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Chronic Antidepressant and Clonidine Treatment Effects on Conflict Behavior in the Rat

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COMMISSARIS, R. L., D. M. ELLIS, T. J. HILL, D. M. SCHEFKE, C. A. BECKER AND D. J. FONTANA. *Chronic antidepressant and clonidine treatment effects on conflict behavior in the rat.* PHARMACOL BIOCHEM BEHAV **37**(1) 167–176, 1990.—The present studies examined the effects of chronic treatment with several antidepressants and clonidine on conflict behavior. In daily ten-minute sessions, water-deprived rats were trained to drink from a tube which was occasionally electrified (0.25 or 0.5 mA). Electrification was signalled by a tone. Chronic desipramine (5 mg/kg, IP, b.i.d.) or clonidine (40 μg/kg, b.i.d.) treatment resulted in time-dependent anticonflict effects, with a latency to onset of approximately 3–4 weeks. In contrast, chronic buproprion (up to 10 mg/kg, IP, b.i.d.), mianserin (up to 10 mg/kg, IP, b.i.d.) or trazodone (up to 40 mg/kg, IP, b.i.d.) treatment resulted in at best only a weak anticonflict effect. The efficacy of these antidepressants and clonidine to increase punished responding when administered chronically correlates well with their efficacy as antipanic agents in man.

Antidepressants Antipanic agents Anxiety Buproprion Clonidine Conflict behavior Desipramine Mianserin Panic disorder Trazodone

PANIC disorder is a serious condition characterized by unexpected and recurrent panic attacks often leading to agoraphobia and constricted lifestyles. As such, panic disorder is classified as an anxiety neurosis different from generalized anxiety disorder (1). The results of pharmacological studies also support this distinction between generalized anxiety disorder and panic disorder. In the 1960s, Klein and coworkers reported that spontaneous panic attacks could be prevented by chronic treatment with tricyclic antidepressants (TCAs), a treatment which did not affect background anxiety (35–37). The antipanic efficacy of TCAs and monoamine oxidase inhibitors (MAOIs) has been demonstrated by several investigators since the original reports of Klein and coworkers (22, 33, 40, 43, 46, 48, 51, 57, 60).

Antipanic efficacy has also been demonstrated with some, but not all, atypical antidepressants. For example, alprazolam exhibits good antipanic efficacy (2, 10, 47, 49), whereas buproprion has been reported to lack antipanic efficacy (50). Finally, chronic treatment with trazodone exhibits only moderate antipanic effects when compared to alprazolam or imipramine (10,42). Antipanic efficacy is not limited to agents with antidepressant activity, however. The benzodiazepine clonazepam (4,54) and the alpha-2-adrenoceptor agonist clonidine (31,39) also have been reported to exhibit antipanic effects in man.

Although several behavioral procedures have been used to study generalized anxiety, the search for an effective "animal model" for the study of panic disorder has resulted in mostly negative findings, with chronic administration of tricyclic antidepressants (TCAs) shown *not* to affect the potentiated startle response (9), social interaction (15), the elevated plus maze (14) or the defensive burying paradigm (3). Recently, two animal conflict procedures have yielded positive results (i.e., "anxiolytic-like" effects) following chronic antidepressant treatment. These are the Novelty-Suppressed Feeding task [NSF: (6)] and the Conditioned Suppression of Drinking paradigm [CSD: (13, 17–19)]. In these procedures, chronic, but not acute, administration of TCAs and MAOIs results in time-dependent anticonflict (i.e., "anxiolytic") effects, with a time-course ("onset" latency of 2–4 weeks) which parallels the time course for the clinical antipanic efficacy of these agents (22, 35, 36, 48, 60). Thus, conflict paradigms such as the NSF and CSD may be useful "animal models" for the study of panic disorder and antipanic agents.

The present study determined the effects of acute and chronic treatment with several agents with varying degrees of clinical antipanic efficacy on CSD conflict behavior. The agents selected

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were the typical antidepressant desipramine, the atypical antidepressants trazodone, buproprion and mianserin and the antipanic alpha-2-agonist clonidine.

GENERAL METHOD

Animals

Female Sprague-Dawley rats (Charles River Farms, Cambridge, MA; 250–300 grams at the start of the experiments) were housed in groups of four or five in a climate-controlled room with a 12-hour light:12-hour dark cycle (lights on 0700–1900 hours). Initially, food and water were available continously. Following a two-week accommodation period and continuing throughout the period of behavioral assessment, all animals were maintained on a restricted water schedule (see below). Food continued to be available in the home cage.

Apparatus

Conditioned Suppression testing was conducted in an apparatus similar to that described by Fontana *et al.* (17). The testing chamber was a rectangular box with Plexiglas® sides and a metal floor and top. Protruding from one wall was a metal drinking tube to which a calibrated (0.5 ml units) length of polyethylene tubing was attached for measuring the volume of water consumed. Programming for the test session was controlled by solid state modular programming equipment (Coulbourn Instruments Co., Lehigh Valley, PA).

General Procedure

For the first few sessions, water-restricted (24-hr deprivation) subjects were placed in the experimental chamber and allowed to consume water freely without the shock contingency. After one week of nonshock sessions, the tone/shock contingency was initiated. The 7-sec tone periods were presented at regular (22-sec ISI) intervals to the subjects. During the last 5 sec of these tone periods, contact between the floor and the metal drinking tube completed a circuit that resulted in the delivery of a shock (0.125, 0.25 or 0.5 mA) to the rat. Shocks were delivered by a Two-Pole Small Animal Shocker (Coulbourn Instruments Inc., Model No. E13-02).

Initially, the shock inhibited fluid consumption in the test chamber. After several days, however, all subjects learned to consume stable volumes of water during the silent periods and made relatively few and very brief contacts with the tube during the tone. The duration of the shock received was equal to the duration of the tube contact (less than 200 msec).

In all experiments, subjects were tested individually in 10-minute sessions at the same time of day. All subjects achieved stable control values (day-to-day coefficients of variation of approximately 30% for individual rats) for punished and unpunished responding by the end of the second week of CSD sessions with the alternating tone:no tone periods. Baseline (i.e., nondrug) CSD testing was continued for two additional weeks before drug testing was initiated. For baseline determinations and throughout each experiment, CSD testing was conducted four days per week (Monday–Thursday) and free access to water was provided on nontest days (Thursday p.m. until Sunday a.m.).

