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TOLERANCE TO COCAINE'S EFFECTS FOLLOWING CHRONIC ADMINISTRATION OF A DOSE WITHOUT DETECTED EFFECTS ON RESPONSE RATE OR PAUSE

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Abstract

To observe tolerance to drug effects on operant behavior, the dose that researchers have often selected for chronic administration is one that disrupts, but does not abolish, responding. Some evidence suggests that tolerance may develop after chronic administration of relatively smaller doses. The purpose of the present experiment was to assess systematically effects of chronic administration of a dose without detected effect on responding. Specifically, response rates and postreinforcement pauses of five pigeons key pecking under a three-component multiple fixed-ratio schedule of food reinforcement were observed under chronic cocaine administration. We evaluated the effects of a range of doses (1.0 mg/kg to 17.0 mg/kg) during acute administration. The largest dose that failed to alter responding acutely then was administered chronically (1.0 mg/kg for one pigeon, 3.0 mg/kg for three pigeons, and 5.6 mg/kg for one pigeon). After 30 consecutive sessions of chronic administration, smaller and larger doses occasionally were substituted for the chronic dose. Pigeons then received pre-session saline administration for 30 consecutive sessions, and the postchronic effects of the series of doses on responding were determined. All subjects developed tolerance to doses of cocaine that initially had caused large decreases in rate, with the magnitude of the effects varying across components of the multiple schedule and subjects. Specifically, tolerance generally was greatest in the components with smaller ratios. Following postchronic saline administration, tolerance was usually diminished. Overall, the results demonstrate that under these conditions, repeated experience with disruptive effects of cocaine on food-maintained responding is not a necessary factor in the development of tolerance.

Keywords

tolerance; cocaine; fixed ratio; key peck; pigeons

Classified clinically as a stimulant, cocaine is thought to exert its effects principally by blocking dopamine reuptake in the brain. A complete understanding of the effects of cocaine, however, includes not only its physiological action but also its behavioral action. In an operant-conditioning paradigm, environmental factors, like the schedule of reinforcement, can cause an interaction between the drug and behavior, largely determining the effects that a drug exerts on behavior, rather than its effects depending solely on known pharmacological properties (Barrett, 1976; Dews, 1955, 1958; Gonzales & Goldberg, 1977; Kelleher & Morse, 1964, 1968). For example, cocaine can produce dose-dependent rate-decreasing effects on responding maintained by fixed-ratio (FR) food reinforcement (e.g., Hoffman, Branch, & Sizemore, 1987) and dose-dependent rate-increasing effects on

responding maintained by fixed-interval (FI) food reinforcement (e.g., Schama & Branch, 1994).

The acute effects of cocaine determine what type of changes in behavior can be considered as tolerance. In general, tolerance is defined as a decreased sensitivity to drug effects after repeated dosing (i.e., chronic administration). A dose that formerly produced an effect no longer may be effective, or a larger dose may be needed to produce effects comparable to initial effects at smaller doses. Cocaine's typical acute effects on responding under an FR schedule are that pausing increases and rates decrease (Johanson, 1978; MacPhail & Seiden, 1975). Therefore, tolerance to cocaine's pause-increasing and rate-decreasing effects would be characterized by a decline in pausing and recovery of response rates.

A number of environmental and behavioral factors have been shown to modulate whether and the degree to which behavioral tolerance develops. Some of these variables include repeated administration (e.g., Branch & Dearing, 1982), whether the dose is administered pre- or postsession (e.g., Pinkston & Branch, 2004, 2010), the reinforcement schedule type and context (e.g., Barrett, 1976; Schuster, Dockens, & Woods, 1966), the degree of stimulus control (e.g., Laties & Weiss, 1966), the subjects' deprivation level (e.g., Hughes, Pitts, & Branch, 1996), reinforcer magnitude (e.g., Durgin, Porter, Bradley, Laraway, & Poling, 2009), response effort (e.g., Makhay, Alling, & Poling, 1994), and reinforcement-schedule parameter (e.g., Hoffman et al., 1987; Nickel, Alling, & Poling, 1993). Though exactly how environmental variables function—contributing to tolerance or lack thereof—remains to be elucidated, the reinforcement-loss hypothesis proposed by Schuster et al. (1966) has accumulated much empirical support and has endured as a viable account in many circumstances. According to the reinforcement-loss hypothesis, tolerance is thought to be a functional mechanism in that it develops only when a drug's behavioral effects decrease rate of reinforcement. If an organism experiences the prevailing contingencies of a schedule in the presence of behaviorally deleterious drug effects (i.e., behavior is disrupted severely enough such that reinforcement is markedly reduced or not obtained), it can learn to adjust its behavior accordingly to compensate for the cost associated with drug-induced losses.

