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Stability of cocaine dose–response functions at different inter-dose intervals ☆

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Abstract

Past research has found that daily administration of cocaine can lead to tolerance to its behavioral effects, and that tolerance can develop even when the dose is varied from day to day. The present experiment examined effects of administering varied doses of cocaine at a variety of inter-dose intervals ranging from once per week to everyday. Pigeons pecked on a fixed-ratio 20 schedule of reinforcement. A dose–response function for cocaine was assessed eight consecutive times during each of four phases of the experiment to assess the stability of effects of each dose. In Phase 1, subjects were administered a dose of cocaine or saline vehicle every seventh day. One subject developed tolerance by the end of this phase and was not studied further. In Phase 2, doses were administered every fourth day. During Phase 3, doses were administered every 2 days. In the final phase, doses were administered everyday. Dose–response curves were generally similar both within and across phases, regardless of inter-dose interval. No subjects developed tolerance during Phases 2, 3, and 4, suggesting that some aspect of the drug regimen prevented the development of tolerance when cocaine was given frequently.

Keywords: Dose–response curve; Cocaine; Tolerance; Inter-dose interval; Dose intermittency; Operant behavior; Pigeon

Tolerance and addiction often develop after prolonged use of cocaine, leading some users to administer higher doses of the drug (NIDA, 2004). It is therefore important to study factors related to the development of tolerance to cocaine. Because drug addiction has important behavioral components, and the most effective treatments for drug dependence include behavioral constituents (Leshner, 1997), an understanding of behavioral factors that influence tolerance to a drug's behavioral effects is imperative. Cocaine dependence usually develops from intermittent long-term use followed by compulsive binges (Gawin and Kleber, 1986). Consequently, it is useful to examine effects of intermittent administration of cocaine.

Tolerance is a common product of repeated drug administration. Tolerance can be demonstrated by a shift to the right in the dose–response curve or in a shift of the effects of a single dose away from acute effects of the drug and toward baseline levels (Hardman et al., 1996; Rang et al., 2003). Many factors can influence drug tolerance such as species (e.g., Byrd, 1975), behavioral procedure (e.g., Nickel et al., 1993), dose timing in relation to behavioral tests (e.g., Carlton and Wolgin, 1971), dose magnitude (e.g., Stafford and Branch, 1996), and dose intermittency (e.g., Stafford et al., 1994). The present experiment focuses on the effects of dose frequency on the development of tolerance.

In much behavioral research, dose–response curves are constructed by the administration of a sequence of doses delivered once or twice weekly (Boren, 1966). Typically, no drug or vehicle is administered on intervening days. It is usually assumed that tolerance will not develop as a result of such a regimen, but that notion has not been fully tested. Because dose–response curves are used to show the initial effects of a drug, or behavioral changes produced by drugs, the development of tolerance during dose–response curve construction may obstruct assessment of effects of a drug. It is best to evaluate tolerance with dose–response curves to ensure that the range of effects produced by different doses of a drug is encompassed. Dose–response assessments allow distinction between tolerance and habituation (Boren, 1966; Carlton, 1983).

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Past research has shown that the administration of a drug at 4-day intervals can lead to the development of tolerance. Emmett-Oglesby and Taylor (1981) conducted an experiment in which rats engaged in a milk-drinking task daily. Subjects were assigned to one of three groups. One group was administered a fixed dose of methylphenidate daily before the milk-drinking task. A second group was administered the same fixed dose of methylphenidate every fourth day before the milk-drinking task. The third group was administered saline daily before the milk-drinking task. The dose of methylphenidate used in this experiment initially produced a substantial disruption in milk-drinking for all rats. Subjects in the group administered methylphenidate daily and those in the group administered methylphenidate every fourth session both developed tolerance. These results showed that intermittent administration of a fixed dose of methylphenidate could lead to tolerance on a milk-drinking task (Emmett-Oglesby and Taylor, 1981).

Wenger et al. (1981) conducted a study in which rats ran on a treadmill to avoid shock. One group was administered a dose of ethanol pre-session for 24 consecutive daily sessions. A second group was administered the same dose post-session for 24 consecutive sessions, except that every fourth day ethanol was administered pre-session rather than post-session. A third group was administered ethanol post-session for 24 consecutive sessions. Initially, ethanol produced more time spent off the treadmill, and this effect was attenuated for both the group administered the drug pre-session daily, and the group administered ethanol pre-session every fourth day. The group administered ethanol post-session daily did not develop tolerance to the motor impairing effect of ethanol. This study demonstrated that occasional pre-session administration of ethanol was sufficient for tolerance to develop to ethanol's motor effects (Wenger et al., 1981).

Intermittent administration of cocaine has also resulted in tolerance in laboratory animals. Stafford, Branch, and Hughes (1994) conducted a study in which three pigeons responded on an FR 30 schedule of reinforcement and were administered intermittent injections of cocaine. Subjects were administered a dose of cocaine, which initially produced a large decrease in rate of responding, for 10 administrations with doses spaced every 8 days. During this drug regimen, one subject developed substantial tolerance to the rate-decreasing effect of cocaine, and for a second subject, the initial reduction in key pecking rate produced by cocaine was partially attenuated. For the subject that developed partial tolerance and the third subject, the inter-dose interval was decreased such that the dose of cocaine was administered every 4 days, then every 2 days, and finally daily. The subject that developed some tolerance with an 8-day inter-dose interval continued to show the same degree of tolerance, and the subject that did not show tolerance with cocaine administered at 8-day intervals did not show tolerance until doses were administered daily (Stafford et al., 1994). These results suggest that daily administration of a fixed dose of cocaine is not necessary for tolerance to develop to rate-decreasing effects of cocaine. Specifically, tolerance can develop when a fixed dose is given less frequently than daily.

