

Anxiolytic-Like Action of Beta-Blockers: Effects of Stimulus Salience

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TERRY, P. AND P. SALMON. *Anxiolytic-like action of beta-blockers: Effects of stimulus salience*. PHARMACOL BIOCHEM BEHAV 39(3) 597-603, 1991.—Eighteen rats were trained on a multiple schedule: lever pressing was rewarded on a Variable Interval (VI 20 s) in both components but, in addition, punished on a similar schedule in one. Shock intensity was individually adjusted to produce high or low degrees of response suppression during punishment periods in two different groups of animals. For some rats in each group, punishment periods were signalled by a flashing light; for others, by a steady light. d,l-Propranolol (2.5-7.5 mg/kg), l-propranolol (3.75, 7.5 mg/kg) and atenolol (20 mg/kg) released responding in animals in which suppression was low. These effects were restricted to the group for which the punishment signal was flashing light. The results are consistent with the view that activation of peripheral beta-adrenoceptors is involved in the suppression of responding by signals of punishment, but only in some conditions. Adding chlordiazepoxide (3.75 mg/kg) to d,l-propranolol (7.5 mg/kg) increased punished responding in the high-suppression group, but reduced it in the low-suppression group.

Punishment	Electric foot-shock	Propranolol	Atenolol	Beta-adrenoceptors	Chlordiazepoxide
Stimulus salience	Rat				

EVIDENCE is contradictory as to whether propranolol and other beta-blocking drugs are anxiolytic in man (10,16). In order to clarify its properties, propranolol has been administered to animals trained on conflict schedules in which rewarded responding during discrete periods is suppressed by punishment with electric shock. Although punished responding can be increased by known anxiolytic drugs, such as benzodiazepines (7), propranolol has had variable effects. Early reports were negative (20, 26, 31), but are hard to interpret; propranolol was administered intraventricularly in one (31) and the remaining two have procedural shortcomings (23).

Some positive results have been described also. Sepinwall et al. (26) reported an increase in punished responding by propranolol when this had already been increased by the benzodiazepine, chlordiazepoxide (CDP). This may be related to a more recent finding that propranolol further increased punished responding in animals in which this had been increased by a different procedure: reducing shock to a very low intensity (23). In experiments in which nonreward rather than shock has been used, moderately suppressed responding has also been preferentially facilitated by propranolol (21). In a further study which found a significant increase of punished responding by propranolol, the authors attributed this to their use of a baseline of higher response rates (maintained by weaker shock) than previously (3), but direct comparison is difficult between their data, from pigeons, and those from the other experiments, in which rats have been used. A more recent study makes it clear that the issue is not yet resolved. Fontana et al. found no anticonflict ef-

fect of propranolol on rats' licking when this was punished by shock at either of two intensities (6).

To confirm a selective effect of propranolol on moderately suppressed responding in animals might help to clarify the clinical conditions under which the drug is anxiolytic. The present experiment provides further data on the relationship between response suppression and its release by propranolol. First, we established whether the influence of shock intensity on the effect of propranolol described previously (23) could be replicated, and we explored the dose-dependence of this drug effect. Since propranolol blocks peripheral beta-adrenoceptors, its effect is of theoretical interest also, because it may indicate that, contrary to the view of Rescorla and Solomon (19), the peripheral nervous system is involved in the effect of conditioned fear stimuli on operant behavior. We therefore extended the previous findings by examining the pharmacological basis of propranolol's effect. Of its isomers, dextro- and laevo-propranolol, only laevo-propranolol is beta-blocking (30), as well as antagonizing serotonin transmission (8,14); nonspecific membrane-stabilizing properties are distributed equally between both. Atenolol, which is primarily a beta₁ antagonist, is also of interest because of its exclusion from the brain after systemic administration (28), and because it has already been reported (3) to disinhibit punished responding in pigeons.

We have previously suggested that shock intensity influences the effect of propranolol by affecting the salience of the shock (23). In the present experiment, we also tested the importance of the salience of the stimulus used to distinguish punishment

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and nonpunishment periods: flashing and steady lights served as signals and their significance was counterbalanced in different groups of animals.

