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Effects of ethanol on cocaine discrimination in rats

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Abstract

Ethanol and cocaine are frequently abused in combination, but little is known about how the subjective effects of the two drugs interact. The ability of ethanol and other $GABA_A$-active compounds to alter the discriminative stimulus effects of cocaine was tested. Male Sprague–Dawley rats were trained to discriminate cocaine (10 mg/kg ip) from saline using either single- or cumulative-dosing methods. In single-dose testing, ethanol (0.1–0.5 g/kg) dose-dependently decreased cocaine-appropriate responding following the training dose of cocaine. Ethanol (0.5 g/kg) produced a rightward shift in the cocaine cumulative dose–effect curve. Ethanol (0.1–1.0 g/kg) failed to substitute for the discriminative stimulus effects of cocaine and the higher doses (1–2 g/kg) completely suppressed responding. Indirect $GABA_A$ agonists diazepam (benzodiazepine site) and pentobarbital (barbiturate site) did not block the discriminative stimulus effects of cumulative doses of cocaine. The $GABA_A$ antagonist pentylenetetrazol (PTZ) (10–40 mg/kg) did not substitute for cocaine. These findings suggest that ethanol can modulate the discriminative stimulus effects of cocaine, and that these effects may not be mediated by the actions of ethanol at the $GABA_A$ receptor.

Keywords: Cocaine; Ethanol; Drug discrimination; $GABA_A$ receptor; Rat

1. Introduction

Coabuse of drugs has been recognized as increasingly common, yet little research is devoted to the effects of drug combinations. Cocaine and ethanol are both widely abused, and many people who abuse cocaine simultaneously consume alcoholic beverages (Substance Abuse and Mental Health Services Administration, 2001). Little is known about the subjective effects of combinations of cocaine and ethanol. A clinical study reported that alcohol enhances and prolongs the euphoria produced by cocaine (McCance-Katz et al., 1993). Unfortunately, there is little research in animal models characterizing the interaction of the discriminative effects of cocaine and ethanol.

Prior studies have reported that cocaine does not substitute for the discriminative stimulus effects of ethanol in mice, pigeons, and Long–Evans rats (Emmett-Oglesby et al., 1988; Grant et al., 1991; Schechter, 1994). A series of studies examined the effects of cocaine and ethanol in rats trained to discriminate cocaine versus saline, cocaine versus ethanol, and cocaethylene versus saline in N/Nih rats (Schechter, 1994, 1995, 1997). In only one of these studies were the effects of ethanol in cocaine-trained (10 mg/kg vs. saline) rats tested. This study reported that a low dose of cocaine (2.5 mg/kg) produced 35% cocaine-appropriate responding, and 0.6 g/kg ethanol in combination with 2.5 mg/kg cocaine increased cocaine-appropriate responding to 71%. Complete characterization of the interaction between the discriminative stimulus effects of cocaine and ethanol has not been reported nor has an analysis of the mechanism for the interaction.

The neural mechanism for an interaction between cocaine and ethanol is not obvious, as cocaine is known to act by blocking the uptake of dopamine, norepinephrine, and serotonin, whereas the effects of ethanol are mediated largely by GABA and NMDA receptors (Koob and Nestler, 1997). However, there is increasing evidence that cocaine may act directly at $GABA_A$ receptors. For example, cocaine increases benzodiazepine binding (Jung et al., 1989) and directly blocks $GABA_A$ receptor function in hippocampal neurons (Ye et al., 1997, 1999).

Behavioral data have been less clear. Pentylenetetrazol (PTZ) (20 mg/kg), a $GABA_A$ antagonist, did not generalize to a low dose of cocaine (1.25 mg/kg) in rats; and diazepam

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(10 mg/kg), a benzodiazepine site agonist, did not block the discriminative effects of cocaine (Emmett-Oglesby et al., 1983). However, a study in rhesus monkeys found that the $GABA_A$ modulator pentobarbital and the high-efficacy benzodiazepine triazolam did block the discriminative stimulus effects of cocaine although the $GABA_A$ agonist muscimol and the low-efficacy benzodiazepine imidazenil did not (Negus et al., 2000). Conversely, in rats trained to discriminate PTZ (20 mg/kg) from saline, high doses of cocaine (20 mg/kg and higher) substituted for PTZ (Shearman and Lal, 1979, 1981), whereas lower doses did not (Harris et al., 1989; Prather and Lal, 1992). Haloperidol, a dopamine antagonist that blocks the discriminative stimulus effects of cocaine (Callahan and Cunningham, 1993), did not block the substitution of cocaine for PTZ (Shearman and Lal, 1981). In the same study, diazepam fully blocked the discriminative stimulus effects of PTZ (Shearman and Lal, 1979) and blocked the substitution of cocaine for PTZ. These findings suggest that the substitution of cocaine for PTZ may be mediated by the $GABA_A$ receptor rather than by the blockade of dopamine uptake.