Schuster et al. (1966) demonstrated that amphetamine tolerance developed in the differential-reinforcement-of-low-rates (DRL) component, but not in the fixed-interval (FI) component, in a multiple schedule. Physiological mechanisms of tolerance, such as changes in metabolism or neurotransmitter receptor sites, cannot fully explain the obtained results given that differential tolerance occurred. Amphetamine's acute effects increased responding in both components, thereby diminishing reinforcement rates in the DRL but not in the FI, which led Schuster et al. to suggest that behavioral tolerance occurs only when the initial effect of the drug is such that behavior becomes incompatible with the contextual contingencies, and therefore contact with reinforcement decreases. Since the initial suggestion that reinforcement loss can be an important factor in the development of tolerance, differential tolerance has been demonstrated across drugs, species, and responses in a multitude of studies (Bowen, Fowler, & Kallman, 1993; Demellweek & Goudie, 1982; Emmett-Oglesby & Taylor, 1981; Foltin & Schuster, 1982; Nickel, Alling, Kleiner, & Poling, 1993; Poling & Nickel, 1993; Smith, 1986, 1990; for reviews see Corfield-Sumner & Stolerman, 1978, and Wolgin, 1989).

The finding that the reinforcement schedule modulates tolerance is interesting because the multiple schedule arrangement reveals that the presence and absence of tolerance can occur within a single session, thus indicating that simple, direct neurophysiological effects cannot be a complete account of tolerance. Such an effect even has been extended to schedule-parameter dependent tolerance to the disruptive effects of cocaine. Hoffman et al. (1987) trained three pigeons to respond under a three-component multiple FR schedule with food

reinforcement. When cocaine was administered acutely, it produced dose-dependent, rate-decreasing effects in all three components. Following chronic administration of a dose that suppressed—but did not entirely eliminate—responding, tolerance developed in the small- and medium-ratio components. Little to no tolerance developed in the large-ratio component. These results were consistent somewhat with the reinforcement-loss hypothesis in that response rates recovered during chronic administration and subjects were able to adjust behavior to achieve reinforcement. The results were inconsistent with the reinforcement-loss hypothesis, however, because tolerance failed to occur in the large-ratio component even though reinforcement loss occurred in that component. Follow-up studies by Branch (1990) and Schama and Branch (1989) revealed that differences in reinforcement rate across components were not associated with differential development of tolerance. Findings reported by Yoon and Branch (2004) and Hughes, Sigmon, Pitts, and Dykstra (2005) showed that differences in unit price also were not associated with differential development of tolerance. Our present understanding of the effect obtained by Hoffman et al., therefore, is that the response requirement is the relevant variable that controls the extent to which tolerance develops.

With respect to repeated administration, typically the largest dose that reduces responding without eliminating it entirely often has been selected. Schuster (1978) suggested that the best dose at which one can observe the development of tolerance during chronic administration is between the effective-dose (ED) 25 and the ED 75. An ED_{25} is a dose that alters (i.e., increases or decreases) responding by 25% relative to baseline, and an ED_{75} would be a dose that alters responding by 75% relative to baseline. Because previous research on repeated administration of cocaine has indicated that tolerance can develop with relatively lower doses but usually does not develop with higher doses that abolish responding (Bowen et al., 1993; Branch, Wilhem, & Pinkston, 2000; Stafford & Branch, 1996), the systematic manipulation and assessment of the chronic dose selection is of critical importance in understanding factors that contribute to the development of tolerance or lack thereof.

