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Behavioural Effects in Mice of Subchronic Buspirone, Ondansetron and Tianeptine. I. Social Interactions

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CUTLER, M. G., R. J. RODGERS AND J. E. JACKSON *Behavioural effects in mice of buspirone, ondansetron and tianeptine. I. Social interactions* PHARMACOL BIOCHEM BEHAV **56**(2) 287–293, 1997—In a continuation of recent work on effects of a benzodiazepine (chlordiazepoxide) and selective monoamine reuptake inhibitors (maprotiline and fluvoxamine), the current study compares 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). Compounds were given daily to mice for 21 days prior to testing and the subsequent behaviour of the animals during social interactions was assessed by ethopharmacological procedures. Buspirone, at 0.75 mg/kg, increased immobility and reduced occurrence of the aggressive act, "attack." At 1.5 and 3.0 mg/kg, it enhanced olfactory exploration of the sawdust substrate, but had no effect on social investigation. Ondansetron increased the duration of environmental exploration at 0.1 μg/kg, while at 100 μg/kg it increased the duration of digging in the substrate. Ondansetron had no effect on the categories of behaviour and failed to induce an anxiolytic-like enhancement of social investigation. Tianeptine produced an anxiogenic-like effect at 10 mg/kg, while at 5 mg/kg it enhanced flight and immobility. The relevance of these findings is discussed in relation of the reported behavioural actions of these compounds and to current pharmacotherapy of anxiety and depression. The apparent anxiogenic effect of tianeptine is a novel finding which requires further study. **Copyright © 1997 Elsevier Science Inc.**

Anxiety Social interaction Anxiolytics Antidepressants Buspirone Ondansetron Tianeptine Mice

CURRENT views indicate that there is considerable commonality in the symptomatology and pharmacotherapy of anxiety and a range of depressive disorders (20,34). Furthermore, it is known that antidepressant agents, such as imipramine, can be effective in treating human anxiety and that a range of anxiolytic agents, including buspirone, ipsapirone, ritanserin and ketanserin, possess antidepressant efficacy (e.g., 44,46). Studies using animal models of anxiety and depression have, in contrast, yielded negative (e.g., 5,8,23,38,42) as well as positive responses (e.g., 3,4,9,11,32) in their detection of anxiolytic and antidepressant effects, since they use very different and highly specific test procedures. Assessment of the effects induced by anxiolytic and antidepressant agents on spontaneously occurring behaviour in animals should provide more sensitive and meaningful information than the standard animal models for detecting anxiolytic or antidepressant activity. Additionally, in view of the clinical patterns, it is of obvious important to examine the effects of treatment following chronic, rather than acute, administration.

Ethopharmacological methods of behavioural analysis have been employed in the current series of experiments. Ethopharmacology provides a powerful tool with which to measure drug effects on the whole range of spontaneous acts and postures in an animal's behavioural repertoire (19), and has, during our earlier experiments, been found to yield reproducible, dose-related and comprehensive drug profiles (16,17, 27,28). In the current studies, the anxiolytic agent, buspirone, the putative anxiolytic agent, ondansetron, and the novel antidepressant, tianeptine, have been examined to obtain further information on the behavioural profiles of anti-anxiety and antidepressants compounds.

Buspirone is well known to be clinically effective as an

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TABLE 1

EFFECTS OF SUBCHRONIC TREATMENT (21 DAYS) WITH BUSPIRONE ON THE FREQUENCY AND DURATION OF MAJOR CATEGORIES OF BEHAVIOUR SHOWN BY MICE IN THE SOCIAL INTERACTION TEST

