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Conditioned Suppression With Cocaine as the Unconditioned Stimulus

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SCHINDLER, C. W., E. B. THORNDIKE, J. D. MA AND S. R. GOLDBERG. *Conditioned suppression with cocaine as the unconditioned stimulus.* PHARMACOL BIOCHEM BEHAV **65**(1) 83–89, 2000.—A conditioned-suppression procedure was used to study drug conditioning using cocaine as the unconditioned stimulus (UCS). Rats were first trained to nose poke for food-reinforcement during daily 60-min sessions. At least 1 week following jugular vein catheterization, a 5-min tone–light compound stimulus was presented 30 min into the food-reinforcement session. Two minutes after the onset of the stimulus, either 0 (saline), 1.0, 3.0 or 5.6 mg/kg cocaine, was administered IV to separate groups of rats. For another group, the stimulus was presented, and the 5.6 mg/kg dose of cocaine was injected in an unpaired fashion (i.e., at different times). After 5 days of training a test was given with the tone–light stimulus presented alone. No disruption of responding during the tone–light stimulus was observed in the saline and 1.0 mg/kg cocaine groups or for the unpaired group. When the tone–light stimulus was paired with 5.6 mg/kg cocaine; however, it produced nearly a 50% reduction in responding, which then gradually extinguished when the stimulus was presented alone for 5 days. The 3.0 mg/kg cocaine group produced intermediate suppression. When the tone–light compound stimulus was shortened to 70 s and the interstimulus interval (ISI) was 0, 30, or 60 s in three separate groups of rats, the most robust conditioned suppression was observed at the 60 s ISI. Therefore, the conditioned suppression procedure, using 3.0 or 5.6 mg/kg IV cocaine doses as the UCS, produced robust conditioning effects comparable to other drugs and more conventional reinforcers. The conditioned suppression procedure may be a useful model for studying the classically conditioned effects of cocaine. © 1999 Elsevier Science Inc.

Cocaine Conditioned suppression Classical conditioning Interstimulus interval Rats

CONDITIONING plays an important role in many theories of drug abuse (25). Wikler (32) proposed over 30 years ago that classical conditioning of drug withdrawal effect plays an important role in relapse to drug abuse, and Siegel (27) has proposed that classical conditioning plays an important role in drug tolerance. Although much research has focused on this issue, almost all of that research has used diverse environmental stimuli as the conditioned stimulus (CS) for drug conditioning. For example, pairing the environment of a locomotor activity chamber with cocaine injections leads to conditioned sensitization (24), or pairing a distinct environment with cocaine injections can produce conditioned place preference (2). Although the environment clearly functions as a conditioned stimulus in these situations, it is not clear which aspects of the environment have been conditioned or whether only the environment as a whole is effective. This stands in marked contrast to the more traditional classical conditioning situation where discrete stimuli such as tones and lights are presented for short periods of time during any one conditioning session (18). We have recently shown that discrete tone and light stimuli can be conditioned to produce locomotor-activating effects when paired with cocaine (21), although even here the tone and light were presented throughout the conditioning session.

One procedure that has been used successfully to condition drug effects to discrete stimuli is conditioned suppression. This procedure was originally used by Estes and Skinner (9) to produce what they termed a "conditioned emotional response." Animals are typically trained to respond on an operant baseline for food reinforcement. A discrete stimulus such as a tone or light is then presented for a short period of time (2–5 min) followed by an unconditioned stimulus (UCS) such as shock presentation. The development of conditioning is

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then measured as a disruption (suppression) in the ongoing operant behavior (3).

This procedure has been used with some success using drugs as the UCS. Drugs that have been shown to support conditioning include chlorpromazine (4), LSD (4,5), psilocybin (5), amphetamine (8,30,31), and pentobarbital (7,30). In opiate-dependent animals, nalorphine will also serve as a UCS (11–13). Although most studies have shown that drugs support conditioned decreases in response rates, conditioned increases have also been reported when a drug produces unconditioned increases in response rates (13,30).

The purpose of the present experiment was to determine whether cocaine injections could also support conditioning within a conditioned-suppression paradigm, and to determine some of the parameters necessary to support such conditioning. Few studies have looked at the importance of dose in supporting conditioned suppression, and none have looked at the role of the interstimulus interval (ISI, time between conditioned stimulus and UCS onsets). In addition, the associative nature of the conditioning (i.e., whether the temporal pairing of the CS and UCS is necessary) has not been definitively established, as no study has used controls for nonassociative factors.