Tolerance to effects of cocaine has also been shown to develop following daily administration of variable doses. An experiment by Branch et al. (2000) was designed to determine whether daily administration of varying doses would produce tolerance or would reveal that cocaine can be administered daily without changing its effects. Pigeons responded on an FR 20 schedule of reinforcement. Subjects were divided into groups matched on their initial sensitivity to the rate-decreasing effects of cocaine. Subjects in the Variable Dosing group were administered one of a range of doses of cocaine before each session. Doses used encompassed the full range of effects and were administered in descending order. Subjects in the Fixed Dosing group were administered the same dose daily, and the dose was the arithmetic mean of the range of doses assigned to a matched partner in the Variable Dosing group. All subjects were given approximately 50 daily cocaine administrations. Subjects in the Fixed Dosing group then continued administration of their fixed dose and subjects in the Variable Dosing group were administered the fixed dose of their matched partner. Most subjects in both groups developed tolerance to cocaine, and most subjects in the Variable Dosing group developed some amount of tolerance during variable dosing. These results suggest that daily administration of a variety of doses that produce the full range of effects of cocaine is likely to produce tolerance. Daily variable dosing, therefore, is not a sound method for assessing acute effects of cocaine (Branch et al., 2000). That daily administration of varying doses generally results in tolerance has also been observed by Miller and Branch (2002) and Yoon and Branch (2004).

Although little research has been conducted on the development of tolerance to cocaine following intermittent administration, another body of research has examined effects of intermittent administration of analgesic drugs on the development of tolerance. Tolerance to effects of morphine and nicotine on analgesic tests can develop when the drugs are administered at a variety of inter-dose intervals including 72 h or 96 h inter-dose intervals (Tiffany et al., 1992, 1991; Cepeda-Benito et al., 2005). Tolerance to morphine has been found to develop more readily with longer inter-dose intervals (e.g. 24 h or 96 h) when morphine was paired with a distinctive environment (Tiffany et al., 1991). Subjects administered morphine in the home cage with saline paired with the distinctive context also displayed tolerance to the analgesic effects of morphine when morphine was administered at 6 h inter-dose intervals, but this was likely to be a product of pharmacological tolerance (Tiffany et al., 1992). Cepeda-Benito et al. (2005) showed that tolerance to the analgesic effects of nicotine could develop when nicotine was administered every 72 h in the context of the tail flick test, even without practice under the effects of nicotine.

To summarize, several experiments investigating intermittent dosing have found that administration at inter-dose intervals ranging from 3 to 8 days of a fixed dose of cocaine (Stafford et al., 1994), ethanol (Wenger et al., 1981), morphine (Tiffany et al., 1991, 1992), or nicotine (Cepeda-Benito et al., 2005) can lead to the development of tolerance. Based on these collective results, it is possible that tolerance might develop during acute dose–response curve construction when variable doses are administered once or twice weekly. Because it is common to administer acute injections of cocaine twice weekly (e.g., Byrd, 1980; Hoffman et al., 1987; van Haaren and Anderson, 1994; Wolgin and Hertz, 1995) when examining behavioral effects, it is possible that

tolerance can develop to effects of cocaine during dose–response curve construction. It is generally assumed that tolerance does not develop during acute dosing of cocaine, but to the best of our knowledge, no experiment has examined this.

The number of assessments of effects of each dose of drug in a dose–response curve has varied across experiments. If each dose is administered only once (e.g., Byrd, 1980; Schuster et al., 1966), it is not possible to evaluate the stability of effects. A single assessment of each dose might be contaminated by sequence effects wherein exposure to one dose alters effects of other doses. To deal with this problem, it is common to administer from two to as many as six administrations of each dose in dose–response assessments (e.g., Hoffman et al., 1987; van Haaren and Anderson, 1994; Smith, 1990) thus permitting assessment of reliability of effects for each dose.

The major purpose of the present experiment was to examine the minimum inter-dose interval that can be used in cocaine dose–response curve construction without a high probability of