The purpose of the present study was to characterize the effects of ethanol on the cocaine discriminative stimulus and to test whether those effects of ethanol are mediated by $GABA_A$ receptors. Initial studies tested the effects of ethanol (0.25–1 g/kg) alone and in combination with cocaine (10 mg/kg) in single-dose experiments. Subsequent experiments utilized cumulative-dosing methods to obtain full dose–effect curves of ethanol (0.1–1.0 g/kg) or PTZ (10–40 mg/kg) alone and of cocaine after administration of ethanol (0.1–0.5 g/kg), diazepam (5 and 10 mg/kg), and pentobarbital (10 mg/kg).

2. Materials and methods

2.1. Subjects

Male Sprague–Dawley rats were obtained from Harlan–Sprague–Dawley (Indianapolis, IN). All rats were housed individually and were maintained on a 12:12 light/dark cycle (lights on at 7:00 a.m.). Body weights were maintained at 320–350 g by limiting food to 20 g/day, which included the food received during operant sessions. Water was freely available. All housing and procedures were in accordance with the guidelines of the Institute of Laboratory Animal Resources, National Research Council (Institute of Laboratory Animal Resources, 1986) and were approved by the University of North Texas Health Science Center Animal Care and Use Committee.

2.2. Discrimination training

Standard operant chambers (Coulbourn Instruments, Allentown, PA) were connected to IBM-PC-compatible computers via LVB interfaces (Med Associates, East Fairfield, VT). The computers were programmed in MED-PC 1.15 (Med Associates) for the operation of the chambers and collection of data.

Rats were trained to discriminate cocaine (10 mg/kg) from saline using a two-lever choice methodology. Food (45-mg food pellets; Bio-Serve, Frenchtown, NJ) was available as a reinforcer under a fixed ratio 10 schedule when responding occurred on the injection-appropriate lever. There was no consequence for incorrect responses. Animals received approximately 60 training sessions in total before use in any behavioral experiment. Animals were selected for use in experiments when they had met the criteria of emitting 85% of responses on the injection-correct lever for both the first reinforcer and total session during their last 10 training sessions.

For single-dose studies, training sessions occurred in a double alternating fashion (D-D-S-S-D, etc.), and tests were conducted between pairs of identical training sessions (i.e., between either two saline or cocaine training sessions). Rats were tested only if they had achieved 85% drug lever responding for both first reinforcer and total session on the two prior training sessions. Before each session, the rats received an injection of either saline or cocaine. Ten minutes later, the rats were placed in an operant chamber. Each training session lasted a maximum of 10 min, and the rats could earn up to 20 food pellets.

During training for cumulative-dose studies, one to four 15-min cycles were conducted each day. Saline or cocaine was administered at the start of each cycle. Ten minutes later, the rats were placed in an operant chamber for training session that lasted a maximum of 5 min during which the rats could earn up to 10 food pellets. Cocaine was given only on the last cycle, except on those days in which four saline cycles were administered. The rats were tested only if they met the 85% criterion for both first reinforcer and total session on each cycle of the two training sessions immediately preceding the test session.

2.3. Test procedures

During single-dose testing, intraperitoneal injections of ethanol (0.25–2 g/kg) or vehicle (0.9% saline) occurred 15 min prior to the start of the test session. Intraperitoneal injections of the training dose of cocaine occurred 10 min prior to the start of the test session. Test sessions lasted for 20 min or until 20 reinforcers had been obtained. At least 3 days elapsed between test sessions.

During cumulative-dose testing, the ability of ethanol (0.1, 0.25, 0.5, and 1.0 g/kg), PTZ (10, 20, and 40 mg/kg), or cocaine (1, 2.5, 5, and 10 mg/kg) to substitute for cocaine was tested. Administration of cocaine occurred 10 min prior to the start of the test session, and administration of ethanol and PTZ occurred 15 min prior to the start of the test session. The test period lasted for 3 min or until one reinforcer had been obtained. On completion of the test period, animals were injected with the next dose of test drug

and tested as above. Subsequent doses increased the cumulative amount of drug to the values given above. The ability of ethanol, diazepam, and pentobarbital to antagonize the discriminative stimulus effects of cocaine was also tested. Injections of ethanol (0.1, 0.25, and 0.5 g/kg), diazepam (5 and 10 mg/kg), or pentobarbital (10 mg/kg) were administered 15 min prior to determination of the cocaine dose–effect curve. At least 4 days elapsed between test sessions.

