EFFECTS OF BETA-BLOCKERS ON PUNISHED RESPONDING AND ON HEART RATE IN PIGEONS

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4301 JONES BRIDGE ROAD
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Name of Candidate: Lynn A. Durel
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Thesis and Abstract Approved:

Jerome E. Singer Committee Chairperson	17 June 1986 Date
James E. Barrett	6-17-86
Committee Member	Date
Andrew S. Baum	6-17-86
Committee Member	Date
David Krantz	17 June 1986
Committee Member	Date
Ethelyn D. Lazar	17 June 86
Committee Member	Date

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Lynn A. Durel
Department of Medical Psychology
Uniformed Services University
of the Health Sciences

ABSTRACT

Title of Dissertation: Effects of Beta-blockers on Punished Responding and on Heart Rate in Pigeons

Lynn Christine AuCoin Durel, Doctor of Philosophy, 1986

Dissertation directed by: David S. Krantz, Ph.D.
Department of Medical Psychology
and
James E. Barrett, Ph. D.
Department of Psychiatry

Beta-adrenergic blocking drugs, widely used in the treatment of cardiovascular disorders, have been reported to produce antianxiety effects in people with bodily anxiety symptoms and in those in acute stress situations. Although earlier animal studies of propranolol failed to detect any substantial behavioral effect in a punishment test usually predictive of clinical antianxiety effects, propranolol and atenolol were recently reported to be active in that test in pigeons. The present study attempted to confirm that finding, to compare the effects of propranolol, metoprolol, and atenolol with that of chlordiazepoxide, a standard antianxiety agent, and to examine whether heart rate is related to the behavioral effect of the drugs.

Key pecking of five pigeons was maintained under a multiple schedule of food presentation. In the presence of one key light stimulus, every fiftieth response produced food. When a different key light stimulus was present, every fiftieth response produced food and electric shock (punishment). Punished responding occurred at approximately 15%

of the high unpunished response rates.

Propranolol, atenolol, and metoprolol doses from 1.0 to 10.0 mg/kg, i.m. and chlordiazepoxide 3.0 to 10.0 mg/kg, i.m. substantially increased punished responding with little effect on unpunished responding. Propranolol increased punished responding approximately twice as much as did the other drugs. The increases were generally dose-related and appeared to be related to previous behavioral and/or pharmacological history. Heart rate increases during punished responding were decreased by the beta-blockers. Propranolol and, to a somewhat lesser extent, metoprolol produced large dose-related decreases. Atenolol's effect was small. Chlordiazepoxide increased heart rate at higher doses. With the beta-blockers, larger increases in punished responding were generally associated with greater heart rate decreases.

Peripheral beta-1 blockade, the only property reportedly shared by the three beta-blockers, decreases cardiac activity. This activity appears to be sufficient to account for increases in moderately suppressed responding and decreases in heart rate produced by these drugs. Additional mechanisms which may account for propranolol's greater effects are suggested. These antipunishment and heart rate effects may have implications for understanding the antianxiety effects of beta-blockers in humans.

THE EFFECTS OF BETA-BLOCKERS ON PUNISHED RESPONDING AND ON HEART RATE IN PIGEONS

BY

LYNN CHRISTINE AUCOIN DUREL

Dissertation submitted to the Faculty of the Department of Medical Psychology
Graduate Program of the Uniformed Services University of the
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requirements for the degree of
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INTRODUCTION

Overview

Although initially developed for and currently widely used in the treatment of cardiovascular disorders such as angina pectoris, hypertension, and arrhythmia (Frishman,1981; Kaplan, 1983), beta-adrenergic blocking agents also exert effects on mood and behavior (Middlemiss, Buxton, and Greenwood, 1981; Patel and Turner, 1982). The most frequently studied psychological effect of beta-blockers has been anxiety reduction. Several controlled studies report significant antianxiety effects of these drugs among both anxious patients and healthy subjects placed in an anxiety provoking situation (see Frishman, Razin, Swencionis, and Sonnenblick, 1981; Noyes, 1982, for reviews). The nature of the influence of beta-blockers on human behavior has remained in question (Middlemiss et al., 1981; Greenblatt and Shader, 1978). In contrast to studies with humans, earlier animal studies of propranolol--the most widely used beta-blocker--noted minor changes in behavior but failed to detect any substantial effect in a test usually predictive of antianxiety activity (e.g., McMillan, 1973c; Sepinwall, Grodsky, Sullivan, and Cook, 1973). Results from a recent study (Durel, Krantz, & Barrett, in press) suggest, however, that beta-blockers may have effects comparable to those of antianxiety drugs. The purposes of the present study were (1) to confirm the recent finding of such effects of beta-blockers in this animal behavioral model, (2) to compare the effects of selected beta-blockers with those of a standard antianxiety agent, and (3) to determine whether a relationship exists between the behavioral and cardiac effects of the beta-blockers.

The first section of this paper (1) presents the relevant pharmacology and physiological effects of beta-blockers, (2) summarizes the literature on the influence of beta-blockers on human mood and behavior, (3) examines the nature and validity of the punishment procedure for testing antianxiety drugs, and (4) reviews the animal studies that have tested the beta-blocker propranolol using this model. The next section discusses the rationale for the present study: that punished behavior is accompanied by heart rate increase and that beta-blocker-induced dampening of heart rate increases may be related to the

and that beta-blocker-induced dampening of heart rate increases may be related to the reported antianxiety effect of these drugs. Also in this section, the choice of drugs and experimental conditions for this study are explained and the hypotheses are presented. The methods, results, and discussion follow.

The Pharmacology and Physiology of Beta-Blockers

The most prominent actions of beta-blockers are on the heart and their primary use is for the treatment of cardiovascular disorders, such as angina pectoris, hypertension, arrhythmia, and the prevention of reinfarction and migraine headache (Frishman, 1981, 1984; Beta-Blocker Heart Attack Study Group, 1981). Logically then, the focus of study of these drugs has been on the cardiovascular effects of beta-blockade. But as newer drugs in the class have been developed, the complexity of their actions and effects--physiological and psychological--is being increasingly recognized (Anderson, 1980; Frishman, 1981; Turner, 1983).

Beta-blockade

Beta-blockers are structurally similar to the body's adrenergic neurotransmitter norepinephrine and neurohormone epinephrine and to agonists which preferentially act at the beta-receptor. These compounds are antagonists which competitively inhibit binding at the beta subset of adrenergic receptors. They have their greatest effect during intense sympathetic nervous system (SNS) activity when the adrenergic transmitters with which they compete for receptor sites would otherwise exert their effects. In other words, their effects are slight when sympathetic activity is minimal ("at rest") and greater when the SNS responds to physical and/or psychological demands (Weiner, 1980). Their effects can be hard to predict, however, because the various drugs differ considerably in pharmacological properties such as selectivity of blockade, membrane stabilizing activity, free drug plasma concentration, lipid solubility, and other parameters (Weiner, 1980; Frishman, 1981).

Since the subclassification of beta-adrenoceptors into beta-1 and beta-2 (Lands, Arnold, McAuliff, Luduena, and Brown, 1967), it has become common practice to

distinguish the beta-antagonists accordingly (Weiner, 1980). Those that primarily block stimulation of the heart are categorized as having beta-1 blocking action; those that block skeletal muscle vasodilatation are referred to as having beta-2 blocking action. Those that have both actions are considered nonselective beta-antagonists. Selectivity is relative, however, and decreases at higher doses. The most apparent and therapeutically beneficial effects of beta-blockade result from effects on the cardiovascular system, predominantly, the heart. Adrenergic activity in the heart increases heart rate, contractility, and conduction velocity. Beta-1 antagonism results in reductions in heart rate and cardiac output. Other physiological functions are also influenced by beta-blockade. (See Frishman, 1981, 1984, and Anderson, 1980, for fuller discussions).

Properties not related to beta-blockade

Not all effects of this class of drugs are due to beta-blockade. Other properties that may influence effects of beta-blockers include membrane stabilizing activity (MSA), intrinsic sympathomimetic activity, and lipophilicity. Membrane stabilizing activity results in a local-anesthetic or quinidine-like effect on the membrane; this activity is unrelated to beta-blockade and occurs only at higher drug doses of some beta-blockers (Frishman, 1981). Intrinsic sympathomimetic activity is a property of several beta-blockers which, while they inhibit binding of agonists and transmitters, provide some (i.e., partial) agonist activity. These drugs cause a less severe decrease in resting cardiovascular activity than do antagonists without intrinsic sympathomimetic activity but block equally at high SNS activity levels (Frishman, 1981).

In discussions of the sites of action of beta-blockers, the issue of lipophilicity has been raised. Drugs which are lipid soluble are better able to cross the blood-brain barrier and concentrate in brain tissue than are those which are more water soluble. This relative ability of some beta-blockers to penetrate the brain might be related to "side effects," e.g., nightmares and depression, thought to be centrally mediated (Frishman, 1981; Neil-Dwyer, Bartlett, McAinsh, and Cruickshank, 1981; Turner, 1983). Table 1 shows the

cardioselectivity, lipophilicity, MSA, half lives of some beta-blockers, and ratios between plasma and brain tissue concentration of several beta-blockers based on studies of humans and in rats.

TABLE 1

Comparative pharmacology of selected beta-blockers

Drug	Cardiac Selectivity	L/H[a]	MSA	Brain/Plasma Ratio		Plasma Half-Life (Hrs)
Propranolol	no	L	++	26[b]	8.36[c]	2-3
Atenolol	yes	H	-	0.2	0.054	6-9
Metoprolol	yes	L	+/-	12	--	3-4
Nadolol	no	H	--	--	--	17-24

a. H=hydrophilic; L-lipophilic; MSA=membrane stabilizing activity
b. ratios determined in rat brain after acute administration, adapted from Day, Hemsworth, and Street, 1977;
c. ratios determined in human brain after chronic use, adapted from Frishman, 1981; Neil-Dwyer et al., 1981.

The Effects Of Beta-Blockers On Human Mood And Behavior

Since the introduction of beta-adrenoceptor antagonists and their use in cardiovascular disorders, there have been reports of a variety of both desirable and untoward psychological effects. Foremost among these are beneficial effects in reducing anxiety. This observation has been made in patients exhibiting chronic anxiety characterized by bodily symptoms as well as in a variety of acute stress situations in healthy subjects and in heart patients. (See reviews by Frishman et al., 1981; Middlemiss et al., 1981; Patel and Turner, 1982; Suzman, 1981; Tyrer, 1976). Other emotional behavior may also be affected by these drugs; reductions in Type A ("coronary-prone ") behavior and anger have recently been reported (see Durel, Krantz, Eisold, et al., 1985). Unwanted psychological effects of beta-blockers have also been observed. Such side effects as fatigue, depression, nightmares, and disturbance of sleep and sexual functioning have been reported (Frishman et al., 1981;

Lazar, Eisold, Gadson, and Tesch, 1984; Moss and Procci, 1982; Patel and Turner, 1982; Weiner, 1980). The psychological effects of beta-antagonists, specifically those on chronic anxiety states and situational stress, have received considerable attention.

Anxiety reduction

First reported by Granville-Grossman and Turner (1966) with propranolol, the ability of beta-blockers to reduce anxiety when compared to placebo in a subset of chronically anxious patients has been confirmed repeatedly and is now well accepted (see the reviews listed above). When compared to other antianxiety drugs such as the benzodiazepines (e.g., chlordiazepoxide), however, beta-antagonists are probably effective primarily in patients whose anxiety is characterized by bodily complaints (Tyrer and Lader, 1974). In other words, when patients describe their anxiety more in terms of palpitations and tremor than as worry and mental tension, their anxiety is likely to be reduced with a beta-blocker. When "psychic" symptoms predominate, beta-blockers are considered much less effective than benzodiazepines (Patel and Turner, 1982). There is some evidence, however, that "psychic" symptoms may be amenable to extended propranolol therapy, especially with higher doses (Suzman, 1971; 1981). An anxiolytic effect of beta-blockers is generally accepted, but the complexity of reported pharmacological actions and physiological and psychological effects contributes to confusion about the mechanisms responsible for anxiety reduction.

Effects during situational stress or anxiety

In addition to evidence that beta-blockers can alleviate chronic anxiety states, reduction of situational stress has been reported. Beta-blockers blunt the increases in cardiovascular activity and in anxiety that often accompany stressful activities such as public speaking, examinations, race car driving, musical performance, and oral surgery (Brisse, Tetsch, Jacobs, and Bender, 1982; Neftel, Adler, Kappelli et al., 1982; see also Middlemiss et al., 1981; Patel and Turner, 1982; Suzman, 1981; Tyrer, 1976). In beta-blocked cardiac patients, a similar effect may be reflected by the lower scores on measures of voice stylistics

(e.g., loud and rapid speech) and cardiovascular activity during a challenging interview (Krantz, Durel, Davia et al., 1982; Schmieder, Friedrich, Neus, Ruddel, and VonEiff, 1983). Propranolol-associated anxiety reduction has also recently been reported for post-myocardial infarction patients whose speech performance, assessed for anxious behavior, improved (Gatchel, Gafney, and Smith, 1983). When situational stress itself leads to a decrement in performance and contributes to anxiety (e.g., the anxiety-induced tremor experienced by some string musicians during public performance), anxiety reduction and/or tremor reduction by beta-blockade reportedly leads to improved performance (Neftel et al., 1982; see also Patel and Turner, 1982; Suzman, 1981).

In sum, beta-blockers generally do reduce reported somatic anxiety in humans and may improve stress-related performance decrements. In animal studies of beta-blockers, the effect of these drugs on conditioned behavior has been investigated. As discussed next, punished behavior is commonly used to assess antianxiety drugs.

The Effect of Antianxiety Drugs on Punished Responding

An animal behavioral test involving punished responding has generally been used to characterize behavioral effects of drugs used clinically to treat anxiety and to screen drugs for their possible efficacy in such treatment (Cook and Davidson, 1973; Geller and Seifter, 1960; Geller, Kulak, and Seifter, 1962; Haefely, 1978; Iversen and Iversen, 1981; Sepinwall and Cook, 1978). In an experimental situation in which behavior maintained by reinforcement is decreased by the response-dependent presentation of shock (i.e., by punishment), drugs that are clinically effective antianxiety agents have typically been found to increase behavior. The next section discusses the punishment procedure, its validity, and findings of a number of studies.