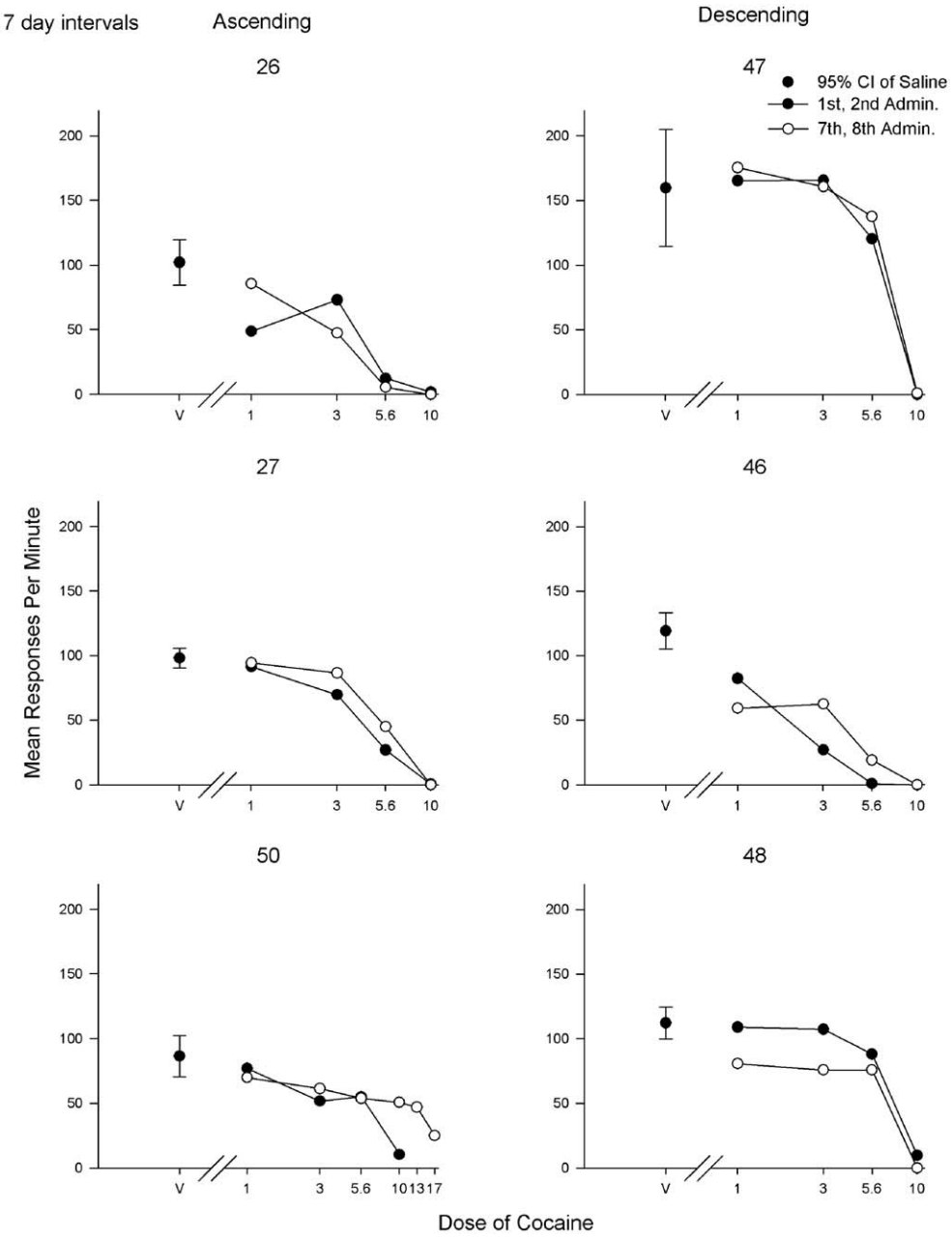


Fig. 1. Each graph shows data from an individual subject with responses per minute plotted as a function of dose (log scale) of cocaine. Data from subjects administered doses in an ascending dose order are presented in the left column, and data from subjects administered doses in a descending dose order are presented in the right column. The points and bars above "v" show the mean and 95% confidence interval (based on the 8 administrations in the phase) from sessions preceded by saline vehicle administration. The filled circles display the average rate of responding from the first and second administration of each dose of cocaine. The open circles show the average rate of responding from the seventh and eighth administration of each dose. Numbers above each graph identify the subject. Administrations occurred once every 7 days.

tolerance developing. More specifically, the present experiment used a within-subject method to determine if tolerance would develop when acute doses of cocaine were delivered 7 days apart, 4 days apart, 2 days apart, or following daily administration. The effects of each dose were assessed eight times in each phase of the experiment to ensure that effects of each dose had been adequately evaluated. The choice of eight administrations encompasses the maximum number of administrations usually employed to establish dose–response functions, and it therefore provides an assessment of the likelihood that tolerance could contaminate the functions at each particular inter-dose interval examined.

1. Method

1.1. Subjects

Subjects were six adult male, racing homer pigeons (Double "T" Farm, Glenwood, IA). All subjects were experimentally naïve and aged approximately 7 months at the beginning of the experiment. Subjects were housed in individual home cages in a windowless colony room on a 16.5/7.5 h light/dark cycle (lights on at 7:00 a.m.). The colony room was maintained between 19.4 °C and 22.8 °C. Subjects had access to vitamin-enriched water at all times in the home cage, and were maintained at 80%

