engaged in 5 min social encounters in a neutral cage (60 × 25 × 25 cm) with an untreated group-housed unfamiliar DBA/2 male partner. Behavior during these 5 min social interactions was recorded on audiotape as a spoken commentary and was simultaneously recorded on videotape.

Behavioral Analysis and Statistics

For analysis, by computer, of the frequency and duration of each behavioral element and category, the spoken commentaries from drug-treated mice and their controls were transcribed onto a floppy disk through direct keyboard input. The categories of behavior comprised non-social activity, social investigation, aggression, flight, and immobility (22).

Data are presented as the means (± SEM) for each group, and the probability values for the significance of differences

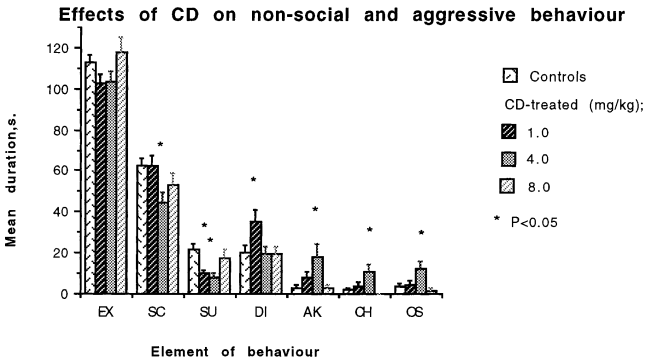

FIG. 1. Effects of subchronic treatment with chlordiazepoxide (CD) on non-social and aggressive behavior in male mice. Data are presented as mean values (duration ± SEM). EX = explore; SC = scan; SU = substrate investigation; DI = dig; AK = attack; CH = chase; OS = offensive sideways posture.

between drug-treated and control groups have been determined by the non-parametric Kruskal–Wallis one-way analysis of variance (ANOVA) and the pair-wise Mann–Whitney *U*-tests.

RESULTS

Chlordiazepoxide

The main effects of chlordiazepoxide (CD) on behavior of the mice occurred at the intermediate dose of 4 mg/kg (Table 1). At this dose, aggressive behavior was increased in frequency and duration whereas non-social activity was reduced. At the higher dose of 8 mg/kg, treatment with CD decreased the frequency but not the duration of non-social activity.

As shown in Fig. 1, the aggressive elements, ''attack/bite'' (AK), ''chase'' (CH), and ''offensive sideways posture'' (OS), as well as the non-social act of ''digging'' (DI), were increased in duration in mice given CD at 4 mg/kg. The time spent in ''scanning'' (SC) was reduced after treatment with CD at 4 mg/kg and ''substrate investigation'' (SU) was decreased by CD at both 1.0 mg/kg and 4 mg/kg.

Additionally, ''exploration'' (EX) was decreased in frequency by CD at 4 and 8 mg/kg (mean frequency ± SE; controls 60.9 ± 2.5; treated; 4.0 mg/kg 49.9 ± 3.2, $p < 0.05$; 8.0 mg/kg 47.8 ± 4.2, $p < 0.01$) although there wre no significant changes to its duration. At 1.0 mg/kg, CD reduced the duration of ''stretch-attend.'' (mean durations ± S.E. controls 2.5 ± 0.4; treated 1.5 ± 0.6, $p < 0.05$).

The only significant effect of CD on social investigation was to increase the duration of ''nose-to-nose contact'' (NO) after drug administration at 8.0 mg/kg (mean durations ± S.E.; controls 17.9 ± 1; CD-treated 26.1 ± 3.8, $p < 0.05$).

Maprotiline

As shown in Table 2, treatment with maprotiline at 2 mg/kg increased aggressive behavior and decreased social investigation (both frequency and duration). The frequency of non-social activity was reduced by maprotiline at 0.5 mg/kg and the duration of immobility was raised in mice given the drug at 10 mg/kg.

Figure 2 shows that the enhancement of aggressive behavior by maprotiline at 2 mg/kg was associated with increased duration of the acts AK and CH. The duration of OS and of DI also showed an increase, but this just failed to reach an acceptable level of statistical significance. However, the duration of DI was significantly raised in mice treated with maprotiline at 0.5 mg/kg.

