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The Effects of Beta-Antagonists and Anxiolytics on Conflict Behavior in the Rat

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FONTANA, D. J., T. C. McCLOSKEY, S. K. JOLLY AND R. L. COMMISSARIS. *The effects of beta-antagonists and anxiolytics on conflict behavior in the rat.* PHARMACOL BIOCHEM BEHAV **32**(3) 807–813, 1989.—The present studies were designed to evaluate the effects of beta-adrenoceptor antagonists and traditional anxiolytics (phenobarbital and diazepam), alone and in combination, on behavior in the Conditioned Suppressioned of Drinking (CSD) conflict paradigm, an "animal model" for the study of anxiety and antianxiety agents. In daily 10-minute sessions, water-deprived rats were trained to drink from a tube which was occasionally electrified (0.5 mA), electrification being signalled by the presence of a tone. Within 2–3 weeks, control responding had stabilized (10–15 shocks/session and 10–15 ml water/session); drug tests were then conducted at weekly intervals. As expected, diazepam (0.6–10 mg/kg) and phenobarbital (10–40 mg/kg) administration resulted in a marked and dose-dependent increase in punished responding at doses which did not markedly alter background responding (water intake). Neither propranolol (0.5–8 mg/kg) nor the beta-1-selective antagonist atenolol (1–16 mg/kg) significantly affected punished responding in the CSD. Both propranolol and atenolol produced significant beta-1-adrenoceptor blockade, as evidenced by the production of significant bradycardic effects in conscious rats at the doses employed. Pretreatment with 2.0 mg/kg propranolol did not alter the anticonflict effects of diazepam (0.6–10 mg/kg) or phenobarbital (10–40 mg/kg). Further, reduction of the shock intensity to 0.125 mA (i.e., decreased suppression) failed to alter the behavioral response to propranolol (1.5–5 mg/kg) or the interaction of 2.0 mg/kg propranolol with diazepam. Finally, chronic administration of propranolol (2.0 mg/kg, twice daily) did not affect punished responding over the course of 5 weeks of treatment. These data suggest that the CSD paradigm, although an effective "animal model" for the study of benzodiazepine and barbiturate anticonflict effects, cannot serve as an "animal model" for the study of the situation-specific (i.e., phobic) anxiety for which propranolol and related agents are presently used.

Anxiolytics Conflict behavior Conditioned suppression Diazepam Phenobarbital Propranolol Anxiety Drug interactions Atenolol

SINCE the introduction of chlordiazepoxide and diazepam in the late 1950s and early 1960s, the benzodiazepines have been the drugs of choice for the treatment of anxiety disorders. These agents are some of the most widely prescribed drugs in medical practice today (20). As a group, the benzodiazepines are clearly superior in anxiolytic activity to other classes of antianxiety agents and are much less toxic at therapeutic doses than their predecessors, the propanediol carbamates and barbiturates (20,22). Nonetheless, because of their potential for the development of addiction and dependence upon chronic administration and rebound withdrawal upon abrupt discontinuation (20,22), alternatives to the benzodiazepines in the treatment of anxiety continue to be explored.

Recently, propranolol and other beta-adrenoceptor blocking agents have been found to be effective in the treatment of situation-specific anxiety, or performance anxiety. Following the original reports by Turner *et al.* (39) and Granville-Grossman and Turner (18), a number of studies have confirmed the antianxiety efficacy of beta-adrenoceptor antagonists [(1, 7, 23, 38); see reviews by (21,26)]. These beta-antagonists appear to be most effective in the treatment of the symptoms associated with "situational anxiety," and their use has been advocated in a number of stressful conditions, including public speaking, concert performance and examination stress (8,19).

Although it is generally believed that "adequate beta-adrenergic blockade is an effective treatment for the symptoms of anxiety" (31) in humans, the experimental evidence relating to beta-adrenoceptor blockade and "antianxiety" actions in animals is sparse and unclear. Most studies examining beta-blockers have reported either weak or no "antianxiety" effects in animal tests predictive of such activity (28, 32, 35); however, some recent reports indicate an "antianxiety" action of propranolol (10, 33, 34).