The effect of meprobamate and barbiturates on punished responding. Geller and Seifter (1960) first described the experimental animal method employing punishment that was sensitive to the actions of the clinically useful antianxiety drug meprobamate, as well as to the barbiturates, which were once used more extensively in treating anxiety. Rats were

trained to respond on a variable-interval (VI) (Ferster and Skinner, 1957) schedule of food presentation during which a response produced food once every two minutes on average (VI 2 min). During periodic segments of the daily session, a sound stimulus signalled a change to a reinforcement schedule during which every response simultaneously produced food and electric shock. For testing meprobamate, the intensity of the electric shock was set high enough to produce a nearly completely suppressed response baseline against which an increase in responding could easily be detected. In the non-drug control situation, responding during the stimulus which signalled the food and electric shock schedule was almost completely suppressed, while the rate of unpunished behavior remained high. Meprobamate, pentobarbital, and phenobarbital greatly increased responding in the presence of the tone which increased shock delivery as well as food presentation. The same drugs only minimally affected the unpunished behavior, indicating that a non-specific stimulant effect could not account for the change in punished responding.

The effect of chlordiazepoxide on punished responding. The antipunishment effect of the benzodiazepine chlordiazepoxide was also reported (Geller et al., 1962). When responding was severely suppressed by a high shock intensity, chlordiazepoxide markedly increased responding; when responding was minimally suppressed by low shock intensity, chlordiazepoxide had little, if any, effect. Thus, chlordiazepoxide's effect on punished responding paralleled that of meprobamate.

Procedural variations. Variations in the Geller-Seifter procedure have often been used in more recent studies. Rather than a continuous punishment schedule, a schedule of intermittent shock has been used. This procedure results in a higher baseline of punished responding than with the original procedure which produced nearly complete suppression. Higher response rates allow dose- and drug-related increases or decreases to be more readily assessed (Cook and Davidson, 1973). The baseline level of response rate has also been manipulated by varying the level of food deprivation and/or the level of shock intensity (Haefely, 1978; McMillan, 1973b, 1973c; Sepinwall and Cook, 1978; Witkin and Barrett,

1976).

Species generality. The response rate-increasing effects of antianxiety drugs on punished responding have been demonstrated in a variety of laboratory animals, including rats (Geller et al., 1962; Miczek, 1973; Robichaud, Sledge, Hefner, and Goldberg, 1973; Sepinwall et al., 1973), monkeys (Cook and Catania, 1964; Hanson et al., 1967), and pigeons (Jeffrey and Barrett, 1979; McMillan, 1973c; McMillan and Leander, 1975; Morse, 1964; and Wuttke and Kelleher, 1970). The effects of these compounds on the punished behavior of a wide variety of species are generally quite comparable (Dews, 1976).

Validity. The Geller-Seifter procedure has gained wide acceptance as a test to discriminate behaviorally the classes of drugs which are clinically effective antianxiety agents (Cook and Sepinwall, 1978; Haefely, 1982; Iversen and Iversen, 1981; Stein, Wise, and Berger, 1973). The benzodiazepines, meprobamate and related drugs, and most barbiturates have consistently produced dose-related increases in punished responding, while other behaviorally active drugs, e.g., the neuroleptic compounds and amphetamines, have not. Pain reduction is unlikely to account for these effects since analgesics such as morphine do not increase punished behavior (see Sepinwall and Cook, 1978). Increase in responding suppressed by response-contingent punishment is regarded as a critical component, however (Cook and Sepinwall, 1978; Iversen and Iversen, 1981; Jeffrey and Barrett, 1979). This procedure also has predictive validity. There are exceptionally high correlations (i.e., r=+.987 and r=+.88) between the drugs and doses which increase punished responding and those found effective in the treatment of anxious patients (Cook and Davidson, 1973; Cook and Sepinwall, 1975a, 1975b).

Extension of the behavioral model to humans. Furthermore, the relevance to human behavior of punished animal behavior in drug testing has been extended to experimental settings with humans (Beer and Migler, 1975; Carlton, Siegel, Murphee, and Cook, 1981; Fischman, Schuster, and Uhlenhuth, 1977). Cook (1982) confirmed the effectiveness of the benzodiazepine diazepam in which behavior maintained by monetary reinforcement was

suppressed by response-dependent money loss.

Advantages of the model. The Geller-Seifter procedure has become a common technique for assessing properties of antianxiety drugs because it provides a number of advantages. The conditions influencing the effects of drugs, e.g., stimulus intensity and level of deprivation, since they can be controlled by the experimenter, can be manipulated precisely in order to characterize more completely the effects of drugs on behavior. For comparison with findings from extensive past use of the model and its strong predictive value, as well as for the advantages noted above, this procedure is the standard for testing agents purported to have an antianxiety effect. An increase in punished responding remains the primary criterion for predicting the clinical efficacy of these drugs (Cook and Sepinwall, 1978).

Propranolol's effect on punished responding

Early studies

Early studies of propranolol in laboratory animals, using a variety of experimental procedures, indicated various changes that resembled a tranquilizing effect (see Middlemiss et al., 1981; Sepinwall et al., 1973). These findings, as well as clinical reports of beta-blocker-induced anxiety reduction, led to three early animal studies which tested propranolol and chlordiazepoxide (McMillan, 1973c; Robichaud et al., 1973; Sepinwall et al., 1973). Each study will be reviewed in some detail to provide information on the conditions under which the drugs were tested.

McMillan (1973c) tested propranolol and the sedative-hypnotic drugs ethchlorvynol and chloral hydrate in three pigeons trained to respond under a fixed ratio 30, fixed interval five minute multiple schedule. In the presence of a one color key light, every thirtieth peck resulted in a four-second grain presentation (fixed-ratio or FR schedule). After each food presentation (or if no response occurred within 60 seconds), the schedule and associated key light were alternated. In the presence of another color key light, the first key peck after five minutes resulted in a four-second grain presentation (fixed-interval or FI schedule). The

drugs were first tested in this multiple schedule without electric shock to assess drug effects on unpunished responding. At lower doses of 3.0 and 10.0 mg/kg, propranolol affected neither the higher rates of responding maintained under the FR schedule nor the relatively lower response rate maintained under the FI schedule. Propranolol severely decreased both FR and FI responding at 17.5 mg/kg and prevented all responding at 30.0 mg/kg. Ethchlorvynol and chloral hydrate failed to increase unpunished behavior over a wide range of doses.

When each response in both schedule components produced a 3.5 mA electric shock administered through electrodes implanted around the pubic bones, the control response rate for FR and FI responding decreased greatly. Under these conditions of severe suppression, propranolol doses of 3.0 and 10.0 mg/kg, produced a very slight increase in FR responding. No responding occurred at 30.0 mg/kg. Chlordiazepoxide doses of 3.0, 5.6, and 10.0 mg/kg produced large increases under both FI and FR schedules.

When shock intensity was lowered to 2.5 mA, the FR control response rates approximately doubled and the FI rates increased even more. Responding after propranolol did not change appreciably at any of the same three doses (3.0, 10.0, and 30.0 mg/kg). Chlordiazepoxide again produced large increases. Even at the lower shock intensity, however, chlordiazepoxide did not increase the continuously punished and severely suppressed responding to half that of the unpunished response rates. The sedative-hypnotics ethchlorvynol and chloral hydrate showed little tendency to increase responding under either punishment intensity. McMillan (1973c) concluded that propranolol, ethchlorvynol and chloral hydrate, unlike chlordiazepoxide, did not increase punished responding.

Robichaud et al. (1973) trained six rats on a multiple VI 2 min food schedule which was interspersed with periods of continuous reinforcement during which both food and electric foot shock were delivered. The punished response rate was greatly suppressed from the unpunished response rate. One group of three rats received propranolol. Propranolol (5.0 mg/kg) had virtually no effect on unpunished or punished responding. In the second group,

chlordiazepoxide (5.0 mg/kg) increased unpunished responding by 42% over control. Punished responding after chlordiazepoxide increased nearly to the level of unpunished responding. When the subjects received both propranolol and chlordiazepoxide, the results were not different from those with chlordiazepoxide alone, suggesting that propranolol was inactive in this test.

Sepinwall et al. (1973), also using rats, employed a punishment task with a multiple VI 30 sec. FR 10 schedule in which foot shock accompanied each food presentation in the FR schedule. This intermittent punishment schedule changed responses from a high unpunished rate to a moderately suppressed level. Chlordiazepoxide increased punished responding in a dose-related manner at six doses ranging from 1.2 - 40.0 mg/kg. The maximal drug effect was an increase of 254% over the control rate. Propranolol slightly increased punished responding at four doses from 10.0 - 80.0 mg/kg. Only the largest increase (26% above control at 20.0 mg/kg) was significant. Thus, the effects of propranolol were not typical of the antipunishment effect produced by a standard antianxiety agent in either the magnitude of the effect or the wide range of effective doses.

The results of these three studies of the effect of propranolol and chlordiazepoxide on punished behavior indicated that propranolol had only a slight attenuating effect on punished responding under various experimental conditions in which chlordiazepoxide revealed a clear-cut antipunishment effect. The McMillan (1973c) study revealed a very small increase with propranolol (3.0 and 10.0 mg/kg) compared with the dose-dependent increases with chlordiazepoxide. In the Sepinwall et al. (1973) study, propranolol slightly increased punished responding at several doses (10.0 - 80.0 mg/kg) but significantly so only at one dose. These relatively small rate-increasing effects have led reviewers to conclude that propranolol does not increase punished responding (McMillan, 1975; Barrett and Tessel, 1984). These results and conclusions are puzzling when compared to the findings of an anxiolytic effect of beta-blockers in the clinical anxiety literature.

Recent results with propranolol and atenolol

Although the punishment studies reviewed here demonstrated little or no behavioral effect with propranolol, there are continuing observations of change in mood and behavior associated with the use of propranolol and other beta-blockers in humans. Additionally, a recent study reports increased punished responding with propranolol and atenolol in pigeons (Durel et al., in press). Since these results are at odds with those of earlier studies, and since that study served as the basis for the study reported here, it will be discussed in some detail.

Three adult White Carneaux pigeons having no previous experience with operant schedules or with drugs, were maintained at approximately 80% of their free-feeding body weights. 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) and was unpunished. In the presence of a red light, every thirtieth response produced both grain and, after stable performance was reached, electric shock. Electric 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 minute component. The two three-minute components of the multiple FR30 schedule alternated regularly and were separated by a 30 second timeout period during which the chamber was dark and responding had no scheduled consequences. Non-drug control performances for the three subjects averaged 1.9 ($\pm$0.4) responses per second for unpunished responding and 0.2 ($\pm$0.1) responses per second for punished responding.

Propranolol or atenolol in a saline vehicle, at a dose from 1.0 to 10.0 mg/kg (expressed as the salt), was injected into the pectoral muscle immediately prior to the session. Punished responding increased at 1.0, 3.0, and 5.6 mg/kg, and effects were dose-related, with both drugs. Both beta-blockers weakly increased unpunished responding irrespective of drug dose. The dose-response curves for propranolol and atenolol were similar over the dose range and indicated considerable antipunishment effects. For punished responding, propranolol was approximately twice as effective as atenolol, with a maximal effect of a

fourfold increase.

The effects of propranolol and atenolol in increasing punished behavior (while only marginally altering unpunished behavior) strongly paralleled the effects of antianxiety drugs in other studies. The dose-response curves were similar to those reported for chlordiazepoxide and other antianxiety agents (Jeffrey and Barrett, 1979; Witkin and Barrett, 1976). Since no standard antianxiety agent was tested, however, the relative effectiveness of these agents compared to a well-characterized anxiolytic drug could not be determined. Furthermore, propranolol and atenolol, which are both used extensively for cardiovascular disorders and are both reported to have antianxiety effects (Neftel, Adler, Kappeli et al., 1982), differ in several properties. Since they differ substantially, the mechanism(s) responsible for propranolol's greater effect could not be assessed.

RATIONALE

Results from studies of beta-blockers in humans and from the recent punishment study (Durel et al., in press) suggest that these drugs can produce a change in behavior similar to that produced by antianxiety drugs. Findings related to such behavior change are far from unanimous, however. The experimental conditions under which the behavioral changes are generated and the properties of these drugs that produce such changes are not well understood.

Punished Response Baseline

In the studies reviewed earlier, several parameters related to drug effects on behavior, for example, shock intensity and frequency, differed making the relative contributions of these conditions to behavior change difficult to determine. For example, McMillan (1973c) did vary shock intensity, with lower intensity associated with a larger effect for chlordiazepoxide but apparently not for propranolol. Both intensities produced severe response suppression, however. An examination of the response rates associated with the non-drug and drug conditions suggests that the effectiveness of both chlordiazepoxide and propranolol might have been related to the baseline level of punished responding. When punished responding was maintained at a very low rate, chlordiazepoxide was less effective than when response rates were somewhat higher. Changes in shock intensity were related to changes in control response rate and to response rate with chlordiazepoxide; lower shock intensity was associated with higher control response rates and greater responding with chlordiazepoxide. Although propranolol was relatively ineffective at both shock intensities, the biggest propranolol-related increase in responding was also inversely related to the level of suppression in this study .

The largest absolute effect for chlordiazepoxide in the studies reviewed occurred when punished responding was relatively less suppressed (Sepinwall et al., 1973). On a smaller scale, the same appears to be the case for propranolol in the earlier studies. The most recent study (Durel et al., in press), on the other hand, maintained a somewhat higher rate of punished responding, a moderately suppressed level, which propranolol and atenolol

punished responding, a moderately suppressed level, which propranolol and atenolol strongly increased.

It is plausible that the increase in punished responding with propranolol and atenolol was a function of the less severe behavioral suppression than was maintained in the earlier studies. Beta-blockers may be effective in increasing only moderately suppressed responding. It is also conceivable that such responding is associated with changes in heart rate. Relevant animal studies of heart rate are discussed below.

Conditioned Heart Rate

Since beta-blockers are used primarily to dampen the effects of sympathetic nervous system activity in the heart, peripheral beta-1 blockade is thought to be the most relevant activity for anxiety reduction as well as for cardiac treatment (Frishman, 1981; Noyes, 1982). It is conceivable that an effect of these agents on punished behavior would involve this ability to prevent some of any increase in heart rate associated with the behavior. If conditioned behavior, especially punished behavior, is associated with increases in heart rate, drugs that dampen heart rate may influence behavior as well. Specifically, if a conditioned heart rate increase occurs and is correlated with punished responding as well as with the key light, it may acquire discriminative features. Beta-blockers that antagonize the heart rate increase may, by altering the conditioned component, affect responding too.