Specific Experiments

Experiment I: Chronic desipramine treatment effects on conflict behavior. Two groups of subjects, trained for CSD testing as described above, received either chronic desipramine (5.0 mg/kg) or saline injections twice daily. The injections were accomplished immediately after CSD testing and again 12 hours later. This schedule of twice daily administration of DMI was selected to minimize fluctuations in DMI concentrations during the course of chronic administration. CSD testing (4 days/week) was conducted for 5 weeks. The daily CSD test sessions were conducted 12–14 hours after the evening injection of the preceding day. This procedure was used to minimize the influence of the acute effects of the chronically administered drug on CSD behavior.

Chronic desipramine or saline treatments were continued for an additional 11 weeks in the absence of CSD testing. Starting at Week 16 of chronic treatment, CSD testing was reinitiated for the purpose of establishing a current intensity response function for chronic desipramine- and saline-treated subjects. This current-intensity response function was determined using a standard counterbalanced design ("ABCCBA"). For the first week (Week 16 of chronic desipramine/saline treatment), the shock intensity was 0.5 mA as used previously. For the second and third weeks (Weeks 17 and 18), the current intensity was reduced by one-half each week (0.25 and 0.125 mA, respectively). For Weeks 19–21, CSD behavior was examined at 0.125, 0.25 and 0.5 mA current intensities, respectively. The chronic desipramine or saline treatments were maintained throughout this period of CSD testing.

Experiment II: Atypical antidepressants: Acute and chronic treatment effects on conflict behavior. Three separate groups of subjects, trained for CSD testing as described above, were used to determine the acute effects of the atypical antidepressants trazodone, buproprion or mianserin on CSD behavior. Following four weeks of nondrug CSD sessions, the subjects received single treatments with various doses of the atypical antidepressant under investigation over the course of several weeks of testing. Each week the effects of a different dose of the agent in question were determined; the order of doses tested was randomized. Drug tests were conducted on Wednesdays and Thursdays each week using a standard "crossover" procedure (18,41). On the Wednesday drug tests, half the subjects received the dose of the drug under examination and half received vehicle. These treatments were reversed on the Thursday drug tests. Thus, each animal served as its own control. In this phase of Experiment II, the atypical antidepressant was administered 10 minutes prior to CSD testing.

Since mianserin treatment has been reported to produce rapid changes in serotonin-2 receptors following only a single dose (5,29), an additional group of subjects was used to examine a brief time course for the effects of a single dose of mianserin on CSD behavior. In this study subjects were tested in control (i.e., nondrug) CSD sessions for four days. Immediately after CSD testing on Day 4, half the subjects received 10 mg/kg mianserin and the other half received vehicle. The subjects were then tested in the CSD paradigm at 24, 48 and 72 hours posttreatment.

Three additional groups of subjects, trained for CSD testing as described above, were used to determine the effects of chronic posttest treatment with these atypical antidepressants on CSD behavior. Following four weeks of nondrug CSD sessions, subjects in each group were assigned into two treatment conditions with comparable levels of punished responding over the last two weeks of these control CSD sessions. Subjects in one treatment condition received chronic posttest treatment with the atypical antidepressant under investigation; controls received comparable vehicle injections. CSD testing (4 days/week) was continued throughout the period of chronic drug treatment. The doses administered (trazodone: 10 mg/kg, b.i.d. for 4 weeks, followed by 20 mg/kg, b.i.d. for 4 weeks, followed by 40 mg/kg, b.i.d. for 4 weeks; buproprion: 5 mg/kg, b.i.d. for 4 weeks, followed by 10 mg/kg, b.i.d. for 4 weeks; mianserin: 5 mg/kg, b.i.d. for 4 weeks, followed by 10 mg/kg, b.i.d. for 4 weeks) were selected because they have been shown to produce behavioral and/or neurochemical changes when administered chronically (5, 7, 11, 16, 21, 28–30,

44, 52, 56). Chronic drug or vehicle treatments were administered immediately posttest and again 12 hours later. As with the chronic desipramine study, the minimum interval between any drug injection and CSD testing in this experiment was 12 hours. CSD testing was continued for three weeks (Test Weeks 13–15) following discontinuation of chronic treatment in the chronic trazodone study.

Experiment III: Clonidine: Acute and chronic treatment effects on conflict behavior. Another group of subjects, trained for CSD testing as described above (shock intensity = 0.5 mA), was used to determine the acute effects of the alpha-2-agonist clonidine on CSD behavior. Following four weeks of nondrug CSD sessions, the subjects received single treatments with various doses of clonidine at various pretreatment times over the course of several weeks of testing. Each week the effects of a different dose or pretreatment time were determined; the order of doses and pretreatment times tested was randomized. Drug tests were conducted on Wednesdays and Thursdays each week using the "crossover" procedure described above. In this experiment, the effects of a wide range of clonidine doses (1.25–80 μg/kg) was examined following either a 10-minute or a 120-minute pretreatment.

An additional group of subjects, trained for CSD testing as described above (shock intensity = 0.25 mA), was used to determine the effects of chronic posttest treatment with clonidine on CSD behavior. Following four weeks of nondrug CSD sessions, the subjects were assigned into two treatment conditions with comparable levels of punished responding over the last two weeks of these control CSD sessions. One group of subjects received chronic posttest treatment with clonidine (40 μg/kg, twice daily); controls received saline injections. CSD testing (4 days/week) was continued throughout the period of chronic drug treatment (seven weeks). Chronic drug or vehicle treatments were administered immediately posttest and again 12 hours later. As with the chronic desipramine study, the minimum interval between any drug injection and CSD testing in this experiment was 12 hours.

