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Drug Discrimination in Pentylenetetrazol-Trained Baboons: Generalization to Buspirone and β-Carboline-3-Carboxylic Acid Ethyl Ester but Not Lorazepam or Pentobarbital

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ABSTRACT

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Pentylenetetrazol (PTZ) has been characterized as producing anxiogenic effects in humans and rats, and PTZ drug discrimination procedures in rats have been used to categorize drug effects as anxiogenic. In the present study, baboons trained to discriminate a subconvulsant dose of PTZ from the no-drug condition showed dose-dependent generalization to PTZ and to β-carboline-3-carboxylic acid ethyl esther [β-CCE; a benzodiazepine (BZ)-receptor inverse agonist] but no generalization to the BZ-receptor antagonist Ro 15-1788 (flumazenil). Ro-1788 produced surmountable antagonism of the β-CCE discriminative stimulus. The novel anxiolytic buspirone also occasioned 100% drug lever responding in the PTZ-trained baboons, although lorazepam and pentobarbital did not. Results with the 5HT ligand 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) were mixed. Lorazepam but not buspirone antagonized PTZ. Observations of baboons after PTZ, buspirone, and β-CCE at doses occasioning PTZ lever responding showed that tremors and agitation occurred after buspirone but not after β-CCE or PTZ.

Key words: Ro-15-1788, flumazenil, 8-OH-DPAT, anxiety

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INTRODUCTION

Drug discrimination studies with pentylenetetrazol (PTZ) as a training drug in drug vs. no-drug procedures showed that tests with certain other convulsants (e.g., bemegride) and stimulants (e.g., cocaine) occasioned selection of the PTZ lever by >80% of the rats [Lal and Emmett-Oglesby, 1983], although drug lever selection in tests with other such drugs has not occurred or has been less reliable (e.g., bicuculline and strychnine [Shearman and Lal, 1980], *d*-amphetamine and methylphenidate [Shearman and Lal, 1979]). Recently, some β-carbolines (harmane, FG 7142, β-CCM, DMCM) occasioned drug lever selection by 75% or more PTZ-trained rats [Lal and Emmett-Oglesby, 1983; Stephens et al., 1984]. Rats chronically treated with diazepam responded on the PTZ lever after the benzodiazepine (BZ) antagonist Ro 15-1788 (flumazenil), although Ro 15-1788 did not occasion PTZ lever selection in the absence of chronic diazepam [Emmet-Oglesby et al., 1983]. Antagonism of the PTZ discriminative stimulus has been demonstrated with a number of sedative/anxiolytics [Lal and Emmett-Oglesby, 1983] but not with all anticonvulsants tested [Shearman and Lal, 1980]. The argument has been made that the unreliable generalization of PTZ-trained rats to convulsants, coupled with the unreliable antagonism of the PTZ discriminative stimulus by anticonvulsants, suggests that the PTZ discrimination is not based on convulsant activity of PTZ. Rather, it has been suggested that the pattern of results of generalization and antagonism studies indicates that the PTZ stimulus is best characterized as "anxiogenic" [e.g., Emmett-Oglesby et al., 1983; Lal and Fielding, 1984].

In the context of drug discrimination research on sedative/anxiolytic drugs in our laboratory, baboons were trained to discriminate PTZ from the no-drug condition. Although we found the expected generalization to the β-carboline β-carboline-3-carboxylic acid ethyl ester (β-CCE) and antagonism of the PTZ discriminative stimulus by a BZ (lorazepam), we found unexpected generalization to the novel anxiolytic buspirone. In previous research, buspirone has not occasioned drug lever responding in baboons or rats trained to discriminate other sedative/anxiolytic drugs [Ator and Griffiths, 1986; Hendry et al., 1983], and, given the clinical efficacy of buspirone as an anxiolytic [Goa and Ward, 1986], the generalization to buspirone by PTZ-trained subjects was surprising.