		Buspirone-treated		
	Injected Controls (n = 35)	0.75 mg/kg daily (n = 16)	1.5 mg/kg daily (n = 16)	3.0 mg/kg daily (n = 15)
		Mean frequency ± SE		
Non-social activity	128.3 ± 6.9	127.3 ± 7.9	131.3 ± 7.5	123.5 ± 7.4
Social investigation	50.6 ± 4.7	39.4 ± 4.0	45.7 ± 3.9	55.7 ± 4.2
Aggression	18.2 ± 7.1	3.1 ± 2.2	5.3 ± 4.3	7.0 ± 6.0
Flight	0.1 ± 0.1	0.3 ± 0.3	0.0 ± 0.0	0.0 ± 0.0
Immobility	0.1 ± 0.1	0.4 ± 0.2	0.1 ± 0.1	0.9 ± 0.7
		Mean duration (s) ± SE		
Non-social activity	228.7 ± 6.2	228.6 ± 6.6	236.4 ± 4.9	225.6 ± 7.6
Social investigation	62.5 ± 5.8	56.4 ± 6.5	60.1 ± 4.4	58.3 ± 5.3
Aggression	11.8 ± 4.2	3.2 ± 1.7	4.9 ± 3.6	3.9 ± 3.0
Flight	0.1 ± 0.1	0.6 ± 0.6	0.0 ± 0.0	0.0 ± 0.0
Immobility	0.1 ± 0.1	2.5 ± 1.5*	0.5 ± 0.5	7.6 ± 6.3

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

anxiolytic only after chronic administration (30,51). Its anxiolytic actions are thought to relate mainly to its significant affinity for 5-HT_{1A} receptors (19,53). It also has been found to act as a "serenic," reducing aggressive behaviour (47), and to have marked to moderate antidopaminergic activity (19).

5-HT_3 receptor antagonists are effective in several, although not all of the preclinical models of anxiety (11,23,36). Effects consistent with anxiolytic action have been observed in the mouse light-dark box, the rat social interaction test and in primate threat tests (marmosets and cynomolgus monkeys), but the compound has been shown to be inactive in the water-lick conflict test (36), the elevated plus maze (23,47), and the social interaction test of File (22).

Tianeptine, an atypical second-generation compound, has shown antidepressant properties in preclinical tests (37,54) and has also exhibited an anxiolytic-like profile during social interactions after subchronic administration in rats (24). Additionally, tianeptine has been reported to counteract the anxiogenic effects of benzodiazepine withdrawal, although it was ineffective in reducing the responses of rats to aversive cat odours (25).

The present study examines effects of these three compounds on the behaviour of mice during social interactions in an unfamiliar cage. A companion paper presents data from a parallel study using the elevated plus-maze (50). To enhance the clinical relevance of this work, each of the substances has been given to mice by daily administration over a three week period.

METHODS

Animals

Adult male CD1 mice (Charles River), weighing 23–45 g, were used in these studies. Animal were housed in groups of 10–11 (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 06.00 h). Testing was conducted between 09.00 and 16.00 h under dim white light (60w) during the dark phase. All mice received an ad lib supply of water and pelleted cubes (SDS, Weltham, Essex), except during the brief test sessions.

Drugs

Drugs used were buspirone hydrochloride (Sigma, U.K.), ondansetron hydrochloride (Glaxo Group Research, U.K.) and tianeptine, sodium salt (Servier, France). All compounds were dissolved in physiological saline and administered by intraperitoneal injection in volume of 1ml/300 g. Injections were given once daily for 21 days and on the last dosing day (day 21) were given at 30 min prior to testing. A group of controls injected with physiological saline and non-injected controls were included in the design in order to assess the effects of chronic handling and injection.

Experimental Procedures

Mice were randomly allocated to one of 11 treatment conditions, uninjected control (n = 16), saline injected control (n = 35), buspirone injected (0.75, 1.5 or 3.0 mg/kg daily, n = 15–16), ondansetron injected (0.1, 10.0 or 100.0 μg/kg daily, n = 15–16) or tianeptine injected (2.5, 5.0 or 10.0 mg/kg daily, n = 15–16).

Ethopharmacological procedures, used in previous studies (e.g., 27), were employed to assess the behavioural responsiveness of experimental mice when engaged in 5 min social encounters with an untreated group-housed unfamiliar DBA/2 male partner in a neutral cage (60 × 25 × 25 cm). Behaviour during these 5 min social interactions was recorded on audiotape as a spoken commentary and was simultaneously recorded on videotape.