One animal procedure which has been used extensively in the study of anxiety and/or antianxiety agents is that Conditioned Suppression of Drinking [CSD; (3–6, 12, 14, 25)], a modification of the Geller-Seifter conditioned conflict test (15–17) and the

Vogel Acute Conflict task (40). Although this CSD procedure has been used in numerous studies examining benzodiazepines and barbiturates (4–6, 14, 24, 25, 27), there are no reports on the effects of propranolol or other beta-adrenoceptor antagonists on CSD behavior. The purpose of the present study, therefore, was to examine the effects of beta-adrenoceptor antagonists and the anxiolytics phenobarbital and diazepam, administered alone and in combination, on CSD behavior.

METHOD

Animals

Subjects in the Conditioned Suppression of Drinking (CSD) studies were female Sprague-Dawley rats (Charles River, Inc., Cambridge, MA) housed in groups of five in a climate-controlled room with a 12-hour light:12-hour dark cycle (lights on 0700–1900 hours). Animals were given ad lib access to food with restricted water (details of water restriction described below in the Procedure section.) Subjects in the cardiovascular studies were male rats from the same supplier. These subjects were housed singly and were given ad lib access to both food and water.

Conditioned Suppression of Drinking

Apparatus. Conditioned suppression testing was conducted in an apparatus similar to that described by Fontana *et al.* (12) and McCloskey *et al.* (27). 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 subjects (food provided ad lib) 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-second tone periods were presented at regular (22 second ISI) intervals to the subjects. During the latter 5 seconds of these tone periods, contact between the floor and the metal drinking tube completed a circuit which resulted in the delivery of a shock to the rat. The duration of the shock received was equal to the duration of the tube contact (less than 200 msec). The shock intensities used were 0.5 mA and 0.125 mA.

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, receiving a consistent number of shocks from day to day. Subjects were tested singly in 10-minute sessions at the same time of day (1400–1600 hr) Tuesday through Friday and were allowed free access to water from Friday p.m. until Monday a.m. This schedule of 4-day/week testing was maintained throughout the course of drug testing.

Specific experiments conducted.

Acute single-drug administration—0.5 mA shock intensity. Acute drug tests were conducted on Thursdays and Fridays each week and used a standard "cross-over" procedure described by Fontana *et al.* (12) and McCloskey *et al.* (27). On the Thursday test days, half the subjects received a dose of the drug under examination and half received the appropriate vehicle. These treatments were reversed on the Friday test days. Thus, each animal served as its own control for the effects of a given drug dose. Initially, all rats received all doses of propranolol, atenolol, phenobarbital and diazepam administered alone. All drugs were administered 10 minutes prior to CSD testing; propranolol effects were also determined following a 60-minute pretreatment interval. Each week the effects of a different dose of a drug were tested; the order of doses and drugs tested was randomized.

Drug combination studies—0.5 mA shock intensity. In a second group of subjects, the effects of various doses of diazepam and phenobarbital were determined in propranolol (2 mg/kg) or saline pretreated subjects using a modification of the procedure by Commissaris *et al.* (6). In these studies, subjects were pretreated (60 minutes prior to testing) with either saline or 2.0 mg/kg propranolol on both the Thursday and Friday test days, while diazepam or phenobarbital and their respective vehicles were administered on alternate days. Thus, the pretreatment was held constant for a given test week, but varied from week to week. At the end of this phase of the study, each animal had received all doses of diazepam (0.6–10 mg/kg) and phenobarbital (10–40 mg/kg) following saline and propranolol pretreatment.

Single drug and drug combination studies—0.125 mA shock intensity. A third group of subjects was used to evaluate the effects of propranolol, diazepam and the combination of diazepam and propranolol on CSD behavior at a 0.125 mA shock intensity. As with the studies at the 0.5 mA shock intensity, the animals were tested for three weeks of control CSD sessions prior to drug testing. The effects of various doses of propranolol (10-minute pretreatment) alone were examined. In addition, the effects of diazepam were determined following saline or propranolol pretreatment (60 minutes). The procedures used for these drug challenges were the same as those described above.

Chronic propranolol administration—0.5 mA shock intensity. In a fourth group of 20 subjects, the effects of chronic propranolol administration on CSD behavior were examined using the methods described by Fontana *et al.* (12). Briefly, following training the subjects were tested in control (i.e., nondrug) CSD sessions for three weeks at the 0.5 mA shock intensity. The subjects were then assigned into two groups with comparable punished responding for these control CSD sessions. One group of subjects received chronic propranolol (2.0 mg/kg, IP twice daily at 0800 and 2000 hours); the controls received comparable saline injections. CSD testing (4 days/week; 1400–1600 hours) and these chronic treatments were continued for 5 weeks.