Several animal studies suggest that, in some species, conditioning involving presentation of an aversive stimulus leads to conditioned heart rate increases (Cohen and Durkovic, 1966; Dantzer and Baldwin, 1974a, 1974b; Kelleher, Morse, and Herd, 1972, 1981). Immobilized pigeons exposed to signalled, unavoidable electric shock responded with conditioned heart rate increases (Cohen and Durkovic, 1966). Operant responding might also be expected to be associated with increases in heart rate. Preliminary data collected after the Durel et al. study (in press) indicated that heart rates increased during unpunished responding and, to a greater extent, during moderately suppressed punished responding. In pigs, severe suppression of responding has been associated with reflexive

decreases in heart rate (Dantzer and Baldwin, 1974a, 1974b).

Drug Effects on Experimentally-Induced Heart Rate Increase

Heart rate in experimental animals is sensitive to drug influence, as well as to aversive stimuli. Propranolol has been shown to antagonize heart rate increases in a dose-dependent manner whether heart rate is increased by a conditioned emotional response (Bergamaschi and Longoni, 1973), an avoidance task (Kelleher et al., 1972), or a challenge with an intravenous infusion of the beta-agonist isoproterenol (Bergamaschi and Longoni, 1973). Benzodiazepines, on the other hand, seem to weaken conditioned emotional cardiac acceleration (Bergamaschi and Longoni, 1973; Dantzer and Baldwin, 1974b) but not that due to an isoproterenol challenge (Bergamaschi and Longoni, 1973). These studies and others suggest that conditioned punished responding and heart rate may be related, and both may be influenced by antianxiety agents. There apparently has been no report of a cardiac index of beta-1 blockade during a punishment procedure.

A Procedure to Measure Heart Rate during Punished Responding

To test the feasibility of measuring heart rate in pigeons during responding, a procedure was devised for recording an EKG from implanted electrodes. In the pigeons used in the Durel et al. study (in press), the pubic bone electrodes that delivered electric shock were used for recording an EKG. The procedures for recording and ground electrode implantation and heart rate measurement are detailed in the Methods section.

Pilot measurements of heart rate and promising preliminary data suggested the feasibility of testing the hypothesis that beta-blockers produce an antipunishment behavioral effect in association with their lowering of the heart rate increases accompanying moderately suppressed responding. Selected doses of propranolol and atenolol, which earlier increased moderately suppressed responding in this procedure, generally lowered heart rate in both punished and unpunished components. If the hypothetical relationship between heart rate and behavioral state in the treatment of anxiety is extrapolated to this animal behavioral

model, then change in heart rate during punished responding should be inversely related in a dose-dependent manner to increases in responding.

Choice of Drugs

As noted in the discussion of the study by Durel and colleagues (in press), the inclusion of a standard antianxiety agent in a punishment test of beta-blockers is necessary for determining the relative effectiveness of the drugs. It is also important for demonstrating the sensitivity of the experimental conditions to the rate-increasing effect of antianxiety agents. Chlordiazepoxide, which is used extensively in studies involving conflict and in the treatment of anxiety, was included as the standard drug.

The choice of beta-blockers was based on clinical and pharmacological factors as well as previous use in animal studies. In addition to their reported clinical antianxiety effects, both propranolol and atenolol increased punished responding (Durel et al., in press). Propranolol produced greater increases in punished responding than did atenolol under moderate response suppression. Since propranolol differs from atenolol in a number of properties, including selectivity and lipophilicity, the mechanism(s) responsible for the difference in behavioral effect could not be determined, An additional beta-blocker, differing in these properties from propranolol and atenolol, was needed to separate the relative contributions of these properties to possible behavioral effects. Metoprolol, like atenolol, is a beta-1 selective beta-blocker but, unlike atenolol, it is lipophilic. So it has ready access to central beta-1 receptors, as well as to the peripheral beta-1 receptors available to atenolol. Metoprolol's similarity to propranolol in lipophilicity and to atenolol in selectivity may be useful in determining the relative influence of these properties in the reported differential antianxiety effect of the beta-blockers. If propranolol again produces greater rate-increasing effects than atenolol, then whether metoprolol effects are more similar to those of either propranolol or atenolol would suggest which property--lipophilicity or beta-2 antagonism--contributed to propranolol's additional antipunishment effect.

Summary

The review of studies of propranolol's influence on punished responding suggests that the level of response suppression is likely to be a determinant of the rate-increasing effect of beta-blockers. These drugs may be most effective at moderate levels of response suppression. Further, literature on conditioned heart rate suggests that heart rate is sensitive to some classes of drugs. If heart rate increases during punished responding and if beta-blockers block such increases, this physiological effect may relate to behavior change. Thus, changes in heart rate may relate to beta-blocker influence on responding.

Hypotheses

The lines of reasoning presented above lead to a number of hypotheses for this study.

(1) Because of their clinical efficacy for anxiety reduction and the rate-increasing effect on moderately suppressed responding the beta-blocking drugs, propranolol, metoprolol, atenolol, and the antianxiety drug chlordiazepoxide will increase punished responding. The four experimental drugs are expected to increase moderately suppressed responding in a dose-related manner. Propranolol may exert a stronger effect than atenolol. To the extent that propranolol's greater behavioral effect is a function of central beta-1-blockade and that beta receptors in pigeon brain are similar to those in human brain, metoprolol's effect should be more similar to those of propranolol than to those of atenolol.

(2) Because heart rate is generally related to behavior, and especially to conditionedresponding, heart rate is expected to be positively related to unpunished and punished responding. Specifically, heart rate during unpunished responding will be higher than during timeout (rest), and heart rate during punished responding will be higher than during unpunished responding.

(3a) Because beta-blockers dampen increases in cardiac activity, propranolol, metoprolol, and atenolol will attenuate heart rate increases associated with punished

responding.

(3b) Because punished responding is expected to be associated with higher heart rates than those occurring during unpunished responding, the beta-blockers are expected to prevent more of the heart rate increase associated with moderately punished responding than that associated with unpunished responding. The beta-blockers, as a function of their direct action on the heart, should be more effective than chlordiazepoxide in preventing the expected heart rate increase.

(3c) Finally, the effects of the beta-blockers on punished responding and on heart rate during punished responding are expected to be related, with increases in punished responding accompanied by decreases in heart rate in a dose-related manner.At highest doses of the drugs, however, when responding will decrease, the inverse relationship will not hold.

Therefore, to address these hypotheses, this study:

(1) provides an opportunity for replication of the finding of increases in punished responding with propranolol and atenolol,

(2) compares the effects of these drugs with those of a standard antianxiety drug chlordiazepoxide and the beta-blocker metoprolol, and

(3) examines heart rate change during responding under control and drug conditions.

METHODS

Subjects. The subjects for this study were five adult male White Carneaux pigeons (Columba livia) (Palmetto Pigeon Plant, Sumter, SC). P-4256 and P-4227 were experimentally naive, one-year old male birds. Four other birds originally trained for this experiment were discontinued when technical problems disrupted their response patterns. The three other birds used for the study were not experimentally naive. P-4217, two years old, had earlier received punishment and had received propranolol, atenolol, and other drugs. P-1989 and P-1976, two years old, had received a variety of drugs, including d-amphetamine, haloperidol, propranolol, and others, but had not received electric shock.

The pigeons were housed in individual living cages with water and crushed oyster shells continuously available. Light (on 0600; off 2000 hours), temperature, and humidity were kept constant throughout the course of the study.

Apparatus. The experimental chamber, a conventional pigeon chamber (Ferster and Skinner, 1957), measuring 29 x 28 x 33 cm, consisted of plexiglass walls and ceiling, except for the front panel, which was aluminum, and a wire grid floor. A plastic response key (R. Gerbrands Co., Arlington, MA) was located behind a two cm diameter opening in the center of the front panel. The key, 15 cm above the grid floor, was transilluminated by pairs of 7W white and red lamps. A key peck of 15 grams (0.15N) 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 opening, six cm above the grid floor, was a 4.5 x 5.5 cm opening through which access to mixed grain was provided. The food magazine, but not the response key, was illuminated only when grain was delivered. The experimental chamber was situated in a grounded metal enclosure (model LEC-006, BRS/LVE, Beltsville, MD) which was ventilated, sound- and light-attenuating, and supplied with white noise.

The operant schedules in this study were programmed with relay circuits using electromechanical equipment. The relay equipment and polygraph were located in a room adjoining that containing the experimental chamber.

Twenty-four gauge stainless steel wires implanted around the pubic bone (Azrin,

Twenty-four gauge stainless steel wires implanted around the pubic bone (Azrin, 1959) and connected through a harness served to detect electrocardiogram (EKG) signals and to deliver electric shock. The harness consisted of an open-front vest of reinforced expanded vinyl fabric which was worn at all times. The pubic bone and ground electrode wires (described below) were attached to the vest in the middle of the bird's back. The pubic bone electrodes were connected to a plug; a coiled telephone cable joined the jack to a swivel connection located on the ceiling of the chamber. The implanted ground wire was threaded through the coil, run across the top of the chamber, brought out of the metal enclosure, and, finally, clipped to a copper cable. This ground cable was attached to the polygraph chassis ground.

On the outside of the top of the chamber the shock/recording electrode wires were attached to two sets of wires, one for delivering shock, the other for recording the EKG signal. Both sets were connected to a relay (inside the chamber) which permitted EKG recording except when switched to deliver electric shock. EKG recording then resumed until the next shock. The EKG leads were attached to the polygraph preamplifier through a Grass EKG input cable.

The ground electrode was fashioned from twenty-four gauge stainless steel wire rolled into a coil approximately 0.8-1.0 cm diameter. A small loop made at the outer end was then soldered to a silver electrode lead wire (Grass). The plastic coated lead wire and the solder joint were covered with Silastic Medical Grade tubing and Silastic Medical Silicone Adhesive. The sterilized coil and wire were surgically implanted subcutaneously in an anesthetized (pentobarbital and ketamine) pigeon just above the rostral end of the breastbone where the clavicle joins it or subcutaneously behind the neck; the coil was secured with a silk suture to the midline connective tissue or, in the case of those connected on the back, to an Autoclip clipped to the skin. The end of the lead wire not connected to the electrode was threaded over the pectoral muscle, above the shoulder joint, and brought through the skin at a small incision at midback. The wire was kept coiled and clipped to the harness when not

being used.

Electric shock (200 msec in duration, 120 V AC,) was delivered through a variable resistor. During training the intensity was manipulated in attempts to maintain punished responding at rates that resulted in one or two shocks per three minute stimulus component.

Heart beats were counted from the R spike of the EKG. EKGs were recorded on a Grass EKG and Polygraph Data Recording System with a Model 79D chassis and a Model RPS7C8B Regulated Power Supply (115 V, 50-60hz). The channel used for the EKG had an EKG-Tachograph Pre-Amplifier Model 7P-4G, and a DC Driver Amplifier Model 7DAG. The second channel, with a low-level DC Pre-Amplifier Model 7P-1F and a DCDriver Amplifier Model 7DAG, recorded response, reinforcement, and stimulus condition signals from the relay devices.

Training Procedures. When their free-feeding body weights remained within ten grams for several days, the pigeons' body weights were gradually reduced (by limiting the daily food allotment to five grams) to 80% of their free-feeding weights. Body weights were maintained at approximately this level for the duration of the study by providing limited post-session grain.

When body weights reached the 80% level, pigeons began preliminary training for the operant procedure (Ferster, 1953). Shaping (reinforcement of successive approximations of the response) was used to train the birds to peck the key. When the response had been shaped into a valid key peck (one which resulted in audible feedback as described above) reinforcement followed each peck (continuous reinforcement). Training sessions on the continuous reinforcement schedule continued for several days. The length of time the grain was available was reduced to three seconds and remained constant for the duration of the study.

When a consistent rate of responding was well developed (stable responding), a transition was made from continuous reinforcement to short fixed ratio (FR) schedules. Training continued until stable responding on a fixed ratio of 50 responses to one

reinforcement (FR 50) developed.

Further training consisted of introducing the remaining aspects of the operant schedule for this study. Every three minutes the white key light was turned off, first for a few seconds and eventually for a 30 second period during which responding had no scheduled consequences (timeout). Daily weekday sessions of the FR 50, timeout 30 seconds (TO 30 sec) schedule, for 10 repetitions at a session, continued until the response pattern was again stable. At this point, the pubic bone electrodes were implanted.

A schedule of two components, each correlated with a different key light, was then introduced. After the first three minute interval, during which the stimulus light was white, the key was transilluminated with a red light for a second three minute interval. When responding under the two component schedule was stable, electric shock was introduced while the red light was on. During this interval, each fiftieth response produced electric shock as described earlier. Thus, responding in the presence of a red light produced both reinforcement and punishment; a fixed ratio 50 response schedule (FR 50) of electric shock presentation occurred conjointly with the FR 50 schedule for food presentation. The response counter reset after each interval so that 50 responses always preceded each grain and shock presentation. Training on the multiple schedule continued until the response pattern in each component stabilized.

The EKG ground electrode was then implanted. Several days after the surgery, final training began in order to stabilize the response pattern and test the EKG recording. EKGs of two birds were recorded before shock was introduced. In these animals, heart rates, as well as response rates, were comparable under the two simulus light conditions. When responding and recording both occurred satisfactorily, experimental sessions began.

Experimental Session. The 35 minute experimental session was composed of five sets of alternating stimulus light presentations separated by 30 sec timeout periods. Sessions were conducted five days per week.

Drug Procedure. The beta-blocking drugs propranolol HCl (Ayerst, NY, NY),

metoprolol tartrate (Geigy Pharmaceuticals, Ardsley, NY), and atenolol HCl (Stuart, Wilmington, DE), and the benzodiazepine chlordiazepoxide HCl (Hoffman-LaRoche, Inc., Nutley, NJ) were administered to each pigeon. The order of the beta-blocker administration was balanced: generally each drug was administered first to two birds, second to two birds, and third to two birds. The benzodiazepine series followed the beta-blockers in all the pigeons.