Behavioural Analysis and Statistics

The spoken commentaries from drug-treated mice and their controls were transcribed onto floppy disc through direct keyboard input for analysis by computer of the frequency and duration of each behavioural element and category. The

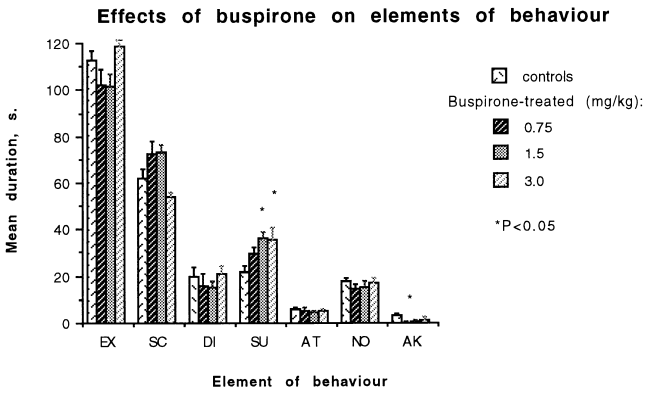

FIG. 1. Significant effects of subchronic treatment with buspirone on the behaviour of male mice. Data are presented as mean values (duration ± SEM). EX = explore; SC = scan; DI = dig; SU = substrate investigation; AT = attend; NO = nose; AK = attack. Kruskal–Wallis H values; EX = 4.9; SC = 3.3; DI = 2.9; SU = 8.8 ($P < 0.01$); AT = 2.9; NO = 4.3; AK = 8.3 ($P = 0.03$).

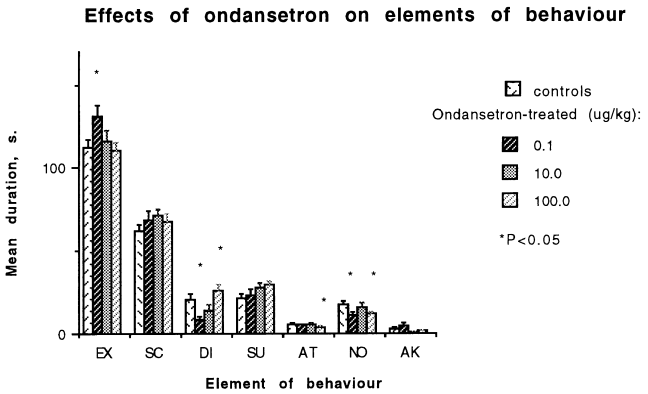

FIG. 2. Significant effects of subchronic treatment with ondansetron on the behaviour of male mice. Data are presented as mean values (duration ± SEM), EX = explore; SC = scan; DI = dig; SU = substrate investigation; AT = attend; NO = nose; AK = attack. Kruskal–Wallis H values; EX = 6.9; SC = 3.1; DI = 7.5 ($P = 0.04$); SU = 2.5; AT = 7.6 ($P = 0.03$); NO = 5.7; AK = 5.8.

categories of behaviour comprised non-social activity, social investigation, aggression, flight and immobility (27).

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

Effects of Buspirone on Behaviour

Table 1 shows that mice treated with buspirone at 0.75 mg/kg spent more time in immobility than their saline-injected controls. From Table 1 it also can be seen that the frequency and duration of aggression was somewhat less in all mice treated with buspirone than in their respective controls. Further analysis of this data (Fisher's exact treatment of the 2 × 2 Tables) demonstrated that aggression was significantly less frequent ($P = 0.04$) in mice given buspirone at 0.75 mg/kg (2/16 mice) that in saline-injected controls (14/35 mice). This effect failed to reach statistical significance in mice treated with the higher doses of buspirone.

Significant effects of buspirone on duration of individual elements of behaviour are illustrated in Fig. 1. At 95% confidence limits, both duration (mean ± SE; controls, 3.3 ± 0.9; treated, 0.3 ± 0.3) and frequency (means ± SE, controls, 7.1 ± 2.2, treated, 0.6 ± 0.5) of the act "attack" were reduced in mice given buspirone at 0.75 mg/kg. "Substrate sniffing" (SU) was increased in duration among drug-treated mice (mean ± SE; controls, 21.7 ± 2.4: treated at 1.5 mg/kg, 36.2 ± 2.7; treated at 3.0 mg/kg, 35.6 ± 5.5; $P < 0.01$) and also was raised in frequency (mean ± SE; controls, 16.8 ± 1.4: treated at 1.5 mg/kg, 24.4 ± 0.9; treated at 3.0 mg/kg, 23.9 ± 1.8; $P < 0.01$).

