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Physiological and Subjective Effects of Acute Cocaine Withdrawal (Crash) in Rats

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GAUVIN, D. V., R. J. BRISCOE, T. J. BAIRD, M. VALLETT, K. L. CARL AND F. A. HOLLOWAY. *Physiological and subjective effects of acute cocaine withdrawal (crash) in rats.* PHARMACOL BIOCHEM BEHAV **57**(4) 923–934, 1997.—The physiological and subjective effects of high acute doses of cocaine and the subsequent homeostatic acute withdrawal syndrome were measured in rats. Radiotelemetry recordings of body temperature and activity were monitored in rats for 48 h after 32 mg/kg cocaine (COC) and saline (SAL) were administered by both intraperitoneal and subcutaneous (SC) routes. COC initially produced hypothermia and hyperactivity, followed by a prolonged hyperthermic and hypoactive rebound that seemed to peak around 12 h after injections. The SC route of administration produced the greatest rebound effect. Eight additional rats were monitored for EEG activity by telemetry for 48 h after SC administration of SAL or 32 mg/kg COC. COC produced an initial decrease in alpha and beta wavelength bands, with a trend toward increases in alpha and beta power demonstrated from the 10th through 14th h after injections. Using a three-choice haloperidol (HDL), saline, and COC drug discrimination task, we demonstrated a COC-like subjective state produced during the 10th through 12th h after a 32-mg/kg SC COC injection with no HDL-like responding engendered during any tested period of the acute or rebound effects of COC. These data provide evidence for an acute COC withdrawal syndrome (crash) in rats occurring 10–14 h after a high-dose COC treatment. © 1997 Elsevier Science Inc.

Cocaine Haloperidol Electrocorticogram Body temperature General activity Acute withdrawal syndrome

UNTIL the early 1980s, most authorities believed that cocaine (COC) was a drug of high abuse potential but was relatively safe with regard to the possibility of true physiological dependence (18,31,54,60). More recently, however, it has been argued that heavy COC users manifest a characteristic syndrome of withdrawal upon abrupt cessation of COC use (18–25,31). These authors have proposed a triphasic model for abstinence symptomatology comprising "crash," "withdrawal," and "extinction" phases (21). Three separate controlled clinical studies have failed to provide robust evidence for the phasic COC withdrawal pattern and have reported only mild changes in mood and COC craving during withdrawal (21, 30,60,74).

Rebound or withdrawal phenomena are natural events and are found a) after the decline of serum blood levels following acute drug administration; b) after withdrawal from chronic exposure to any active drug; and c) as a physiological compensatory mechanism of the central nervous system without drugs (51). Solomon and Corbit (65,66), Solomon (64), and many others (57,61,67,78) have suggested a standard pattern of affective dynamics to explain the relationship between hedonic stimuli and the after-reaction emerging upon stimulus termination. The compensatory mechanisms initiated by the primary drug effect can either a) reduce the intensity of the primary reaction and produce an opposite "B state," contributing to the development of *tolerance* (57), or b) be isodirectional to the initial drug effect, contributing to the development of *sensitization* (67,75,78).

Dackis and Gold (4–6,23) have postulated that chronic abuse of COC leads to a functional depletion of dopamine, citing hyperprolactinemia (8) and pseudoparkinsonism (7) in human COC abusers and decreased levels of brain dopamine in animals after chronic COC exposure (70). It is this dopamine depletion that Dackis and Gold (4–6) and Koob and Bloom (45) have postulated underlies the rebound or COC withdrawal syndrome. Kleber and Gawin (43) have ques-

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tioned this hypodopaminergic state hypothesis in COC abusers. Jaffe et al. (28) have shown plasma prolactin levels in COC abusers to be within normal limits, and their sleep, appetites, and moods to be normal for a hospitalized population. Jaffe et al. (28) also reported that 15 min after administration of an intravenous bolus of COC, self-ratings of "craving" and "wanting" were significantly increased. This increase in reports of craving after COC administration may suggest an isodirectional compensatory process that drives or contributes to sensitization to COC craving over repeated administrations (67,75,78).

Although there is a vast and venerable literature examining the acute effects of COC administration in a number of nonhuman subjects, there is a paucity of data on the acute COC withdrawal or "crash" that follows those acute effects. In the present study, we used three physiological measures [body temperature, activity, and electrocorticograms (ECoG)] that have been previously demonstrated to be affected by COC administration (1,3,9,11,15,26,44,49,50,55,56,58,68,71,72, 79). Our goal was to measure changes in the core body temperature, general activity, and ECoG immediately following acute high-dose administration of COC and to continue to record these measures over the duration of the acute intoxication, homeostatic rebound, and recovery phases. To capture the temporal dynamics of the acute COC withdrawal syndrome, subjects were monitored by radiotelemetry for 48 continuous hours after a single injection of COC.

Recently, this laboratory has reported the successful training of rats in a three-choice haloperidol–saline–COC (HDL-SAL-COC) drug discrimination task (17). The hypothesized affective dimension correlated with the training injections was based on the euphoria–dysphoria/anhedonia affective continuum characteristically involved in acute and withdrawal symptomatology of COC (45). In the present study, we attempted to a) quantify the temporal changes in subjective effects across this hypothetical affective continuum after injections of both drug training stimuli, and b) assess whether the subjective effects of acute COC withdrawal in rats were similar to those in humans in that high dose pretreatments of COC would induce an isodirectional (COC-like) or opponent directional (HDL-like) rebound.

METHODS

Subjects

Sixteen drug and experimentally naive male Sprague–Dawley rats (300–325 g) were purchased from Sasco, Inc. (Omaha, NE, USA); six other male Sprague–Dawley rats, initially purchased from the same breeder and previously trained in a three-choice HDL-SAL-COC discrimination task, were also used (17). Rats were allowed to acclimate to the laboratory colony room for 1 week and then were reduced to 85% of their free-feeding weights. Each rat was allowed to gain 10 g of body weight per month throughout the study to allow for normal growth. Strict adherence to the National Institutes of Health guidelines for the care and use of animals in research was maintained during the course of these experiments. All protocols had prior approval of the Institutional Animal Care and Use Committee of the University of Oklahoma Health Sciences Center.

Radiotelemetry Studies

A Dataquest III (Mini-mitter Co., Inc., Sunriver, OR, USA) was interfaced with a DataSciences (St. Paul, MN, USA) telemetry data collection system. Twenty-four-hour remote monitoring was accomplished through a 386DX IBM-clone personal computer system (American Neuroscience Research Foundation, Yukon, OK, USA) interfaced with the eight Dataquest radio receivers (RA1010) through a BCM100 consolidation matrix and DQ1088 interface card (Minimitter Co., Inc.). Core body temperature was determined by a thermistor-based temperature sensor; raw frequency data were radiotransmitted to the computer and converted to temperature readings from a standard thermistor characteristic curve by the Dataquest software. ECoG waveforms were radiotransmitted to the computer coded by the frequency of digital pulse trains. These data epochs were examined through the short-term frequency changes from the input device. Each channel's frequency was serially collected at a rate of 500 cycles/s for 30 s every 10 min. General activity was radiotransmitted to the computer by recording each input as an "event." Each event was represented by a digital pulse indicating either a vertical or horizontal position change within the shoe-box cage. The computer accumulated the total number of pulses (events) that had been transmitted during the recording interval (10 min). When the sampling interval had elapsed, the system stored the total activity count in a permanent record.