For each of the drugs, at least four doses ranging from 1.0 to 10.0 mg/kg, expressed as the total salt, were given in a mixed sequence with a low dose between high doses. At least one determination was made at each dose, with additional determinations made when responding at a particular dose fell outside of the dose-effect curve indicated by responding at other doses. When the highest or lowest dose increased responding, an additional dose was administered. The drugs were dissolved in 0.9% saline. Beta-blocker solutions were kept refrigerated. Chlordiazepoxide was mixed fresh daily. At doses of 5.6 mg/kg and above, atenolol solutions were mixed with two drops of Tween to improve dissolving. The drugs were injected into the pectoral muscle in a volume of 1.0 ml/kg of body weight. A beta-blocker dose was administered immediately prior to the session. A chlordiazepoxide dose was administered 60 minutes before the session. An equal volume of the vehicle was generally given during one or two drug series for each bird to serve as control injections. Drugs were administered on Tuesdays and Fridays given that control responding remained stable.

Data Analysis. Response rates in responses/sec for the total session time were calculated for the behavioral measure. Control rates of responding were determined separately during the four drug series and were generally based on three non-injection control days. Drug effects at each dose were calculated as comparisons of response rates with the average control response rates for each bird. Drug effects on behavior are reported as percent of control responding.

Behavioral data were analyzed statistically for individual subjects' data by

establishing confidence intervals of two standard deviations above and below the control means for each drug series. Response rates outside the intervals were considered statistically significant at less than the 0.05 level of probability.

Calculation of heart rate in beats/minute was made by counting R spikes from the EKG for short intervals, usually six seconds, and converting to beats/minute. Representative segments during unpunished responding, punished responding, and timeouts over the session were used to figure average heart rates during those periods and for the session. Heart rates during the same periods were calculated for drug sessions. The results are presented as the changes in heart rate for comparable periods. To the extent possible, heart rates were figured for the sessions used in reporting behavioral data, although, due to technical problems, there were fewer heart rate data.

RESULTS

Behavior

Control Performance

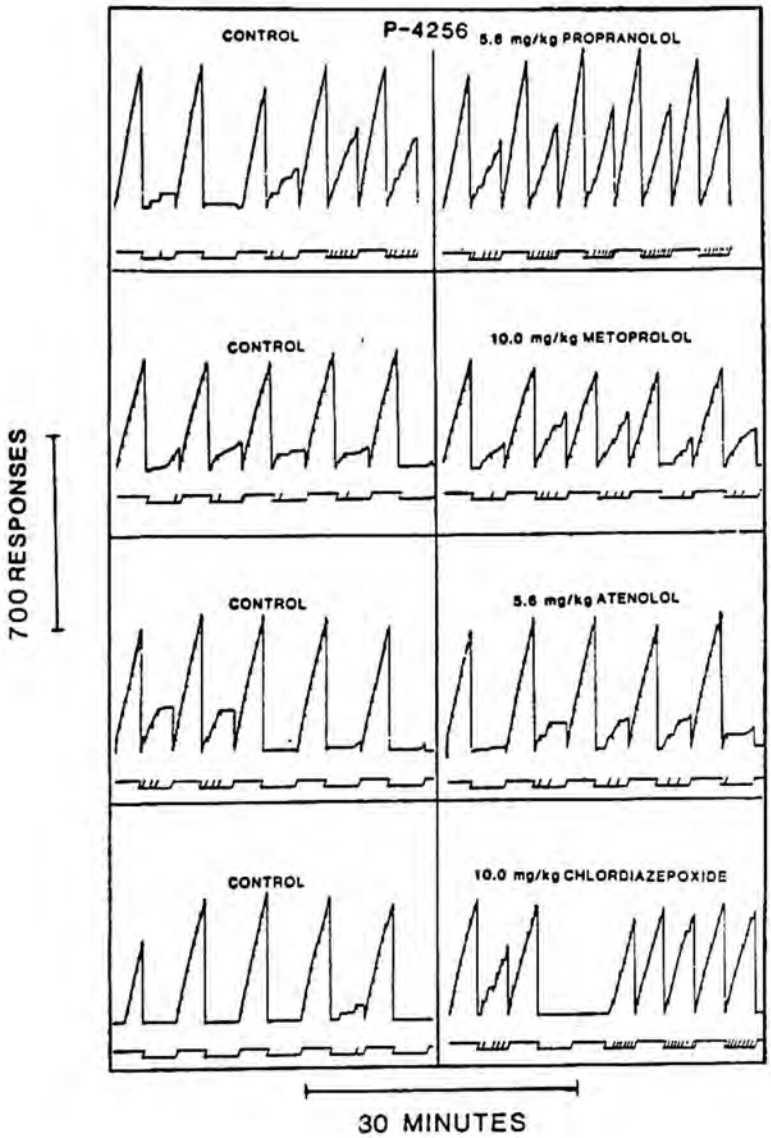
Before shock was introduced, responding was comparable under the white and red light conditions. During the punishment component of the multiple schedule, responding decreased to approximately 15% of unpunished rates. The average rates of unpunished and punished responding for the study were 2.5 (±0.5) responses per second (resp/sec) and 0.3 (±0.2) resp/sec, respectively. Average unpunished response rates for the five birds ranged from 1.8 - 3.0 resp/sec and average punished responding ranged from 0.20 - 0.55 resp/sec. Appendix 1 lists individual control rates and means for unpunished and punished responding over the four drugs series. Electric shock intensity and the order of beta-blocker administration for each bird are also given.

Control patterns of unpunished responding were characteristic of those maintained under a fixed ratio 50 schedule. Figure 1 shows typical cumulative records of control responding for one of the original subjects (P-4256) (see the left side of Fig.1 for cumulative records for the four drug series). Unpunished responding occurred at a rapid and consistent rate until a response produced the presentation of grain; a short pause followed the reinforcement period. Punished responding occurred at lower rates than responding under the schedule of positive reinforcement alone. Although the rate of responding during a run of 50 responses often slowed only slightly, there were usually longer pauses before the punished response runs. Occasionally, pauses occurred during these runs, a pattern not evident in unpunished responding. Responding typically produced several shocks in a thirty minute session. Patterns of both unpunished and punished responding remained relatively similar in the five subjects over the course of the study.

Drug Effects

Propranolol, metoprolol, atenolol, and chlordiazepoxide typically increased

Figure 1. Cumulative responses are on the ordinate and time on the abscissa. The pens reset to baseline before each three minute component. (Timeout periods were not recorded.) The short diagonal strokes of the upper (response) pen indicate food delivery. Shock presentations are indicated on the lower (event) tracing which also shows the alternating components; the higher line represents the period during which food only was available and the lower line represents the period during which both food and shock were available. Panels on the left side represent control performances for the days preceding drug administration. Panels on the right side represent drug performances for 5.6 mg/kg propranolol, 10.0 mg/kg metoprolol, 5.6 mg/kg atenolol, and 10.0 mg/kg chlordiazepoxide, respectively.


P-4256
CONTROL
5.6 mg/kg PROPRANOLOL
CONTROL
10.0 mg/kg METOPROLOL
CONTROL
5.6 mg/kg ATENOLOL
CONTROL
10.0 mg/kg CHLORDIAZEPOXIDE
700 RESPONSES
30 MINUTES

punished responding but not unpunished responding in the five subjects (Fig. 2). The four drugs generally produced dose-related increases in punished responding within the dose range of 1.0 - 10.0 mg/kg with the beta-blockers and 3.0 - 10.0 mg/kg with chlordiazepoxide. Increases exceeding 300% of control were produced by propranolol in three of the five birds. Increases exceeding 150% of control were common with the other drugs. Maximal increases with propranolol typically occurred at 5.6 mg/kg, whereas with atenolol, the largest increases depended more on the individual pigeons and were between 1.0 and 10.0 mg/kg. Peak effects with metoprolol also were related to the individual pigeons and did not parallel those of either propranolol or atenolol; however, as with atenolol, the largest increases occurred across a broad range of doses (1.0 -10.0 mg/kg). In most pigeons the rate-increasing effects of the three beta-blockers were in the following orders of magnitude: propranolol>atenolol>metoprolol or atenolol>propranolol> metoprolol. Only P-4227 was an exception to these effects. In this pigeon propranolol and metoprolol produced comparable effects except that the metoprolol curve was shifted to the left.

In contrast to the general rate-increasing effects of the beta-blockers in all pigeons, chlordiazepoxide produced large increases in punished responding only in two animals (P-4217 and P-1976). Effects were smaller or did not occur with the other pigeons.

The four drugs decreased punished responding from maximal levels at 10.0 or 17.0 mg/kg except for one instance each with propranolol and chlordiazepoxide (in P-4227 and P-4217, respectively).

Unpunished responding remained approximately at control levels with the beta-blockers at doses that increased punished responding. It typically decreased slightly at higher doses when punished responding decreased from maximal levels and was virtually eliminated when a dose of 56.0 mg/kg was administered in one pigeon (P-4227). Chlordiazepoxide typically increased unpunished responding slightly at doses that increased punished responding and decreased it at higher doses (see Fig. 2).

Individual rates of punished and unpunished responding, as well as percent of control rates for each drug series and saline administrations are presented in Appendix 2. The number of determinations at each dose and significant changes (values exceeding two standard deviations of control) in behavior are noted.

Behavioral performances for P-4256 at doses of the drugs which produced maximal increases in punished responding are shown in Figure 1. Compared to preceding days' control levels, the very high rates of unpunished responding increased slightly with propranolol and decreased slightly with metoprolol and chlordiazepoxide. Punished responding increased to a level approaching unpunished responding at the end of the session with 5.6 mg/kg propranolol and with chlordiazepoxide (10.0 mg/kg). Metoprolol (10.0 mg/kg) substantially increased punished responding, while atenolol (5.6 mg/kg) increased it slightly.