Geller-Seifter type conflict paradigms use response-contingent grid floor scrambled footshock (24,25), while the CSD conflict paradigm uses direct punishment of the consummatory response (mouth shocks applied via a two-pole shocker). The final experiment was conducted to examine the effects of chronic posttest clonidine administration on behavior in a modification of the CSD where the punisher was a response-contingent grid floor scrambled footshock rather than the CSD standard two-pole shock to the mouth area. The apparatus and procedures for this experiment were identical to those described above with two exceptions. First, tube contacts during the latter 5 seconds activated a grid floor shocker (Model No. E13-08), rather than a two-pole shocker, for the duration of the tube contact (less than 200 msec). Second, the shock intensity was 0.5 mA (rather than 0.25 mA). Based upon pilot studies examining a range of two-pole mouth versus grid floor scrambled shock intensities, this shock intensity was found to be comparable to 0.25 mA shock intensity administered to the mouth in terms of both baseline (i.e., nondrug) shocks received and in terms of the anticonflict effects of acute benzodiazepine treatment (Becker *et al.*, unpublished). Following four weeks of baseline conflict testing, clonidine (40 μg/kg) or saline were administered twice daily for seven weeks. Conflict testing was conducted 4 days/week throughout this period of chronic treatment.

Drugs

Desipramine hydrochloride and clonidine hydrochloride were purchased from Sigma Chemical Company (St. Louis, MO). Mianserin hydrochloride was purchased from Research Biochemicals, Inc. (Natick, MA). Trazodone hydrochloride was received as a gift from the Bristol-Myers Company (Evansville, IN). Buproprion hydrochloride was received as a gift from the Burroughs Wellcome Company (Research Triangle Park, NC). Desipramine, clonidine and trazodone were dissolved in saline; mianserin and buproprion were dissolved in distilled water. All drugs were administered intraperitoneally in a volume of 1 ml/kg body weight.

Statistical Analyses

The effects of the acute administration of single doses of various agents on CSD performance were compared to vehicle controls using *t*-tests for paired values. For the chronic treatment studies, pretreatment (i.e., baseline) water intake and punished responding were compared using *t*-tests for unpaired values. The effects of chronic drug or vehicle treatments on these parameters were compared using 2 × "X" factorial ANOVAs ("X" = the number of Test Weeks + Baseline) with repeated measures (Main Effects: Chronic Drug/Vehicle and Test Weeks). The effects of chronic posttest clonidine administration on conflict behavior were evaluated using a 2 × 2 × 8 factorial ANOVA (Main Effects: Clonidine/Saline treatment; Two-Pole/Grid Floor shock; Baseline + 7 Test Weeks) with repeated measures. Post hoc least significant differences (lsd) tests were used to detect Test Weeks in which the Drug versus Vehicle change scores were significantly different. Current-intensity functions in chronic desipramine and saline-treated subjects were evaluated by 2 × 3 factorial ANOVA with repeated measures (Main Effects: Desipramine/Saline; Current Intensities). In all statistical comparisons, $p<0.05$ was used as the criterion for statistical significance (55).

RESULTS

Baseline CSD performance for all subjects in the CSD paradigm at the 0.5 mA shock intensity was 13.9 ± 1.1 (mean ± SEM) shocks accepted and 11.1 ± 0.3 ml water/session. Baseline responding for subjects at the 0.25 mA shock intensity was 38.1 ± 6.1 shocks/session and 10.6 ± 0.5 ml water/session. It should be noted that the number of tube contacts during the shock component (10–20 per session) was insignificant when compared to the number of tube contacts during the unpunished component (2000–3000 per session). Thus, the volume of water consumed accurately reflects unpunished responding in the CSD.

Experiment I: Chronic Desipramine Treatment Effects on Conflict Behavior

The upper panel of Fig. 1 illustrates the effects of chronic desipramine treatment on punished responding in the CSD. The pretreatment baselines for punished responding in the two groups were not statistically different (saline: 7.1 ± 1.6; desipramine: 10.5 ± 2.9; $t = 1.01$, n.s.). Desipramine-treated subjects exhibited a slight depression of punished responding (relative to baseline values) in the first Test Week, followed by a gradual increase in punished responding over Weeks 2–5. Statistically, there was a significant Main Effect for the various Test Weeks, $F(4,32) = 15.85$, $p<0.05$. There was also a statistically significant Main Effect for the Desipramine/Saline treatments, $F(1,8) = 9.14$, $p<0.05$. Finally, there was a significant interaction of Desipramine/Saline × Test Weeks, $F(4,32) = 17.71$, $p<0.05$. Post hoc lsd comparisons revealed that chronic desipramine-treated rats accepted significantly more shocks than did saline controls at Test Weeks 3, 4 and 5 of chronic treatment.

The lower panel of Fig. 1 illustrates the effects of chronic desipramine or saline treatment on water consumption in the CSD. Water intake did differ between the two groups prior to initiation

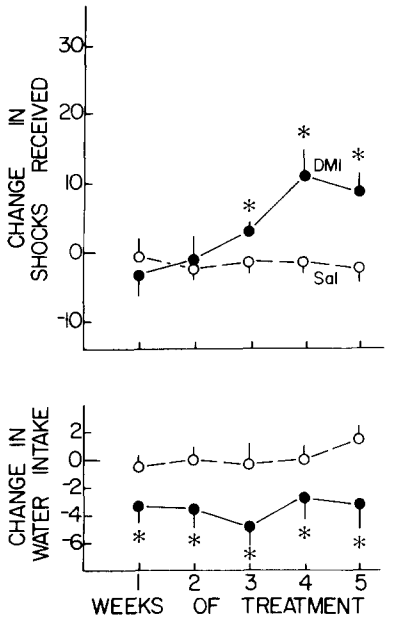

FIG. 1. The effects of chronic administration of desipramine on CSD behavior. The change in shocks received (upper panel) and change in water consumed (lower panel) in CSD sessions during the course of 5 weeks of chronic saline (Sal; open circles) or desipramine (DMI; 5.0 mg/kg, b.i.d.; filled circles) administration are plotted. Each symbol represents the mean ± SEM from five subjects. Desipramine was administered at least 12 hours prior to CSD testing. *$p<0.05$: desipramine-induced change from baseline significantly different from saline-induced change at the indicated Test Week, post hoc lsd test following factorial ANOVA.

