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Modulation of the Discriminative Stimulus and Rate-Altering Effects of Cocaine by Competitive and Noncompetitive *N*-Methyl-D-Aspartate Antagonists

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KANTAK, K. M., M. A. EDWARDS AND T. P. O'CONNOR. *Modulation of the discriminative stimulus and rate-altering effects of cocaine by competitive and noncompetitive* N-*Methyl-D-aspartate antagonists.* PHARMACOL BIOCHEM BEHAV **59**(1) 159–169, 1998.—The purpose of this study was to determine the extent to which *N*-methyl-D-aspartic acid (NMDA) antagonists modified the discriminative stimulus effects of cocaine in rats trained to discriminate 5 mg/kg cocaine from vehicle on a fixed-ratio schedule of food presentation as well as the rate-altering effects of cocaine in rats maintained on a fixed-interval schedule of food presentation. NMDA-associated ion channel blockers (dizocilpine, phencyclidine, and magnesium chloride) and competitive NMDA antagonists (NPC 17742 and CGP 37849) displayed similar behavioral effects when administered alone: each drug engendered intermediate levels of cocaine-appropriate responses and rate-dependent effects on food-reinforced operant responding. Selected doses of dizocilpine, magnesium chloride, and phencyclidine given in combination with 1 mg/kg cocaine produced more cocaine-appropriate responses than this dose of cocaine alone. In addition, dizocilpine and magnesium chloride each attenuated the discriminative stimulus effects of higher doses of cocaine. The competitive NMDA antagonists did not appreciably modify the discriminative stimulus effects of any dose of cocaine. Under the fixed-interval schedule, each NMDA antagonist attenuated the effects of 3 mg/kg cocaine, which normally produced maximal increases in response rate. Attenuation of the rate-decreasing effects of the highest dose of cocaine (30 mg/kg) also were observed after pretreatment with dizocilpine and magnesium chloride. These findings demonstrated differences in the way that NMDA-associated ion channel blockers and competitive NMDA antagonists interact with cocaine, and suggest that some NMDA-associated ion channel blockers may either enhance or antagonize the effects of cocaine, depending on the dose and type of behavioral procedure. © 1998 Elsevier Science Inc.

CGP 37849 Cocaine Dizocilpine Drug discrimination Magnesium chloride MK-801 NMDA antagonists NPC 17742 Phencyclidine Schedule-controlled behavior

COCAINE acts in the central nervous system by inhibiting the uptake of dopamine (DA) and other monoamines (norepinephrine, 5-hydroxytryptamine) into presynaptic terminals (22,37,39,50). Although cocaine blocks the transporters and alters the synaptic levels for all three monoamines, there is a positive correlation between the relative affinities of drugs for cocaine binding sites on the DA transporter and their potencies for producing cocaine-like behavioral effects (3,38,52,61). Consequently, DA principally mediates many of the behavioral effects of cocaine, but several different neurotransmitter systems also have been implicated as modulators of these effects. Among these are the noradrenergic (28,63), serotonergic (12, 57), and opiate (59,60) neurotransmitter systems.

Recent observations further suggest that drugs acting selectively at the *N*-methyl-D-aspartic acid (NMDA) receptor complex can modulate the behavioral effects of cocaine and other stimulants. Concurrent treatment with the NMDA-associated ion channel blocker dizocilpine (MK 801) has been

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shown to block the development of sensitization to the locomotor-stimulant effects and stereotypy induced by repeated administration of cocaine to rats and mice (36). In addition, the competitive NMDA antagonist 2-amino-5-phosphonovaleric acid (APV) has been reported to reduce locomotor activity induced by an acute injection of cocaine in rats (49). Finally, dizocilpine, as well as another ion channel blocker phencyclidine (PCP), and the competitive NMDA antagonists 3-(2-carboxy-piperazine-4-yl)propyl-1-phosphonic acid (CPP) and NPC 12626, have been shown to protect against cocaine-induced convulsions and/or lethality (26,53,65). Collectively, these findings suggest that inhibition of NMDA-mediated neurotransmission might serve to attenuate at least some of the effects of cocaine in vivo.

In addition to studies reporting an inhibitory influence of NMDA antagonists on the behavioral effects of cocaine, other studies indicate that NMDA antagonists may have behavioral effects in common with cocaine. Clineschmidt et al. (9), for example, reported that dizocilpine increased locomotor activity in mice and induced ipsilaterally rotation in rats with a unilateral nigrostriatal lesion produced by 6-hydroxydopamine. Dizocilpine, PCP, and APV also have been shown to induce a behavioral syndrome in rats, which includes stereotypy and hyperlocomotion (41,42). In addition to these motor-activating effects of NMDA antagonists, findings from drug discrimination studies demonstrated that under a low-dose (2 mg/kg) cocaine training condition, dizocilpine, PCP, as well as magnesium chloride ($MgCl_2$) can engender discriminative stimulus (DS) effects that partially mimic those of cocaine (33). In contrast to the effects of the NMDA-associated ion channel blockers, the competitive NMDA receptor antagonist [2R,4R,5S-(2-amino-4,5-(1,2-cyclohexyl)-7-phosphonoheptanoic acid)] (NPC 17742) did not engender appreciable cocaine-like DS effects (33), suggesting some differences in the way different types of NMDA antagonists may interact with cocaine.

The effects of dizocilpine and PCP also have been evaluated on schedule-controlled behavior maintained on either a fixed-interval (FI) or differential reinforcement of low-rate (DRL) schedule of food presentation (2,20,24). Both drugs produced rate-increasing effects after low-to-intermediate doses and rate-decreasing effects after higher doses, resulting in a bitonic dose–response curve characteristic for psychomotor stimulant drugs. How these and other NMDA antagonists might modify the rate-altering effects of cocaine have not yet been evaluated. The purpose of the present study was to determine the extent to which different types of NMDA antagonists might mimic and/or modify the DS effects of cocaine in rats trained to discriminate an intermediate dose of cocaine from vehicle on a fixed-ratio (FR) schedule of food presentation as well as the rate-increasing and rate decreasing effects of cocaine in rats trained on a FI schedule of food presentation. To optimize the degree of drug interaction in the drug discrimination studies, 5.0 mg/kg cocaine was chosen as the training dose rather than a higher dose, for which NMDA antagonists do not substitute, or a lower dose, for which more extensive discrimination training is required (33). The drugs studied were the NMDA-associated ion channel blockers dizocilpine, PCP, and $MgCl_2$ (51,70) and the competitive NMDA antagonists NPC 17742 and CGP 37849 (16,17).

METHOD

Subjects

Male Wistar rats (Charles River Breeding Labs, Portage, MI) were housed in individual stainless steel cages (24 × 18 × 18 cm) within a temperature (74 ± 4°F)- and light (0800 h on, 2000 h off)-controlled vivarium. Four experimentally naive rats were used to study the effects of drugs on fixed-interval schedule-controlled behavior and four previously trained rats (33) were used to study the effects of drugs on cocaine discrimination (see below). Between experimental sessions, the rats had continuous access to water in their home cages; food was restricted to 16 g per day. This ration of food maintained body weights at approximately 85% of ad lib values throughout the duration of each study (444 ± 9 g to 475 ± 10 g in the drug discrimination study; 251 ± 9 g to 370 ± 10 g in the fixed-interval schedule-controlled behavior study).

