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Behavioural Effects in Mice of Subchronic Buspirone, Ondansetron and Tianeptine. II. The Elevated Plus-Maze

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RODGERS, R. J., M. G. CUTLER AND J. E. JACKSON. *Behavioural effects in mice of subchronic buspirone, ondansetron and tianeptine. II. The elevated plus-maze.* PHARMACOL BIOCHEM BEHAV **56**(2) 295–303, 1997.—In follow-up to recent work on benzodiazepines (chlordiazepoxide) and selective monoamine reuptake inhibitors (maprotiline and fluvoxamine), the present study compares the effects of the 5-HT_{1A} receptor partial agonist, buspirone (0.75–3.0 mg/kg), the 5-HT_3 receptor antagonist, ondansetron (0.1–100 μg/kg), and the novel antidepressant, tianeptine (2.5–10.0 mg/kg), on the behaviour of mice in the elevated plus-maze test of anxiety. Compounds were administered daily for 21 days prior to testing, and an ethological scoring technique was used to generate comprehensive behavioural profiles. Results show that subchronic treatment with ondansetron failed to influence the behaviour of mice in the plus-maze, while the limited changes induced by buspirone could not be attributed to anxiety-related processes. In contrast, tianeptine produced unambiguous anxiogenic-like effects at the top dose tested (10.0 mg/kg), a profile that was not secondary to changes in general levels of locomotor activity or exploration. Data are discussed in relation to current pharmacotherapy of anxiety and depressive disorders, and the nature of anxiety induced by animal models. **Copyright © 1997 Elsevier Science Inc.**

Anxiety Plus-maze Anxiolytics Antidepressants Buspirone Ondansetron Tianeptine Animal models Mice

CURRENT views on the relationship between anxiety and depression emphasize considerable commonality in symptomatology, genetic risk factors and pharmacotherapy (37,43,54, 55,73). From the viewpoint of drug therapy, panic disorder has been successfully treated with both traditional (tricyclics and monoamine oxidase inhibitors (e.g., 55,56,62,69)) and novel (i.e. serotonin-selective reuptake inhibitors (SSRIs) (e.g., 3,21,42,58,74) antidepressant compounds. Conversely, recent evidence suggests that generalized anxiety disorder may respond just as well to imipramine treatment as to benzodiazepines (37,41,61,73). In view of these data, it is somewhat surprising that antidepressants have generally not produced positive profiles in animal models of anxiety. This applies equally well to tests based on conditioned responses (e.g., 26,36,44) as to those involving unconditioned responses (e.g., 8,13,16,22,28,48,59,74). Nevertheless, the potential clinical relevance of animal studies in this field is supported by the observation that acute antidepressant treatment (particularly SSRIs) can result in an enhancement of anxiety both in patients (3,55,75) and animals (5,7,31,32,35,57,60).

Clearly, one important difference between the clinical management of anxiety disorders and animal research concerns treatment duration. In this context, although some negative data have been reported (13,24,60), anxiolytic-like effects have been observed in several animal models following chronic treatment with both first- (e.g., imipramine, amitriptyline, phenelzine) and second- (e.g., mianserin, paroxetine) generation antidepressants (6,9,14,25–27,31,32,40,45,63). In view of this pattern of results, we have recently undertaken a large-scale study to compare the behavioural effects in mice of subchronic treatment with a range of antianxiety and antidepressant agents. In this work, we have employed two ethological models (social encounters, (e.g., 27); elevated plus-maze, (e.g., 68)) to generate comprehensive behavioural profiles of

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drug action. Using such methods, we have found distinct similarities (both models) in the behavioural profiles of chlordiazepoxide and the noradrenaline reuptake inhibitor, maprotiline, as well as major differences between these compounds and the SSRI, fluvoxamine (19,67).

In the present paper, we report a direct comparison of the subchronic effects of the novel 5-HT_{1A} anxiolytic, buspirone (70), the putative 5-HT_3 anxiolytic, ondansetron (29) and the atypical antidepressant, tianeptine (76), in the murine plus-maze. A companion paper (20) presents data from a parallel study using the murine social interaction test.

METHODS

Animals

Subjects were adult male CD1 mice (Charles River, U.K.), weighing 23–45g and housed in groups of 10 (cage size: 45 × 28 × 13 cm) for 3 weeks prior to the experiment. They were maintained under a reversed 12h LD cycle (lights off: 0700h) in a temperature (21 ± 1°C)- and humidity (50 + 5%)-controlled environment. Food and water were freely available. All mice were experimentally naive.