2.4. Drugs

Diazepam was obtained from Research Biochemicals International (Natick, MA). PTZ and pentobarbital sodium were purchased from Sigma (St. Louis, MO). (−)-Cocaine hydrochloride was obtained from the National Institute on Drug Abuse. Diazepam was prepared as a suspension in 2% methyl cellulose. All remaining drugs were dissolved in 0.9% saline. All drugs were administered intraperitoneally. Ethanol was administered in a concentration of 15% (wt/vol). All remaining drugs were administered in a volume of 1 ml/kg.

2.5. Data analysis

Drug discrimination data were expressed as the mean percentage of responses made on the cocaine-appropriate lever prior to completion of the first fixed ratio. Percent cocaine-appropriate responding and response rate were plotted as a function of the dose of the test compound (log scale). Graphs for cumulative-dose studies were plotted as a function of the cumulative dose of the test compound (log scale). Percent cocaine-appropriate responding was shown only if at least three rats completed the first fixed ratio. Full substitution was defined as >80% cocaine-appropriate responding and partial substitution as $\geq$40% and

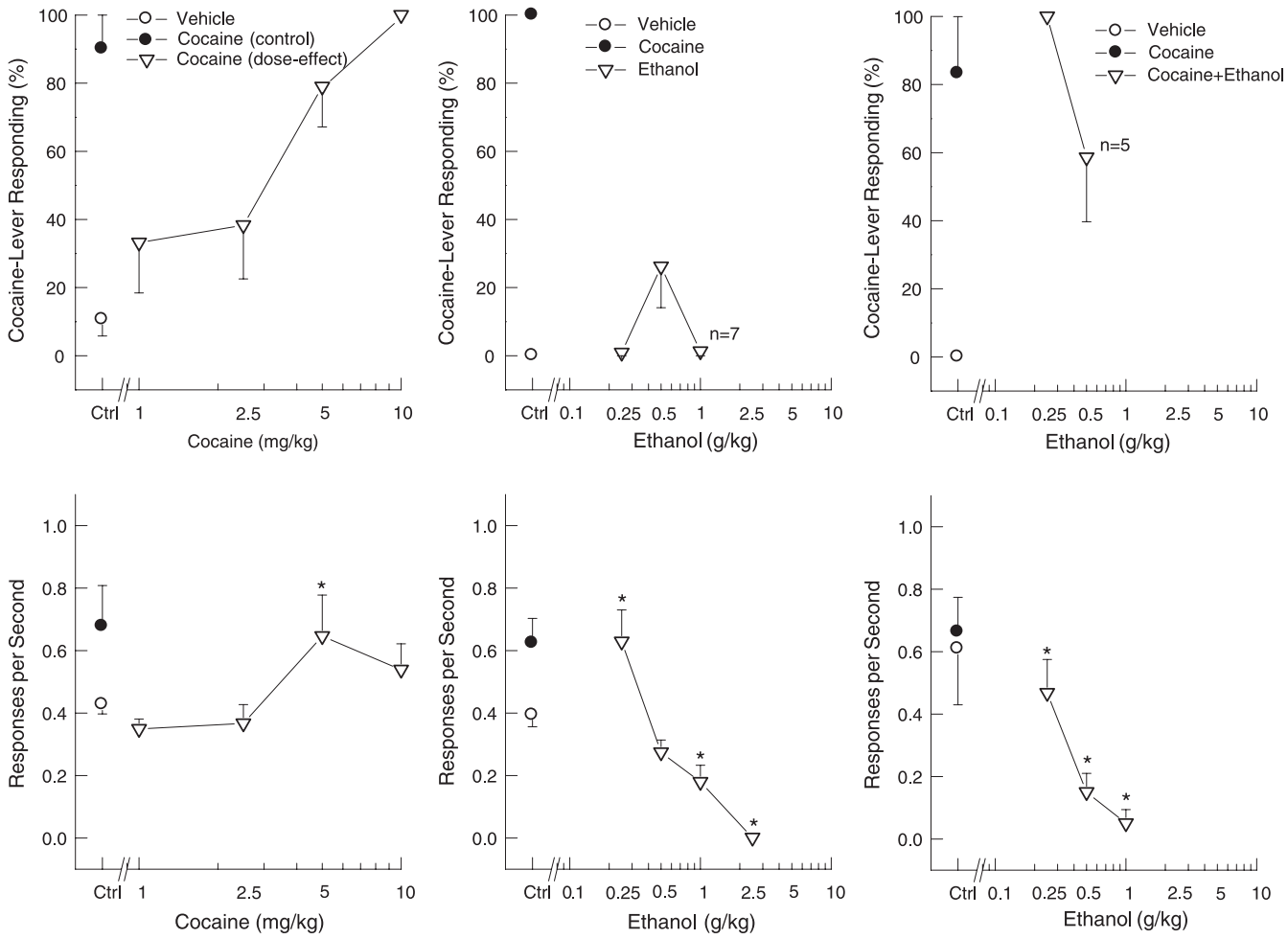

Fig. 1. The left panels show the effects of cocaine alone (n = 10). The center panels show the effects of ethanol alone (n = 10). The right panels show the effects of ethanol in combination with cocaine (n = 6). The upper panels show the mean (±S.E.M.) percentage of responses emitted on the cocaine-appropriate lever during the first fixed ratio as a function of dose for doses with three or more rats completing the first fixed ratio. The lower panels show the mean response rate (±S.E.M.) as a function of dose for all subjects tested. To the left of the axis break, control (Ctrl) data are shown for the vehicle (0.9% saline) and for the training dose of cocaine (10 mg/kg). For the substitution studies (left and center panels), asterisks show points different from the saline control (P < .05). For the antagonism study (right panel), asterisks show points different from cocaine alone (P < .05).