Effects of Ondansetron on Behaviour

As can be seen from Table 2, ondansetron induced no significant changes to the categories of behaviour in these studies, although it did modify the occurrence of specific elements. Figure 2 shows that treatment with ondansetron produced dose-related increases in duration of the act, "dig" (DI), an increase in the duration of exploration (EX) at 0.1 μg/kg and decreases in duration of the social elements, "attend" (AT) at 100 μg/kg and "nose" (NO) at 0.1 and 100 μg/kg. At 100 μg/kg, ondansetron also reduced the frequency of "attend" (mean ± SE; controls, 12.9 ± 0.7; treated, 9.9 ± 0.8; $P < 0.05$), but did not significantly modify the frequency of non-social "exploration" and "digging."

Effects of Tianeptine on Behaviour

Table 3 shows that treatment of the mice with tianeptine at 5 mg/kg increased the frequency and duration of flight and immobility. Mice given tianeptine at 10 mg/kg showed a reduction in the frequency and duration of social investigation, a decrease in the frequency of non-social activity and an increase in the frequency of immobility.

Significant effects of tianeptine on the duration of behavioural elements are illustrated in Fig. 3. This shows that the time spent by the mice in scanning (SC) was reduced by tianeptine at 10 mg/kg and that substrate sniffing (SU) was decreased by tianeptine at 5 mg/kg. Substrate sniffing also was decreased in frequency by tianeptine 5 mg/kg (mean ± SE, controls 21.7 ± 2.4. treated 15.4 ± 2.3., $P < 0.05$).

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

Non-injected controls spent more time in the acts "wash and self-groom" ($P < 0.05$) than saline-injected controls (Mean ± SE; SAL 3.2 ± 0.5, CON 2.0 ± 0.4; $P < 0.05$). There were no other significant differences in behaviour between the saline-injected and non-injected control groups.

DISCUSSION

The current results have shown that daily handling and saline-injection of the CD1 mice for three weeks induced little change to their behaviour during social interactions. These findings closely parallel the results obtained by Rodgers et al, (50) in a companion study using the elevated plus-maze.

It is pertinent to note that the behaviour of mice differs considerably from strain to strain (6,40). Furthermore, behaviour can change when mice of the same strain are tested in

TABLE 2

EFFECTS OF SUBCHRONIC TREATMENT (21 DAYS) WITH ONDANSETRON ON THE FREQUENCY AND DURATION OF MAJOR CATEGORIES OF BEHAVIOUR SHOWN BY MICE IN THE SOCIAL INTERACTION TEST

		Ondansetron-treated		
	Injected Controls (n = 35)	0.1 mg/kg daily (n = 15)	10.0 mg/kg daily (n = 16)	100.0 mg/kg daily (n = 15)
		Mean frequency ± SE		
Non-social activity	128.3 ± 6.9	134.1 ± 9.2	144.8 ± 9.6	135.3 ± 5.2
Social investigation	50.6 ± 4.7	43.1 ± 4.7	48.2 ± 4.7	39.9 ± 3.8
Aggression	18.2 ± 7.1	33.4 ± 12.5	7.4 ± 5.6	13.9 ± 5.5
Flight	0.1 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Immobility	0.1 ± 0.1	0.0 ± 0.0	0.4 ± 0.4	0.0 ± 0.0
		Mean duration (s) ± SE		
Non-social activity	228.7 ± 6.2	241.2 ± 7.0	239.0 ± 5.4	241.5 ± 6.3
Social investigation	62.5 ± 5.8	45.9 ± 6.1	55.3 ± 6.2	49.3 ± 5.0
Aggression	11.8 ± 4.2	18.3 ±6.6	5.3 ± 3.0	9.3 ± 3.9
Flight	0.1 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Immobility	0.1 ± 0.1	0.0 ± 0.0	1.9 ± 1.9	0.0 ± 0.0

different social environments (e.g., 14). Thus, a standardized regimen has been employed to assess effects of the compounds on social interactions in the earlier (17) and current behavioural studies.