Drugs

Drugs used were buspirone hydrochloride (Sigma, U.K.), ondansetron hydrochloride (formerly GR38032F; Glaxo Group Research) and tianeptine (Servier, France). All compounds were dissolved in physiological saline and administered intraperitoneally in a volume of 1 ml/300 g. Injections were given once daily for 21 days, with the side of injection alternated to avoid peritoneal irritation. Non-injected controls were included in the design in order to assess the effect of chronic handling and injection.

Apparatus

The elevated plus-maze was a modification of that validated for NIH mice by Lister (48), and comprised two open arms (30 × 5 cm) and two enclosed arms (30 × 5 × 15 cm) which extended from a common central platform (5 × 5 cm). The configuration formed the shape of a plus-sign, with like arms arranged opposite one another, and the apparatus was elevated 60 cm above floor level on a central pedastel. The maze floor was made of black Plexiglas while the side- and end-walls of the enclosed arms were made from clear Plexiglas. As reported previously (10–13), grip on the open arms was facilitated by inclusion of a small raised edge (0.25 cm) around their perimeter and open arm activity was further encouraged by testing under dim red light (4 × 60 W indirect).

Experimental Procedure

Mice were randomly allocated to one of 11 treatment conditions (n = 7–16): uninjected control, saline, 0.75, 1.5 or 3.0 mg/kg buspirone, 0.1, 10.0 or 100.0 μg/kg ondansetron, or 2.5, 5.0 or 10.0 mg/kg tianeptine. Animals were tail-marked for individual recognition, and treated once daily for 21 days with final injections given 30 min prior to testing. All treatments and behavioural testing were performed during the dark period of the light-dark cycle when mice are normally most active (0930–1230h). To facilitate habituation, animals were transported to the laboratory from the holding room at least one hour before testing. 30 minutes following the final injection, animals were individually placed onto the central square of the maze facing an open arm. A 5 minute test duration was used and, between subjects, the maze was thoroughly cleaned with both damp and dry cloths. Test sessions were recorded by an overhead video camera linked to a monitor and video recorder in an adjacent room.

Behavioural Analysis

Videotapes were scored blind by a highly trained observer using ethological software ('Hindsight') developed in this laboratory by Scott Weiss. Using separate location and behaviour keys, this software permits the real-time scoring of acts and postures by direct keyboard entry to a PC. Data can then be collated by treatment condition and downloaded for statistical treatment. Both conventional and ethological parameters were recorded (68).

The conventional measures comprised: number of open and closed arm entries (arm entry defined as all four paws entering an arm) and time spent on different sections of the maze (including the central platform). The distribution of behaviour on the maze was calculated as 'percent total' for frequency (percent open entries; open/total × 100) and duration (percent time spent in open, centre & closed sections; e.g., open time/300 × 100). As pilot studies had indicated that CD1 mice show high levels of open arm entries compared with other strains (e.g., DBA/2 & T1, 10), entries into, and time spent on, the ends of the open arms (defined as distal half of open arm) were also recorded; from these values, percent scores for end-open entries (end-open entries/total × 100) and end-open time (end-open time/300 × 100) were derived.

In addition to the conventional measures, a range of behaviours (encompassing elements of the murine defensive repertoire) were recorded (68). These ethologically-derived acts and postures comprised rearing frequency and duration (all rearing occurred against the walls of the closed arms i.e. supported rearing); the frequency of discrete behaviours such a head-dipping (exploratory movement of head/shoulders over the sides of the maze) and stretched attend postures (SAP; an exploratory posture in which the mouse stretches forward and retracts to original position without locomoting forward); and the duration (s) of prolonged behaviours such as sniffing (olfactory exploration of maze floor and walls with occasional air-sampling), grooming (species-typical sequence beginning with snout, progressing to ears, and ending with whole-body groom), and flat-back approach behaviour (exploratory locomotion where the animal stretches to its full length and cautiously moves forward). It should be noted that control levels of closed arm returns, a measure normally recorded in studies with DBA/2 mice in our laboratory (e.g., 10–13), were extremely low in CD1 mice and were not therefore scored.

As thigmotactic cues play an important role in plus-maze exploration (72), head-dipping, stretched attend, sniffing, and flat back approach were further differentiated as a function of whereabouts on the maze they were performed. The closed arms and central platform were together designated protected areas of the maze (i.e. offering relative security), while the open arms were designated unprotected areas. Data for the above behavioural elements are therefore given as percent protected scores (%p; protected/total × 100) as well as behaviour totals. Finally, to complement the measurement of end-open entries and end-open time, the frequencies of end-open head-dips and end-open SAP were also recorded.

