Buspirone in Animal Models of Anxiety

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Chapter 4

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I. INTRODUCTION AND OVERVIEW

The successful treatment of psychopathology by chlorpromazine in the 1950's initiated various attempts to develop sensitive, reliable methods for use with animals that could evaluate and predict the clinical efficacy of psychotherapeutic compounds. At first, many of these tests consisted of activity or locomotor measures to evaluate sedation, ataxia and muscular impairment. Other tests of taming or aggression were used to assess the potential anti-aggressive and fear-reducing actions of drugs. However, many of these procedures were not objective, dose-response functions were difficult to establish, and they were often not capable of clearly distinguishing classes of drugs which had different clinical actions. Tests employing such unconditioned behaviors were gradually supplemented by procedures involving conditioned behavior. The use of conditioned avoidance methods, for example, in which animals were allowed to avoid shocks by climbing a rope or pressing a lever during a stimulus period preceding the delivery of foot shock, were the first procedures widely used to assess the effects of antipsychotic compounds (Cook and Weidley, 1957; Courvoisier et al., 1953). Generally, these drugs decreased responses occurring during the pre-shock stimulus (i.e., avoidance responses) but did not impair responses to shock (escape responses). The avoidance procedure fulfilled many of the criteria deemed essential for assessing preclinical drug effects in animals: it was sensitive to variations in dose levels, it was objective and, further, was capable of differentiating among compounds from different pharmacological classes. For example, barbiturates and other sedative hypnotics decreased responding during both the pre-shock stimulus and shock presentation.

With the discovery of compounds that were effective in the treatment of anxiety and depression, the need for additional diverse behavioral methods to assay these drugs was heightened still further. Concomitantly, as research

focusing on the neuropharmacological mechanisms underlying the effects of antipsychotic drugs increased, thereby identifying and clarifying the potential role of dopamine, so did the number of animal models used to evaluate those effects. Thus, research involving the blockade by antipsychotic drugs of apomorphine- and amphetamine-induced stereotypy also became established models for determining potential efficacy of antipsychotic drugs. More recently, techniques for identifying and localizing neurotransmitters in various brain regions, together with radiolabelled ligand procedures for identifying receptor populations, have spawned additional methods for establishing newer animal models based on lesions and brain stimulation techniques.

At present, a wide variety of behavioral, neuropharmacological and neurophysiological procedures are used to evaluate the efficacy and mechanisms of action of psychotherapeutic compounds. In general, these procedures are complementary in that there is, for the most part, good agreement across the different procedures in the identification of drugs with particular therapeutic effects. On occasion, however, compounds are discovered that do not show the same "profile" yet are clinically effective agents (e.g., the novel antipsychotic compound clozapine). When this occurs, it reveals one of the recognized shortcomings of all these procedures: novel compounds with different mechanisms of action, yet similar therapeutic efficacy, are not likely to be detected. There is no easy or currently available solution to this problem (Eison, 1984). When such compounds are discovered, however, they raise new and exciting questions. Ultimately, such discoveries may not only result in the development of drugs with even greater selectivity, but they may also clarify the mechanisms underlying the psychopathological disorder being treated, as well as the basic processes by which pharmacological treatments alter the

course of the disorder. This appears to be the case with buspirone, a novel clinically effective anxiolytic which differs substantially from other antianxiety agents. Unlike other anxiolytic drugs, buspirone is not an anticonvulsant or sedative-hypnotic; it does not bind to gamma aminobutyric acid (GABA) receptors in the central nervous system, nor is it a muscle relaxant. As such, research with buspirone promises to yield valuable information for the understanding and treatment of anxiety and the neurobiological and psychological processes involved in this disorder.

This chapter briefly reviews various animal models used in the evaluation of drugs with anxiolytic activity. A number of reviews have appeared recently which critically and thoroughly evaluate various methods and procedures used to assess and predict the efficacy of compounds with potential clinical utility (Crawley, 1985; Liebman, 1985; Treit, 1985). The majority of this chapter, therefore, is devoted to summarizing recent research on buspirone using behavioral models so that the actions of this novel and intriguing compound can be integrated and synthesized with extant information on traditional anxiolytics.

It is appropriate to comment briefly on the concept of an "animal model," a term which should not be used without adequately understanding that, with regard to psychopathology, no animal method currently in use faithfully "models" or mimics a disease. At best, the effects of drugs on behavior under certain procedures correlate quite well with clinical effects in humans. However, there may be little or no relationship between the "model" used to predict clinical outcome and the disease process itself. Thus, there is no clear reason why drug effects under procedures using avoidance conditioning should predict antipsychotic efficacy. In a strict sense, then, the procedures are

not models but are, instead, assay systems or methods with correlational but not isomorphic relevance.

II. ANIMAL MODELS IN PRECLINICAL PSYCHOPHARMACOLOGY OF ANTIANXIETY DRUGS

A. Behavioral Models

As with procedures used to evaluate chlorpromazine, methods for testing antianxiety drugs have evolved considerably over the more than 20 years that have elapsed since the introduction of chlordiazepoxide and diazepam. Generally, two approaches to the behavioral study of anxiolytic drug actions have been used. One method involves the use of unconditioned behavior where a particular response is selected for study that is normally part of the animal's repertoire. Usually, these involve exploratory or locomotor activity, eating, drinking or, perhaps aggression elicited by shock or isolation. Alternatively, various conditioning procedures have also often been employed in which behavior is conditioned or established by arranging for certain consequences to follow behavioral responses. Typically, these methods use punished or conflict behavior or drug discrimination procedures. This section will highlight the major methodologies used to evaluate the preclinical anxiolytic actions of compounds, particularly as these methods have been used to evaluate the effects of buspirone.

1. *Unconditioned behaviors*

a. Eating and drinking: It has been known for some time that benzodiazepines increase the intake of food and water (Randall et al., 1960). These effects occur in non-deprived and deprived animals, as well as in animals pre-fed with a highly palatable diet (review by Cooper and Estall, 1985). However, this effect is not pharmacologically specific because non-benzodiazepine compounds such as cyproheptadine and chlorpromazine also

increase food consumption (Mansbach et al., 1984). Increases in eating produced by the benzodiazepines are, however, mediated through the benzodiazepine receptor since the benzodiazepine antagonist Ro 15-1788 (Hunkeler et al., 1981) and the inverse agonist ß-CCE (ethyl ß-carboline-3-carboxylate) reverse diazepam-induced eating but not that produced by cyproheptadine or chlorpromazine. Although increases in consummatory behavior with anxiolytic drugs occur in several different species and across a wide range of conditions, the occurrence of these effects with non-anxiolytic agents would appear to limit the utility of consummatory behavior as a method capable of differentiating compounds effective in the management of anxiety.

