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Tolerance and Sensitization to the Behavioral Effects of Cocaine in Rats: Relationship to Benzodiazepine Receptors

N. E. GOEDERS,[1] B. D. IRBY, C. C. SHUSTER AND G. F. GUERIN

Departments of Pharmacology and Therapeutics and Psychiatry, Louisiana State University Medical Center, Shreveport, LA 71130-3932

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GOEDERS, N. E., B. D. IRBY, C. C. SHUSTER AND G. F. GUERIN. *Tolerance and sensitization to the behavioral effects of cocaine in rats: Relationship to benzodiazepine receptors.* PHARMACOL BIOCHEM BEHAV **57**(1/2) 43–56, 1997.—Tolerance and sensitization to the behavioral effects of cocaine were investigated in rats responding under a fixed-consecutive-number eight schedule of food reinforcement. The development of tolerance or sensitization was induced by delivering the drug either immediately before or after each behavioral session during chronic administration. Chronic cocaine administered before each session resulted in tolerance, as indicated by the shift to the right in the cocaine dose–response curve. This tolerance was more likely to develop in the presence of an external discriminative stimulus. On the other hand, when cocaine was delivered after each session, the injections did not disrupt responding and sensitization or increased sensitivity rather than tolerance developed. This sensitization was more likely to occur when the external discriminative stimulus was not present. These data suggest that either tolerance or sensitization to the behavioral effects of cocaine can occur following the same number of chronic injections, with the effect dependent on the context under which the drug is delivered. Significant differences in benzodiazepine receptor binding measured autoradiographically using [^{3}H]flumazenil were observed between rats that received cocaine before or after each session, suggesting that the development of tolerance and sensitization may be mediated through changes in benzodiazepine receptors in discrete brain regions. © 1997 Elsevier Science Inc.

Cocaine Tolerance Sensitization Fixed-consecutive-number Schedule-controlled behavior Benzodiazepine receptors Autoradiography

A variety of clinical and animal data suggest that repeated exposure to cocaine and other psychomotor stimulants can result in marked changes in the behavioral responses to the drug. These changes can be assessed in the laboratory by generating dose–response relationships. Sensitization or reverse tolerance is defined as a shift to the left in the dose–response gradient, with lower doses of the drug producing effects previously observed following a single acute administration of higher doses of the drug (7). On the other hand, tolerance can be demonstrated by a shift to the right in the dose–response gradient, suggesting that a higher dose is required to reinstate the acute responses to the drug. However, these apparently opposite behavioral actions can sometimes result from similar chronic dosing schedules, with the effect dependent on the behavior under observation. Important factors related to the generation of sensitization include both the time interval between chronic injections and the environmental context (36,37,39). The development of either tolerance or sensitization with chronic stimulant administration also depends on whether the drug-induced behavioral changes produce a loss of reinforcement (48) and on the degree of control exerted by environmental stimuli over the behavior (10).

The fixed-consecutive-number (FCN) schedule of reinforcement has proven useful for investigating the involvement of external (i.e., environmental) discriminative stimuli in the behavioral effects of drugs (41). Under this schedule, a minimum number of consecutive responses (e.g., eight) on one lever (i.e., work operandum) is required before a single response on a second lever (i.e., reinforcement operandum) is reinforced (31). Responding on the second lever before the

[1]Requests for reprints should be addressed to N. E. Goeders, Department of Pharmacology and Therapeutics, Louisiana State University Medical Center, P.O. Box 33932, Shreveport, LA 71130-3932.

minimum number of responses on the first lever is made resets the response requirement. Two primary variations of the FCN schedule have been investigated (27,56). Under the first variant of the schedule (FCN-S^D), an external discriminative stimulus is presented following the completion of the required number of consecutive responses on the work lever, while under the second variant of the schedule (FCN), there is no programmed presentation of an external stimulus. Although the response requirement is the same under both variations of the schedule, responding under one version (FCN-S^D) is controlled by an external discriminative stimulus, while responding under the other (FCN) is under internal discriminative control. Comparable rates of responding are typically engendered under both of these modifications of the schedule (27). However, accuracy (i.e., the percentage of consecutive responses resulting in reinforcer presentation) and efficiency (i.e., emitting just the required minimum number of responses on the work lever before switching to the reinforcement lever) are both enhanced in the FCN-S^D version of the schedule when compared to the FCN schedule without an added external discriminative stimulus (27), suggesting increased stimulus control under the FCN-S^D variant. Therefore, the role of the environment (i.e., the presentation of an external discriminative stimulus) on the development of behavioral tolerance or sensitization can be determined by comparing the effects of drugs under these two variations of the schedule.

While initial cocaine use has been reported by humans to produce profound subjective feelings of well-being and a decrease in anxiety (12,13), major symptoms associated with withdrawal often include severe anxiety, restlessness, and agitation (9,13,53). The drug has even been reported to precipitate episodes of panic attack in neurobiologically vulnerable individuals (1,2,57). Benzodiazepines (e.g., intravenous diazepam) are also often used in the emergency room for the treatment of convulsions that may become manifest following an acute cocaine overdose (14,53), suggesting that anxiety and related effects at benzodiazepine receptors may be involved in the etiology and neurobiology of cocaine use and withdrawal in humans. Preclinical data from our laboratory have also suggested a potential involvement of benzodiazepines in some of the behavioral and neurobiologic effects of cocaine in rats. Chronic cocaine administration [20 or 40 mg/kg, intraperitoneally (IP)] for 15 days resulted in differential effects on benzodiazepine receptor binding in various regions of the rat brain (16,17), which were mediated in part through a dopaminergic mechanism. Benzodiazepine receptor binding was also compared between animals that self-administered cocaine and animals that received simultaneous, yoked infusions of cocaine or saline to determine the potential involvement of these receptor systems in cocaine reinforcement (18). Benzodiazepine receptor binding was significantly altered in "reinforcement-relevant" brain regions associated with ascending dopaminergic systems (e.g., medial prefrontal cortex, nucleus accumbens), suggesting that these effects may be related to cocaine reinforcement. Pretreatment with the benzodiazepine receptor agonists chlordiazepoxide (15) or alprazolam (19) attenuated intravenous cocaine self-administration in rats, possibly by decreasing the reinforcing effects of the drug, while exposure to noncontingent electric foot-shock increased the acquisition of low-dose cocaine self-administration (20). These data suggest that many of the behavioral and neurobiologic effects of cocaine may be mediated, at least in part, through interactions at benzodiazepine receptors.

This study was designed to investigate the effects of acute and chronic cocaine administration in rats on responding maintained under both the FCN-S^D and FCN variants of the schedule described above. The development of tolerance or sensitization to the acute effects of the drug was determined by delivering the drug either immediately before or immediately after each behavioral session during chronic cocaine administration. Animals receiving cocaine before each experimental session were expected to show tolerance to the effects of the drug on schedule-controlled responding, which would be demonstrated by a shift to the right in the dose–response curve. The rats receiving cocaine injections immediately after each session were anticipated to become sensitized to the effects of the drug, with lower doses resulting in increased behavioral responses. The effects of acute and chronic cocaine administration on responding maintained by pigeons under these modifications of the FCN schedule have previously been described (8). However, the effects of cocaine on responding maintained by rats under this schedule have not been reported. In addition, although the effects of pre- and postsession administration of chronic amphetamine on responding maintained under these variations of the FCN schedule have been reported (41), the effects of cocaine have not. Finally, the effects of the different treatment conditions on benzodiazepine receptor binding were also measured, since these receptors appear to be involved in many of the behavioral and neurobiologic effects of cocaine.

METHOD

Subjects

Forty-eight experimentally naive male Wistar rats 90–120 days old at the start of the experiments were used. The animals were housed communally in a temperature- and humidity-controlled, American Association for the Accredidation of Laboratory Animal Care (AAALAC)-accredited animal care facility on a reversed 12 L:12 D cycle until the start of the experimental procedures. At this time, the rats were isolated in individual cages with free access to water. These rats were maintained at 85–90% of their free-feeding body weights by presentations of food pellets (45 mg; Bio-Serve, Frenchtown, NJ) during the behavioral sessions and by supplemental postsession feeding (Purina Rat Chow; Bioserve).

Apparatus

Standard plastic and stainless-steel sound-attenuating operant conditioning chambers (Med-Associates, Inc., St. Albans, VT) were used. Each experimental chamber was equipped with two retractable response levers (Med-Associates, Inc.) mounted on either side of a food pellet dispenser on one wall of the chamber. A stimulus light was located above each response lever, and a houselight was centrally mounted at the top of the opposite wall of the chamber. The chambers were also equipped with an exhaust fan which supplied ventilation and white noise to mask extraneous sounds. An IBM-compatible personal computer and interface system (Med-Associates, Inc.) was used to program the procedure and collect the experimental data.