Statistical Analysis

Data were analysed by single factor (drug treatment) or two-factor (drug treatment × location; repeated measures on

TABLE 1

ANOVA SUMMARY STATISTICS FOR THE EFFECTS OF EXPERIMENTAL MANIPULATIONS (21-DAY HANDLING/ INJECTION; 21-DAY TREATMENT WITH BUSPIRONE, ONDANSETRON, TIANEPTINE) ON PLUS-MAZE BEHAVIOUR IN CD1 MICE

Variable	*F*	*p*
Total entries	0.53	N.S.
Open entries	0.66	N.S.
Closed entries	0.97	N.S.
Total rears	0.94	N.S.
% Open entries	1.14	N.S.
% End-open entries	0.91	N.S.
% Open arm time	2.22	0.03
% End-open time	1.77	N.S.
% Centre time	1.33	N.S.
% Closed arm time	1.27	N.S.
Total head-dips	3.36	0.001
End-open head-dips	2.45	0.01
Total SAP	1.53	N.S.
End-open SAP	2.55	0.009
Rearing duration(s)	1.00	N.S.
Sniff duration(s)	2.06	0.04
Grooming duration(s)	1.00	N.S.
Flat back approach duration(s)	0.78	N.S.
%p head-dips	1.51	N.S.
%p SAP	2.64	0.007
%p sniff	2.22	0.02
%p flat back approach	1.37	N.S.

SAP = stretched attend postures. Degrees of freedom = 10,103. N.S. = non-significant.

TABLE 2

THE EFFECTS OF DAILY HANDLING AND INJECTION (21 DAYS) ON THE BEHAVIOUR OF CD1 MICE IN THE ELEVATED PLUS-MAZE

Variable	Uninjected Control (n = 16)	Saline Control (n = 14)
Total entries	30.0 ± 1.5	30.4 ± 2.9
Open entries	17.9 ± 1.5	19.1 ± 2.6
Closed entries	12.1 ± 0.7	11.2 ± 0.8
Total rears	17.3 ± 1.9	18.5 ± 2.1
% Open entries	58.6 ± 2.8	59.1 ± 4.1
% End-open entries	22.9 ± 1.0	23.3 ± 2.7
% Open arm time	31.1 ± 2.3	34.7 ± 4.0
% End-open time	13.2 ± 1.0	15.8 ± 2.3
% Centre time	35.0 ± 2.9	28.6 ± 2.0
% Closed arm time	33.9 ± 2.2	36.7 ± 3.4
Total head-dips	14.3 ± 1.2	13.9 ± 2.0
End-open head-dips	4.0 ± 0.5	4.1 ± 0.9
Total SAP	9.0 ± 0.7	9.5 ± 0.7
End-open SAP	1.9 ± 0.2	3.0 ± 0.5
Rearing duration(s)	11.6 ± 1.9	14.0 ± 2.6
Sniff duration(s)	30.5 ± 1.7	41.3 ± 6.8
Grooming duration(s)	13.1 ± 4.0	14.7 ± 3.1
Flat back approach duration(s)	20.0 ± 1.6	17.9 ± 2.5
%p head-dips	44.5 ± 6.3	40.1 ± 6.6
%p SAP	61.5 ± 3.7	49.9 ± 6.1
%p sniff	68.5 ± 2.2	59.0 ± 4.5
%p flat back approach	22.4 ± 2.9	30.2 ± 5.1

SAP = stretched attend postures. Data are presented as mean values ± SEM. No significant differences were observed between the two control groups.

location) analyses of variance (ANOVA). Where indicated by significant/near significant F-values, further tests (Dunnett's t-statistic) were performed using the appropriate error variance terms from the ANOVA summary tables.

RESULTS

Table 1 summarizes the main ANOVA statistics, and reveals significant treatment effects on several of behavioural measures. For clarity, the results of follow-up analyses are presented under appropriate sub-headings.

Control Profiles: Effect of Handling and Injection

Table 2 compares the behavioural profiles of uninjected and saline-injected control animals. In comparison with previous studies using male DBA/2 and T1 mice (e.g., 10), male CD1 mice generally showed higher levels of plus-maze activity and exploration and, on both conventional (% open entries and time) and ethological indices (e.g., total SAP & percent protected SAP), displayed a lower baseline anxiety profile. Results also showed that daily handling and injection for 21 days had mimimal effects on plus-maze behaviour, with no statistically-significant differences evident.

Effects of Buspirone

The effects of subchronic treatment with buspirone are summarized in Table 3. Only very modest behavioural changes were observed with this compound. At 0.75–1.5 mg/kg, the only change noted was a reduction in the number of end-open SAP while, at the highest dose tested, significant reductions in total head-dipping and end-open head-dipping were evident. A 2-factor ANOVA on percent time data (treatment × maze location; location = open arms, centre platform, closed arms) revealed a significant main effect for location $F(2, 206) = 104.5$, $P < 0.001$ and a treatment by location interaction $F(20, 206) = 1.65$ $P < 0.02$. Follow-up tests showed that control animals preferred the open and closed arms relative to the centre platform (i.e. open = closed > centre), a profile that was altered by 3.0 mg/kg buspirone such that open arms were preferred over both the closed arms and centre platform (open > closed = centre).