Cardiovascular Testing

In order to verify that beta-1-adrenoceptor blockade was being produced by the propranolol and atenolol treatments, the effects of these agents and saline on mean arterial pressure and heart rate were assessed in conscious rats.

Surgical procedure. Chronic indwelling catheters were placed in the femoral artery of rats as described by Commissaris and Davis (2) and Oxenkrug *et al.* (29). Briefly, animals were anesthetized with 65 mg/kg pentobarbital, IP; a hybrid PE-10/PE-20 catheter was then inserted into the femoral artery and "snaked" toward the heart to terminate in the abdominal portion of the descending aorta. The catheter was then secured to the femoral artery and the PE-20 portion was guided under the skin to protrude from the back of the neck. The animals were allowed to recover for 1–2 days prior to testing.

Testing procedure. The testing procedure for blood pressure and heart rate measurements was similar to that used by Commissaris and Davis (2) and Oxenkrug *et al.* (29). Initially, a 15-minute baseline period was obtained. The drug or saline was then administered IP and subsequent blood pressure and heart rate readings were made at 10, 20, 30, 60, 90 and 120 minutes

posttreatment. Each animal was tested only once.

Drugs

Diazepam, pentobarbital sodium and phenobarbital sodium were obtained through NIDA. *d,l*-Propranol HCl and atenolol HCl were purchased from Sigma Chemical Co. (St. Louis, MO). Pentobarbital, phenobarbital, propranolol and atenolol were dissolved in saline; diazepam was administered in a 0.5% methylcellulose suspension. Except for diazepam, doses were calculated as the respective salt and all drugs were administered IP in a volume of 1 ml/kg body weight.

Statistical Analyses

The effects of single doses of various drugs on CSD performance were compared to drug vehicle using *t*-tests for paired values. The effects of propranolol versus saline pretreatment on the actions of diazepam (or phenobarbital) were analyzed by two-way ANOVA [main effects: propranolol/saline, diazepam (or phenobarbital) doses] with repeated measures.

For the chronic treatment study, pretreatment (i.e., baseline) water consumed and punished responding were compared using *t*-tests for unpaired values. The effects of chronic propranolol or saline treatments on these parameters were examined by first converting weekly averages to change scores (relative to baseline), followed by a 2×5 factorial ANOVA (main effects: propranolol/saline, test weeks 1–5) with repeated measures.

Baseline mean arterial pressures and heart rates in the various treatment groups were compared by one-way ANOVA. The effects of various treatments on mean arterial pressure and heart rate were evaluated by paired *t*-tests relative to baseline values. In all statistical comparisons, $p<0.05$ was used to establish statistical significance (37).

RESULTS

Conditioned Suppression of Drinking

Baseline (i.e., nondrug) responding in the CSD paradigm at the 0.5 mA shock intensity, 12.4 ± 3.8 shocks/session and 12.5 ± 0.6 ml water/session, was quite stable throughout the course of this study. It should be noted that the number of tube contacts during the shock component was insignificant when compared to the number of tube contacts during the unpunished component (2500–3000 per session). Thus, the volume of water consumed accurately reflects unpunished responding in the CSD.

Table 1 summarizes the effects of various doses of propranolol, atenolol, diazepam and phenobarbital on CSD performance. The traditional anxiolytics diazepam and phenobarbital produced a dose-dependent increase in punished responding. These agents also produced a slight increase in water consumed at the lowest doses and a decrease in water consumed at the higher doses. In contrast to diazepam and phenobarbital, neither propranolol (10- or 60-minute pretreatment) nor atenolol administration significantly affected punished responding at any of the doses tested. Propranolol slightly decreased water consumed at most of the doses examined. Atenolol reduced water consumed slightly at all doses employed.

The upper panel of Fig. 1 illustrates the anticonflict effects of diazepam and phenobarbital in subjects pretreated with either saline or 2.0 mg/kg propranolol. As can be seen, diazepam and phenobarbital again produced a dose-dependent increase in punished responding. Propranolol pretreatment did not affect the response to either diazepam or phenobarbital, as indicated by the lack of a propranolol/saline main effect [diazepam: $F(1,72)<1.0$, n.s.; phenobarbital: $F(1,38)<1.0$, n.s.] and the lack of a propranolol/saline × diazepam/phenobarbital dose interaction [diazepam: $F(4,72)<1.0$, n.s.; phenobarbital: $F(2,36)<1.0$, n.s.]. Thus, propranolol pretreatment did not alter the anticonflict effects of either diazepam or phenobarbital.