Behavioral Procedure

The rats were trained to respond under a discrete-trial, fixed-consecutive-number eight schedule of food reinforcement (27,40). Both retractable response levers were extended into the chamber 60 s after the behavioral session was started. During training under the signalled component of the schedule

(FCN-S^D), the light located above the right lever was illuminated as an external discriminative stimulus, and a single response resulted in the delivery of a 45-mg food pellet. Following reinforcer presentation, the stimulus light was extinguished, a houselight was illuminated, and both response levers were retracted for 3 s. Both levers were reextended into the chamber after the timeout, and a new discrete trial was initiated. Each session consisted of 100 trials or 30 min. When the animals were successfully trained to respond on the right lever, sessions began with the illumination of the stimulus light above the left lever. A single response on the left lever extinguished the left stimulus light and illuminated the right stimulus light. A single response on the right lever then resulted in food presentation and the termination of the trial. The response requirement on the left lever was gradually increased to a final value of eight or more consecutive responses. If fewer than the required number of consecutive responses were made on the left lever before the right lever was pressed, both stimulus lights were extinguished without the presentation of the food reinforcer, and the levers were retracted for 3 s. Following this timeout, both levers were extended into the chamber and a new trial was initiated. Once the rats successfully completed the response requirement during $>$ 90% of the trials for five consecutive sessions, the second component of the multiple schedule was introduced. For this unsignalled (FCN) component, all conditions were the same except that the lights above the response levers were extinguished (i.e., the external discriminative stimulus to control the switch from the left to the right lever was no longer present), and the houselight was illuminated to indicate reinforcer availability. During the multiple schedule, 10 trials were conducted during the FCN-S^D component followed by 10 trials under the FCN component of the multiple schedule. The two components alternated in this manner until 50 trials were completed under both components (total 100 trials) or 30 min elapsed. Sessions were conducted 5 days/week.

Pharmacologic Procedure

Once stable baselines of responding under the multiple FCN-S^D/FCN schedule were obtained (approximately 30 sessions), acute dose–response curves were generated in each animal. The rats were injected with cocaine (1, 3, 10, 17, or 30 mg/kg, IP) or saline (1 ml/kg, IP) immediately before the start of the experimental session. Rats were injected on Tuesdays and Fridays provided that responding returned to baseline levels between drug tests. Each dose of cocaine and saline was tested in a random order at least twice in each animal.

When the acute dose–response curves were completed in each animal and stable baselines of responding were again observed, the rats were randomly divided into four equal treatment groups. The rats in the first group received daily injections of saline (1 ml/kg, IP) before each experimental session (saline-before). The rats in the second group were injected with saline after each session (saline-after). The rats in the third group received injections of cocaine (10 mg/kg, IP) immediately before the start of each behavioral session (cocaine-before). The animals in the last group were injected with the same concentration of cocaine immediately after each session (cocaine-after). Although sessions were not conducted on weekends and holidays, all animals were still injected with cocaine or saline, respectively. Following approximately 60 days exposure (8 wk) to chronic cocaine or saline injections, chronic dose–response curves were evaluated in each animal by substituting each dose of cocaine in a random order for presession injections twice per week as described above. On test days, all animals received the test dose of cocaine before the behavioral session and saline (1 ml/kg) after the session. If the test dose was less than the chronic dose of cocaine (i.e., 10 mg/kg), the remainder of the dose was administered immediately after the session. Chronic daily injections of cocaine or saline, administered before or after the behavioral sessions, were continued until the completion of the dose–response curves. Following the completion of the chronic dose–response curves, chronic daily injections of cocaine or saline were discontinued, and the animals were killed and the brains harvested and stored at −70°C for subsequent receptor autoradiography as described below.

Tissue Preparation

Twenty-four hours following the completion of the chronic dose–response curves, all animals were anesthetized with sodium pentobarbital (50 mg/kg, IP) and were perfused via the left ventricle of the heart with 0.9% NaCl, 50 mM sodium phosphate (pH 7.5), followed by 0.3 M sucrose and 50 mM sodium phosphate. The brains were rapidly removed, embedded in brain paste, and frozen onto brass microtome chucks over dry ice. Ten-micrometer coronal sections were cut in a cryostat-microtome (Reichert-Jung, Buffalo, NY), and the sections were thaw-mounted onto chrome-alum/gelatin-subbed slides and stored at −70°C until processed for quantitative autoradiography.

Autoradiography

Benzodiazepine receptors were visualized using [^{3}H]flumazenil under standard autoradiographic conditions (17,59,60). Briefly, slide-mounted tissue sections were incubated for 40 min at 4°C with 2 nM [^{3}H]flumazenil (79.8 Ci/mmol; New England Nuclear, Boston, MA) in 0.17 M Tris-HCl buffer (pH 7.4 at 4°C). Nonspecific binding was estimated by including 1 μM clonazepam in the incubation. Following incubation, the sections were washed for 2 min in ice-cold buffer to reduce nonspecific binding. The slides were briefly dipped in ice-cold distilled water and immediately dried under a stream of cool, dry air. Slides were affixed to mounting board, placed in X-ray cassettes with radioactive standards (Amersham, Buckinghamshire, UK) and apposed to [^{3}H]Ultrofilm (LKB Industries, Gaithersburg, MD). After a 4-wk exposure, the film was developed using previously reported procedures (26,55) and the autoradiograms were quantified using computer-assisted (Loats Associates, Inc., Westminster, MD) microdensitometry (25,26). Brain regions analyzed included: medial prefrontal cortex, sulcal prefrontal cortex, frontal cortex, cortex, nucleus accumbens (rostral and caudal), olfactory tubercle, caudate nucleus (rostral and caudal), globus pallidus, anterior hypothalamus, medial forebrain bundle, thalamus, amygdala, central medial nucleus of the amygdala, substantia nigra, and ventral tegmental area.

Data Analysis

Data collected included the number of reinforced trials, during which the rats pressed the work lever eight or more consecutive times, the overall rates of responding, and the time required to switch to the reinforcement lever following the completion of eight or more consecutive responses on the work lever during both the FCN and FCN-S^D components of the schedule. The time from the delivery of the reinforcer and the end of the time out until a response was made (i.e.,

TABLE 1

EFFECTS OF ACUTE AND CHRONIC COCAINE ADMINISTRATION, DELIVERED BEFORE OR AFTER THE BEHAVIORAL SESSIONS, ON THE NUMBER OF REINFORCED TRIALS (50 MAXIMUM) FOR FIXED-CONSECUTIVE-NUMBER EIGHT FOOD-REINFORCED RESPONDING WITH (FCN-S^D) AND WITHOUT (FCN) AN EXTERNAL DISCRIMINATIVE STIMULUS

	Reinforced Trials							
	Saline Before		Cocaine Before		Saline After		Cocaine After	
Dose	Acute	Chronic	Acute	Chronic	Acute	Chronic	Acute	Chronic
FCN-S^D								
Saline	49.09 ± 0.37	49.40 ± 0.31	48.82 ± 0.42	48.73 ± 0.30	47.90 ± 0.67	49.60 ± 0.16	49.10 ± 0.28	49.30 ± 0.30
1.0	47.58 ± 0.42	49.25 ± 0.30	47.67 ± 0.81	49.00 ± 0.33	49.20 ± 1.26	49.20 ± 0.33	48.78 ± 0.36	42.67 ± 1.92
3.0	42.75 ± 1.91	45.25 ± 1.60	44.36 ± 1.97	49.00 ± 0.26*	46.90 ± 1.38	47.70 ± 0.76	47.44 ± 0.69	42.17 ± 2.66
10	28.09 ± 1.76	33.50 ± 4.18	27.25 ± 2.98	47.22 ± 1.12*	35.78 ± 4.28	30.60 ± 1.83	34.77 ± 3.03	19.71 ± 5.25*
17	18.55 ± 1.30	15.82 ± 5.21	27.00 ± 3.22	46.75 ± 1.88*	22.50 ± 4.56	22.33 ± 1.85	20.33 ± 2.33	6.71 ± 1.13*
30	1.17 ± 0.51	1.27 ± 0.89	3.00 ± 1.61	1.55 ± 1.09	2.22 ± 0.78	4.20 ± 1.33	3.09 ± 1.56	0.64 ± 0.39
FCN								
Saline	44.73 ± 0.87	46.40 ± 0.60	45.64 ± 1.25	48.25 ± 0.84	44.10 ± 1.31	42.40 ± 0.93	42.55 ± 1.68	45.13 ± 0.99
1.0	44.67 ± 0.63	45.92 ± 0.69	45.90 ± 1.23	46.00 ± 1.20	43.60 ± 1.07	43.80 ± 1.17	48.42 ± 0.43	41.58 ± 1.41*
3.0	38.67 ± 1.19	39.08 ± 1.40	39.33 ± 1.94	43.38 ± 1.92	37.80 ± 1.46	39.10 ± 2.30	46.70 ± 0.97	28.67 ± 4.17*
10	19.36 ± 1.71	18.67 ± 1.10	10.10 ± 2.10	28.60 ± 3.85	18.00 ± 2.22	18.70 ± 3.81	31.73 ± 3.22	15.00 ± 2.77*
17	7.27 ± 1.31	8.91 ± 0.94	7.33 ± 1.72	25.29 ± 3.12	6.00 ± 1.26	8.78 ± 1.30	24.27 ± 2.90	6.70 ± 1.26*
30	0.67 ± 0.36	1.82 ± 0.64	1.42 ± 0.90	1.75 ± 1.49	1.22 ± 0.60	1.00 ± 0.70	1.73 ± 0.70	0.73 ± 0.51

Values are the means (±SEM) for double determinations with $n = 12$/treatment condition. Significance of the differences between treatment means was determined with a two-way analysis of variance followed by Student's *t*-tests.