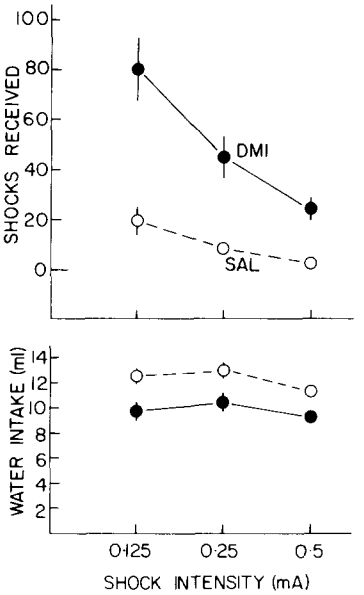

FIG. 2. Intensity-response function for CSD behavior in rats chronically treated with saline or desipramine. Plotted are the number of shocks received (upper panel) and the volume of water consumed (lower panel) in animals chronically treated with saline (SAL; open circles) or desipramine (DMI; 5.0 mg/kg, b.i.d.; filled circles) for 16–21 weeks. Each symbol represents the mean ± SEM from five subjects. Desipramine was administered at least 12 hours prior to CSD testing.

of chronic DMI/Saline treatment (saline: 11.9 ± 0.8; desipramine: 8.7 ± 1.0; $t = 2.58$ $p<0.05$). Chronic desipramine treatment further reduced water intake, as evidenced by a statistically significant Main Effect for Desipramine/Saline treatments, $F(1,8) = 18.62$, $p<0.05$. There was also a significant Main Effect for Test Weeks, $F(4,32) = 4.54$, $p<0.05$. There was no significant interaction of Desipramine/Saline × Test Weeks, $F(4,32) = 1.66$, n.s., on water intake.

The upper panel of Fig. 2 illustrates the effects of current intensity on punished responding in the CSD in chronic desipramine- or saline-treated subjects. As can be seen, desipramine-treated subjects accepted more shocks than saline controls at all intensities examined. This is supported by a significant Main Effect for Desipramine/Saline treatment, $F(1,8) = 27.82$, $p<0.05$. As expected, there was also a significant Main Effect for Current Intensity, $F(2,16) = 21.25$, $p<0.05$, with lower shock intensities resulting in a greater number of shocks received. There was also a significant Desipramine/Saline × Current Intensity interaction, $F(2,16) = 6.16$, $p<0.05$, with the magnitude of the desipramine effect (i.e., desipramine–saline) increasing as shock intensity decreased. It should be noted that the magnitude of the desipramine versus saline difference at Week 16 (saline: 3.2 ± 0.6; desipramine: 23.5 ± 5.0) was similar to that observed at Week 5 (saline: 4.9 ± 1.4; desipramine: 19.1 ± 3.5).

The lower panel of Fig. 2 illustrates the effects of various current intensities on water intake in the CSD in these subjects. As can be seen, regardless of current intensity, desipramine-treated subjects consumed significantly less water than saline controls. This is supported by a significant Main Effect for Desipramine/Saline treatment, $F(1,8) = 14.41$, $p<0.05$. There was a significant Main Effect for Current Intensity, $F(2,16) = 4.81$, $p<0.05$, with subjects consuming more water at the 0.25 mA intensity than at either the 0.5 or 0.125 mA intensity. Finally, there was no Desipramine/Saline × Current Intensity interaction, $F(2,16)<1$, n.s., on water intake.

Experiment II: Atypical Antidepressants: Acute and Chronic Treatment Effects on Conflict Behavior

Table 1 illustrates the effects of acute administration of these atypical antidepressants on CSD behavior. Trazodone did not affect punished responding at the 5 or 10 mg/kg doses, but decreased punished responding at 20 mg/kg. Buproprion tended to increase punished responding at the 5 and 10 mg/kg doses, but this effect was not statistically significant. Mianserin significantly increased punished responding at the 2.5 mg/kg dose, but not at any other dose examined. With all three agents, both punished (shocks received) and unpunished (water intake) responding were significantly decreased at the highest doses examined (20 mg/kg trazodone, 40 mg/kg buproprion, 20 mg/kg mianserin). Although it has been shown to affect serotonin receptors within 24 hours after a single 10 mg/kg treatment (5,29), acute treatment with 10 mg/kg mianserin did not affect CSD behavior at any time up to 72 hours postadministration (data not shown).

The upper panel of Fig. 3 illustrates the effects of chronic trazodone treatment on punished responding in the CSD. The pretreatment baselines (shock intensity = 0.25 mA) for punished responding in the two groups were comparable (vehicle: 26 ± 5; trazodone: 28 ± 6, $t = 0.26$, n.s.). All subjects accepted fewer shocks over the course of 12 weeks of CSD testing. Statistically, this was supported by a significant Main Effect for the various Test Weeks, $F(12,96) = 4.46$, $p<0.05$. Trazodone-treated subjects tended to accept more shocks than saline controls at the highest dose examined (40 mg/kg, b.i.d.; Test Weeks 9–12); this effect was not

TABLE 1

EFFECTS OF ACUTE TREATMENT (10-MINUTE PRETREATMENT) WITH THE ATYPICAL ANTIDEPRESSANTS TRAZODONE, BUPROPRION OR MIANSERIN ON CSD BEHAVIOR

	Change in Shocks Received	Change in Water Intake (ml)
Trazodone Dose (mg/kg); 0.25 mA Shock		
5.0	5.9 ± 3.6	−0.8 ± 1.0
10.0	−2.0 ± 3.8	−2.4 ± 1.1*
20.0	−12.1 ± 5.0*	−7.5 ± 1.8*
Buproprion Dose (mg/kg); 0.25 mA Shock		
2.5	+1.1 ± 4.5	−0.7 ± 1.0
5.0	+22.2 ± 16.0	+1.4 ± 0.8
10.0	+16.6 ± 10.3	+0.2 ± 0.7
20.0	+1.0 ± 13.4	−6.0 ± 1.4*
40.0	−31.3 ± 12.5*	−8.0 ± 0.8*
Mianserin Dose (mg/kg); 0.5 mA Shock		
1.25	0.3 ± 0.6	−0.4 ± 0.4
2.5	8.2 ± 2.6*	0.4 ± 0.6
5.0	1.9 ± 1.6	−2.4 ± 1.0*
10.0	−1.6 ± 1.4	−6.3 ± 1.1*
20.0	−12.1 ± 0.6*	−14.1 ± 0.6*

Values represent the mean ± SEM change from baseline (Drug − Vehicle) from 20 subjects/group.
*$p<0.05$, t-test for paired values.

statistically significant, however, as there was no significant Main Effect for the Trazodone/Vehicle treatment, $F(1,8)<1.0$, n.s., nor was there a significant interaction of Trazodone/Vehicle × Test Weeks, $F(12,96)=1.45$, n.s. The number of shocks received in subjects which had received trazodone treatment returned to control levels over the course of three weeks of CSD testing in the absence of chronic Trazodone/Vehicle treatments (Test Weeks 13–15).