Effects of Ondansetron

The effects of ondansetron treatment on plus-maze behaviour are summarized in Table 4. Over the dose range tested, this 5-HT_3 receptor antagonist was completely devoid of significant behavioural effects. Follow-up tests on the significant

TABLE 3

EFFECTS OF SUBCHRONIC TREATMENT WITH BUSPIRONE (0.75-3.0 mg/kg, DAILY 21 DAYS) ON THE BEHAVIOUR OF CD1 MICE IN THE ELEVATED PLUS-MAZE TEST OF ANXIETY

Variable	saline (n = 14)	0.75 mg/kg (n = 7)	1.5 mg/kg (n = 10)	3.0 mg/kg (n = 10)
Total entries	30.4 ± 2.9	31.0 ± 2.1	26.1 ± 2.2	26.9 ± 3.3
Open entries	19.1 ± 2.6	18.6 ± 1.6	15.4 ± 2.0	17.0 ± 2.7
Closed entries	11.2 ± 0.8	12.4 ± 1.1	10.7 ± 0.8	9.2 ± 1.3
Total rears	18.5 ± 2.1	18.7 ± 3.0	19.5 ± 1.9	16.1 ± 2.1
% Open entries	59.1 ± 4.1	59.9 ± 2.6	56.9 ± 4.0	64.3 ± 3.6
% End-open entries	23.3 ± 2.7	21.9 ± 0.9	20.9 ± 2.7	24.6 ± 3.4
% Open time	34.7 ± 4.0	28.8 ± 2.6	28.7 ± 4.0	41.9 ± 3.8
% End-open time	15.8 ± 2.3	11.1 ± 1.2	10.7 ± 1.9	17.2 ± 3.0
% Centre time	28.6 ± 2.0	34.1 ± 2.7	33.4 ± 4.4	27.1 ± 1.7
% Closed time	36.7 ± 3.4	37.1 ± 3.4	37.9 ± 4.5	31.0 ± 3.5
Total head-dips	13.9 ± 2.0	9.3 ± 1.1	11.2 ± 1.6	5.4 ± 0.9**
End-open head-dips	4.1 ± 0.9	1.9 ± 0.5	1.9 ± 0.5	1.1 ± 0.5**
Total SAP	9.5 ± 0.7	8.4 ± 0.7	7.9 ± 1.0	6.7 ± 0.8
End-open SAP	3.0 ± 0.5	1.4 ± 0.2*	1.4 ± 0.4*	1.9 ± 0.3
Rearing duration(s)	14.0 ± 2.6	13.6 ± 2.5	13.3 ± 1.9	14.1 ± 2.1
Sniff duration(s)	41.3 ± 6.8	22.2 ± 3.1	23.1 ± 2.9	23.7 ± 2.4
Grooming duration(s)	14.7 ± 3.1	25.1 ± 10.0	19.1 ± 5.0	17.1 ± 6.4
Flat back approach duration(s)	17.9 ± 2.5	17.0 ± 3.7	14.6 ± 2.3	12.5 ± 2.2
% p head-dips	40.1 ± 6.6	44.5 ± 5.5	48.3 ± 6.6	31.0 ± 5.7
% p SAP	49.9 ± 6.1	64.3 ± 4.6	65.3 ± 4.7	43.1 ± 5.2
% p sniff	59.0 ± 4.5	65.4 ± 3.7	62.1 ± 5.7	51.2 ± 4.9
% p flat back approach	30.2 ± 5.1	19.0 ± 5.2	16.5 ± 4.4	11.6 ± 4.4

SAP = stretched attend postures. * $P < 0.05$, ** $P < 0.01$ versus saline.

2-factor ANOVA (details above) confirmed that treatment with this compound also failed to alter the spatiotemporal preference profile (open = closed > centre) seen in the saline control condition.

Effects of Tianeptine

The effects of tianeptine are summarized in Fig. 1 and Table 5. The most prominent effects were observed at the highest dose tested (10.0 mg/kg), and comprised significant reductions in % open arm time and end-open SAP (also reduced at 2.5 & 5.0 mg/kg) together with significant increases in % protected sniffing and % protected SAP (Fig. 1). Several other measures closely approached an acceptable level of significance, including reductions in % end-open time and % protected head-dipping. Follow-up tests on the significant 2-factor ANOVA (details above) revealed that tianeptine altered the control profile (open = closed > centre) such that, at 5 mg/kg, a preference for the closed arms over both the centre platform and open arms was evident and, at 10.0 mg/kg, the closed arms and centre platform were preferred to the open arms ($P < 0.001$).