b. Aggression: Early research suggested that benzodiazepines acted to decrease aggressive responses (Randall et al., 1960) and, quite frequently the taming or anti-aggressive effects of drugs have been used initially to characterize various compounds. For example, buspirone has been reported to inhibit aggressive behavior in rhesus monkeys (Tompkins et al., 1980). However, several studies conducted within the past few years have indicated that the effects of benzodiazepines on aggression are quite variable. At least part of the variability is attributable to the fact that aggression is not a unitary behavior but depends very much on the context in which it occurs and on the methods used to produce it (Rodgers and Walters, 1985; Treit, 1985). Consequently, anxiolytic drugs have been shown to increase or decrease aggression depending on a host of factors. Further research which blends detailed ethological analyses with suitable behavioral techniques could clarify many issues but, at present, it appears that anti-aggressive effects of drugs are not a suitable means of delineating compounds that might be effective in treating anxiety.

c. Exploratory activity and social behavior: A number of procedures based on exploratory activity and/or social behavior have been proposed and examined for their ability to provide sensitive, selective means for evaluating the anxiolytic actions of drugs (Crawley, 1985; File 1985a,b). These models are derived in part from the tendency of rodents to explore novel environments. Two of the more recent tests have an added feature of manipulating the level of illumination to study the frequency of crossings between bright and dark portions of a compartment (Crawley, 1985) or the effects of illumination on social interaction (File, 1985a,b). Under these test conditions benzodiazepines increase the number of movements between compartments in mice and also elevate measures of social interaction between rats under levels of high illumination. The effects seen with the light-dark transition procedures appear best suited for mice in that a number of rat strains do not show high baseline levels of exploratory behavior, nor does diazepam increase transition scores (Crawley, 1985). Additionally, stimulants such as amphetamine produce effects comparable to those of the benzodiazepines, thereby necessitating a further test for non-specific increases in general locomotor activity. Compounds which both increase transitions and locomotion are, therefore, considered stimulants rather than anxiolytics.

In the social interaction test, morphine produces effects partially comparable to those of the benzodiazepines. Consistent with its atypical profile under other procedures, buspirone has no effect (File, 1985b). Thus, although effects of various drugs in models based on exploratory behavior appear to correlate reasonably well with anxiolytic activity, problems with species or pharmacological specificity or the need for multiple test procedures indicate that these results must be cautiously interpreted. Additionally, adaptation or

habituation to the testing apparatus, and the possible heterogeneous nature of the behaviors involved (e.g., the social interaction test appears to provide undifferentiated measures of both affiliative and aggressive behavior) must also be considered in interpreting results using these procedures.

2. Conditioned Behaviors

a. Punishment or conflict procedures: The first test to be employed widely and reliably to assess anxiolytic activity was that developed by Geller and Seifter (1960). These investigators studied the effects of various compounds on the lever-pressing responses of rats that were established and maintained by food delivery. In certain segments of the experimental session, a distinctive stimulus was presented during which responses produced both food and shock. In the absence of drugs, responding during the stimulus period was suppressed or punished, an outcome that frequently has been termed "conflict" behavior. Geller and his colleagues demonstrated that drugs with sedative-hypnotic and anxiolytic effects (e.g., meprobamate, pentobarbital and chlordiazepoxide) increased punished behavior, whereas other drugs which lacked these effects, such as chlorpromazine and amphetamine, did not. This basic methodology, with some variations, was validated in extensive studies (Cook and Sepinwall, 1975; Sepinwall and Cook, 1978) and studied systematically (McMillan, 1975). The increases in punished responding were not due to analgesia, general stimulation, muscle relaxation, or to the anticonvulsant actions of these agents. For the most part, antianxiety compounds produced similar effects on punished behavior of all species studied, including humans (Beer and Migler, 1975; Fischman et al., 1977).

As was true with antipsychotic drugs, various neurotransmitter systems were suggested to play a role in anxiolytic drug action. The current emphasis

remains on systems involving GABA and serotonin (5-HT), although the precise mechanisms and specific contribution of these systems remain unclear (Sepinwall, 1983). Additionally, modified behavioral techniques were promoted because they provided a more rapid means of evaluating potential anxiolytic drug activity. One method which has been widely adopted since its initial report by Vogel et al. (1971) utilizes water-deprived rats which are allowed timed access to a water spout after which they receive shock with each lick. As under the Geller-Seifter procedure, most compounds which alleviate clinical anxiety attenuate the suppression of drinking produced by lick-contingent shock. However, this procedure may screen for drugs which affect deprivation-induced fluid consumption more than for effects on punished behavior per se (Leander, 1983). For example, isoproterenol increases punished licking although it is not an effective anxiolytic (Patel and Malick, 1980). None the less, this procedure has the distinct advantage of not requiring any specific training nor does it require the time-consuming establishment of stable baselines.

For the most part, procedures used with animals to predict anxiolytic actions in humans have been quite effective. However, there are exceptions. Perhaps most notable are many of the serotonin antagonists (e.g., cyproheptadine, methysergide and mianserin) which increase punished responding in animals (Brady and Barrett, 1985), but apparently are not uniformly effective in the treatment of anxiety in humans. It is interesting that methysergide has recently been shown to alleviate benzodiazepine-resistant anxiety in humans that was apparently produced by exposure to high environmental cations (Gianini et al., 1983). It remains almost certain that anxiety is not a unitary condition and that it can be differentiated in several ways (see

Section IIc, this chapter). Further research will undoubtedly clarify the relative contributions of various environmental conditions and neurotransmitter systems involved in the expression and treatment of various disorders now only globally characterized as anxiety.

b. Procedures using other conditioned behaviors: Treit (1985) has recently reviewed the results of studies which have examined the effects of anxiolytic drugs on conditioned taste aversions and on conditioned defensive burying. Conditioned taste aversions, developed by pairing a novel solution with the injection of a drug such as lithium chloride, have been shown to diminish with the administration of many anxiolytics but, as yet, it has been difficult to separate the attenuating effects from the general tendency of these compounds to elevate drinking. Thus, the utility of such procedures remains uncertain at present. The second procedure, that of conditioned defensive burying, occurs with rats that have been shocked with a stationary prod; under conditions where bedding material is available rats will bury the prod. A number of anxiolytic compounds produce dose-dependent decreases in burying, whereas most nonanxiolytic drugs do not. One advantage of this procedure is that no specific deprivation is involved, thereby obviating the frequent criticism that drug effects are due to an appetite-enhancing or dipsogenic effects. It is also apparently easily established but, unfortunately, may be too species specific to test for generality. Furthermore, additional research is necessary to more adequately differentiate between the effects produced by antipsychotic drugs and anxiolytics.