MATERIALS AND METHODS

Adult male baboons (*Papio anubis*) were housed in standard primate squeeze cages, with an intelligence panel mounted on the rear wall [apparatus is fully described in Ator and Griffiths, 1983, 1986]. The intelligence panel contained two levers with a jewel light over each lever. A food tray into which 1 g banana-flavored pellets were delivered was centered on the intelligence panel 15 cm above the right lever. An automated drinking spout through which drugs could be administered orally was mounted above the left lever, and a small translucent light panel was in the upper right quadrant of the panel. Weights of the baboons ranged from 27.4 to 32.8 kg, except one PTZ-trained baboon (ST) weighed 17.0–18.5 kg.

The drug discrimination training session procedures were previously described [Ator and Griffiths, 1983]. Sessions were preceded by a time out, which equalled the pretreatment time for the training or test drugs or their vehicles. White noise was turned on at the beginning of the presession time out and continued until the end of the session. During time out, the translucent panel was illuminated and lever responses were counted but had no programmed consequences. At the end of time out, the panel light went off and the two jewel lights were illuminated, beginning a 20-min period of food-pellet availability. Responses on either lever in the presence of the jewel lights produced a 0.1 sec feedback tone. During training sessions, pellet delivery depended on a fixed number of consecutive responses on the lever appropriate to the drug or no-drug condition in effect; responses on the inappropriate lever reset the response requirement. During training, the response requirement was manipulated to be one

that maintained criterion level performance and generated a high, steady rate of responding in each baboon (final values ranged from 15 to 35 for individual baboons). A 5 sec time out followed each pellet delivery. Drug and no-drug training sessions generally alternated.

Four baboons had been trained to discriminate lorazepam (1.8 mg/kg p.o.) from the no-drug condition and had served in previous drug discrimination studies [Ator and Griffiths, 1983, 1985, 1986]. PTZ training initially was attempted with three other baboons, with PTZ delivered orally. The oral dosing procedure is one used successfully for a number of years with lorazepam and pentobarbital as training drugs [Ator and Griffiths, 1985, 1986]. It involves training the baboon to accept 60 ml of an orange drink laced with quinine sulfate (0.32 mg/ml) and then adding drug. The initial PTZ training dose was 18 mg/kg, with a pretreatment time of 30 min. (In pilot work, a dose of 32 mg/kg resulted in vomiting and failure to consume food pellets.) Although training initially proceded smoothly, the baboons began rejecting the PTZ; decreasing the dose to 10 mg/kg did not improve acceptance of the PTZ solution. Consequently, route of administration was changed to i.m., and i.m. training was completed in two baboons (the third baboon did not continue for reasons unrelated to this study). PTZ training dose was 10 mg/kg i.m. for baboon SC but was raised to 13.3 mg/kg i.m. for baboon ST to maintain criterion performance.

Testing began after responding in the drug and no-drug training sessions met the following criteria for at least four consecutive sessions: 1) 95–100% of the total responses had to be on the reinforced lever and 2) at the beginning of the session, the required number of consecutive responses must have been made first on the reinforced lever. For the PTZ-trained baboons, the first test sessions were conducted with the PTZ training dose and saline. If criterion performance occurred in those test sessions, then test sessions with other PTZ doses were conducted. Dose-effect curves were determined for lorazepam, PTZ/lorazepam combinations, β-CCE, buspirone, Ro 15-1788, β-CCE/Ro 15-1788 combinations, pentobarbital, 8-OH-DPAT, and buspirone/PTZ combinations. Before beginning tests with each novel drug condition, the reliability of the PTZ discrimination performance was redetermined in test sessions with PTZ training dose and saline. In test sessions, conditions were identical to those in training sessions except that the usual required number of consecutive repsonses on either lever produced food. The order of drug and no drug training sessions between test sessions was counterbalanced so that test sessions were as often preceded by a drug as by a no-drug training session. To study time course of drug action on some test days, additional sessions were conducted after the first session. That is, the experimental session was turned on again under test conditions at predetermined times after drug administration. These later sessions were preceded by a 5 min time out and were 10 min long. Sessions were 7 days per week, except that 2 days without an experimental session always followed days on which PTZ was given.