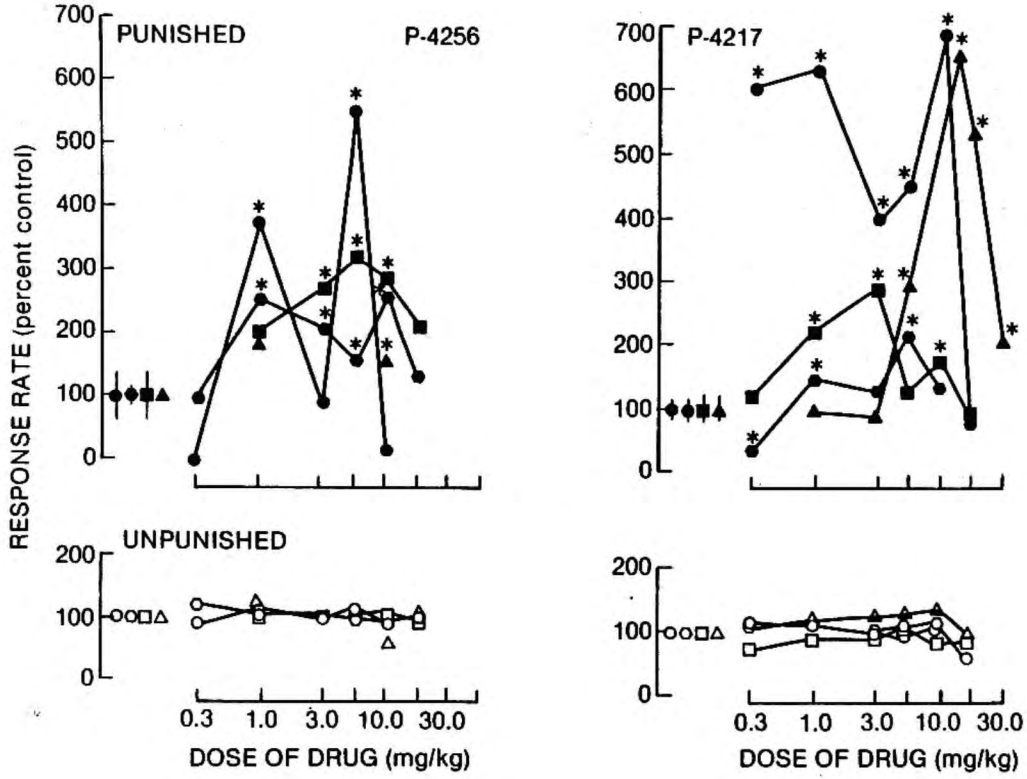
Heart Rate

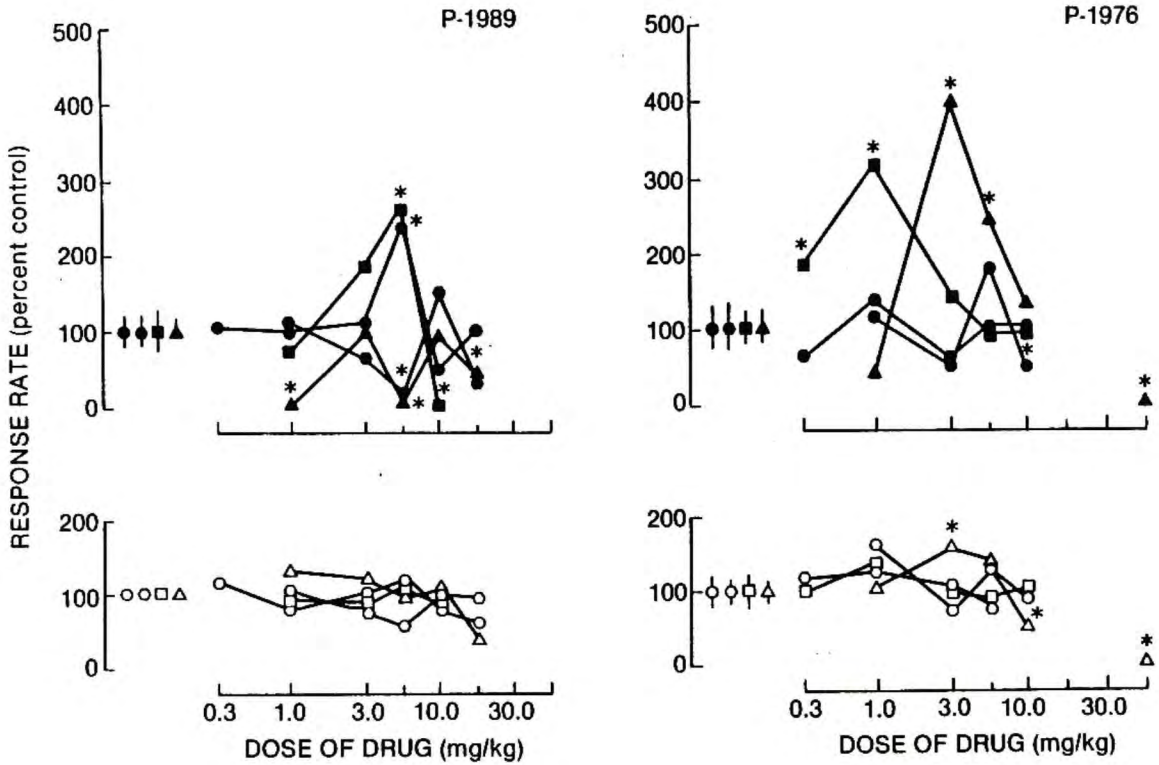
Control Rates

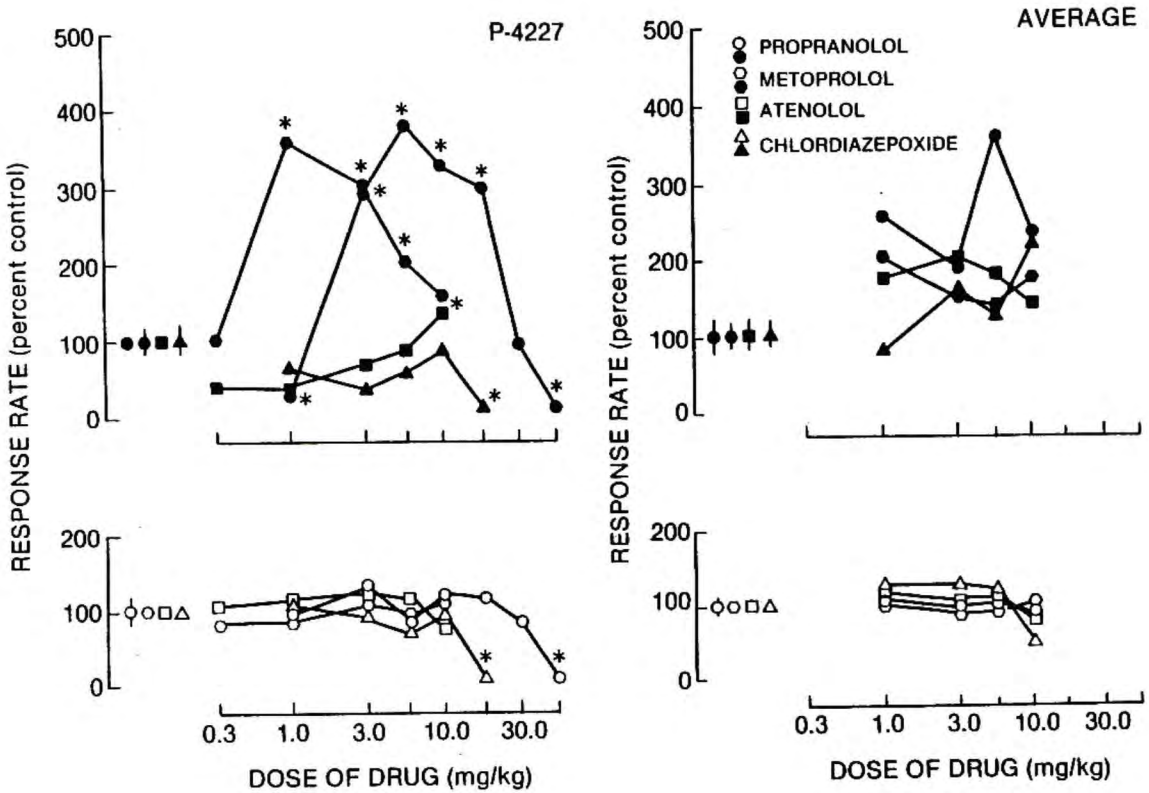
Heart rates varied under the stimulus conditions of the experimental session. The average heart rates during timeout (resting periods), unpunished responding, and punished responding were 121, ($\pm$ 17), 146 ($\pm$ 22), and 170 ($\pm$ 20) bpm, respectively. Heart rates during control periods of unpunished and punished responding for each bird are listed in Appendix 4. The number of data points is also given. Heart rate averages reported here represent fewer control and drug sessions than reported for behavior due to missing data, so data of individual birds are not presented. Losses appeared to be evenly distributed across birds, drugs, and doses, so it is unlikely that systematic error occurred.

Control patterns of heart rate during unpunished (left side) and punished (right side) responding, for the subject whose performances are presented in Figure 1, are shown in EKG segments in Figure 3. Control patterns of heart rate for the five birds generally

Figure 2. Effects of propranolol, metoprolol, atenolol, and chlordiazepoxide on punished responding (filled symbols) and unpunished responding (unfilled symbols) under the multiple schedule in the individual pigeons and as averages for the group. Vertical lines in the unconnected symbols on the left of the curves denote $\pm$ 1 SEM from the mean control rate based on the average of control days (Thursdays) for each drug series. Drug effects are graphed as percent of control rates. For individual pigeons an asterisk denotes a change that is statistically significant at the .05 level.


PUNISHED
P-4256
P-4217
UNPUNISHED
RESPONSE RATE (percent control)
700
600
500
400
300
200
100
0
0.3
1.0
3.0
10.0
30.0
DOSE OF DRUG (mg/kg)


P-1989
P-1976
RESPONSE RATE (percent control)
500
400
300
200
100
0
200
100
0
0.3
1.0
3.0
10.0
30.0
DOSE OF DRUG (mg/kg)


P-4227
AVERAGE
PROPRANOLOL
METOPROLOL
ATENOLOL
CHLORDIAZEPOXIDE
RESPONSE RATE (percent control)
500
400
300
200
100
0
0.3
1.0
3.0
10.0
30.0
DOSE OF DRUG (mg/kg)

varied during the session according to the stimulus condition and behavior. During unpunished responding, heart rates were typically consistent over the session and fairly stable, usually varying no more than 30 bpm over the time during which the 50 responses were made. During punished responding, heart rates were higher and less consistent. They tended to vary both with response rate and with the regularity of responding. Responding that was inconsistent was usually accompanied by short-term changes in heart rate that exceeded those accompanying unpunished responding. Typically, heart rate was lower before a punished response run and higher at the end of the run than at comparable parts of unpunished response runs. Heart rates increased sharply when shock occurred, but usually decreased within seconds (see Fig. 3). Heart rate patterns varied considerably among the birds, and varied somewhat for individual birds over the course of the study. Abrupt increases and arrhythmias also occurred occasionally during the punished response component.

Drug Effects

Propranolol, metoprolol, and atenolol generally dampened heart rate increases associated with punished responding (see Fig. 4). Propranolol and metoprolol decreased heart rates in a generally dose-related manner. The effect of propranolol, with greater than a 50 bpm reduction at 10.0. mg/kg, was slightly greater. With atenolol, heart rates were approximately 10 bpm lower than the control level but the decrease was unrelated to dose. Heart rates varied from little change at the lower doses to an increase at higher doses with chlordiazepoxide.

Changes in heart rate during unpunished responding generally paralleled the changes during punished responding but were of smaller magnitude. Individual and average heart rates during unpunished and punished responding are listed in Appendix 4 for the drug series; the number of data points is also given.

Drug effects on heart rate during unpunished and punished responding are shown

in EKG segments for P-4256 in Figure 3. Heart rates during unpunished responding changed only slightly from control levels. At doses that typically produced maximal increases in punished responding in this bird, much of the heart rate increase associated with punished responding and shock was dampened with propranolol and metoprolol. Little or no change in heart rate occurred with atenolol or chlordiazepoxide at these doses. Decreased heart rate was associated with increased punished responding at 5.6 mg/kg propranolol and 10.0 mg/kg metoprolol. The slight increase in punished responding with 5.6 atenolol was not accompanied by a change in heart rate. Unlike the pattern seen with the beta-blockers, both heart rate and punished responding increased with 10.0 mg/kg chlordiazepoxide. Although the heart rate increase accompanying punished responding before shock was greater than during control levels in this panel, the increase was not maintained during subsequent increased responding.

In all five birds propranolol clearly decreased heart rates during punished responding, with maximal decreases exceeding 50 bpm (see Appendix 4). Metoprolol also decreased heart rates in all birds but, with one exception (P-4256), less consistently and less strongly. With atenolol, heart rates varied considerably among the birds and across the doses but decreases did not exceed 30 bpm. Chlordiazepoxide was also associated with heart rate changes that varied considerably; increases and decreases reached 40 bpm and occurred across the doses. Some differences among the birds in the effects of the drugs on heart rate during punished responding were evident. Propranolol and metoprolol produced heart rate decreases at lower doses in P-4256, P-4227, and P-4217 than in P-1989 and P-1976. P-4256 exhibited heart rate decreases at all doses of the four drugs and the decreases were frequently larger than those occurring in the other birds.

With few exceptions, increases in punished responding in the five pigeons were associated with heart rate decreases with the beta-blockers and chlordiazepoxide (see Appendices 2 and 4). At higher doses, decreases in punished responding were

Figure 3. EKG segments (upper tracing) and corresponding responses (lower tracing) from control and drug sessions. The shorter response tracing at the end of a response series indicates the fiftieth response which was reinforced with grain (unpunished) or with grain and electric shock (punished). Panels on the left are segments of control and drug records during unpunished responding. Panels on the right are segments of control and drug records during punished responding for the same session as shown on the left. Drug doses are those shown for the same animal's cumulative record in Figure1: 5.6 mg/kg propranolol, 10.0 mg/kg metoprolol, 5.6 mg/kg atenolol, and 10.0 mg/kg chlordiazepoxide. Marks below the EKGs represent six second intervals and numbers represent heart rate in beats/minute.

P-4256

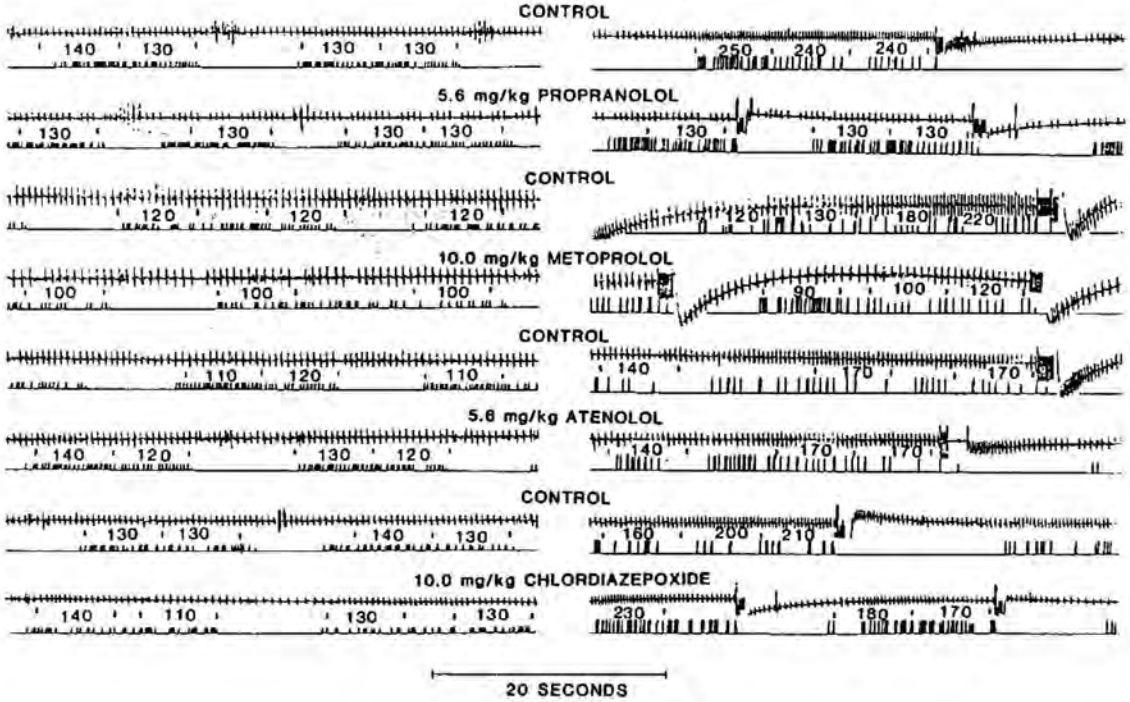
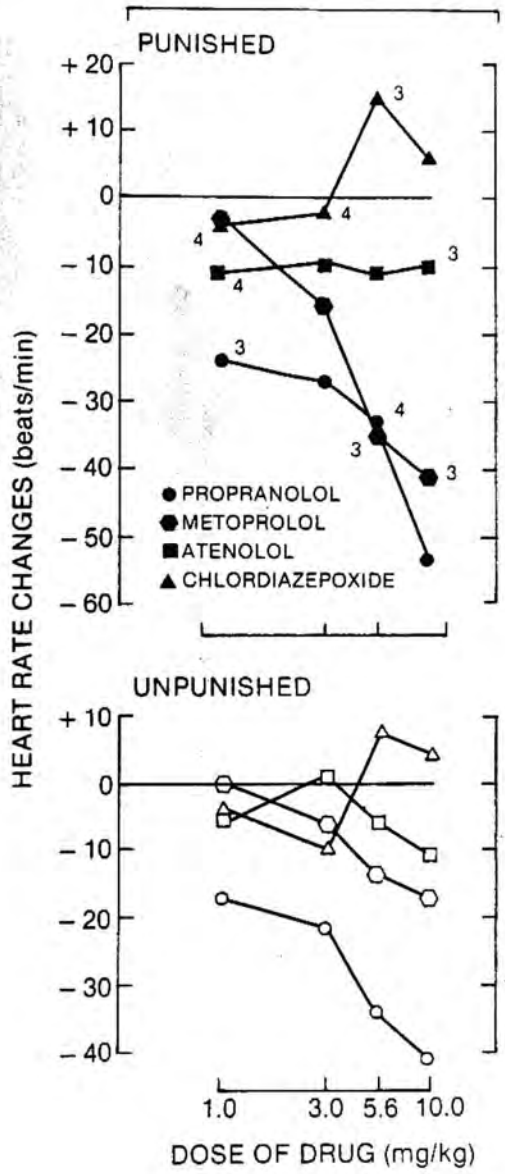

CONTROL
140 130 130 130
250 240 240
5.6 mg/kg PROPRANOLOL
130 130 130 130
130 130 130
CONTROL
120 120 120
120 130 180 220
10.0 mg/kg METOPROLOL
100 100 100
90 100 120
CONTROL
110 120 110
140 170 170
5.6 mg/kg ATENOLOL
140 120 130 120
140 170 170
CONTROL
130 130 140 130
160 200 210
10.0 mg/kg CHLORDIAZEPOXIDE
140 110 130 130
230 180 170
20 SECONDS

Figure 4. Effects of propranolol, metoprolol, atenolol, and chlordiazepoxide on heart rate during punished and unpunished responding computed as change from control rates.


