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Situational Specificity of Tolerance to Decreased Operant Responding by Cocaine[1]

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SMITH, J. B. *Situational specificity of tolerance to decreased operant responding by cocaine*. PHARMACOL BIOCHEM BEHAV **36**(3) 473–477, 1990.—Responding of rats was maintained in three different environmental situations each day. Interruption of a photobeam was maintained under a shock avoidance schedule in the first session, lever pressing was maintained under a 5-min fixed-interval (FI) schedule of food presentation in a second session, and nose-key pressing was maintained under a 30-response fixed-ratio (FR) schedule of food presentation in a third session. After receiving once-weekly injections of cocaine (3–17 mg/kg) prior to each of the sessions, animals received daily administration of 13 mg/kg *after* responding in the third daily session for four weeks, *before* responding in the third session for four weeks, *before* responding in the second daily session for four weeks, and then *before* responding in the first daily session for four weeks. Tolerance that developed in the environment that was coincident with the pharmacological actions of cocaine did not extend to operants in other environmental situations. Instead, tolerance to the behavioral effects of cocaine was specific to particular stimulus conditions associated with drug administration, indicating that the expression of tolerance depended on both pharmacologic action as well as concurrently operating behavioral processes.

Cocaine Behavioral tolerance Fixed ratio Fixed interval Avoidance Rat

IT is well established that experiences with specific features of the environment can influence the occurrence and form of behavior. This association of environmental stimuli and behavior was both conjectured (7) and observed (14) in the last century, and the concept has been prominent ever since in theories of learning and performance [see (11,16)].

The association between environmental stimuli and physiological reflexes is most often studied with the experimental procedure developed by Pavlov, whereas the association between environmental stimuli and acquired operant behavior is most often studied with the experimental procedure developed by Skinner. Both of these procedures have been very useful for studying the behavioral effects of drugs (12, 20, 26, 30), and an understanding of both Pavlovian and operant functions of drug-produced stimuli has been fundamental for studying the liability for dependence and misuse of chronically administered drugs [see (2,29)].

However, it is important to recognize that tolerance and misuse are not inevitable consequences of long-term drug administration, but instead are influenced by the history of situational stimuli that are coincident with that drug administration. It has been reported, for example, that a large majority of men admitting to narcotic addiction in Vietnam gave up their habit upon returning home without showing signs of drug dependence (15), and this may have been a result of the markedly different situational circumstances surrounding their drug use and their drug abstinence. Moreover, drug lethality itself can depend on situational circumstances, and well-tolerated doses of clinically prescribed opiates can cause death when the only major difference in drug administration has seemed to be the physical setting in which the drug was taken [(20), pp. 155–157]. In laboratory experiments as well, lethality of well-tolerated doses of pentobarbital is influenced by the environment in which animals receive drug (27). Results from these experiments are consistent with the view that tolerance to the behavioral effects of drugs is not entirely dispositional [see (5)], but depends as well on behavioral processes occurring at the time of pharmacologic effects of a drug.

The present experiment studied the effects of cocaine on operant responding during repeated dosing that was associated with markedly different environmental circumstances. Individual rats were studied in three different environmental situations each day, and the presence of cocaine coincided with each separate condition. Recent experiments have demonstrated the effectiveness of this multi-environment procedure and have documented associative influences on development of tolerance to behavioral effects of phencyclidine, *l*-nantradol, and clonidine (23–25), as well as cocaine (3). A recent experiment has also used a similar procedure and documented associative influences on sensitization to effects of cocaine (28).

METHOD

Subjects

Five experimentally naive male Charles River CD albino rats

[1]Animals used in this study were maintained in accordance with guidelines of the Animal Care Committee of the Worcester Foundation for Experimental Biology and of the "Guide for Care and Use of Laboratory Animals" of the Institute of Laboratory Animal Resources, National Research Council, Department of Health, Education and Welfare, Publication Number (NIH)85-23, revised 1985.

were maintained at 300 g body weight and were approximately 6 months old at the start of the experiment. Water was always available in living cages.