3. Drug Discrimination Models

One of the more recent methods to attract widespread experimental attention has been the drug discrimination procedure. Developed originally to

study state-dependent learning and the use of drugs as discriminative stimuli (Overton, 1984), the focus and utilization of this method has shifted somewhat from the analysis of stimulus control to that primarily of drug classification. In short, this procedure involves establishing a drug as a discriminative stimulus by reinforcing one response in the presence of the drug (e.g., after i.m. administration) and a different response in the drug's absence (e.g., after saline). Once established as a discriminative stimulus, the dose of the training drug can be varied or other compounds can be substituted to determine whether those compounds exert control that is similar to the training drug (generalization) or to saline. For the most part, there is good agreement with this procedure; drugs within the same pharmacological class or related classes produce similar behavioral control when substituted for the training drug. Additionally, pharmacologically specific antagonists are usually capable of blocking the discriminative control established by the drug, thereby yielding effects comparable to those found after saline administration (Schuster and Balster, 1977). Such findings are generally viewed as indicating that drug discrimination procedures allow statements about receptor-mediated drug actions.

Recently a model has been proposed that uses compounds which produce behavioral and physiological effects similar to those of anxiety. Lal and Emmett-Oglesby (1983) have summarized research in which pentylenetetrazol was used as the training drug. Although a convulsant at high doses, lower pentylenetetrazol doses have been reported to be anxiogenic in humans (Rodin and Calhoun, 1970). Animals trained to discriminate pentylenetetrazol from saline responded to other putative anxiogenic compounds such as the methyl ester of beta-carboline-3-carboxylic acid (ß-CCM) by responding on the lever corre-

lated with the administration of pentylenetetrazol. Further, withdrawal from chronic diazepam administration, induced by administration of Ro 15-1788, or simply by cessation of diazepam injections, also produced responding similar to that produced by the pentylenetetrazol stimulus. Finally, discriminations developed by pentylenetetrazol are decreased in a dose-dependent manner by anxiolytic drugs.

At the present time, it does not appear that buspirone has been studied in pentylenetetrazol-trained animals. However, in squirrel monkeys responding under schedules of food or shock presentation, buspirone does not block or reverse the effects of ß-CCE (unpublished studies); effects of ß-CCE are, however, blocked by chlordiazepoxide (Barrett et al., 1985). Since there is generally good agreement between drug antagonism and drug discrimination studies, it would appear that buspirone would not block a discrimination based on pentylenetetrazol and, again, would show atypical effects for an anxiolytic.

Studies focusing on buspirone as a training drug have found it difficult to establish a discrimination because of buspirone's rate-decreasing effects at the higher doses required to be effective as a discriminative stimulus (Hendry et al., 1983). Nevertheless, in animals trained with 0.75 mg/kg buspirone, a dose that did not produce substantial response disruption, there was no generalization to either oxazepam or pentobarbital when these drugs were substituted for buspirone. With animals trained to discriminate oxazepam, which was more easily established as a discriminative stimulus than was buspirone, there was also no evidence of generalization of the stimulus properties of buspirone although there was for pentobarbital. Similarly, baboons and rats trained to discriminate either lorazepam or pentobarbital from saline also showed no generalization to buspirone (Ator and Griffiths, submitted).

Thus, in these procedures designed to mimic either the subjective effects of anxiety or the stimuli correlated with anxiolytic drugs, buspirone again presents an atypical profile.

B. Neurophysiological and Neuroanatomical Models

Research directed towards better understanding the various mechanisms contributing to anxiolytic drug action has also been directed towards the development of neurophysiological and neuroanatomical models. Although relatively little research has been conducted with buspirone using these methods, advances in related areas that have identified regional distribution of receptors and sites of drug action suggest that these procedures will be used increasingly in the future. Two of the major methods will be discussed, focusing on i) the function of the locus coeruleus in anxiety and ii) studies using electrical stimulation of the brain.

1. Locus coeruleus: Electrolytic lesions and electrical stimulation of the noradrenergic nucleus locus coeruleus were found to produce changes in the behavior of monkeys (Macaca arctoides) suggesting that this area of the brain was involved in the expression of anxiety (Redmond, 1977; Redmond and Huang, 1979). For example, stimulation of the locus coeruleus produced a cluster of behaviors such as opening and closing of the mouth, scratching and yawning that have been characterized as conflict, fear or anxiety. Bilateral lesions of the locus coeruleus, on the other hand, decreased the occurrence of these behaviors. Additional support for a role of the locus coeruleus in anxiety was suggested by pharmacological experiments. Drugs such as the alpha-2 adrenergic antagonists piperoxane and yohimbine, which block autoreceptors and, presumably, increase impulse flow in the locus coeruleus, produce effects comparable to those found with electrical stimulation. Other drugs,

such as clonidine, which stimulate alpha-2 adrenergic receptors and limit activity in the locus coeruleus, as well as the benzodiazepines and morphine, reduce the frequency of behaviors characterized as anxiety.

Although reservations have been expressed about the specificity and selectivity of the lesion and pharmacological studies implicating the locus coeruleus in anxiety (Mason and Fibiger, 1979), a few studies have examined the effects of buspirone on locus coeruleus activity. In one experiment (Sanghera et al., 1983), diazepam decreased the firing rate of locus coeruleus cells, whereas buspirone increased impulse flow. This study also examined the effects of diazepam and buspirone on the major metabolite of norepinephrine 3-methoxy-4-hydroxyphenylglycol sulfate (MOPEG-SO_4). Diazepam decreased MOPEG-SO_4 in forebrain, whereas buspirone slightly increased levels of this metabolite. In further research, the metabolite of buspirone [1(-2 pyrimidyl) piperazine or 1-PP] and a buspirone analogue (MJ 13805) also increased locus coeruleus impulse flow (Sanghera and German, 1983). Trulson and Henderson (1984) have also demonstrated that buspirone increases locus coeruleus neuronal activity in vitro. Taken together, these findings reaffirm the unique properties of buspirone in proposed animal models of anxiety. Further, these results suggest that reductions in the activity of noradrenergic neurons in the locus coeruleus are not uniformly related to actions of anxiolytic drugs.

2. Electrical stimulation of the brain: A number of investigators have recently proposed that brain stimulation studies may help clarify mechanisms underlying anxiety and anxiolytic drug activity (Graeff, 1984, 1986; Liebman, 1985). Techniques employing electrical brain stimulation were proposed some time ago as being potentially useful in screening compounds for anxiolytic drug action (Olds et al., 1956). Electrical stimulation of the

brain can elicit a wide variety of behaviors ranging from feeding and drinking to sexual activity, defensive aggression and withdrawal (Olds, 1962). It has also been known for some time that brain stimulation can maintain responding when it follows a particular response, thereby serving as a reinforcer. Further, brain stimulation can also maintain responding when it is withdrawn or terminated and can suppress responding depending on the localization of the electrode (Olds, 1960). Thus, electrical stimulation of the brain, like other salient events, can function in multiple ways and can produce diverse behavioral effects (Barrett and Katz, 1981; McKearney and Barrett, 1978; Morse and Kelleher, 1970, 1977).