PUNISHED
+ 20
+ 10
0
− 10
− 20
− 30
− 40
− 50
− 60
HEART RATE CHANGES (beats/min)
PROPRANOLOL
METOPROLOL
ATENOLOL
CHLORDIAZEPOXIDE
UNPUNISHED
+ 10
0
− 10
− 20
− 30
− 40
1.0
3.0
5.6
10.0
DOSE OF DRUG (mg/kg)

accompanied by large heart rate decreases, particularly with propranolol and metoprolol. With propranolol, which generally decreased heart rate substantially in all birds, punished responding typically increased substantially as well. Occasionally, however, at doses of propranolol that typically increased punished responding, the heart rate decreases were associated with decreases in punished responding (P-4227 at 1.0 mg/kg, P-4256, P-1989, and P-1976 at 3.0 and 10.0 mg/kg and for P1989 also at 5.6 mg/kg). Somewhat less consistently, with metoprolol and atenolol increases in punished responding were also related to decreases in heart rate. Occasionally with metoprolol and atenolol, increases in responding occurred when heart rate increased (P-4217 and P-1976 at 1.0 mg/kg of metoprolol and P4217 at 1.0 mg/kg and P19989 at 3.0 mg/kg of atenolol). When increases in punished responding occurred with chlordiazepoxide, heart rates also typically decreased.

DISCUSSION

The behavioral data reported here indicate that propranolol, metoprolol, and atenolol were similar to chlordiazepoxide in increasing punished responding. These results support the primary hypothesis of this study. The already high rates of unpunished responding increased no more than slightly with any drug, whereas levels of punished responding typically increased to two or three times control levels. All of the drugs increased punished responding, although the magnitude and consistency of effects differed across birds. Propranolol typically produced the largest and most consistent increases, followed by atenolol, then metoprolol, and chlordiazepoxide.

These results appear to replicate a recent study which also reported increases in punished responding with propranolol and atenolol in White Carneaux pigeons (Durel et al., in press). The increases in punished response rates and the effective dose range under the fixed ratio schedules of the present and previous studies were similar. In both, propranolol produced some increases in punished responding that exceeded 500% of control level but rates of punished responding in the present study were higher than those previously reported (3.5 vs 1.7 resp/sec at maximal levels).

The inclusion in the present study of metoprolol which differs from propranolol and atenolol provides additional support for the rate-increasing effects of beta-blockers. The inclusion of chlordiazepoxide allows the beta-blockers to be compared with an antianxiety agent which increases suppressed responding (Geller et al., 1962: Jeffrey and Barrett, 1979; McMillan, 1973b; Sepinwall et al., 1973). The beta-blockers resembled chlordiazepoxide in increasing suppressed responding across a range of doses except that propranolol produced larger effects.

Heart rate data in the present study indicated increases during punished responding averaging 24 bpm above that recorded during unpunished responding, and nearly 50 bpm above the levels recorded during timeout (rest) periods. These findings provide support for the hypothesis that heart rates during the session are related to the behavior occurring during different stimulus conditions. The heart rate increases during punished

support for the hypothesis that heart rates during the session are related to the behavior occurring during different stimulus conditions. The heart rate increases during punished responding were associated with response rates that were lower than unpunished response rates, indicating that motor activity could account for little of the increase associated with punished responding. The heart rate increase during punished responding, over that occurring during unpunished responding, parallels the 26 bpm conditioned increase reported for immobilized pigeons under a signalled unavoidable shock schedule (Cohen and Durkovic, 1966).

The beta-blockers decreased response-related heart rates in a generally dose-related manner, as expected. Also as hypothesized, heart rates decreased more during punished responding than during unpunished responding. Heart rate decreases produced by propranolol and metoprolol were clearly dose-related, however larger decreases occurred with propranolol. Heart rate decreases were small at higher doses of atenolol under both schedules.[1] Chlordiazepoxide produced variable effects on heart rate. Although small changes in heart rate occurred across the range of doses, changes of 30-40 bpm were also common. The changes were unrelated to dose and occurred in all pigeons.

Comparison of the performance and EKG data in Figure 3 and in the dose-effect curves for performance and heart rate suggests that the hypothesized relationship between beta-blocker-produced increases in punished responding and decreases in heart rate associated with that behavior has obtained some support. Furthermore, the pigeons that were more responsive to the response rate-increasing effects of the beta-blockers appear also to have been more responsive to their heart rate-decreasing effects (see the data for individual pigeons in Appendices 2 and 4). These data are not presented, however, and this apparent relationship should be considered preliminary, because the sample size is small and there are fewer heart rate data than behavior data. With chlordiazepoxide increases in punished responding were usually associated with decreases in heart rate, and failure of the drug to

increase responding was commonly associated with increases in heart rate. Benzodiazepines have been reported to dampen heart rate increases occurring during a stimulus signalling shock presentation (Bergamaschi and Longoni 1973; Dantzer and Baldwin, 1974b). Since, in the present study increases in responding also occurred when heart rate did not decrease, however, heart rate decreases do not appear to be a necessary component of the behavior change produced by chlordiazepoxide.

Taken as a whole, the findings of this study support the hypotheses of (1) increased punished responding with beta-blockers and chlordiazepoxide, (2) heart rate increases during nondrug unpunished and, especially, punished responding, and (3) reductions in heart rate accelerations that are generally related to the increases in punished responding produced by the beta-blockers.

Determinants of Drug Effects

Drug History

Although the four drugs used in this study increased punished responding, they produced behavioral changes that differed somewhat among the pigeons. Due to technical problems during the beginning of the study, some of the original subjects were replaced with others that had been involved in previous experiments. P-4256 and P-4227 were retained and were naive at the start of the study. P-4217 had participated in a drug study involving punishment and had received several drugs. P-1989 and P-1976 had extensive drug histories but had not received electric shock. The punished responding of P-1989 and P-1976 was increased less and at fewer doses of the drugs, a pattern unlike that of the other three birds. Differences in the drug effects with these pigeons may have been due to a number of factors that, recently, have been shown to alter drug action. For example, prior drug history and drug-behavior interaction histories have been shown to produce significant alteration in drug effects (Brady and Barrett, 1986; Glowa and Barrett, 1983; Smith and McKearney, 1977). When d-amphetamine increases responding that results in a decrease in

reinforcement frequency, subsequent increases in responding do not occur (Smith and McKearney, 1977). Under other circumstances, administration of a drug under one experimental condition has been shown to modify the effects of that drug under different conditions. Since P-1989 and P-1976 did not respond typically to the beta-blockers or to chlordiazepoxide, their behavior in this study may have been influenced by their experimental histories. In addition, chlordiazepoxide failed to increase punished responding when it was preceded immediately by atenolol (in P-4227 and P-1989) (see Appendices 1 and 2 for drug administration order and drug effects on responding). In these instances, atenolol produced small and inconsistent increases compared to those in the other birds when it had been administered earlier in the drug sequence. Thus, when administered last in the beta-blocker sequences, atenolol produced its smallest increases and subsequent responding with chlordiazepoxide was also lower than when this drug followed increases produced by atenolol. In this study, then, the behavioral effects of the drugs may have been influenced by earlier behavioral and drug histories and by the consequences of responding during drugs administered earlier in the drug sequence.

In addition, when experimental history is considered, control rates of responding may have been related to drug effects in some birds. Among the less experienced and generally more drug-responsive, birds (P-4256, P-4227, and P-4217), but not in the more experienced pigeons (P-1989 and P-1976), larger absolute levels of punished responding produced by the beta-blockers were associated with higher levels of control responding. Drug-produced rates greater than 1.0 resp/sec occurred only when control rates exceeded 0.25 resp/sec in the less experienced birds. The issue of level of responding will be discussed in greater detail below. To some exent, then, the greater increases with propranolol in P-4256 and P-4217 may have been related to higher control response rates during that series than during the metoprolol and atenolol series. While this possiblity makes the present comparison of effect size among the drugs more difficult, it strengthens the

assumption that beta-blockers are effective in increasing moderate, but not low, rates of punished responding.

Pharmacological Mechanisms of Action

The differences in effects among the beta-blockers and differences in their mechanisms of action may be related. Propranolol was generally twice as effective behaviorally and produced larger heart rate decreases than metoprolol and atenolol. Propranolol blocks beta-1 and beta-2 receptors and, being lipophilic, readily penetrates the central nervous system (Weiner, 1980). Presynaptic beta-2 receptor activation has been reported to increase norepinephrine release (Langer, 1976), and blockade of this receptor has been suggested as a possible antihypertensive mechanism for beta-blockers (see Robertson, 1983). Inhibition of this positive feedback loop could possibly contribute to propranolol's effects. Atenolol blocks beta-1 receptors but is reported to possess little other pharmacological activity (Weiner, 1980). Therefore, the properties that are responsible for differences in effects between propranolol and atenolol cannot be determined when only the two beta-blockers are compared, as was the case in the Durel et al. (in press) study. For this reason, metoprolol was included in the present study. If beta-2 antagonism plays a prominent role in the behavioral effects of beta-blockers, then the effects of metoprolol should resemble those of atenolol. If, on the other hand, lipophilicity, a physical property of this drug, is more important, the effects of metoprolol should more closely resemble the effects of propranolol, unless blockade of central beta-2 receptors contributes significantly to propranolol's effects.

The behavioral data reported here place metoprolol near atenolol in effect size while heart rate data place it between propranolol and atenolol. However, access to the central nervous system does not mean that propranolol and metoprolol have the same activity there. Compared to the predominant beta-1 receptors in mammalian brain, avian cerebral membranes possess atypical beta-receptors which are not characteristic of mammalian beta-1

receptors (Nahorski, 1977). They bind propranolol (Nahorski and Smith, 1977) but may not strictly correspond to mammalian beta-2 receptors either (Dickinson and Nahorski, 1981; Nahorski, personal communication to S. D. Iversen, September 3, 1985). In the avian species used in this study, then, metoprolol is apparently unlikely to block central beta receptors typical of those in humans. So, mere access to bird brain by metoprolol would not be sufficient to allow inference of activity equivalent to that in human brain. Possible central mechanisms related to metoprolol's effects in this study cannot be determined. Since beta-blockers increase punished responding and dampen heart rate increases in pigeons and since central beta-receptors in birds differ from those in humans, the pigeon may be a useful model of the peripheral actions of beta-blockers.

In addition, activity unrelated to beta-blockade may also occur with these drugs (Weiner, 1980). Some beta-blockers, notably propranolol, but not atenolol, have been reported to block 5-hydroxytryptamine (serotonin) receptors (Middlemiss, Blakeborough, and Leather, 1977). Propranolol, but not metoprolol or atenolol, has been reported to have quieting effects upon animal behavior similar to those found with other serotonin blockers (Weinstock and Weiss, 1980; Green, Hall, and Rees, 1981; Green and Grahame Smith, 1976). The serotonergic system has been linked to punished behavior, and drug interference with this system is associated with antianxiety effects (see Sepinwall and Cook, 1978). So propranolol-induced antipunishment effects may be mediated centrally by serotonin blocking activity as well as peripherally by beta-blocking activity. Propranolol also has membrane stabilizing activity but metoprolol and atenolol do not. This property has apparently not been linked to behavioral effects, however (Frishman, 1984).

Assuming that atenolol is limited in action to peripheral beta-1 blockade and that metoprolol also acted predominantly at peripheral beta-1 receptors in this study, the increased punished responding produced by atenolol and metoprolol would not appear to be primarily accounted for by a direct central action of these drugs. Furthermore, since peripheral

beta-blockade is the only property usually ascribed to the three beta-blockers used in this study, and since the three beta-blockers prevented at least some of the heart rate increase associated with punished responding, it seems likely that peripheral beta-1 blockade cannot be ruled out as a mechanism that accounts, at least in part, for the suggested antipunishment effects of beta-blockers. That greater increases in punished responding appear to be associated with larger decreases in heart rate in this study also is consistent with a peripheral explanation.

Taken together, then, the behavioral and heart rate data presented here suggest a role for cardiac beta-1-blockade in some behavioral effects of the beta-blockers. The mechanism or mechanisms responsible for the larger results with propranolol cannot be determined from these data, however. The greater increases in punished responding and the greater decreases in heart rate produced by propranolol in this study may have multiple determinants. Several mechanisms other than peripheral beta-1 blockade, including central beta-blockade, peripheral beta-2 blockade, and serotonin blockade, remain plausible as contributors to the effects found with propranolol.

Punished Response Baseline

The final issue to be addressed is why this and the preceding study (Durel et al., in press) found increased punished responding, while the studies of propranolol carried out a decade ago failed to find such activity. There is no evidence that either the species or the fixed ratio schedules of the current studies is responsible for the different results with propranolol. White Carneaux pigeons were used by McMillan (1973c) and a fixed ratio punishment schedule was employed by Sepinwall and colleagues (1973) . With the results of the present study, however, there is increased support for the suggestion made earlier that control levels of punished responding influence the beta-blocker effects.