The findings from the present work provide a direct comparison of the subchronic effects of buspirone, ondansetron and tianeptine on the social behaviour of mice. Buspirone, a 5-HT_{1A} receptor partial agonist (4), was found, at 0.75 mg/kg to increase immobility and reduce aggressive behaviour. This may have some parallels with earlier reports that buspirone has a modest anti-conflict efficacy (52). Such effects, typical of serenic agents (e.g. fluprazine and eltoprazine) are thought to be due to reduced glucose utilization in such areas of the brain as the hippocampus and dentate gyrus, although glucose utilization is increased in a few other sites of the brain (31). The increase of substrate sniffing induced by the higher dose levels of buspirone in the present studies might possibly arise from its blocking of presynaptic dopamine receptors (19). For example, the D2 dopamine agonist, quinpirole, which reduces metabolism of dopamine, has likewise been shown to enhance substrate sniffing in mice (29).

In contrast to the present findings, it was found in an earlier study that buspirone increased social investigation when given to CD1 male mice for 12–14 days in the drinking fluid (27). Thus, differences in the mode of administration or treatment duration may have contributed to the difference between the present results and the findings reported earlier. The anxiogenic effects of buspirone in handling-habituated animals (1) may also be of possible relevance to the present findings. (i.e., The current handling/injection regimen might have counteracted or reduced and anxiolytic-like enhancement of social investigation by the drug). However, many workers have reported that buspirone shows an apparent lack of anxiolytic activity in several animal species, despite its demonstrated

TABLE 3

EFFECTS OF SUBCHRONIC TREATMENT (21 DAYS) WITH TIANEPTINE ON THE FREQUENCY AND DURATION OF MAJOR CATEGORIES OF BEHAVIOUR SHOWN BY MICE IN THE SOCIAL INTERACTION TEST

		Tianeptine-treated		
	Injected Controls (n = 35)	2.5 mg/kg daily (n = 15)	5.0 mg/kg daily (n = 15)	10.0 mg/kg daily (n = 16)
		Mean frequency ± SE		
Non-social activity	128.3 ± 6.9	124.7 ± 7.4	121.4 ± 8.5	105.1 ± 8.2*
Social investigation	50.6 ± 4.7	43.1 ± 4.6	41.3 ± 5.2	35.7 ±4.5*
Aggression	18.2 ± 7.1	7.3 ± 4.5	25.4 ± 9.7	15.7 ± 6.8
Flight	0.1 ± 0.1	0.1 ± 0.1	1.3 ± 1.0*	0.4 ± 0.4
Immobility	0.1 ± 0.1	0.5 ±0.2	1.3 ± 0.8†	1.3 ± 0.8*
		Mean duration (s) ± SE		
Non-social activity	228.7 ± 6.2	246.2 ± 6.3	223.3 ± 7.4	227.8 ± 10.3
Social investigation	62.5 ± 5.8	56.3 ± 6.8	56.8 ± 5.6	50.8 ± 5.4*
Aggression	11.8 ± 4.2	5.3 ± 2.8	19.1 ± 6.8	13.5 ± 5.6
Flight	0.1 ± 0.1	0.1 ± 0.1	3.2 ± 2.5*	1.7 ± 1.7
Immobility	0.1 ± 0.1	2.0 ± 1.3	8.7 ± 6.1*	12.8 ± 11.1

* $P < 0.05$, † $P < 0.01$, betwen drug-treated and control mice by the Kruskal-Wallis and Mann-Whitney U tests.

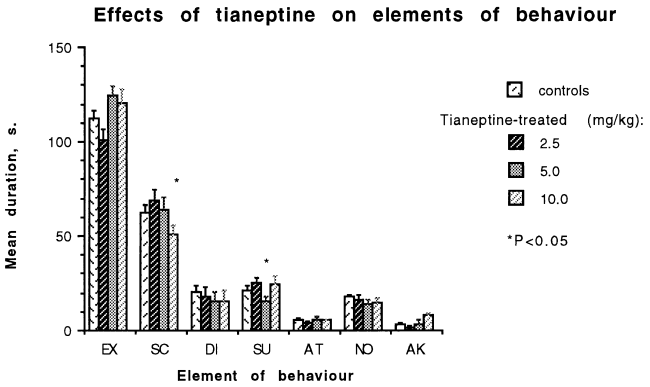

FIG. 3. Significant effects of subchronic treatment with tianeptine on the behaviour of male mice. Data are presented as mean values (duration ± SEM). EX = explore; SC = scan; DI = dig; SU = substrate investigation; AT = attend; NO = nose; AK = attack. Kruskal–Wallis H values; EX = 4.5; SC = 6.5; DI = 1.3; SU = 6.1; NO = 5.1; SK = 2.3.

anxiolytic efficacy in man (e.g, 7,41,45,51). It was, for example, found to be without effect in a mouse operant punishment paradigm (41). It is thus possible that buspirone induces anxiolytic effects via different pathways from those utilized by the benzodiazepines or barbiturates.