Early experiments with electrical stimulation of the brain demonstrated that many anxiolytic compounds were capable of elevating the threshold required to produce components of aggressive behavior (Malick, 1970; Panksepp, 1971). Other initial studies also demonstrated that chlordiazepoxide could increase the latency of lever-pressing behavior that switched off electrical stimulation delivered to brain sites that were able to maintain responding by the presentation as well as termination of stimulation of these sites (Panksepp et al., 1971). Subsequent research by Graeff and his colleagues (reviews by Graeff, 1984, 1986) has shown that chlordiazepoxide also increases the latency of lever pressing that turns off continuous electrical stimulation of the dorsal periaqueductal gray. Additionally, chlordiazepoxide increases food- or water-maintained responding that has been suppressed by brief electrical stimuli delivered to the dorsal periaqueductal gray following each response. Although these results parallel those found with more traditional punishment studies, this is not always the case. For example, Morato de Carvalho et al. (1981) have shown that, in contrast to their effects on

behavior suppressed by peripheral punishment (i.e., footshock or tailshock), the serotonin antagonists cyproheptadine and methysergide do not increase responding suppressed by periaqueductal gray stimulation. Furthermore, amphetamine also increases punished responding suppressed by periaqueductal gray stimulation, a finding which also contrasts with the effects of this drug on behavior punished by peripherally-delivered shock. Research using electrical stimulation of the brain has yet to be explored systematically and extensively using various sites and compounds with a view towards the development of a suitable animal model. Additional studies are required to document the pharmacological and regional specificity of many of the findings now being reported. For example, as in the case with benzodiazepines, opiates have also been shown to block lever pressing maintained by escape from periaqueductal gray stimulation (Jenck et al., 1983; Kiser and German, 1978). It would be necessary to demonstrate pharmacological specificity between these compounds unless one is interested in possible interrelationships between nociception and anxiety. Finally, to the extent that results with these models do not parallel clinical effects, they may be of limited utility. Nevertheless, such procedures may aid in the clarification and understanding of drug action.

C. Psychopharmacological Models

The discovery of compounds capable of producing behavioral states characterized by an anxiety-like syndrome that are blocked by both the benzodiazepines and benzodiazepine-receptor antagonists has had considerable impact in the development of theoretical and pharmacological approaches to the understanding and treatment of anxiety. Recently, Insel et al. (1984) have outlined models of anxiety based on compounds that induce anxiety-like conditions which are differentially antagonized by various agents. For example, the ben-

zodiazepine receptor-mediated model is based on the induction of elevated heart rate, blood pressure and cortisol levels by ß-CCE or FG-7142. These effects are blocked by diazepam and Ro 15-1788. A noradrenergic model, however, is based on yohimbine-induced increases in plasma MHPG, the appearance of "alarm" behaviors and, as mentioned earlier, by increased firing of the locus coeruleus. These effects are antagonized by clonidine. Insel et al. (1984) have also proposed models of anxiety based on sodium lactate (blocked by imipramine) and caffeine (blocker unknown), both of which are mediated through different receptor systems with sites of action currently unknown. The proposed psychopharmacological models remain to be examined in greater detail but may be useful in delineating more precisely the various pathophysiological and neuropharmacological substrates now only globally subsumed under the term "anxiety." It will be of considerable interest to evaluate the effects of buspirone on these different psychopharmacological models of anxiety. If, in fact, as information now suggests, buspirone exerts its main actions through non-traditional substrates, the proposed models must be extended to encompass still another mechanism through which anxiety is manifested.

III. BEHAVIORAL EFFECTS OF BUSPIRONE

A. Punishment Studies

Most research on the behavioral effects of buspirone as a potential anxiolytic compound has focused on its effects on punished or conflict behavior. As a whole, the data on buspirone's effects on punished behavior are somewhat inconsistent. Initially, buspirone was reported to produce increases in punished responding of cynomologus monkeys and rats at doses (0.5-5.0 mg/kg, intramuscular) that were equipotent to those of diazepam (Geller and Hartmann,

1982). In addition to producing marked anticonflict activity shortly after administration, buspirone effects persisted for nearly two weeks. Although some subsequent animal studies have also reported increases in suppressed behavior by buspirone, none have reported such long-lasting effects nor have the effects of buspirone usually been comparable in magnitude to those of the benzodiazepines (see below). At present, the lengthy duration of action and efficacy of buspirone found in the Geller and Hartmann study appears to be either idiosyncratic to the cynomologus monkey or to certain procedures or conditions unique to this particular experiment.

Despite its proven clinical efficacy (see Tunicliff et al., and Robinson, this volume), buspirone has not uniformly produced increases in punished responding (Sanger et al., 1985; Sepinwall, 1985). Further, when increases do occur, at least with rats and monkeys, they are generally not comparable in magnitude to those of the benzodiazepines. For example, in one study with squirrel monkeys (Weissman et al., 1984), every 30th lever-pressing response produced a pellet of food. In the presence of a white light, no other consequence occurred; however, during a red light, every 30th response also produced a mild, brief electric shock to the tail which suppressed responding. Buspirone increased the low punished response rates to approximately 300 percent of control at the most effective dose (3.0 mg/kg) and, except at the highest dose (30 mg/kg), had relatively little effect on unpunished responding. In comparison, the benzodiazepine midazolam produced increases in punished responding to over 2000 percent of control at doses that did not markedly alter unpunished behavior.

Table 1 summarizes the effects of buspirone on behavior using various punishment procedures and provides an analysis by species, dose and route of

administration. There appear to be no consistent variables such as route, dosage, or species which might account for the differences in buspirone's

Insert Table 1 about here

effects. Although details of the shock intensity or duration were not always stated, in cases where they were comparable, effects were not necessarily consistent. Even when buspirone increased punished behavior the effects were generally rather weak. Obviously, these exceptions to the generally uniform correspondence between anticonflict activity and clinical anxiolytic efficacy are intriguing.

In contrast to the either weak activity or lack of effects produced by buspirone on punished behavior of rats and monkeys, effects obtained in White Carneaux pigeons are extraordinarily robust (Figure 1), quite reliable and of the same magnitude as those produced by the benzodiazepine, chlordiazepoxide (Witkin and Barrett, 1986; Barrett et al., 1986). Buspirone, however, is at least ten times more potent than chlordiazepoxide in this species (Figure 2). Pigeons were studied under the same general procedures described for squirrel

Insert Figure 1 about here

monkeys above. This procedure is a slight variation on traditional conflict-type procedures described in Section 2a of this chapter, and has been used quite extensively to examine various drug effects. With pigeons, it appears to be selective and sensitive to compounds having anxiolytic actions, even those such as buspirone that are somewhat atypical and generally do not exert

Insert Figure 2 about here

substantial activity in other procedures of this type (e.g., the beta blockers propranolol and atenolol also increase punished responding of pigeons, Durel et al., submitted manuscript). However, compounds from other classes, such as the psychomotor stimulants, opiate analgesics, and tricyclic antidepressants, as well as the antipsychotic drugs, do not produce increases in punished responding. Thus, when used with pigeons, this procedure may be quite effective in detecting unique, atypical anxiolytic agents (Barrett, 1985). The precise reasons for this unique sensitivity to potentially novel anxiolytic compounds remain unclear at the present time.