< 80% cocaine-appropriate responding. Full antagonism was defined as < 20% cocaine-appropriate responding, and partial antagonism was defined as ≥ 20% and ≤ 60% cocaine-appropriate responding.

One-way repeated measures analysis of variance (ANOVA) was used for single-dose experiments and cumulative-dosing substitution experiments to analyze response rate data. Planned comparisons (a priori contrast) were conducted for each dose against vehicle control in substitution experiments and against cocaine control in antagonism experiments. Two-way repeated measures ANOVA was used to analyze dose–effect curves (Group × Dose) for cumulative-dosing experiments in which ethanol, diazepam, or pentobarbital were administered in combination with cocaine. Planned comparisons (a priori contrast) were conducted at each dose to detect differences from the cocaine alone group. Criterion for statistical significance was set a priori at $P < .05$.

3. Results

3.1. Single-dose ethanol experiments

Fig. 1 shows the effects of cocaine and ethanol alone and combined on cocaine-lever responding and response rate. Saline control tests occasioned no more than 17% cocaine-appropriate responding, whereas cocaine control tests occasioned from 83% to 100% cocaine-appropriate responding. Cocaine dose-dependently increased cocaine-appropriate responding to 100% at 10 mg/kg but had no significant overall effect on response rate [$F(4,36) = 2.54$, $P = .056$]. Planned comparisons (a priori contrast) against vehicle control showed a significant difference for the 5.0 mg/kg doses of cocaine.

Ethanol did not substitute for cocaine (Fig. 1) and produced maximal cocaine-appropriate responding of 26% at 0.5 g/kg. Ethanol dose-dependently decreased responding