Ondansetron, a 5-HT_3 receptor antagonist that has been reported to have anxiolytic-like properties at extremely low dose levels (36), was found in the present experiments, using 0.1 to 100 μg/kg, to have relatively minor effects on behaviour. These effects included a dose-related enhancement of substrate digging, an increase of exploration at 0.1 μg/kg and a reduced occurrence of specific social acts, such as "nose" and "attend" at 100 μg/kg.

In earlier experiments in this laboratory, a single dose of the 5-HT_3 receptor antagonist, BRL 46470, was found to induce a dose-related increase of "digging" by CD1 mice (28) and also an increase of social investigation (15,28). Subchronic administration of BRL 46470 in drinking fluid was found likewise to increase social investigation by CD1 mice (27). However, there was no increase of social investigation in male DBA mice given granisetron for 5–10 days in their drinking fluid (14) or in CD1 intruder mice treated with a single dose of this drug (15). These findings correspond with reports by other workers that, in tests for anxiolytic activity, 5-HT_3 receptor antagonists can induce both positive and negative effects (11,22,23,36,48).

In this context it has been suggested (33) that 5-HT_3 receptor antagonists may be behaviourally inert under conditions in which endogenous neurotransmitter tone at the 5-HT_3 receptor is low, but that this receptor is activated in response to specific pharmacological or environmental stimuli. When 5-HT_3 receptors are activated, the antagonists can induce a wide range of behavioural changes (2,10–13,21,47). Nonetheless, due to the variability of experimental findings, and disappointing results from clinical trials (39), it appears that the therapeutic value of 5-HT_3 receptor antagonists (e.g., as anxiolytics) has yet to be fully delineated.

Tianeptine, a selective 5-HT reuptake enhancer (43), showed an anxiogenic-like profile at the higher dose levels in the present studies. It increased immobility and flight in mice at 5 mg/kg, and showed a greater range of behavioural changes at 10 mg/kg (e.g., reducing non-social activity and social investigation and increasing immobility of the mice). In parallel experiments, tianeptine exhibited an anxiogenic-like behavioural profile in male mice tested in the plus-maze (50). These effects of tianeptine differed from those of the antidepressants, maprotiline and fluvoxamine, which failed to induce such marked anxiogenic-like activity in the social interaction test (17,49), although each of these antidepressants was found to induce immobility at some of the dose levels tested.

The present findings differ markedly from earlier reports of behavioural effects produced by tianeptine. In previous studies, tianeptine had been shown to reduce stress-induced behavioural deficits (53,55) and induce anxiolytic-like effects in the rat social interaction test (24). It also had been found to counteract some of the anxiogenic effects associated with benzodiazepine- and with ethanol withdrawal (25,26), and to show reactions indicative of an antidepressant action (37).

The reason for the difference between the present and earlier experiments requires further study, perhaps by a direct comparison between the effects of chronic administration of tianeptine with those of a single dose. It is possible that after chronic treatment, the drug or its metabolites may accumulate in body tissues with adverse effects. Nonetheless, recent clinical trials, do not indicate adverse reactions, but report that tianeptine shows a good therapeutic efficacy in patients classified as "anxious-depressed" (35). The effects of tianeptine in primary anxiety have not yet been studied (55), and it is possible that tianeptine may be effective in certain forms of anxiety and depression and not in others.

In summary, the present results show that buspirone and ondansetron (contrary to effects found with maprotiline and chlordiazepoxide under similar tests conditions), fail to produced evidence of anxiolytic activity. These results are consistent with other animal (and human) data. However, aversive effects from tianeptine have not previously been reported, and further research on this finding is warranted. In this respect, one vitally important issue is the nature of "anxiety" expressed in each of the tests.

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