The effects of diazepam and phenobarbital on water consumed in saline- and propranolol-pretreated subjects are depicted in the lower panel of Fig. 1. Diazepam tended to increase water consumed at the low (0.6–2.5 mg/kg) doses and produced a depression of water consumed at the high (10.0 mg/kg) dose. Overall, there was a significant main effect for diazepam dose, $F(4,72) = 12.73$, $p<0.05$, on water consumed. There was no main effect for propranolol/saline pretreatment on the change in water consumed in diazepam-treated rats, $F(1,18)<1.0$, n.s., nor was there a diazepam dose × propranolol/saline pretreatment interaction on this measure, $F(4,72)<1.0$, n.s. There was also a

TABLE 1

THE EFFECTS OF BETA-ANTAGONISTS AND ANXIOLYTICS ON CSD BEHAVIOR

Agent and Dose (mg/kg)	Change in Shocks Received	Change (ml) in Water Consumed
Phenobarbital (10-min pre-TX)		
5	+2.5 ± 3.2	+1.5 ± 0.3*
10	+12.4 ± 2.2*	+2.1 ± 0.5*
20	+33.4 ± 5.6*	+2.7 ± 0.5*
40	+57.0 ± 7.6*	+0.9 ± 0.9
Diazepam (10-min pre-TX)		
0.6	−1.7 ± 3.4	+0.5 ± 0.9
1.25	+8.3 ± 3.1*	+0.3 ± 0.3
2.5	+17.2 ± 7.6*	+0.6 ± 1.0
5	+18.0 ± 4.4*	−2.8 ± 1.0*
10	+31.5 ± 9.6*	−1.6 ± 1.2
Propranolol (10-min pre-TX)		
0.25	+6.0 ± 5.1	−0.1 ± 0.4
0.5	−5.8 ± 5.1	−0.1 ± 0.4
1	−1.0 ± 2.0	−0.5 ± 0.5
2	−2.3 ± 1.5	−0.2 ± 0.4
4	+1.4 ± 1.8	+0.6 ± 0.3
8	−6.0 ± 4.1	−2.3 ± 0.7
Propranolol (60-min pre-TX)		
0.5	+0.6 ± 1.2	−1.8 ± 0.6*
1	−1.0 ± 2.2	−0.3 ± 0.5
2	−0.8 ± 4.0	−0.3 ± 0.5
4	+4.2 ± 4.4	+0.2 ± 0.4
Atenolol (10-min pre-TX)		
1	−1.8 ± 1.9	−1.0 ± 0.4*
2	−0.5 ± 1.3	−2.1 ± 0.3*
4	−0.5 ± 2.8	−1.1 ± 0.3*
8	−0.5 ± 1.6	−1.3 ± 0.6*
16	−2.3 ± 1.8	−1.7 ± 0.5*

Values represent the mean ± SEM, change from vehicle treatment ($n = 20$).

*$p<0.05$, compared to vehicle injection, paired *t*-test.