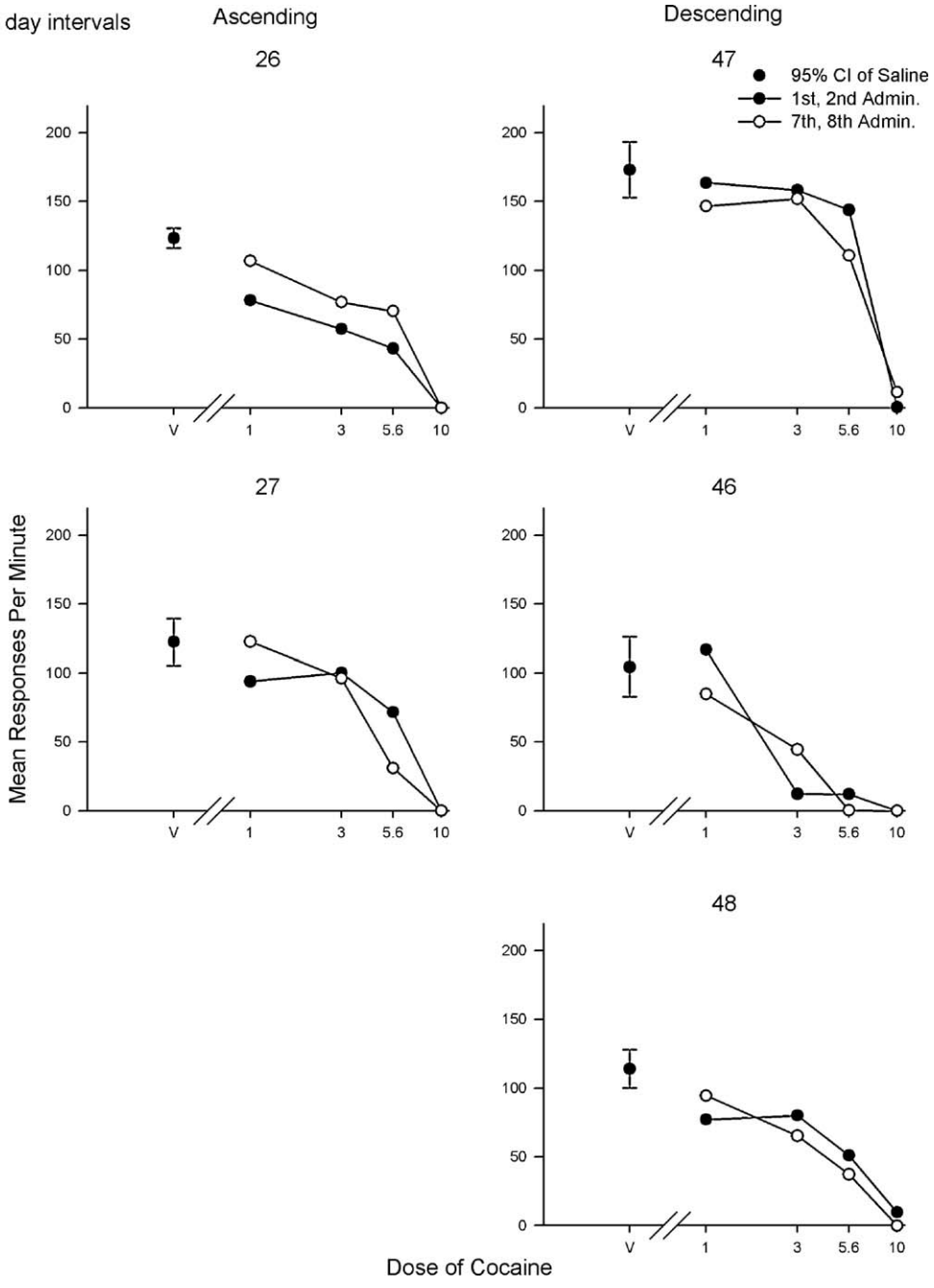


Fig. 2. Dose–response functions obtained when injections occurred every fourth day. Details are as in Fig. 1.

of their free-feeding body weight by post session feeding (Purina ProGrains for Pigeons) delivered immediately, if needed, after each session.

1.2. Apparatus

Experimental sessions were conducted in a standard three-key pigeon operant test chamber measuring 31.0 cm × 36.5 cm × 35.0 cm, enclosed in a sound-attenuating cubicle. The center key was 2.5 cm in diameter and located on the intelligence panel 8.7 cm from the ceiling and equidistant from both side walls. The key could be illuminated from behind by a 28-V DC light. To register a response, the key required a force of approximately 0.11 N. A 28-V DC houselight was centered 2.2 cm from the ceiling on the intelligence panel, and illuminated the chamber during the experimental session. Only the center key was used in this experiment, and was illuminated white when the FR schedule was in effect. The other keys remained dark and inoperative. Mixed grain could be made available through a 5.5 cm × 5.0 cm aperture centered at the base of the intelligence panel 20.0 cm from the ceiling. A speaker in the experimental room produced white noise (95 dB) to mask extraneous sounds. Experimental events were arranged and recorded by EC-BASIC (Palya et al., 1995) software on a computer located in another room. A cumulative recorder in