METHOD

Subjects

The subjects were male Sprague–Dawley rats, weighing approximately 200 g upon arrival in the laboratory. They were housed individually in a temperature- and humidity-controlled room with a 14L:10D cycle (lights on at 0600 h EST) and had free access to food and water. Once an animal reached approximately 375 g they were deprived to 85% of that free-feeding weight by limiting food access.

For IV drug administration, jugular-vein catheters were implanted according to procedures described in detail elsewhere (22). In brief, approximately 4 cm of Silastic tubing (Dow Corning, 0.44 mm i.d., 0.9 mm o.d.) was inserted into the right jugular vein and connected to vinyl tubing (Dural Plastics, 0.5 mm i.d., 1.0 mm o.d.), which exited the back at the midscapular region, and was plugged with an obturator. A 20-mm nylon screw was cemented to the skull immediately after catheter implantation to serve as a head mount for connecting the metal catheter protecting spring to the animal. Catheters were flushed before and after each training session with 0.1 ml of a saline solution containing 1.25 units/ml heparin and 0.08 mg/ml gentamicin.

All animals used in this study were maintained in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC). All procedures were conducted in accordance with the guidelines of the Institutional Care and Use Committee of the NIDA/IRP and the Guide for the Care and Use of Laboratory Animals (6).

Apparatus

Operant chambers (Model E10-18, Coulbourn Instruments) were enclosed individually in sound-attenuation chambers. Each chamber had a grid floor. On the front wall there were two nose-poke holes on either side of a food trough. The nose-poke holes could be illuminated from inside the hole by a dim yellow light. Only the left nose-poke hole was used in the current experiment. A 4500-Hz auditory stimulus (#628 Sonalert operated at 8.75 V) and a shielded houselight (#1820) served as stimuli, and were situated above and between the nose-poke holes. Food pellets (Bio-Serv #F0021, 45 mg) could be delivered into the food trough. Cocaine or saline was delivered through Tygon tubing wrapped in a metal spring and suspended from the ceiling by a single-channel fluid swivel (Alice King Chatham). The spring was attached to the animal's head mount. The swivel was attached to a syringe pump (Harvard, model 22). Experimental events were controlled by a MED-PC computer system (Med Associates).

Experiment 1—Direct Effects of Cocaine on Operant Behavior

Six naive rats were first trained to nose poke for food by reinforcing each nose poke with a food pellet. The start of the session was indicated by illumination of the nose-poke hole. The schedule of reinforcement was gradually increased to a tandem variable-interval (VI) 60-s fixed-ratio (FR) 4. On this schedule, the first four response ratio completed after an average period of time of 60 s was reinforced with a food pellet. However, there were no stimulus changes associated with the completion of the ratio prior to reinforcement. This schedule was chosen based on a previous conditioned suppression study using amphetamine as the unconditioned stimulus (8). Sessions were 80 min in duration. Once responding stabilized on this schedule, an intravenous catheter was implanted as described above. Following recovery from surgery, the rats were returned to the tandem schedule and trained until responding was again stable. Typically, there were only minor disruptions in behavior following surgery. The rats were then tested with a variety of doses of cocaine (0, 1, 3, and 5.6 mg/kg IV) to assess the direct effects on operant behavior. The animals were allowed to respond on the tandem schedule for approximately 30 min, and then given the IV injection. Responding on the tandem schedule was then monitored for an additional 50 min. Only one dose was tested per day, and there were at least 3 days between tests where no drug was given. Each rat received all doses. During this and all subsequent experiments, the food schedule remained in effect throughout the session, and was independent of stimulus or drug presentations.