Apparatus

Four experimental chambers for rats (Gerbrands, Model A, Waltham, MA) were each equipped with two response levers, mounted 7.6 cm apart, and a pellet dispenser, which emitted an audible click during delivery of 45 mg food pellets (Noyes, Traditional Formula, Lancaster, NH) to a receptacle located between the levers. Each chamber was enclosed within a sound-attenuating cubicle equipped with an overhead light to provide general illumination and a fan to provide ventilation and mask extraneous sounds. Experimental events were controlled by a 286 AT-compatible computer that was programmed in Medstate Notation and connected to an interface (Med Associates, East Fairfield, VT).

Drugs

The drugs studied were cocaine hydrochloride and PCP hydrochloride (NIDA, Rockville, MD), dizocilpine maleate [(+)-MK 801] (Research Biochemicals Inc., Natick, MA), NPC 17742 (NOVA Pharmaceutical Corp., Baltimore, MD), $MgCl_2$ (Fisher Scientific, Medford, MA), and CGP 37849 (Ciba-Geigy Limited; Basel, Switzerland). Except for NPC 17742, drugs were dissolved and diluted to desired concentrations in either sterile 0.9% saline or sterile distilled water. NPC 17742 (30 mg/ml) was first dissolved in 100 mM sodium hydroxide and then diluted to desired concentrations with sterile distilled water. All drugs were administered as a bolus injection 15 min before the session either by the subcutaneous route in a volume of 3.0 ml/kg body weight ($MgCl_2$) (35) or by the IP route in a volume of 1.0 ml/kg body weight (other drugs).

Drug Discrimination Procedure

Rats, which were previously trained to discriminate 10 mg/kg cocaine from vehicle and had substitution tests with 10 different NMDA-related or DA-related drugs over a 8-month period (33), were retrained to discriminate 5 mg/kg cocaine from vehicle for the present investigation. After administration of 5 mg/kg cocaine, 10 responses (FR 10) on one lever resulted in delivery of a food pellet, whereas after administration of saline, 10 responses on the other lever produced a food pellet. There were no consequences for incorrect responses. A different sequence of randomly assigned saline and drug training sessions was used for each subject to ensure that any olfactory cues associated with the two levers (15) would not bias the discrimination. Training sessions were conducted daily (Monday–Friday) and lasted 15 min in duration. Training under these conditions continued until 1) there were at least 10 consecutive sessions in which ⩾ 90% of responses were made on the injection-appropriate lever, 2) the total number of responses on both levers did not exceed 12 before the first food pellet was delivered in each session, and 3) a significant reduction in

ED_{50} was established in substitution tests. These three criteria were met after 26 retraining sessions for all subjects.

Following training, drug test sessions were conducted once or twice per week, with training sessions scheduled on intervening days. Test sessions were conducted only if performance during the preceding training session met the first two criteria described above. Test sessions were identical to training sessions except that 10 responses on either lever resulted in delivery of a food pellet. A range of doses of cocaine (1.0–10 mg/kg), dizocilpine (0.03–0.3 mg/kg), PCP (1.0–5.6 mg/kg), $MgCl_2$ (10–300 mg/kg), CGP 37849 (3.0–18 mg/kg), and NPC 17742 (3.0–18 mg/kg) was studied in all subjects to determine the degree to which each compound substituted for the 5 mg/kg training dose of cocaine. Doses of dizocilpine (0.18 mg/kg), PCP (1.8 mg/kg), $MgCl_2$ (30 mg/kg), CGP 37849 (10 mg/kg), and NPC 17742 (10 mg/kg), which were shown to be behaviorally effective in this or previous studies (24,31,35,68), were selected to administer in combination with a full range of doses of cocaine. To ensure that the interactions were not due to variations in individual drug effects, drugs were studied in different orders with different subjects and each dose of cocaine and saline was examined on two to three occasions in each subject at various times during the experiment. Results for NPC 17742 were based on the performance of three subjects as one subject died before this portion of the study was completed.

Fixed-Interval Scheduled-Controlled Behavior Procedure

After shaping and training naive rats to respond under a FR10 schedule of food presentation, rats were then trained to respond on a 1-min FI schedule of food presentation, for which the left lever was designated as the active lever. Responding on the right lever had no scheduled consequences and the average response rate on this lever was generally less than 0.01 responses per second for the entire study. Daily test sessions (Monday–Friday) were 15 min in duration, which permitted a maximum of 14 food pellets per session.

Experiments with drugs began after stable rates and patterns of responding were observed from day to day. Six saline control sessions preceded the first drug test session. Drug test sessions were conducted twice per week, with noninjection control sessions at the beginning of each week and saline control sessions on intervening days. A range of doses of cocaine (1.0–30 mg/kg), dizocilpine (0.01–0.18 mg/kg), PCP (0.1–3.0 mg/kg), $MgCl_2$ (30–560 mg/kg), and NPC 17742 (0.3–30 mg/kg) was studied in all subjects to determine the degree to which each compound altered the rate of responding. Doses of dizocilpine (0.03 and 0.1 mg/kg), PCP (0.3 and 1.8 mg/kg), $MgCl_2$ (100 and 178 mg/kg), and NPC 17742 (1.0 and 10.0 mg/kg), which were approximately equi-effective in increasing or decreasing responding when given alone, were selected to administer in combination with a full range of doses of cocaine.

Analysis of Drug Effects

In the drug discrimination study, the percentage of cocaine-appropriate responses was determined by dividing the number of responses on the cocaine-associated lever by the total number of responses on both levers. Data were not used in these analyses if the corresponding response rate was $\leq$0.01 resp./s. When appropriate, the dose of a drug estimated to engender 50% cocaine-appropriate responses (ED_{50} ± 95% CI) was calculated by linear regression analysis over the ascending portion of the log dose–response curve. Single-factor (drug dose) repeated measures ANOVA and Dunnett's tests were used to analyze differences in the percentage of cocaine-appropriate responses during substitution tests. In drug interaction studies, dose–response curves were analyzed using two-factor (cocaine dose × pretreatment drug) repeated measures ANOVA and Dunnett's tests to determine differences in the level of cocaine-appropriate responses. An additive drug effect was defined as an increase in cocaine-appropriate responses following the combination of a pretreatment drug with cocaine that was significantly greater than either drug alone. An infra-additive drug effect was defined as an increase in cocaine-appropriate responses following the combination of a pretreatment drug with cocaine that was significantly greater than cocaine alone, but was not significantly different from the pretreatment drug alone. For purposes of this study, full substitution for cocaine was defined as $\geq$90% cocaine-appropriate responses.

FR rates of responding were calculated by dividing the total number of responses on both levers by the total session length. Response-rate data were expressed as percentage of the saline control value for individual subjects and data from all subjects were used in these analyses. For analysis of drug effects on FI behavior, rates of responding after each dose of a drug or saline (averaged over the study) were calculated for individual subjects as the percentage of the noninjection control rates (averaged over the study) for individual subjects. In each study, single-factor (drug dose) or a two-factor (cocaine dose × pretreatment drug) repeated measures ANOVA were computed and the Dunnett's test was used to determine differences in FR or FI response rates. Complete attenuation of the rate-altering effects of cocaine was defined as a change in response rate after the combination of cocaine and a test drug that was significantly different from cocaine alone and not significantly different from the test drug alone. Incomplete attenuation of the rate-altering effects of cocaine was defined as a change in response rate after the combination of cocaine and a test drug that was significantly different from either drug alone. In all drug interaction studies, dose–response curves also were analyzed using the parallel line assay of Finney (18) to ascertain differences in slope.