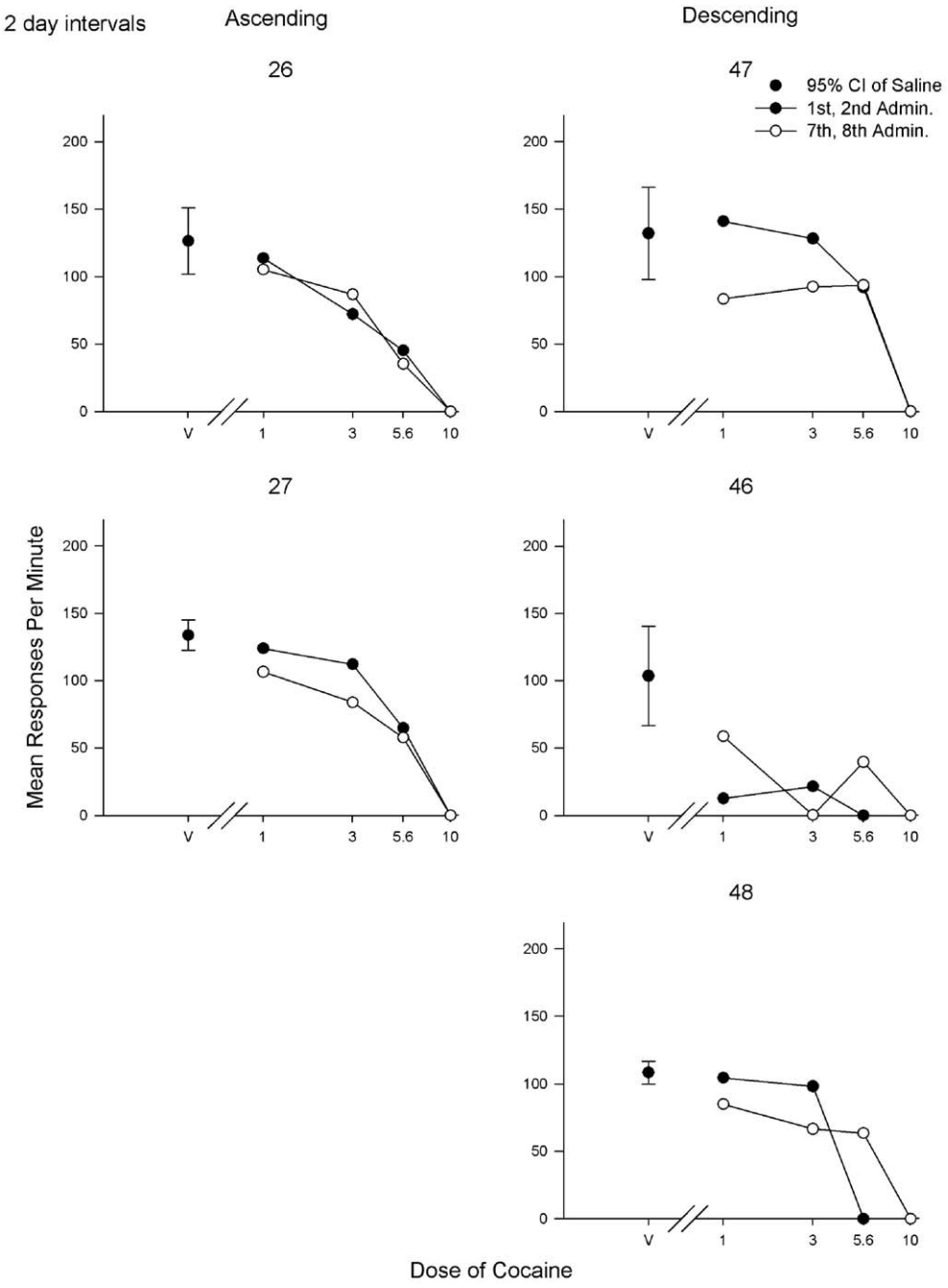


Fig. 3. Dose–response functions obtained when injections occurred every second day. Details are as in Fig. 1.

another room recorded responses as a function of time during daily sessions.

1.3. Procedure

1.3.1. Training

Subjects were trained, through the method of successive approximations, to peck the center key when it was illuminated white. After all subjects reliably pecked the key, they were put on a continuous reinforcement schedule (CRF) for one session. Sessions ended after 30 min or 20 grain presentations, which ever came first. Subjects then underwent FR training. During FR training, the session began with an FR 1 and incremented by one to four responses per reinforcer up to FR 20. Fixed-ratio training that incremented within the session terminated after 40 grain presentations or 30 min, which ever came first. Ratio training was completed within one session for two subjects. The remaining subjects, except one whose behavior was not well controlled by training under incrementing FR schedules, were placed on various FR schedules that incremented across sessions for two to seven sessions until they responded on FR 20. This last subject was trained on a random ratio (RR) schedule that incremented across sessions to RR 25 over eight sessions before being placed on the FR 20 baseline. The

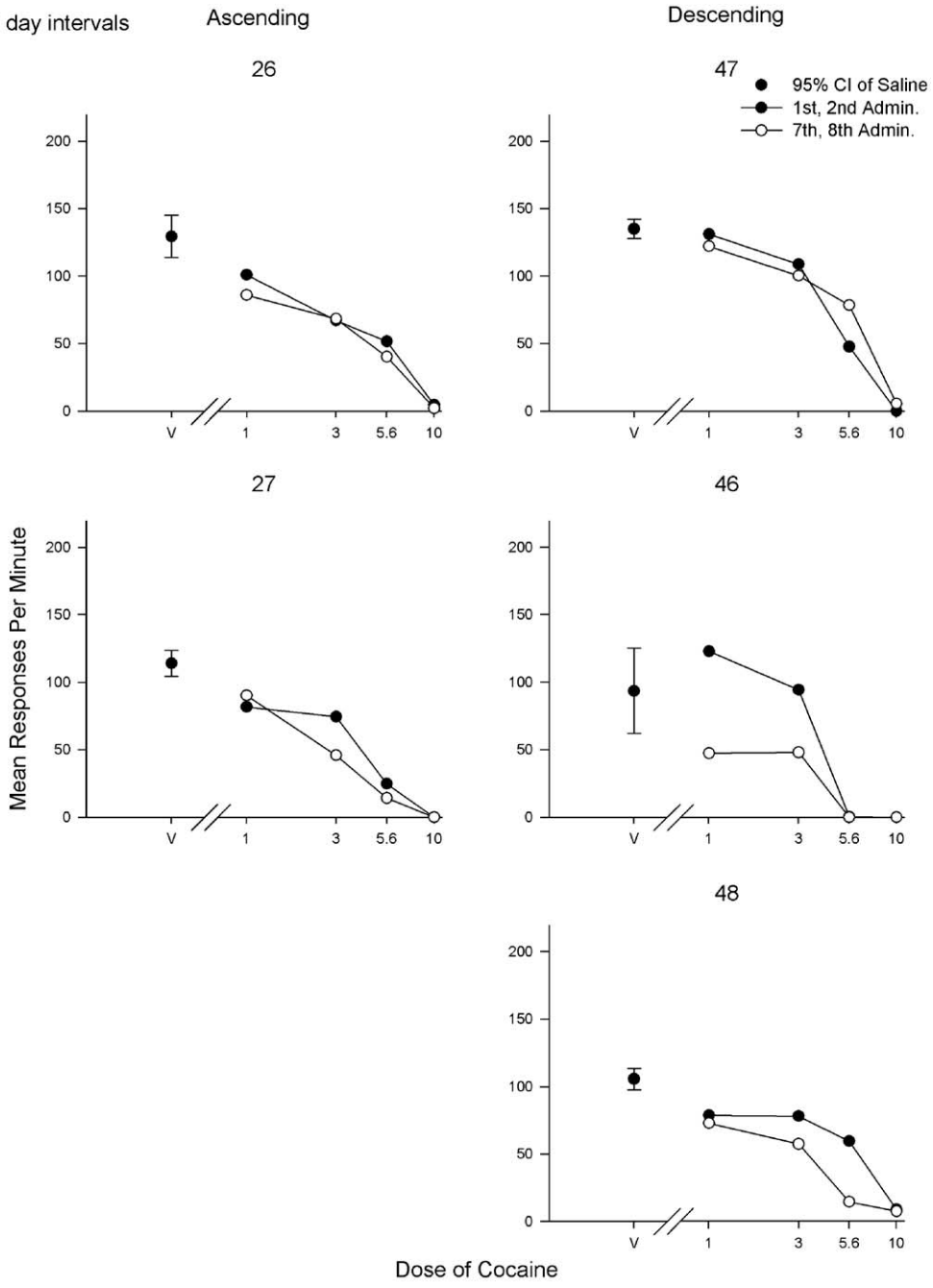


Fig. 4. Dose–response functions obtained when injections occurred daily. Details are as in Fig. 1.