Surgical Implantations

Each rat was pretreated, prior to surgery, with 0.1 ml of atropine sulfate (0.54 mg/ml). Surgical anesthesia was accomplished with 40 mg/kg sodium pentobarbital and 10 mg/kg ketamine HCl. Eight radiotelemetry discs (model XMFH, Minimitter Co., Inc.) selectively tuned for core body temperature and general activity monitoring were used for experiment 1. The small nickle-sized discs were implanted in the abdominal cavity by making a 2.5-cm incision through the abdominal wall, inserting the telemetry device, and then suturing the fascia and skin. For experiment 2, eight rats were each surgically implanted (abdominal cavity) with radiotelemetry devices selectively tuned for electrocorticographic, core body temperature, and general activity monitoring (TA10ETA-F40, DataScience Inc., St. Paul, MN, USA). A small 2.5-cm incision was made and the telemetry device was implanted. The fascia was sutured with Chromosorb suture and the ECoG leads were threaded through the subcutaneous fascia with a trocar instrument and attached to stainless steel skull screws (3 mm posterior and lateral to bregma). The skull screws and lead wire tips were covered with cranioplast cement for stability and insulation. The skull and abdominal dermal incisions were sutured with surgical silk and treated with a topical antibiotic ointment. After surgery, each rat was placed on a warming pad to reduce the effects of hypothermia associated with the anesthetic. A 2-week recovery period preceded telemetry recordings.

Experiment 1

Eight rats were implanted with temperature/activity transmitter devices. After the 2-week recovery period, each rat received injections on four occasions of either SAL or 32 mg/kg COC administered by either intraperitoneal (IP) or subcutaneous (SC) routes. Each injection was randomized across subjects, and a 2-week washout period was imposed between injections. All injections occurred 2 h into the lights-on period (0800 h).

The temporal constraints of analyzing the long-term series of individual ECoG recordings for the duration planned in the present study limited the number of treatment epochs to be monitored. Livezey and Sparber (49) have previously re-

ported a relationship between core body temperature and ECoG changes engendered by COC. Therefore, we initially monitored only body temperature and activity in eight rats following acute injections of either SAL or 32 mg/kg COC via IP and SC routes of administration. Visual inspection of the data determined that SC administration of COC produced the most dramatic acute COC withdrawal syndrome. Therefore, we decided to record ECoG activity for 48 continuous hours after SC administration of 32 mg/kg COC.

Experiment 2

Eight rats were instrumented with the ECoG/temperature/activity transmitters and allowed 2 weeks to recover from the surgical procedure within an isolated colony room that was used exclusively for the computerized monitoring of this protocol. Each home cage was placed on a radio receiver and recorded continuously for 48 h after SC injection of SAL or 32 mg/kg COC. Each rat's ECoG (30-s epochs at 500 Hz once per 10 min) was sequentially monitored from eight rats over 48-h periods.

Experiment 3: Drug Discrimination Task

Six rats were successfully trained in a three-choice HDL-SAL-COC discrimination task; the initial dose—response functions for both COC and HDL were previously reported by this laboratory (17). The illumination of the house light and the three response-lever lights signaled the beginning of the experimental session. The subjects were trained to the food pellet dispenser and to operate any of the three levers by the method of successive approximation. Each response was reinforced (FR1) by delivery of one 45-mg food pellet. Once this initial lever-press response had been demonstrated, drug discrimination training began.

Prior to the commencement of training, a drug/SAL (stimulus) presentation schedule was created for each rat such that over a 30-day period each rat would be maintained on a training-stimulus presentation ratio of 1:1:1 to ensure that a) each of the discriminative stimuli was presented equally often, and b) the training condition varied across animals each day. These procedures were designed to reduce the probability of a response bias and to ensure that the only predictive cue available to the subject (in locating the correct lever) was the drug or SAL injection. Each rat received two IP injections prior to a training session on alternating sides of the abdomen. On SAL training days, each rat received an injection of SAL (1 ml/kg) 2 h and again 15 min prior to the session. On COC training days, each rat received a SAL injection 2 h before and a 10-mg/kg COC injection 15 min before the training session. On HDL training days, each rat received 0.1 mg/kg HDL 2 h before and a 1-ml/kg SAL injection 15 min before the training session. This specific injection schedule was maintained to ensure that the specific time of handling and subsequent injection could not be used as a functional stimulus to solve the discrimination task. HDL training sessions were always followed by a day off to ensure that no acute or carry-over effects of the HDL injection were present for the next training session. Administration of one of these latter injections (hereafter referred to as training stimuli) determined the appropriate lever to select for obtaining food. Training sessions lasted for 20 min or until 50 reinforcements with food delivery, whichever occurred first. The number of responses required for food delivery was raised across successive sessions until five consecutive responses (FR5) were required. Once the contingencies for reinforcement were raised above the initial FR1 requirement, responses on any stimulus-inappropriate lever reset the ratio requirement on the stimulus-appropriate lever. Training sessions were conducted 5–7 days per week and continued until each rat met the criteria of emitting fewer than 10 responses prior to the first reinforcer delivery and of emitting at least 90% of the total session responses on the stimulus-appropriate lever for 3 consecutive days. Each rat was then required to meet these criteria for six more consecutive sessions in a double alternation sequence (i.e., HDL-HDL-SAL-SAL-COC-COC).

Discrimination Testing

When discriminative control was established, dose–response functions were generated with HDL and COC [previously reported by this laboratory: (17)]. Test sessions were identical to training sessions except that, during test sessions, five consecutive responses on any lever produced food. Training and test sessions were alternated throughout the week, ensuring that three separate training stimuli were presented between each test day. A typical week's sequence was: train COC, train HDL, day off, train SAL, test, etc. If a rat did not meet the criteria for stimulus control during a training session, further testing was postponed until the criteria for HDL-SAL-COC training days were achieved. Test sessions were conducted at various time intervals after rats were injected with 32 mg/kg of COC (SC) and the two training doses of training drugs (0.1 mg/kg HDL, 10 mg/kg COC). Tests were conducted once every 2 weeks. After any 32-mg/kg COC dose was tested, a 2-day washout period in the rat's home cage was imposed. Time–effect functions were determined by conducting individual test sessions 15, 30, 45, 60, 90, 120, 150, 180, and 240 min after injecting the rats with the 10-mg/kg COC training dose. Additional time–effect functions were determined by testing at 5, 10, 20, 30, 45, 60, 90, 120, 150, 180, and 240 min after injecting the rats with the 0.1-mg/kg HDL training dose. Test sessions were always preceded by three consecutive HDL, SAL, and COC training sessions. Time–effect functions and the acute COC withdrawal tests were conducted only once per subject in a pseudorandom order.