Experiment 2—Conditioned Suppression with Cocaine as UCS

Naive rats in this study were trained identically to those in Experiment 1 up to the point of drug testing, except that sessions were 1 h in duration. Following stabilization on the tandem schedule after surgery, a 5-min tone–light CS was presented approximately 30 min into the training session. For one group of rats ($n = 7$), an IV injection of saline was given 2 min into the CS. For two other groups, an IV injection of either 1 mg/kg cocaine ($n = 6$) or 5.6 mg/kg cocaine ($n = 8$) was given 2 min into the stimulus. Finally, for an unpaired group ($n = 7$), 5.6 mg/kg cocaine was given IV 10–20 or 40–50 min into the session, and the CS was presented at the other time period. The order of stimulus presentation was reversed in about half the sessions, and whether cocaine or the stimulus was presented first on day 1 was counterbalanced across rats. For all groups, training continued for 5 days, with tone–light stimulus presentations occurring each day. On day 6, all rats were injected with saline instead of cocaine, and responding during the tone–light stimulus was monitored. Following this suppression test, the 5.6 mg/kg cocaine-trained rats continued to receive the tone–light stimulus and IV injection of saline for an additional 4 days. Most other studies of conditioned suppression with drugs as the UCS have used a habituation period for the CS. A habituation period (presentation of the CS alone prior to conditioning) was not used in these studies to avoid the possibility of latent inhibition influencing the results (17).

Experiment 3—Dose–Effect Function for Cocaine

Training for this experiment was identical to that of Experiment 2, except that a VI 240-s schedule was used to maintain responding. This schedule was used to determine whether suppression would be affected by a schedule that maintained a lower rate of responding. Following restabilization of behavior after surgery, separate groups of naive rats were given suppression training using IV injections of saline ($n = 5$), 1 mg/kg cocaine ($n = 5$), 3 mg/kg cocaine ($n = 6$), or 5.6 mg/kg cocaine ($n = 6$) as the UCS. Stimulus parameters were otherwise the same as Experiment 2, and there were again 5 days of training followed by a test day, during which saline was substituted for cocaine.

Experiment 4—ISI Effects on Conditioned Suppression

Initial training for this experiment was identical to that of Experiment 2, except that a VI 60-s schedule was used to maintain responding. A VI 60-s schedule was used to maintain higher response rates than the VI 240-s schedule used in Experiment 3. With the shorter ISI values used in this experiment, changes in rate would be easier to detect than with the slower rates of the VI 240-s schedule. Following stabilization on the VI schedule after surgery, a 70-s tone–light CS was presented approximately 30 min into the session. The stimulus duration was shortened so that the stimulus would not be on for a long period of time following UCS presentation. Three groups of four naive rats each were then trained, with 3.0-mg/kg cocaine as the UCS, with ISIs of 0, 30, and 60 s. Training continued for 8 days, with stimulus presentations occurring each day. On day 9, all rats were injected with saline instead of cocaine. Following this suppression test, the rats continued to receive the tone–light stimulus and saline for an additional 4 days.

Drug

Cocaine hydrochloride (NIDA, Baltimore, MD) was dissolved in sterile saline at a concentration of 8.0 mg/ml and injected at a rate of 3.0 ml/min. The duration of the injection was adjusted for the weight of the animal and dose. Doses are expressed as the salt.

Data Analysis

Responses were collected in 1-min bins throughout the session, and response rates were tabulated. All stimulus onset times were set to occur at the beginning of these 1-min bins. Responding during a 2–5-min period prior to stimulus (drug injection UCS in Experiment 1, tone–light CS in Experiments 2–4) presentation was used as the baseline. A 5-min period was used for Experiments 1–3, where the longer 5-min stimulus times were analyzed. A shorter 2-min period was used as the baseline in Experiment 4, for comparison with the shorter 70-s tone–light stimulus period, and for the training phase of Experiment 2, where only the 2-min stimulus period prior to injection of cocaine was used for analysis. On average, these baseline rates were consistent with response rates during the entire session prior to stimulus presentation. Where appropriate, data were analyzed using ANOVA with follow-up tests using the Fisher LSD method (33). Comparisons to 100% of baseline were made using paired *t*-tests.

RESULTS

Experiment 1—Direct Effects of Cocaine on Operant Behavior

Rats responded at a high rate on the tandem VI-FR reinforcement schedule. Baseline rates of responding for the saline, 1, 3, and 5.6-mg/kg test sessions were 86.4 ± 10.0, 81.7 ± 11.0, 75.9 ± 9.0, and 94.2 ± 11.3, responses/min (resp/min), respectively. The injection of saline had little effect on responding, with response rates remaining near baseline levels throughout the remainder of the session (Fig. 1). At the lowest dose (1 mg/kg) tested, cocaine produced a small increase in responding 10–15 min following the injection, with rates returning to baseline by 25 min. At the 3-mg/kg dose, cocaine produced a clear decrease in responding immediately following the injection, with rates recovering toward baseline 15 min following the injection, and then increasing above baseline for much of the remainder of the session. At the highest dose (5.6 mg/kg), cocaine depressed responding for at least 20 min following the injection. Because the 5.6-mg/kg dose produced only decreases in response rates and the 1.0-mg/kg dose produced only increases, albeit very small, those doses were chosen for conditioning in Experiment 2.

