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The Antianxiety Effect of Beta-Blockers on Punished Responding

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DUREL, L. A., D. S. KRANTZ AND J. E. BARRETT. *The antianxiety effect of beta-blockers on punished responding.* PHARMACOL BIOCHEM BEHAV 25(2) 371–374, 1986.—Clinically effective anxiolytic drugs generally increase responding that is suppressed by punishment. Although beta-adrenergic antagonists have been reported to reduce anxiety in humans, such effects have not been reported reliably in animal punishment procedures. In the present study, three pigeons were trained to key peck under a multiple schedule. In the presence of a white light every thirtieth response produced grain. In the presence of a red light every thirtieth response produced grain and electric shock which suppressed responding to approximately 10 percent of that occurring in the alternate component. Propranolol (1.0–5.6 mg/kg) and, less reliably, atenolol significantly increased punished responding in a dose-related manner; propranolol effects were approximately twice as large as those of atenolol. Both drugs no more than weakly increased unpunished response rates at doses that increased punished responding. These results suggest that (1) beta-blockers have an antianxiety effect on punished behavior, and that (2) peripheral beta-blockade, the predominant action of beta-blockers regardless of whether they readily penetrate the brain, is likely to be involved in this effect.

Beta-blockers Punished responding Propranolol Atenolol Anxiolytic drugs Behavioral effects Anxiety

SINCE their introduction for the treatment of cardiovascular disorders, the beta-adrenergic antagonists have been associated with a variety of behavioral effects [18,22]. Anxiety reduction has been reported in controlled studies of these drugs in anxious patients and in healthy subjects placed in anxiety-provoking situations (see [7, 9, 21] for reviews). Peripheral beta-blockade, which reduces sympathetically-mediated activity such as increased heart rate and cardiac contractility, is generally thought to be sufficient to account for the antianxiety effect of these drugs [18, 27, 28].

Shortly after the initial reports of anxiety reduction by beta-blockers, several animal studies were performed with propranolol, the most widely used beta-blocker. In contrast to the studies with humans, these studies noted minor changes in behavior but generally failed to detect any substantial antianxiety effect in a test usually predictive of such activity [16, 23, 24].

The standard animal behavioral procedure used to characterize drugs prescribed clinically to treat anxiety and to test drugs for their possible efficacy in such treatment is a procedure during which responding produces both reinforcement and punishment [11]. Behavior suppressed by punishment procedure is typically increased by benzodiazepines and other clinically effective antianxiety agents [3, 10, 12, 25]. Results of human and animal studies of the benzodiazepines, barbiturates, and meprobamate have led reviewers to conclude that the punishment procedure is a valid test to discriminate the classes of drugs which are clinically effective antianxiety agents [3, 12, 25, 13]. Exceptionally high correlations link the efficacy and potency of the antianxiety agents in animal punishment studies with dosages of drugs found effective in the treatment of anxious patients [2, 4, 5].

Although the animal studies of propranolol have reported either weak or no anti-punishment effects [16, 23, 24], there are continuing observations of change in mood and behavior associated with the use of propranolol and other beta-blockers in humans (see [7,8]). The present study reexamined punished responding using propranolol and the newer beta-blocker atenolol. Atenolol differs from propranolol on several pharmacological parameters. For example, as a cardioselective beta-blocker, it antagonizes fewer of epinephrine's noncardiac actions; in addition, it has only a very weak ability to penetrate the brain [22,28]. However, it has been related to human anxiety reduction [19].

METHOD

Animals

Three adult White Carneaux pigeons were maintained at approximately 80% of their free-feeding body weights. The birds were experimentally naive, having no previous exposure to operant schedules, shock presentation, or drugs.

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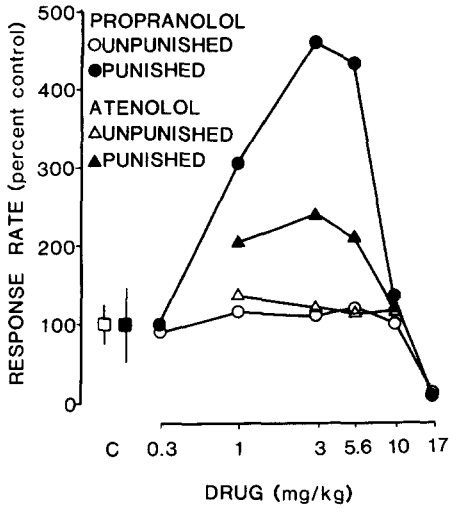

FIG. 1. Averaged drug effects on punished responding are represented as filled symbols. Averaged drug effects on unpunished responding are represented as open symbols. Propranolol effects are shown as circles, atenolol effects as triangles. Squares represent the mean ± one standard deviation of control rates.