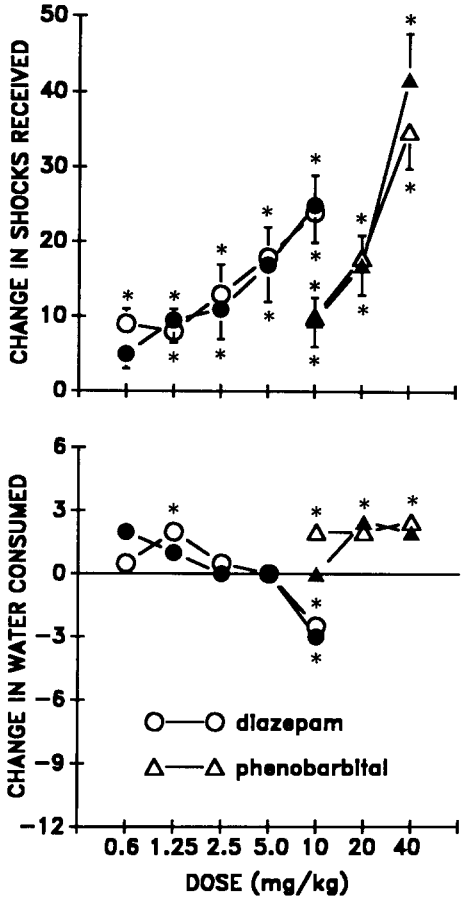

FIG. 1. Effects of propranolol pretreatment on the anticonflict actions of diazepam or phenobarbital in the CSD (0.5 mA shock intensity). Plotted are the mean change in shocks received (top panel) and water consumed (bottom panel) produced by various doses of diazepam (circles) and phenobarbital (triangles) given 10 minutes before testing, following either saline (open symbols) or 2.0 mg/kg propranolol (filled symbols) and pretreatment (60 minutes prior to test). Each symbol represents the mean ± SEM from 20 subjects. *$p<0.05$, diazepam or phenobarbital dose significantly different from vehicle control, *t*-test for paired values. Propranolol pretreatment did not alter the dose-effect curve for diazepam or phenobarbital in the CSD (see the Results section for details).

significant main effect for phenobarbital dose on water consumed, $F(2,38)=5.19$, $p<0.05$. There was also a significant main effect for propranolol/saline pretreatment on change in water consumed in the phenobarbital-treated rats, $F(1,18)=3.99$, $p<0.05$, with propranolol-pretreated subjects exhibiting less of a phenobarbital-induced increase in water consumed than saline-pretreated subjects. There was no phenobarbital dose × propranolol/saline pretreatment interaction on water consumed, $F(2,36)=1.94$, n.s. Thus, as with punished responding, propranolol pretreatment did not reliably alter the effects of diazepam or phenobarbital on unpunished responding (i.e., water consumed).

Table 2 summarizes both baseline characteristics and the effects of various doses of propranolol on CSD behavior at the 0.125 mA shock intensity. As can be seen, decreasing the shock intensity dramatically increased punished responding, with little affect on water intake. Even at this reduced level of control behavioral suppression, however, propranolol treatment failed to affect punished or unpunished responding in the CSD.

TABLE 2

BASELINE CHARACTERISTICS AND THE EFFECTS OF PROPRANOLOL ON CSD BEHAVIOR—0.125 mA SHOCK INTENSITY

	Shocks Received*	Water Intake†
Baseline	125 ± 26	12.7 ± 0.5
	Change in Shocks Received	Change in Water Intake
Propranolol		
1.0 mg/kg	+4.2 ± 0.3	+0.6 ± 0.5
2.0 mg/kg	+3.2 ± 11.0	−0.4 ± 0.3
4.0 mg/kg	+4.0 ± 11.3	−0.4 ± 0.3

*Values represent mean ± S.E.M. from 20 subjects.

†Values represent mean ± S.E.M. change (propranolol − Saline) from 20 subjects. No significant differences were found.

Figure 2 illustrates the effects of diazepam and the combination of diazepam and propranolol on CSD behavior at the 0.125 mA shock intensity. Diazepam treatment again produced a robust and