RESULTS

Drug Discrimination

Training performances and effects of cocaine. After reduction in training dose to 5 mg/kg cocaine, rats made an average of 98.4% ± 1.3 of responses on the cocaine-associated lever following training injections of 5 mg/kg cocaine (rates of responding averaged 0.82 ± 0.11 responses per s) and an average of 0.6% ± 0.6 of responses on the cocaine-associated lever following training injections of saline (rates of responding averaged 1.15 ± 0.11 responses/s). Thus, over the course of the study with various drugs, discriminative stimulus control by 5 mg/kg cocaine was consistently maintained. In substitution tests (Table 1), cocaine (1–10 mg/kg) engendered significant, $p < 0.01$, dose-related increases in the percentage of cocaine-appropriate responses, reaching a maximum average of 99% after 5 mg/kg. The ED_{50} was significantly lower after retraining rats to discriminate 5 mg/kg cocaine (ED_{50} = 1.9 mg/kg; 95% CI = 1.5–2.3) compared to the initial 10 mg/kg cocaine training dose exposure (ED_{50} = 3.6 mg/kg; 95% CI = 2.9–4.1). Significant, $p < 0.01$, reductions in FR response rate were observed after doses $\geq$ 5 mg/kg.

Effects of NMDA antagonists

In substitution tests, the NMDA-associated ion channel blockers dizocilpine, PCP, and $MgCl_2$ each engendered in-

TABLE 1

COCAINE-APPROPRIATE RESPONSES AND FR RESPONSE RATES DURING DRUG SUBSTITUTION TESTS WITH COCAINE AND NMDA ANTAGONISTS* AND RESPONSE RATES FOLLOWING COCAINE AND NMDA ANTAGONIST TREATMENTS UNDER A FI 1 MIN SCHEDULE OF FOOD PRESENTATION†

Drug	Dose	Cocaine Substitution	FR Response Rate	FI Response Rate
Vehicle		0.03% ± 0.01	100%	97% ± 7
Cocaine	1.0	22.2% ± 12	85% ± 12	115% ± 8
	3.0	87.4% ± 8§	72% ± 11	142% ± 6‡
	5.0	99.8% ± 0.3§	50% ± 8§	
	10	99.2% ± 2§	35% ± 9§	60% ± 17‡
	30			0.3% ± 0.1§
Dizocilpine	0.01			129% ± 15
	0.03	0.04% ± 0.02	83% ± 10	156% ± 22‡
	0.06			127% ± 12
	0.10	0.11% ± 0.05	72% ± 13	88% ± 11
	0.18	49.0% ± 11§	14% ± 2§	29% ± 10‡
	0.3	—	0.7% ± 0.2§	
PCP	0.1			120% ± 9
	0.3			143% ± 13‡
	1.0	0.1% ± 0.1	83% ± 10	110% ± 23
	1.8	57.0% ± 25‡	54% ± 16	73% ± 19
	3.0	87.0% ± 7§	13% ± 9§	17% ± 6§
	5.6	—	0.6% ± 0.4§	
$MgCl_2$	10	0.16% ± 0.1	92% ± 4	
	30	10% ± 9	87% ± 9	117% ± 8
	100	0.5% ± 0.04	67% ± 6‡	142% ± 19‡
	178			82% ± 14
	300	46.0% ± 29‡	29% ± 9§	64% ± 22
	560			7% ± 3§
CGP 37849	3.0	0.2% ± 0.2	86% ± 8	
	10	27.0% ± 8	6% ± 4§	
	18	48.0% ± 10§	2% ± 1§	
NPC 17742	0.3			123% ± 8
	1.0			142% ± 5‡
	3.0	33.0% ± 32	54% ± 25	111% ± 8
	10	33.0% ± 33	49% ± 29	79% ± 4
	18	43.0% ± 29	15% ± 7§	63% ± 11‡
	30			20% ± 3§

*Values (expressed in percent cocaine-appropriate responses and percent of control responses per second) are means ± SEM determined in four rats, except for NPC 17742 ($n = 3$). The control rate of FR responding was 1.32 ± 0.16 responses per second.

†Values (expressed in percent baseline responses per second) are means ± SEM determined in four rats. The control rate of FI responding was 0.57 ± 0.1 responses per second.

‡$p < 0.05$ and §$p < 0.01$ compared to vehicle control value.

creases in the percentage of cocaine-appropriate responses that differed significantly from saline after one or more doses. As shown in Table 1, the maximum average percentages of cocaine-appropriate responses reached 49% after 0.18 mg/kg dizocilpine ($p < 0.01$), 87% after 3.0 mg/kg PCP ($p < 0.01$), and 46% after 300 mg/kg $MgCl_2$ ($p < 0.05$). All three NMDA-associated ion channel blockers produced significant decreases in FR response rate after the two highest doses ($p < 0.05$ or 0.01).

The competitive NMDA antagonist CGP 37849 also engendered significant increases in the percentage of cocaine-appropriate responses (Table 1), with a maximum average of 48% after 18 mg/kg ($p < 0.01$). NPC 17742, on the other hand, did not engender statistically significant changes in the percentage of cocaine-appropriate responses, although it did engender a maximum average of 43% cocaine-appropriate responses after 18 mg/kg. Both competitive NMDA antagonists produced significant decreases in FR response rate after one or more doses ($p < 0.01$).

Effects of cocaine combined with NMDA antagonists

For all drugs studied, analyses of the percentage of cocaine-appropriate responses revealed significant main effects for the dose factor ($p < 0.001$), but not for the pretreatment factor. Drugs did differ with respect to their interaction effects with cocaine. The interactions were significant between dose of cocaine and dizocilpine pretreatment, $F(4, 12) = 17.6$, $p < 0.001$, $MgCl_2$ pretreatment, $F(4, 12) = 4.08$, $p < 0.026$, and PCP pretreatment, $F(4,12) = 3.50$, $p < 0.041$. As suggested by significant decreases in the slope of the cocaine dose–response curve after both dizocilpine, $t(28) = 2.63$, $p < 0.05$, and $MgCl_2$, $t(28) = 2.05$, $p < 0.05$, the predominant effect of these two agents on the percentage of cocaine-appropriate responses was to flatten the cocaine dose–response curve (Figs. 1 and 2 , left panels). The predominant effect of PCP was to nominally shift the cocaine dose–response curve to the left (Fig. 3 , left panel). Specifically, pretreatment with dizocilpine, $MgCl_2$ and PCP produced significant, $p < 0.05$, increases in the percentage of cocaine-appropriate responses after 1.0 mg/kg cocaine compared to this dose of cocaine alone. The increase was additive for $MgCl_2$ ($p < 0.01$) and infra-additive for dizocilpine and PCP. In addition, dizocilpine pretreatment significantly decreased the percentage of cocaine-appropriate responses after 3.0 and 10 mg/kg cocaine ($p < 0.05$) and $MgCl_2$ pretreatment significantly decreased the percentage of cocaine-appropriate responses after 3.0 and 5.0 mg/kg cocaine ($p < 0.05$). In contrast to dizocilpine and $MgCl_2$, PCP pretreatment produced no significant changes in the percentage of cocaine-appropriate responses after doses $\geq$ 3.0 mg/kg cocaine, the slope of the dose–response curve, or the ED_{50} value (0.71 mg/kg, 95% CI = 0.63–13.2). Pretreatment with the competitive NMDA antagonists NPC 17742 and CGP 37849 did not modify the percentage of cocaine-appropriate responses after any dose of cocaine (Figs. 4 and 5, left panel), the slope of the dose–response curves or the ED_{50} values (1.41 mg/kg for NPC 17742 pretreatment, 95% CI = 1.05–3.72; 0.78 mg/kg for CGP 37849 pretreatment, 95% CI = 0.72–10.72).