Experiment 2—Conditioned Suppression with Cocaine as UCS

Figure 2 shows the course of conditioning during training sessions for the 5.6 mg/kg cocaine group compared to the saline controls. On day 1 of training, response rates were suppressed for both groups with the presentation of the novel tone–light stimulus. This suppression habituated rapidly for the saline group, while responding for the conditioning group remained depressed.

Following 5 days of training, all the rats were tested with only the tone–light stimulus and injection of saline on day 6. The results of that test are shown in Fig. 3. There were clear differences between the groups, $F(3, 23) = 13.1$, $p < 0.001$. Responding during the stimulus for the group conditioned with 5.6-mg/kg cocaine was depressed below baseline ($p < 0.05$). This group also differed from all three of the other groups. In contrast, responding during the stimulus in the sa-

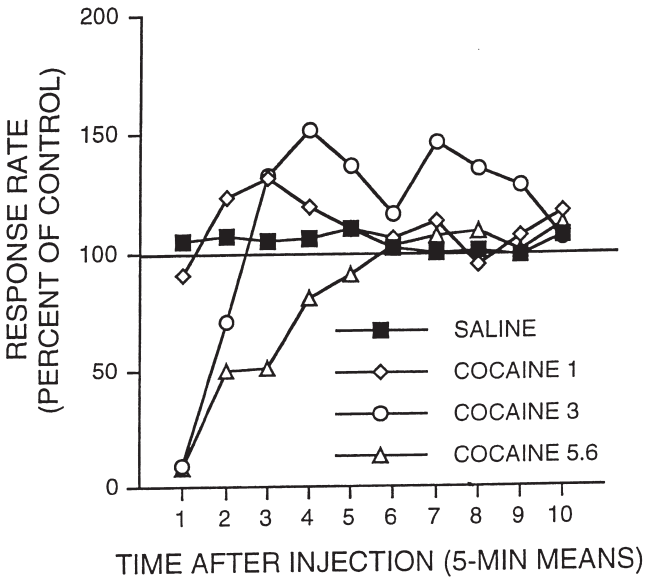

FIG. 1. The unconditioned effects of cocaine on responding in rats maintained on a tandem VI 60-s FR 4 schedule of food reinforcement in Experiment 1. Cocaine was given IV approximately 30 min into the 80-min session. Data are presented as a percent of control, with the 5-min just prior to the injection used as the control. The first data point is the 5 min immediately following the injection. Doses are in mg/kg.

line and the 1-mg/kg cocaine conditioning groups did not differ from baseline, nor did these groups differ from each other. Responding during the stimulus for the unpaired group was actually elevated above baseline ($p < 0.05$), and responding for this group also differed from the other three groups. Following conditioning, rats in the 5.6-mg/kg cocaine group continued to be trained with saline as the UCS (extinction). Figure 4 shows that responding gradually returned to near baseline levels by day 5 of extinction (study day 10).

Baseline responding was not affected by the conditioning procedure. On day 1 of training (prior to any stimulus presentation), the baseline response rate was 90.9 ± 6.6 resp/min for the saline group, while for the day 6 test session the baseline response rate was 100.2 ± 10.9 resp/min. The same day 1/day 6 comparisons for the other conditioning groups were: cocaine 1 mg/kg, 100.9 ± 14.0/102.9 ± 9.0 resp/min; cocaine 5.6 mg/kg, 80.5 ± 10.6/79.7 ± 10.1 resp/min. Baseline rates for the unpaired group on day 1 of testing prior to the drug injection were 85.1 ± 10.5 resp/min. On the test day, baseline rates for the unpaired group were 74.0 ± 3.4 resp/min.

Experiment 3—Dose–Effect Function for Cocaine

The use of the VI 240-s schedule led too much lower response rates. Baseline response rates on day 1 of testing were 28.2 ± 3.2, 25.8 ± 10.5, 30.5 ± 9.7, and 29.7 ± 7.3 resp/min for the saline, 1.0, 3.0, and 5.6-mg/kg groups, respectively. Conditioning did not systematically affect baseline response rates, with the test day baseline rate being 28.8 ± 7.7, 33.7 ± 13.2, 18.4 ± 4.0, and 29.7 ± 5.4 resp/min for the same groups, respectively.