Finally, we investigated the relationship between response suppression and the effect of propranolol in a second way: by an attempt to replicate the drug interaction with CDP reported by Sepinwall et al. (26) and described above.

METHOD

Subjects

Eighteen Sprague-Dawley rats (Olac Ltd., Bicester, UK) were individually housed on a 12/12-hour light/dark cycle. Testing was during the light phase. One rat died after the second drug trial. Food deprivation began two weeks before testing; rats were then fed 15 g standard diet each day. During the experiment this was given directly after behavioral testing. Water was freely available in the home cage. Mean body weights at the start and end of the experiment were 315 g and 379 g respectively.

Apparatus and Training

Rats were tested in six purpose-built 2-lever Skinner boxes (31 cm × 26 cm × 25 cm high) with metal rail floors (rails 0.5 cm diameter, 2 cm apart) in sound-attenuating, light-proof chambers. Only the left-hand lever of each box operated, and required a force of 5 g to register a response. Reinforcement was by single 45 mg Noyes pellets, and signalled by a 3 s illumination of the food tray. A 2.8-W bulb directly above the left lever provided the stimulus light (see below). Ambient illumination was by a 2.8-W bulb in the box roof. A shock generator and scrambler (Campden Instruments, models 521C, 521S) were connected to the floor rails of each box. On-line control and response recording was by an Acorn "Master" microcomputer programmed in "Spider" Basic (Paul Fray Ltd., Cambridge, UK).

The rats were first trained to lever-press over 3 days, then on Fixed Ratio 2 for 4 days. Sessions were 30 min. Variable interval (VI) training then followed. The mean interval was gradually increased from 5 to 20 s over 9 days. VI 20 continued for 34 days before discrimination training began. Sessions were then extended to 32 min, and divided into 162-min periods separated by 1 s time out. VI 20 continued during 8 (UNPUN) periods; during the remaining (PUN) periods, responses continued to be reinforced on the same schedule but, in addition, were punished by a 0.5 s electric footshock (see below) according to a similar, but independent, VI 20 schedule (independence ensures that shock should acquire no predictive value for nonreward, and so prevents its aversiveness being affected by counterconditioning). The order of VI and PUN periods was chosen daily from 4 sequences chosen randomly with the constraint that no more than three periods of the same kind could be consecutive. The stimulus light shone steadily or flashed (being lit for 1 s in every 2) to signal the component in force; the significance of the signal was counterbalanced between two different sets of animals. Discrimination training continued for 54 sessions.

From the start of discrimination training, animals were divided into two equal groups: High- and Low-shock. Within each group, 4 or 5 animals were in each stimulus condition (steady or flashing light). All rats began discrimination training with shock intensity at 0.05 mA. It was then adjusted, in steps of 0.05 mA, for each animal independently according to the following protocol. In the Low-shock group, the target was to maintain each animal's level of responding during PUN periods between 50–80% of its UNPUN response rate. When saline PUN

responses exceeded or fell short of this range on two consecutive days, shock was increased or decreased accordingly. For High-shock animals, the target range of PUN responses was 5–30% of UNPUN responses. When an animal's mean saline responses fell outside of this range over any drug trial (see below), it was excluded from the analysis of that trial. Mean shock intensities over all trials for High- and Low-shock groups were 0.17 and 0.07 mA for animals punished in flashing light, 0.15 and 0.08 mA for steady light.

Drug Testing

Drugs were injected IP in 1 ml isotonic saline/kg body weight; doses refer to the HCl salt. Vehicle alone was injected on saline days. The minimum interval between drug trials was one day. The order of trials was: d,l-propranolol 10, 5, 2.5, 7.5, 1, 10 mg/kg; l-propranolol 3.75 mg/kg; atenolol 10, 20, 40 mg/kg; d-propranolol 7.5 mg/kg; l-propranolol 7.5 mg/kg; d,l-propranolol 10 mg/kg. The second trial of d,l-propranolol at 10 mg/kg was to find whether generalized suppressant effects apparent in the first trial had habituated. Each dose was tested in a trial lasting 8 days on an ABBAABBA design (A=saline; B=drug), apart from those of atenolol and the second trial of d,l-propranolol at 10 mg/kg, which lasted 4 days (ABBA). Finally, d,l-propranolol (7.5 mg/kg) and CDP (3.75 mg/kg) were tested alone and in combination in a single design. In 4 successive blocks, each of 4 days, rats received one day each with saline, propranolol alone, CDP alone or both drugs. The order of treatments was balanced in a Latin square. All injections were 5 minutes before testing.