*$p < 0.05$.

postreinforcement pause data) was also collected. Responding less than eight times on the work lever and then responding on the reinforcement lever was recorded as a nonreinforced trial or error. The significance of the differences between treatment means was determined with a two-way analysis of variance (ANOVA) followed by Student's *t*-tests. The autoradiographic data are presented as fentomole per milligram tissue. The significance of the differences between the different treatment conditions was assessed with an ANOVA followed by Student's *t*-tests.

RESULTS

Control Responding

One rat in the saline-after group died unexpectedly before the end of the experiment and was not included in any of the data analyses. Data collected during baseline and vehicle control sessions indicated that there were no significant differences in baseline responding between the four treatment groups in either the FCN-S^D or FCN components of the schedule. Mean accuracy levels (i.e., percent reinforced trials) following vehicle (i.e., saline) administration for the four groups were: saline-before: 98% (range 98–100%); saline-after: 96% (range 86–100%); cocaine-before: 98% (range 92–100%); and cocaine-after: 98% (range 98–100%) during the FCN-S^D component of the schedule. During the FCN component, mean accuracy levels were: saline-before: 90% (range 82–100%); saline-after: 88% (range 72–98%); cocaine-before: 91% (range 74–100%); and cocaine-after: 85% (range of 66–96%). Accuracy levels for each group were consistently higher during the FCN-S^D component compared with the FCN component of the schedule (Table 1). There were no significant differences in response rates between the four treatment groups or between the FCN-S^D and FCN components of the schedule, although response rates were generally slightly reduced during the FCN variant (Table 2). Mean response rates were 64 responses/min (range 58–74) during the FCN-S^D variant and 59 responses/min (range 51–67) during the FCN variant. Switch times (i.e., the time to switch responding from the work to the reinforcement lever) were also not significantly different among the four treatment groups, although there was a slight increase in switch times during the FCN component of the schedule (Table 3). There were also no significant differences in post reinforcement pause times among the four treatment groups (Table 4).

Acute Cocaine Administration

There were no significant differences in the acute cocaine dose–response curves among any of the four treatment groups. There was a main effect of cocaine dose on mean accuracy levels in each of the four treatment groups during the FCN-S^D component [$F(1, 71) = 2.7604$, $p < 0.01$, cocaine-before; $F(1, 71) = 3.4872$, $p < 0.01$), cocaine-after; $F(1, 71) = 5.6683$, $p < 0.01$, saline-before; $F(1, 65) = 15.2393$, $p < 0.01$, saline-after] and the FCN component of the schedule [$F(1, 71) = 3.0146$, $p < 0.01$, cocaine-before; $F(1, 71) = 6.0939$, $p < 0.01$, cocaine-after; $F(1, 71) = 10.4909$, $p < 0.01$, saline-before; $F(1, 65) = 20.6561$, $p < 0.01$, saline-after]. Mean accuracy levels were not affected by the 1.0-mg/kg dose of cocaine under either variant of the schedule (Table 1). The acute administration of the other doses of cocaine resulted in dose-related decreases in accuracy levels during both components of the schedule, although these effects were generally greater during the FCN component. Mean accuracy levels decreased to an average of 93% of saline control, with a range of 87–98% among treatment groups, with the 3.0-mg/kg dose during the FCN-S^D component. Accuracy fell to 65% (range 54–74%), 45% (range 37–55%), and 5% (range 2–6%) of saline control levels at the 10-, 17-, and 30-mg/kg doses, respectively. Accuracy was also decreased to 92% during the FCN component

TABLE 2

EFFECTS OF ACUTE AND CHRONIC COCAINE ADMINISTRATION, DELIVERED BEFORE OR AFTER THE BEHAVIORAL SESSIONS, ON RESPONSE RATES (RESPONSES PER SECOND) FOR FIXED-CONSECUTIVE-NUMBER EIGHT FOOD-REINFORCED RESPONDING WITH (FCN-S^D) AND WITHOUT (FCN) AN EXTERNAL DISCRIMINATIVE STIMULUS

	Response Rate							
	Saline Before		Cocaine Before		Saline After		Cocaine After	
Dose	Acute	Chronic	Acute	Chronic	Acute	Chronic	Acute	Chronic
FCN-S^D								
Saline	1.041 ± 0.056	0.948 ± 0.021	1.239 ± 0.072	1.159 ± 0.080	0.965 ± 0.103	0.976 ± 0.033	1.019 ± 0.063	1.033 ± 0.043
1.0	0.937 ± 0.023	0.923 ± 0.014	1.192 ± 0.071	1.225 ± 0.076	1.095 ± 0.028	1.014 ± 0.023	0.999 ± 0.055	0.978 ± 0.042
3.0	0.904 ± 0.020	0.867 ± 0.020	1.049 ± 0.076	1.078 ± 0.047	0.973 ± 0.046	0.963 ± 0.038	0.916 ± 0.044	0.798 ± 0.015
10	0.463 ± 0.023	0.518 ± 0.086	0.467 ± 0.051	0.845 ± 0.048*	0.596 ± 0.080	0.513 ± 0.046	0.764 ± 0.045	0.334 ± 0.020
17	0.305 ± 0.029	0.238 ± 0.034	0.289 ± 0.047	0.850 ± 0.071*	0.463 ± 0.047	0.352 ± 0.052	0.311 ± 0.023	0.185 ± 0.018
30	0.047 ± 0.015	0.028 ± 0.006	0.017 ± 0.007	0.052 ± 0.029	0.076 ± 0.028	0.125 ± 0.044	0.056 ± 0.019	0.027 ± 0.019
FCN								
Saline	0.864 ± 0.041	0.936 ± 0.032	1.124 ± 0.072	1.199 ± 0.085	1.059 ± 0.034	0.937 ± 0.021	0.964 ± 0.046	1.002 ± 0.051
1.0	0.918 ± 0.025	0.914 ± 0.015	1.219 ± 0.088	1.249 ± 0.084	1.061 ± 0.024	1.017 ± 0.032	0.997 ± 0.084	0.947 ± 0.031
3.0	0.825 ± 0.031	0.815 ± 0.036	0.948 ± 0.060	1.178 ± 0.061*	0.914 ± 0.036	0.951 ± 0.043	0.925 ± 0.122	0.394 ± 0.021
10	0.349 ± 0.023	0.435 ± 0.038	0.363 ± 0.043	0.688 ± 0.053*	0.352 ± 0.047	0.378 ± 0.030	0.504 ± 0.021	0.356 ± 0.056
17	0.203 ± 0.020	0.231 ± 0.076	0.170 ± 0.045	0.710 ± 0.074*	0.257 ± 0.059	0.346 ± 0.029	0.280 ± 0.036	0.219 ± 0.040
30	0.031 ± 0.011	0.008 ± 0.004	0.004 ± 0.003	0.023 ± 0.015	0.018 ± 0.011	0.114 ± 0.054	0.053 ± 0.025	0.006 ± 0.005

Values are the means (±SEM) for double determinations with $n = 12$/treatment condition. Significance of the differences between treatment means was determined with a two-way analysis of variance followed by Student's *t*-tests.

*$p < 0.05$.