For all drugs studied, except NPC 17742, analyses of FR response rates revealed significant main effects for the dose factor ($p < 0.02$). The pretreatment factor was significant in experiments involving dizocilpine and CGP 37849 ($p < 0.005$). For the interaction effect, FR responses rates (Figs. 1–5, middle panels) associated with the different doses of cocaine varied as a function of pretreatment with dizocilpine, $F(4, 12) = 9.7$, $p < 0.001$, PCP, $F(4, 12) = 4.57$, $p < 0.016$, CGP 37849, $F(4, 12) = 12.9$, $p < 0.001$, and NPC 17742, $F(4, 8) = 6.7$, $p < 0.011$. Following 0.18 mg/kg dizocilpine and 10 mg/kg CGP 37849 pretreatments, response rates were significantly lower, $p < 0.05$, than each dose of cocaine alone. Following 1.8 mg/kg PCP pretreatment, the response rate associated with 1 mg/kg cocaine was significantly decreased, $p < 0.05$, and following 10 mg/kg NPC 17742 pretreatment, the rate-decreasing effect of 10 mg/kg cocaine was completely attenuated, $p < 0.05$. Pretreatment with 30 mg/kg $MgCl_2$ did not further modify the rate-decreasing effects of cocaine.

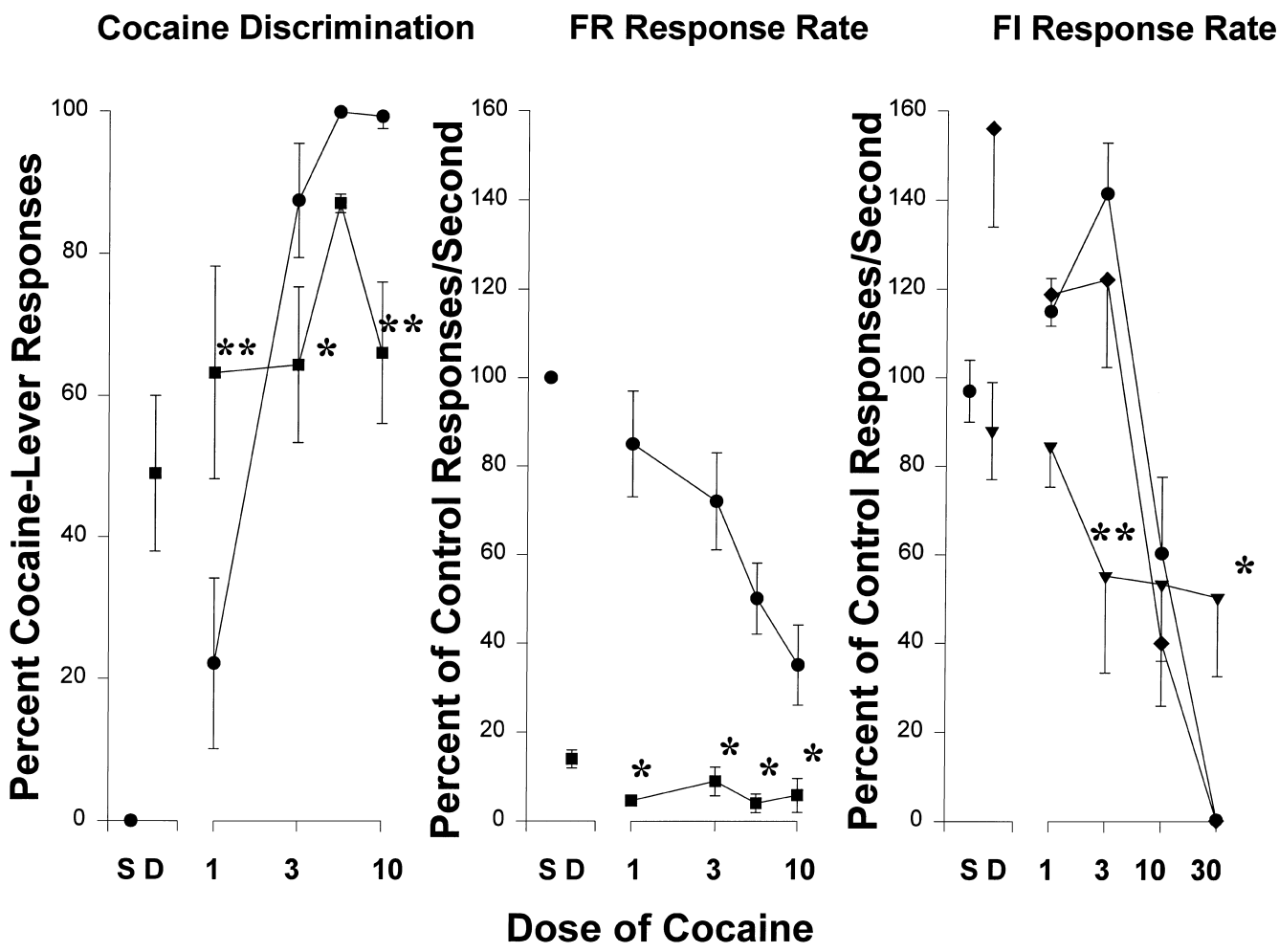

FIG. 1. Effects of dizocilpine (D) pretreatment on cocaine-appropriate responses (left panel; symbols: ● cocaine alone and ■ cocaine + 0.18 mg/kg dizocilpine), FR response rates (middle panel; symbols: ● cocaine alone and ■ cocaine + 0.18 mg/kg dizocilpine), and FI response rates (right panel; symbols: ● cocaine alone, ◆ cocaine + 0.03 mg/kg dizocilpine, and ▼ cocaine + 0.1 mg/kg dizocilpine). Abscissae: dose, log scale; ordinates: percentages of responses. Points are based on four rats. Vertical lines show ± SEM. Points above S show the effects of saline. $*p < 0.05$ and $**p < 0.01$.

Fixed-Interval Schedule-Controlled Behavior

Control performances and effects of cocaine. During noninjection control sessions, rates of responding averaged 0.60 ± 0.1 responses per second for the group of four rats. Administration of saline had no systematic effect on the rate of responding, which averaged 0.57 ± 0.1 responses/s (97% of the noninjection control rate). Baseline rates of responding were, therefore, consistently maintained over the course of the study with various drugs.

Administration of cocaine altered response rate as a bitonic function of dose (Table 1). Responding reached an average maximum increase of 142% of control, $p < 0.05$, after a dose of 3.0 mg/kg. Decreases in responding were observed following 10.0, $p < 0.05$, and 30.0, $p < 0.01$, mg/kg doses of cocaine.

Effects of NMDA antagonists. Administration of dizocilpine, PCP, $MgCl_2$, and NPC 17742 each altered response rate as a bitonic function of dose (Table 1). Responding reached average maximum increases of 142–156% of control, $p < 0.05$, after intermediate doses of 0.03 mg/kg dizocilpine, 0.3 mg/kg PCP, 100 mg/kg $MgCl_2$, and 1.0 mg/kg NPC 17742. Significant, $p < 0.05$ or 0.01, decreases in responding were observed following higher doses of 0.18 mg/kg dizocilpine, 3.0 mg/kg PCP, 560 mg/kg $MgCl_2$, and 18.0 and 30.0 mg/kg NPC 17742.

Effects of cocaine combined with NMDA antagonists. For all drugs studied, analyses of the percentage of control responses revealed significant main effects for the dose factor ($p < 0.01$), but not for the pretreatment factor, except for NPC 17742 ($p < 0.005$). Interaction effects were significant for dizocilpine, $F(8, 24) = 6.0$, $p < 0.001$, $MgCl_2$, $F(8, 24) = 2.5$, $p < 0.039$, PCP, $F(8, 24) = 4.0$, $p < 0.004$, and NPC 17742, $F(8, 24) = 8.8$, $p < 0.001$. Most importantly, as shown in the right panels of Figs. 1–4, an incomplete, but significant, attenuation of the rate-decreasing effects of the highest dose of cocaine (30 mg/kg) was observed only following 0.1 mg/kg dizocilpine and 100 mg/kg $MgCl_2$ pretreatments, $p < 0.05$. Additionally, each of the NMDA antagonists attenuated, in a dose-related manner, the rate-increasing effects of cocaine. Dunnett's comparisons revealed that the effects of 3 mg/kg cocaine, which normally produced the maximal increase in response rate, were completely attenuated, $p < 0.05$ or 0.01, following 0.1 mg/kg dizocilpine, 178 mg/kg $MgCl_2$ and 1.8 mg/kg PCP. Doses of 0.3 mg/kg PCP or 1.0 and 10.0

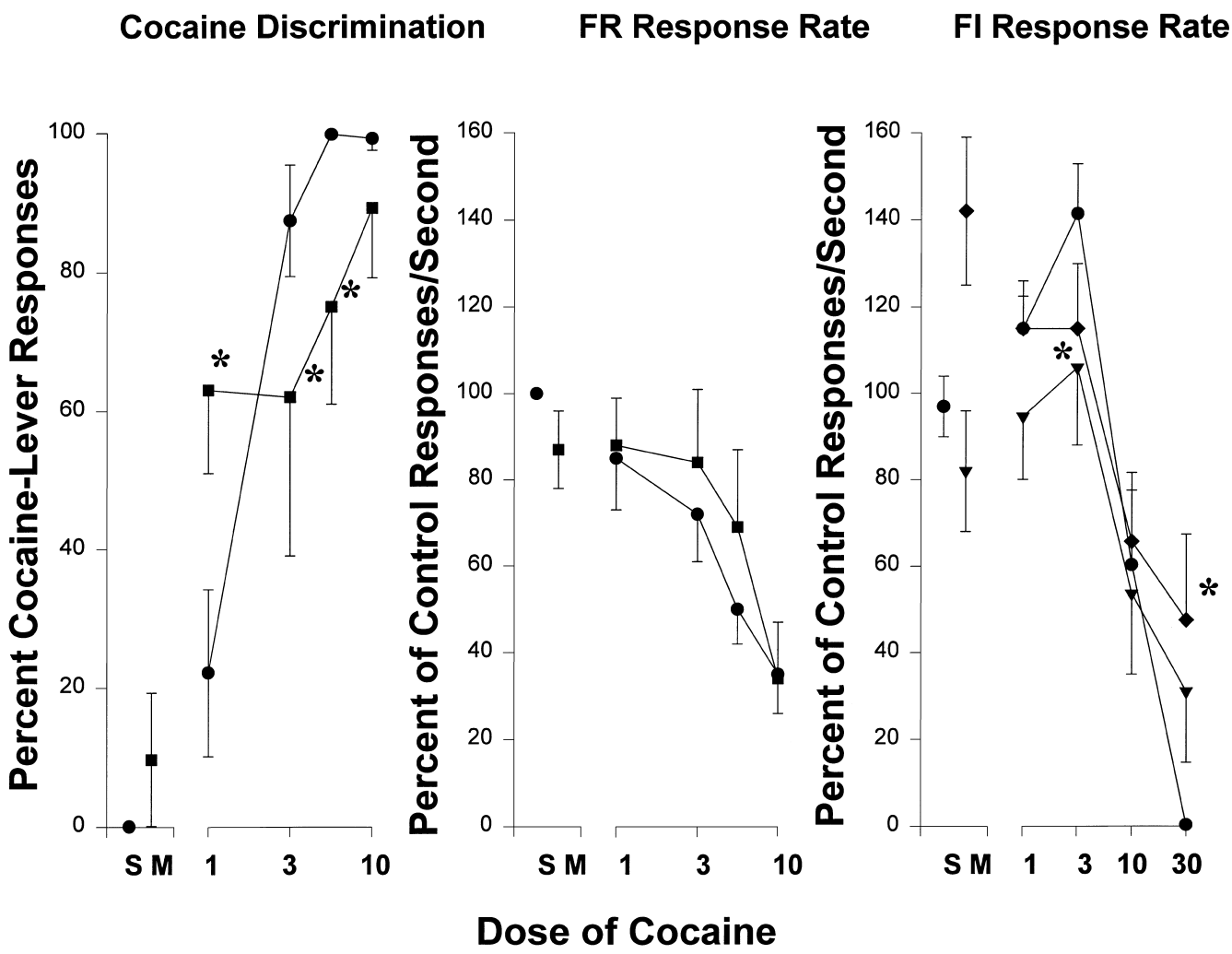

FIG. 2. Effects of $MgCl_2$ (M) pretreatment on cocaine-appropriate responses (left panel; symbols: ● cocaine alone and ■ cocaine + 30 mg/kg $MgCl_2$), FR response rates (middle panel; symbols: ● cocaine alone and ■ cocaine + 30 mg/kg $MgCl_2$), and FI response rates (right panel; symbols: ● cocaine alone, ◆ cocaine + 100 mg/kg $MgCl_2$, and ▼ cocaine + 178 mg/kg $MgCl_2$). Other details are as in Fig. 1.

mg/kg NPC 17742 also completely attenuated the rate-increasing effects of 3.0 mg/kg cocaine, but response rates were more greatly reduced than with the test drug dose alone, $p < 0.01$. Additionally, the slope was significantly decreased after 0.1 mg/kg dizocilpine pretreatment, $t(28) = 3.2, p < 0.01$.

DISCUSSION

The results of the present study demonstrated that the 5 mg/kg training dose of cocaine was functionally intermediate to those previously used to examine the effects of NMDA antagonists and other drugs in rats discriminating different doses of cocaine (33,62). In substitution tests, the NMDA-associated ion channel blockers dizocilpine, $MgCl_2$ and PCP engendered intermediate levels of cocaine-appropriate responses ranging from 46 to 87%. Under a 10 mg/kg training dose condition, these same drugs only engendered 4 to 33% cocaine-appropriate responses, while under a 2 mg/kg training dose condition, cocaine-appropriate responses ranged from 73 to 96% (33). These findings further support the view that the cocaine-like DS effects of the NMDA-associated channel blockers are cocaine training dose dependent. In contrast, training dose dependency was not apparent for the competitive NMDA antagonists. Across a range of training doses of cocaine (2, 5 and 10 mg/kg), NPC 17742 and/or CGP 37849 consistently engendered between 37 and 48% cocaine-appropriate responses [present findings; (33)].