Data Analysis

Data from the telemetry study were analyzed with Dataquest III software. The spectral content of the ECoG real-time data series was conducted by a linear taper function. A fast Fourier transformation (FFT) was computed on the autocorrelation function and the magnitude of the spectrum was computed from the results of the FFT. The resulting power density spectra for each 30-s epoch were further segmented into four frequency bands, each representing the integrated power over a certain frequency range (American Neuroscience Research Foundation). The mean integrated power data were expressed for four wavelength bands categorized as delta (0–3.75 Hz), theta (4–8 Hz), alpha (8.25–14 Hz), and beta (14.25–30 Hz). The ECoG power data for these four bands were averaged across animals for each 10-min sample. The core body temperatures were averaged across subjects for each of the six temperature recordings per hour. General actograms were constructed by averaging each rat's general activity count for each 10-min interval. A subject $\times$ treatment $\times$ time multiple analysis of variance (MANOVA) was used to test for significance. Due to the size of the files, data were analyzed in 12-h epochs. Once the 12-h epochs were analyzed, post hoc specific-effects tests were conducted using smaller time epochs to specifically examine the acute and withdrawal effects of COC.

The time factors used for analysis of the specific-effects analyses of variance (ANOVAs) were determined by visual inspection of the graphs. Due to differences in the onset of action between IP- and SC-administered COC, differential time factors were used.

The data from the drug discrimination task are presented as the percentage of the total session responses emitted on the HDL-, SAL-, and COC-appropriate levers. The partial generalization to a training drug stimulus appears to reflect an accurate assessment of the degree of quantitative and/or qualitative similarity between the test drug or drug condition and the training stimulus. A test drug or drug condition was considered to produce "complete generalization," i.e., discriminative effects similar to those of the HDL or COC training stimuli, if at least 80% of the total session responses were emitted on the HDL- or COC-appropriate lever, respectively. The average response rates during the test session are expressed in responses per second. Such response rates provide a second measure of the behavioral effects of the drug or drug-associated state that appears to be independent of the distribution of response choice on the two levers. All data were analyzed using a mixed-factor (subject × treatment, repeated measures) MANOVA with a posteriori tests for individual treatment conditions (Duncan's multiple-range test).

All data were analyzed using the personal computer statistical package "Complete Statistical System: Statistica" (CSS; Statistica, Tulsa, OK, USA).

Drugs

Cocaine HCl and ketamine HCl were purchased from Sigma Chemical Corporation (St. Louis, MO, USA). Haldol® brand of HDL as the lactate with 1.8 mg methylparaben, 0.2 mg propylparaben, and lactic acid for pH adjustment to 3.0–3.6 (5 mg in 1-ml vials) (McNeil Pharmaceutical, Spring House, PA, USA), sodium pentobarbital, atropine sulfate, and normal sterile SAL were purchased from the pharmacy of the University Hospital (Oklahoma City, OK, USA). All doses of COC, ketamine HCl, and Haldol were diluted in SAL and expressed in mg/kg as the salt. COC was mixed in a concentration of 1.2 mg/ml. We have previously demonstrated that this low concentration of COC requires injection of relatively large volumes (5–10 ml) of solution, but provides benign injection sites when administered by either IP or SC routes [cf. (10)]. More importantly, these injections did not produce any evidence of dermal necrosis or tissue damage. Each drug was prepared daily in a photographic darkroom. Haldol was diluted in normal SAL and stored in a light-impermeable bottle (amber serum bottles, wrapped in aluminum foil and tape) to prevent oxidation by light.

RESULTS

Experiment 1

Telemetry recordings of core body temperature (Fig. 1) and general activity (Fig. 2) demonstrated significantly pronounced and prolonged changes after both IP (middle panels) and SC (bottom panels) administration of 32 mg/kg COC. Both routes of administration of SAL produced similar temperature and activity responses (all $ps > 0.8$; test–retest reliability of 0.959 for temperature and 0.94 for activity), so the group means were pooled and plotted in a single graphic (upper) panel. SAL injections produced an initial *hyper*thermic response with no significant changes in the general activity measure. There was a circadian rhythm evident in the core body temperature changes across the 2-day recording period, whereas general activity demonstrated a pattern best described as an ultradian rhythm, with many peaks and ebbs in activity occurring each day. COC (32 mg/kg) administered intraperitoneally (Fig. 1, middle panel) produced an initial significant *hypo*thermic response (Table 2; first 2 h) and a significant *hyper*thermic rebound (Table 2; 10–14 h). Subcutaneous administration of 32 mg/kg COC (Fig. 1, lower panel) also produced a significant *hypo*thermia (Table 2; first 2 h) followed by a pronounced and prolonged period of *hyper*thermic rebound (Table 2; 10–14 h). The patterns and degree of the initial hypothermia and the rebound hyperthermia were significantly different between IP and SC routes of administration (Table 2). The SC route produced a significant change in core body temperature across all four of the 12-h recording epochs (Table 1). The IP route resulted in a significant change only dur-

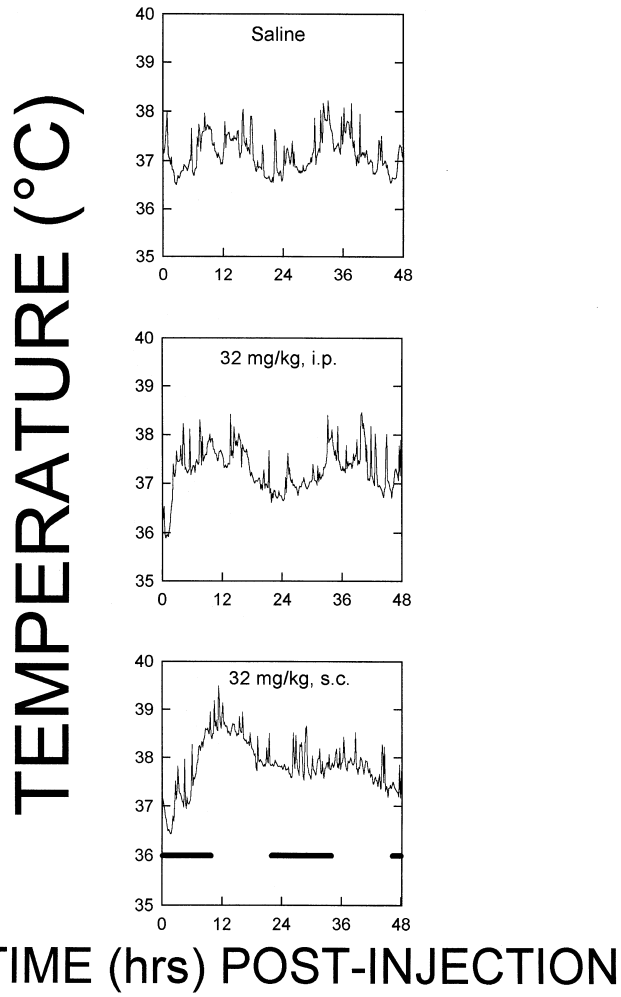


FIG. 1. Core body temperature changes (°C) remotely recorded by telemetry from eight rats every 10 min over a 48-h period after injections of saline (top panel), 32 mg/kg IP-administered cocaine (middle panel), and 32 mg/kg SC-administered cocaine (bottom panel). Saline was administered by both SC and IP routes. Because no significant differences were found between the two routes of administration and the test–retest reliability was found to be 0.959, the data were pooled. The top panel reflects the grand mean of two observations from each of the eight rats after saline administration. Statistical results are presented in Tables 1 and 2.