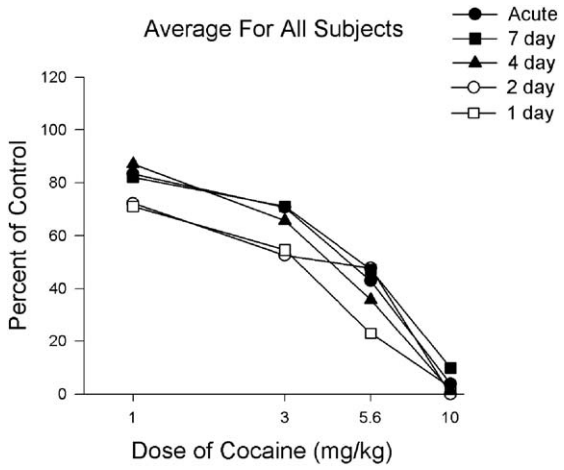


Fig. 5. Data averaged for all subjects with responses per minute plotted as a function of dose of cocaine. Data are plotted as percent of values obtained after administration of saline vehicle for each phase of the experiment. Filled circles show the acute effects of cocaine, defined as the average rate of responding from the first and second administration of each dose of cocaine administered at 7-day intervals. The remaining functions are averages of the seventh and eighth administration of each dose. Filled squares display data from the phase when administrations occurred at 7-day intervals. Filled triangles show data from the phase when doses were administered at 4-day intervals. Open circles are data from the 2-day interval phase. Open squares are results from the phase with 1-day intervals.

session time limit was then reduced to 20 min. Throughout the experiment, pecks were reinforced with 3-s access to mixed grain.

1.3.2. Baseline

Sessions began with a 5 min blackout, during which key pecking had no programmed consequence. This was followed by an FR 20 schedule of reinforcement for 20 min or until 40 reinforcers were obtained, whichever came first. After 30–49 sessions, responding was determined to be stable by visual analysis of graphs of daily session-wide response rates and cumulative response records. Sessions were conducted 7 days a week at approximately the same time everyday.

1.3.3. Drug regimen

Past research in which variable doses of cocaine were given daily found that an ascending dose series led to tolerance somewhat more quickly than a descending dose series (Miller and Branch, 2002). Therefore subjects were randomly assigned to the Descending Group or the Ascending Group (3 subjects per group). Subjects in the Descending Group were administered doses in a repeating cycle of saline, 10.0 mg/kg, 5.6 mg/kg, 3.0 mg/kg, and 1.0 mg/kg. Subjects in the Ascending Group were administered doses in a fixed cycle of saline, 1.0 mg/kg, 3.0 mg/kg, 5.6 mg/kg, and 10.0 mg/kg. In each phase of the experiment, each dose of cocaine and saline was administered eight times. During the first phase of the experiment, doses of cocaine or saline were administered once every 7 days. If successive dose–response functions were similar across a phase, subjects progressed to the following phase of the experiment. If a subject's data indicated that tolerance had developed, the subject was removed from the experiment. During the second phase, saline or cocaine doses were administered every 4 days. The third phase consisted of administration of saline or cocaine doses every 2 days. During the final phase, cocaine doses or saline were administered daily. All phases of the experiment began with the administration of the saline vehicle, which followed the previous drug dose by the number of days specified by the inter-dose interval of the upcoming phase.

Occasional errors in dosing occurred. If no injection occurred on the day an injection was scheduled, the dose was administered the following day, and the remaining doses were shifted forward 1 day. This did not occur more than once for any subject throughout the experiment. If the wrong dose was administered, the data from that dose were excluded, the dose that was scheduled was skipped, and the drug regimen continued as scheduled. Incorrect doses were administered a maximum of once per phase for all subjects except for the following: Subject 26 was administered the wrong dose twice in Phase 1; Subject 27 was administered the wrong dose twice in Phase 1, three times in Phase 3, and twice in Phase 4; and Subject 50 was administered the wrong dose twice in Phase 1.

1.3.4. Drug procedure

Cocaine hydrochloride was dissolved in a sterile 0.9% sodium chloride solution. Doses were determined by the weight of the salt, and injection volume was 1 ml/kg. Drug was administered via intramuscular (i.m.) injections in the breast muscle, immediately before the experimental session. Injections alternated sides of the breast muscle to prevent bruising.

The experimental protocol was approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Florida, and followed the *Guide for the Care and Use of Laboratory Animals*.