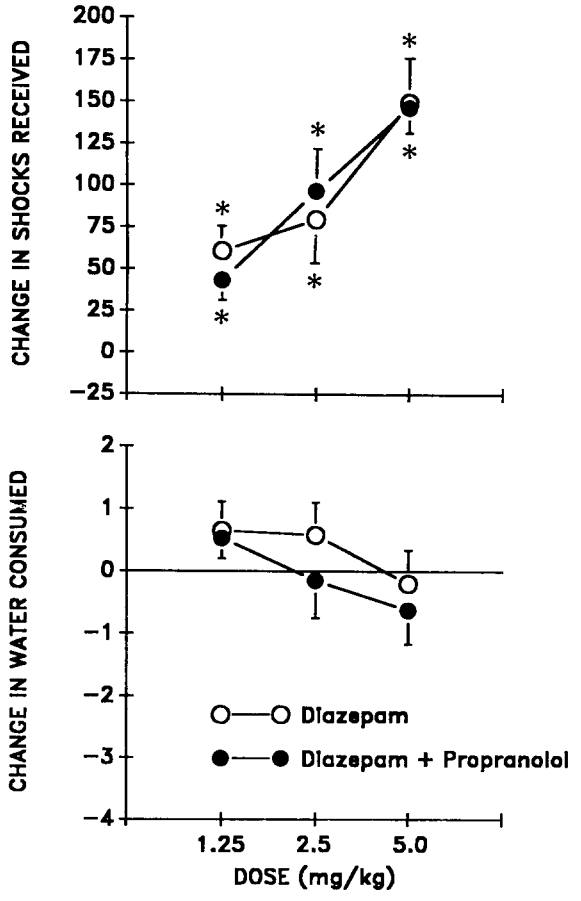

FIG. 2. Effects of propranolol pretreatment on the anticonflict effects of diazepam in the CSD (0.125 mA shock intensity). See Fig. 1 for details. *$p<0.05$, diazepam dose significantly different from vehicle control, *t*-test for paired values. Propranolol pretreatment did not alter the dose-effect curve for diazepam in the CSD (see the Results section for details).

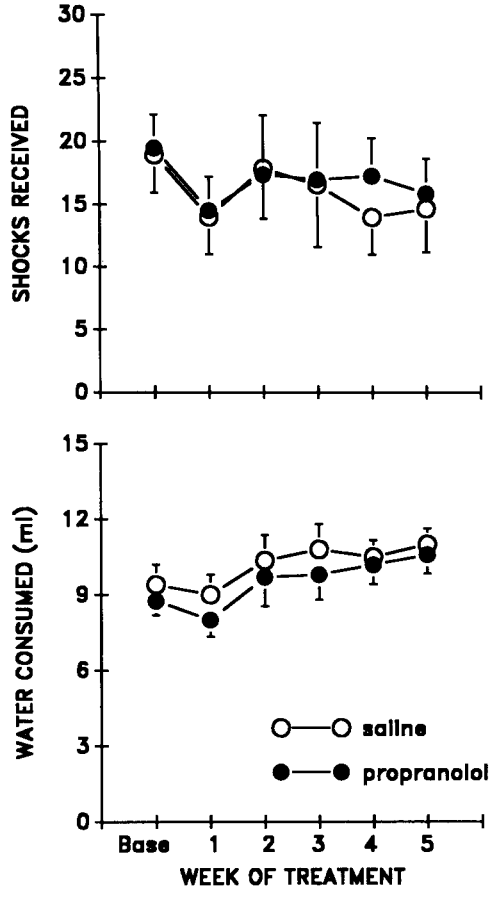

FIG. 3. The effects of chronic propranolol or saline administration on behavior in the CSD paradigm. The number of shocks received (upper panel) and volume of water consumed (lower panel) in CSD sessions before (Base) and during the course of 5 weeks of chronic saline (open circles) or propranolol (2.0 mg/kg, twice daily; filled circles) administration. Each symbol represents the mean ± SEM from 10 subjects. Chronic propranolol treatment did not affect CSD behavior over the course of 5 weeks of chronic treatment.

dose-dependent anticonflict effect, which was supported by a significant main effect for diazepam dose, $F(2,38)=17.56$, $p<0.05$. The absolute magnitude of the diazepam anticonflict was quite impressive, with subjects receiving approximately 150 shocks more than their vehicle baseline following 5 mg/kg diazepam. There was no main effect for propranolol/saline treatment, $F(1,19)<1.0$, n.s., nor was there a propranol/saline × diazepam dose interaction, $F(2,38)=2.11$, n.s. Thus, propranolol pretreatment again failed to alter the anticonflict action of diazepam.

The lower panel of Fig. 2 depicts the effects of propranolol, diazepam and the combination of diazepam and propranolol on water consumed in the CSD at the 0.125 mA shock intensity. Administered alone, there was no significant effect of propranolol on water consumed in the CSD. There was no main effect for diazepam dose, $F(2,38)=2.91$, n.s., or propranolol/saline pretreatment, $F(1,19)<1.0$, n.s., on this measure, nor was there a diazepam dose × propranolol/saline pretreatment interaction, $F(2,38)<1.0$, n.s.

The upper panel of Fig. 3 illustrates the effects of chronic propranolol/saline treatment on punished responding on the CSD. Pretreatment baselines for punished responding in the two treatment groups (saline: 18.94 ± 3.24; propranolol: 19.42 ± 2.65) were comparable, $t=(18)0.22$, n.s. As expected, chronic saline administration had no effect on punished responding throughout the study. Moreover, chronic propranolol treatment did not alter punished responding over the course of 5 weeks of administration. Factorial ANOVA revealed no significant main effect for propranolol versus saline treatment, $F(1,18)<1$, n.s. There was a significant main effect for test weeks, $F(4,72)=3.82$, $p<0.05$, with both saline and propranolol-treated subjects accepting fewer shocks in the first week of chronic treatment. Finally, there was no propranolol/saline × test week interaction, $F(4,72)<1$, n.s.