TABLE 3

EFFECTS OF ACUTE AND CHRONIC COCAINE ADMINISTRATION, DELIVERED BEFORE OR AFTER THE BEHAVIORAL SESSIONS, ON SWITCH TIMES (SECONDS) FOR FIXED-CONSECUTIVE-NUMBER EIGHT FOOD-REINFORCED RESPONDING WITH (FCN-S^D) AND WITHOUT (FCN) AN EXTERNAL DISCRIMINATIVE STIMULUS

	Switch Time							
	Saline Before		Cocaine Before		Saline After		Cocaine After	
Dose	Acute	Chronic	Acute	Chronic	Acute	Chronic	Acute	Chronic
FCN-S^D								
Saline	2.91 ± 0.53	2.44 ± 0.32	2.23 ± 0.22	2.02 ± 0.34	2.25 ± 0.28	2.31 ± 0.27	2.29 ± .021	2.41 ± 0.20
1.0	2.74 ± 0.45	2.48 ± 0.31	2.60 ± 0.18	1.87 ± 0.30	2.06 ± 0.26	1.93 ± 0.30	2.06 ± 0.15	2.25 ± 0.18
3.0	2.24 ± 0.41	2.36 ± 0.37	2.45 ± 0.36	1.51 ± 0.25	1.89 ± 0.30	1.89 ± 0.22	1.89 ± 0.18	1.59 ± 0.10
10	1.46 ± 0.33	1.71 ± 0.27	1.02 ± 0.10	1.44 ± 0.33	1.27 ± 0.13	1.13 ± 0.08	1.31 ± 0.28	1.79 ± 0.17
17	2.18 ± 0.55	1.52 ± 0.29	1.04 ± 0.08	1.48 ± 0.23	2.12 ± 1.05	1.86 ± 0.57	1.50 ± 0.28	2.45 ± 0.21
30	8.17 ± 0.73	19.11 ± 17.12	11.73 ± 9.61	1.79 ± 0.95	7.77 ± 5.09	5.19 ± 3.32	9.16 ± 1.00	118.25 ± 92.84
FCN								
Saline	3.68 ± 0.53	3.27 ± 0.29	2.52 ± 0.20	2.42 ± 0.37	2.64 ± 0.24	2.52 ± 0.25	2.51 ± 0.16	2.60 ± 0.22
1.0	3.51 ± 0.47	3.78 ± 0.60	3.13 ± 0.27	2.15 ± 0.28*	2.38 ± 0.26	2.34 ± 0.27	2.46 ± 0.15	2.68 ± 0.17
3.0	3.64 ± 0.49	3.36 ± 0.48	3.12 ± 0.30	1.99 ± 0.27*	2.42 ± 0.27	2.51 ± 0.28	2.40 ± 0.14	2.93 ± 0.23
10	4.11 ± 0.75	3.79 ± 0.58	2.24 ± 0.35	1.94 ± 0.27	3.49 ± 0.87	2.98 ± 0.35	3.69 ± 0.40	6.01 ± 0.45
17	3.98 ± 0.95	5.97 ± 1.64	23.56 ± 11.73	2.21 ± 0.33	6.66 ± 2.09	5.29 ± 1.19	11.31 ± 2.74	6.09 ± 0.60
30	8.96 ± 1.37	11.46 ± 5.31	27.60 ± 20.56	2.16 ± 1.22	9.56 ± 1.43	8.73 ± 3.06	7.69 ± 0.36	13.52 ± 4.44

Values are the means (±SEM) for double determinations with $n = 12$/treatment condition. Significance of the differences between treatment means was determined with a two-way analysis of variance followed by Student's *t*-tests.

*$p < 0.05$.

of the schedule with 3.0 mg/kg cocaine. This fell to 45% (range 22–74%), 26% (range 14–57%), and 3% (range 2–4%) of saline control levels at the 10-, 17-, and 30-mg/kg cocaine doses, respectively, during the FCN variant. There was also a main effect of cocaine dose on mean response rates (Table 2) in each of the four treatment groups during the FCN-S^D component [$F(1, 71) = 5.5755$, $p < 0.01$, cocaine-before; $F(1, 71) = 3.4584$, $p < 0.01$, cocaine-after; $F(1, 71) = 8.9003$, $p < 0.01$, saline-before; $F(1, 65) = 9.2063$, $p < 0.01$, saline-after] and the FCN component of the schedule [$F(1, 71) = 5.1931$, $p < 0.01$, cocaine-before; $F(1, 71) = 2.5637$, $p < 0.01$, cocaine-after; $F(1, 71) = 7.3199$, $p < 0.01$; saline-before; $F(1, 65) = 20.2902$, $p < 0.01$, saline-after]. Mean response rates were decreased 10% from saline control following 3.0 mg/kg cocaine during both components of the schedule. Response rates were decreased to 55% (range 38–75%), 32% (range 23–48%), and 5% (range 1–8%) of saline control at the 10-, 17-, and 30-mg/kg doses, respectively, during the FCN-S^D variant. During the FCN component, response rates were decreased to 39% (range 32–52%), 22% (range 15–29%), and 3% (range 1–6%) of saline control levels at the 10-, 17-, and 30-mg/kg cocaine doses, respectively. A main effect of cocaine dose on switch times (Table 3) was not found in any of the four treatment groups during either the FCN-S^D component [$F(1, 71) = 0.9276$, cocaine-before; $F(1, 71) = 1.0652$, cocaine-after; $F(1, 71) = 1.2389$, saline-before; $F(1, 65) = 0.9376$, saline-after] or the FCN component of the schedule [$F(1, 71) = 1.0444$, cocaine-before; $F(1, 71) = 0.9833$, cocaine-after; $F(1, 71) = 0.9382$, saline-before; $F(1, 65) = 1.5351$, saline-after]. Although switch times were not affected at the 17-mg/kg dose of cocaine under the FCN-S^D variant, switch times were increased during the FCN component of the schedule. Switch times were also increased during both variants of the schedule following pretreatment with the 30-mg/kg dose. A significant main effect of cocaine dose on postreinforcement pauses (Table 4) was also not observed in any of the four treatment groups [$F(1, 71) = 0.9412$, cocaine-before; $F(1, 71) = 1.4101$, cocaine-after; $F(1, 71) = 0.9489$, saline-before; $F(1, 65) = 0.8356$, saline-after]. Pretreatment with cocaine (1.0, 3.0, and 10 mg/kg) did not affect the postreinforcement pause, and there was only a slight increase at the 17-mg/kg dose. However, postreinforcement pause times were further increased following 30 mg/kg cocaine.

Chronic Cocaine Administration

All rats were injected with saline or cocaine, before or after each session, for at least 60 days before the chronic cocaine dose–response curves were generated, and these chronic injections continued until the completion of the dose–response curves (approximately 6 additional wk). There were no significant differences between saline control values generated during the acute and chronic dose–response curves for any data collected in any of the four treatment groups and in either the FCN-S^D or FCN component of the schedule, indicating that baseline and control accuracy levels, response rates, switch times, and postreinforcement pauses remained relatively stable over the course of the experiment. Furthermore, there were no significant differences between the acute and chronic cocaine dose–response curves for either the saline-before or saline-after control groups.

The chronic administration of cocaine (10 mg/kg, IP) immediately before each behavioral session resulted in the development of tolerance to the effects of the drug, and this effect was more evident during the FCN-S^D than the FCN variant of the schedule. There was a main effect of chronic cocaine treatment on mean accuracy levels during the FCN-S^D component [$F(1, 71) = 3.9989$, $p < 0.05$), but not during the FCN component of the schedule [$F(1, 71) = 0.5564$). The number of reinforced trials during the FCN-S^D component of the schedule following pretreatment with 1.0–17 mg/kg cocaine was no longer significantly different from saline control (Fig. 1 and Table 1). To a lesser degree, tolerance also appeared to develop to the effects of the 10- and 17-mg/kg doses on the number of reinforced trials during the FCN component (Fig. 2 and Table 1). Tolerance did not develop to the effects of the highest dose tested (30 mg/kg) under either component of the schedule. A main effect of chronic cocaine treatment on response rates was observed under both the FCN-S^D component [$F(1, 71) = 4.0126$, $p < 0.05$) and the FCN component of the schedule [$F(1, 71) = 16.0449$, $p < 0.01$). The rate-decreasing effects of 10 and 17 mg/kg cocaine during the FCN-S^D variant (Fig. 3 and Table 2) and 3.0, 10, and 17 mg/kg cocaine during the FCN component of the schedule (Fig. 4 and Table 2) were also attenuated. Although switch times were also generally reduced back toward saline control values, these effects were only significant at the 1.0- and 3.0-mg/kg doses of cocaine during the FCN variant [$F(1, 71) = 4.9268$, $p < 0.05$) of the schedule (Table 3). No consistent effects on postreinforcement pause times were noted (Table 4).