DISCUSSION

The current study involved daily handling and injection of subjects for 21 days. In view of the possible impact of such experience on behavioural baselines (64), the design incorporated both saline-injected and uninjected controls. Our results (Table 2) confirm earlier findings (67) in that the chronic handling/injection regimen employed had minimal effect upon behavioural baselines in male CD1 mice. It is also pertinent to note that the behavioural profile of intact male CD1 mice in the elevated plus-maze differs from that previously observed with DBA/2 and T1 mice (10). In particular, CD1 mice showed higher levels of open arm entries (resulting in high baseline scores for % open entries) and a greater proportion of time spent on the aversive open arms, and did not display closed arm returns to a recordable level. Thus, in order to maintain the sensitivity of the test, and particularly those measures most closely related to the conventional indices of anxiety, our scoring method was adapted to incorporate measures of end-open arm activity, which other laboratories (e.g., 15,18) have used successfully in the detection of changes in anxiety.

Although buspirone (a 5-HT_{1A} receptor partial agonist (70)) is a clinically effective anxiolytic, it has presented problems for animal models where, by comparison with benzodiazepines, it is either ineffective or only weakly effective (4,35,38,50,71). For example, in the elevated plus-maze test, acute treatment with the compound has been found to produce effects ranging from anxiolysis, through no effect, to anxiogenesis (for reviews: 30,35,64). Few studies have examined the effects of chronically-administered buspirone in this model.

TABLE 4

EFFECTS OF SUBCHRONIC TREATMENT WITH ONDANSETRON (0.1–100 μg/kg, DAILY 21 DAYS) ON THE BEHAVIOUR OF CD1 MICE IN THE ELEVATED PLUS-MAZE TEST OF ANXIETY

Variable	saline (n = 14)	0.1 μg/kg (n = 9)	10.0 μg/kg (n = 10)	100.0 μg/kg (n = 9)
Total entries	30.4 ± 2.9	30.3 ± 2.8	31.1 ± 2.5	28.6 ± 3.3
Open entries	19.1 ± 2.6	19.5 ± 1.9	18.3 ± 1.5	17.3 ± 2.7
Closed entries	11.2 ± 0.8	10.8 ± 1.5	12.8 ± 1.1	11.2 ± 1.0
Total rears	18.5 ± 2.1	18.4 ± 3.6	23.0 ± 3.0	17.8 ± 3.0
% Open entries	59.1 ± 4.1	64.6 ± 3.1	59.0 ± 1.4	58.8 ± 3.0
% End-open entries	23.3 ± 2.7	26.3 ± 1.7	22.4 ± 1.7	19.8 ± 3.1
% Open time	34.7 ± 4.0	34.3 ± 3.5	33.0 ± 1.9	31.2 ± 4.6
% End-open time	15.8 ± 2.3	14.0 ± 1.4	13.9 ± 1.4	12.7 ± 2.2
% Centre time	28.6 ± 2.0	34.5 ± 3.0	30.1 ± 2.2	29.7 ± 3.0
% Closed time	36.7 ± 3.4	31.2 ± 2.1	36.9 ± 2.0	39.1 ± 5.3
Total head-dips	13.9 ± 2.0	14.4 ± 1.0	13.1 ± 1.1	13.7 ± 1.3
End-open head-dips	4.1 ± 0.9	3.6 ± 0.4	3.5 ± 0.7	2.8 ± 0.8
Total SAP	9.5 ± 0.7	9.1 ± 0.5	9.3 ± 0.9	8.9 ± 0.9
End-open SAP	3.0 ± 0.5	2.5 ± 0.4	2.4 ± 0.3	2.3 ± 0.5
Rearing duration(s)	14.0 ± 2.6	10.7 ± 1.7	15.0 ± 3.2	13.1 ± 2.6
Sniff duration(s)	41.3 ± 6.8	45.4 ± 12.6	39.1 ± 9.1	42.9 ± 10.7
Grooming duration(s)	14.7 ± 3.1	9.9 ± 1.8	13.0 ± 3.3	24.7 ± 14.7
Flat back approach duration(s)	17.9 ± 2.5	14.6 ± 2.6	15.9 ± 3.0	17.0 ± 2.9
% p head-dips	40.1 ± 6.6	37.9 ± 5.8	36.8 ± 3.5	43.2 ± 7.7
% p SAP	49.9 ± 6.1	53.9 ± 5.0	51.4 ± 4.9	58.4 ± 6.5
% p sniff	59.0 ± 4.5	60.1 ± 3.8	60.7 ± 3.3	64.4 ± 5.0
% p flat back approach	30.2 ± 5.1	22.8 ± 3.7	14.1 ± 4.2	26.8 ± 8.0

SAP = stretched attend postures. Statistical analysis failed to reveal any treatment effects.