PTZ, β-CCE, buspirone HCl, and 8-OH-DPAT HBr were administered i.m. PTZ, buspirone, and 8-OH-DPAT were dissolved in 0.9% sterile saline. β-CCE base was dissolved in 0.1 normal hydrochloric acid; two drops of Tween were added and then q.s. to total volume, which was never less than 2 ml. Lorazepam, Ro 15-1788, and pentobarbital Na were administered p.o. in 60 ml of the orange-flavored quinine (0.325 mg/ml) solution into which 1 g/liter of a suspending agent (Bio-Serv Agent K; Bio-Serv, Frenchtown, NJ) had been blended. Oral dosing with drug or vehicle typically was accomplished in 5 min and in no more than 15 min. In the drug interaction conditions in which both drugs had the same pretreatment time, oral dosing occurred first, followed by the i.m. injection. Doses are expressed according to the form of the drug administered. Pretreatment times were 30 min for PTZ, lorazepam, and pentobarbital; 60 min for buspirone; 10 min for β-CCE and Ro 15-1788; and 15 min for 8-OH-DPAT.

RESULTS

In test sessions with PTZ, both PTZ-trained baboons showed dose-dependent generalization to PTZ and responding tended to be all-or-none on the PTZ lever in these sessions (Fig.

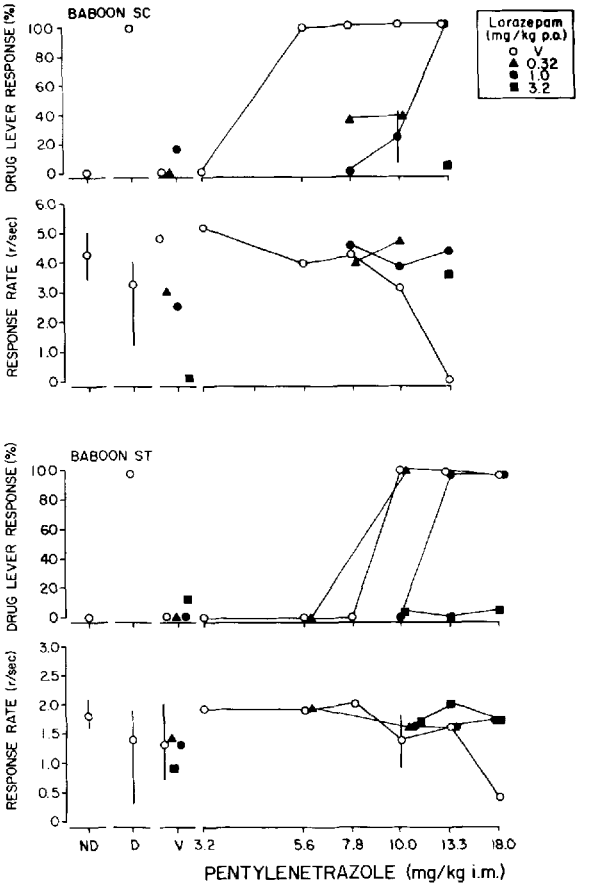

Fig. 1. Drug lever responding and response rates for baboons trained to discriminate PTZ from the no-drug condition. Points over ND and D represent mean responding in the no-drug and drug training sessions, respectively, that immediately preceded test sessions. Other points represent test sessions preceded by PTZ, lorazepam, vehicles (V), or their combinations. Each point represents a single observation, except N = 2 for SC PTZ 10 + lorazepam and ST PTZ 10 + lorazepam vehicle; N = 18–20 for the ND and D points. Vertical bars indicate ranges.

1). Lorazepam did not occasion PTZ lever responding in these baboons up to a dose that clearly decreased response rates (Fig. 1). In combination with PTZ, lorazepam produced surmountable, dose-dependent antagonism of the PTZ-discriminative stimulus, and there was mutual antagonism of the response rate-decreasing effects of the highest PTZ and lorazepam doses.

When lorazepam and PTZ were studied in lorazepam-trained baboons, a lorazepam dose (1.0 mg/kg) slightly below the 1.8 mg/kg training dose occasioned ~ 80% lorazepam-lever responding in all four baboons; 1.8 mg/kg and higher doses occasioned 100% drug lever responding. No dose of PTZ occasioned lorazepam lever responding (Fig. 2) Lorazepam in combination with PTZ produced dose-dependent, surmountable antagonism of the lorazepam discriminative stimulus. The intermediate responding at some PTZ/lorazepam dose combinations (i.e., 40–80% drug lever responding) shown in Figure 2 reflects not only the fact that individual baboons did respond on both levers but also that the dose combinations that

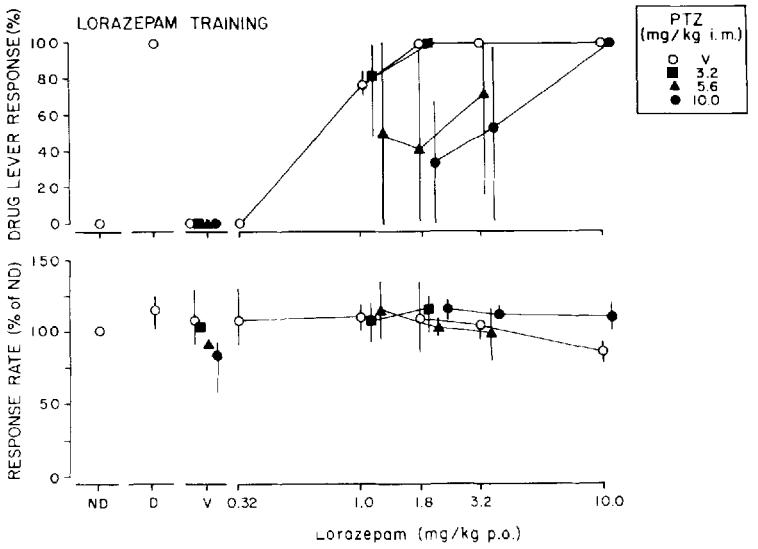

Fig. 2. Drug lever responding and response rates for baboons trained to discriminate lorazepam from the no-drug condition. Each test session point represents the mean of one to three determinations in three or four baboons; N = 19–28 sessions per subject for the ND and D points. Response rates in D training sessions and in test sessions are given as percentages of the mean response rate in ND training sessions. Mean ND response rates ranged from 0.6 to 2.4 r/sec; vertical bars indicate range of means for individual baboons. Other details are as for Figure 1.

demonstrated complete antagonism of the lorazepam discriminative stimulus (i.e., 0% lorazepam-lever responding) differed across baboons.

β-CCE occasioned 100% PTZ lever responding in both baboons at 0.1 mg/kg (Fig. 3). At higher doses, baboon ST responded on the PTZ lever, but responding was completely suppressed in baboon SC. When time-course determinations were conducted with baboon SC at 0.32 mg/kg, however, responding did occur in later sessions and was on the PTZ lever (Fig. 4). At 30 min after 0.32 mg/kg β-CCE, response rate was virtually zero, but by 60 and 90 min response rate was over 3 r/sec, and responding was 100% on the PTZ lever (open triangles). Reliability of the discriminative performance under this time course procedure is demonstrated by the fact that responding was always on the no-drug lever when the same time course determinations were made under vehicle conditions (open circles).