In contrast, tolerance was not observed, and the effects of cocaine were retained and even enhanced following the chronic administration of 10 mg/kg cocaine immediately after each behavioral session; this effect was more evident during the FCN

TABLE 4

EFFECTS OF ACUTE AND CHRONIC COCAINE ADMINISTRATION, DELIVERED BEFORE OR AFTER THE BEHAVIORAL SESSIONS, ON POSTREINFORCEMENT PAUSE TIMES (SECONDS) FOR FIXED-CONSECUTIVE-NUMBER EIGHT FOOD-REINFORCED RESPONDING

	Postreinforcement Pause							
	Saline Before		Cocaine Before		Saline After		Cocaine After	
Dose	Acute	Chronic	Acute	Chronic	Acute	Chronic	Acute	Chronic
Saline	3.32 ± 0.15	3.45 ± 0.30	3.49 ± 0.16	3.50 ± 0.21	4.00 ± 0.29	3.86 ± 0.15	3.48 ± 0.19	3.48 ± 0.09
1.00	3.32 ± 0.17	3.42 ± 0.19	3.58 ± 0.22	3.40 ± 0.20	3.72 ± 0.14	3.57 ± 0.13	3.45 ± 0.09	3.61 ± 0.18
3.0	3.12 ± 0.20	2.86 ± 0.16	3.65 ± 0.25	3.22 ± 0.20	3.57 ± 0.16	3.44 ± 0.13	3.07 ± 0.16	3.39 ± 0.22
10	2.40 ± 0.22	2.57 ± 0.13	2.59 ± 0.14	2.89 ± 0.19	4.18 ± 0.60	3.42 ± 0.37	3.90 ± 0.49	4.21 ± 0.25
17	5.70 ± 2.27	4.16 ± 0.86	4.97 ± 0.91	4.20 ± 0.48	3.06 ± 0.36	4.15 ± 0.47	6.89 ± 2.87	7.38 ± 0.87
30	15.13 ± 7.40	13.63 ± 4.91	9.00 ± 2.43	5.93 ± 3.59	10.70 ± 8.75	12.01 ± 8.01	54.75 ± 42.97	431.34 ± 122.67

Values are the means (± SEM) for double determinations with $n = 12$/treatment condition. Significance of the differences between treatment means was determined with a two-way analysis of variance followed by Student's *t*-tests.

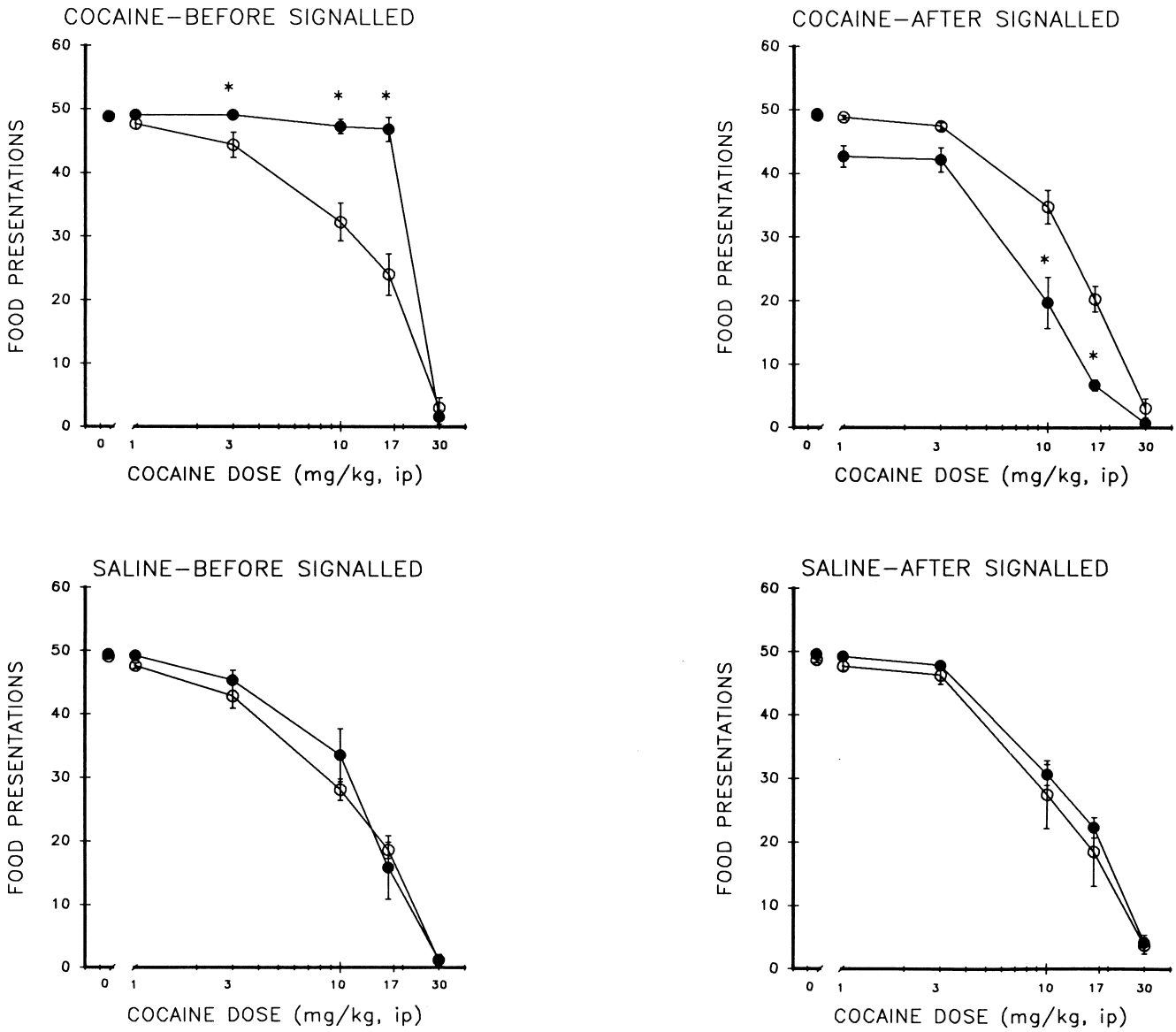

FIG. 1. Effects of cocaine on the number of reinforced trials (accuracy) during fixed-consecutive-number eight food-reinforced responding in the presence (FCN-S^D) of an external discriminative stimulus (SIGNALLED) before (○) or after (●) chronic cocaine or saline administration delivered before or after the behavioral sessions. Values are the means (±SEM) for double determinations with $n = 12$/treatment condition. Significance of the differences between treatment means was determined with a two-way analysis of variance followed by Student's *t*-tests; *$p < 0.05$.

component of the schedule. There was a main effect of chronic cocaine treatment on mean accuracy levels during the FCN-S^D component [$F(1, 71) = 10.9931$, $p < 0.01$) as well as the FCN component of the schedule [$F(1, 71) = 34.8870$, $p < 0.01$). The number of reinforced trials was significantly decreased from acute cocaine values with 1.0–17 mg/kg cocaine following chronic cocaine administration during the FCN component of the schedule (Fig. 2 and Table 1), while the number of reinforced trials during the FCN-S^D variant was significantly reduced from acute values following only the 10- and 17-mg/kg doses (Fig. 1 and Table 1). However, a main effect of chronic cocaine treatment on response rates was not observed under either the FCN-S^D component [$F(1, 71) = 2.4885$) or the FCN component of the schedule [$F(1, 71) = 1.7419$), even though the rate-decreasing effects of the drug appeared to be augmented following 3.0, 10, and 17 mg/kg cocaine during the FCN-S^D variant (Fig. 3 and Table 2) and following 3.0 and 10 mg/kg during the FCN variant (Fig. 4 and Table 2). Switch times were not consistently affected and only appeared to be lengthened following the 17-mg/kg dose of cocaine during the FCN-S^D component and the 10-mg/kg dose during the FCN variant of the schedule (Table 3). Postreinforcement pause times were generally increased following chronic cocaine administration, but these increases did not reach statistical significance because of the high degree of individual variability among rats (Table 4).