However, although Moser (53) found 16-day pretreatment to be ineffective in male rats, recent work in our own laboratory (12) has shown 15-day pretreatment to produce anxiolytic-like effects in male mice. Unfortunately, as with acute treatment, the most convincing anti-anxiety effects (2.5–5.0 mg/kg) were accompanied by behavioural suppression leading to doubts about behavioural selectivity. In the present study, a lower dose range (0.75–3.0 mg/kg; daily 21 days) was employed in an attempt to circumvent such interpretative difficulties. However, our findings show that buspirone had rather few effects under present test conditions. Low doses (0.75–1.5 mg/kg) reduced risk assessment at the ends of the open arms while, at 3 mg/kg, reductions in total head-dipping and end-open head-dipping were observed. The high dose also resulted in an alteration in spatiotemporal patterning, with mice preferring the open arms to other parts of the maze. However, in the absence of other behavioural changes (e.g., increases in % open entries or % open time relative to saline controls), any effects of buspirone on anxiety-related processes must be considered minimal. Of possible relevance in this context is a report that buspirone produces anxiogenic effects in handling-habituated animals (1). Perhaps, therefore, any anxiolytic action of chronically-administered buspirone in the present study was countered by an opposing influence of chronic handling/injection. However, it is important to emphasize that the injection regimen employed in the present study did not alter behavioural baselines and that no evidence of such an interaction was apparent in a previous study from this laboratory (12).

Ondansetron is a highly selective 5-HT_3 receptor antagonist with putative anxiolytic-like properties at extremely low systemic doses. It has been studied extensively in animal models but, as for buspirone, with highly variable results (e.g., 4,30,34). In the plus-maze, similar numbers of positive and negative findings have been reported, a pattern that cannot readily be accounted for by variations in dosage (64). Although previous work from this laboratory failed to find evidence of anxiolytic activity with acute ondansetron (1–100 μg/kg) (66), the possibility remained that anxiolytic effects would be seen following chronic treatment (e.g., 17). However, as present data show, 21-day pretreatment with ondansetron (0.1–100 μg/kg) failed to uncover an anxiolytic action of this compound; indeed, Table 4 confirms that the compound was without any behavioural effect under present test conditions. Of relevance in this context is the observation that another 5-HT_3 receptor antagonist, zacopride, only produces anxiolytic-like effects in handling-naive animals (1). Although present negative findings may be attributable to the chronic handling/injection schedule used, it is perhaps more parsimonious to conclude that ondansetron, administered acutely or subchronically, is without effect on the type of anxiety induced in mice by exposure to the elevated plus-maze. While this conclusion would be entirely consistent with the disappointing results of recent