Apparatus

Experiments were conducted with individual rats placed either in one of two Model C Gerbrands Rat Cages or in a smaller clear lucite chamber measuring 25 cm long × 15 cm wide × 15 cm high. Each Model C cage contained a 5-cm square opening leading into a recessed plastic enclosure (F7020 food cup, Gerbrands Corp.). One of the Model C cages had standard walls, and the recessed enclosure was connected to a solenoid-operated pellet dispenser (G5100, Gerbrands). This chamber was used to study FI responding, and experimental sessions were accompanied by masking noise and a 7-W white light mounted directly over the lever. The other Model C cage was darkened with black construction paper and the recessed enclosure was monitored by a photobeam and light-sensitive receiving cell. This chamber was used to study avoidance responding, and experimental sessions were accompanied by a low-frequency clicking sound and a 7-W blue light mounted outside a false wall near the recessed plastic enclosure. Scrambled electric stimuli could be delivered to the avoidance chamber through the grid floor by a Grason-Stadler Model 700 constant current shock generator. The smaller clear lucite chamber contained a translucent response key (G6315, Gerbrands Corp.) and a food cup (F7020, Gerbrands) on one wall and a speaker and a water tube on the opposite wall. This chamber was used to study FR responding, and experimental sessions were accompanied by a masking noise and a 7-W white light mounted outside a false wall behind the nose-key. All chambers were enclosed in larger sound-attenuating boxes. The control and recording of all scheduled events used an IBM AT-compatible computer with additional hardware and BehaviorPlus™ software developed by Princeton Economics, Inc. (Princeton, MA).

Behavioral Procedure

Avoidance responding required no special training. Whenever electric stimulation was delivered to inexperienced rats, they readily moved their heads into the dimly lit 5 cm hole and thereby interrupted the photobeam and terminated the stimulation (1.6 mA, 0.5 sec). A single interruption was counted as a response, and repeated interruption was required for subsequent responses. Interruption of the photobeam was accompanied by a brief interruption of the blue light that illuminated the recessed enclosure and by a click from a nearby relay. Watchful spacing of electric stimulation insured that animals repeatedly put their heads into the small hole after shock, and subsequent exposure to these conditions generated and maintained repeated, steady interruption of the photobeam by head movement. In the absence of responding, electric stimulation was delivered every 5 sec (shock-shock, or S-S interval). Each response postponed electric stimulation for 30 sec (response-shock, or R-S interval), and appropriately spaced responding could result in the complete absence of electric stimulation throughout the session (18). Sessions terminated after 60 min or whenever the S-S interval elapsed 60 consecutive times. This latter condition prevented excessive electric stimulation whenever drugs suppressed responding.

Nose-key and lever pressing in the other chambers was established by selectively reinforcing desired features of behavior, and responding was initially maintained under a 1-response fixed-ratio schedule which delivered single food pellets (0.045 g, Noyes Formula A) in the presence of the white light mounted over the lever of the Model C cage (FI) or behind the nose-key of the smaller lucite cage (FR). The fixed-ratio (FR) requirement was gradually increased to 40. Responding was subsequently maintained under an FI 5-min schedule in the Model C cage (three food pellets per reinforcer) or an FR40 schedule in the smaller lucite cage (one food pellet per reinforcer). The FR session terminated after 60 min, and the FI session terminated after 12 fixed-interval segments. Individual FI segments ended with a reinforcer or whenever responding failed to occur at the end of the 5-min period or during an additional 30-sec grace period.

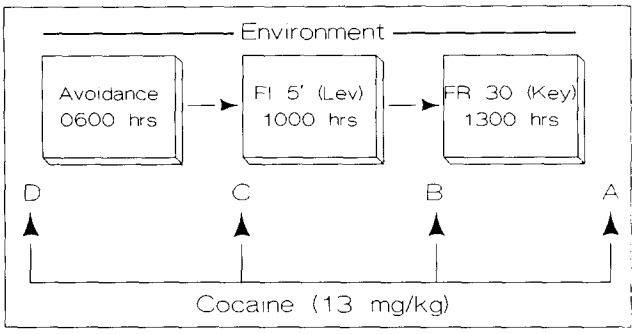

FIG. 1. Depiction of the multi-environment procedure. Schedules and session times are shown in the boxes, and injection times are shown by the arrows. Directional lines between boxes are not in real-time scale, but only describe the sequence of 60-min sessions.

During daily sessions, responding was first studied under the avoidance schedule at 6:00 a.m. in the darkened Model C cage, then at 10:00 a.m. under the FI schedule in the brighter Model C cage, and finally at 1:00 p.m. under the FR schedule in the smaller lucite chamber. With exceptions noted below for acute dosing, animals responded in all three sessions Monday–Friday. Animals responded under these conditions until variability of response rate for each schedule was within 20% for two successive weeks. The multi-environment procedure is illustrated in Fig. 1.

Drug Procedure

Cocaine hydrochloride was dissolved in 0.9% sodium chloride and injected IP in a volume of 0.25 ml/kg. Sodium chloride vehicle served as control injection. After initial training and development of stable performance, each animal received at least 5 injections of each of several doses of cocaine (3–17 mg/kg) once weekly immediately prior to each experimental session. Cocaine has a rapid onset of action and the immediate preinjection permitted observation of initial behavioral effects. When animals received acute injections of cocaine prior to the first or second session, they were not studied on that day in following sessions. Each animal received at least 7 injections of vehicle once weekly immediately prior to each experimental session, and the average of these sessions was used for comparing predrug control responding with effects of both acutely and chronically administered cocaine.