Doses of the isomers were selected in the following way. Racemic propranolol is 50% laevo-, 50%-dextro-propranolol. Virtually all of the beta-blocking property of the racemic drug is attributable to the laevo-isomer. Therefore, to obtain a dose of laevo-propranolol which is equivalent in beta-blocking potency to a given dose of the racemic mixture, half the racemic dose would be chosen. Since nonspecific effects are distributed equally between the isomers, an equivalent nonspecific effect of dextro-propranolol would be obtained by a dose equal that of the racemic drug. Since 7.5 mg/kg proved to be the highest effective dose of racemic propranolol, doses were chosen in relation to this. The additional trial of laevo-propranolol (7.5 mg/kg) was carried out so that the isomers could also be compared at the same dose.

Data Collection and Analysis

Responses/minute were averaged separately across PUN and UNPUN periods in each daily session, and square root transformed to normalize their distributions for analyses of variance. Preliminary analyses included two between-subject treatments: Light (distinguishing animals for which steady or flashing light signalled punishment periods) and Shock. There were two within-subject terms: Days (describing successive pairs of days) and Drug (distinguishing the drug and saline days within each pair). PUN responses were analyzed after adjustment for covariance with UNPUN. This has statistical advantages over the use of a suppression ratio (23). For the trial in which both CDP and propranolol were given, Days described successive sets of 4 days; the terms Propranolol and CDP distinguished days on which the respective drugs were present or absent. In preliminary analyses, apart from that of the mixture, significant drug effects on PUN responses interacted with Light. Therefore separate analyses of variance (or, for PUN, covariance) were performed for each Light condition; these are the results presented.

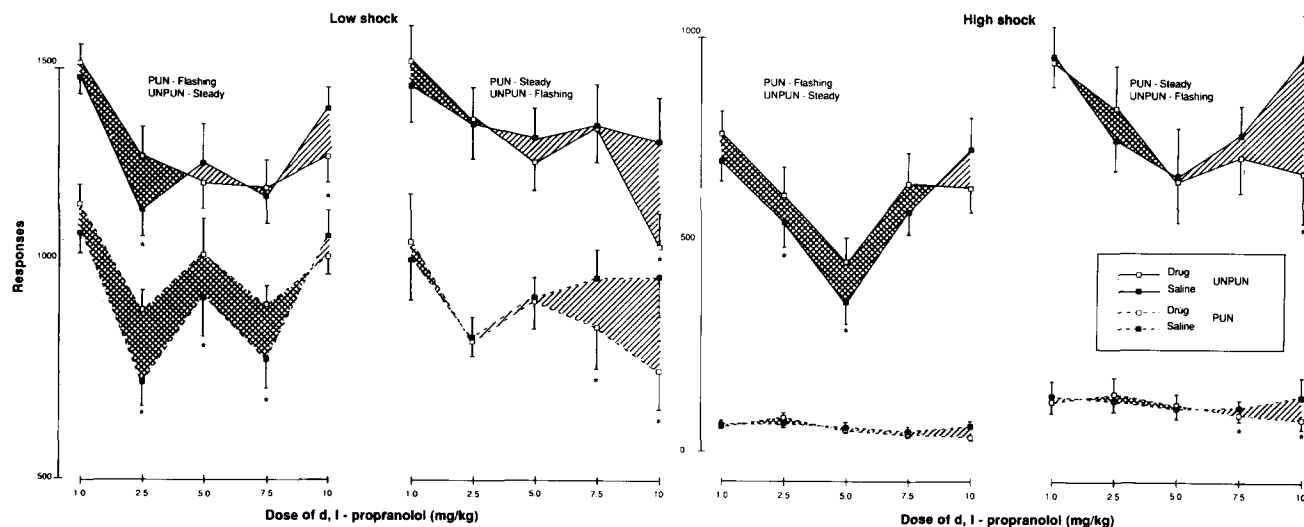


FIG. 1. Mean daily responses (and SEM) after saline or propranolol during the unpunished and punished components of the multiple schedule. Separate groups received high or low shock; steady or flashing light signalled PUN or UNPUN in different groups. *Drug effect which reaches statistical significance (see text for details). Crossed shading indicates drug responding greater than saline; single shading indicates the reverse.