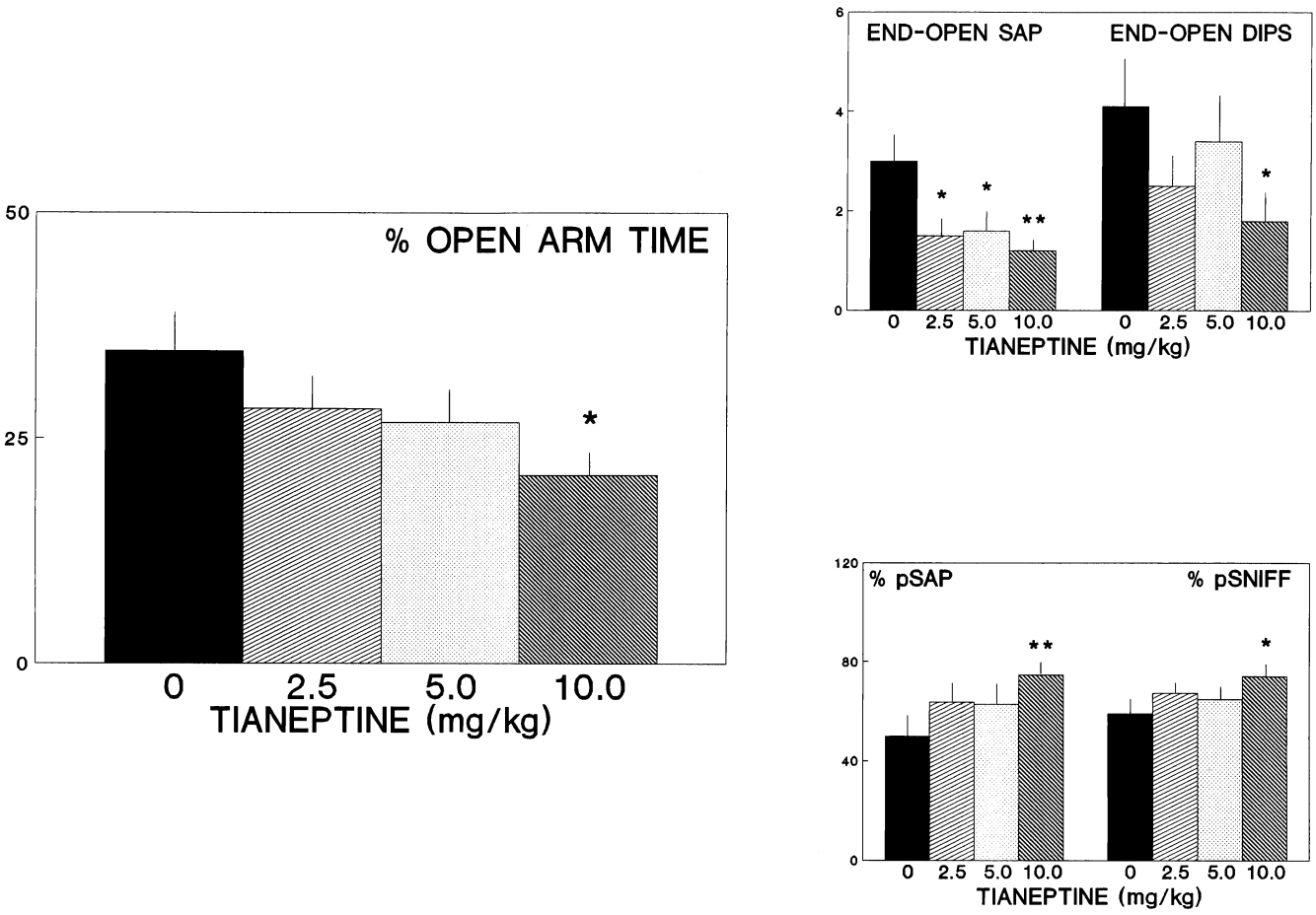

FIG. 1 The effects of subchronic tianeptine (2.5-10.0 mg/kg; daily for 21 days) on behaviours displayed by male CD1 mice in the elevated plus-maze test of anxiety. Data are presented as mean values (± SEM). See Table 5 for complementary data. %p = percent protected; SAP = stretched attend postures. $*P < 0.05$, $**P < 0.01$ vs saline control.

clinical trials with 5-HT_3 receptor antagonists (46,47), there may be certain types of anxiety which would respond to agents of this class. Certainly, the negative results obtained with ondansetron (and buspirone) contrast sharply with those reported for chlordiazepoxide and maprotiline under identical test conditions (67), an observation that lends further credence to the growing view that different animal models are tapping into different facets of anxiety (e.g., 23). In this context, it is pertinent to note that Glaxo are currently focussing on the development of 5-HT_3 receptor antagonists for the treatment of panic (e.g., 52), and that the murine plus-maze has been found insensitive to both established (13) and putative (65) panicolytic agents.

Tianeptine, a modified tricyclic belonging to the dibenzothiazine series, has been shown to have antidepressant efficacy in a number of clinical studies (review: 76). The compound has been classed as intermediate in position between stimulant and sedative antidepressants (49), and is highly unusual in that it enhances (rather than inhibits) 5-HT reuptake (2,51). In animal studies, tianeptine has been shown to reduce pituitary-adrencocortical responses to stress and to antagonize stress-induced behavioural deficits (review: 76). Furthermore, acute treatment with this agent (2.5-10.0 mg/kg) has been shown to produce a weak anxiolytic-like effect in the rat elevated plus-maze but not the social interaction test, whereas 5-day treatment produces a weak anxiolytic-like effect in the social interaction test but not the elevated plus-maze (25).

Present results show that subchronic treatment with tianeptine produced an anxiogenic-like behavioural profile in male mice tested in the plus-maze. This effect was most evident at the highest dose tested (10 mg/kg) and consisted of a reduction in percent time spent on the open arms, reductions in end-open SAP and head-dips, and increases in percent protected forms of SAP and sniffing. In addition, analysis of spatiotemporal preferences confirmed a dose-dependent increase in open arm avoidance, while several other anxiety-related measures showed non-significant trends towards anxiety enhancement e.g., percent end-open time and total head-dipping. These effects bear direct comparison with profiles obtained for well-established anxiogenic drugs under similar test conditions (e.g., pentylenetetrazol, FG7142; (65)), and are not confounded by changes in general activity levels: total arm entries, rearing and, most importantly, closed arm entries (68) were unaffected by drug treatment. In view of the importance of behavioural baselines in animal models of anxiety, the detection of tianeptine-induced anxiogenesis in the present study may have been facilitated by the relatively high levels of open arm activity in CD1 mice compared with other strains (e.g., DBA/2 and T1 (10)). Importantly, however, the pattern of behavioural change seen in plus-maze is consistent with the