In the behavioral literature on drug action, surprisingly few studies have attempted to assess the role of the chronic dose when it is administered pre-session. Bowen et al. (1993) found that acute cocaine administration dose-dependently decreased responding in a milk-drinking task in rats. Rats then either received 8.0 mg/kg, 16.0 mg/kg, or 32.0 mg/kg cocaine chronically. They found that dose-specific tolerance occurred to the lowest dose tested (i.e., 8.0 mg/kg), but that tolerance failed to generalize when higher doses were substituted for the chronic dose. Following the moderate-dose chronic administration, tolerance was observed across a range of doses tested, and the highest dose tested (32.0 mg/kg) produced hardly any tolerance. Stafford and Branch (1996) reported a similar pattern of findings when they assessed cocaine's acute rate-decreasing effects under an FR 30 schedule in pigeons. The combined results from these studies corroborate the well-known fact that the degree of tolerance can be affected by the dose selected for chronic administration; however, neither study addressed this variable in the context of a multiple schedule, which also has been shown to modulate the degree of tolerance (e.g., Hoffman et al., 1987).

Pinkston and Branch (2004) aimed to assess tolerance to cocaine's rate-decreasing effects in a multiple FR 5 FR 100 schedule following pre-session chronic administration of a small dose. For all six pigeon subjects, they found that tolerance developed in the small-ratio component but not in the large-ratio component. That is, following chronic administration of a small dose, acute effects (i.e., decreased response rates at high doses) were attenuated. Of particular interest is that the small chronic dose produced no noticeable effect on response rates in the small-ratio component, suggesting that tolerance may develop after pre-session administration of a behaviorally inactive dose. Unfortunately, one limitation in their study

was the criterion for selection of the “small” dose. The chronic, pre-session small dose was chosen because in a previous condition of the experiment it was defined as one that did not affect within-session responding when administered post-session. The problem with the definition is twofold. First, by the end of the post-session chronic administration condition, responding had decreased in the large-ratio component for three of seven subjects and had decreased in the small-ratio component for one subject. Second, when the small dose then was administered chronically pre-session, it reduced responding, albeit slightly, in the large-ratio component; thereby the “small” dose still had some behavioral action on responding.

The purposes of the present experiment were to (a) evaluate the development of tolerance after chronic administration of a dose that failed to reduce responding acutely and (b) determine whether the FR parameter modulated the degree of tolerance. To do so, we arranged a three-component multiple schedule, under which five pigeons' responding was maintained by access to grain. Once baseline responding had stabilized, an acute dose-effect determination was conducted. The largest dose that failed to disrupt responding acutely then was administered chronically. To evaluate whether, and the degree to which tolerance developed, we reassessed the effect of a series of doses on responding by conducting a during-chronic dose-effect determination. The development of tolerance to larger doses of cocaine following pre-session chronic administration of a dose without detected effects on rate and pause not only would confirm findings reported by Bowen et al. (1993), Stafford and Branch (1996), and Pinkston and Branch (2004), but also provide evidence against the reinforcement-loss hypothesis, in that tolerance need not require learning and behavioral compensation due to the presence of decreased reinforcement rate under drug effects.

Method

Subjects

Five experimentally-naïve adult male White Carneau pigeons (numbered 1082, 1163, 1166, 1186, and 1859) were obtained from Double-T Farms, Glenwood, Iowa. We maintained the pigeons at 85% of their free-feeding body weight via post-session feedings consisting of mixed grain and pellets (Purina Pigeon Chow Checkers) in equal proportions. Outside of daily sessions, the pigeons were individually housed in a temperature- and humidity-controlled colony room with a 16:8-hr light:dark cycle. In their home cages, the pigeons freely had access to water and health grit.

Apparatus

The experiment was conducted in two pigeon operant-conditioning chambers (interior dimensions 35 × 30 × 35 cm). The front panel of the chambers contained a houselight positioned 30 cm from the chamber floor, and 7 cm below the houselight were three horizontally-positioned keys. The keys measured 2.5 cm in diameter and were positioned 8 cm from the walls and 5.5 cm apart. Only the center key—illuminated white, red, or green—was used; its activation required a minimum force of 0.098 N. A 30-ms tone, produced by a Mallory Sonalert®, accompanied each successful response to the key. Located 10 cm directly below the center key and 11 cm from the chamber floor there was a 5-cm by 5.5-cm aperture through which access to a solenoid-operated hopper filled with buckwheat, milo, and hempseed could be provided. During reinforcer presentations, the aperture and raised hopper were illuminated, and all other lights in the chamber were extinguished. In one of the chambers, an additional 5-cm by 5.5-cm aperture for pellet delivery was located 3.5 cm to the left of the grain aperture, but it served no function in this experiment. White noise at approximately 95 dB masked extraneous sounds in the rooms containing the operant chambers. In an adjacent room, computers running EC-BASIC software (Palya & