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Cocaine self-administration under variable-dose schedules in squirrel monkeys

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Abstract

Squirrel monkeys self-administered cocaine under a variable-dose schedule, with the dose varied from injection to injection. As in earlier studies with rats, post-injection pauses varied as a monotonic function of dose, allowing a cocaine dose-effect curve to be obtained during each session. These curves were shifted by pretreatment with dopamine antagonists, demonstrating that this procedure may provide an efficient means of evaluating treatments that affect drug self-administration. However, drug intake eventually became "dysregulated" after extensive training (100–300 sessions), with relatively short pauses following all doses. Dose-sensitivity was restored by adding a 60-s timeout period after each injection, suggesting that dysregulation occurred because the monkeys developed a tendency to self-administer another injection before the previous injection had been adequately distributed. Finally, when the response requirement under the variable-dose schedule was increased from 1 to 10, both the post-injection pause and the rate of responding following the pause ("run rates") were found to vary with dose. The dose-dependency of run rates suggests that post-injection pauses reflect not only motivational factors, such as satiety, but also the direct effects of cocaine on leverpressing.
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Under controlled conditions, animals tend to self-administer drugs in highly-regular patterns (Lynch et al., 1998; Pickens et al., 1981; Wise et al., 1995a,b; Yokel and Pickens, 1974). The amount of time between self-injections varies as a direct function of the dose per injection, with longer post-injection pauses (latencies) occurring after higher doses. In most studies, the dose is held constant within each session and varied between sessions. However, the relationship between latency and dose is robust even when the dose is varied from injection to injection within the same session using a "variable-dose" schedule (Gerber and Wise, 1989; Panlilio and Schindler, 2000; Panlilio et al., in press; Solinas et al., 2004; Wise et al., 1995b; see also Lynch et al., 1998). Although a variable-dose schedule has been implemented in only a handful of studies – and only in rats – this schedule is worthy of further attention because (1) it may provide information about the mechanisms involved in the self-regulation of drug intake and (2) it may provide an efficient means of evaluating potential therapeutic treatments for drug abuse.

Variable-dose procedures allow a dose–effect curve for the self-administered drug to be obtained during each session of the study. Thus, within a single test session, it is possible to determine the effects of a treatment drug across a range of doses of the self-administered drug (Gerber and Wise, 1989). This application of the variable-dose schedule may be advantageous for rapidly determining the effects of treatment drugs or other manipulations (e.g., see Panlilio et al., in press; Solinas et al., 2004) and for examining therapeutic effects as they develop over the course of chronic treatment.

To evaluate the potential of this schedule for studying treatment drugs in non-human primates, we trained squirrel monkeys under a variable-dose schedule of cocaine self-administration. Although the study involved only a small number of monkeys, there was a high degree of consistency both between and within subjects. To determine the usefulness

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of this procedure, two dopaminergic drugs known to affect cocaine self-administration under fixed-dose procedures were given as pre-session treatments: the D1 antagonist, SCH 23390, and the D2 antagonist, eticlopride. Because intravenous catheters can be maintained in squirrel monkeys over much longer periods than in rats, we were also able to examine changes in self-administration behavior (i.e., a dysregulation of drug intake) that developed only after the monkeys had extensive experience with the procedure. In the final phase of the study, the response requirement under the variable-dose schedule was increased to 10 responses for each injection. This modification provided further insight into the phenomenon of post-injection pausing and the regulation of drug intake, an area that has received much recent attention (Ahmed and Koob, 1989, 1999; Panlilio et al., 2003; Tornatzky and Miczek, 2000; Tsibulsky and Norman, 1999; see review by Lynch and Carroll, 2001 and the commentaries that accompany their review).

1. Methods

1.1. Subjects

Three adult male squirrel monkeys (*Saimiri sciureus*) weighing 850–1100 g were housed in individual cages in rooms with light, temperature and humidity controlled. Fresh water was continuously available in the home cage. The monkeys were provided daily with five biscuits of high protein monkey diet (Lab Diet 5045; PMI Nutrition International, Richmond, Ind., USA) and two pieces of Banana Softies (Bio-Serv, Frenchtown, N.J., USA), and they also received fresh fruits or vegetables daily as part of an environmental enrichment program. Monkeys were implanted with a chronic, indwelling venous catheter (jugular, femoral or iliac vein) for the delivery of cocaine. If catheters failed during the experiment, testing was suspended while a new catheter was implanted in the same or a different vein. The general surgical procedure has been described in detail elsewhere (Goldberg, 1973). In brief, polyvinyl chloride catheters (inside diameter: 0.38 mm, outside diameter: 0.76 mm) were implanted during anesthesia with isoflurane–oxygen mixtures (1.75–2.00% isoflurane). The distal ends of the catheters were passed s.c. through the skin in the middle of the back. Monkeys wore nylon-mesh jackets (Lomir Biomedical, Canada) at all times to protect the catheters. Catheters were flushed with saline before and after each experimental session, and they were sealed with stainless steel obturators when not in use. Two monkeys (#M7661 and #D6258) were experimentally naive prior to this study. The other monkey (#F3397) had served in previous experiments involving passive administration of i.v. cocaine (but not self-administration) while seated in a chair and chamber similar to the one used in this study. Monkey #F3397 had also received intramuscular injections of several dopaminergic compounds during some sessions in the previous study, but had not received any drugs for three months prior to the present study. The facilities were fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, and all procedures were conducted in accordance with the guidelines of the Institutional Care and Use Committee of the National Institute on Drug Abuse/Intramural Research Program and the Guide for the Care and Use of Laboratory Animals (National Research Council, 1996).