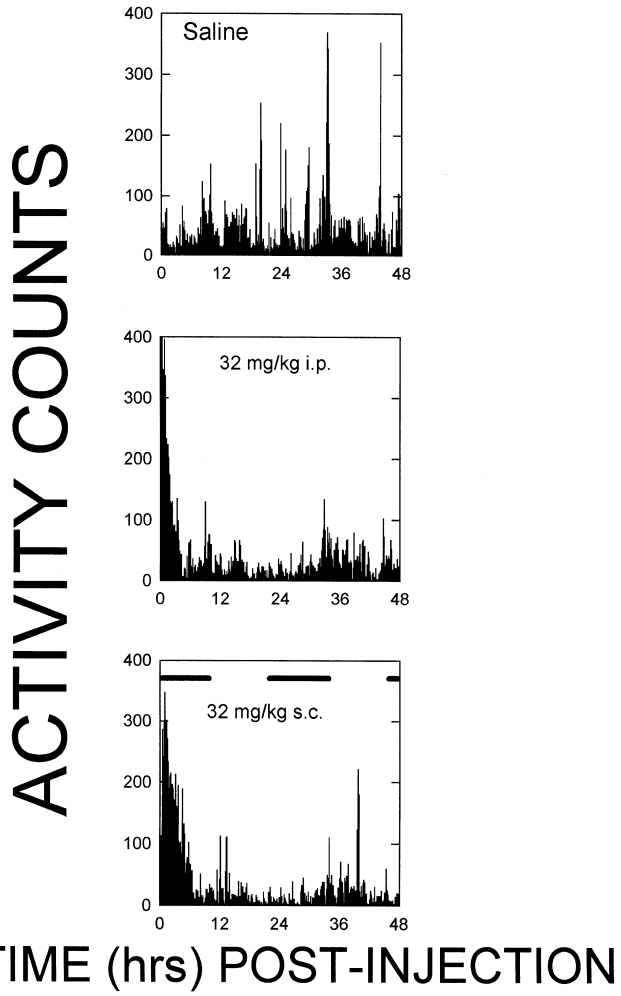


FIG. 2. General locomotor activity changes (counts/10 min) remotely recorded by telemetry from eight rats every 10 min over a 48-h period after injections of saline (top panel), 32 mg/ kg IP-administered cocaine (middle panel), and 32 mg/kg SC-administered cocaine (bottom panel). Saline was administered by both SC and IP routes. Because no significant differences were found between the two routes of administration and the test–retest reliability was found to be 0.94, the data were pooled. The top panel reflects the grand mean of two observations from each of the eight rats after saline administration. Statistical results are presented in Tables 3 and 4.

ing the last 12-h epoch (hours 36–48; Table 1). Both SC and IP routes of COC administration produced significant changes in general activity measures (Tables 3, 4). Both routes significantly increased general activity over SAL baseline activity counts for the first 12-h epoch. The SC route of COC administration produced a greater degree of hyperactivity than did the IP route. The general activity counts demonstrated a significant and prolonged opponent hypoactivity rebound from the initial COC-induced hyperactivity. The SC route initiated a significantly longer hypoactivity rebound effect, extending for the full 48-h recording period. The IP route of COC administration also produced a significant hypoactivity rebound, but the third 12-h epoch did not differ significantly from SAL baseline activity counts. In general, the greatest response to COC administration in both physiological measures of temperature and activity were demonstrated after SC administration. Therefore, ECoG recordings were recorded for 48 h after SC administration of 32 mg/kg COC.

Experiment 2

The group mean changes in the four ECoG wavelength bands across the 48-h recording period after SC administration of SAL (dashed lines) and 32 mg/kg COC (solid lines) are shown in Fig. 3. Each 12-h epoch was analyzed (Table 5) along with post hoc specific comparisons with the first 8 h and the acute COC withdrawal period (10–14 h). The negative log of power is plotted as a function of the 48-h recording period. It should be noted that an upward change in the negative log of the power function reflects an actual reduction in the power values. Therefore, it can be clearly seen that the initial response to 32 mg/kg COC was a reduction in power in all four wavelength bands; only the alpha and beta wavebands reached statistical significance over the first 12-h recording epoch (Table 5: Acute effects). After this initial decline in the wavelength power there was a prolonged but nonsignificant *increase* (defined as a downward trend in the negative log functions) in both alpha and beta wavelengths for approximately the first 30 h after COC administration. Each epoch produced significant time and effect × time interaction effects [all Fs(27, 189) > 1.4, ps < 0.05].

Experiment 3

Volumetric control injection tests were conducted using the large bolus volumes required to administer the low concentrations of COC used during SC administration. Large volumes of IP and SC injections were tested with no significant alterations in either the response-choice or rates-of-responding measures. The time–effect functions for the 10-mg/kg COC (Fig. 4) and 0.1-mg/kg HDL (Fig. 5) training stimuli were conducted in individual weekly test sessions. The 10-mg/kg COC training stimulus demonstrated a statistically significant, time-dependent decrease in the percentage of total session responses emitted on the COC-appropriate lever [main time effect: $F(7, 35) = 18.27$, $p < 10^{-6}$]. During these time course tests, responding was distributed on the COC- and

TABLE 1
STATISTICAL RESULTS: TEMPERATURE MAIN EFFECTS

		Cocaine IP	Cocaine SC
Epoch 1 (0–12 h)	Tx	$F(1, 7) = 1.75, p = 0.23$	$F(1, 7) = 8.55, p = 0.02$
Epoch 1 (12–24 h)	Tx	$F(1, 7) = 0.97, p = 0.37$	$F(1, 7) = 32.22, p = 0.0007$
Epoch 1 (24–36 h)	Tx	$F(1, 7) = 0.02, p = 0.87$	$F(1, 7) = 32.51, p = 0.0007$
Epoch 1 (36–48 h)	Tx	$F(1, 7) = 4.64, p = 0.06$	$F(1, 7) = 7.91, p = 0.026$

F-values reflect tests conducted between saline (IP and SC pooled) and cocaine injection conditions (32 mg/kg injected IP or SC). Tx, treatment.

TABLE 2
STATISTICAL RESULTS:
TEMPERATURE POST HOC SPECIFIC COMPARISONS

Acute effects (0–2 h)		
IP vs. saline	Tx	$F(1, 7) = 36.5, p = 0.005$
	Time	$F(11, 77) = 2.45, p = 0.001$
	Tx × Time	$F(11, 77) = 2.95, p = 0.002$
SC vs. saline	Tx	$F(1, 7) = 5.54, p = 0.05$
	Time	$F(11, 77) = 5.49, p = 2 \times 10^{-6}$
	Tx × Time	$F(11, 77) = 1.78, p = 0.07$
IP vs. SC	Tx	$F(1, 7) = 13.12, p = 0.008$
	Time	$F(11, 77) = 1.9, p = 0.05$
	Tx × Time	$F(11, 77) = 2.46, p = 0.01$
Withdrawal effects (10–14 h)		
IP vs. saline	Tx	$F(1, 7) = 7.46, p = 0.03$
	Time	$F(27, 189) = 1.95, p = 0.005$
	Tx × Time	$F(27, 189) = 2.43, p = 0.0002$
SC vs. saline	Tx	$F(1, 7) = 65.59, p = 0.00008$
	Time	$F(27, 189) = 0.91, p = 0.59$
	Tx × Time	$F(27, 189) = 2.46, p = 0.0002$
IP vs. SC	Tx	$F(1, 7) = 39.7, p = 0.0004$
	Time	$F(27, 189) = 1.28, p = 0.17$
	Tx × Time	$F(27, 189) = 2.11, p = 0.002$

Tx, Treatment.