Percent responding during the stimulus compared to baseline on the day 6 test is shown in Fig. 5, $F(3, 18) = 5.8$, $p < 0.01$. Follow-up tests indicated that responding for the 5.6-mg/kg cocaine group was significantly lower than both the saline and 1-mg/kg group, while responding for the 3.0-mg/kg groups was significantly lower than the 1.0-mg/kg group. The difference between the 3.0-mg/kg and saline groups approached significance ($p = 0.091$). The 5.6- and 3.0-mg/kg groups did not differ.

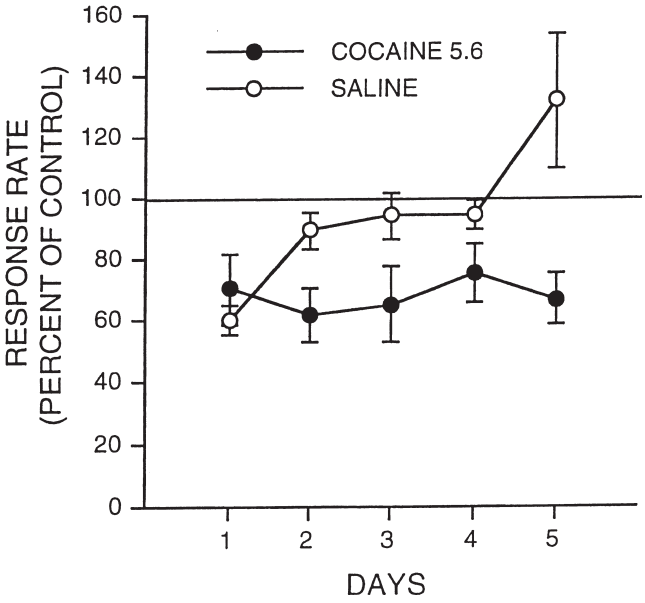

FIG. 2. Response rates for the 5 training days for rats given stimulus and 5.6 mg/kg cocaine pairings or stimulus and saline pairings in Experiment 2. Data are presented as percent of control response rates during the 2-min period of the tone–light stimulus prior to the cocaine injection, using the 2-min period just prior to the stimulus as the control. Note that the tone–light stimulus initially disrupted responding for both groups.

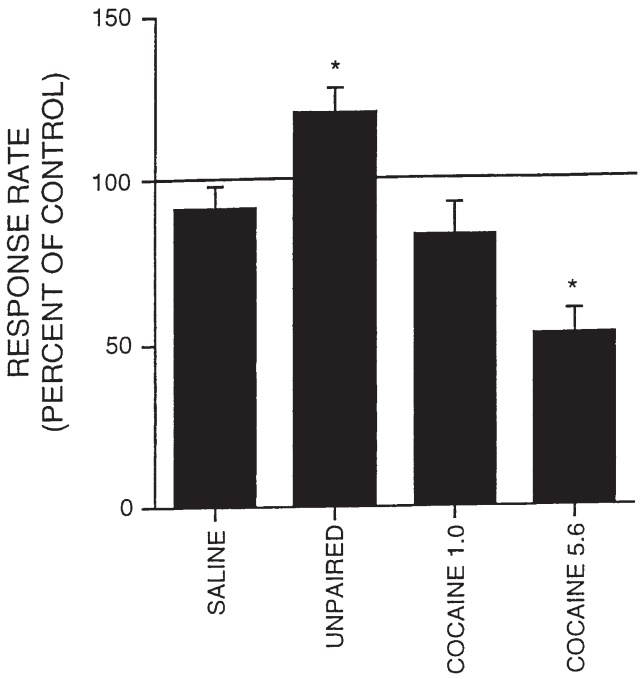

FIG. 3. On the sixth day of testing for conditioned suppression in Experiment 2, the animals were given the tone–light stimulus paired with a saline injection. Percent of control response rates are calculated for the 5-min period of the tone–light stimulus, with the 5 min just prior to the stimulus serving as the control. Doses are in mg/kg. The saline, 1.0-mg/kg cocaine, and 5.6-mg/kg cocaine groups had previously received five pairings of a 5-min tone–light compound stimulus with the appropriate drug. The unpaired group had received five stimulus presentations and 5.6 mg/kg cocaine injections in an unpaired manner. *$p < 0.05$ from 100% of baseline.