1.2. Apparatus

During experimental sessions, the monkey sat in a Plexiglas chair in a ventilated, sound-attenuating chamber (Model AC-3; Industrial Acoustics Co., Inc., Bronx, NY) that provided continuous white noise to mask extraneous sounds. The monkeys were fully adapted to the chair and chamber prior to catheter implantation. Facing the chair, there were two levers (left and right; Model 121-05; BRS/LVE Corp., Laurel, MD) on a stainless steel panel. Pressing the lever with a force greater than 0.2 N produced an audible click and recorded a response. Above the levers, there were two white cue lights on the panel. The chamber was illuminated by a white houselight. Cocaine was delivered by a motor-driven syringe pump (Model 57-6496; Harvard Apparatus, South Natick, MA) outside of the chamber. The concentration of the cocaine solution was 0.54 mg/ml and the injection volume ranged from 0.016 to 0.611 ml. Operation of the experimental chambers and data collection were controlled using the MED-PC software package (Med Associates, East Fairfield, VT).

1.3. Procedure

1.3.1. Basic procedure

Training sessions were conducted 5 days/week. Under the basic procedure, a single response on the right-hand lever was required to produce an injection of cocaine, which was accompanied by flashing of the cue light at 5 Hz. After each injection, the latency to the next response was recorded. In some sessions, a 60-s timeout was added after each injection. During timeout, the houselight was turned off and responding had no scheduled consequences. Responses made during the injection and timeout were not included in the latency measure. Although response rates can be derived from the inverse of the latencies (with a decrease in latency corresponding to an increase in response rate), latencies were analyzed rather than response rates because a direct measure of response rate requires sequential injections of the same dose.

The dose of each injection was controlled by the duration of the syringe pump activation (0.3–11.5 s). To fill the catheter and assure the accuracy of subsequent doses, the first two injections of each session were always 100 μg/kg/injection, and the data from these initial injections were not included in the analysis. During the remainder of the session, four possible doses were made available (10, 30, 100 and 300 μg/kg/injection). To determine the order of the doses in each session, doses were chosen without replacement from a list in which each dose appeared twice. When the list was exhausted, the procedure was repeated three more times, for a total of 34 injections. Although this method of varying the dose per injection confounds dose with injection duration, we have reported earlier (Panlilio et al.,

1998) that within the range of values used in the present study, changing the injection duration has little or no effect on cocaine self-administration if the dose per injection is held constant in rhesus monkeys.

1.3.2. Fixed-ratio10 variable-dose schedule

In the final phase of the study (which lasted approximately 30 sessions), the schedule was altered to require a fixed ratio of 10 responses (FR10) for each injection. During this phase, the following data were recorded: (1) the latency to the first response after each injection, not including responses during the injection and 60-s timeout period; (2) "run time", the amount of time taken to complete the 10 responses once the first response had occurred; and (3) "inter-injection interval", the total amount of time between injections, equal to the sum of response latency and run time.

1.3.3. Pretreatment procedure

During some sessions, a test drug or vehicle was administered intramuscularly approximately 5 min before the start of the session. These test sessions were conducted no more than twice per week. One test drug, SCH 23390, was examined during the "basic" variable-dose cocaine schedule with no timeout. The other test drug, eticlopride, was studied using the FR10 version of the variable-dose schedule with a 60-s timeout.

1.4. Drugs

Cocaine hydrochloride (National Institute on Drug Abuse, Baltimore, MD), SCH 23390, and eticlopride were dissolved in sterile physiological saline vehicle. SCH 23390 and eticlopride were obtained from Sigma (St. Louis, MO).