SAL-appropriate levers only [main lever selection effect: $F(2, 10) = 245.4, p < 10^{-6}$; main time × lever selection interaction: $F(14, 70) = 92.9, p < 10^{-6}$]. The median effective time interval (METI) for the COC training cue was 50.5 (±4.5) min. The response topography demonstrated in test sessions conducted after the 0.1-mg/kg HDL training stimulus demonstrated a different pattern of responding. Rats emitted a large percentage of total session responses on the COC-appropriate lever (75%) within 10 min after the HDL administration; the median effective time interval for this initial COC-like interoceptive cue was 5.8 (±1.0) min. After this initial COC-like responding, there was an exclusive shift to HDL-appropriate responding. The median effective time interval for the onset of the HDL stimulus was 56.2 (±3.7) min. The median effective time interval for the time course of the HDL stimulus was 193 (±1.6) min. This time-dependent distribution in the pattern of responding on the three training stimulus levers resulted in a nonsignificant main time effect [$F(10, 50) = 1.0$, $p = 0.45$], but significant main lever selection [$F(2, 10) = 267.8$, $p < 10^{-6}$] and main time × lever selection interaction [$F(20, 100) = 111.5$, $p < 10^{-6}$] effects. Individual hourly discrimination test sessions conducted during the 10th through 14th h after 32 mg/kg of SC administered COC, corresponding to the peak in the temperature rebound effects (Fig. 1), demonstrated time-dependent isodirectional rebound responding on the COC-appropriate lever during the 10th through 12th h of testing (Fig. 6). Opponent-like HDL-appropriate responding was not demonstrated in any rat tested; all responding was emitted on the COC- or SAL-appropriate levers. The COC withdrawal tests demonstrated nonsignificant main time effects [$F(4, 20) = 1.0, p = 0.43$] but significant response choice [$F(2, 10) = 155.4$, $p < 10^{-6}$] and significant time × response choice interaction [$F(8, 40) = 47.3, p < 10^{-6}$] effects.

Because of the low fixed-ratio 5 schedule of reinforcement used in the present study, there were no significant changes in the rates of responding across any test or training stimulus condition.

DISCUSSION

We have demonstrated that acute high-dose COC treatments in rats produced biphasic patterns in core body temperature, general activity, and electrocorticographic activity. Nayak, Misra, and Mule (52) have previously reported that the SC route of administration of COC results in an effective half-life of 1.8–2 h, compared with the intravenous and IP half-lives of 0.3 h and 0.25 h (34,46,53). The time course and

TABLE 3
STATISTICAL RESULTS: ACTIVITY MAIN EFFECTS

Epoch 1 (0–12 h)	Tx	$F(1, 7) = 30.91, p = 0.0008$	$F(1, 7) = 52.45, p = 0.0001$
Epoch 1 (12–24 h)	Tx	$F(1, 7) = 6.03, p = 0.04$	$F(1, 7) = 6.56, p = 0.03$
Epoch 1 (24–36 h)	Tx	$F(1, 7) = 1.84, p = 0.22$	$F(1, 7) = 5.12, p = 0.06$
Epoch 1 (36–48 h)	Tx	$F(1, 7) = 4.36, p = 0.07$	$F(1, 7) = 4.21, p = 0.08$

F-values reflect tests conducted between saline (IP and SC pooled) and cocaine injection conditions (32 mg/kg injected IP or SC). Tx, treatment.

TABLE 4
STATISTICAL RESULTS: ACTIVITY POST HOC SPECIFIC COMPARISONS

Acute effects (0–4 h)		
IP vs. saline	Tx	$F(1, 7) = 42.2, p = 0.0003$
	Time	$F(11, 77) = 5.18, p < 10^{-6}$
	Tx × Time	$F(11, 77) = 2.85, p = 0.00006$
SC vs. saline	Tx	$F(1, 7) = 33.34, p = 0.0007$
	Time	$F(11, 77) = 4.30, p < 10^{-6}$
	Tx × Time	$F(11, 77) = 3.65, p = 0.000001$
IP vs. SC	Tx	$F(1, 7) = 0.54, p = 0.48$
	Time	$F(11, 77) = 6.02, p < 10^{-6}$
	Tx × Time	$F(11, 77) = 1.98, p = 0.007$
Withdrawal effects (10–14 h)		
IP vs. saline	Tx	$F(1, 7) = 10.44, p = 0.01$
	Time	$F(27, 189) = 2.25, p = 0.0008$
	Tx × Time	$F(27, 189) = 1.40, p = 0.09$
SC vs. saline	Tx	$F(1, 7) = 1.89, p = 0.21$
	Time	$F(27, 189) = 1.44, p = 0.08$
	Tx × Time	$F(27, 189) = 1.83, p = 0.01$
IP vs. SC	Tx	$F(1, 7) = 0.34, p = 0.57$
	Time	$F(27, 189) = 1.35, p = 0.12$
	Tx × Time	$F(27, 189) = 1.98, p = 0.004$

Tx, treatment.

magnitude of the acute and withdrawal effects of COC in the present study were dependent on route of administration. The acute temperature response to COC administration in the present study was similar to those demonstrated in other laboratories [cf. (50)]. A COC dose of 32 mg/kg produced acute hypothermia followed by rebound hyperthermia in each rat. The SC route of administration produced a slower onset to the peak in acute hypothermia, the magnitude of which was less than with the IP route; however, the SC route produced a more pronounced and prolonged hyperthermic rebound when compared with the IP route. Similar to other reports, COC produced acute hyperactivity in each rat (3,9,15,56,71,72). Again, the IP route of administration produced an initially greater degree of hyperactivity, but the SC route maintained the hyperactivity for almost 7 h when compared with SAL baseline levels. The results of the telemetry recordings of experiment 1 replicate the acute responses to COC previously reported by a number of other laboratories and provide the unique finding of a significant homeostatic compensatory rebound effect for both temperature and activity. The hyperthermia and hypoactivity seemed to oppose the acute effects. This compensatory rebound occurred 8–14 h after acute injection of COC. It is interesting that HDL has been reported to produce an acute hypothermia in rats (48) similar to the acute COC effects reported here.