In related studies with punished behavior of pigeons, we have found that the buspirone analogue MJ 13805 (gepirone) also produced increases comparable to those found with buspirone (Barrett et al., 1986). A buspirone metabolite, 1-PP (MJ 13653), however, did not increase punished responding of pigeons and, in this species, does not appear as a metabolite of buspirone or MJ 13805 (D. Taylor, personal communication). Comparisons of the effects of buspirone, MJ 13805 and 1-PP are shown in Figure 3.

Insert Figure 3 about here

Since these effects in pigeons were in marked contrast to those reported thus far with most other species, further behavioral and neurochemical studies (Weissman, this volume) were designed to determine the possible mechanisms through which buspirone produces these effects.

B. Drug Interaction Studies

In view of the marked actions of buspirone on dopaminergic systems (McMillen et al., 1983; Riblet et al., 1984; Taylor et al., 1982), we initially examined the effects of dopamine agonists and antagonists alone and

in combination with buspirone in pigeons (Witkin and Barrett, 1986). The effects of buspirone on punished and unpunished behavior were unaffected by either apomorphine (Figure 4) or haloperidol (Figure 5). However, the rate decreases produced by higher doses of apomorphine were reversed by doses of buspirone that had no effect when administered alone. The lack of direct

Insert Figure 4 about here

dopaminergic activity in mediating buspirone effects was also confirmed in studies with the buspirone analogue MJ 13805 described above (Figure 3). This compound, which has no significant effects on central dopamine systems, produced increases in punished behavior of pigeons that were comparable to those

Insert Figure 5 about here

of buspirone. Thus, data from behavioral studies do not substantiate the direct involvement of dopamine in mediating the anxiolytic effects of buspirone.

Effects of buspirone on punished behavior of pigeons also do not appear to involve the benzodiazepine-GABA receptor complex. Although buspirone has been reported to facilitate the binding of benzodiazepine ligands under some conditions (Oakley and Jones, 1983; Weissman, this volume), the benzodiazepine receptor antagonist Ro 15-1788 does not alter effects of buspirone on punished behavior of rats, pigeons or squirrel monkeys (Barrett et al., 1986; Weissman et al., 1984). Further studies with other drugs having relatively selective effects on serotonergic systems will provide additional information but, at the present time, it appears that buspirone produces its unique actions through multiple neurotransmitter systems (Eison and Eison, 1984).

Perhaps compounds with mixed actions would be best suited to further analyze the mechanisms involved in buspirone's effects.

C. Implications for Animal Models of Anxiety

Unlike most other clinically effective anxiolytic compounds, buspirone does not appear to produce robust, reliable increases in punished responding in any species except the pigeon. With regard to a satisfactory preclinical screen or model for evaluating potentially novel anxiolytics, it appears that, at present, the pigeon provides the requisite features. Both typical and atypical anxiolytic agents produce increases in punished behavior in this species, yet compounds that are non-effective anxiolytics do not. It is interesting that ketamine also increases punished behavior of pigeons (Brandão et al., 1980; Wenger, 1980), although these effects are much smaller than those obtained with pentobarbital. There appear to be no reports of anxiolytic activity by ketamine, though it may be important that certain doses of both buspirone and ketamine produce similar effects on gross behavior of baboons (R. Lamb, personal communication). It may be the case that, although punished behavior in the pigeon currently appears to be the most sensitive and selective model for revealing the potential actions of both typical and atypical anxiolytics, newer effective compounds may not produce similar effects.

Results with buspirone in the pigeon also suggest that this species may be useful in drug discrimination studies for probing compounds which might produce similar discriminative stimulus effects. As mentioned earlier, it has been difficult to use buspirone as a training drug because the high doses required to produce discriminative control also result in large behavioral effects. The sensitivity of the pigeon's behavior to doses of buspirone as

low as 0.03-0.1 mg/kg indicate that it should be relatively easy to develop stimulus control with this compound. This would allow an additional means of assessing the system or systems through which buspirone produces its unique effects.

Perhaps no single method will provide the necessary features for evaluating new drugs. It may be necessary to develop a battery of tests based on some of the procedures described in this chapter to provide the most suitable means of predicting anxiolytic drug action. In view of the multiple characteristics and determinants of anxiety, it seems only appropriate to assume that a non-unitary pathological condition will not easily be modeled by a single test or, perhaps, even a few tests. Progress in the treatment of anxiety with pharmacologically selective agents such as buspirone will aid in clarifying basic behavioral and neurochemical processes involved in this disorder. Designing tests to evaluate these newer agents will be a continuing challenge to psychopharmacologists such that both clinical and preclinical research will profit by these developments.

IV. CONCLUSIONS

The discovery of buspirone as an effective anxiolytic essentially devoid of most of the traditional biochemical, physiological and behavioral characteristics normally associated with this class of drugs has initiated an exciting new phase in the psychopharmacology of anxiety. Together with the parallel and substantial developments in benzodiazepine receptor pharmacology, these findings have generated new questions, challenged old assumptions and created tremendous research activity. The vigor associated with these efforts is likely to radically revise our current concepts of anxiety and provide a better understanding of factors involved in the etiology, assessment and treat-

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Figure Legends

Figure 1: Illustration of control performances and effects of 0.1 mg/kg buspirone in the pigeon. Each key-pecking response incremented the pen; every 30th response produced food delivery which is indicated by the diagonal stroke of the pen. During alternate 3-minute segments of the session, the colors on the key changed from white to red to denote, respectively, whether each 30th response also produced shock. Punishment components are indicated by the deflection of the pen beneath each record for the 3-min period; shock deliveries are indicated by deflections on both recordings.