1.5. Data analysis

Data were analyzed using Proc Mixed (SAS Institute, Cary, NC), which is capable of analyzing data sets for which some subjects were not tested under all conditions. This was necessary because monkey #F3397 had to be dropped from the study for health reasons and therefore did not receive two doses of SCH 23390 and was not exposed to the timeout procedure. Paired comparisons were performed using the Tukey–Kramer procedure with an overall significance level of 0.05 for each set of tests. To analyze the effects of extended training, data from periods during which SCH 23390 was not being studied were divided into four phases, the first two of which were defined by changes in the monkeys' behavior: (1) "early" training, during which dose–effect curves for cocaine were stable, with latencies increasing monotonically across the three highest doses during each session, and treatment drugs were not being administered; (2) "extended" training, during which the curves became flattened, with latencies failing to increase monotonically across the three highest doses during each session; and (3) a "timeout" phase, during which a 60-s timeout period followed each injection. Thus, the early phase corresponded to sessions 37–59 for #F3397, 106–118 for #D6258 and 21–45 for #M7761. The extended phase corresponded to sessions107–117 for #F3397, 223–234 for #D6258 and 309–329 for #M7761. The timeout phase corresponded to sessions 305–328 for #D6258 and 414–442 for #M7761. For the FR10 variable-dose schedule, only two monkeys could be tested, so linear regression was performed for each monkey's data to quantify the slope of the dose–effect functions for response latencies and run times. Statistical analysis of inter-injection intervals was not performed for the data obtained under the FR-10 variable-dose schedule; although this is an important measure when considering drug intake, this analysis would not be independent from those of response latencies and run times.

2. Results

2.1. Initial training and effects of treatment with SCH 23390

Dose-dependent responding developed in all three monkeys during the initial phase of training, with consistent behavior observed both within and between subjects (see "baseline" data in Fig. 1). The highest dose of cocaine (300 μg/kg) began to produce longer latencies than the lower doses within the first few sessions for all three monkeys. Latencies following the second highest dose (100 μg/kg) did not become differentiated from the two lowest doses until about the 20th session in two monkeys, and in one monkey (#F3397) this differentiation did not become reliable. Latencies for the two lowest doses (10 and 30 μg/kg) did not become clearly differentiated from each other in any of the monkeys. As seen in Fig. 1, orderly dose–effect curves were obtained within single sessions, and shifts in these curves were readily detected when the D1-receptor antagonist, SCH 23390, was given before cocaine self-administration sessions. SCH 23390 produced dose-dependent decreases in latencies, mainly affecting the latencies that followed the highest doses of cocaine.

Statistical analysis of the data in Fig. 1 confirmed that baseline latency curves were dose-dependent. For analysis, data for the three baseline sessions were averaged within monkeys #D6258 and #M7761. The interaction of cocaine dose and SCH 23390 dose was significant [$F(9,22)=10.3$, $p<0.001$]. Under the baseline condition, paired comparisons revealed that the highest dose of cocaine produced significantly longer latencies than each of the other three doses, and the second highest dose also produced significantly longer latencies than the two lower doses. The highest dose of cocaine continued to produced significantly longer latencies than each of the other three doses even when the cocaine dose effect curve was significantly shifted by treatment with SCH 23390. Relative to baseline, the 0.01 mg/kg dose of SCH 23390 produced a significant decrease in latencies at the highest dose of cocaine, and the 0.03 mg/kg dose of SCH 23390 produced significant decreases at both of the two highest doses of cocaine.

2.2. Extended training

Although performances were stable in each monkey for about 100–300 sessions, the original dose-sensitivity of