In experiment 2, the high-dose SC treatments with COC initially produced reductions in the amplitude of power in all four wavelength bands. After this initial decline, there was a trend toward an opponent-like compensatory rebound increase in amplitude for both alpha and beta wavelength bands. The "minor" alterations in mean power amplitudes demonstrated across the full waveband spectrum by COC administration are similar to clinical electroencephalogram reports discussed by Herning et al. (26) and Knott (44). Again, the unique nature and direction of the opponent compensatory rebound effect suggests that development of tolerance to the initial effects should occur over repeated exposure to these high acute

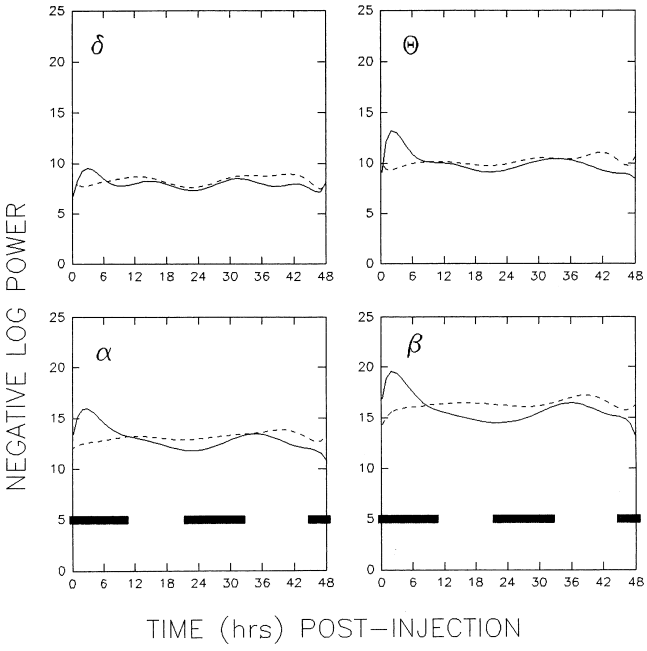


FIG. 3. Electrocorticograms remotely and serially recorded by telemetry from eight rats every 10 min over a 48-h period after SC injections of either saline (dashed lines) or 32 mg/kg cocaine (solid lines). Each individual recording was visually inspected, fast Fourier transformed, and separated into wavelength bands. All rats' sorted wavelength bands (delta, theta, alpha, beta) for each 10-min epoch were pooled; the grand mean, expressed as the negative log of power, is plotted as a function of time after injection. An upward change in the mean negative log of power actually reflects a *decrease* in the actual power value, and vice versa. Statistical results are presented in Table 5.

TABLE 5
STATISTICAL RESULTS: EEG DATA

		Delta	Theta	Alpha	Beta
Main effects					
Epoch 1 (0–12 h)	Tx	$F(1, 7) = 0.20, p = 0.66$	$F(1, 7) = 2.46, p = 0.16$	$F(1, 7) = 5.36, p = 0.05$	$F(1, 7) = 5.85, p = 0.04$
Epoch 2 (12–24 h)	Tx	$F(1, 7) = 0.74, p = 0.42$	$F(1, 7) = 1.66, p = 0.24$	$F(1, 7) = 2.05, p = 0.19$	$F(1, 7) = 6.94, p = 0.03$
Epoch 3 (24–36 h)	Tx	$F(1, 7) = 0.19, p = 0.67$	$F(1, 7) = 0.10, p = 0.76$	$F(1, 7) = 0.61, p = 0.45$	$F(1, 7) = 1.44, p = 0.27$
Epoch 4 (36–48 h)	Tx	$F(1, 7) = 4.92, p = 0.06$	$F(1, 7) = 4.32, p = 0.08$	$F(1, 7) = 1.71, p = 0.23$	$F(1, 7) = 1.60, p = 0.25$
Post hoc specific effects					
Acute effects (0–8 h)	Tx	$F(1, 7) = 0.63, p = 0.45$	$F(1, 7) = 2.44, p = 0.16$	$F(1, 7) = 4.43, p = 0.07$	$F(1, 7) = 6.36, p = 0.03$
Withdrawal effects (10–14 h)	Tx	$F(1, 7) = 0.40, p = 0.54$	$F(1, 7) = 0.05, p = 0.81$	$F(1, 7) = 0.45, p = 0.52$	$F(1, 7) = 1.03, p = 0.34$

F-values reflect tests conducted between saline (SC) and cocaine (32 mg/kg SC). Tx, treatment.

doses of COC. Both of the previously controlled clinical electroencephalogram studies of Herning et al. (26) and Alper et al. (1) were conducted in patients previously self-exposed to multiple COC administrations. The different acute effects found in the present study and those of these other authors may reflect prior development of tolerance to the acute effects of COC over the course of prior self-administration of COC in these clinical populations. The present study demonstrated the long-term recording of ECoGs in undisturbed (rat) subjects and the presence of an opponent-like compensatory ECoG response to acutely administered COC, which occurred approximately 10–14 h after SC administration.

Analysis of the temporal profile of the subjective effects of COC by using a three-choice drug discrimination task in experiment 3 demonstrated the presence of an *isodirectional* compensatory response to the acute effects and suggests a role for *sensitization* processes during adaptation to a course of chronic COC exposure. We have also demonstrated a rapid and short-lived opponent-like acute subjective effect of HDL administration. Rats engendered approximately 75% of the

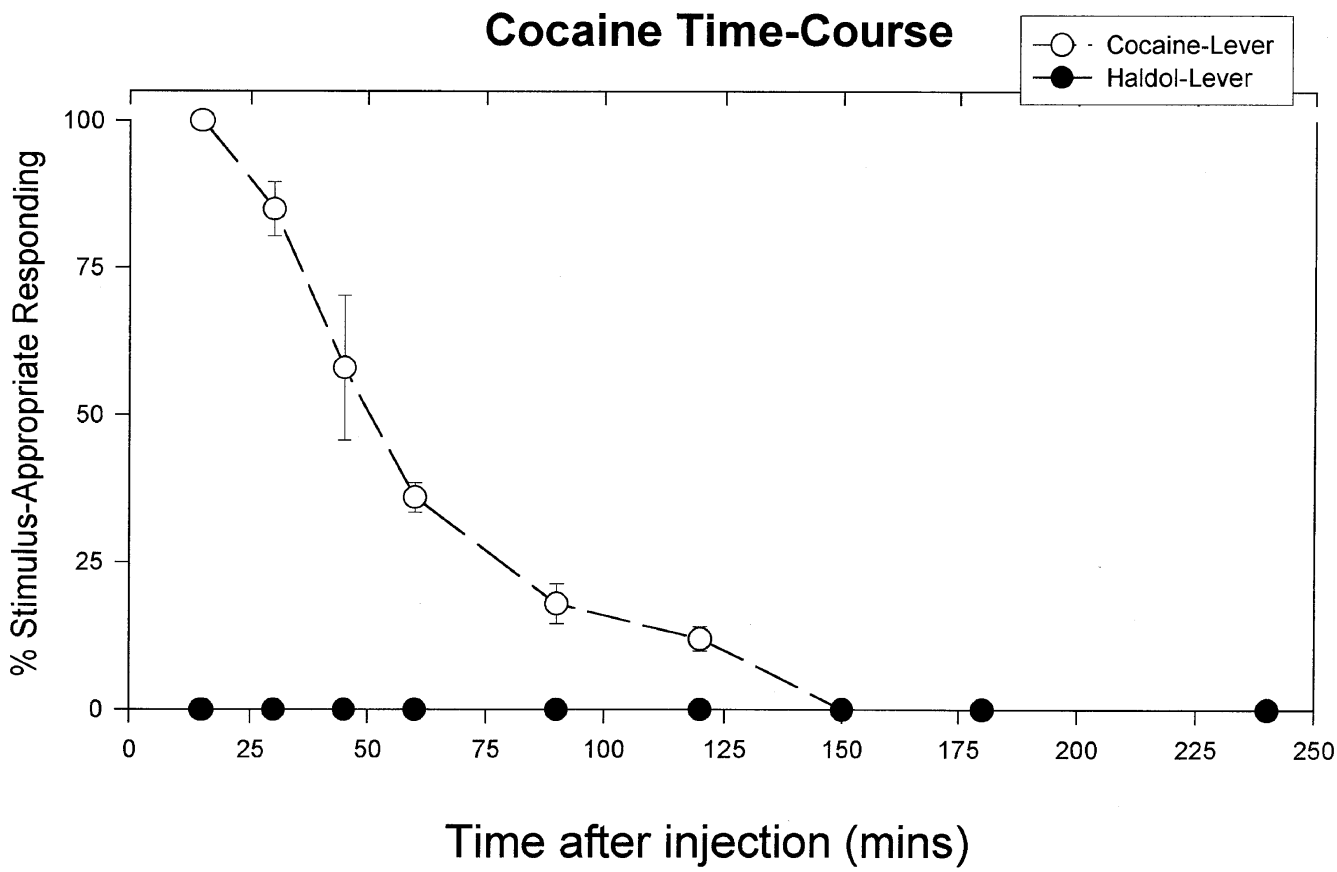


FIG. 4. Time–effect functions for cocaine administered with saline. The percentages of total session responses emitted on the COC- and HDL-appropriate levers are expressed as a function of pretreatment time of the COC training dose. Rats were trained in a three-choice HDL (0.1 mg/kg)–SAL–COC (10 mg/kg) discrimination task. All responses were engendered on the COC- and SAL-appropriate levers only. The median effective time interval for the COC training stimulus was 50.5 min. Each point represents the mean of six trained rats.

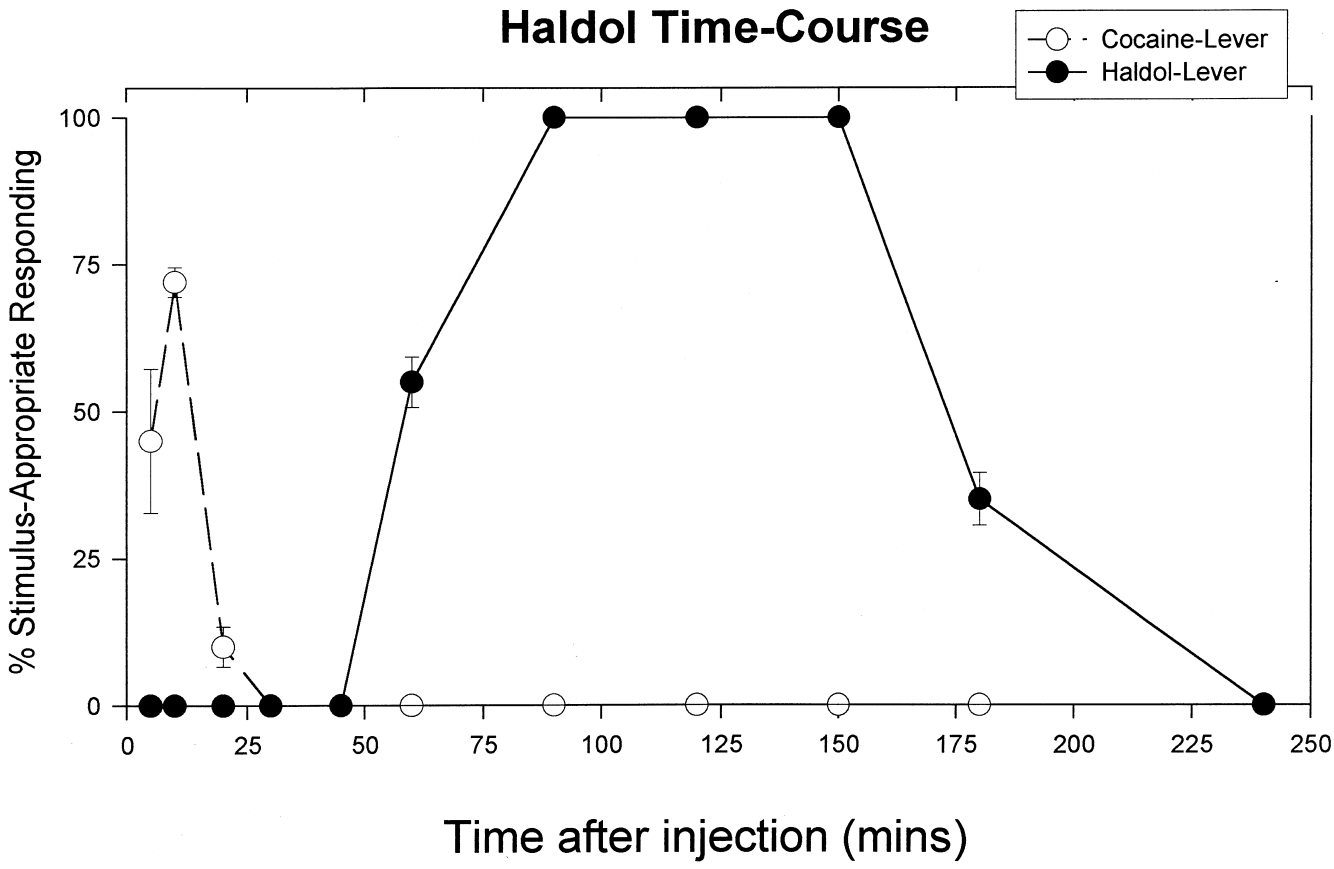
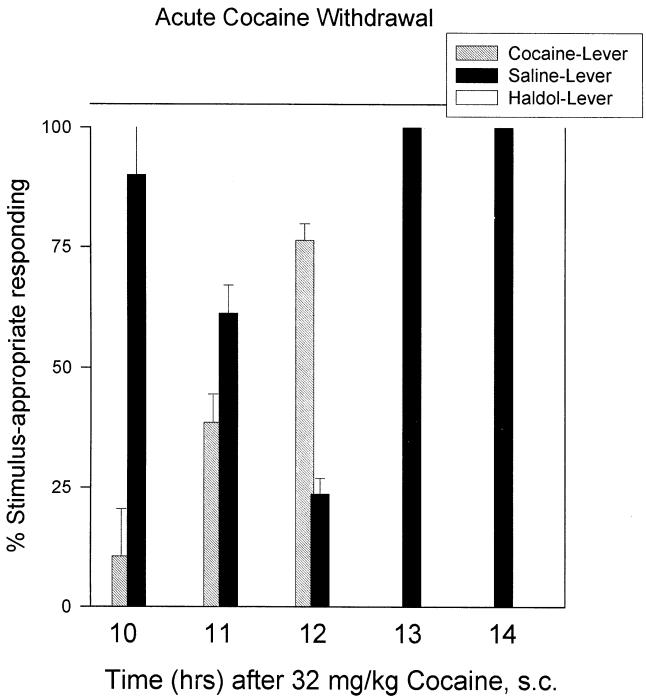


FIG. 5. Time–effect functions for haloperidol administered with saline. The percentages of total session responses emitted on the COC- and HDL-appropriate levers are expressed as a function of pretreatment time of the HDL training dose. Rats were trained in a three-choice HDL (0.1 mg/kg)–SAL–COC (10 mg/kg) discrimination task. Responses were distributed on all three active levers. The median effective time interval for the HDL training stimulus was 192 min. Each point represents the mean of six trained rats.



total test session responses on the COC-appropriate lever 10 min after an acute injection of the training dose of HDL. This COC-like effect was short-lived and may represent the endogenous release of dopamine by administration of the dopamine antagonist HDL. This conclusion is similar to those of previous reports of potentiation or release of DA activity by administration of its antagonist (2,25,27,29,33,35,47,73,77) and may be related to the negative efficacy of the antagonist itself [cf. (36,37)]. As noted earlier, HDL produces acute hypothermia in rats (48), similar to the acute effect of COC.