TABLE 3

THE EFFECTS OF SALINE, PROPRANOLOL AND ATENOLOL ON MEAN ARTERIAL PRESSURE AND HEART RATE IN CONSCIOUS RATS

Treatment	Mean Arterial Pressure (mmHg)	Heart Rate (beats/min)
Saline (n = 5)		
Baseline	120 ± 4	356 ± 8
10	121 ± 4	356 ± 7
20	120 ± 4	350 ± 3
30	120 ± 4	354 ± 4
60	122 ± 4	352 ± 9
90	121 ± 3	354 ± 7
120	120 ± 3	360 ± 7
2.0 mg/kg Propranolol (n = 4)		
Baseline	121 ± 3	358 ± 10
10	123 ± 4	298 ± 5*
20	122 ± 4	288 ± 5*
30	119 ± 4	298 ± 5*
60	120 ± 3	313 ± 5*
90	121 ± 5	305 ± 6*
120	121 ± 3	325 ± 10
4.0 mg/kg Atenolol (n = 4)		
Baseline	117 ± 3	355 ± 10
10	115 ± 4	310 ± 17*
20	114 ± 5	308 ± 15*
30	115 ± 6	308 ± 14*
60	119 ± 5	323 ± 13
90	119 ± 4	320 ± 11*
120	119 ± 3	335 ± 10

Values represent the mean ± SEM from 4 or 5 subjects.
*$p<0.05$ compared to preinjection baseline values, paired t-test.

The effects of chronic propranolol/saline treatment on water consumed are illustrated in the lower panel of Fig. 3. Pretreatment baselines for water consumed (saline: 9.4 ± 0.8; propranolol: 8.75 ± 0.56) did not differ between the two groups, $t(18)=0.65$, n.s. Collapsed across test weeks, chronic propranolol treatment did not significantly affect water consumed relative to saline treatment, $F(1,18)<1$, n.s. There was a significant main effect for test weeks for this measure, $F(4,72)=20.5$, $p<0.05$, with both saline- and propranolol-treated subjects consuming more water/session over the course of the five weeks of CSD testing. As seen with punished responding, however, there was no saline/propranolol × test week interaction on water consumed, $F(4,72)<1$, n.s.

Cardiovascular Studies

Baseline (i.e., preinjection) mean arterial pressures (MAPs) were comparable in all groups prior to treatment, $F(2,11)<1.0$, n.s. Similarly, baseline heart rates were comparable prior to

treatment, $F(2,11)<1.0$, n.s. Table 3 illustrates the effects of saline, 2 mg/kg propranolol or 4 mg/kg atenolol on MAP and heart rate in conscious rats. As expected, saline administration did not affect either MAP or heart rate at any test interval. Both propranolol and atenolol administration resulted in significant bradycardia relative to baseline values. These effects were statistically significant at all test intervals except 120 minutes postinjection for propranolol and 60 and 120 minutes postinjection for atenolol. Neither the propranolol nor the atenolol treatments significantly affected mean arterial pressure at any of the test intervals examined.

DISCUSSION

The CSD procedure has been used extensively to study anxiety and/or the actions of antianxiety agents (3–6, 24, 25, 27). Although considerable work has been done on the effects of barbiturates and benzodiazepines on CSD behavior, the effects of the beta-antagonist antianxiety agents have not been investigated. The present studies examined the effects on CSD behavior of beta-antagonist agents relative to diazepam and phenobarbital.

Consistent with previous reports (5, 6, 14, 25, 27), diazepam and phenobarbital produced a marked and dose-dependent increase in punished responding in the CSD and depressed background behavior (water intake) only at the highest doses employed. This anticonflict effect is consistent with the dramatic antianxiety effects of these agents in man (20). In contrast to the effects of diazepam and phenobarbital, neither propranolol nor the beta-1-selective antagonist atenolol significantly affected punished responding in the CSD. This failure to produce an antianxiety effect in the CSD is consistent with the results of other investigations. Using a multiple VI-FR conflict paradigm, Sepinwall and co-workers (35) found that propranolol did not produce the anticonflict pattern typical of traditional anxiolytics. Moreover, Robichaud *et al.* (32) failed to demonstrate an "antianxiety" response with propranolol in two different experimental animal models predictive of clinical antianxiety activity.