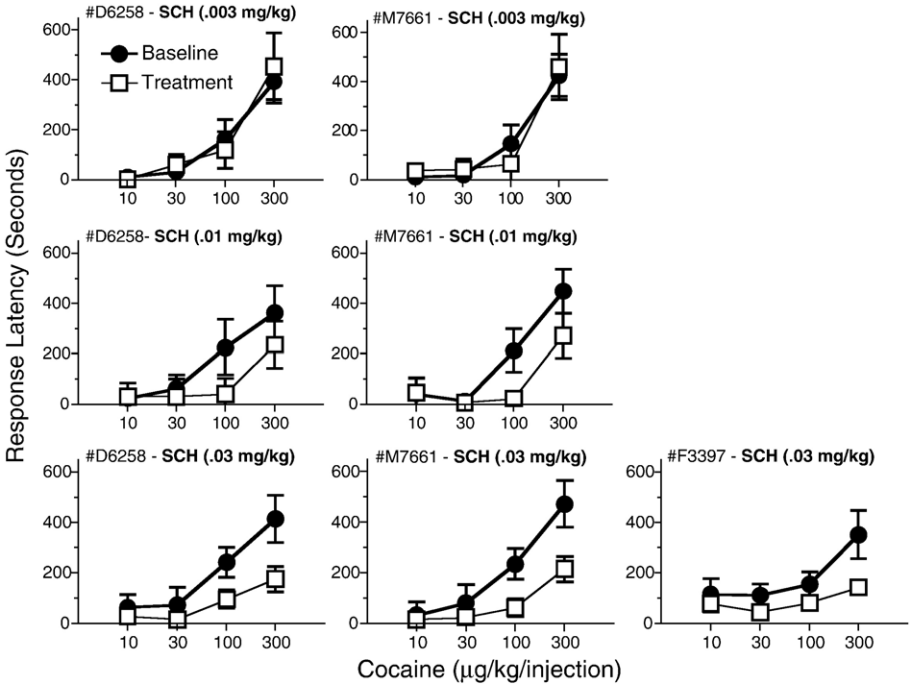

Fig. 1. Acute effects of SCH 23390 treatment on within-session dose–effect functions for cocaine in individual monkeys. Each curve represents data from a single session. Two monkeys received three doses of SCH 23390 (0.003, 0.01 and 0.03 mg/kg), but monkey #D6258 was only tested at one dose (0.03 mg/kg). *Solid circles* represent mean latencies during the baseline (vehicle) session on the day preceding the test session, and *open squares* represent latencies during the SCH 23390 test session. Error bars indicate the within-session standard error of latencies for each dose.

response latencies was eventually lost in all three monkeys, with the latency curves becoming considerably flatter (see Fig. 2). During this period, latencies following the two highest doses of cocaine were shorter than before, and the second highest dose was no longer differentiated from the two lower doses. For the data in Fig. 2, the interaction of training phase and cocaine dose approached significance [$F(6,18)=2.64$, $p<0.051$]. While latencies following the highest dose were significantly longer than each of the other doses during the "early" phase (p's<0.05), none of the doses differed from each other during the "extended" phase (all p's>0.33). This loss of dose-sensitivity was due mainly to changes in the latencies produced by the highest dose of cocaine; for this dose, latencies were significantly shorter during "extended" training compared to "early" training ($p<0.05$).

Because it appeared that the loss of dose-sensitivity during extended training might be due to the monkeys self-administering more cocaine before the previous injection had been adequately distributed throughout the body, a 60-s timeout was added to the schedule. The addition of a timeout effectively increased latencies at the higher doses and increased the slope of the curves (see Fig. 2). Analysis of the data in Fig. 2 confirmed that, when the timeout was added, the highest dose again produced significantly longer latencies than the other three doses, as it had during the early phase of training (p's<0.05).

The increases in latency when the timeout was added were not simply a result of the timeout period being included in the latency measure, because the increases in latency were substantially longer than the duration of the timeout. Without the timeout procedure (i.e., in the "early" phase of training), the minimum possible latency was 0.3–11.5 s, but the obtained latencies for the lowest dose were about 60 and 100 s for monkeys #M7661 and #D6258, respectively. When the timeout procedure was added, the minimum possible latency was 60.3–71.5 s, but the obtained latencies for the lowest dose were about 150 and 200 s for monkeys #M7661 and #D6258. Thus, it is clear that that the monkeys did not simply respond as soon as the timeout ended and drug became available. In addition, it should be noted that responses during the timeout were extremely rare. Therefore, the latencies reported during the "timeout" phase of training in Fig. 2 represent an accurate measure of the monkeys' post-injection pauses under this procedure.

2.3. FR10 variable-dose schedule

In the final phase of the study, an FR10 contingency was added to the variable dose schedule. All three measures obtained during this phase of the study (response latency, run time, and inter-injection interval) were found to increase monotonically as a function of injection dose (Fig. 3). This dose-dependency was observed when data were combined across sessions (as seen in Fig. 3) and also during individual sessions (as seen in the "baseline" data from single sessions presented in Fig. 4). For both monkeys exposed to this schedule, the slope of the dose-effect function was significantly different from zero for both response latency and run time (p's<0.001). Regression analysis on the logarithms of the data in Fig. 3 revealed that – although the intercepts were higher for response