The present examination of the subjective effects of acute COC withdrawal in the rat demonstrated a unique *isodirectional* COC-like response pattern during the 10–14-h post-injection interval that paralleled the peak in hyperthermic rebound. This isodirectional rebound subjective state implies a role for sensitization mechanisms in the development of adap-

FIG. 6. Subjective effects of acute cocaine withdrawal in rats trained in a three-choice HDL (0.1 mg/kg)–SAL–COC (10 mg/kg) discrimination task. Each of the six trained rats received 32 mg/kg COC SC and was tested in individual 10-min test sessions every hour from the 10th through 14th h after COC administration. No HDL-appropriate lever responding was emitted by any rat. An isodirectional (COC-like) rebound was demonstrated in a time-dependent fashion, peaking at 12 h after the 32-mg/kg COC injection.

tive responses to repeated COC administration. These data would support a prediction that the development of sensitization to the COC cue should occur over repeated COC administration in the rat. These data and predictions parallel the unique COC-induced craving previously reported in COC abusers by Jaffe et al. [(28); see below].

Recently, some authors have suggested that intermittent COC administration produces sensitization and continuous administration results in tolerance to subsequent challenge doses of COC (39–42). Under this view, the acute intermittent injections used in experiments 1 and 2 and the relatively long-term or chronic administration used in the drug discrimination task of experiment 3 in the present study may reflect different underlying mechanisms. However, we do not believe that the data from the present study can be used to infer differential adaptations to COC administration for the following reasons. a) Tolerance or sensitization does not develop to COC, but rather to the behavioral effects of COC (62,63). b) Tolerance or sensitization occurs to certain effects of the drug but not to others, and is manifested to different effects of the drug in the same organism (32). Finally, c) the development of sensitization to those behaviors comprising the psychomotor stimulant-induced behavioral (PSIB) continuum (12,13,69) is relatively unaffected by administration parameters (38). As summarized by Kilbey and Sannerud (38), relatively few exposures to psychomotor stimulants at relatively long intervals are sufficient to demonstrate sensitization, as measured by augmentation of the initially induced component of the PSIB continuum, and longer periods of exposure result in sensitization, as measured by shifts to more extreme forms of PSIB than those originally seen following a unit dose (p. 314). In addition, Kilbey and Sannerud (38) suggested that studies that have reported tolerance to continuous exposure to psychomotor stimulants may actually represent sensitization of more extreme forms of PSIB.

Data from our drug discrimination study do not suggest that tolerance or sensitization to the behaviorally disruptive or discriminative effects of COC had developed over the course of the study. The 50 ($\pm$4)-min median effective time interval (METI) for the COC discriminative cue in the present three-choice drug discrimination task is similar to the 60 ($\pm$6)-min METI we previously reported for a similar 10-mg/kg COC cue in a more typical two-choice COC vs. SAL drug discrimination task (16). The 192 ($\pm$1.6)-min METI for the HDL discriminative cue in the present study seems to parallel the time course of HDL's effects on central nervous system dopamine [cf. (2,27)]. The rates of responding engendered by COC during the present set of studies were not significantly different from the initial rates of responding during the initial training phase of discrimination (17). Finally, an extended 3-week washout period occurred between the data collection period described in our previous report (17) and the period associated with the present results. If tolerance or sensitization had occurred during the initial training and testing period, a change in discriminative and rate-altering effects to baseline levels would have been predicted over the long washout period. During the first 3 days of retraining, the rats engendered >90% discriminative accuracy, and no significant rate-altering effects were produced by any of the three training stimuli.

We have demonstrated acute COC withdrawal in the rat analogous to the COC "crash" (21) associated with human COC abuse. Acute withdrawal from COC is characterized by hyperthermia, hypoactivity, minor elevations in the amplitude of relative power for both alpha and beta brain wavelengths, and a subjective or interoceptive COC-like state.

Dackis and Gold (5–7,23) have postulated that chronic abuse of COC leads to a functional depletion of dopamine. Dackis and Gold (5–7) and Koob and Bloom (45) have further postulated that this dopamine depletion underlies the rebound or COC withdrawal syndrome. The presence of a COC withdrawal syndrome and the subjective effects of COC craving have been suggested to be causal links to continued COC administration. Self-medication or escape from the aversive attributes of withdrawal symptoms has been suggested to play an important role in the addictive process (5–7,30,45). The data from the present study do suggest that the acute COC crash occurs in an opponent fashion to the acute or immediate effects of COC. However, our data identify a number of physiological changes that occur across the intoxication and withdrawal phases of COC and do not support any conclusions regarding any one underlying neurotransmitter change which may produce these effects.

We suggest that the COC-like subjective effects engendered in rats in the drug discrimination task of the present study, occurring approximately 13 h after SC administration of 32 mg/kg COC, are similar to the verbal reports of COC craving in humans occurring 15 min after an intravenous (IV) bolus administration of COC described by Jaffe et al. (28). This conclusion is based on the hypothesis that the acute withdrawal syndrome is correlated with the rate of change in the declining serum/brain COC levels as they approach zero (31). Jones (31) has concluded that serum COC levels do not adequately reflect brain COC levels, and the brain levels are the important determinants of the subjective effects. Because humans have a relatively high level of cholinesterase, the half-life of COC is relatively short (31); rats, on the other hand, have relatively low levels of cholinesterases (31), so SC administration of COC in rats in the present study had a half-life of approximately 2 h (52). Wesson and Smith (76) have described the experience of IV-administered COC as an intense rush occurring within 2 min; because the effects of COC dissipate rapidly, there is an intense need for another shot 10 min later. Resnick and coworkers (59) and Fischman et al. (14) found that the significant cardiovascular changes occurring in humans after IV administration of 32 mg/kg COC occurred in 2 min, peaked in 5–10 min, and then declined. The increase in craving scores in the Jaffe et al. study (28) occurred at a time when serum COC levels would have been on the declining slope of the COC kinetic function, approaching zero. Although not specifically assayed in the present study, the large dose of 32 mg/kg of COC administered to rats in the present study would have produced an effective dose of 0.37 mg/kg at the peak of the isodirectional (COC-like) rebound and on the declining slope of the serum COC clearance function. Because of the differential species-specific and route of administration-dependent time courses of the effects of COC, direct temporal comparisons of the present animal analogue with the human COC crash should not be inferred. The general phenomenon of the COC-like crash in rat subjects, occurring as the COC levels approach zero, may serve as a useful model of the human condition for assessing the efficacy of pharmacological and therapeutic interventions that may be useful in clinical settings.

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