Further distinctions between the effects of competitive NMDA antagonists and NMDA-associated ion channel blockers were apparent in drug discrimination pretreatment studies. Pretreatment with the competitive NMDA antagonists NPC 17742 and CGP 37849 did not modify the cocaine dose–response curve. In contrast, pretreatment with the NMDA-associated ion channel blockers dizocilpine, $MgCl_2$, and PCP enhanced the DS effects of 1 mg/kg cocaine. An enhancement of the DS effects of a low dose of cocaine by dizocilpine, $MgCl_2$ and PCP extends the findings that each drug fully substituted for cocaine in the majority of subjects tested under a low-dose (2 mg/kg) training condition (33). Unlike dizocilpine and $MgCl_2$, PCP did not attenuate the DS effects of doses of cocaine $\geq$ 3 mg/kg. The different effects of PCP vs. dizocilpine and $MgCl_2$ on attenuating the DS effects of higher

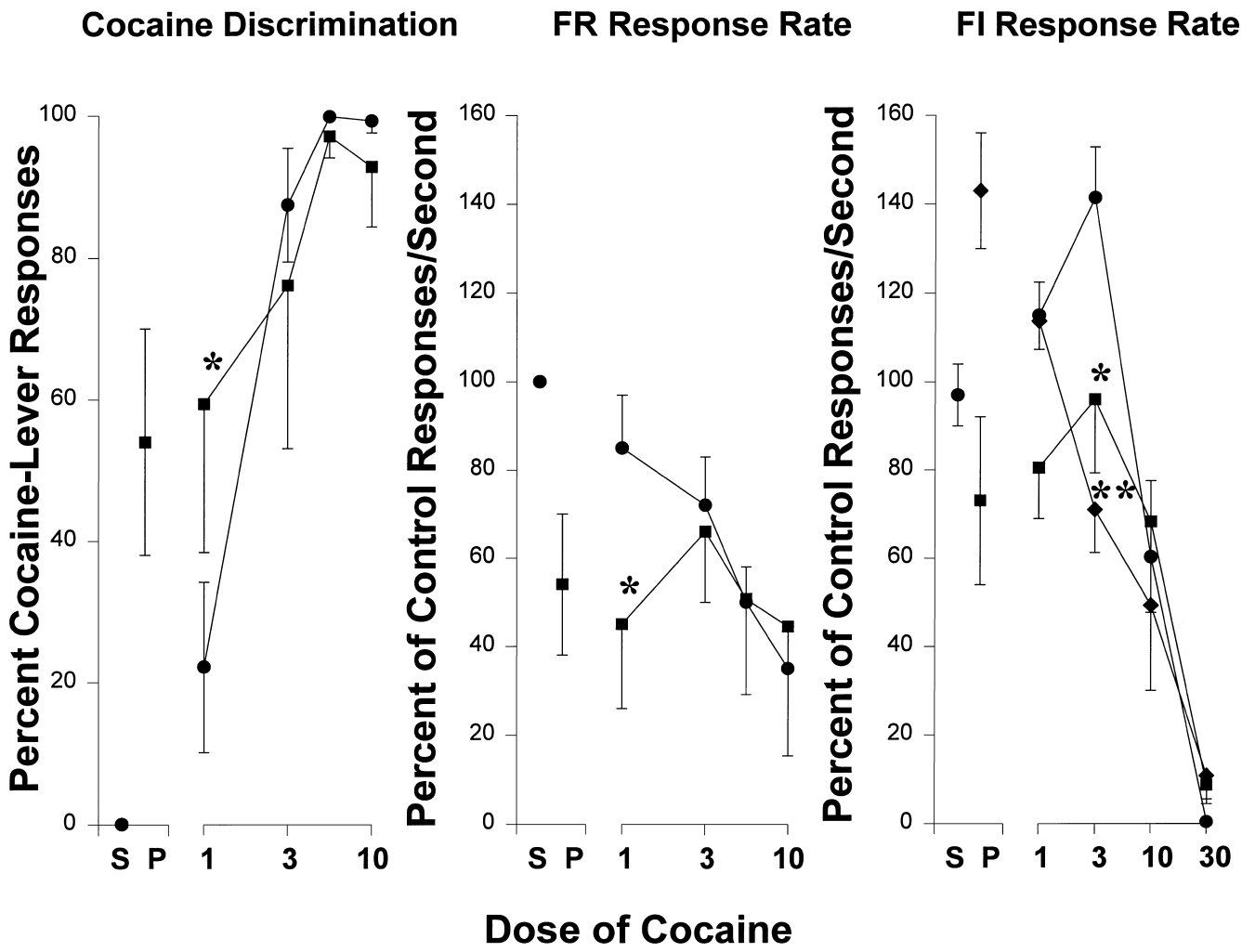

FIG. 3. Effects of PCP (P) pretreatment on cocaine-appropriate responses (left panel; symbols: ● cocaine alone and ■ cocaine + 1.8 mg/kg PCP), FR response rates (middle panel; symbols: ● cocaine alone and ■ cocaine + 1.8 mg/kg PCP), and FI response rates (right panel; symbols: ● cocaine alone, ◆ cocaine + 0.3 mg/kg PCP, and ■ cocaine + 1.8 mg/kg PCP). Other details are as in Fig. 1.

doses of cocaine may be related to the higher potency by which PCP also inhibits DA uptake (IC_{50} = 0.46 μM in striatal tissue) compared to dizocilpine (IC_{50} = 129 μM) and $MgCl_2$ (IC_{50} = 10 mM) (1,55). Because the IC_{50} for striatal DA uptake inhibition by cocaine is approximately 0.4 μM (27), PCP might remain more cocaine-like than dizocilpine and $MgCl_2$, and with increasing doses of cocaine, continue to act synergistically and not block its effects. This possibility is supported by the substitution tests in the present study showing that PCP engendered more cocaine-appropriate responses (87%) than either dizocilpine (49%) or $MgCl_2$ (46%). However, it should be noted that in another cocaine discrimination study using different training dose and testing conditions, the majority of rats (five out of seven) selected the cocaine-appropriate lever after injections of PCP, while the all rats (seven out of seven) selected the cocaine-appropriate lever after injections of dizocilpine (40). Although these findings suggest that DA uptake inhibition may not play a more prominent role in the cocaine substitution effects of PCP vs. dizocilpine, it may still be important for explaining the interaction effects between PCP and cocaine vs. other NMDA-associated ion channel blockers and cocaine. One factor-limiting interpretation of this difference among NMDA-associated ion channel blockers is that only a single dose of each drug was used in combination with cocaine. Although a higher pretreatment dose of PCP might reveal an effect consistent with dizocilpine and $MgCl_2$, the results reported in Table 1 show that there would be a very narrow range of relevant doses to use because 5.6 mg/kg PCP eliminates responding. Pretreatment with 3.0 mg/kg PCP would be an appropriate dose to evaluate in this regard.