Experiment 4—ISI Effects on Conditioned Suppression

Baseline response rates were higher on the VI 60-s schedule than on the VI 240-s schedule, but were generally not as high compared to the tandem schedule. On day 1 of training, baseline rates of responding for the 0-, 30-, and 60-s ISI groups were 45.1 ± 11.2, 43.4 ± 18.2, and 64.2 ± 18.7 resp/min, respectively. The conditioning procedure did not alter those baseline rates, with baseline rates on the test day being 52.9 ± 11.2, 45.5 ± 5.5, and 50.8 ± 14.6 resp/min, respectively.

Figure 6 shows the response rates during the test as a percent of the baseline control rate. The 60-s ISI appeared to produce the largest effect, although the groups were not significantly different, $F(2, 10) = 0.5$. Both the 0- and 60-s groups were different from the expected baseline rate ($p < 0.05$). Following 5 days of extinction, the 60-s group remained below baseline at 39.7% of control ($p < 0.05$), while the 0- and 30-s groups returned towards baseline (84.8 and 91.6%, respectively).

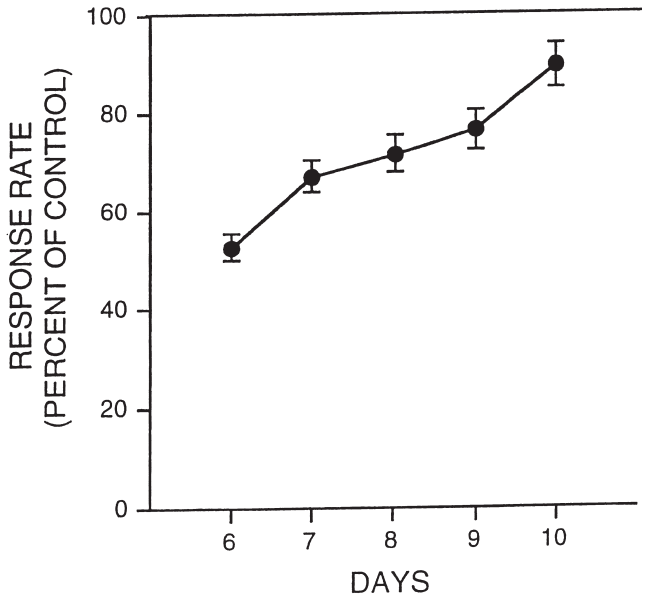

FIG. 4. Following the sixth day of testing for Experiment 2, the 5.6 mg/kg cocaine-trained animals continued to receive the tone–light stimulus paired with saline for 4 more days (extinction). Over the course of this extinction testing, response rates during the tone–light stimulus gradually returned towards baseline. Data are calculated as in Fig. 3. Day 6 is the test day data presented in Fig. 3.

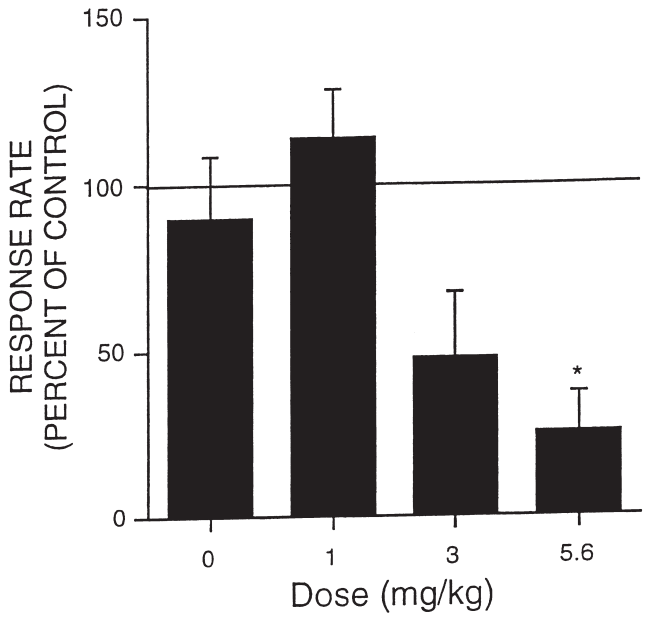

FIG. 5. Conditioned suppression tests for those animals trained with the VI 240-s schedule in Experiment 3. During the conditioned suppression test on the sixth day, the animals were given the tone–light stimulus paired with a saline injection. Data are presented as percent of control response rates during the 5-min tone–light stimulus, with the 5 min just prior to the stimulus as the control. Animals were trained with either saline, 1, 3, or 5.6 mg/kg cocaine as the UCS. $^*p < 0.05$ from 100% of baseline.