In addition, to check whether the occurrence of the first shock in each PUN period contributed to response suppression over and above the effect of the signal light, PUN response rates in each session were cumulated, but separately from the start of the period to receipt of the first shock (preshock), and from this to the end of the period (postshock). To confirm the difference between these two rates which appeared in every drug trial, the mean pre- and postshock response rates on the saline days in each trial were entered into a single analysis of variance; between-subject treatments were Period and Light.

Analyses were by the GENSTAT 5 program (Rothamstead Experimental Station).

RESULTS

Manipulation of Shock Intensity

Mean UNPUN responses over all trials were 1342 and 793 in low- and high-shock animals, respectively. Mean PUN responding was within the target ranges in every trial. In every trial, the main effect of Shock on both UNPUN and PUN responding was significant, confirming the higher rates of both baseline and punished responding in the low-shock animals. Within PUN periods, response rates after the first shock had been received were lower than before, but the decline was greater in steady light than in flashing (18.7 vs. 6.0 responses/minute). This difference was confirmed by the analysis of mean pre- and postshock values on the saline days in each trial [Period \times Light: $F(1,22) = 99.6, p < 0.001$].

Racemic Propranolol

Effects at 10 mg/kg were similar in each of the two trials: results refer to the second.

Effects on UNPUN response rates were few and inconsistent (Fig. 1). At 2.5 mg/kg these were increased in animals punished in flashing light, irrespective of shock level, $F(1,42) = 5.08, p < 0.05$. At 5 mg/kg they were increased in the high-shock animals punished in flashing light [Drug \times Shock: $F(1,42) = 13.78, p < 0.001$]. UNPUN responses were decreased generally at 10 mg/kg

[PUN-Flashing group: $F(1,15) = 5.72, p < 0.05$; PUN-Steady group: $F(1,18) = 13.56, p < 0.01$].

Mean PUN responses are shown in Fig. 1. There was no significant effect at the lowest dose, 1 mg/kg. Effects of the higher doses depended on the stimulus light. There were no facilitatory effects on responding in animals punished in steady light, although responding was reduced by the two higher doses, 7.5 and 10 mg/kg [respectively: $F(1,42) = 6.69, p < 0.05$; $F(1,18) = 11.26, p < 0.01$]. Facilitatory effects were seen only in flashing light. Responses were increased at 2.5 mg/kg, $F(1,42) = 4.50, p < 0.05$. Figure 1 suggests that the increase tended to be greater in low-shock animals, but the interaction of Drug \times Shock became significant, confirming this differential effect, only at the higher doses: 5.0 and 7.5 mg/kg [respectively, $F(1,42) = 9.12, 7.52, ps < 0.01$]. At the highest dose, 10 mg/kg, the decrease in responding in flashing light, irrespective of shock level, approached significance, $F(1,15) = 4.33, p = 0.06$.

Isomers

Mean responses are shown in Fig. 2. Dextro-propranolol had no effect on either PUN or UNPUN responses. Laevo-propranolol (3.75 mg/kg) increased UNPUN responding in the rats punished in flashing light irrespective of the shock level, $F(1,42) = 6.99, p < 0.001$, but an increase at 7.5 mg/kg was further restricted to the high-shock condition [Drug \times Shock: $F(1,35) = 6.41, p < 0.05$]. PUN responding was released consistently by laevo-propranolol at both 3.75 and 7.5 mg/kg. The analyses confirmed the suggestion in Fig. 2 of an effect similar to that of the racemic mixture at 7.5 mg/kg: it was confined to animals punished in flashing light, and the Drug \times Shock interaction in these animals confirmed that it was present only at low-shock levels [3.75 mg/kg: $F(1,42) = 9.89, p < 0.005$; 7.5 mg/kg: $F(1,35) = 8.44, p < 0.01$]. Graphically, the effect at each dose was of similar order to that of racemic propranolol at 7.5 mg/kg.