Benzodiazepine Receptor Autoradiography

Statistically significant changes in benzodiazepine receptor binding resulting from the different treatment conditions are

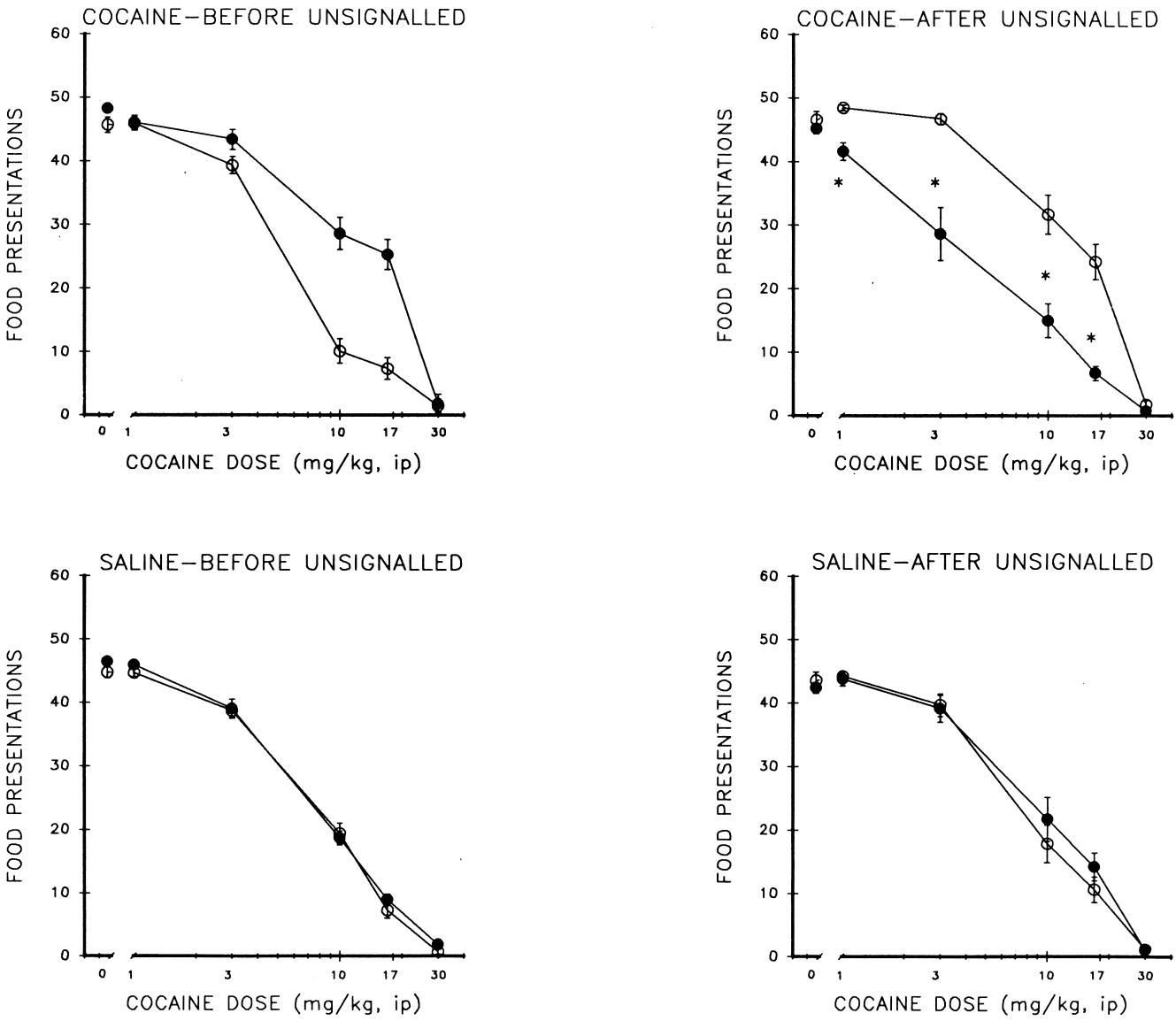

FIG. 2. Effects of cocaine on the number of reinforced trials (accuracy) during fixed-consecutive-number eight food-reinforced responding in the absence (FCN) of an external discriminative stimulus (UNSIGNALLED) before (○) or after (●) chronic cocaine or saline administration delivered before or after the behavioral sessions. Values are the means (±SEM) for double determinations with $n = 12$/treatment condition. Significance of the differences between treatment means was determined with a two-way analysis of variance followed by Student's *t*-tests; $^*p < 0.05$.

presented in Fig. 5. A main effect of treatment was observed in the medial prefrontal cortex [$F(3, 35) = 10.0728$, $p < 0.01$), globus pallidus [$F(3, 27) = 3.6393$, $p < 0.05$), anterior hypothalamus [$F(3, 30) = 11.6263$, $p < 0.01$), medial forebrain bundle [$F(3, 30) = 8.3659$, $p < 0.01$), hippocampus [$F(3, 27) = 10.3199$, $p < 0.01$), central medial nucleus of the amygdala [$F(3, 31) = 3.8064$, $p < 0.05$), substantia nigra [$F(3, 35) = 4.067$, $p < 0.05$), and ventral tegmental area [$F(3, 32) = 27.5498$, $p < 0.01$). Comparisons between rats from the cocaine-before and saline-before treatment groups revealed statistically significant decreases in binding in the anterior hypothalamus [(−31%), $t = 3.3402$, $p < 0.01$), medial forebrain bundle [(−29%), $t = 2.7268$, $p < 0.05$), and ventral tegmental area [(−56%), $t = 8.6153$, $p < 0.01$). Similar decreases in binding were observed in the anterior hypothalamus [(−40%), $t = 5.4751$, $p < 0.01$), medial forebrain bundle [(−38%), $t = 3.3438$, $p < 0.01$), and ventral tegmental area [(−37%), $t = 4.2547$, $p < 0.01$) of rats from the cocaine-after group compared with those from the saline-after treatment group. Benzodiazepine receptor binding was increased in the hippocampus of rats from both the cocaine-before [(+59%), $t = -6.1330$, $p < 0.01$) and cocaine-after [(+25%), $t = -2.2869$, $p < 0.05$) treatment groups compared with their respective saline controls. Statistically significant increases in binding were also found in the central medial nucleus of the amygdala [(+34%), $t = -3.6047$, $p < 0.01$) and substantia nigra [(+54%), $t = -2.4456$, $p < 0.05$) of rats from the cocaine-before treatment group compared with saline controls that were not seen in rats from the cocaine-after group. However, benzodiazepine receptor binding was significantly increased in the medial prefrontal cortex of rats from the cocaine-after group compared with rats from either the saline-after [(+30%), $t = -4.2101$, $p < 0.01$) or even the cocaine-

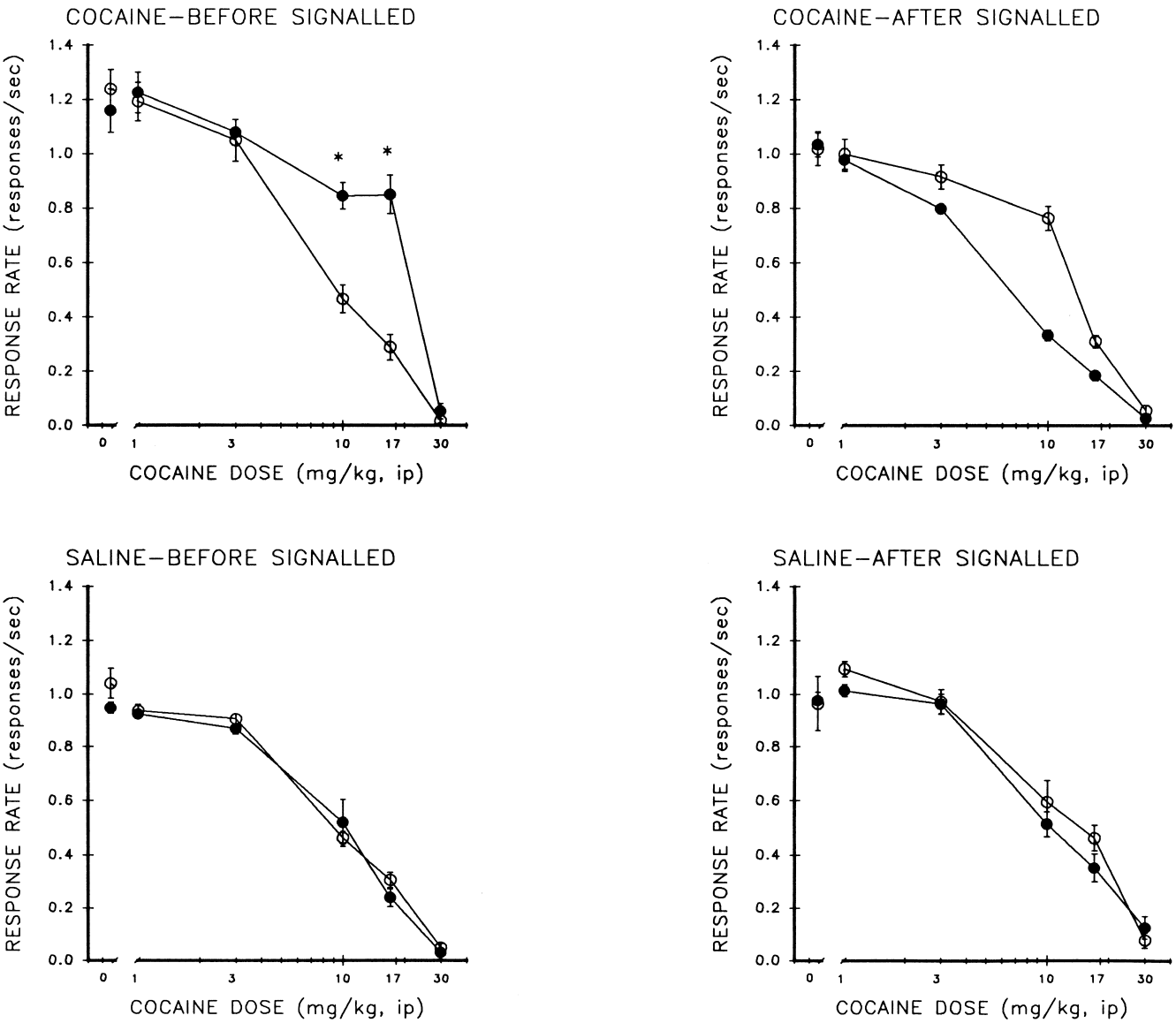

FIG. 3. Effects of cocaine on response rates (responses per second) during fixed-consecutive-number eight food-reinforced responding in the presence (FCN-S^D) of an external discriminative stimulus (SIGNALLED) before (○) or after (●) chronic cocaine or saline administration delivered before or after the behavioral sessions. Values are the means (±SEM) for double determinations with $n = 12$/treatment condition. Significance of the differences between treatment means was determined with a two-way analysis of variance followed by Student's t-tests; $*p < 0.05$.