The ISI appeared to affect the development of tolerance to the response rate disruption following cocaine administration. On day 1 of training, response rates during the 2 min following the administration of cocaine were 2.4 ± 1.5, 4.5 ± 3.7, and 0.25 ± 0.1 for the 0-, 30-, and 60-s ISI groups. By day 8 of training, however, response rates following cocaine were 41.1 ± 13.5, 46.9 ± 8.1, and 21.9 ± 3.1 for the same three groups. In fact, for the 0- and 30-s groups, rates following cocaine were higher than the baseline rates for that day, while for the 60-s group they were at approximately 65% of control.

DISCUSSION

The results of the current study show conclusively that cocaine as a UCS produces conditioned suppression in the rat. This agrees with the results for a number of other drugs (4,5,8,11,12,30), including the psychomotor stimulant amphetamine (8,30). Further, this conditioned suppression is the result of associative conditioning, as suppression was not observed for the unpaired condition. Thus, the classically conditioned effects of cocaine can alter ongoing learned-operant behavior.

The development of the conditioned response (response suppression) was also affected by parameters known to affect the development of classically conditioned responses, including conditioned suppression. For example, it is known that the intensity of the UCS can affect conditioning (3), and changes in the dose of cocaine affected the development of conditioning. Only the higher doses of cocaine produced conditioned suppression. At the 1 mg/kg dose of cocaine, no conditioned suppression of responding was observed when either the tandem or VI 240-s schedule-maintained responding. While no conditioned suppression of responding was observed at 1 mg/kg cocaine, no conditioned enhancement of responding was observed either. This was not entirely expected, as this dose of cocaine produced small increases in response rate when given alone. Previous investigators have shown that for drugs that increase operant response rates (13,30), conditioned increases in response rates are observed to the CS. However, the increase in response rate to cocaine was relatively small (<50%), and was not reliably seen until at least 5 min following the injection. At this time, CS would have terminated in the present study.

Another parameter known to affect the development of conditioned suppression is the ISI (18). One could argue that, because there was little difference among the groups, ISI did not affect suppression in the current study. This might not be all that surprising, as with only one trial per day, the relative relationship between stimulus duration and session time was not that much different between groups. The relative ISI duration has been shown to influence conditioning (16), including conditioned suppression (29). Nevertheless, in the current study, the 60-s ISI appeared to be optimal. The 60-s ISI produced the greatest suppression, and that suppression was sustained though five extinction sessions, while the suppression at the 0- and 30-s ISI recovered to baseline more quickly. However, the other ISIs also supported conditioning, including the 0-s ISI condition. Typically, a 0-s ISI will not support conditioning (18), but suppression was observed in the current study at this ISI. The most likely explanation for this is that the onset of the peak drug effect is probably delayed by a few seconds, even for IV administration. Therefore, even though a 0-s IS was arranged, the actual ISI may have been longer. An interesting finding in the ISI study was that response rate following cocaine administration appeared to re-