Atenolol

UNPUN responding was unaffected except for a slight increase at the lowest dose, 10 mg/kg, in the animals punished in

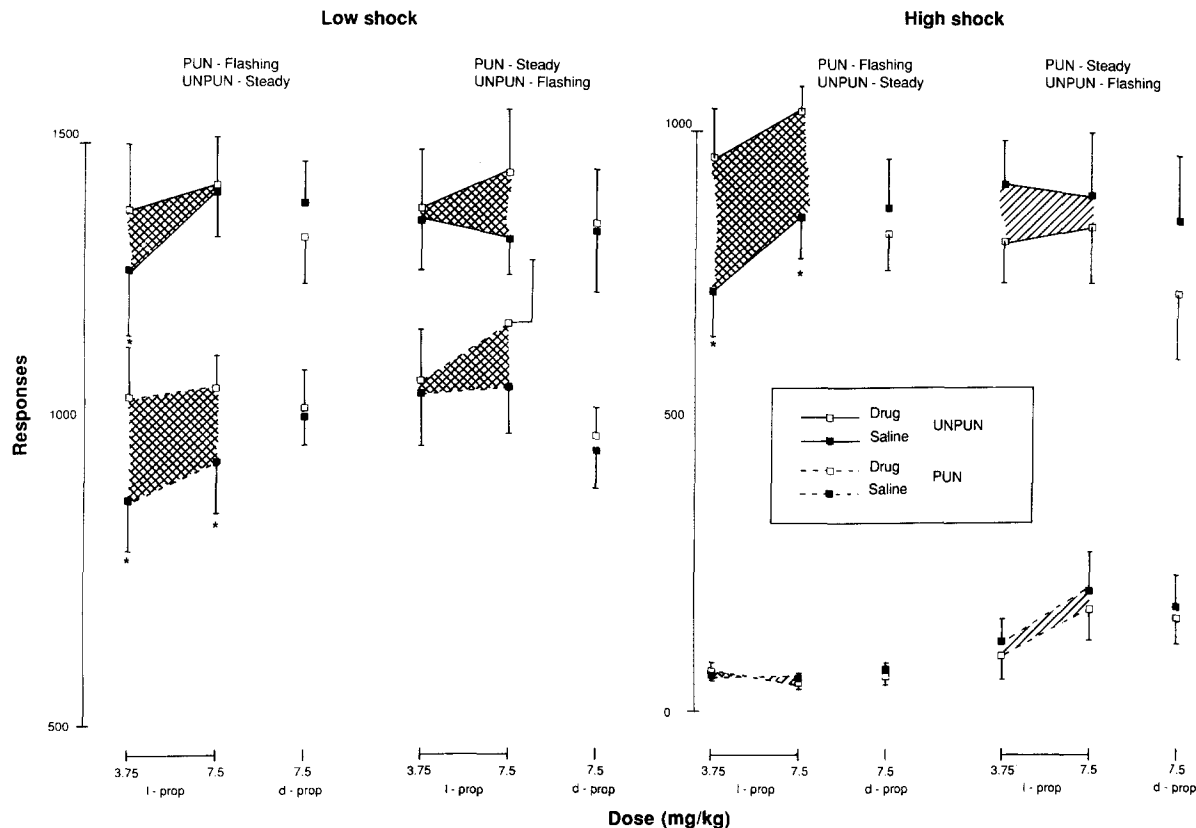


FIG. 2. Mean daily responses (and SEM) after saline or d- or l-propranolol. Details as for Fig. 1.

steady light, $F(1,18) = 5.14$, $p < 0.05$ (Fig. 3). Means for PUN responses are shown in Fig. 3. Again, there was no effect in steady light ($F_s < 1.0$), but responding was increased by the higher doses in flashing light; this reached significance at 20 mg/kg, $F(1,18) = 5.65$, $p < 0.05$, and approached significance at 40 mg/kg, $F(1,15) = 4.25$, $p < 0.10$. Graphically, this effect approached the magnitude of that seen with racemic and laevo-propranolol. Although Fig. 3 shows that the effect was attributable to the low-shock animals, the interaction of Drug \times Shock fell short of significance.