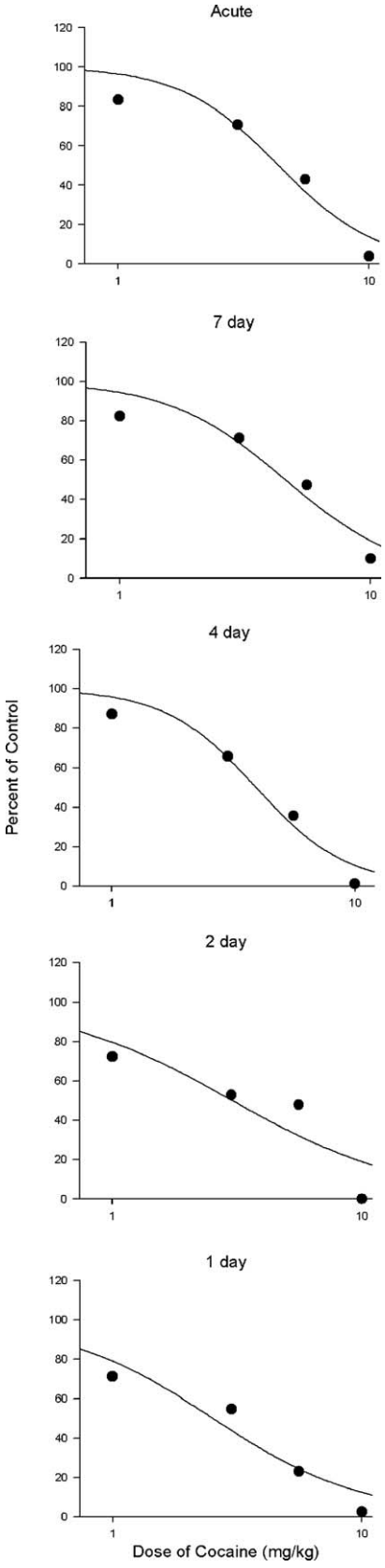
2. Results

Fig. 1 displays dose–response curves from the first phase of the experiment in which doses of cocaine were administered every 7 days. Compared are the first two and last two administrations of the phase.

Subject 50 was the only pigeon to display a substantial change in the dose–response curve, a shift to the right across the phase. This subject showed tolerance to the effects of 10.0 mg/kg cocaine after the fifth administration of that dose, and the tolerance persisted across the remaining administrations. Following the eighth administration of each dose, Subject 50 was delivered single administrations of 13.0 mg/kg and 17.0 mg/kg cocaine at 1-week intervals and responded near control rates under effects of these high doses. Because Subject 50's curve shifted following administration of doses at 7-day intervals, it was not studied further.

The curves for the five other subjects (26, 27, 46, 47, and 48) did not change substantially when cocaine was administered every 7 days (see Fig. 1). The apparent difference in curves for Pigeon 46 was not consistent across the later portions of the phase.

Fig. 2 shows dose–response curves from the second phase of the experiment in which injections occurred every 4 days. Again the curves compare the first two and last two administrations. Subject 26 had an anomalous rate of responding following the



eighth administration of 5.6 mg/kg cocaine and was therefore delivered one more administration of each dose, totaling nine administrations of each dose and saline vehicle. Therefore the open circles represent the average rate of responding from the eighth and ninth administration of each dose for this subject. During administration of cocaine at 4-day intervals no substantial shifts in dose–response curves developed. The differences in effects apparent for Pigeon 26 were not consistent.

Fig. 3 shows dose–response curves from the third phase of the experiment in which injections occurred every other day. Again, no consistent changes in the curves developed in this phase. Subject 46's response rates were generally lower in this phase. Although it appears that Subject 48's curve shifted slightly upward at 5.6 mg/kg cocaine, the rate of responding shown for the first two administrations of this dose was uncharacteristically low for this subject (compare to Figs. 1 and 2). The rate of responding following the last two administrations of 5.6 mg/kg cocaine for Subject 48 is similar to the rate in previous phases. Rate of responding after small doses of cocaine (1.0 mg/kg and 3.0 mg/kg) decreased modestly across this phase for some subjects (47, 27, and 48).

Fig. 4 shows dose–response curves from the fourth phase of the experiment in which injections occurred daily. Once again, no consistent changes in the functions were evident. Dose–response curves for Subjects 27, 46, and 48 were shifted slightly to the left by the end of the phase. Rate of responding under effects of 5.6 mg/kg cocaine for Subject 47 gradually increased across the last half of the phase, but did not exceed the level observed in previous phases.

Fig. 5 shows dose–response curves for response rate plotted as percent of saline vehicle rate (i.e., normalized), averaged across subjects. The value for saline for each pigeon was the mean from all eight administrations in the phase. The figure displays that overall there was little difference in the mean curve across phases. A two-factor (dose × phase) repeated-measures analysis of variance of the normalized rate of responding of the five subjects that completed the experiment confirmed that there was a statistically significant effect of dose ($F=49.346$, $p<.001$), and no significant effect of phase ($F=1.674$, $p>.05$). The interaction between dose and phase also was not significant ($F=1.411$, $p>.05$).

For each phase, a two-parameter logistic function was fit to the percent control data averaged from the five subjects that completed the experiment. The functions are shown in Fig. 6. These functions suggested that slope decreased somewhat in the 2-day and everyday conditions; however, a repeated-measures analysis of variance on the slope for each function for each subject that completed the experiment revealed that the difference in slope was not statistically significant ($F=1.58$, $p>.05$). Also, a repeated measures analysis of variance on the median effective dose (ED_{50}) for each subject that completed the experiment at each

Fig. 6. Group-mean dose–response functions for the acute phase (first two administrations with a 7-day inter-administration interval) and the last two administrations of each dose in each of the four phases of the experiment. Each function shows data from one phase of the experiment. The *Y*-axes display mean response rate as a percentage of the saline control level. *X*-axes show dose of cocaine (log scale). The fitted lines are from a two-parameter logistic regression, with the maximum fixed at 100 and the minimum fixed at 0 (SigmaPlot 9.0).

phase showed that the differences among ED_{50} values were also not significant ($F=0.94$, $p>.05$).

3. Discussion

Because the different dose orders did not lead to any notable differences in effects, the results will be discussed without regard to dose order. Overall, the present experiment found that tolerance was not likely to develop when a variety of doses of cocaine were delivered at any of the intervals, including, surprisingly, when administrations occurred everyday. Tolerance was defined as a consistent shift in the dose–response curve at the end of a phase to the right, compared to the dose–response curve at the beginning of a phase. Five of the six subjects did not develop tolerance when cocaine administrations were spaced 7 days apart. The tolerance seen in one subject did not develop until after five administrations of each dose. These results suggest that spacing acute doses of cocaine by 7 days and delivering up to five administrations of each dose during dose–response curve construction is therefore a relatively safe method of dose–response curve construction, in that values are unlikely to reflect the development of tolerance or sensitization. In addition, none of the other subjects developed consistent tolerance when inter-dose intervals were subsequently shortened to 4-day, 2-day, and finally 1-day intervals. The 7-day and 4-day average functions were very similar, whereas when doses were spaced by 2 days or 1 day the average curves were somewhat flatter, although the differences among curves were not statistically significant. Although not definitive, the present data suggest that administering the drug at 4-day intervals is likely not to result in significant changes over repeated assessments.