Additional drug discrimination pretreatment studies should be conducted to include other doses of the various drugs used in this study to verify the observed differences on the DS effects of cocaine. The importance of conducting those studies lies in the fact that there were no systematic effects among subclasses of NMDA antagonists on altering the rate-decreasing effects of cocaine under the FR schedule. This is most likely related to the particular doses selected to use in combination with cocaine. It should further be noted that the selected dose of dizocilpine (0.18 mg/kg) was so rate suppressing that the modulation of the DS effects of cocaine by dizocilpine may not be meaningful. A case could be made,

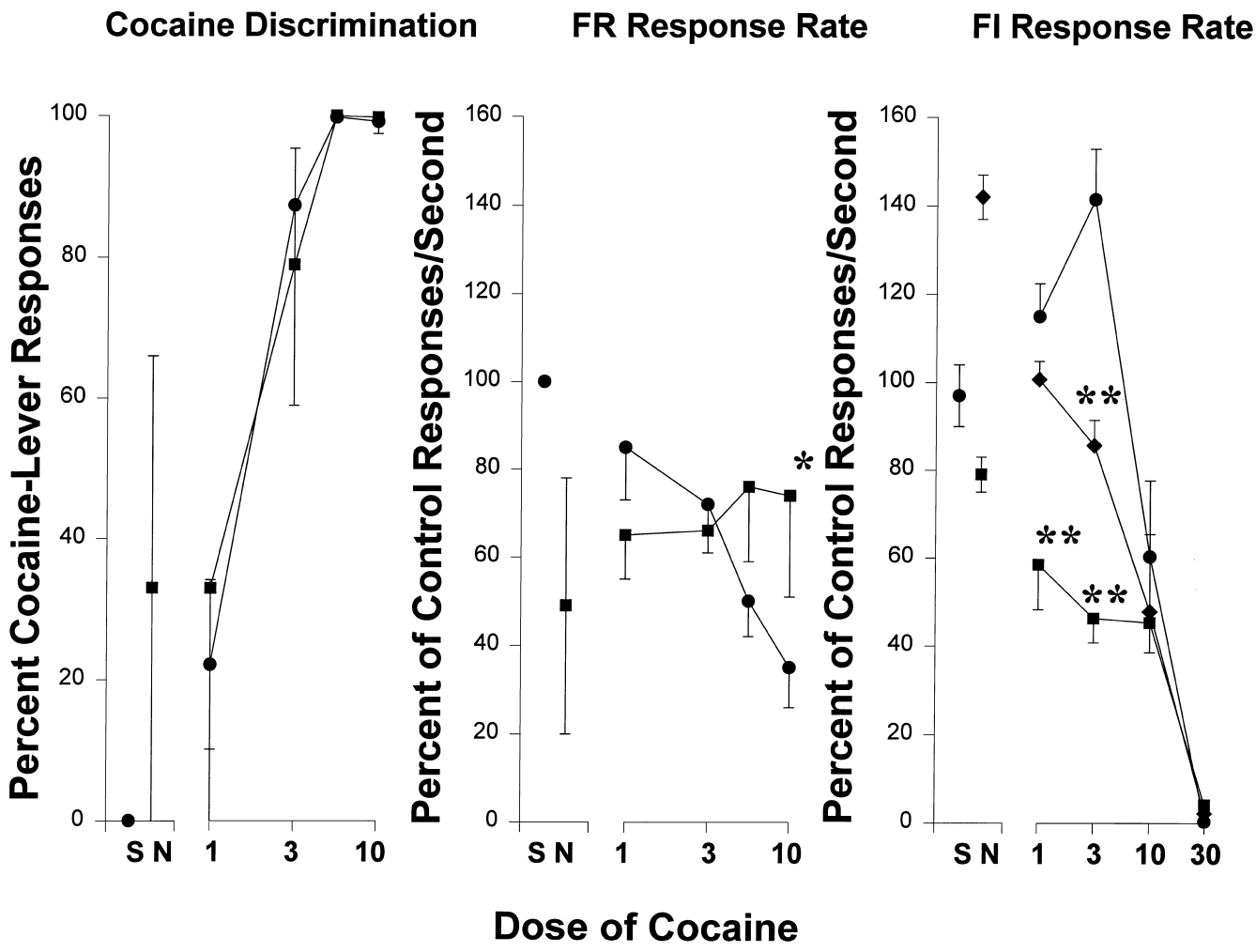

FIG. 4. Effects of NPC 17742 (N) pretreatment on cocaine-appropriate responses (left panel; symbols: ● cocaine alone and ■ cocaine + 10 mg/kg NPC 17742), FR response rates (middle panel; symbols: ● cocaine alone and ■ cocaine + 10 mg/kg NPC 17742), and FI response rates (right panel; symbols: ● cocaine alone, ◆ cocaine + 1.0 mg/kg NPC 17742, and ■ cocaine + 10 mg/kg NPC 17742). Points are based on three rats. Other details are as in Fig. 1.

however, that this effect was meaningful because a comparable rate-suppressing dose of CGP 37849 (10 mg/kg) did not modify the DS effects of any dose of cocaine and a nonrate-suppressing dose of $MgCl_2$ (30 mg/kg) modified the DS effects of cocaine in a manner similar to dizocilpine. The rate-decreasing effects of cocaine were minimally affected by PCP and NPC 17742, yet they modified the DS effects of cocaine differently. Thus, there was no relationship between the way the DS effects of cocaine were modified and the way FR response rates were modified in this study. However, there does appear to be pharmacological specificity to the rate-decreasing effects of these drugs. NPC 17742 was less potent than CGP 37849, and PCP was less potent than dizocilpine in decreasing the FR response rate, as would be expected from previous NMDA receptor binding studies and behavioral studies (17,24,40,70).

An alternative interpretation for the attenuating effects of dizocilpine and $MgCl_2$ pretreatments is that these drugs were producing a perceptual masking, rather than pharmacological antagonism, of the DS effects of higher doses of cocaine. Masking, or the obscuring of one drug stimulus by another (19,71), would yield randomly distributed lever responses and incomplete attenuation of the DS effects without concomitant attenuation of the rate-altering effects; pharmacological antagonism would attenuate both the DS effects and response rate in a surmountable manner [e.g. (58)] In the present study, the percentage of cocaine-lever responses was statistically the same after the combination of dizocilpine with 1, 3, and 10 mg/kg cocaine (values ranged from 63 to 66%) and after the combination of $MgCl_2$ with 1, 3, and 5 mg/kg cocaine (values ranged from 63 to 75%). These findings do show near-randomly distributed lever responses across a range of doses of cocaine. Furthermore, neither dizocilpine nor $MgCl_2$ attenuated the rate-decreasing effects of cocaine obtained under the FR schedule of food presentation. Clearly, additional studies are required to explain the different effects of PCP vs. dizocilpine and $MgCl_2$ on the DS effects of higher doses of cocaine.