Mixture

For both UNPUN and PUN response rates, inspection of means for each light condition revealed a similar pattern in each, although effects on PUN responses were more accentuated in flashing light. For simplicity, values in Fig. 4 are therefore averaged across light conditions. CDP increased UNPUN responses. Although propranolol was without any effect on UNPUN when given alone, it abolished this effect of CDP. This pattern is confirmed by the CDP \times Propranolol interaction, $F(1,78) = 7.37$, $p < 0.01$. Comparisons which reached significance within this interaction included the increased responding after CDP compared with saline and the mixture ($t_s = 3.33, 3.56$, respectively; $p_s < 0.01$). In PUN responses, the drug interaction differed between the high- and low-shock groups [CDP \times Propranolol \times Shock: $F(1,77) = 7.38$, $p < 0.01$]. At low shock intensity, the mixture decreased responding by comparison with propranolol and CDP alone ($t_s = 2.03$, $p < 0.05$). At high shock

the mixture did not differ from CDP alone (Fig. 4); there was an indication that, after allowing for differences in UNPUN response rates by analysis of covariance, however, the mixture was more effective than CDP alone: the mixture, but not CDP, increased responding by comparison with both propranolol alone ($t = 3.23$, $p < 0.01$) and saline ($t = 2.56$, $p < 0.05$).

DISCUSSION

As in previous experiments (23), the response-increasing effect of propranolol on punished responding could not be accounted for by a general rate-increasing action. It was present at doses at which no increase in UNPUN responding was seen, and remained after adjustment for covariance with UNPUN responses. The effect was modest and confined to a narrow range of doses. Nevertheless, its relationship to level of suppression was consistent with a previous report (23) that propranolol increased responding when this was mildly suppressed by weak electric shock, but not when greater suppression was maintained by more intense shock. This contrasts with CDP which tends generally to show a greater effect at higher levels of suppression (18). In the schedules of punishment on which propranolol has shown facilitatory effects, shock has been either of low intensity, as in the present case, or has been delivered on a relatively sparse schedule (3, 22, 23). It may be that a property of the shock such as its salience, which could be a product of intensity and frequency, counters the disinhibitory effect of propranolol.

It remains to explain the absence of an anticonflict effect on lick-suppression by either high (0.5 mA) or low (0.125 mA)