The lower panel of Fig. 3 illustrates the effects of chronic trazodone or vehicle treatment on water intake in the CSD. Pretreatment water intake did not differ between the two groups (vehicle: 8.7 ± 1.7; trazodone: 9.7 ± 1.9; $t=0.84$, n.s.). Statistically, there was a significant Main Effect for Test Weeks, $F(12,96)=3.35$, $p<0.05$. There was not a significant Main Effect for the Trazodone/Vehicle treatment, $F(1,8)<1.0$, n.s., nor was there a Trazodone/Vehicle × Test Weeks interaction, $F(8,96)=1.12$, n.s.

The upper panel of Fig. 4 illustrates the effects of chronic buproprion treatment on punished responding in the CSD. The pretreatment baselines (shock intensity = 0.25 mA) for punished responding in the two groups were not different (vehicle: 47 ± 15; buproprion: 65 ± 15, $t=0.83$, n.s.). As with the trazodone experiment, all subjects accepted fewer shocks over the course of 8 weeks of CSD testing. Statistically, this was supported by a significant Main Effect for the various Test Weeks, $F(8,56)=4.28$, $p<0.05$. There was no statistically significant Main Effect for the Buproprion/Vehicle treatment, $F(1,7)=1.12$, n.s., nor was

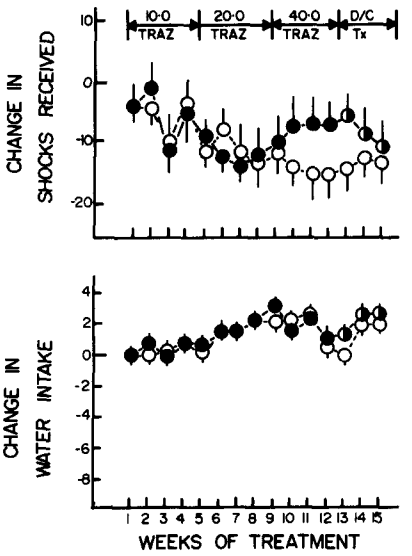

FIG. 3. The effects of chronic administration of trazodone on CSD behavior. The change in shocks received (upper panel) and change in water consumed (lower panel) in CSD sessions during the course of 12 weeks of chronic saline (Sal; open circles) or trazodone (TRAZ; 10 mg/kg, b.i.d., for Test Weeks 1–4, 20 mg/kg, b.i.d. for Test Weeks 5–8, 40 mg/kg, b.i.d. for Test Test Weeks 9–12, No Treatment for Test Weeks 13–15; filled circles) administration are plotted. Each symbol represents the mean ± SEM from five subjects. Trazodone was administered at least 12 hours prior to CSD testing. *$p<0.05$: trazodone-induced change from baseline significantly different from saline-induced change at the indicated Test Week, post hoc lsd test following factorial ANOVA.

there a significant Buproprion/Vehicle × Test Weeks interaction, $F(8,56)<1$, n.s.

The lower panel of Fig. 4 illustrates the effects of chronic buproprion or vehicle treatment on water consumption in the CSD. Pretreatment water intake did not differ between the two groups (vehicle: 12.7 ± 1.7; buproprion: 12.0 ± 0.9; $t=0.46$, n.s.). Chronic treatment with the highest buproprion dose (10 mg/kg, b.i.d.) decreased water intake relative to vehicle-treated controls. Statistically, there was no significant Main Effect for Chronic Buproprion/Vehicle treatment on water intake, $F(1,7)=2.94$, n.s., nor was there a significant Main Effect for Test Weeks, $F(8,56)=1.98$, n.s. There was, however, a statistically significant Buproprion/Vehicle × Test Weeks interaction, $F(8,56)=2.68$, $p<0.05$. Post hoc lsd comparisons revealed that chronic buproprion-treated rats consumed significantly less water than did vehicle controls at Test Weeks 5, 6 and 7 of chronic treatment.

The upper panel of Fig. 5 illustrates the effects of chronic mianserin treatment on punished responding in the CSD. The pretreatment baselines (shock intensity = 0.5 mA) for punished responding in the two groups were comparable (vehicle: 12.2 ± 2.0; mianserin: 12.6 ± 1.2, $t=0.16$, n.s.). Statistically, there was a significant Main Effect for the various Test Weeks, $F(7,112)=8.38$, $p<0.05$, with both vehicle- and mianserin-treated subjects exhibiting an overall depression of punished responding (relative to pretreatment Baseline values). Although there was no statistically significant Main Effect for the Mianserin/Vehicle treatment, $F(1,16)=1.45$, n.s., there was a significant interaction of Treatment × Test Week, $F(7,112)=3.04$, $p<0.05$. Post hoc lsd comparisons revealed that chronic mianserin-treated rats accepted significantly fewer shocks than did vehicle controls at Test Weeks 4 and 7 of chronic treatment. At no Test Week did the mianserin-

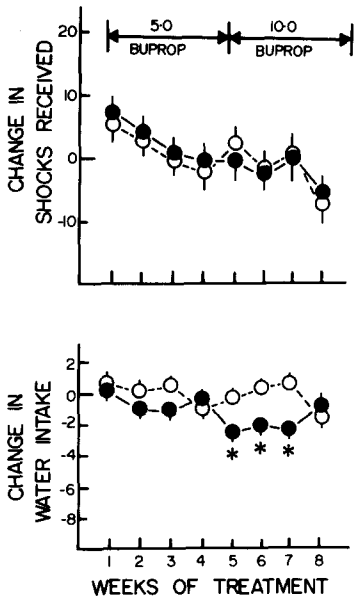

FIG. 4. The effects of chronic administration of buproprion on CSD behavior. The change in shocks received (upper panel) and change in water consumed (lower panel) in CSD sessions during the course of 8 weeks of chronic distilled water (VEH; open circles) or buproprion (BUPROP; 5.0 mg/kg, b.i.d., Test Weeks 1–4, 10 mg/kg, b.i.d. for Test Weeks 5–8, filled circles) administration are plotted. Each symbol represents the mean ± SEM from five subjects. Buproprion was administered at least 12 hours prior to CSD testing. *$p<0.05$: buproprion-induced change from baseline significantly different from saline-induced change at the indicated Test Week, post hoc lsd test following factorial ANOVA.