Figure 2: Comparison of effects of buspirone and chlordiazepoxide on punished and unpunished behavior of the pigeon. Control points ± 1 S.E. are indicated on the left by the unconnected points. The dashed line denotes no change from control levels. (Adapted from Barrett et al., 1986)

Figure 3: Effects of buspirone, MJ-13805 and 1-PP on punished (top) and unpunished (bottom) behavior of pigeons. Control measures, ± 1 S.E., are indicated on the left by the unconnected points. (Adapted from Barrett et al., 1986)

Figure 4: Effects of buspirone and apomorphine alone and in combination on punished and unpunished behavior of pigeons. Filled unconnected points on left represent control measures, ± 1 S.E; open symbols denote effects of apomorphine alone and in combination with buspirone. (Adapted from Witkin and Barrett, 1986)

Figure 5: Effects of haloperidol and buspirone alone and in combination on punished and unpunished behavior of pigeons. Details as in Figure 4. (Adapted from Witkin and Barrett, 1986)

Figure 6: Effects of the benzodiazepine receptor antagonist Ro 15-1788 and buspirone alone and in combination on punished and unpunished behavior of pigeons. Details are the same as those in Figure 4. (Adapted from Barrett et al., 1986).

Table 1

BUSPIRONE EFFECTS ON PUNISHED BEHAVIOR

Species	Procedure	Dosage and Route	Increase	Reference
Rat	lever pressing	0.5-5.0 mg/kg, IM,PO	yes	Geller & Hartmann, 1982
	drinking	10-80 mg/kg, PO	yes	Oakley & Jones, 1983
	drinking	50 mg/kg, PO	no	Goldberg et al.,1983
	drinking	0.5-5.0 mg/kg, PO	yes	Weissman et al., 1984
	drinking	1.25-20 mg/kg, PO	no	Sullivan et al., 1983
	drinking	1.0-10 mg/kg, IP	no	Sanger et al., 1985
Monkey				
cynomalogous	lever pressing	0.5-5.0 mg/kg, IM	yes	Geller & Hartmann, 1982
squirrel	lever pressing	10.0 mg/kg, PO	no	Goldberg et al., 1983
	lever pressing	3.0-30 mg/kg, PO	yes	Weissman et al., 1984
	lever pressing	1.25-5.0 mg/kg, PO	no	Sullivan et al., 1983
Pigeon	key pecking	0.03-10 mg/kg, IM	yes	Witkin & Barrett, 1986
	key pecking	0.01-10 mg/kg, IM	yes	Barrett et al., 1986

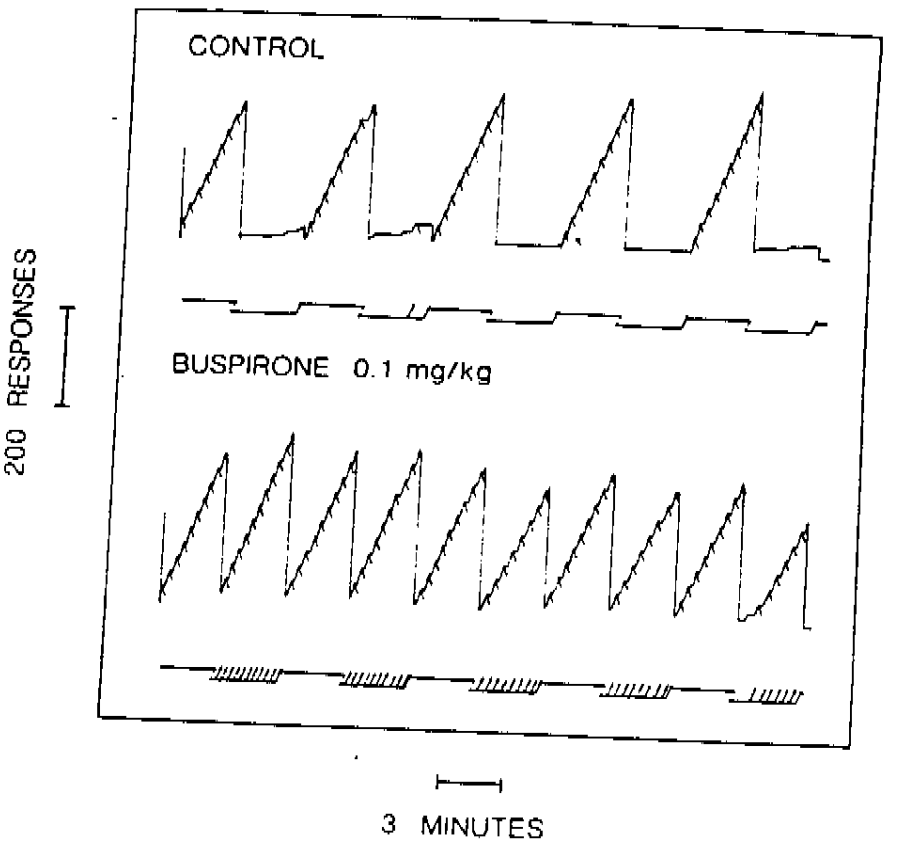

Figure 1

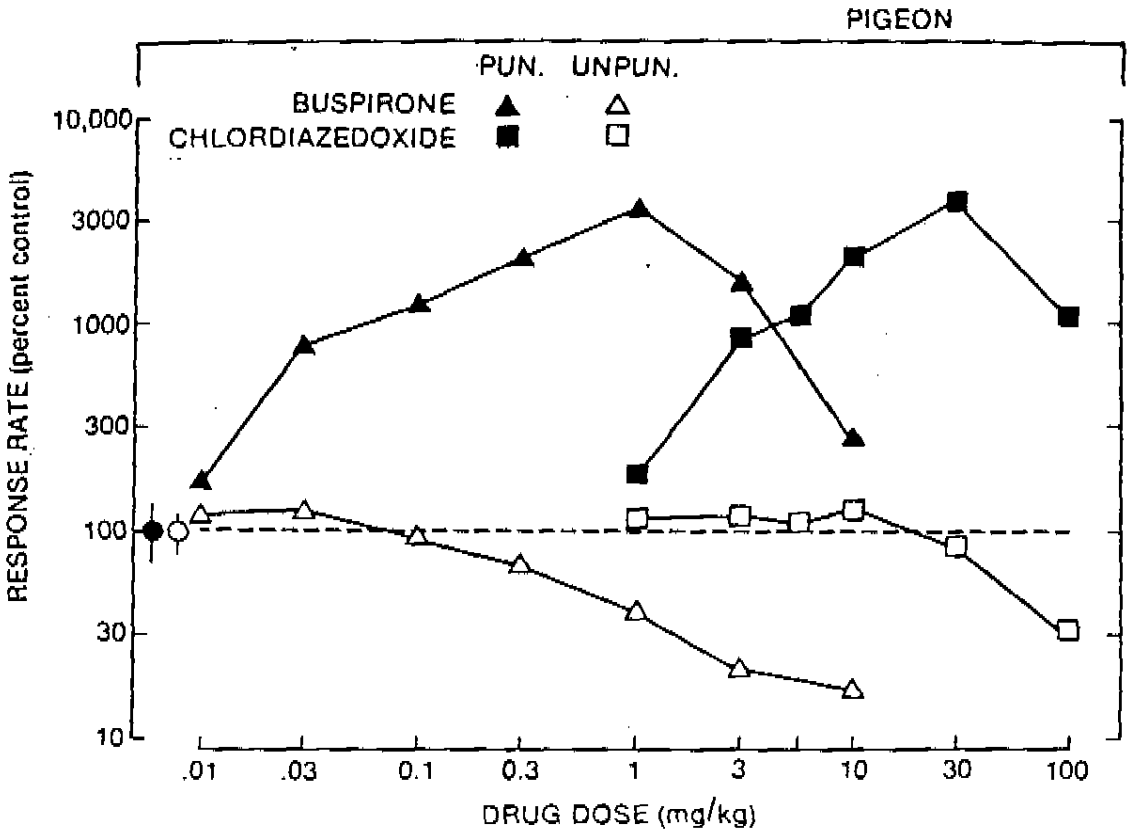
PIGEON
PUN. UNPUN.
BUSPIRONE
CHLORDIAZEDOXIDE
RESPONSE RATE (percent control)
10,000
3000
1000
300
100
30
10
.01
.03
0.1
0.3
1
3
10
30
100
DRUG DOSE (mg/kg)