After determination of acute dose effects, animals received 13 mg/kg/day cocaine for 4 weeks immediately *after* fixed-ratio responding in the third daily session (Fig. 1, Condition A). Then, animals received the same daily dose for 4 weeks *before* fixed-ratio responding in the third daily session (Fig. 1, Condition B); for 4 weeks *before* fixed-interval responding in the second daily session (Fig. 1, Condition C); and then for 4 weeks *before* avoidance responding in the first daily session (Fig. 1, Condition D). Throughout chronic drugging, cocaine was administered at noon on weekends.

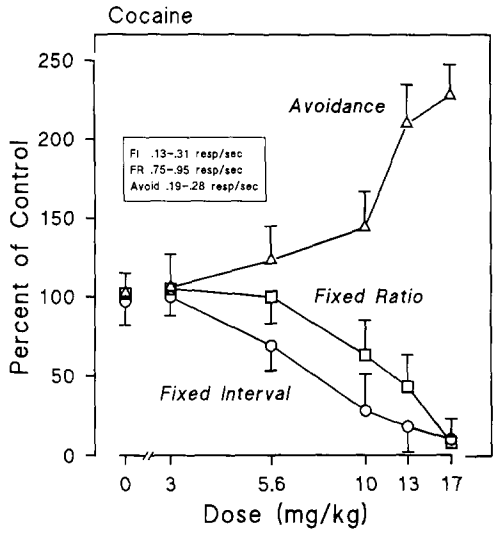

FIG. 2. Effects of cocaine on percent change in responses/min under avoidance (triangles; control mean = 0.246 ± 0.04 SD), fixed-ratio (squares; control mean = 0.85 ± 0.09 SD), and fixed-interval (circles; control mean = 0.23 ± 0.08 SD) schedules of reinforcement. Unconnected points show the average of at least 7 control sessions (± 1 SD) and connected points show the average of 5 sessions at each dose for each animal (± 1 SD).

RESULTS

Control Responding

Head-moving of rats under the avoidance schedule was similar to that reported previously for the same species studied under similar circumstances (21). Responding was maintained at moderate, steady rates (0.19–0.28 responses/sec; mean = 0.25 ± 0.04), and there were generally 20–30 electric stimuli delivered each session. Approximately two-thirds of these stimuli always occurred in the first 5–15 min of a session, and animals never received more than 7 S-S stimuli. Lever pressing under the FI schedule also occurred at moderate overall rates (0.13–0.31 responses/sec; mean = 0.23 ± 0.08) and was characterized by a pause after food delivery followed by comparatively steady responding until the next food delivery. Key pressing under the FR schedule occurred at a higher, sustained rate (0.75–0.95 responses/sec; mean = 0.85 ± 0.09), and there were generally 40–50 reinforcers per 60-min session.

Acute Drug Effects

Responding under the FI and FR schedules of food presentation was decreased as the dose of cocaine increased (Fig. 2, circles and squares), and performance was totally suppressed at 13 mg/kg. Avoidance responding was markedly increased as the dose of cocaine increased (Fig. 2, triangles), and response rate was nearly doubled at 13 mg/kg.

Chronic Drug Effects

Fixed-interval and fixed-ratio responding were not affected when cocaine was given for 4 weeks *after* the third daily session (Fig. 1, Condition A), but avoidance responding in sessions occurring 16 hours later was disrupted and animals received more electric shocks than under control conditions (Fig. 3A).