No standard baseline level of punished responding has emerged in studies testing chlordiazepoxide and other antianxiety drugs. Studies of the effect of chlordiazepoxide on

punished responding have reported baseline levels ranging from virtually complete suppression (<0.001 resp/sec, Geller et al., 1962, and McMillan, 1973b) to moderate levels (0.25 resp/sec, Sepinwall et al., 1973, and 0.36 resp/sec, McMillan, 1973a). Chlordiazepoxide increased punished responding across the reported range of baseline levels in these and other studies. Absolute response levels were smaller when control rates were very low and generally higher (e.g, 0.9 resp/sec, Sepinwall et al., 1973) when control rates were higher. The opposite pattern is noted for relative changes. In the present study, chlordiazepoxide produced absolute levels of punished responding that were greater than 1.5 resp/sec in two birds with baseline rates of 0.4 and 1.1 resp/sec. These rates represented relative increases (184-397%) which are consistent with those reported in other studies employing less severely suppressed baseline rates (Sepinwall et al., 1973; McMillan, 1973a; McMillan and Leander, 1973; McMillan, 1976; Jeffrey and Barrett, 1979). The rates of punished responding were severely suppressed in two of the earlier studies of propranolol and chlordiazepoxide (McMillan, 1973c; Robichaud et al., 1973). The higher rate (0.3 resp/sec) employed by Sepinwall et al. (1973) was associated with the only significant increase reported for propranolol in the earlier studies. Propranolol and atenolol increased punished responding when control rates averaged 0.2 resp/sec (Durel et al., in press). In the present study, propranolol, metoprolol, and atenolol increased punished responding when control rates averaged 0.38, 0.31, and 0.21 resp/sec, respectively. There is, then, a fairly clear difference in level of suppressed responding between studies reporting increases or no increases with propranolol. Thus, there is some evidence for the assumption that higher punished response rates influenced the effects found here with beta-blockers.

The higher levels of control and drug-related responding reported here are consistent with the idea that the rate-increasing effect of beta-blockers is a function of the moderately suppressed rate of responding. Drug effects on punished responding are importantly determined by parameters that affect rate of responding (Geller and Seifter, 1962;

McMillan, 1973c, 1975; Wuttke and Kelleher, 1970). Drugs failing to increase punished responding under one set of experimental parameters may increase punished responding when experimental conditions are varied. For example, etchlorvynol and chloral hydrate, as well as propranolol, did not increase punished responding under the severe suppression reported by McMillan (1973c). Recently, however, under different conditions, both ethchlorvynol and choral hydrate increased punished responding (Witkin, 1984). The baseline for punished responding in the Witkin (1984) study was considerably higher than that reported by McMillan (1973c). Thus, ethchlorvynol and chloral hydrate in one study, and propranolol in another, have increased punished responding under experimental conditions that produced less severe suppression than employed in earlier studies reporting no increase with these drugs. A similar finding may be noted in the antipunishment effect of ethanol. Ethanol generally does not increase punished responding except at less than severely suppressed response levels (see Sepinwall and Cook, 1978). Apparently, the rate-increasing effects of some drugs are strongly influenced by baseline levels of responding and are unlikely to be demonstrated under the baseline of severely suppressed responding that has often been employed to test the benzodiazepines, barbiturates, and meprobamate. The data reported here suggest that when control rates are perhaps 0.2 resp/sec and above, punished behavior may be affected by the beta-blockers in a manner similar to that produced by drugs commonly found to increase punished responding.

Finally, the punished response baseline used in this study may have influenced drug effects in an additional way. Although the beta-blockers produced increases in punished responding that were generally dose-related, smaller than maximal increases occasionally occurred at middle doses of the beta-blockers. The moderate level of punished responding used in this study may have contributed indirectly to the variability seen in control and in drug-produced punished responding. The successful effort to maintain moderate punished response levels appeared to produce responding that was less stable than that produced with

a baseline of severely suppressed responding. Similar variability in control rates of moderately suppressed responding has been reported earlier (McMillan, 1973a), and such variability is more likely with relatively high response rates than with severely suppressed responding.

Age in White Carneaux Pigeons

Another factor which may have contributed to differences between the present study and the earlier study reporting no increased responding in pigeons involves sympathetic nervous system reactivity in White Carneaux pigeons. A decrease in sympathetic responsivity in five year old birds of this strain, compared with one year olds, has been reported (Fronek and Alexander, 1981). The birds used in the two recent beta-blocker studies reporting increased punished responding were less than three years old. Classically conditioned heart rate increases have been reported in birds less than a year old (Cohen and Durkovic, 1966). Since the conditioned heart rate increases are reported to be sympathetically mediated (Cohen and Pitts, 1968), beta-blockers would be expected to be less effective in animals with reduced sympathetic responsivity. Age was not reported in the study reporting no increased responding with propranolol in White Carneaux (McMillan, 1973c), but, since the birds had experimental histories, they may have been older than those used more recently. Thus, it is at least plausible that age in White Carneaux pigeons is a determinant of beta-blocker effects.

A number of factors that might influence the effects of beta-blockers upon punished responding have been mentioned. Among these, an influence of drug history on the subsequent behavioral effects of drugs (Glowa and Barrett, 1983) cannot be ruled out in the propranolol studies reported a decade ago or in some birds in the present study. The rats in the Sepinwall et al. (1973) study had received chlordiazepoxide before propranolol was administered. The rats in the Robichaud et al. (1973) study were naive before the study but it cannot be determined if chlordiazepoxide had been administered before propranolol in that

study. Although chlordiazepoxide was administered after propranolol to the White Carneaux pigeons in the McMillan (1973c) study, the birds had received drugs previously.

Need for Further Testing

Further testing of beta-blockers in the punishment procedure may help to clarify several of the issues that have been discussed. First, examination of rates of responding as a determinant of the effects of beta-blockers and other suggested antianxiety drugs might reconcile different results of earlier studies. As noted by others (Witkin and Barrett, 1976; McMillan, 1973c, 1975), attempts to assess the effects of drugs on punished behavior without specifying the parameters related to the punishment schedule are likely to result in incomplete understanding in this area. Further, it seems plausible that the effects of beta-blockers on punished responding may also be influenced by experimental history (in prior studies, in the order of drug administration, and in the effects produced earlier by drugs) and, at least in White Carneaux pigeons, age. Clearly, age and experimental history should be taken into account in future studies with this strain. Finally, the differential effects found with the three beta-blockers provide an indication that, given comparable control response rates, possible differences in potency and efficacy among beta-blockers relating to this behavioral effect can be determined in an animal test.

The heart rate data collected in this study provide evidence that pigeon heart rate can be measured during an operant procedure, and that heart rate is sensitive to behavioral contingencies. How heart rate varies according to differences in schedule parameters is of interest because the conditions under which heart rate might be increased or decreased might be related to behavioral differences produced by different experimental conditions. Heart rate decreases during conditioning involving unavoidable shock (Cohen and Durkovic, 1966) and during severe suppression of responding with punishment (Dantzer and Baldwin, 1974a, 1974b) have been reported. In the present study with response dependent shock, responding was related to heart rate increases. It is reasonable to assume that punishment conditions that

produce virtually no responding also produce no sustained heart rate increase. If punishment conditions producing differential behavioral effects also produce differential effects on heart rate, then the behavioral effects of drugs whose predominant action is on heart rate, might well be more sensitive to one condition than the other. Thus, beta-blockers would be predicted to increase punished responding primarily in situations in which heart rate increases occur. It is further conceivable that other drugs that have been reported ineffective in punishment procedures studies but are thought to decrease anxiety in humans, for example, ethanol, might produce differential results with different levels of punished responding and such results might, perhaps, be related to heart rate.

Clinical Implications

Finally, the results presented here have implications for understanding the circumstances in which beta-blockers have antianxiety effects in humans. The roles of increased cardiac activity in punished responding and of decreased cardiac activity produced by beta-blockers have received support in this animal study. The feasibility of studying heart rate change as a correlate of punished response change and of beta-blockade has been shown. It may also be relevant to the concept of anxiety as noted next.

Experimental situations in which responding is both positively reinforced and punished have been conceptualized as "conflict" (Cook, 1982; Cook and Sepinwall, 1978; Geller, 1962; Geller and Seifter, 1968; Geller et al., 1962; Haefely, 1976). Examination of the concept of conflict may shed light on implications for the clinical generalizability of the antianxiety effects of beta-blockers. As noted earlier, beta-blockers are reported effective in decreasing anxiety states characterized by somatic symptoms such as palpitations and tachycardia. Further, they are more often reported effective in decreasing anxiety related to specific situations, for example, situations involving public performance, than in anxiety that can be characterized as free-floating or neurotic. It might be reasoned, then, by analogy to the conflict test, that beta-blockers increase responding in situations in which ongoing

behavior is suppressed (e.g., preparation for and/or engaging in public performance). This analysis is consistent with the pioneering notions of conflict (Hovland and Sears, 1938) in which conflict, conceptualized as opposing tendencies to approach and avoid a goal, results in anxiety or fear when the hypothesized accompanying drive state is high (see also Dollard and Miller, 1950: Epstein, 1982; Miller, 1944). This reasoning suggests that anxiety, conceptualized as involving greater or lesser tendency to approach, may involve higher or lower response rates. Perhaps a high tendency to approach, with its assumed higher drive state, is more likely to involve sympathetically mediated cardiovascular activity. If heart rate serves as an index of this activity, conflict behavior accompanied by increased heart rate, and a presumed high tendency to respond, may be particularly sensitive to the antianxiety effects of beta-blockers. Clinically, then, increased heart rate associated with anxiety and/or situational stress may predict which persons might benefit from the antianxiety effects of beta-blockers.

Further, the present findings suggest that the psychological effects of beta-blockers may be influenced by earlier drug use. Perhaps beta-blockers are more apt to be effective in anxious persons who do not have extensive drug histories. Particularly, the antianxiety effects of beta-blockers may be masked or attenuated in people who have earlier used another drug, particularly an antianxiety drug such as chlordiazepoxide. Caution is suggested, then, in subject selection when the psychological effects of beta-blockers are investigated. Similar caution may be justified in expectations for clinical efficacy of beta-blockers in chronically anxious persons who have received previous drug treatment.

FOOTNOTE

1. Tween was added to enhance solubility of doses of 5.6 mg/ml and higher and the drug appeared to remain in solution. The manufacturer does not report any problems with solubility or attenuated physiological effect with the drug at these concentrations (Dr. McCurty, ICI Americas, personal communication, May 19, 1986). Centrifuging solutions of 5.6 and 10.0 mg/ml, the concentrations used during the study, did not result in precipitation. Furthermore, increases in punished responding frequently did occur at the higher doses. At present, therefore, the reason atenolol failed to produce heart rate decreases similar to those seen with propranolol and metoprolol,while still increasing punished responding, is not apparent.

Mean control response rates (response/second)

for unpunished (UNP) and punished (PUN) responding

		DRUG				
		PROP	METOP	ATEN	CDAP	MEAN
Subject #						
4256	UNP	3.592^{3}	2.603^{3}	2.853^{4}	2.743^{2}	2.948
AMP* 2.0**	PUN	0.532	0.495	0.175	1.014	0.554
4227	UNP	1.967^{2}	2.478^{4}	2.727^{2}	2.334^{4}	2.343
MPA 2.5	PUN	0.133	0.303	0.316	0.258	0.208
4217	UNP	3.128^{5}	2.838^{2}	3.073^{3}	2.568^{4}	2.901
PAM 4.0	PUN	0.483	0.138	0.169	0.103	0.223
1989	UNP	2.187^{2}	2.502^{4}	2.499^{2}	2.267^{4}	2.364
PMA 4.5	PUN	0.306	0.195	0.103	0.118	0.200
1976	UNP	1.577^{2}	1.880^{3}	1.699^{2}	1.856^{4}	1.797
MAP 2.0	PUN	0.439	0.396	0.274	0.443	0.402
MEAN	UNP	2.490	2.460	2.570	2.354	2.471
	PUN	0.401	0.305	0.207	0.379	0.317

*: Order of drug administration (P = propranolol, M = metoprolol, A = atenolol)

**: Shock intensity in mAmperes

Note: Superscripts indicate the number of data points represented.

APPENDIX 1

Unpunished responding in responses/second (Rate) and percent control (%)

PROPRANOLOL

DOSE (mg/kg)

Control	0.3	1.0	3.0	5.6	10.0	17.0	30.0	saline	
Subject #									
4256 Rate	3.592	3.053	3.712	3.158[2]	3.790	2.889[2]			
%		85	103	88	106	80			
4227 Rate	1.967		1.761	2.406[2]	1.678	2.164	2.229	1.437[a]	2.650
%			90	122	85	110	113	73	135
4217 Rate	3.128	3.563	3.427	3.233[2]	3.096[2]	3.584	2.077[2]		3.244
%		114	110	103	99	115	66*		104
1989 Rate	2.187	2.588	1.882[2]	2.143[2]	2.427[2]	1.897	1.192		
%		118*	86*	98	111*	87*	55*		
1976 Rate	1.577		1.900	1.084	2.044	1.329			
%			158	69	130	84			
Mean	2.490		2.536	2.405	2.607	2.373			
%			109	96	106	95			

*$p < 0.05$

[a]At 56.0, 0.125 resp/sec and 6%*.

Note: Birds generally receive each dose on one occasion. Superscripts indicate two or three administrations.

APPENDIX 2

Unpunished responding in responses/second (Rate) and percent control

METOPROLOL

DOSE (mg/kg)

		Control	0.3	1.0	3.0	5.6	10.0	17.0	saline
Subject #									
4256	Rate	2.603	2.969	2.714	2.501[2]	2.256	2.209	2.254	
	%		114*	104	96	86*	85*	87*	
4227	Rate	2.478	1.945	2.145	2.575[2]	2.256	2.328		2.273
	%		79	87	104	91	94		92
4217	Rate	2.838	3.100	3.205	3.040	3.279	3.399		
	%		109	113	107	116	120*		
1989	Rate	2.502		2.395	1.964	1.408[2]	2.250	2.243	2.452
	%			96	79	56*	90	90	98
1976	Rate	1.880	2.181	2.368	1.869	1.284	-		
	%		116	126	99	68	-		
Mean		2.460	2.549	2.565	2.391	2.097	2.547		
	%		105	105	97	83	97		

*$p<0.05$

Note: Birds generally received each dose on one occasion. Superscripts indicate two or three administrations.