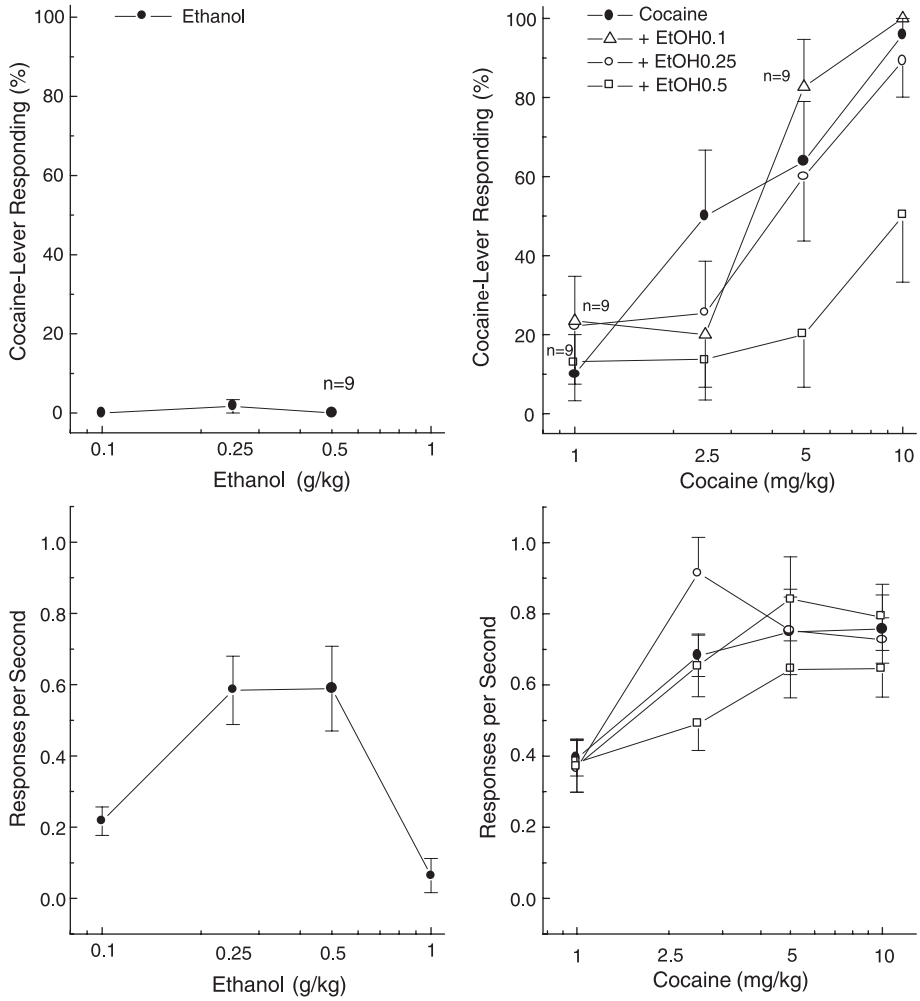

Fig. 2. The effects of ethanol in rats trained to detect cocaine, 10 mg/kg ($n = 10$, except where shown). The left panels show the effects of cumulative doses of ethanol alone ($n = 10$). The right panels show the effects of ethanol (g/kg) in combination with cumulative doses of cocaine. The upper panels show the mean (± S.E.M.) percentage of responses emitted on the cocaine-appropriate lever as a function of dose for doses with three or more rats completing the session. The lower panels show the mean response rate (± S.E.M.) as a function of dose for all subjects tested.

[$F(4,36) = 15.56$, $P < .001$] and completely suppressed responding following 2.0 g/kg. Planned comparisons (a priori contrast) against vehicle control showed significant differences for the 0.25, 1.0, and 2.0 g/kg doses of ethanol.

When given in combination with cocaine, ethanol partially antagonized the discriminative stimulus effects produced by 10 mg/kg of cocaine (Fig. 1). The partial antagonism (59% drug-appropriate responding) occurred following 0.5 g/kg. Ethanol dose-dependently decreased responding [$F(3,15) = 17.29$, $P < .001$], with five out of six rats failing to complete the first fixed ratio when tested following 1.0 g/kg. Planned comparisons (a priori contrast) against cocaine control showed significant differences for the 0.25, 0.5, and 1.0 g/kg doses of ethanol.

3.2. Cumulative-dose ethanol experiments

Cumulative doses of ethanol occasioned essentially no cocaine-appropriate responding (Fig. 2), but significantly altered response rates [$F(3,27) = 16.88$, $P < .001$]. Intermediate doses of ethanol (0.25 and 0.5 g/kg) increased response rates, whereas 8 out of 10 rats failed to complete testing following 1.0 g/kg.

Cumulative doses of cocaine produced dose-dependent increases in cocaine-appropriate responding to near maximal levels (Fig. 2). When administered before cocaine, 0.1 and 0.25 g/kg ethanol did not affect cocaine-lever responding, but a rightward shift was evident following 0.5 g/kg ethanol. At this dose, mostly saline-appropriate responding was seen following 1–5 mg/kg cocaine, and only 50% cocaine-appropriate responding was seen following 10 mg/kg cocaine. Cocaine increased response rates [$F(3,108) = 24.00$, $P < .001$] reaching a maximum of 0.6–0.8 responses by 5 mg/kg. Ethanol at the doses tested did not significantly alter rates of responding following cumulative doses of cocaine [$F(3,36) = 1.12$, $P = .355$], and there was no interaction between cocaine and ethanol dose [$F(9,108) = 1.59$, $P = .128$]. When a higher dose of ethanol (1 g/kg) was administered in combination with cocaine, responding was completely suppressed (data not shown).