Figure 2

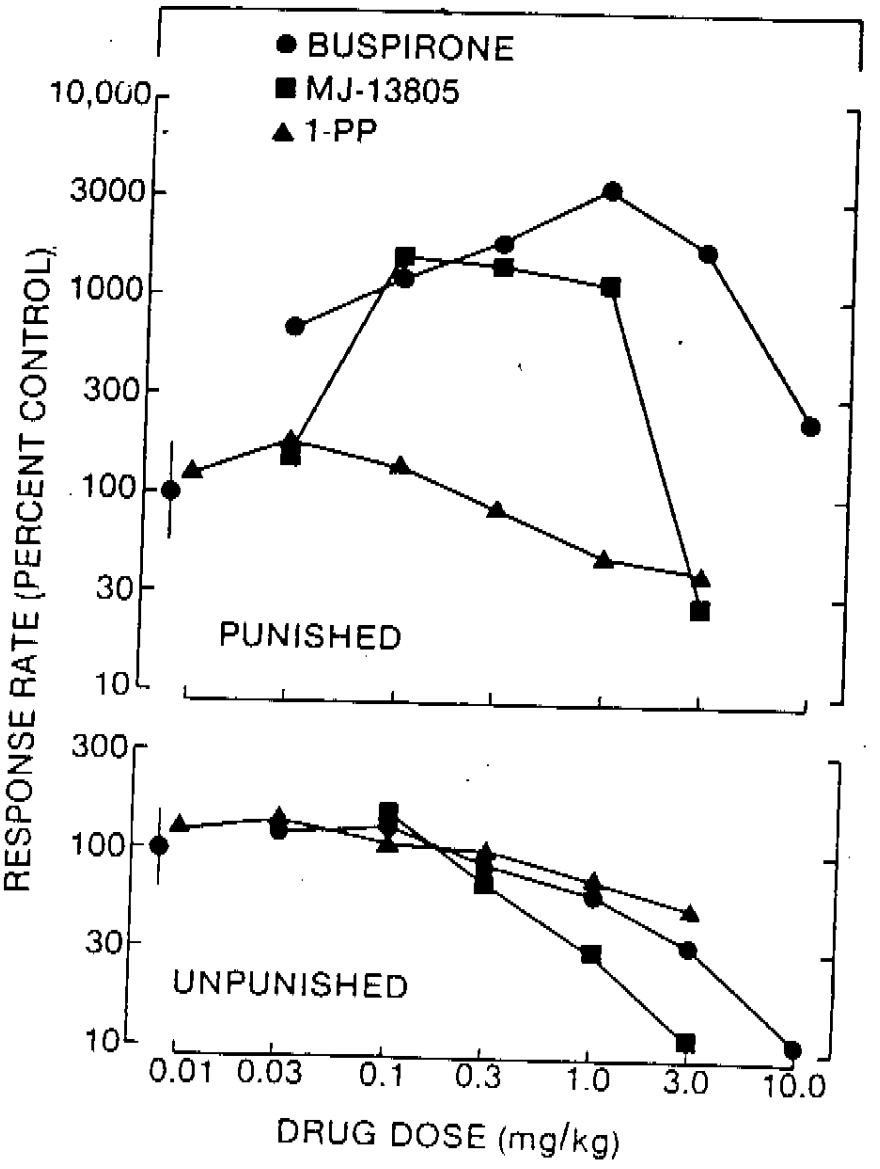
BUSPIRONE
MJ-13805
1-PP
10,000
3000
1000
300
100
30
10
PUNISHED
300
100
30
10
UNPUNISHED
RESPONSE RATE (PERCENT CONTROL)
0.01
0.03
0.1
0.3
1.0
3.0
10.0
DRUG DOSE (mg/kg)

Figure 3

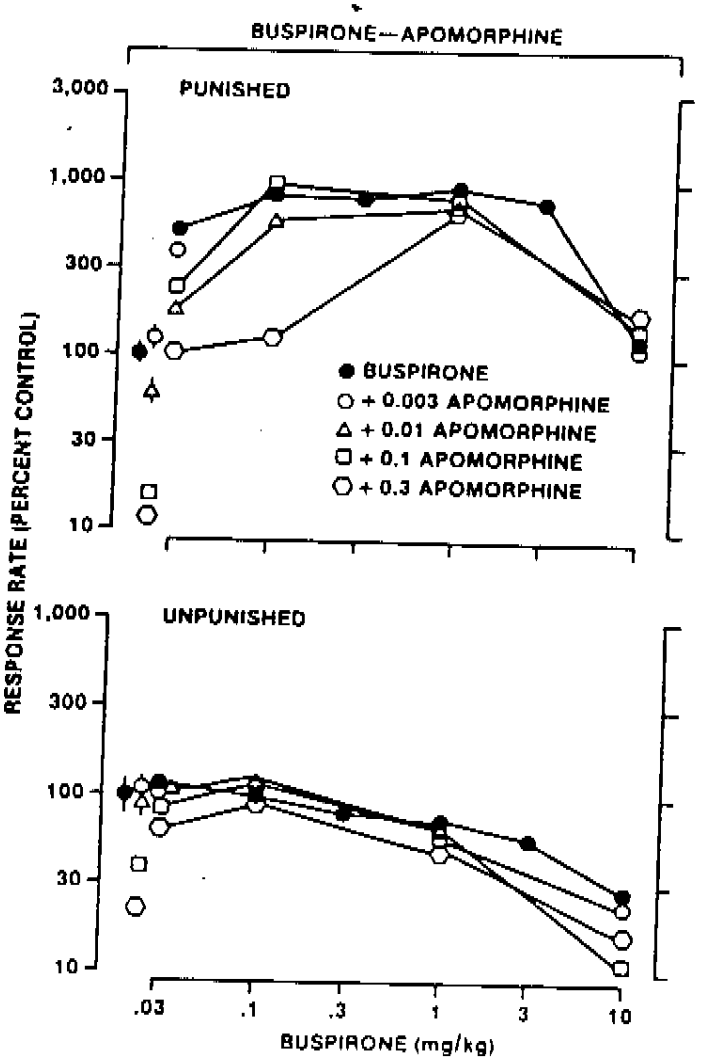
BUSPIRONE—APOMORPHINE
PUNISHED
3,000
1,000
300
100
30
10
BUSPIRONE
+ 0.003 APOMORPHINE
+ 0.01 APOMORPHINE
+ 0.1 APOMORPHINE
+ 0.3 APOMORPHINE
UNPUNISHED
1,000
300
100
30
10
RESPONSE RATE (PERCENT CONTROL)
.03
.1
.3
1
3
10
BUSPIRONE (mg/kg)