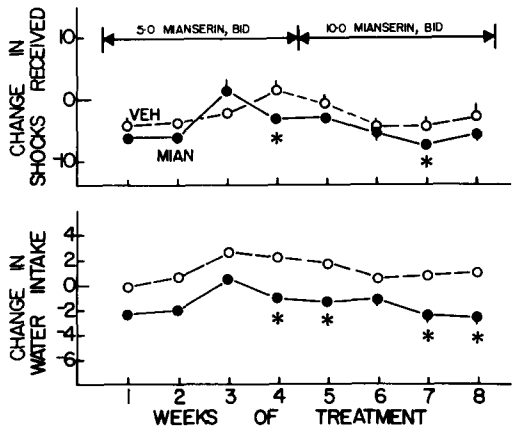

FIG. 5. The effects of chronic administration of mianserin on CSD behavior. The change in shocks received (upper panel) and change in water consumed (lower panel) in CSD sessions during the course of 8 weeks of chronic vehicle (VEH; open circles) or mianserin (MIAN; 5.0 mg/kg, b.i.d., for Test Weeks 1–4, followed by 10 mg/kg, b.i.d., for Test Weeks 5–8; filled circles) administration are plotted. Each symbol represents the mean ± SEM change (relative to pretreatment Baseline) from nine subjects. Mianserin was administered at least 12 hours prior to CSD testing. *$p<0.05$: mianserin-induced change from baseline significantly different from vehicle-induced change at the indicated Test Week, post hoc lsd test following 2 × 8 factorial ANOVA.

TABLE 2

EFFECTS OF ACUTE TREATMENT (10- OR 120-MINUTE PRETREATMENT) WITH CLONIDINE ON CSD BEHAVIOR

	Change in Shocks Received	Change in Water Intake (ml)
0.5 mA Shock; 10-Minute Pretreatment; Dose (μg/kg)		
1.25	+0.7 ± 0.2	−0.6 ± 0.6
5.0	−7.4 ± 2.3*	−2.7 ± 0.3*
20.0	−4.4 ± 2.3	−7.1 ± 0.7*
80.0	−7.4 ± 5.4	−11.7 ± 0.5*
0.5 mA Shock; 120-Minute Pretreatment; Dose (μg/kg)		
2.5	−0.7 ± 1.0	−0.1 ± 0.7
5.0	+0.1 ± 3.4	−1.3 ± 0.5*
10.0	−4.5 ± 2.1	−2.9 ± 0.4*
20.0	−9.4 ± 3.4*	−4.2 ± 0.6*
40.0	−9.0 ± 2.6*	−6.4 ± 0.5*

Values represent the mean ± SEM change from baseline (Clonidine − Vehicle) from 20 subjects/group.

*$p<0.05$, t-test for paired values.

treated subjects exhibit an increase in punished responding relative to vehicle controls.

The lower panel of Fig. 5 illustrates the effects of chronic mianserin or vehicle treatment on water consumption in the CSD. Pretreatment water intake did not differ between the two groups (vehicle: 9.3 ± 0.9; mianserin: 10.5 ± 1.0; $t=0.92$, n.s.). Statistically, there was a significant Main Effect for Test Weeks, $F(7,112)=11.26$, $p<0.05$. There was also a statistically significant Main Effect for the Mianserin/Vehicle treatment, $F(1,16)=11.24$, $p<0.05$, with the mianserin-treated subjects consuming significantly less water than their vehicle-treated controls across all Test Weeks. There was no significant interaction of Treatment × Test Week, $F(7,112)=1.37$, n.s., on water intake. Post hoc lsd comparisons revealed that chronic mianserin-treated rats consumed significantly less water than did vehicle controls at Test Weeks 4, 5, 7 and 8 of chronic treatment.

Experiment III: Clonidine: Acute and Chronic Treatment Effects on Conflict Behavior

Table 2 illustrates the effects of acute clonidine treatment on CSD conflict behavior. As can be seen, across a wide range of doses and pretreatment times, acute clonidine administration did not increase punished responding. Doses greater than 2.5 μg/kg reliably decreased unpunished responding (water intake) in the CSD paradigm.

The upper panels of Fig. 6 illustrate the effects of chronic posttest administration of clonidine on conflict behavior under conditions in which behavior is suppressed by either a two-pole shock administered to the mouth (standard CSD) or a scrambled grid floor shock administered to the feet (Geller-Seifter like). The pretreatment baselines for punished responding were not statistically different in any of the four groups (Mouth Shock/Saline:

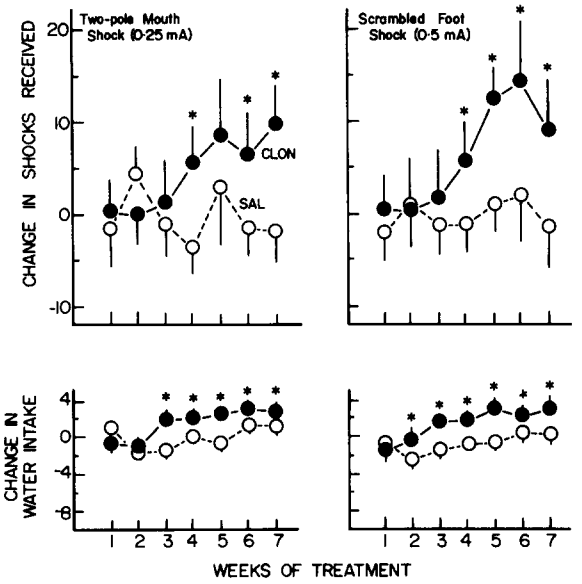

FIG. 6. The effects of chronic administration of clonidine on conflict behavior. The change in shocks received (upper panels) and change in water consumed (ml; lower panel) during the course of 7 weeks of chronic vehicle (SAL; open circles) or clonidine (CLON; 40 μg/kg, b.i.d.; filled circles) administration are plotted. Right panel figures illustrate the data obtained using a 0.25 mA shock administered to the mouth area; left panel figures illustrate the data obtained using a 0.5 mA shock administered through a scrambled grid floor shocker. See text for further details. Each symbol represents the mean ± SEM change relative to pretreatment Baseline) from 4–5 subjects. Clonidine was administered at least 12 hours prior to CSD testing. *$p<0.05$: clonidine-induced change from baseline significantly different from vehicle-induced change at the indicated Test Week, post hoc lsd test following 2 × 2 × 8 factorial ANOVA.