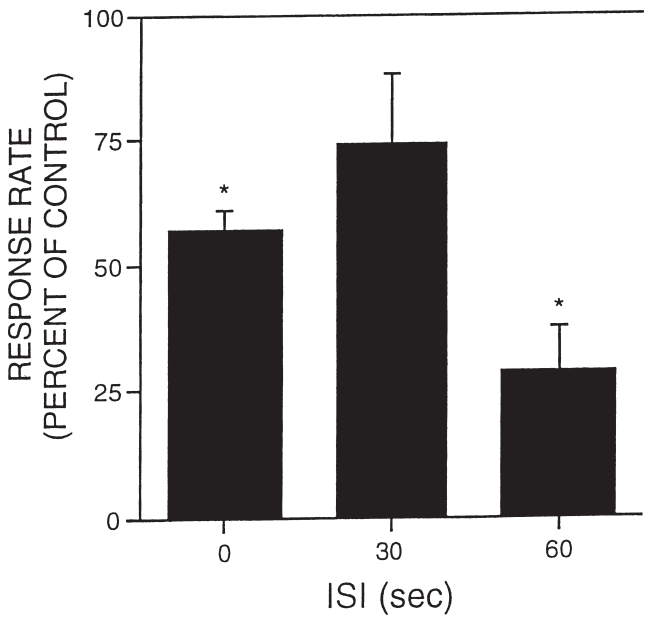

FIG. 6. Conditioned suppression tests for those animals trained with the VI 60-s schedule in Experiment 4. During 8 training days a 70-s tone–light compound stimulus was paired with a 3.0-mg/kg cocaine injection with either a 0, 30, or 60-s ISI. During the conditioned suppression test on the ninth day, the animals were given the tone–light stimulus paired with a saline injection. Data are presented as percent of control response rates during the 70-s tone–light stimulus with the 2 min just prior to the stimulus as the control. $*p < 0.05$ from 100% of baseline.

cover faster with the shorter ISIs. This suggests that behavioral tolerance may be influenced by the relationship of the CS to the drug administration.

Conditioned suppression has often been interpreted as the disruption of responding by conditioning of the aversive effects of the UCS (9). In contrast, when a positive reinforcer is used as the UCS, a number of theories would suggest that responding would be increased (23) when a conditioned stimulus for that positive reinforcer is presented on an operant baseline for food reinforcement. In this regard, it may be surprising that cocaine suppressed responding, because cocaine is well known as a positive reinforcer. However, previous research with more conventional positive reinforcers such as food and water often report that they produce suppression of ongoing positively reinforced behavior, a phenomenon known as positive conditioned suppression (1,19,20). Typically, positive conditioned suppression is observed when two different positive reinforcers are used to maintain operant responding and to serve as the UCS (1), and suppression is more likely with shorter CS durations and ISIs (19,20). Therefore, the effects seen here may be analogous to the previous observations of positive conditioned suppression. In addition, as noted above, another psychostimulant that can serve as a positive reinforcer, amphetamine, also produces conditioned suppression (8,30). The exact mechanisms for producing positive conditioned suppression are not known. Perhaps the simplest explanation is that behaviors incompatible with operant responding, such as movement toward the food trough, are conditioned to the CS. Alternatively, it may be similar to incentive–contrast effects, which are observed with taste-aversion learning (14). That is, the contrast between the strong positive reinforcer cocaine and the weaker food reinforcer is sufficient to produce suppression of the food-maintained behavior.

We cannot, however, rule out the possibility that under the conditions of the present experiment, cocaine was functioning as an aversive stimulus similar to shock. The doses used here to support conditioning (3.0–5.6 mg/kg) were higher than those typically used to support self-administration of cocaine in rats (26), and cocaine is known to have effects similar to aversive stimuli under certain conditions (10,15,28). Therefore, the exact nature of the suppression observed here is unclear. It may be analogous to the positive conditioned suppression reported for other positive reinforcers, or it may be analogous to the conditioned suppression produced by shock if cocaine's aversive properties predominate at the doses used.

In conclusion, conditioned suppression was observed to a discrete tone–light compound stimulus using cocaine as the UCS. Therefore, cocaine's effects can be classically conditioned to discrete stimuli as well as to diffuse environmental stimuli. This conditioning appears to be analogous to the conditioned suppression observed with more conventional reinforcers, in that it was associative in nature and was dependent on the UCS intensity (cocaine dose) and the interstimulus interval. Cocaine, as a UCS, has been shown to support a number of different types of conditioned responses, including conditioned activity (21) and place preference (2). The current results extend the types of conditioned responses to a cocaine UCS to include changes in operant behavior. Although conditioned decreases were observed here, further work will be necessary to determine if conditioned increases in operant rate can also be observed. Nevertheless, these results clearly show that the classically conditioned effects of cocaine can alter ongoing learned-operant behavior. The exact nature of that interaction will also require further study.

Because of the clear importance conditioning plays in the maintenance, acquisition, extinction, and relapse to drug abuse (25), a model of conditioning using a drug as a UCS with clearly defined CS parameters should be helpful in further elucidating the behavioral and physiological mechanisms involved in that conditioning. The conditioned suppression procedure should be ideal for those types of studies, as experimenters will be able to focus on a defined period of time (the CS) to observe conditioning influences.

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