Apparatus

The experimental chamber, measuring 29×28×33 cm, consisted of Plexiglas walls and ceiling, except for the aluminum front panel and a wire mesh floor. A plastic response key (R. Gerbrands Co.) was located behind a two cm diameter opening in the center of the front panel. The key was transilluminated by pairs of red and white 7 W lamps. A key peck of 15 grams (0.15 N) or more was defined as a response and resulted in an audible click of a feedback relay located behind the front panel. Below the key was an opening through which acess to mixed grain was provided. The food magazine, but not the response key, was illuminated when grain was delivered. The experimental chamber was situated in an enclosure which was ventilated, sound- and light-attenuating, and supplied with white noise.

Electric shock was delivered through stainless steel wires implanted around the pubis bone. The wires were connected by a phone jack through a harness to a swivel connection at the top of the chamber. Shock (200 msec in duration, 120 V AC) was delivered through a variable resistor.

Procedure

The pigeons were trained to key peck on a multiple schedule of two components, one in which responding was unpunished and one in which it was punished. In the presence of a white key light, every thirtieth response produced a two-second grain presentation (an FR 30 schedule). In the presence of a red light, every thirtieth response produced grain and, after stable performance was reached, also produced electric shock. Shock intensity (3–4 mA) was adjusted for each pigeon to maintain punished responding at a level that typically resulted in one or two shocks per three-min component. The two three-min components alternated regularly and were separated by a 30 sec timeout period during which the chamber was dark and responding had no scheduled consequences. The 35-min experimental session was composed of five presentations of each component and was conducted five days per week.

TABLE 1

PUNISHED RESPONSE RATES (IN RESPONSES/SECOND) AND MAXIMAL DRUG EFFECTS

	Control		Maximal Drug Effects	
Subj No.	Mean	1 Standard Deviation	Propranolol	Atenolol
P-2229-1	0.286	0.106	1.134*	NA
P-2229-2	0.315	0.138	0.925*	0.811*
P-4258	0.140	0.094	1.666*	0.602*
P-4741	0.086	0.045	0.236*	0.116

*$p<0.05$ Note: atenolol was not utilized during the first dose-response series for P-2229 (see text).

Propranolol or atenolol (in a saline vehicle) was injected into the pectoral muscle immediately prior to the session. Solutions of the drug or the saline vehicle were given in a volume of 1.0 ml/kg of body weight. Propranolol was administered first in two birds; atenolol preceded propranolol in the other. Four doses ranging from 1.0 to 10.0 mg/kg (salt) of body weight were given in an irregular order once or twice for each drug series. (In order to find the range of effective doses, the first propranolol series in P-2229 was expanded to include doses of 0.3 and 17.0 mg/kg, that is, doses just above and below the range of doses which had affected responding in that animal. Punished and unpunished responding under the lower dose were virtually the same as the control rates and so the lower dose was omitted during the rest of the study. At 17.0 mg/kg, both types of responding were significantly decreased, an effect taken to be an indication of nonspecific behavioral toxicity, and this dose was omitted for the remaining drug series in all animals.) Drugs were administered no more than twice weekly, typically on Tuesdays and Fridays, given that control patterns and rates of responding remained relatively consistent compared to performances that had stabilized prior to the beginning of drug studies.

Data Analysis

The behavioral measure used in this study was the average response rate for each bird for the total session time in unpunished or punished responses per second. The average of each bird's response rates for Thursday (non-drug) sessions over the course of the study served as the measure of control performance. (One animal, P-2229, received two series of propranolol doses. Control rates for the first series are based on the control data points for that series alone; control rates for the second series are based on control data for the atenolol series and the second propranolol series). Drug effects were calculated as comparisons with the average control response rates for each bird at each dose. The determination for each bird that significant changes in responding occurred after drug administration was made by a confidence interval bracketing the control mean by two standard deviations on either side. Response rates outside of the interval were considered statistically significant.

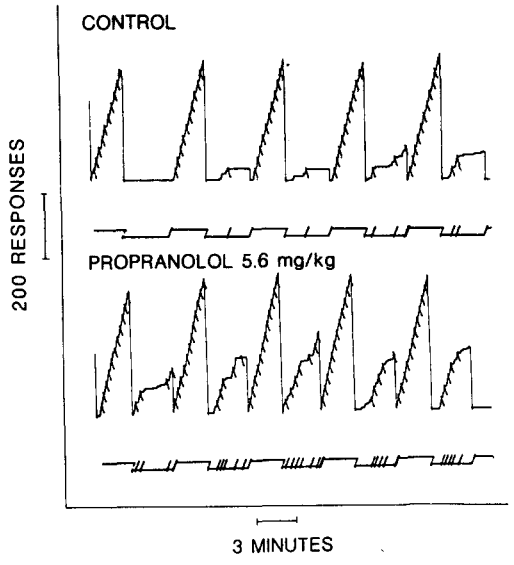

FIG. 2. Cumulative responses are on the ordinate and time on the abcissa, with the pen resetting after each three minute component. Downward pips in the odd-numbered components represent food presentation; downward pips in the even-numbered components represent food and shock presentations. Shocks are also recorded on the bottom tracing.