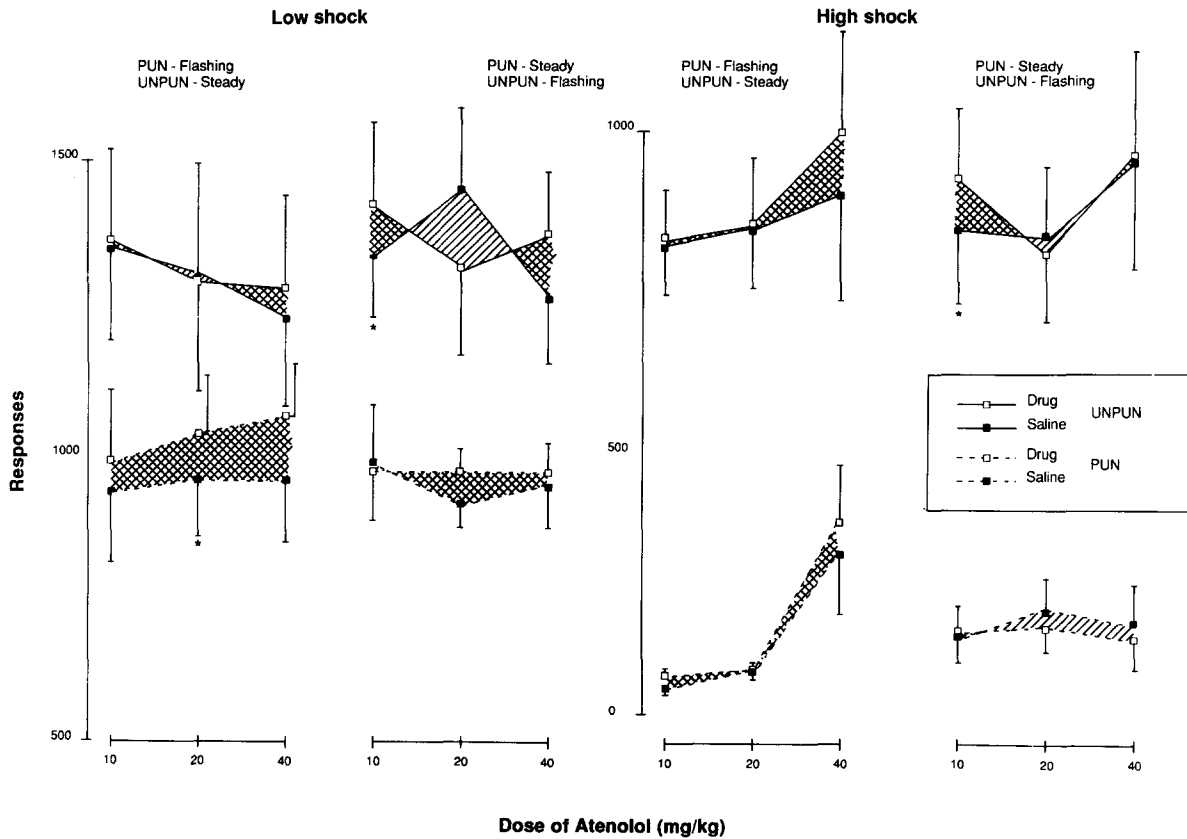


FIG. 3. Mean daily responses (and SEM) after saline or atenolol. Details as for Fig. 1.

shock in Fontana et al.'s recent experiment (6). In that case, however, responding at the lower dose was still suppressed by a factor of 3.5, a greater amount than in the present experiment. It may also be that the shock was more salient in their lick-suppression procedure, in which it followed every lick during the final 5 s of the 7 s signal, than in the present experiment where it was delivered intermittently. In addition, our results suggest that the effect of propranolol is relatively modest; to separate it from error may require the repetition of drug and saline days at a single dose—as in the present experiment.

In the present experiment, an additional factor circumscribed the effect of propranolol: responding was increased only in animals for which punishment periods were signalled by flashing light. In steady light, the only effect was an inhibitory one at higher doses. This unexpected finding shows that anticonglict effects of propranolol depend on relatively subtle features of the experimental procedure. Although this frustrates the attempt to compare results between experiments, it suggests that to identify these features might elucidate the conditions under which propranolol has anxiolytic properties in man. It might be that the drug interacts with the arousing properties of the flashing light (24). However, when flashing and steady lights have been compared as signals for nonreward, propranolol has had no differential effect between them (25). Another, speculative, possibility arises from the observation that the shock was apparently a part of the stimulus complex which controlled response suppression: response rate during the punishment periods was reduced after presentation of the first shock, but this effect was much less if the nominal signal was the more salient, flashing, light. There-

fore, propranolol might only increase punished responding when suppression is not appreciably controlled by the shock itself.

Because effects of racemic propranolol could be reproduced by laevo-, but not dextro-propranolol, it is more likely that beta-blockade is involved than the nonspecific local anesthetic effect, although a role for 5-HT antagonism is also possible (8,14). The response-increasing effects of laevo-propranolol failed to decline at the higher dose (7.5 mg/kg) which, in terms of beta-blocking potency, is equivalent to 15 mg/kg of racemic propranolol—a dose which exceeds that (10 mg/kg) at which the disinhibitory effect was reversed. Loss of this effect at high doses of racemic propranolol might therefore result from non-specific activity rather than beta-blockade.