The reduction of social investigation by maprotiline at 2 mg/kg involved significant decreases in duration of the acts, NO and ''investigate'' (IN). The duration of IN was also decreased in animals treated with maprotiline at 0.5 and 10.0 mg/kg.

TABLE 2

EFFECTS OF SUBCHRONIC TREATMENT (21 DAYS) WITH MAPROTILINE THE FREQUENCY AND DURATION OF MAJOR CATEGORIES OF BEHAVIOUR SHOWN BY MICE DURING SOCIAL ENCOUNTERS

Group dose (*n*)	Injected controls (35)	Maprotiline-treated (mg/kg daily) 0.5 (16)	2.0 (16)	10.0 (16)
	Mean frequency (± S.E.)			
Non-social activity	128.3 ± 6.9	98.9 ± 7.1*	119.2 ± 5.0	108.7 ± 6.9
Social investigation	50.6 ± 4.7	50.0 ± 3.0	35.6 ± 3.1*	52.1 ± 4.6
Aggression	18.2 ± 7.1	30.5 ± 9.9	54.3 ± 11.9**	4.8 ± 2.8
Flight	0.1 ± 0.1	0.0 ± 0.0	0.1 ± 0.1	0.1 ± 0.1
Immobility	0.1 ± 0.1	0.0 ± 0.0	0.6 ± 0.4	1.9 ± 1.0
	Mean duration (s) (± S.E.)			
Non-social activity	228.7 ± 6.2	219.0 ± 5.4	225.3 ± 3.1	228.1 ± 8.0
Social investigation	62.5 ± 5.8	68.0 ± 5.6	42.5 ± 3.9*	68.1 ± 6.9
Aggression	11.8 ± 4.2	18.0 ± 5.3	32.6 ± 6.7**	4.0 ± 2.3
Flight	0.1 ± 0.1	0.0 ± 0.0	0.1 ± 0.1	0.3 ± 0.3
Immobility	0.1 ± 0.1	0.0 ± 0.0	2.1 ± 1.8	4.8 ± 2.9*

*$p < 0.05$, **$p < 0.01$, between drug-treated and control mice by the Kruskal–Wallis and Mann–Whitney *U*-tests.

TABLE 3

EFFECTS OF SUBCHRONIC TREATMENT (21 DAYS) WITH FLUVOXAMINE THE FREQUENCY AND DURATION OF MAJOR CATEGORIES OF BEHAVIOUR SHOWN BY MICE DURING SOCIAL ENCOUNTERS

Group dose (*n*)	Injected controls (35)	Fluvoxamine-treated (mg/kg daily) 2.0 (16)	4.0 (16)	8.0 (16)
	Mean frequency (± S.E.)			
Non-social activity	128.3 ± 6.9	115.2 ± 8.2	112.4 ± 6.2	108.3 ± 4.7
Social investigation	50.6 ± 4.7	48.8 ± 4.1	55.6 ± 5.9	52.3 ± 4.7
Aggression	18.2 ± 7.1	13.6 ± 5.6	1.7 ± 0.9	3.1 ± 1.5
Flight	0.1 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	0.4 ± 0.4
Immobility	0.1 ± 0.1	1.4 ± 0.7**	0.1 ± 0.1	0.6 ± 0.2
	Mean duration (s) (± S.E.)			
Non-social activity	228.7 ± 6.2	228.4 ± 5.1	229.2 ± 8.9	227.8 ± 8.1
Social investigation	62.5 ± 5.8	57.6 ± 3.7	73.2 ± 8.7	70.5 ± 7.5
Aggression	11.8 ± 4.2	10.4 ± 3.8	1.7 ± 0.7	3.6 ± 1.5
Flight	0.1 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	0.9 ± 0.8
Immobility	0.1 ± 0.1	7.7 ± 5.1*	0.1 ± 0.1	1.1 ± 0.4

*$p < 0.05$, **$p < 0.01$, between drug-treated and control mice by the Kruskal–Wallis and Mann–Whitney *U*-tests.