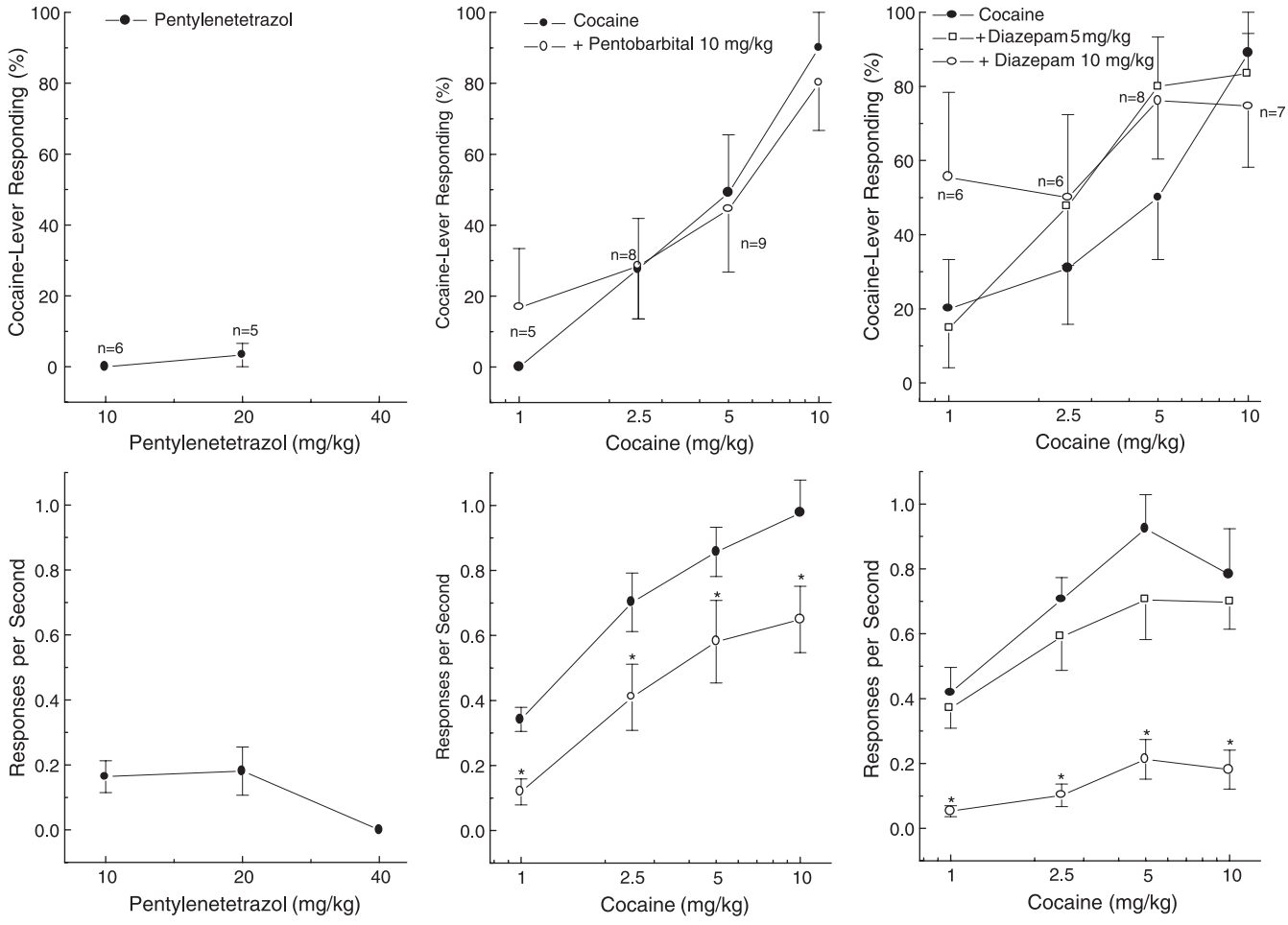

Fig. 3. The effects of cumulative doses of cocaine in combination with diazepam (right panels, $n = 11$) or pentobarbital (center panels, $n = 10$). The left panels show the effects of cumulative doses of PTZ alone ($n = 9$). The upper panels show the mean (±S.E.M.) percentage of responses emitted on the cocaine-appropriate lever as a function of dose for doses with three or more rats completing the session. The lower panels show the mean response rate (±S.E.M.) as a function of dose for all subjects tested. To the left of the axis break, control (Ctrl) data are shown for the vehicle (0.9% saline) and for the training dose of cocaine (10 mg/kg). Asterisks show points different from cocaine alone ($P < .05$).