Ro 15-1788 did not occasion drug lever responding up to 3.2 mg/kg (Fig. 3) or 10 mg/kg (not shown). Ro 15-1788 antagonized the β-CCE discriminative stimulus and response rate effects (Fig. 3). This antagonism was surmountable in baboon ST at the 10 min pretreatment time, but at this pretreatment time for baboon SC all Ro 15-1788 doses combined with all β-CCE doses completely antagonized the response rate suppression after β-CCE alone and resulted in 0% PTZ lever responding. Surmountability of Ro 15-1788 antagonism of β-CCE for baboon SC was demonstrated in the time-course determinations with 0.32 mg/kg β-CCE. When 0.1 mg/kg Ro 15-1788 was given, there was no responding at 10 min but 100% PTZ lever responding at 30 min (0.4 r/sec). When 0.32 mg/kg Ro 15-1788 was given (Fig. 4, closed triangles), there was no responding at 10 min, 57% PTZ lever responding at 30 min, and >80% PTZ-lever responding at 60 and 90 min. A higher dose of Ro 15-1788 (1 mg/kg) completely antagonized the discriminative stimulus effects of this β-CCE dose at all time points (closed triangles). When 1.0 Ro 15-1788 was given, response rate was high, and responding was completely on the no-drug lever at all times studied (closed circles). Figure 4

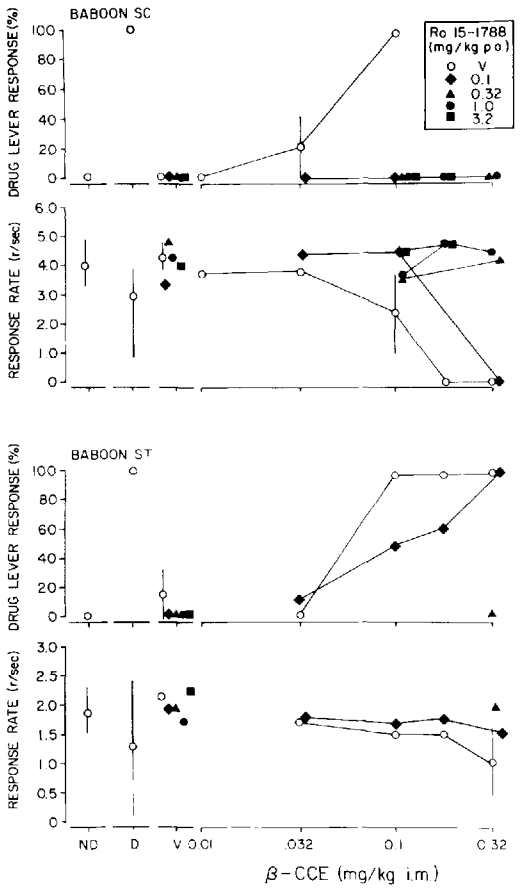

Fig. 3. Drug lever responding and response rates for baboons trained to discriminate PTZ from the no-drug condition. Test sessions were preceded by β-CCE, Ro 15-1788, their vehicles, or combinations of those compounds. Each test session point represents one or two observations; N = 16–32 for the ND and D points. Discrepancies between the number of points for percentage of drug lever responding and response rates occur because percentage of drug lever responding was included only if at least one pellet was obtained in the test session. Other details are as for Figure 1.

also shows that antagonism of β-CCE-induced response rate decreases did not completely parallel antagonism of the β-CCE discriminative stimulus.

Buspirone occasioned 100% drug lever responding in both baboons (Fig. 5) at i.m. doses that did (SC) or did not (ST) result in large decreases in responding. When 0.56 mg/kg i.m. buspirone was administered in combination with the training dose of PTZ, both baboons made 100% of their responses on the PTZ lever (data not shown). When buspirone was given orally, dose-related increases in drug lever responding did not generally occur, although the first exposure to 10 mg/kg occasioned 100% PTZ lever responding in baboon SC. At 32 mg/kg p.o., baboon SC did not respond and also did not respond when 10.0 mg/kg p.o. was redetermined. Baboon ST stopped accepting oral buspirone after 10 mg/kg p.o. and could not be tested at higher doses.

8-OH-DPAT was studied across the ranges of 0.0032–0.032 mg/kg in baboon SC and 0.032–0.18 mg/kg in baboon ST (Fig. 6). For each baboon, all responding was on the no-drug

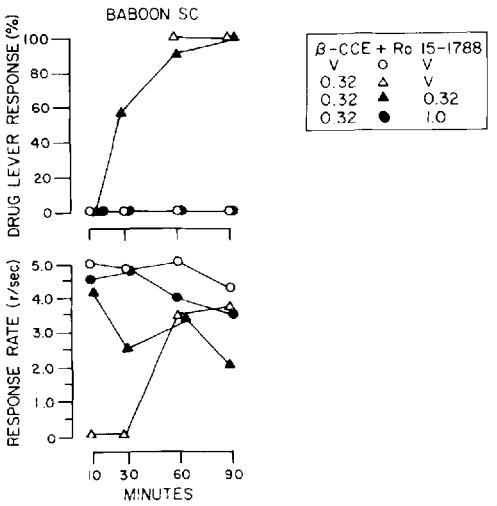

Fig. 4. Drug lever responding and response rates in four successive test sessions after administration of combinations of β-CCE 0.32 or V and Ro 15-1788 for baboon SC. Test sessions were conducted at 10, 30, 60, and 90 min after drug administration. Other details are as for Figure 3.

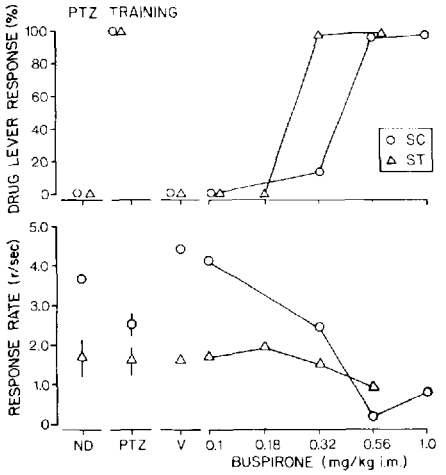

Fig. 5. Drug lever responding and response rates for baboons (SC and ST) trained to discriminate PTZ from the ND condition. Test session points represent single determinations; N = 4 for ND and D points. Other details are as for Figure 1.

lever after the lowest dose, and responding was completely suppressed after the highest dose. At the intermediate doses, baboon ST showed 24–27% PTZ lever responding; baboon SC showed 95% PTZ lever responding after 0.018 mg/kg and variable PTZ lever responding across three determinations of 0.01 mg/kg.

Pentobarbital (3.2, 10, 18 mg/kg) did not occasion drug lever responding in the PTZ-trained baboons; response rates were decreased in a dose-dependent manner below the range of control no-drug rates by all pentobarbital doses and were ~ 50% of control rates at 18 mg/kg (data not shown).

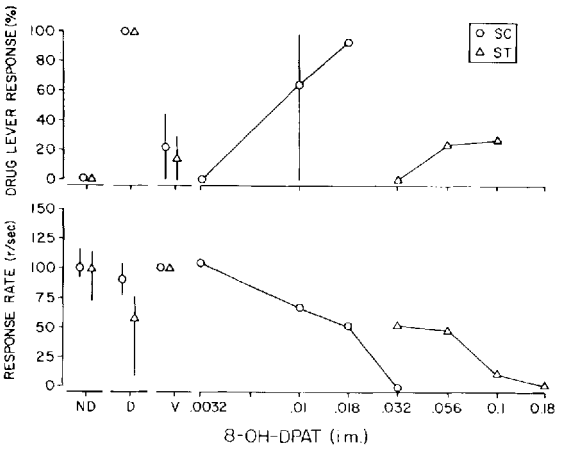

Fig. 6. Drug lever responding and response rates for baboons (SC and ST) trained to discriminate from the ND condition. Test session points represent single determinations except saline (N = 2) 0.01 mg/kg for baboon SC (N = 3); N = 5–7 for ND and D points. Other details are as for Figu

Observation of the PTZ-trained baboons revealed more overt behavioral effects of buspirone and 8-OH-DPAT doses studied than of the PTZ and β-CCE doses. For exam within 10 min after 1.0 mg/kg i.m. buspirone, baboon SC vomited and began show constant limb tremors. By 50 min after the injection, the tremors were sporadic, and baboon began lever pressing as soon as the session began. A similar effect, without vomiti occurred after the 0.56 mg/kg buspirone dose when it was given alone and in combination v PTZ. All such effects were gone by the end of the session (i.e., by 80 min after buspiro Similar effects were observed in other work with buspirone i.v. in baboons (R.R. Griffi unpublished observations). After 0.18 mg/kg 8-OH-DPAT, baboon ST sat motionless on floor of the cage with eyes turned toward the intelligence panel and arms wrapped around torso for over 45 min. Once the baboon began to operate the lever, however, beha appeared normal. In contrast, no unusual signs or behaviors were observed with the dose β-CCE or PTZ used. When the baboons failed to respond after an injection, they merely on the end of the bench away from the intelligence panel, and movements appeared norn

DISCUSSION

As in studies with rats [Lal and Emmett-Oglesby, 1983], baboons could be trainec discriminate a subconvulsant dose of PTZ from the no-drug condition and dose-depenc generalization to novel PTZ doses was shown. A BZ agonist, lorazepam, antagonized the F discriminative stimulus. Conversely, PTZ antagonized the lorazepam discriminative stimu in lorazepam-trained baboons. These results are consistent with previous reports of antagon of the PTZ stimulus in PTZ-trained rats [Lal and Emmett-Oglesby, 1983] and of F displacement of benzodiazepines in vitro [Chweh et al., 1983].

Inverse agonist β-carbolines other than β-CCE have been tested in PTZ-trained rats have occasioned drug lever responding [Lal and Emmett-Oglesby, 1983; Stephens et 1984]. Generalizations from PTZ to β-CCE in the present experiment is mirrored generalization from β-CCE to PTZ reported in β-CCE-trained rhesus monkeys [Takada et 1986]. Although β-CCE has been reported to produce a syndrome in rhesus monkeys sim to that of human anxiety [Ninan et al., 1982], β-CCE occasioned PTZ lever responding baboons at doses that did not produce overt behavioral excitation. Observational studies

β-CCE i.m. in baboons showed that behavioral effects (abnormal postures, tremors, twitches, vomiting, and convulsions) occurred only at very high doses, 32 mg/kg [Sannerud et al., 1987].

Ro 15-1788 dose-dependently antagonized the discriminative and response rate effects of β-CCE in PTZ-trained baboons and did not occasion drug lever responding when given alone. Comparable antagonism of the β-CCE discriminative stimulus was shown in rhesus monkeys, but Ro 15-1788 s.c. given alone did occasion β-CCE lever responding in that study [Takada et al., 1986].

Despite the clinical efficacy of buspirone [Goa and Ward, 1986], buspirone generalization has not been found in rats, squirrel monkeys, and baboons trained with sedative/anxiolytic compounds, including lorazepam, midazolam, oxazepam, and pentobarbital [Ator and Griffiths, 1986; Hendry et al., 1983; Spealman, 1985]. Conversely, buspirone-trained rats or pigeons did not show generalization to oxazepam, pentobarbital, or midazolam [Hendry et al., 1983; Mansbach and Barrett, 1987]. Thus the finding that buspirone did occasion drug lever responding in PTZ-trained baboons (and in β-CCE-trained rhesus monkeys; Takada, personal communication) suggests greater similarity in discriminative stimulus effects of buspirone to drugs that are suggested to produce anxiety and/or excitation than to drugs believed to produce anxiolysis and/or sedation. That PTZ-trained baboons do show selectivity in generalization is indicated by failure to respond on the drug lever after otherwise behaviorally active doses of lorazepam and pentobarbital. The fact that buspirone did not block the PTZ discriminative stimulus may be the first drug with prominent anxiolytic activity to fail do so and thus would seem to call into question the reliability of this model for screening potentially anxiolytic drugs [see Emmett-Oglesby et al., 1983; Lal and Fielding, 1984]. Because the model has been worked out in rats, however, it remains to be determined whether such an effect is species-specific. Previous work with buspirone p.o. in baboons found neither generalization nor response rate effects up to the highest dose tested, 32 mg/kg, yet large response rate decreases occurred with buspirone at 0.32 to 1.0 mg/kg i.m. [Ator and Griffiths, 1986].