Other effects of maprotiline on the elements of behavior included reduction in the frequency of EX when given at 2 and 10 mg/kg (mean ± S.E.; controls 68.9 ± 1.5; treated, 2 mg/kg, 49.6 ± 2.3, $p < 0.01$; mg/kg, 47.9 ± 3.1, $p < 0.01$) and decrease in the frequency of ''scanning'' after maprotiline administration at 2 mg/kg, (mean ± S.E.; controls 43.4 ± 2.5; treated 33.2 ± 2.0, $p < 0.05$).

Fluvoxamine

Fluvoxamine at 2.0 mg/kg increased the frequency and duration of immobility (Table 3). At 4 mg/kg, it suppressed aggressive behavior to a level that was close to statistical significance ($p < 0.05$).

Figure 3 illustrates the few significant effects of fluvoxamine on elements of behavior. These involved an increase in the duration of EX after fluvoxamine administration at 8.0 mg/kg and a reduction of SU when this drug had been given at 4.0 mg/kg.

Behaviour of Saline-Injected (SAL) Versus Non-Injected Controls (CO)

CO spent more time in the acts ''wash and self-groom'' ($p < 0.05$) than SAL (mean ± S.E.; SAL 3.2 ± 0.5, CO 2.0 ± 0.4; $p < 0.05$). There were no other significant differences in behavior between these two control groups.

DISCUSSION

These experiments have compared the effects on social behavior of CD-1 mice following subchronic administration

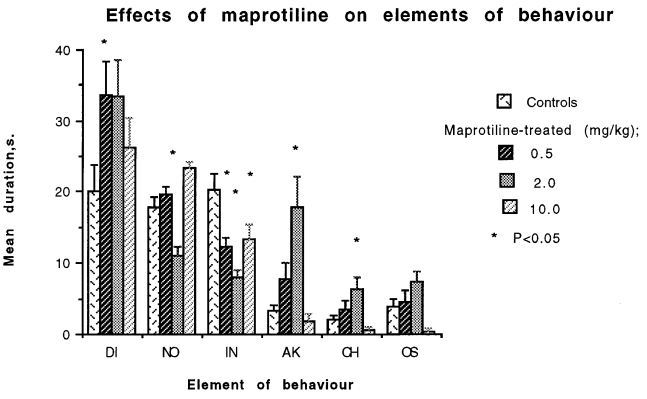

FIG. 2. Effects of subchronic treatment with maprotiline on elements of behavior in male mice. Data are presented as mean values (duration ± SEM). DI = dig; NO = nose; IN = investigate; AK = attack; CH = chase; OS = offensive sideways posture.

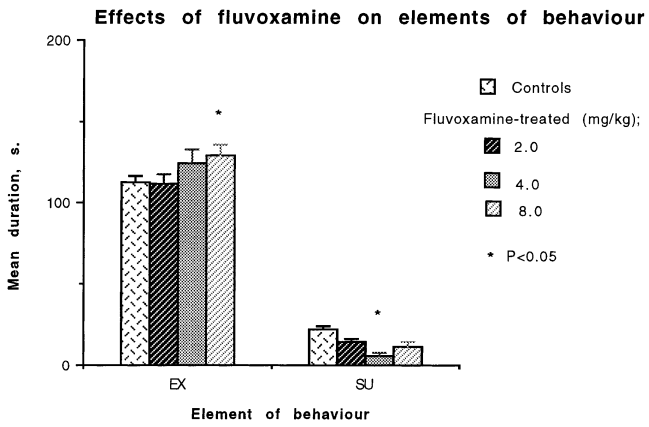

FIG. 3. Effects of subchronic treatment with fluvoxamine on elements of behavior of behavior in male mice. Data are presented as mean values (duration ± SEM). EX = explore; SU = substrate investigation.

of a traditional anxiolytic (chlordiazepoxide), a NA-selective reuptake inhibitor (maprotiline) and a 5-HT selective reuptake inhibitor (fluvoxamine). The experiments have also examined the behavioral effects induced by daily handling and injection of the mice. The results demonstrated that there were minimal changes to behavior after this handling of the animals.

It was found that administration of chlordiazepoxide (4.0 mg/kg) and maprotiline (2 mg/kg) for 21 days increased aggression by the mice. This effect may represent an increase of dominant behavior by the animals (14). There was no enhancement of aggression by treatment of the mice with fluvoxamine. The increase of aggression in male rodents following chronic treatment with benzodiazepines, (as occurred in the present studies), is a frequent finding (31,43,44). Acute administration of benzodiazepines also can increase aggressive behavior in some instances, (e.g., maternal aggression), although this effect would not appear to involve a specific action at benzodiazepine receptor sites (36,44,52). Nonetheless, benzodiazepines are also widely known to reduce aggressive behavior in animals and humans, especially after acute administration in situations characterized by defensive aggression (31,43,44). This latter effect probably involves interaction with benzodiazepine receptors. Maprotiline, like most antidepressants (31), has been found to reduce aggressive behavior after acute administration and to have the reverse effect when given chronically (40). Its enhancement of aggression in the present experiments, shows a resemblance to the effects of chlordiazepoxide. Indeed, there is some evidence that patients with anxious depression will respond favorably to maprotiline (39).

Both chlordiazepoxide and maprotiline, when given at smaller dose levels than those which increased aggressive behavior were found in the present experiments to increase digging of the unfamiliar sawdust. This may represent a state of behavioral unrest. Increased digging of the sawdust in a neutral cage has been noted after the administration of many anxiolytics to mice (12), and is thought to arise because unfamiliar sawdust is mildly aversive (2).

Chlordiazepoxide, as typifies a benzodiazepine (29), was characterized by sedative actions (decrease of non-social activity) when given at the higher doses of 4 and 8 mg/kg. Acute treatment with maprotiline is also associated with sedative action (40) and the present subchronic experiments show that it reduced activity of the mice at each of the dose levels tested (i.e., at 0.5 mg/kg, it reduced the frequency of exploration and scanning, at 2 mg/kg it reduce the frequency of social investigation and at 10 mg/kg it increased the duration of immobility). Additionally, at each of the tested doses, maprotiline reduced investigation of the partner's fur, perhaps reflecting an impairment of olfactory responsiveness.

The 5-HT reuptake inhibitor, fluvoxamine, showed a very different profile of behavioral action from that induced by chlordiazepoxide and maprotiline. Fluvoxamine induced the sedative effect of increased immobility at 2 mg/kg, while at 4 mg/kg it reduced substrate investigation, and at 8 mg/kg increased the duration but not the frequency of non-social exploratory activity (an effect indicative of perseveration). Fluvoxamine had no effect on aggressive behavior in the present studies and Duncan et al. (16) and Rodgers et al. (45) reported it to be without effect in the elevated plus-maze, although Alder and Morinan (1) had found it to have an anxiolytic profile of action. Fluvoxamine is known to be effective in the treatment of certain anxiety disorders as well as in depression (14,28,51) and is reported to be neither sedative nor stimulating (8).

In rodents, the related 5-HT re-uptake inhibitor, fluoxetine, showed a different profile of behavioral action, in that it increased aggressive behavior after chronic administration and suppressed aggression when it had been given acutely, as did a range of other anxiolytic/antidepressant agents (7,33,34). The current findings may in part arise from a species difference in 5-HT functioning (32,44). Alternatively, they could be due to differences in the behavioral effects of different antidepressants, such as fluoxetine and fluvoxamine (25).

It has, for many years, been assumed that non-adrenergic reuptake blockers would be of particular value in treating retarded depression, whereas those which act mainly on 5-HT mechanisms would be more beneficial in agitated/anxious depression (7,19,51). The SSRIs are effective in treating panic disorder but not in the control of generalized anxiety disorder (3,14,50).

In summary, the present findings thus show several similarities between the behavioral effects in mice of maprotiline (an inhibitor of noradrenaline reuptake) and chlordiazepoxide (an anxiolytic acting at benzodiazepine receptor sites), and a major difference from the effects induced by the serotonin reuptake inhibitor (SSRI), fluvoxamine. Not only do these findings bear close resemblance to those obtained in our parallel study in which mice were tested in the elevated plus-maze (45), but also indicate that there is a correlation between effects of drugs acting at noradrenaline and benzodiazepine receptors. It appears that the present situation of behavioral testing provides a sensitive measure for detecting agents that are effective in the management of generalized anxiety disorder. The negative findings with fluvoxamine (an established panicolytic agent) indicates that a different test procedure is needed for the detection of panic-like responses. Finally, it is apparent that further research is needed to identify drugs which are selective for treating the different types of anxiety and depression.

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