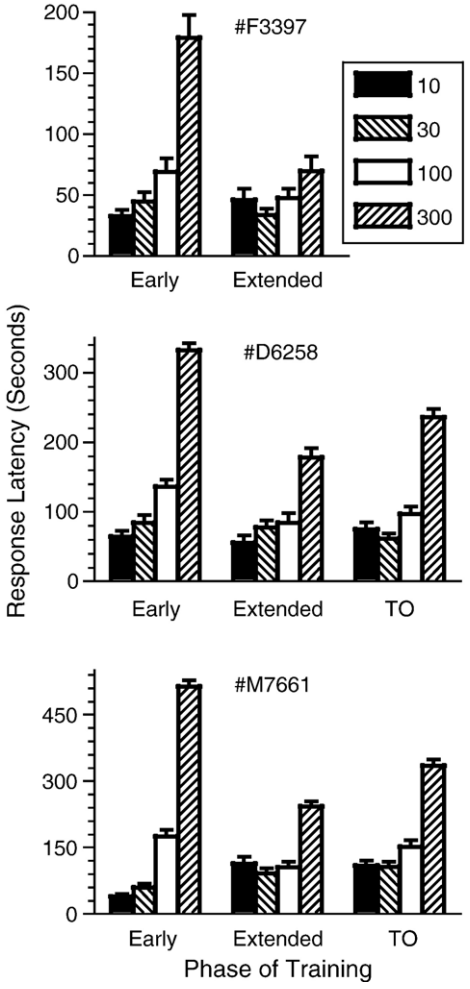

Fig. 2. Mean response latencies for individual monkeys during specific phases of training with the variable dose schedule. Latencies from the sessions within each phase were averaged for each monkey. Error bars represent the standard error of all injections included in each mean. Doses are indicated by shading of bars, as shown in the figure legend. The first set of data bars in each panel represents latencies during early training, once response patterns had stabilized. The second set of bars in each panel represents latencies during extended training under the same conditions, but after dose–effect functions became less distinct. The third set of bars (for monkeys #D6258 and #M7661) represent latencies during subsequent training with a timeout (TO) added after each injection.

latency than run time, indicating higher absolute values for the response latency measure – the slopes for these two measures were nearly identical within each subject (0.38 and 0.39 for monkey #D6258, and 0.35 and 0.34 for monkey #M7761, respectively), indicating that response latency and run time were equally dose-dependent.

To demonstrate that the FR10 version of the variable-dose schedule was viable as a baseline for evaluating the effects of pharmacological treatments, the effects of three doses of the D2-antagonist, eticlopride, were examined in one monkey. When given for a single session, eticlopride dose-dependently decreased response latencies, run times and inter-injection intervals (Fig. 4). Like SCH 23390 in the earlier phase of the study, eticlopride mainly affected the latencies that followed the highest doses of cocaine.

3. Discussion

3.1. Regulation of drug intake

The variable-dose schedule of cocaine self-administration produced orderly within-session dose–effect curves for cocaine, and these curves were shifted to the right by acute treatment with a dopaminergic antagonist. However, behavior became less sensitive to the injection dose after extended training. This loss of dose-sensitivity appears to have been due to a tendency to self-administer another injection before the previous injection had been adequately distributed to the brain. Addition of a timeout after each injection prevented this "premature" responding and increased the slope of the dose–effect curves. It is unclear why this tendency developed only after extensive training.

This loss of control resembles the increased rate of drug intake seen in rats after extensive exposure to cocaine self-administration procedures (Bozarth and Wise, 1985; Fitch and Roberts, 1993; Ahmed and Koob, 1989, 1999). In contrast, the loss of sensitivity to dose observed here did not involve an increase in the *variability* of responding like that observed when rats are exposed to extended "binge" sessions of cocaine self-administration (Tornatzky and Miczek, 2000); the variability of latencies did not increase during the "extended" training phase of the present study (see error bars in Fig. 2). This phenomenon also appears to differ from the tolerance to self-administered cocaine described by Emmett-Oglesby and Lane (1992) and Emmett-Oglesby et al. (1993), who found that tolerance developed quite rapidly in rats that were chronically exposed to high doses of cocaine under a schedule that included a 30-s timeout. However, it cannot be ruled out that tolerance might have developed only to the effects of cocaine that occur during the first 60 s following an injection, leaving intact the effects that occur after 60 s.

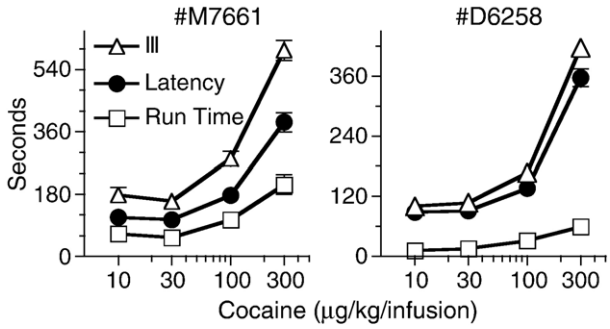

Fig. 3. Mean response latencies (*solid circles*), inter-injection intervals ("III"; *open triangles*) and run times (*open squares*) for two monkeys (*left panel*: #M7661; *right panel*: #D6258) during training with the FR10 version of the variable-dose schedule. Data from the 10th through 20th sessions under this schedule were combined for each monkey, and error bars represent the standard error of all injections at each dose of cocaine. Error bars not seen are covered by the symbol. Run time indicates the number of seconds between the first response and the tenth response for each injection. Thus, inter-injection interval was the sum of response latency and run time. Although the run time curves appear relatively flat due to the scale of the figure, it should be noted that the mean run time under the highest dose of cocaine was about five times greater than under the lowest dose for monkey #D6258 and three times greater for #M7661.