TABLE 5

EFFECTS OF SUBCHRONIC TREATMENT WITH TIANEPTINE (2.5–10.0 mg/kg, DAILY 21 DAYS) ON THE BEHAVIOUR OF CD1 MICE IN THE ELEVATED PLUS-MAZE TEST OF ANXIETY

Variable	saline (n = 14)	2.5 mg/kg (n = 9)	5.0 mg/kg (n = 10)	10.0 mg/kg (n = 9)
Total entries	30.4 ± 2.9	29.4 ± 2.8	25.5 ± 2.7	27.9 ± 3.4
Open entries	19.1 ± 2.6	17.2 ± 2.2	14.2 ± 2.3	14.6 ± 2.1
Closed entries	11.2 ± 0.8	12.2 ± 2.5	11.3 ± 1.0	13.3 ± 1.8
Total rears	18.5 ± 2.1	19.0 ± 2.5	14.6 ± 1.5	14.1 ± 1.9
% Open entries	59.1 ± 4.1	58.0 ± 3.9	54.1 ± 3.3	51.8 ± 3.2
% End-open entries	23.3 ± 2.7	18.9 ± 2.5	20.1 ± 1.7	20.5 ± 1.7
% End-open time	15.8 ± 2.3	9.7 ± 1.8	11.1 ± 1.6	9.4 ± 1.2
% Centre time	28.6 ± 2.0	32.0 ± 3.0	29.6 ± 2.7	37.9 ± 2.6
% Closed time	36.7 ± 3.4	39.7 ± 3.6	43.7 ± 4.6	41.2 ± 2.4
Total head-dips	13.9 ± 2.0	13.6 ± 2.0	12.1 ± 1.8	9.2 ± 1.5
Total SAP	9.5 ± 0.7	10.3 ± 1.1	8.2 ± 0.8	9.9 ± 0.7
Rearing duration(s)	14.0 ± 2.6	14.3 ± 2.1	9.9 ± 1.4	7.3 ± 1.1
Sniff duration(s)	41.3 ± 6.8	25.6 ± 3.6	24.3 ± 1.3	23.1 ± 1.8
Grooming duration(s)	14.7 ± 3.1	13.1 ± 3.4	33.2 ± 13.8	13.4 ± 1.9
Flat back approach duration(s)	17.9 ± 2.5	14.9 ± 2.6	15.8 ± 2.3	15.6 ± 2.3
% p head-dips	40.1 ± 6.6	50.5 ± 9.0	44.2 ± 7.0	63.6 ± 5.9
% p flat back approach	30.2 ± 5.1	18.7 ± 5.7	21.1 ± 4.7	25.7 ± 5.7

SAP = stretched attend postures. See Fig. 1 for complementary data.

anxiogenic-like profile of tianeptine in parallel studies on mouse social interaction (20). Since recent clinical trials indicate good therapeutic efficacy for tianeptine in patients classified as anxious-depressed (33,39), our findings together with the variable results reported by File's group (25) would suggest that the type of anxiety experienced by such patients may not be equivalent to that studied in (at least some) animal models. In this context, however, it is important to note that tianeptine has not yet been studied in patients with primary anxiety (76). As we have previously shown that subchronic treatment with the selective 5-HT reuptake inhibitor, fluvoxamine, is largely without effect under present test conditions (67), the possibility exists that the effects currently observed with tianeptine may not be due to its action on 5-HT mechanisms. Thus, while apparently without significant affinity for any known receptors, this compound has been found to increase extracellular dopamine and acetyl choline concentrations in rat forebrain (76). The importance of these actions to the anxiogenic profile of tianeptine is unknown. Furthermore, as tianeptine (albeit acute administration) has been shown to enhance acquisition in a spatial learning task (25), present data may reflect facilitated spatial learning leading to lower scores for open arm activity.

In summary, present results show that (1) contrary to effects found with chlordiazepoxide and maprotiline under identical test conditions, subchronic treatment with buspirone and ondansetron fails to produce evidence of anti-anxiety activity in the murine plus-maze, and (2) contrary to the lack of effect previously observed with fluvoxamine, the 5-HT reuptake-enhancing antidepressant, tianeptine, produces a profile consistent with anxiety enhancement in this paradigm. The former result is consistent with other animal (and human) data, while the latter strongly suggests the need for more research on the behavioural effects of tianeptine. One vitally important issue in this regard would appear to be the nature of anxiety expressed in different test situations.

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