RESULTS

When the data from the four propanolol series and three atenolol series were averaged across subjects, non-drug control performances for the three subjects averaged 1.9 responses per second for unpunished responding and 0.2 responses per second for punished responding. The average results of the study are represented graphically in the dose-response curves of Fig. 1. Drug effects are the mean effects for the three birds given as the percent of control.

Punished responding was greatly increased and effects were related to drug dose for both drugs, although effects were more consistent and stronger for propranolol. Unpunished responding was increased only weakly, if at all, with both beta-blockers, irrespective of drug dose within the effective dose range. While the two dose-response curves were similar for the dose range and indicate considerable anxiolytic effect at 1.0, 3.0, and 5.6 mg/kg, propranolol was approximately twice as effective as atenolol in releasing punished responding. Neither unpunished nor punished responding changed from control levels in response to injections of saline. No influence of the order of administration on the effects of the drugs was evident.

Control and maximal drug effect data for the individual birds are given in Table 1. Propranolol significantly increased punished responding at 5.6 mg/kg in all three birds; at 1.0 and 3.0 mg/kg, the increase was significant in two birds (P-2229 and P-4258). In one bird (P-2229), the increase in punished responding was significant at 10.0 mg/kg of propranolol, as well as at the three lower doses. A second propranolol series following the administration of atenolol in this bird again yielded significant results at 1.0, 3.0, and 5.6 mg/kg.

Although less effective than propranolol, atenolol generally increased punished response rates at the same doses as propranolol in two of the birds. Punished responding was significantly increased at 1.0, 3.0, and 5.6 mg/kg in one bird (P-4258), at 3.0 mg/kg in another (P-2229), and not at any dose in the third (P-4741).

Figure 2 shows typical cumulative response records of a control session (top) and a session the following day under an effective drug dose (bottom). During the control session, unpunished responding occurred at a consistent and rapid rate after each brief pause following food; punished responding was sporadic and suppressed. Propranolol (5.6 mg/kg) increased punished responding to a level four times greater than that occurring under control conditions; unpunished responding was only slightly increased.

DISCUSSION

Both beta-blockers, propranolol and atenolol, substantially increased punished responding. With propranolol, the effect was large and statistically significant in all three birds. While effective at the same doses as propranolol, atenolol resulted in a smaller increase in punished responding that was significant in fewer instances. For both drugs, the increases in punished responding were dose-related and occurred over the same dose range. The results of this study are also in accord with clinical reports of antianxiety effects for propranolol and, more recently, atenolol [19].

The findings of the present study suggest that some parameter or parameters which differ from the earlier studies are necessary for the rate-increasing effect of propranolol upon punished responding to occur. The four studies of the phenomenon varied in a number of ways. One possibly relevant factor is the difference in control response rates. The levels of punished responding in this study and in the only earlier study to report a significant effect for propranolol [24] were only moderately suppressed and were considerably higher than the severely suppressed punished responding reported by the other two earlier studies [16,23]. The effects of drugs on punished responding are influenced by a number of parameters such as shock intensity and level of food deprivation which also affect control response rates [15,17]. Very low rates of punished responding may not be increased even by well-established antianxiety agents [1, 14, 15]. It is plausible, then, that the significant increases in punished responding in the present study are a function of less severely suppressed responding.

Control rates were related to the magnitude of drug effects for both propranolol and atenolol (see Table 1). The lowest maximal drug effects for both drugs occurred at the lowest control rate and the highest maximal effect for atenolol occurred at the highest control rate. The three highest control rates resulted in robust increases with propranolol. This analysis suggests that the failure of two of the earlier studies to find any anti-punishment effect for propranolol may have been a function of their quite severely suppresssed control rates. In contrast, the present study produced strong increases in punished responding with propranolol against an average baseline of moderately suppressed responding.

The mechanisms that may be responsible for the behavioral effects of these drugs, and for the difference in effect size between propranolol and atenolol, remain undetermined. The prevailing thought in the human clinical literature is that decreases in heart rate and cardiac contractility rather than central actions are the most relevant effects of beta-blockers for anxiety reduction, as well as for cardiac treatment [6, 18, 20, 21, 26]. The results reported here suggest that propranolol may be more anxiolytic than atenolol. In this regard, propranolol and atenolol differ along

several parameters that influence the extensiveness of their peripheral actions, as well as their access to the brain (see [7,22] for a discussion).

The relative effect of these drugs compared to a standard antianxiety agent is also undetermined since such as agent was not tested in this study. However, under similar procedures, chlordiazepoxide produces effects that resemble those of propranolol in magnitude [3,10]. Therefore, the present findings of increased punished responding with propranolol and atenolol warrant examination of (1) the suggested anti-punishment effect of beta-blockers relative to that of a standard antianxiety drug and (2) mechanisms such as heart rate change which may mediate this effect.

SUMMARY

In this study, propranolol and, less strongly, atenolol increased punished behavior while only marginally altering unpunished behavior in pigeons. These findings strongly parallel the effects of standard antianxiety drugs in other studies. These results also parallel the antianxiety effects in humans reported for beta-blockers.

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