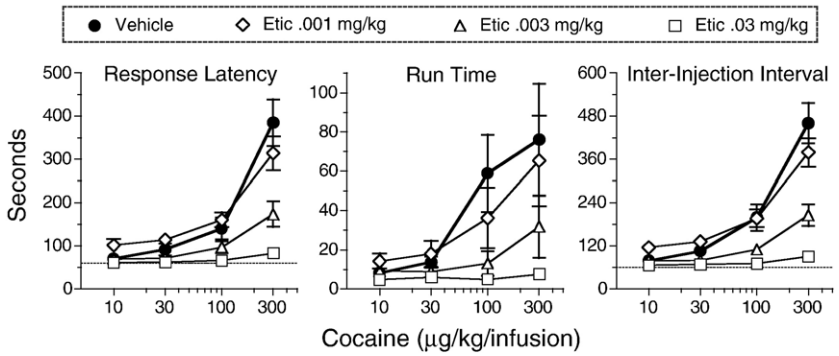

Fig. 4. Acute effects of eticlopride on responding under the FR10 version of the variable dose schedule in one monkey (#D6258). Data are presented for vehicle pretreatment (*filled circles*) and each dose of eticlopride, with each curve representing a single session. Error bars indicate the within-session standard error for each point. Error bars not seen are covered by the symbol. *Dashed lines* indicate minimum value allowed by timeout. *Left panel*: mean within-session response latencies. *Center panel*: mean within-session run time. *Right panel*: mean inter-injection intervals. Eticlopride doses were 0.001 (*open diamonds*), 0.003 (*open triangles*) and 0.03 mg/kg (*open squares*).

The effectiveness of the timeout in improving the slopes of the dose–effect curves suggests that the loss of dose-sensitivity and the shortening of latencies following the highest dose were not caused by either tolerance to cocaine or a partial loss of catheter patency. When catheters did lose patency or iv lines were accidentally disconnected, it immediately became apparent from the response latencies, which became extremely short. When new catheters were implanted, as was occasionally necessary over the course of the study, this did not restore the dose-sensitivity seen in the original dose–effect curves.

Although it is difficult to make comparisons across species, there is some indication that regulated intake may develop more readily in rats than in squirrel monkeys. In the present study, the highest dose was not reliably differentiated until after several sessions of training, and the second highest dose was not differentiated until after a substantial number of sessions. In earlier studies with rats that were initially trained with a fixed-dose schedule, orderly dose–effect curves for four doses of heroin or remifentanil were obtained in the first two sessions of exposure to a variable-dose schedule (Panlilio and Schindler, 2000; Solinas et al., 2004). In a recent experiment with cocaine, 16 of 22 rats showed monotonically increasing dose–effect curves for three doses of cocaine (0.1, 0.3 and 1.0 mg/kg/injection) during the first session of exposure to a variable-dose schedule, with the curve peaking at the highest dose for every subject (Panlilio et al., in press).

Three basic mechanisms have been proposed to account for the regular patterns of drug self-administration that are typically observed in animals (Katz, 1989; Lynch and Carroll, 2001; Panlilio et al., 2003). First, drugs that alter ongoing operant behavior when delivered passively (Barrett, 1987) can also have "direct" effects on response rate when self-administered by the animal (e.g., see Spealman and Kelleher, 1979). Second, high levels of drug may accumulate and become noxious, suppressing responding through a punishment process (e.g., see Goldberg et al., 1983). Third, responding may cease due to a homeostatic satiety mechanism when sufficient drug levels are reached (Ahmed and Koob, 1989; Ranaldi et al., 1999; Tsibulsky and Norman, 1999; Wise et al., 1995a,b; Lynch et al., 1998).

Most studies of regulated drug intake have used FR1 schedules, with one response required for each injection. For example, the fixed-dose FR1 study of Tsibulsky and Norman (1999) and the variable-dose FR1 study of Wise et al. (1995b) have provided the strongest evidence that rats tend to self-administer the next injection of cocaine when whole-body levels of cocaine or nucleus accumbens levels of dopamine, respectively, drop below a specific threshold. Unlike these earlier studies of regulated intake, the variable-dose schedule in the present study was modified to include an FR10 contingency. Under these conditions, both response latency and run time were found to be dose-dependent. After the monkeys received a high dose of cocaine, they not only took longer to re-initiate responding, they responded more slowly while completing the 10 required responses (i.e., run times increased). This dose-dependency of run times is consistent with a "direct effects" hypothesis in which responding is altered by higher doses of cocaine (see Katz, 1989; Panlilio et al., 2003), but it is not easily explained in terms of satiety. Thus, latencies appear to be influenced at least in part by the direct effects of cocaine.