The most surprising result of the present study was the absence of tolerance when administrations occurred daily. One possibility is that the particular drug regimen used in the present experiment somehow prevented the development of tolerance to cocaine. Based on previous research (Branch et al., 2000; Miller and Branch, 2002; Yoon and Branch, 2004), it was expected that subjects would develop tolerance when doses of cocaine were administered everyday. In fact, in those experiments shifts of the dose–response curve to the right of up to a half log unit were common (Branch et al., 2000; Miller and Branch, 2002).

Before examining effects of daily dosing, Branch et al. (2000), Miller and Branch (2002), and Yoon and Branch (2004) began with acute dosing that consisted of a dose of cocaine or saline vehicle administered once per week. Each dose was administered at least twice, and occasionally up to six times, yet most pigeons subsequently became tolerant under daily dosing. Their acute dosing procedures, which are similar to the procedures of Phase 1 of the present study, did not prevent the development of tolerance.

In the studies of Branch et al. (2000) and Yoon and Branch (2004), doses were given daily in a descending order. Each dose of cocaine and saline vehicle was administered 10 (Branch et al., 2000) or 15–26 times in Experiment 1 (Yoon and Branch, 2004). Branch et al. (2000) found consistent tolerance in most subjects after seven to nine administration of each dose; Yoon and Branch (2004) did not report when tolerance was first evident in most subjects. Miller and Branch (2002) administered a variety of doses of cocaine to pigeons daily in a descending, ascending, or sawtooth (ascending followed by descending) dose order. Each dose of cocaine and saline vehicle was administered 13 times. Most subjects showed consistent tolerance after 3 to 10 administrations of each dose. Despite the fact that each dosing regimen in the present experiment lasted for only eight administrations, as compared to 10–26 administrations in previous work on variable dosing of cocaine (Branch et al., 2000; Miller and Branch, 2002; Yoon and Branch, 2004), it was reasonable to expect to see some tolerance in several subjects in the present experiment based on previous research (Branch et al., 2000; Miller and Branch, 2002; Yoon and Branch, 2004). The failure to observe tolerance may be due in some way to the long history of intermittent dosing with variable inter-dose intervals to which the subjects in the present experiment were exposed. Additional research comparing subjects with and without such a history will be needed to discover if that is the case.

The present findings make it clear that the exact timing of spaced administrations is an important factor in determining if tolerance to cocaine's behavioral effects will develop under the conditions of our experiment. By the end of the study each of the behaviorally active doses had been administered 32 times, seemingly more than enough than needed normally to observe tolerance.

The present results suggest that there may well be a difference in effects of intermittent dosing depending on whether the dose is fixed or varies. In the Stafford et al. (1994) study in which pigeons were administered a fixed dose of cocaine every 8 days, one subject developed substantial tolerance after three administrations, and another subject developed partial tolerance. The subject that did not develop tolerance to effects of a fixed dose of cocaine delivered every 8 days did develop tolerance when the same fixed dose was administered daily. Prior to daily cocaine administration, inter-dose intervals were 8 days, 4 days, and 2 days, similar to the present study. Results of the present experiment are therefore not in concordance with those of Stafford et al. (1994) because most subjects in the present experiment did not develop tolerance to effects of cocaine when it was administered at 7-day intervals, nor did they following a shortening of inter-dose interval across phases. An obvious possibility for these conflicting results is that Stafford et al. (1994) used a fixed dose and the present experiment used varying doses.

A potentially important difference between the present study and those using fixed doses is the frequency with which behavioral disruption occurs. In the study by Stafford et al. (1994), and in studies using other drugs (Emmett-Oglesby and Taylor, 1981; Wenger et al., 1981) the fixed dose produced a substantial decrease in the rate of responding. In contrast, in the present experiment, subjects received a dose that produced a large decrease in rate of responding only once or twice every five administrations. It is therefore possible that tolerance may develop from intermittent administrations of varying doses of cocaine only when relatively large doses are administered with close enough temporal spacing. Given the literature shows for a variety of species, responses, and drugs that "drugged practice" can be an important determinant of tolerance (Wolgin, 1989), future research directly examining this possibility seems warranted.

The failure to see tolerance in the present study can be contrasted to reports of substantial tolerance in cocaine addicts (O'Brien, 1996). In fact, research with non-humans generally has not revealed substantial tolerance to cocaine's effects. Those studies showing tolerance (e.g., Branch et al., 2000) generally indicate dose–response–function shifts of half a log unit or less, and many studies show sensitization rather than tolerance (Stewart and Badiani, 1993). It may well be that current animal models do not capture effectively the essential aspects of repeated cocaine use by humans. Those that reveal tolerance, however, might be worth pursuing in attempts to develop better models.

To conclude, the present results indicate that determination of stable acute effects of cocaine on food-maintained operant behavior (at least under small FR schedules) usually can be accomplished safely with 7-day inter-administration intervals. Dose–response functions remained stable for 5 of 6 pigeons across 8 replications, and for all subjects across 4 replications. Individual and group-mean functions remained stable when the inter-administration interval was shortened to 4 days, suggesting that 4-day intervals may be appropriate as well, but flattened slightly at the two shorter inter-administration intervals. The results also suggest that previous experience with a variety of doses of cocaine may retard the development of tolerance when dosing becomes frequent.

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