Appendix 2 (Continued)

Unpunished responding in responses/second (Rate) and percent control (%)

ATENOLOL

DOSE (mg/kg)

		Control	0.3	1.0	3.0	5.6	10.0	17.0	saline
Subject #									
4256	Rate	2.853		2.910[2]	2.761[2]	3.013[3]	2.838[3]	2.333	2.867
	%			102	97	106	99	82	101
4227	Rate	2.727	2.772	2.867	2.670[2]	3.093	1.897		
	%		102	105	104	113*	70		
4217	Rate	3.073	2.275	2.801	2.917	3.303	2.714	2.840	
	%		74	91	95	108	88	92	
1989	Rate	2.499		2.331	2.320[2]	2.720[2]	2.231		
	%			93	93	109	89		
1976	Rate	1.699	1.645	2.279	1.592	1.457	1.652		
	%		97	134	94	86	97		
Mean		2.570		2.638	2.452	2.517	2.266		
%				105	97	104	89		

*$p<0.05$

Note: Birds generally received each dose on one occasion. Superscripts indicate two or three administrations.

APPENDIX 2 (Continued)

Unpunished responding in responses/second (Rate) and percent control (%)

CHLORDIAZEPOXIDE

DOSE (mg/kg)

		Control	1.0	3.0	5.6	10.0	17.0	30.0
Subject #								
4256	Rate	2.743	3.121			1.991		
	%		114*			73*		
4227	Rate	2.334	2.154	2.016[2]	1.614[2]	0.64	0.002	
	%		93	86	69	27*	<1*	
4217	Rate	2.568	3.151	3.373	3.454[2]	3.628	2.767	2.680
	%		123	131	134	141*	108	104
1989	Rate	2.267	2.962	2.622	2.259[2]	2.260	0.815[2]	
	%		131*	116	100	100	36*	
1976	Rate	1.856	1.910	2.842[2]	2.446	0.841		0.00
	%		102	153*	132	45*		0*
Mean		2.354	2.660	2.670	2.443	1.872		
%			113	122	109	77		

*p<0.05

( ) Estimated missing value.

Note: Birds generally received each dose on one occasion. Superscripts indicate two or three administrations.

APPENDIX 2 (Continued)

Punished responding in responses/second (Rate) and percent control (%)

PROPRANOLOL

DOSE (mg/kg)

	Control	0.3	1.0	3.0	5.6	10.0	17.0	30.0	saline
Subject #									
4256 Rate	0.532	0.0	1.990	0.492[2]	2.090	0.096[2]			
%		0	374*	92	545*	18			
4227 Rate	0.133		0.043	0.378	0.493	0.424	0.383	0.109[a]	0.084
%			32*	284*	371*	319*	288*	82	63*
4217 Rate	0.483	2.194	3.069	1.949	2.197[2]	3.353	0.395		0.667
%		604*	636*	404*	455*	695*	82		138
1989 Rate	0.306	0.321	0.320[2]	0.336[2]	0.741[2]	0.215	0.424		
%		105	105	110	242*	70	139		
1976 Rate	0.439		0.488	0.224	0.765	0.201			
%			111	52	174	48			
Mean	0.379		1.182	0.676	1.257	0.858			
%			252	188	357	230			

*$p<0.05$

[a] At 56.0, 0.0 resp/sec and 0%*.

Note: Birds generally received each dose on one occasion. Superscripts indicate two or three administrations.

APPENDIX 2 (Continued)

Punished responding in responses/second (Rate) and percent control (%)

METOPROLOL

DOSE (mg/kg)

		Control	0.3	1.0	3.0	5.6	10.0	17.0	saline
Subject #									
4256	Rate	0.495	0.481	1.252	1.043[2]	0.830	1.280	0.674	
	%		97	253*	211*	168*	259*	136	
4227	Rate	0.303	0.338	1.072	0.8772	0.5972	0.455		0.054
	%		99	354*	289*	197*	150		18*
4217	Rate	0.138	0.050	0.209	0.184	0.302	0.193		
	%		36*	151*	133	219*	140		
1989	Rate	0.195		0.216	0.129	0.018[2]	0.293	0.075	0.069
	%			111	66	9*	150	38*	35*
1976	Rate	0.396	0.443	0.535	0.210	0.384	-		
	%		112	135	53	97			
Mean		0.305	0.328	0.657	0.489	0.426	0.555		
%			86	201	150	138	175		

*p<0.05

Note: Birds generally received each dose on one occasion. Superscripts indicate two or three administrations.

APPENDIX 2 (Continued)

Punished responding in responses/second (Rate) and percent control (%)

ATENOLOL

DOSE (mg/kg)

		Control	0.3	1.0	3.0	5.6	10.0	17.0	saline
Subject #									
4256	Rate	0.175		0.359[2]	0.474[2]	0.565[3]	0.510[3]	0.373	0.002
	%			205	270*	323*	291*	213	1
4227	Rate	0.316	0.120	0.108	0.097[2]	0.254	0.393		
	%		38	34	60	80	124*		
4217	Rate	0.169	0.206	0.376	0.496	0.220	0.305	0.166	
	%		122	224*	294*	130	181*	98	
1989	Rate	0.103		0.074	0.190[2]	0.268[2]	0.0		
	%			72	185	260*	0*		
1976	Rate	0.274	0.490	0.861	0.381	0.268	0.266		
	%		179*	315*	139	98	97		
Mean		0.207		0.356	0.328	0.315	0.295		
%				170	190	178	139		

*$p<0.05$

Note: Birds generally received each dose on one occasion. Superscripts indicate two or three administrations.

APPENDIX 2 (Continued)

Punished responding in responses/second (Rate) and percent control (%)

CHLORDIAZEPOXIDE

DOSE (mg/kg)

Subject #		Control	1.0	3.0	5.6	10.0	17.0	30.0
4256	Rate	1.014	1.865			1.593		
	%		184*			157*		
4227	Rate	0.258	0.144[2]	0.078[2]	0.128[2]	0.190	0.0	
	%		56	30	50	74	0*	
4217	Rate	0.103	0.106	0.095	0.307[2]	0.677	0.555	0.216
	%		103	92	299*	659*	540*	210*
1989	Rate	0.118	0.001	0.115	0.002[2]	0.111[2]	0.054	
	%		<1*	97	2*	94	46*	
1976	Rate	0.443	0.164	1.759[2]	1.069	0.573		0.0
	%		37	397*	241*	129		0*
Mean		0.379	0.456	0.512	0.377	0.577		
%			76	154	148	223		

*$p<0.05$

Note: Birds generally received each dose on one occasion. Superscripts indicate two or three administrations.

APPENDIX 2 (Continued)

Average control heat rates in beats/minute

DRUG		Subject # 4256	4227	4217	1989	1976	Mean	(S.D.)
	TO*	147	100	155	130	120	130	±22
PROP	UNP	160	115	215	140	150	156	±37
	PUN	190	153	180	160	180	173	±16
	TO	125	84	110	130	134	117	±20
METOP	UNP	132	108	153	150	154	139	±20
	PUN	185	140	160	160	180	165	±18
	TO	110	86	132	130	122	118	±19
ATEN	UNP	133	115	108	165	140	147	±26
	PUN	165	158	163	174	180	168	±9
	TO	112	93	110	130	155	120	±24
CDAP	UNP	137	116	150	150	153	141	±15
	PUN	202	138	160	170	196	173	±26
	TO	126	91	127	130	133	121	±17
MEAN	UNP	141	114	175	151	149	146	±22
	PUN	186	147	166	166	184	170	±20

*TO = timeout, UNP = unpunished, PUN = punished

APPENDIX 3

Heart rate in beats/minute during unpunished responding

DOSE (mg/kg)

PROPRANOLOL

Subject #		Control	1.0	3.0	5.6	10.0	17.0
4256	Rate	160^{2}	130	123^{2}	123	135^{2}	
	Change		-30	-37	-37	-25	
4227	Rate	115^{3}	103	102^{2}	-	90	95
	Change		-12	-13	-	-25	-20
4217	Rate	215^{2}	-	170	130	150	105
	Change		-	-45	-85	-65	-110
1989	Rate	140^{2}	-	150	140	110	
	Change		-	+10	0	-30	
1976	Rate	150^{2}	140	130	140	100	
	Change		-10	-20	-10	-50	
Mean	Rate	146	124^{3}	135^{5}	133^{4}	117^{5}	
	Change		-17	-21	-33	-39	

Note: Superscripts indicate a mean based on that number of data points. Other values represent a single administration.

APPENDIX 4

Heart rate in beats/minute during unpunished responding

METOPROLOL

DOSE (mg/kg)

		Control	1.0	3.0	5.6	10.0	17.0
Subject #							
4256	Rate	132^{2}	130	118^{2}	-	105	120
	Change			-2	-14	-	-27	-12
4227	Rate	108^{3}	115	115	105	100	
	Change			+7	+7	-3	-8
4217	Rate	153^{3}	153	135	135	-	
	Change			0	-18	-18	-
1989	Rate	150^{3}	135	150	140	135	110
	Change			-15	0	-10	-15	-40
1976	Rate	154^{2}	165	153^{5}	135	-	
	Change			+9	-4	-22	-
Mean	Rate	139	140^{5}	134^{5}	129^{4}	113^{3}	
	Change			0	-6	-13	-17

Note: Superscripts indicate a mean based on that number of data points. Other values represent a single administration.

APPENDIX 4 (Continued)

Heart rate in beats/minute during unpunished responding

ATENOLOL

DOSE (mg/kg)

		Control	0.3	1.0	3.0	5.6	10.0	17.0
Subject #								
4256	Rate	133[2]		118[2]	115[2]	109[2]	122[2]	
	Change			-15	-18	-24	-11	
4227	Rate	115[2]		110	125[2]	123	115	
	Change			-15	+10	+8	0	
4217	Rate	180[3]		210	210	175	-	
	Change			+30	+30	-5	-	
1989	Rate	165[3]		140	165	150[2]	140	
	Change			-25	0	-15	-25	
1976	Rate	140	160	-	130	140	145	
	Change		+20	-	-10	+8	-5	
Mean	Rate	147		148[4]	149[5]	139[5]	136[4]	
	Change			-6	+2	-6	-10	

Note: Superscripts indicate a mean based on that number of data points. Other values represent a single administration.

APPENDIX 4 (Continued)

Heart rate in beats/minute during unpunished responding

CHLORDIAZEPOXIDE

DOSE (mg/kg)

Subject #		Control	1.0	3.0	5.6	10.0	17.0	30.0
4256	Rate	137	121	-	-	138		
	Change		-16	-	-	+1		
4227	Rate	116^3	110	98^2	142^2	158		
	Change		-6	-18	+26	+42		
4217	Rate	150	-	160	-	-	150	
	Change			+10	-	-	0	
1989	Rate	150^3	160	140	160^2	150	120	
	Change		+10	-10	+10	0	-30	
1976	Rate	153^2	150	135	140	130		
	Change		-3	-18	-13	-23		
Mean	Rate	141	135^4	133^4	147^3	144^4		
	Change		-4	-9	+8	+5		

Note: Superscripts indicate a mean based on that number of data points. Other values represent a single administration.

APPENDIX 4 (Continued)

Heart rate in beats/minute during punished responding

PROPRANOLOL

DOSE (mg/kg)

		Control	1.0	3.0	5.6	10.0	17.0	30.0
Subject #								
4256	Rate	190^{2}	140	140^{2}	130	137^{2}		
	Change		-50	-50	-60	-53		
4227	Rate	153^{3}	130	124^{2}	-	100	110	
	Change		-23	-29	-	-53	-43	
4217	Rate	180^{2}	-	150	128	150	120	
	Change		-	-30	-52	-30	-60	
1989	Rate	160^{2}	-	145	160	100		
	Change		-	-15	0	-60		
1976	Rate	180^{2}	180	170	160	111		
	Change		0	-10	-20	-69		
Mean	Rate	173	150^{3}	146^{5}	145^{4}	120^{5}		
	Change		-24	-27	-33	-53		

Note: Superscripts indicate a mean based on that number of data points. Other values represent a single administration.

APPENDIX 4 (Continued)

Heart rate in beats/minute during punished responding

METOPROLOL

Dose (mg/kg)

Subject #		Control	1.0	3.0	5.6	10.0	17.0
4256	Rate	185^{2}	160	145^{2}	-	115	115
	Change		-25	-40	-	-70	-70
4227	Rate	140^{3}	130	125	110	97	
	Change		-10	-15	-30	-43	
4217	Rate	160^{3}	160	130	125	-	
	Change		0	-30	-35	-	
1989	Rate	160^{3}	145	165	-	150	135
	Change		-15	+5	-	-10	-25
1976	Rate	180^{2}	213	182^{2}	140	-	
	Change		+33	+2	-40	-	
Mean	Rate	165	162^{5}	149^{5}	125^{3}	121^{3}	
	Change		-3	-16	-35	-41	

Note: Superscripts indicate a mean based on that number of data points. Other values represent a single administration.

APPENDIX 4 (Continued)

Heart rate in beats/minute during punished responding

ATENOLOL

DOSE (mg/kg)

Subject #		Control	0.3	1.0	3.0	5.6	10.0	17.0
4256	Rate	165^{2}		138^{2}	156^{2}	139^{2}	144^{2}	
	Change			-27	-9	-26	-21	
4227	Rate	158^{2}		140	145^{2}	155	150	
	Change			-18	-13	-3	-8	
4217	Rate	163^{3}		190	150	154	-	
	Change			+27	-13	-9	-	
1989	Rate	174^{3}		145	180	160^{2}	-	
	Change			-29	+6	-14	-	
1976	Rate	180	207	-	160	177	178	
	Change		+27		-20	-3	-2	
Mean	Rate	168		153^{4}	158^{5}	157^{5}	157^{3}	
	Change			-12	-10	-11	-10	

Note: Superscripts indicate a mean based on that number of data points. Other values represent a single administration.

APPENDIX 4 (Continued)

Heart rate in beats/minute during punished responding

CHLORDIAZEPOXIDE

DOSE (mg/kg)

Subject #		Control	1.0	3.0	5.6	10.0	17.0	30.0
4256	Rate	202	165	-	-	197		
	Change		-37	-	-	-5		
4227	Rate	138[3]	140	133[2]	178	178	-	
	Change		+2	-5	+40	+40	-	
4217	Rate	160	140	170	165	160	130	
	Change		-20	+10	+5	0	-30	
1989	Rate	170[3]	-	165	-	200	195	
	Change		-	-5	-	+30	+25	
1976	Rate	196[2]	235	190	196	160	-	
	Change		+39	-6	0	-36	-	
Mean	Rate	173	170[4]	165[4]	180[3]	179[5]		
	Change		-4	-2	+15	+6		

Note: Superscripts indicate a mean based on that number of data points. Other values represent a single administration.

APPENDIX 4 (Continued)

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