Figure 4

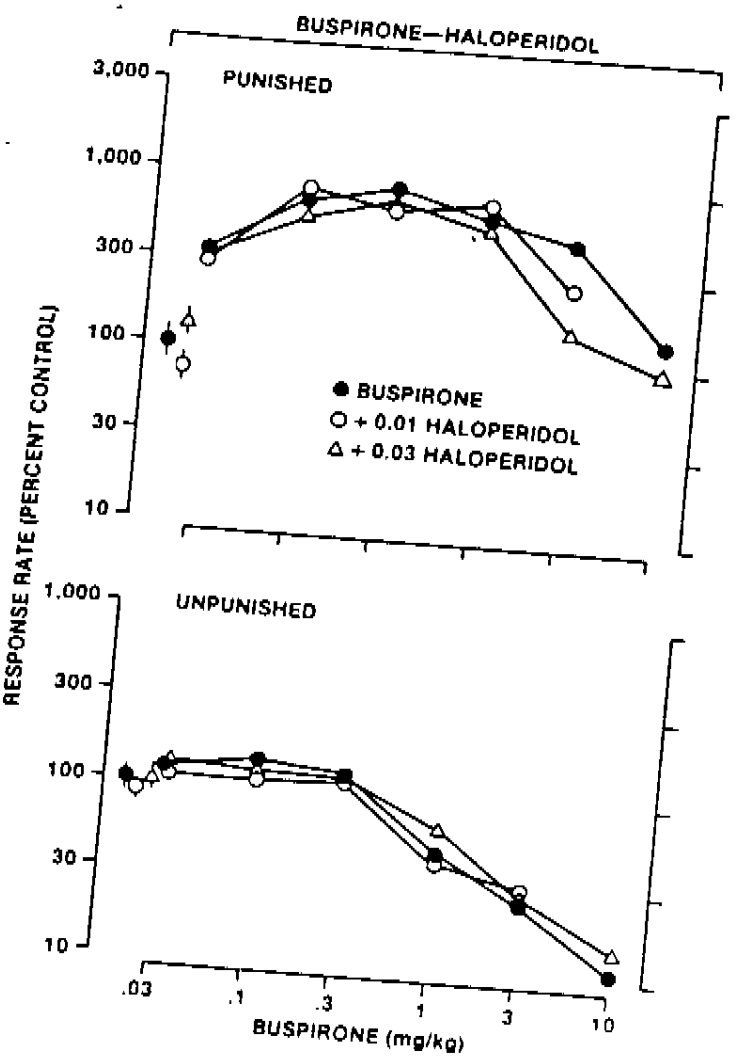
BUSPIRONE—HALOPERIDOL
PUNISHED
3,000
1,000
300
100
30
10
BUSPIRONE
+ 0.01 HALOPERIDOL
+ 0.03 HALOPERIDOL
UNPUNISHED
1,000
300
100
30
10
RESPONSE RATE (PERCENT CONTROL)
.03
.1
.3
1
3
10
BUSPIRONE (mg/kg)

Figure 5

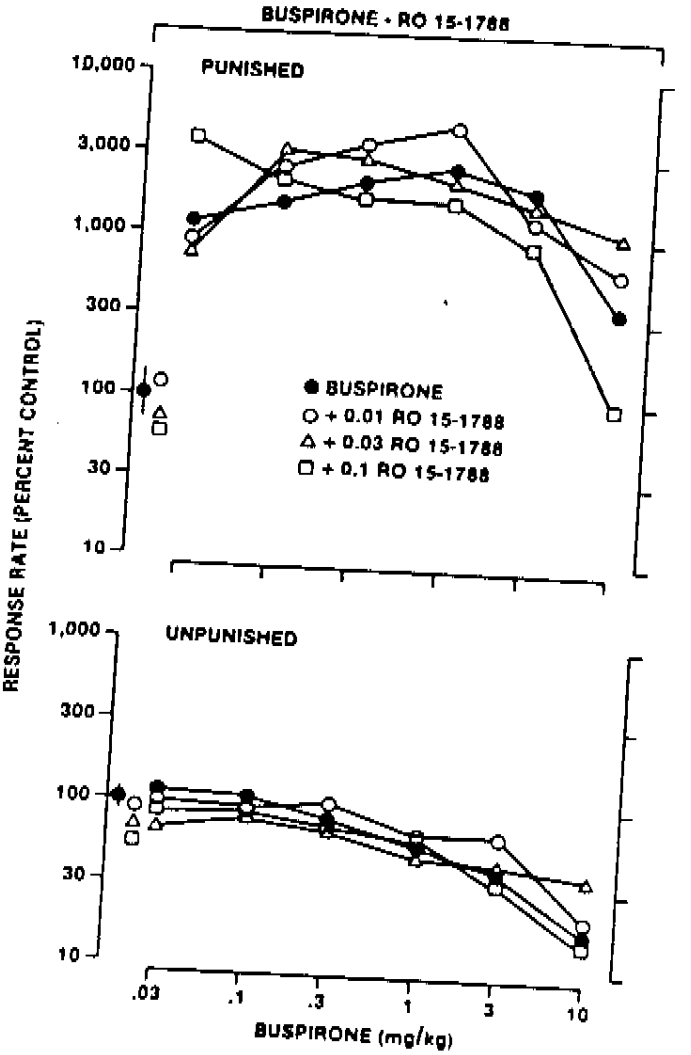
BUSPIRONE + RO 15-1788
PUNISHED
10,000
3,000
1,000
300
100
30
10
BUSPIRONE
+ 0.01 RO 15-1788
+ 0.03 RO 15-1788
+ 0.1 RO 15-1788
UNPUNISHED
1,000
300
100
30
10
.03
.1
.3
1
3
10
BUSPIRONE (mg/kg)
RESPONSE RATE (PERCENT CONTROL)

Figure 6