3.3. Effects of $GABA_A$-selective compounds on cocaine discrimination

PTZ (10–40 mg/kg) failed to produce cocaine-appropriate responding (Fig. 3) and decreased rates of responding at all doses [$F(2,16) = 5.82$, $P = .013$]. The highest dose (40 mg/kg) completely suppressed responding. No tremors or seizures were observed. Pentobarbital (10 mg/kg) administered 15 min before testing did not alter cocaine-appropriate responding. Pentobarbital did reduce response rates at all doses of cocaine [$F(1,18) = 7.80$, $P = .012$]. When given in combination with cocaine, diazepam (5 mg/kg) did not alter cocaine-appropriate responding, but the 10 mg/kg dose increased the amount of cocaine-appropriate responding seen at the lowest dose of cocaine. Diazepam dose-dependently decreased response rates [$F(2,27) = 20.41$, $P < .001$] and markedly suppressed response rates following 10 mg/kg.

4. Discussion

The dose–effect curves for cocaine were comparable in rats trained with either single- or cumulative-dose methods, as noted in previous studies (Lane et al., 1992; Peltier et al., 1994, 1996). The cumulative-dosing method allows for determination of the complete dose–effect range in a single session and the examination of the effects of antagonists on multiple doses of cocaine, not just the training dose. Ethanol did not substitute for the discriminative stimulus effects of cocaine in either single- or cumulative-dose studies, a finding that agrees with earlier studies (Emmett-Oglesby et al., 1988; Grant et al., 1991; Schechter, 1994).

Pretreatment with ethanol (0.5 g/kg) decreased cocaine-appropriate responding to 59% following 10 mg/kg of cocaine. In the cumulative-dosing experiment, the same dose of ethanol shifted the cocaine dose–effect curve to the right, such that doses of cocaine (2.5–5 mg/kg) that typically produce intermediate levels of cocaine-appropriate responding were completely ineffective. Cocaine-appropriate responding following 10 mg/kg cocaine was decreased to 50%. Whether the blockade by ethanol was completely surmountable could not be determined, as higher doses of cocaine were not tested due to the high incidence of seizures at such doses. Higher doses of ethanol completely suppressed responding in both single- and cumulative-dosing experiments.

An earlier study reported that 0.6 g/kg ethanol increased cocaine-appropriate responding following a marginally effective dose of cocaine to 71% in N/Nih rats (Schechter, 1994), whereas 0.5 g/kg ethanol decreased cocaine-appropriate responding at the same dose (2.5 mg/kg) in the present study. Why the two studies do not agree is not clear. The earlier study did not test ethanol against the training dose of cocaine (10 mg/kg), so it is possible that a decrease in cocaine-appropriate responding might have been seen in the earlier study, had that combination been tested. Also, the amount of cocaine-appropriate responding produced by cocaine 2.5 mg/kg was higher in the present study. It is possible that ethanol acts like a low-efficacy compound, which is increasing the effects of low doses of a high-efficacy compound, while decreasing the effects of high doses of the high-efficacy compound. This could explain why ethanol increased the small effects of 2.5 mg/kg cocaine in the earlier study and decreased the larger effects of 2.5 mg/kg cocaine in the present study. This does not account for why ethanol did not increase the effects of 1.0 mg/kg in the present study, but this may be due to strain differences or to the small differences in the ethanol dose used in the two studies.

Not only did ethanol attenuate the effects of a large dose of cocaine in the present study, but it also fully blocked the discriminative stimulus effects of low doses of cocaine. These data are of clinical interest as they suggest that ethanol may be used in combination with cocaine to blunt the less desirable effects of cocaine. If such is the case, it could explain why people report that alcohol enhances and prolongs the euphoria produced by cocaine (McCance-Katz et al., 1993).

A possible explanation for these results is that ethanol reduces the level of cocaine in the blood and brain. Instead, studies have shown that ethanol slightly increases levels of cocaine in both plasma and brain (Hedaya and Pan, 1996, 1997; Pan and Hedaya, 1999). Alternatively, administration of ethanol before cocaine results in production of cocaethylene, which is present in both blood and brain at levels high enough to produce behavioral effects at the time points tested in the present study (Hedaya and Pan, 1997; Pan and Hedaya, 1999). However, cocaethylene fully substitutes for cocaine (Schechter, 1994) and so would not likely contribute to a decrease in cocaine-lever selection following administration of ethanol. These findings suggest that ethanol is blocking the discriminative stimulus effects of cocaine rather than decreasing levels of cocaine or its bioactive metabolites.