before [(+24%), $t = -2.6599$, $p < 0.05$) treatment groups. Interestingly, benzodiazepine receptor binding was significantly higher in the ventral tegmental area [(+33%), $t = 4.0190$, $p < 0.01$) of rats from the saline-before group compared with rats from the saline-after treatment group.

DISCUSSION

The effects of cocaine on food-maintained responding under a fixed-consecutive-number eight schedule of reinforcement were investigated under four conditions: in the presence (FCN-S^D) and absence (FCN) of an external discriminative stimulus and with the chronic cocaine injections delivered before or after each behavioral session. Average accuracy levels and rates of responding following vehicle administration were slightly higher during the FCN-S^D variant of the schedule, although differences between the two components were generally < 10%. However, the acute effects of some doses of cocaine were significantly greater during the FCN component. Accuracy levels and response rates were similarly affected during both components of the schedule following the 1.0- or 3.0-mg/kg dose, but accuracy levels were decreased an average of 20% more and response rates decreased 10–15% more during the FCN variant of the schedule following pretreatment with 10 or 17 mg/kg of cocaine. Following the administration of the highest dose (30 mg/kg), the rats would typically complete fewer than five reinforced trials under either component. These data are in general agreement with investigations of other psychomotor stimulants, which reported increased effects of amphetamine, methylphenidate, and caffeine under FCN schedules compared with FCN-S^D schedules (28,32,40,41). Although a recent report did not find any differences in the

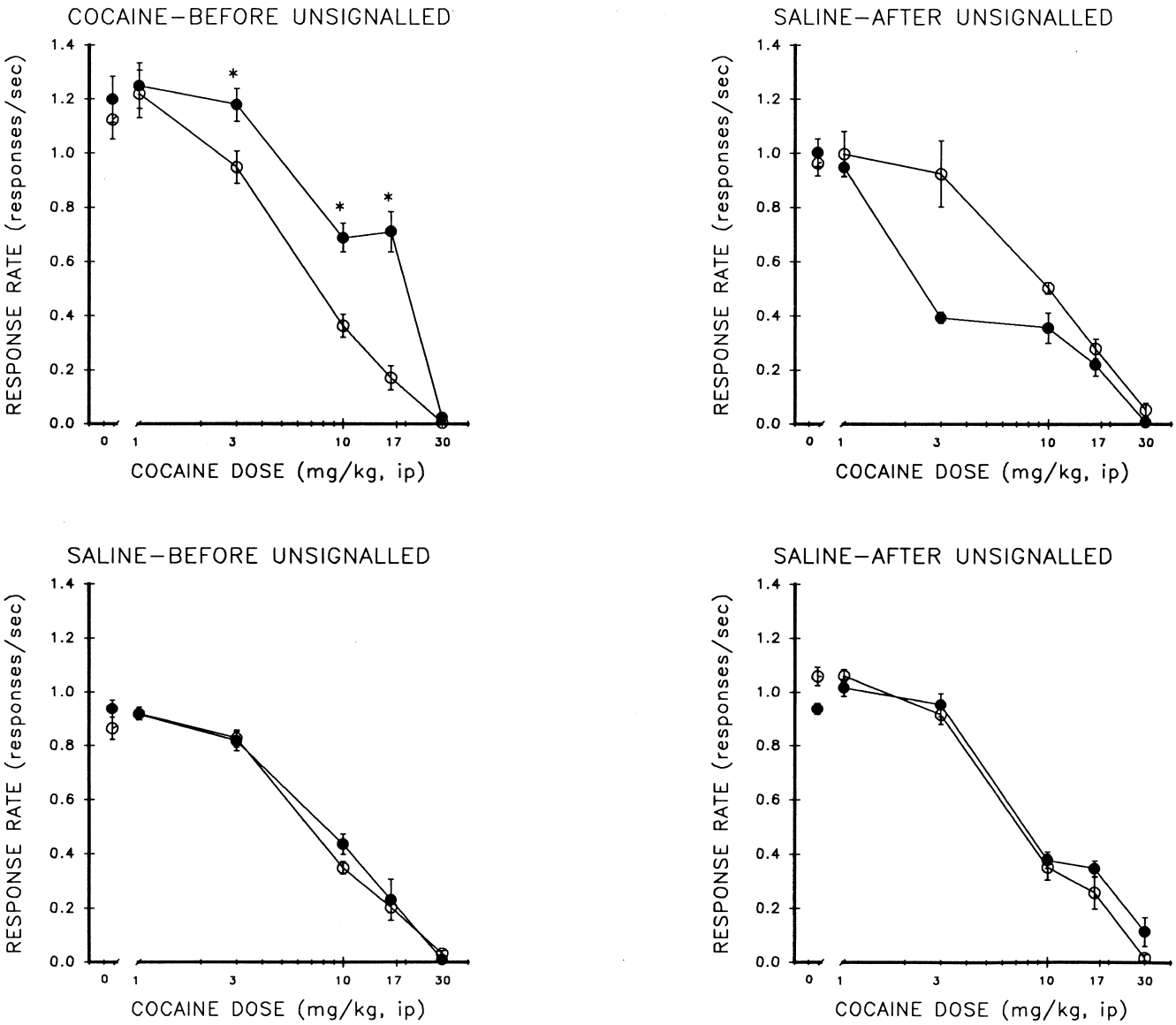

FIG. 4. Effects of cocaine on response rates (responses per second) during fixed-consecutive-number eight food-reinforced responding in the absence (FCN) of an external discriminative stimulus (UNSIGNALLED) before (○) or after (●) chronic cocaine or saline administration delivered before or after the behavioral sessions. Values are the means (±SEM) for double determinations with $n = 12$/treatment condition. Significance of the differences between treatment means was determined with a two-way analysis of variance followed by Student's t-tests; $^*p < 0.05$.

effects of cocaine between these two components of the schedule in pigeons (8), the authors suggest that certain doses of cocaine would likely disrupt behavior more under the FCN than the FCN-S^D variant.

Tolerance to the behavioral effects of cocaine developed when the drug was administered chronically before each experimental session, and this effect was much more evident during the FCN-S^D than the FCN component of the schedule, suggesting that the presence of an external discriminative stimulus facilitates the development of tolerance. Accuracy levels were not significantly different from vehicle with doses as high as 17 mg/kg following the chronic administration of 10 mg/kg cocaine before each behavioral session. Although a slight tolerance did develop to the effects of 10 and 17 mg/kg cocaine during the FCN component, accuracy levels were still decreased 40–50% from saline control values. On the other hand, the development of tolerance to the effects of cocaine on response rates was similar between the two variants of the schedule. These data are in agreement with a report of the effects of chronic amphetamine administration on fixed-consecutive-number eight food-reinforced responding in rats, where a similar differential degree of tolerance developed with accuracy levels, while comparable tolerance developed to the effects of the drug on response rates under both components of the schedule (41). Chronic cocaine administration has also been reported to produce tolerance in pigeons responding under this schedule, although tolerance developed to a similar degree under both the FCN and FCN-S^D components of the schedule (8). Repeated daily injections of cocaine or amphetamine have also been reported to result in tolerance to the disruptive effects of these drugs on behavior in a variety of species under various operant schedules of reinforcement in-