27 ± 4; Mouth Shock/Clonidine: 26 ± 5; Grid Shock/Saline: 22 ± 4; Grid Shock/Clonidine: 21 ± 3; n.s.). In marked contrast to the lack of effect observed with acute clonidine treatment, chronic posttest clonidine administration resulted in a gradual but significant increase in punished responding over the course of the 7 Test Weeks. This effect was observed in both the Mouth Shock and the Grid Floor Shock conditions. Statistically, there was a significant Main Effect for the various Test Weeks, $F(7,91)=3.93$, $p<0.05$. There was also a significant interaction of Clonidine/Saline × Test Weeks, $F(7,91)=4.29$, $p<0.05$. There was no Main Effect for Clonidine/Saline treatment, $F(1,13)<1.0$, n.s. or Mouth/Grid Shock, $F(1,13)=1.01$, n.s. The interactions of Clonidine/Saline treatment × Mouth/Grid Shock, $F(1,13)<1.0$, n.s., Mouth/Grid Shock × Test Weeks, $F(7,91)<1.0$, n.s., and Clonidine/Saline × Mouth/Grid Shock × Test Weeks, $F(7,91)<1.0$, n.s., were not significant. Post hoc lsd comparisons revealed that, irrespective of shock type, chronic clonidine-treated rats accepted significantly more shocks than did saline-treated controls for almost all Test Weeks beyond Test Week 3 (Test Weeks 4, 6 and 7 in the Mouth Shock condition; Test Weeks 4–7 in the Grid Shock condition).

The lower panels of Fig. 6 illustrate the effects of chronic posttest administration of clonidine on water intake (unpunished responding) under conditions in which behavior is suppressed by either a two-pole shock administered to the mouth or a scrambled grid-floor shock administered to the feet. Pretreatment baselines for this measure did differ across the four groups (Mouth Shock/Saline: 13.6 ± 0.9; Mouth Shock/Clonidine: 11.1 ± 0.4; $t=3.08$, $p<0.05$; Grid Shock/Saline: 12.0 ± 0.8; Grid Shock/Clonidine: 10.9 ± 0.05, $t=1.08$, n.s.). Chronic administration of saline did not affect water intake relative to pretreatment baseline values, while water intake in both chronic clonidine treatment groups increased relative to baseline values over the course of the experiment. Statistically, there was a significant Main Effect for the various Test Weeks, $F(7,91)=14.27$, $p<0.05$. There was also a significant interaction of Clonidine/Saline × Test Weeks, $F(7,91)=7.38$, $p<0.05$. There was also a significant Main Effect for Mouth/Grid Shock, $F(1,13)=3.26$, $p<0.05$. There was no Main Effect for Clonidine/Saline treatment, $F(1,13)<1.0$, n.s. The interactions of Clonidine/Saline treatment × Mouth/Grid Shock, $F(1,13)=3.26$, n.s., Mouth/Grid Shock × Test Weeks, $F(7,91)<1.0$, n.s., and Clonidine/Saline × Mouth/Grid Shock × Test Weeks, $F(7,91)<1.0$, n.s, were not significant. Post hoc lsd comparisons revealed that, relative to pretreatment baseline values, chronic clonidine-treated rats increased their water consumption relative to saline-treated controls for almost all Test Weeks beyond Test Week 1 (Test Weeks 3–7 in the Mouth Shock condition; Test Weeks 2–7 in the Grid Shock condition).

GENERAL DISCUSSION

The antidepressant agents desipramine, trazodone and buproprion vary in their efficacy in the treatment of panic disorder. Desipramine and other tricyclic antidepressants (TCAs) are regarded as efficacious antipanic agents (22, 35–37, 40, 43, 46); buproprion has been reported to be devoid of antipanic efficacy (50); finally, trazodone has been found to be only moderately efficacious in the management of panic disorder (10,41). The clinical antipanic efficacy of mianserin has not been determined. In addition to the antidepressants, the alpha-2-agonist clonidine has also demonstrated clinical antipanic efficacy (30,39). The present studies examined the effects of acute and chronic treatment with these agents in the CSD conflict paradigm, a potential "animal model" for the study of panic disorder and antipanic treatments.

Across a wide range of doses, trazodone, buproprion and mianserin failed to elicit reliable anticonflict effects following acute treatment. Higher doses of these agents depressed unpunished responding (water intake), perhaps a reflection of the mild sedative effects of these agents. It should be noted that acute treatment (10-minute pretreatment; up to 10 mg/kg) with desipramine does not result in an anticonflict effect in either the NSF task (6) or the CSD paradigm (17). The lack of an anticonflict effect following acute administration of the antidepressant agents is not surprising, since antipanic treatments must be administered chronically for effect, with a clinical latency to onset of antipanic effect of approximately 3–5 weeks (10, 22, 35, 46, 48, 49).