Within the framework of the present investigation, response rate data obtained under the FI schedule of food presentation suggest that dizocilpine and $MgCl_2$ can antagonize the effects of a high dose of cocaine. Under a FI schedule of food presentation, an increase in low rates of responding produced by a high dose of 30 mg/kg cocaine was only achieved by dizocilpine and $MgCl_2$. Clearly, simple additivity of the

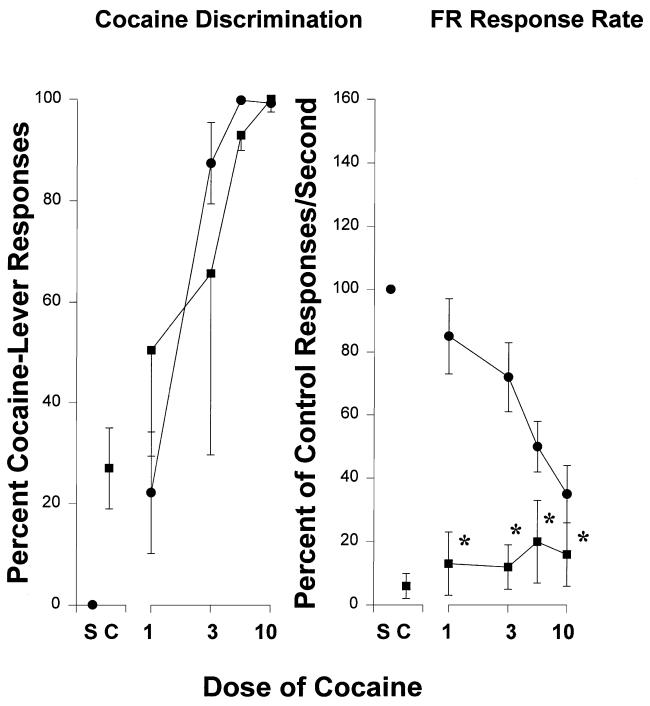

FIG. 5. Effects of CGP 37849 (C) pretreatment on cocaine-appropriate responses (left panel; symbols: ● cocaine alone and ■ cocaine + 10 mg/kg CGP 37849) and FR response rates (right panel; symbols: ● cocaine alone and ■ cocaine + 10 mg/kg CGP 37849). Other details are as in Fig. 1.

rate effects of dizocilpine and $MgCl_2$ cannot account for the increase in low rates of responding produced by 30 mg/kg cocaine because, at least in the case of dizocilpine, this effect was achieved with a moderate rate-decreasing dose. A rate-increasing dose of $MgCl_2$ did attenuate the rate-decreasing effects of 30 mg/kg cocaine; thus $MgCl_2$ may be increasing the low rate of responding produced by cocaine via additivity of their rate effects. However, rate-increasing doses of dizocilpine, PCP, and NPC 17742 failed to modify responding suppressed by 30 mg/kg cocaine, making this explanation less plausible. It is more likely that these findings reflect some degree of pharmacological blockade of the effects of a high dose of cocaine by dizocilpine and $MgCl_2$. In this regard, several other studies have shown various degrees of blockade of the behavioral and physiological effects of cocaine by dizocilpine [e.g. (7,36,53,54)]and $MgCl_2$ [e.g. (21,31,32)]. Perhaps most relevant to the present study are the findings showing that $MgCl_2$ increased the low rates of responding produced by a high dose of cocaine in squirrel monkeys responding under a FI schedule of food presentation (31). It should also be noted that the acute behavioral effects of cocaine are sometimes enhanced by dizocilpine or $MgCl_2$ pretreatment [e.g. (30,69)]. Furthermore, it has been shown that $MgCl_2$ and dizocilpine can have effects in common with cocaine [e.g. (11,34,44,45)]. Thus, the pharmacological interactions between cocaine and dizocilpine or $MgCl_2$ are complex and the direction of change may depend on factors such as dose of cocaine and the nature of the task.

In addition to the distinctions among NMDA antagonists noted above, some similar behavioral effects were observed as well. Although FR response rates from the drug discrimination study and FI response rates from the schedule-controlled behavior study were not obtained in exactly parallel experiments, their comparison revealed that dizocilpine, MgCl2, PCP, and NPC 17742 produced either rate-dependent or schedule-dependent effects. Each NMDA antagonist produced an inverted [U]-shaped dose–response curve for responding maintained by the FI schedule of food presentation; rate-increasing, followed by rate-decreasing effects were measured after escalating doses of each drug. Rate-increasing doses of each NMDA antagonist produced either no change or rate-decreasing effects under the FR schedule of food presentation, thus demonstrating possible rate-dependent or schedule-dependent effects of these drugs. Similar effects of dizocilpine and PCP have been reported previously by Balster and Chait (2) and Genovese and Lu (20), and the present results extend these findings to other NMDA antagonists.

Another common effect of all four NMDA antagonists was that they dose dependently attenuated the rate-increasing effects of 3.0 mg/kg cocaine under the FI schedule of food presentation. One possibility is that the attenuation of the rate-increasing effects of cocaine may reflect a simple additivity of the rate effects of these drugs with cocaine. An additivity of the rate effects of dizocilpine, $MgCl_2$, PCP, or NPC 17742 with those of cocaine could at most explain the attenuation of the rate-increasing effects of 3.0 mg/kg cocaine by the moderate rate-decreasing doses of each NMDA antagonist, but could not explain the similar effect produced by the lower rate-increasing doses. Other possibilities are that the attenuation of the rate-increasing effects of cocaine could have resulted from either pharmacological enhancement or antagonism of cocaine by these drugs. Whichever the case, both competitive and noncompetitive NMDA antagonists appear to blunt the psychomotor stimulant effect of cocaine, which may have bearing on their ability to block the toxic and sensitizing effects of cocaine (21,26,36,53,65). However, the overall pattern of effects for NMDA antagonists suggests that these drugs were not acting solely to either pharmacologically block or enhance the rate-altering effects of cocaine (4,5,56,57). When the results of both the drug discrimination and fixed-interval schedule-controlled behavior studies are viewed together, even though doses differed in the two procedures, it appears that some NMDA antagonists (specifically dizocilpine and $MgCl_2$) may concurrently enhance and block the DS and rate-altering effects of cocaine, while other NMDA antagonists (specifically PCP, NPC 17742, and CGP 37849) are less consistent in this regard. The type of pharmacological interaction shown by dizocilpine and $MgCl_2$ is not unique; it resembles the way partial agonists modify the DS effects of a full agonist [e.g., (8,10,13,14,47,48).

Although the mechanism(s) by which dizocilpine and $MgCl_2$ exert their influence on cocaine are not clear at this time, studies have shown that perfusion with dizocilpine can increase the release of DA above basal (nonstimulated) concentrations in the nucleus accumbens and/or caudate nucleus (6,23,25) and that Mg^2+ can enhance the nonvesicular release of DA, which involves a reversal of the high-affinity DA transporter, as well as augment amphetamine-induced DA release (46). Other studies have reported that both dizocilpine and Mg^2+ inhibit glutamate- or NMDA-stimulated DA release (29,43,67). Thus, under some conditions, dizocilpine and $MgCl_2$ can indirectly enhance DA neurotransmission, and under other conditions they can indirectly block DA neurotransmission. The different effects on DA neurotransmission may reflect the three different modes of interaction (presynaptic facilatory, presynaptic inhibitory postsynaptic) that exist between glutamatergic and dopaminergic neurons (43,64,66).

In conclusion, the present study has demonstrated that in

contrast to some similar behavioral effects of NMDA-associated ion channel blockers and competitive NMDA antagonists when they are administered alone, there are important differences in the way they modify the behavioral effects of cocaine. If it can be conclusively determined that certain NMDA-associated ion channel blockers can enhance and block the effects of cocaine, then some agents from this class of compounds might modify the effects of cocaine relevant to counteracting its abuse and/or toxicity through an indirect mechanism. Development of agents from this class of compounds might include novel drugs acting at NMDA-associated ion channel target sites as well as additional target sites for noncompetitive NMDA antagonism such as glycine, polyamine, and nitric oxide synthase sites.

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