When cocaine was then administered *before* fixed-ratio re-

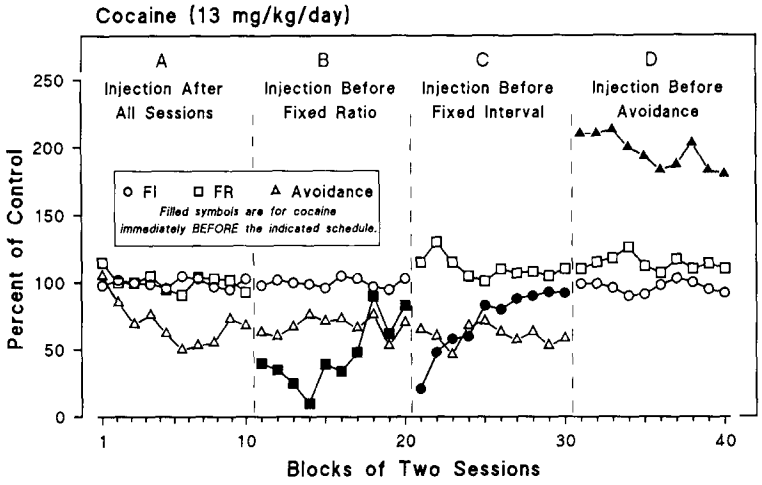

FIG. 3. Effects of daily administration of 13 mg/kg cocaine. The ordinate shows percent change in control response rate and the abscissa shows effects for blocks of two sessions. Panels A–D show effects for daily drug administration at times corresponding with Conditions A–D in Fig. 1. Response rate was compared for selected sessions of each panel, and *t*-tests for dependent-samples verified visual inspection. FR responding during Session 11 (filled square, panel B) was lower than FR responding during Session 10 [open square, panel A; $t(4) = 7.59$, $p < 0.001$], but was not different than that after acutely administered 13 mg/kg cocaine, $t(4) = 0.528$. FI responding during Session 21 (filled circle, panel C) was lower than FI responding during Session 20 [open circle, panel B; $t(4) = 10.813$, $p < 0.001$], but was not different than that after acutely administered 13 mg/kg cocaine, $t(4) = 0.315$. Avoidance responding during Session 31 (filled triangle, panel D) was higher than avoidance responding during Session 30 [open triangle, panel C; $t(4) = 19.673$, $p < 0.001$], but was not different than that after acutely administered 13 mg/kg cocaine, $t(4) = 0.498$.

sponding in the third session (Fig. 1, Condition B), effects were comparable to those after acute administration of the same dose, indicating that pharmacologic action during 20 postsession injections did not produce tolerance to the behavioral effects of the drug (Fig. 3B). As cocaine continued to be injected before responding, tolerance developed to decreased fixed-ratio responding within 4 weeks. When cocaine was subsequently administered *before* responding in the second daily session (Fig. 1, Condition C), fixed- interval performance was markedly suppressed (Fig. 3C). Tolerance developed to decreased FI responding within 2 weeks. The initial suppression of FI responding occurred after 8 weeks of daily cocaine administration and clearly indicated that tolerance did not develop to behavioral effects on fixed-interval responding while cocaine was experienced outside circumstances associated with fixed-interval performance.

Finally, when cocaine was given immediately *before* avoidance responding (Fig. 1, Condition D), performance was enhanced just as it had been during acute dosing (compare triangles in Fig. 2 and Fig. 3D). It is not evident why the same dose of cocaine disrupted avoidance responding over a 12-week period when administered approximately 16 hr *before* daily experimental sessions (Fig. 1, Conditions A–C), but then increased that same responding when first injected immediately prior to sessions (Fig. 1, Condition D). Nevertheless, the present results indicate that 3 months of daily cocaine administration did not result in tolerance to all of its acute behavioral effects.

DISCUSSION

Responding was readily controlled and maintained in three different environmental situations by fixed-ratio and fixed-interval schedules of food presentation, and by a nondiscriminated schedule of shock postponement. It is not known from the present procedure whether there were multiple schedule interactions among these widely separated components in different chambers, but rates and patterns of performance were comparable to those commonly reported for similar schedules and parameters presented individually.

Responding under the fixed-interval and fixed-ratio schedules of food presentation was decreased, and responding under the nondiscriminated shock avoidance was increased, at increasing doses of cocaine. These effects are consistent with previous reports for fixed-ratio and avoidance responding in rodent and primate [e.g., (6,8)], and for fixed-interval responding in rodent (10).

When animals received daily injections of cocaine, tolerance only developed for responding in the presence of environmental stimuli that were coincident with pharmacologic effects of the drug, and did not generalize to operants occurring in different environmental stimuli. Previous experiments have shown that tolerance does not develop to the behavioral effects of a variety of drugs on operant responding when the drug is administered *after* experimental sessions and pharmacologic effects do not coincide with the performance under study (13, 17, 22). Previous experiments have also shown that tolerance which has developed to the analgesic effects of morphine on one reflexive behavior does not extend to another reflexive behavior (1, 9, 19). Similarly, the expression of tolerance to the analgesic effects of nicotine is reduced when drug administration occurs in a novel environment (4), and comparatively gross features of environmental circumstances can function in association with drug-produced stimuli to control "place-learning" (3). Additionally, previous experiments from this laboratory have shown that tolerance to rate-decreasing effects of morphine and the cannabinoid *l*-nantradol are specific to environmental circumstances associated with drug action (24). In the present experiment, tolerance which might have developed when drug action coincided with living cages did not extend to fixed-ratio responding in the third daily session. Similarly, tolerance which subsequently developed to decreased fixed-ratio responding in the third daily session did not extend to fixed-interval responding in the second daily session, and tolerance which then developed to decreased fixed-interval responding in the second daily session did not extend to avoidance responding in the first daily session. It is not readily apparent which aspects of the successive experimental situations was most important for reducing generalization of tolerance, since the present experiment included conditions for manipulanda, schedule, reinforcers, and chamber configuration that were maximally different. Ongoing experiments are studying associative influences on tolerance development by systematically varying features of response topography, schedule parameter, discriminable external stimuli, and order of experimental session.

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