Given the evidence that cocaine acts directly on $GABA_A$ receptors (Jung et al., 1989; Ye et al., 1997, 1999), it is reasonable to assume that compounds active at $GABA_A$ receptors could modulate the discriminative stimulus effects of cocaine, particularly as pentobarbital and triazolam blocked the discriminative stimulus effects of cocaine in rhesus monkeys (Negus et al., 2000). However, in the present study, neither the benzodiazepine agonist diazepam nor the barbiturate agonist pentobarbital blocked the discriminative stimulus effects of cocaine in rats. The dose of pentobarbital tested was behaviorally active, as it produced decreases in response rates. Lower doses were not tested, as it was unlikely they would produce any greater effect, and higher doses (25 mg/kg) produce marked sedation. When tested alone in rats trained to discriminate cocaine, pentobarbital produced no cocaine-appropriate responding (Barrett et al., 2001).

Diazepam also dose-dependently decreased response rates. Given the large reduction in response rates following

10 mg/kg diazepam, it is not clear whether the increase in cocaine-appropriate responding was due to an enhancement of the cocaine discriminative stimulus or to a general disruption of discriminative abilities. Prior studies have reported that diazepam does not substitute for the discriminative stimulus effects of cocaine (Kleven et al., 1999; Schuster and Johanson, 1985), which suggests that a disruption of the discrimination may be more likely. It is possible that a direct $GABA_A$ agonist would have been effective in rats, although muscimol, a $GABA_A$ agonist, did not block the discriminative stimulus effects of cocaine in rhesus monkeys (Negus et al., 2000).

Although large doses of cocaine (20 mg/kg and higher) substitute for PTZ in rats trained to discriminate PTZ (20 mg/kg) from saline (Shearman and Lal, 1979, 1981), PTZ did not substitute for cocaine in the present study. Lower doses of cocaine (less than 20 mg/kg) do not substitute for PTZ (Harris et al., 1989; Prather and Lal, 1992; Shearman and Lal, 1979). In addition, in one study in which cocaine did substitute for PTZ, haloperidol did not block the effects of cocaine, whereas diazepam did (Shearman and Lal, 1981), which suggests that cocaine substitution for PTZ may be mediated by cocaine's actions at $GABA_A$ rather than on dopamine uptake. Finally, an earlier study found that PTZ did not substitute in rats trained to a low dose of cocaine (1.25 mg/kg), and diazepam (10 mg/kg) did not block the discriminative effects of that dose of cocaine (Emmett-Oglesby et al., 1983). The findings suggest that high doses of cocaine are necessary to produce effects at $GABA_A$ receptors, which is in agreement with electrophysiological studies that reported that higher concentrations of cocaine reduce GABA-induced currents in rat hippocampal neurons (Ye et al., 1997, 1999). These findings imply that it might be possible for PTZ to substitute for cocaine if a larger training dose of cocaine were used (e.g., 20 mg/kg). Such a large dose is seldom used due to the increased risk of seizures. However, this possibility still does not account for why some $GABA_A$ agonists were effective at blocking the discriminative stimulus effects in rhesus monkeys but not in rats. Primates may be more sensitive to the GABAergic effects of cocaine; but to date, there is no research exploring such possibilities.

There are a number of other possible mechanisms for the blockade of the cocaine discriminative stimulus by ethanol. Ethanol could modulate the discriminative stimulus effects of cocaine through its effects on other receptors. $GABA_B$ receptors could not, as studies in both rhesus monkeys and rats have reported that the $GABA_B$ agonist baclofen does not modulate the discriminative stimulus effects of cocaine (Munzar et al., 2000; Negus et al., 2000). Glutamate receptors are another major site of action for ethanol, and NMDA receptor channel blockers have been reported to attenuate the discriminative stimulus effects of cocaine (Cunningham and Appel, 1982; Koek et al., 1989, 1995).

Another possibility is that there is no direct pharmacological interaction between ethanol and cocaine. What brain mechanisms might be responsible for mediating such an effect are not known and could reflect modulation of various signaling pathways triggered by cocaine's blockade of dopamine uptake or even cortical processes. Methods for determining whether one drug stimulus is masking the effects of another drug stimulus without producing direct pharmacological antagonism have been previously described (Gauvin and Young, 1989; Overton, 1983) and provide an alternate line of investigation of the interaction between ethanol and cocaine.

Finally, it might be argued that ethanol could generally disrupt operant behavior. However, the dose of ethanol (1.25 g/kg) used to train an ethanol discrimination in Sprague–Dawley rats (Colpaert and Koek, 1995; Mhatre et al., 2000) is higher than the dose that decreased rates of responding in the present study. Taken together, these findings suggest that ethanol can partially block the discriminative stimulus effects of cocaine in rats and that these effects are not mediated by the actions of ethanol at $GABA_A$ receptors. What mediates this interaction between ethanol and cocaine is not clear and requires additional investigation.

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