Although the FR 1 schedule provides a straightforward way to measure drug intake, reinforcing efficacy is typically measured by varying the "cost" of the drug using progressive-ratio or other fixed-ratio schedules with relatively high response requirements (e.g., to perform a behavioral economics analysis). It is important to consider that intake can be largely independent of reinforcing efficacy. For example, intake can be altered in the absence of changes in reinforcing efficacy (Solinas et al., 2004), and reinforcing efficacy can be altered in the absence of changes in intake (Panlilio et al., in press). Although no manipulations were performed to directly evaluate this possibility in the present study, increasing the response requirement of the variable dose from 1 to 10 might make the schedule more sensitive to changes in reinforcing efficacy.

The present results demonstrate that a timeout procedure may be necessary to maintain the slope of the latency curve after extensive training with the variable-dose schedule, when animals may develop a tendency to respond "too soon" after a high dose. It has been noted that, with low-value fixed-ratio schedules of cocaine self-administration that do not include a

timeout, there may be little or no ascending limb of the dose–effect curve for response rate (Sizemore et al., 1997). Norman and Tsibulsky (2001) have suggested that timeout periods may artificially decrease the rate of drug intake at low unit doses under fixed-dose schedules, creating the appearance of an ascending limb for a response-rate dose–effect curve that should theoretically have only a descending limb. However, this potential effect of timeout procedures at low doses does not apply to variable-dose schedules. As noted below, latency functions under variable-dose schedules are inherently monotonic because latencies are short following low or even non-reinforcing doses. In the variable-dose schedule of the present study, addition of a timeout increased the inter-injection intervals at the lowest doses, but it did not create a bitonic latency function.

3.2. Evaluation of treatment effects

Cocaine dose–effect curves obtained with the variable-dose schedule were clearly sensitive to acute pretreatment with dopamine antagonists, which produced an immediate decrease in response latencies (i.e., an increase in response rate). The dopamine antagonists had effects similar to reducing the dose of cocaine: increasing the rate of injection and inducing rapid responding like that typically seen during extinction (e.g., as seen in the present study when iv lines were disconnected or catheter patency failed). The effects of dopamine antagonists in this study were comparable to those observed earlier with a variable-dose schedule of cocaine self-administration in rats (Gerber and Wise, 1989) and were also consistent with previous cocaine self-administration studies that used fixed-dose rather than variable-dose procedures. In most of these studies, dopamine antagonists increased response rates and cocaine intake rates, especially at higher doses of cocaine (e.g., Corrigal and Coen, 1991; Glowa and Wojnicki, 1996; Koob et al., 1987). Based on their work with a schedule that also included periods of food-reinforced responding, Glowa and Wojnicki concluded that dopamine antagonist-induced increases in cocaine self-administration could be attributed equally well to reductions in the reinforcing effects of cocaine or to reductions in the direct, rate-decreasing effects of cocaine.

In some previous fixed-dose studies that used low doses of cocaine during baseline and testing, certain dopamine antagonists (including SCH 23390 and eticlopride) produced only decreases in cocaine self-administration responding in rhesus monkeys (Winger, 1994; Woolverton, 1986; Woolverton and Virus, 1989). In contrast, in the present study and the variable dose-study of Gerber and Wise (1989), dopamine antagonists had little effect on response latencies following low doses of cocaine. This demonstrates a difference between variable- and fixed-dose studies with respect to low doses of the self-administered drug. Treatments that reduce response rates under low doses of the reinforcing drug in a fixed-dose schedule may have no effect or even an opposite effect in a variable-dose schedule. This difference stems from the fact that, under a fixed-dose schedule, a low dose is always followed by the same low dose, and responding is only weakly maintained. In contrast, when a low dose is received under a variable-dose schedule, the next response may produce a higher, more reinforcing dose. Thus, variable-dose schedules produce monotonic dose–effect functions for latency, corresponding to the descending limb of the dose–effect curve for response rate. If the set of doses used for a variable-dose schedule were not chosen carefully, high rates of responding could appear to be maintained by very low doses that would fail to maintain responding under a fixed-dose schedule.