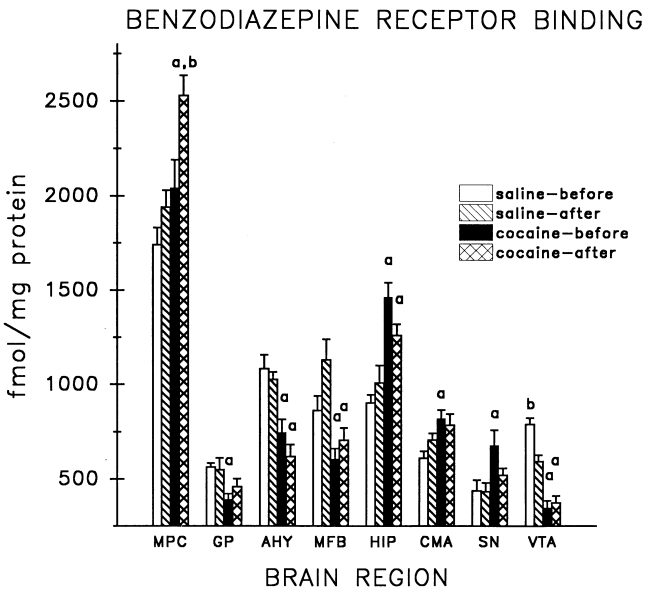

FIG. 5. Statistically significant changes in benzodiazepine receptor binding measured autoradiographically using [^{3}H]flumazenil in rats injected chronically with saline or cocaine (10 mg/kg, IP) before or after the daily fixed-consecutive-number eight behavioral sessions. Significance of the differences was determined with an analysis of variance followed by Student's *t*-tests with (a) $p < 0.05$ cocaine vs. saline, or (b) $p < 0.05$ before vs. after. MPC, medial prefrontal cortex; GP, globus pallidus; AHY, anterior hypothalamus; MFB, medial forebrain bundle; HIP, hippocampus; CMA, central medial nucleus of the amygdala; SN, substantia nigra; VTA, ventral tegmental area.

cluding fixed-interval responding by squirrel monkeys (4) and pigeons (46), various fixed-ratio schedules of responding by pigeons (21), delayed-matching-to-sample performance (5), and repeated acquisition and performance of response sequences (54) by pigeons, complex operant responding by squirrel monkeys (6), and food-reinforced responding by rats on fixed-ratio and differential reinforcement of low rate schedules of reinforcement (58). These data suggest that when the effects of a drug interfere with the ability of an animal to meet the contingencies required for reinforcer presentation, then the animal is more likely to become tolerant to these effects.

On the other hand, psychomotor stimulant-induced behavioral sensitization has also been systematically documented in a variety of animal models and species, although motor components of behavior (e.g., hyperactivity and stereotypy) have been most frequently associated with these effects (24,38,39). Chronic daily injections of cocaine or amphetamine result in progressive increases in stereotypy in rats (23,30,33, 35,50,52) and rhesus monkeys (34) and in increased locomotor activity and hyperactivity in rats (33,35) and mice (50). Furthermore, the disruptive effects of cocaine and amphetamine on milk intake in rats are decreased following chronic administration when the injections precede the experimental session, while animals receiving an equal number of injections immediately following the sessions become more sensitive to the effects of the drug (3,11,58). In the present experiment, accuracy levels were decreased from acute values when the chronic cocaine injections followed each experimental session, and this effect was more pronounced during the FCN component of the schedule, suggesting that the presence of an external discriminative stimulus interferes with the development of sensitization. Accuracy levels were decreased an average of 40% more than acute values for the 3.0-, 10-, and 17-mg/kg doses and 20% more for the 1.0-mg/kg dose during the FCN component. During the FCN-S^D variant, accuracy levels were decreased approximately 30% from acute values, but only for the 10- and 17-mg/kg doses. These data suggest that when the animals receive cocaine after the session, drug-induced behavioral changes do not result in a loss of reinforcement and tolerance to the disruptive effects of the drug does not develop (41).

Significant changes in benzodiazepine receptor binding measured autoradiographically using [^{3}H]flumazenil were observed when rats from the chronic cocaine-treated groups were compared with respective saline-treated controls. Significant decreases in binding were found in the anterior hypothalamus, medial forebrain bundle, and ventral tegmental area, with significant increases in binding evident in the hippocampus, of rats from both the cocaine-before and cocaine-after treatment groups, suggesting that these effects may be associated with the general pharmacologic effects of cocaine and are likely unrelated to the development of tolerance or sensitization. The changes in the anterior hypothalamus may be related to the neuroendocrine effects of cocaine (29,43–45), while the changes in the ventral tegmental area might reflect actions of the drug at dopamine terminals (22,42). The increases in binding in the hippocampus may be involved in the potentially toxic (e.g., increased susceptibility to convulsions) effects of cocaine (14,18,53). Increases in benzodiazepine receptor binding were observed in the central medial nucleus of the amygdala and substantia nigra, and decreases in the globus pallidus, of rats from the cocaine-before treatment group which were not evident in rats from the cocaine-after treatment group, suggesting that changes in binding in these brain regions may be associated with the development of tolerance. On the other hand, increases in binding were found in the medial prefrontal cortex of rats from the cocaine-after treatment group compared with rats from either the saline-after or cocaine-before treatment groups, suggesting that these changes might be related to the development of sensitization (47,51).

Previously, our laboratory reported that daily injections of cocaine (20 or 40 mg/kg, IP) for 15 days produced differential effects on benzodiazepine receptor binding within the two major ascending dopaminergic systems (17). In these previous experiments, binding was decreased in the medial prefrontal cortex and nucleus accumbens and increased in the caudate nucleus. In the present experiments, binding was increased in the medial prefrontal cortex of rats from only the cocaine-after group, increased in the substantia nigra and decreased in the globus pallidus of rats from only the cocaine-before group, and decreased in the ventral tegmental area of rats from both cocaine-treated groups. There are varied reasons which could account for these apparently disparate data, including the strain of the rats, the cocaine dose, the number of days of exposure to the drug, and training and subsequent responding under a fixed-consecutive-number eight schedule of food reinforcement. In the previous experiments (17), rats derived from the Fischer 344 strain were intraperitoneally injected with cocaine (20 or 40 mg/kg) once a day for only 15 days and were transferred to a separate holding cage for 60 min following each injection. In the present investigation, Wistar rats were exposed to repeated cocaine injections (10 mg/kg, IP), delivered immediately before or after a food-reinforced operant behavioral session, for approximately 100 days. Nevertheless, the data from both experiments suggest that benzodiazepine receptors in brain regions associated with

ascending dopaminergic neurons may be involved, in part, in some of the behavioral and neurobiologic effects of cocaine.

Benzodiazepines can be used in the emergency room for the treatment of some of the medical complications associated with cocaine intoxication. Convulsions are often apparent following an acute cocaine overdose, and these seizures can be treated with intravenous diazepam (14,53), but not dilantin (53). Some of the major symptoms associated with cocaine withdrawal also often include severe anxiety, restlessness, and agitation (9,13,53), suggesting that anxiety and related effects at benzodiazepine receptors may be involved in the etiology and neurobiology of cocaine use and withdrawal in humans. Pretreatment with the benzodiazepine receptor agonists chlordiazepoxide (15) or alprazolam (19) alters intravenous cocaine self-administration in rats, suggesting that these receptors may also be involved in the reinforcing effects of the drug (18). However, even though anxiety appears to be involved in the etiology of cocaine use and withdrawal in humans, diazepam is clinically useful in the treatment of acute cocaine intoxication, and benzodiazepine-receptor agonists decrease cocaine self-administration in rats, benzodiazepines are not usually recommended as the treatment of first choice for cocaine withdrawal because of the concern that the use of these drugs might result in a secondary dependence.

In summary, chronic cocaine injections administered before the start of each behavioral session were more likely to result in tolerance to the effects of the drug on fixed-consecutive-number eight food-reinforced responding. Tolerance was more likely to develop during the FCN-S^D (signalled) component of the schedule, indicating that the presence of an external discriminative stimulus may contribute to this effect. The disruptive effect of cocaine on the ability of the rats to complete the response requirement successfully likely plays a role as well. On the other hand, chronic cocaine injections delivered immediately following each behavioral session did not induce tolerance and were more likely to result in sensitization or increased sensitivity to the effects of the drug. Sensitization was more likely to develop during the FCN (unsignalled) component of the schedule, indicating that the lack of an external discriminative stimulus may contribute to this effect. Since the chronic injections were delivered after each behavioral session, cocaine did not disrupt responding during the session so that increased sensitivity rather than tolerance to the effects of cocaine was more likely to develop. These data suggest that either tolerance or sensitization to the effects of cocaine on fixed-consecutive-number eight food-reinforced responding may occur following the same number of chronic injections depending on the context under which the drug is delivered. These effects may be mediated, in part, through changes in benzodiazepine receptor binding in discrete brain regions.

ACKNOWLEDGEMENTS

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