Acute clonidine treatment has been reported to exert anxiolytic effects, particularly in situations characterized by excessive noradrenergic activity [e.g., morphine, ethanol withdrawal; (26,59)]. The lack of an anxiolytic-like effect of acute clonidine treatment in the CSD paradigm is contrary to the findings by some investigators examining the effects of this agent in the Geller-Seifter and other conflict paradigms (8, 32, 38, 45, 53), but in agreement with several other reports in which clonidine failed to increase punished responding (23, 27, 45). Sepinwall and Cook (45) have reported that acute treatment with clonidine failed to elicit an anticonflict effect except when control levels of behavioral suppression were relatively extreme. Although acute clonidine treatment does not increase punished responding in the CSD conflict paradigm when the shock intensity is 0.25 mA [baseline shocks received equals approximately 35; (20)], the effects of acute clonidine treatment on CSD behavior using even higher shock intensities (i.e., even lower baselines) has not been determined. In a recent study

Soderpalm and Engel (53) reported that clonidine exerts anxiolytic-like effects at doses of 6.25 μg/kg (Vogel conflict task) and 10 μg/kg (elevated plus maze task), but not at lower doses (e.g., 3 μg/kg). Thus, an anxiolytic-like effect of acute clonidine treatment might have been masked in the present study by the significant depression of unpunished responding (water intake) produced by relatively low doses (5 μg/kg and above) of this agent.

In marked contrast to their lack of effect when administered acutely, chronic posttest administration of desipramine or clonidine produced a time-dependent increase in punished responding, with a latency to "onset" of 3–4 weeks. This delay to "onset" of anticonflict effect is consistent with previous reports in which chronic administration of TCAs (imipramine or amitriptyline) or MAOIs (phenelzine or pargyline) produced anticonflict effects in the CSD (17–19) and the Novelty-Suppressed Feeding (NSF) task (6), and is in accordance with the "onset" latency (2–4 weeks) observed with the clinical use of these agents in treating panic disorder (22, 31, 35, 36, 39, 48, 60).

The magnitude of the anticonflict effect associated with chronic desipramine treatment did not change appreciably between Test Weeks 5 and 16 of chronic treatment. Similarly, the increase in punished responding associated with chronic clonidine administration also appeared to asymptote at or around 5 weeks of chronic treatment. Thus, although the anticonflict effect of these chronic treatments clearly was not maximal after three weeks, it appears that an asymptotic level of punished responding had been reached by approximately Week 5. Both the desipramine- and saline-treated subjects accepted more shocks as the current intensity was reduced, indicating that the asymptotic level of punished responding observed in the desipramine-treated subjects at the 0.5 mA intensity was not the result of a "ceiling effect." Finally, it should be noted that desipramine-treated subjects accepted more shocks than saline-treated controls at all shock intensities examined.

When compared to behavior suppressed by two-pole shocks delivered directly to the mouth area, drinking tube contacts during the tone were suppressed less effectively by scrambled grid floor shocks. However, after doubling the shock intensity in the grid floor condition, punished responding in the absence of drug treatments was comparable in the two conditions. The increase in punished responding associated with chronic posttest administration of clonidine did not differ under these two shock conditions. Comparable anticonflict effects following acute benzodiazepine administration have also been observed under these different shock conditions (Becker *et al.*, unpublished). It appears, therefore, that the procedural difference of response-contingent punishment (used in the Geller-Seifter paradigm) versus direct punishment of the consummatory response (used in the CSD paradigm) does not markedly affect the anticonflict effects associated with drug treatments. Thus, it would be predicted that chronic posttest clonidine treatment would increase punished responding in the Geller-Seifter conflict paradigm.

In contrast to the time-dependent anticonflict effects associated with chronic treatment with TCAs, MAOIs, clonidine and alprazolam observed in this study and previous studies (6, 13, 17–19), chronic buproprion or mianserin treatment for up to eight weeks failed to exert a significant anticonflict effect in the CSD paradigm. Chronic trazodone treatment resulted in at best a slight increase in punished responding at the highest dose examined.

The negative data with buproprion are consistent with a clinical report indicating that buproprion is *not* effective in the treatment of panic disorder (50). The lack of a statistically significant anticonflict effect with chronic trazodone treatment is perhaps surprising, since this agent has been reported to be clinically effective in the treatment of panic disorder (10,42). It should be noted, however, that there was a tendency (although not statistically significant) for an anticonflict effect at the highest dose (40 mg/kg, b.i.d.) of trazodone (higher doses were not examined because of overt toxicity to the subjects). Moreover, when compared to the efficacious antipanic agents imipramine and alprazolam, trazodone exhibits only moderate antipanic efficacy in man (10). Thus, perhaps only a modest anticonflict effect would be predicted with chronic trazodone treatment.

The hypothesis that the anticonflict effect observed in the present study with desipramine relates to its antipanic (and not antidepressant) effects is supported by three observations. First, conflict paradigms such as the Geller-Seifter conditioned conflict task (24,25), the Vogel acute conflict task (58) and the CSD (12, 34, 41) traditionally have been utilized as animal models for the study of "anxiety" and antianxiety agents. Although the effects of antipanic drug treatments have not been reported in the Vogel acute conflict task or the Geller-Seifter paradigm, Bodnoff *et al.* (6) have reported that chronic but not acute desipramine treatment exerts an "anxiolytic" effect in a nonshock conflict paradigm. Second, the lack of anticonflict effect associated with chronic buproprion or mianserin treatment suggests that the CSD is not an effective "animal model" for the study of depression and/or antidepressant agents. This conclusion is based, in part, on the observation that treatment with mianserin (at the dose employed in the present study: 10 mg/kg) *is* effective in alleviating the deficits in shuttlebox avoidance training associated with the Learned Helplessness "animal model" for depression (52), but is *not* effective in the CSD. Third, and perhaps most critical, chronic posttest clonidine (antipanic, but *not* antidepressant) administration results in a time-dependent anticonflict effect. Thus, the time-dependent anticonflict effects observed following chronic treatment with TCAs, MAOIs or alprazolam (6, 13, 17–19) appears not to relate to their antidepressant actions. To the extent that the CSD is a potential "animal model" for the study of panic disorder and antipanic agents, the present data suggest that mianserin will *not* be clinically effective in the treatment of panic disorder. Clearly, however, this hypothesis remains to be tested in clinical trials of mianserin as an antipanic agent.

In summary, chronic posttest treatment with the clinically effective antipanic agents desipramine or clonidine resulted in a time-dependent increase in punished responding, with a latency to onset of 3–4 weeks. Chronic posttest treatment with the weakly efficacious or nonefficacious compounds trazodone or buproprion, respectively, failed to increase punished responding in the CSD paradigm. These data are consistent with the hypothesis that conflict paradigms such as the CSD may be effective "animal models" for the study of panic disorder and potential antipanic agents.

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