Evidence to date suggests that a major action of PTZ is to reduce γ-aminobutyric acid (GABA)-mediated inhibition in the central nervous system (CNS), through the picrotoxinin site on the GABA/BZ receptor complex, thereby enhancing CNS excitability [Franz, 1985]. Thus the lorazepam/PTZ interaction results may be due to noncompetitive blockade of enhanced GABA function produced by BZ. β-Carbolines appear to act through the benzodiazepine site on the GABA/BZ receptor complex [O'Brien et al., 1981]. Antagonism of β-CCE by the BZ-receptor antagonist Ro 15-1788 suggests this mechanism for the discriminative stimulus effects of β-CCE in the PTZ-trained baboons. Although buspirone has shown activity in both the dopaminergic and serotonergic systems, evidence now seems to indicate that serotonergic activity is particularly strong and may underlie the anxiolytic effects of buspirone [Bockaert et al., 1987; McMillen et al., 1983; Vandermaelen et al., 1986]. Activity at the GABA/BZ receptor complex has seemed weak [Vandermaelen et al., 1986]. The buspirone discriminative stimulus in buspirone-trained pigeons appears to be mediated via the $5HT_{1A}$ receptor in that there was drug key responding after the $5HT_{1A}$ ligand 8-OH-DPAT but not after haloperidol [Mansbach and Barrett, 1987]; pigeons and rats trained to discriminate 8-OH-DPAT or the $5HT_{1A}$ ligand spiroxatrine showed generalization to buspirone [Barrett, in press; Cunningham et al., 1987]. In the present study, however, 8-OH-DPAT occasioned drug lever responding inconsistently in the two baboons, suggesting that the effect of buspirone occasioning drug lever responding in PTZ-trained baboons may not be predominantly a $5HT_{1A}$ effect.

Given the dissimilarities in the molecular mechanisms of action of PTZ, β-CCE, and buspirone, it seems likely that cross-generalization among these drugs is a function of a more general common effect. β-CCE and PTZ have been reported to produce "anxiety" symptoms in primates [Ninan et al., 1982; Rodin, 1958], although observations in the present study made it clear that overt behavioral signs of tremor or agitation were not concommitant with

responding on the PTZ lever. Buspirone has not, to our knowledge, been reported to produce such effects in experimental studies, although clinical reports of buspirone-induced "jitteriness" have emerged [Goa and Ward, 1986; Liegghio et al., 1988]. Buspirone has been reported to increase secretion of the stress-sensitive hormones prolactin and corticosterone in unstressed rats similar to increases in these hormones under a conditioned-fear paradigm [Urban et al., 1986]. It may be that the seemingly paradoxical effects of buspirone are a function of release of "stress-sensitive" hormones. On the other hand, such effects are consistent with dopaminergic activity. Given buspirone's demonstrated activity at dopamine receptors [e.g., McMillen et al., 1983], this possibility remains to be explored experimentally.

NOTE ADDED IN PROOF

Gepirone is a buspirone analogue that shows potential as an anxiolytic and differs from buspirone primarily in not binding potently to brain dopamine receptors [Csanalosi et al., J. Clin. Psychopharm. 7: 31-33, 1987]. Gepirone was administered i.m. to PTZ-trained baboons (0.56 to 5.6 mg/kg for baboon ST and 0.1, 0.18, and 0.32 mg/kg for baboon SC); the highest dose completely suppressed responding. The maximum percentage of drug lever responding at any dose was 11%. These data suggest that the dopaminergic activity of buspirone was sufficient to occasion the drug response in the PTZ-trained baboons.

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