In certain respects, atenolol also had a similar effect to propranolol. Punished responding was increased to a similar extent; once again, this was restricted to rats punished in flashing light. The only discrepancy is that the tendency for a greater effect at low shock intensities (Fig. 3) did not reach significance. Had the trials continued for as long as those of propranolol, statistical support might have been expected. Since the pharmacological properties of atenolol are a subset of those of propranolol, it is reasonable to attribute the effects of both drugs to these: that is, to peripheral beta (particularly beta₁-)blockade. This suggests that peripheral beta-adrenergically mediated stimuli may be involved in the suppression of responding by fear, but only where control by salient external stimuli (strong or frequent shock) is absent. Internal and environmental stimuli may "compete" for control over behavior in a similar way to that identified in man (17).

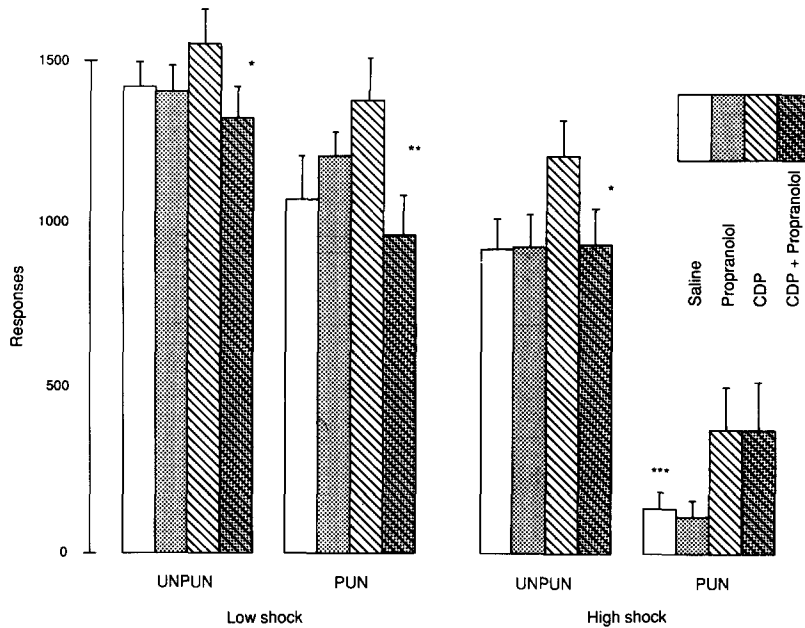


FIG. 4. Mean daily responses (and SEM) in unpunished and punished components of the multiple schedule after saline, and after CDP and dl-propranolol in combination and separately. *Mixture decreases responding by comparison with CDP alone; **Mixture decreases responding by comparison with propranolol and CDP; ***Mixture increases responding by comparison with propranolol and saline.

Although speculative, this view can help to make sense of some of the disparate effects of beta-blockers in man. An anxiolytic action has been described in situations in which a salient external anxiety-provoking stimulus is difficult to identify: for example in public speaking or stage performance (5, 12, 13, 15). By contrast, negative results are typical when more discrete stressors are used, such as simulated aircraft flight (4), mental arithmetic (11), hypnotic suggestion (2) and exposure to spiders and snakes in phobic people (1). This contrast may apply to clinical practice, also. Tyrer (29) found that the anxiety patients who benefitted from treatment with propranolol were the ones who failed to identify external sources of anxiety.

Finally, treatment of anxiety patients by propranolol and a benzodiazepine has been found to be more effective than by either alone (9,27). Consistent with this, Sepinwall et al. (26) reported that propranolol (40 mg/kg) enhanced the effect of CDP (both drugs given PO) on responding which was suppressed by shock of relatively high intensity, although having no effect alone. The interaction may be specific to particular doses or dose ratios, because Fontana et al. (6) could not repli-

cate Sepinwall et al.'s results using diazepam and a relatively low dose (2 mg/kg IP) of propranolol. At high shock intensities, the present results resemble those of Fontana et al. (6): adding CDP increased punished responding by comparison with saline or propranolol alone (after allowing for changes in baseline (UNPUN) responding), although the effect was not shown to be superior to that of CDP alone. The importance of our results, however, is to show that these drugs can also interact in a negative way. That is, adding CDP to propranolol under conditions where the latter alone was effective was counterproductive: at low shock the mixture further suppressed responding. Study of a wider range of doses and dose ratios is necessary to establish the conditions which lead to negative and positive interactions.

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