In the present study, pretreatment with propranolol did not alter the anticonflict effects of diazepam or phenobarbital. Thus, the beta-antagonist agents do not mimic or alter the effects of benzodiazepines or barbiturates in the CSD paradigm. This finding is in agreement with that of Robichaud *et al.* (32) who reported that pretreatment with propranolol (5.0 mg/kg, IP) did not influence the anticonflict effects of chlordiazepoxide. This finding has been questioned by Salmon and Gray on the basis that propranolol was administered 90 minutes before testing and this delay may have resulted in low tissue levels of the drug (34). However, our data on the cardiovascular effects of 2.0 mg/kg propranolol IP suggest substantial beta-blockade at 90 minutes posttreatment as demonstrated by a significant bradycardic effect at that time. Another study examining the effects of propranolol pretreatment on the antianxiety action of chlordiazepoxide found that a high dose of propranolol (40 mg/kg, PO) potentiated the actions of chlordiazepoxide (35). Although the mechanism for this effect was not discussed, nonadrenergic [e.g., serotonergic (36)] effects must be considered.

It has been suggested (34) that the failure to detect an anticonflict effect for propranolol in several earlier studies may be due to the severe level of behavioral suppression employed in these studies. In support of this notion are the studies by Durel *et al.* (10) and Salmon *et al.* (34) who demonstrated a disinhibition of punished responding by propranolol only when the control level of suppression was low. These investigators concluded that a strong anticonflict action of propranolol could be detected only under conditions of moderately suppressed baseline (i.e., non-drug) responding. In the present study, reducing the shock intensity from 0.5 to 0.125 mA decreased the suppression of punished responding from approximately 30-fold to 3.5-fold. Even at this reduced level of response suppression (125 ± 12 shocks/session), however, propranolol did not exert an anticonflict effect, nor did it alter the anticonflict effects of diazepam. It should be noted that, when expressed as the absolute change from baseline, the *magnitude* of the diazepam anticonflict effect was substantially greater at the 0.125 mA shock intensity relative to the 0.5 mA shock intensity. Although such a finding might be predicted based upon "rate-dependency," for the highly-effective 5 mg/kg dose, there was no correlation between baseline and the anticonflict effect (drug − vehicle) observed at either the 0.5 mA ($r = -.28$, n.s.) or 0.125 mA ($r = .21$, n.s.) shock intensity.

In cardiovascular studies, both 2 mg/kg propranolol and 4 mg/kg atenolol produced significant bradycardic effects when administered to conscious subjects, indicating that these treatments were indeed producing a significant beta-adrenoceptor blockade. Thus, the negative findings with the beta antagonist agents in the CSD cannot be explained on the basis of dose and/or pretreatment time selections. There were no significant changes in mean arterial pressure associated with either agent, although there was a tendency for the atenolol treatment to reduce mean arterial pressure. Indeed, a higher dose (8 mg/kg) of atenolol has been shown to produce a significant hypotensive effect (Fontana and Commissaris, unpublished).

The possibility that chronic administration is necessary to produce an anticonflict effect with propranolol was also examined in the present study. Chronic treatment with propranolol did not affect behavior in the CSD. This finding is in agreement with Salmon and Gray (33) who reported that chronic propranolol treatment had no "antianxiety" effects in differential reinforcement of low rates of responding (DLR) paradigm.

In summary, consistent with their efficacy in the treatment of generalized anxiety, both diazepam and phenobarbital markedly increased punished responding in the CSD. In contrast, neither propranolol nor atenolol treatment affected punished responding in the CSD. Furthermore, pretreatment with propranolol did not alter the anticonflict effects of diazepam or phenobarbital. Finally, chronic treatment with propranolol also failed to affect CSD behavior. These data suggest that the CSD paradigm, previously shown to be an effective "animal model" for the study of generalized anxiety (3, 4, 6, 14, 25, 27) and panic disorder (11–13), may not be an effective "animal model" for the study of the situation-specific (i.e., phobic) anxiety for which propranolol and related agents are used.

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