Because of this aspect of variable-dose schedules, a zero dose was not included in the set of cocaine doses used in present study. However, some indication of the behavior that would be engendered by a zero dose can be gleaned by considering non-reinforced responses under the FR10 version of the variable-dose schedule as a proxy for responses following a zero dose. For example, in monkey #M7661, the mean latency for the lowest dose of cocaine (10 mg/kg) was >30 s during early training (with no timeout) under the FR 1 variable-dose schedule. The mean latency between non-reinforced responses during the "run time" period of the FR10 schedule (averaged across the four doses) for this monkey was approximately 10 s.

3.3. Advantages of variable-dose schedules

The results obtained here with cocaine suggest that variable-dose schedules would be useful for rapidly determining dose–effect curves for other drugs in monkeys. To study a drug with a much slower onset or longer duration of action than cocaine, it would probably be necessary to alter schedule parameters such as the timeout duration and the number of injections made available per session. However, in rats we find that the same parameters can be used to study cocaine, remifentanil (which is substantially shorter acting than cocaine) and heroin (which is substantially longer acting than cocaine). Nonetheless, further study will be required to compare the effectiveness of this procedure to other procedures for studying the intake of various drugs in monkeys.

A different procedure that allows within-session determination of dose–effect functions for self-administered drugs has been used fairly extensively with rats (Caine and Koob, 1995; Emmett-Oglesby et al., 1993; Martin et al., 1996; Sizemore et al., 1997) and monkeys (Caine et al., 2000; Carey and Bergman, 1997; Winger, 1994; Winger and Woods, 1996; Winger et al., 1989; see also Negus, 2003, 2004). In this procedure, sometimes referred to as a "multi-dose" schedule, several doses are made available during a session that is divided into components, with a different fixed dose available within each component. Like variable-dose schedules, multi-dose schedules produce within-session dose–effect functions that are sensitive to pharmacological treatments. Unlike variable-dose schedules, multi-dose schedules can produce inverted U-shaped dose–response curves. Thus, multi-dose schedules may be preferable to variable-dose schedules in many situations, especially when the ascending limb of the dose–response function is of particular interest. However, variable-dose procedures may have advantages over multi-dose procedures in some situations.

In multi-dose schedules, the order in which the doses are presented is confounded with time in the session, and the order of doses may influence the shape of the dose–effect curve. For example, Caine and Koob (1995) found that an ascending limb was only obtained with a multi-dose schedule when an ascending dose order was used. In contrast, dose and time are independent under variable-dose schedules. Thus, variable-dose schedules may be useful for observing the time-course of changes in the dose–effect function within a session.

Another advantage of variable-dose schedules stems from the fact that injections of the same dose are not grouped together as they are in multi-dose and fixed-dose schedules. When the same dose is given repeatedly, each injection signals what the dose will be for the remainder of the schedule component. In some multi-dose studies, there is also an explicit exteroceptive stimulus signaling what dose is available in the component. These kinds of discriminative stimuli can exert powerful control over behavior, making the animal's responding less sensitive to moment-to-moment changes in drug levels (Panlilio et al., 1996, 2000; Weiss et al., 2003). In contrast, variable-dose schedules have no interoceptive or exteroceptive discriminative stimulus signaling the dose of the next injection. Thus, variable-dose schedules may provide the most clear-cut demonstration that self-administration responding is controlled by the current level of drug effect rather than other stimuli.

In light of this possibility, it should be noted that some of the phenomena observed with variable-dose schedules in the present study – the gradual development of regulated intake and its malleability once established – appear consistent with a learning process. Cocaine and other drugs of abuse can have reinforcing effects, punishing effects and discriminative-stimulus effects, as well as "direct" effects on behavior. Therefore, it is likely that the regulation of drug intake involves both: (1) unlearned processes, involving direct effects of the drug, and (2) experience-derived processes, involving learning about the consequences of self-administering more drug, given the current level of drug effect.

3.4. Conclusions

The variable-dose schedule of cocaine self-administration provided orderly within-session dose–effect curves for cocaine, and these curves were clearly shifted by treatment with dopamine antagonists. This efficient procedure could be useful for measuring the effects of treatments over time, either within a session or over the course of chronic treatment with a potential therapeutic agent. Although regulated drug intake was disrupted after extensive exposure to cocaine under the self-administration procedure, regular patterns were restored when a post-injection timeout period was added to the schedule. These results suggest that, without a timeout, drug intake became dysregulated because the monkeys developed a tendency to self-administer more cocaine before the previous injection had been adequately distributed to the brain. In the final phase of the study, the FR10 version of the variable-dose schedule revealed that the direct effects of cocaine on response rates may be one factor that influences post-injection pauses, and therefore the pattern of drug intake. Thus, regulated drug intake appears to be a multiply determined process that develops over time and that becomes disrupted under certain conditions. Variable-dose schedules may have some unique advantages for studying these changes and their role in addiction.

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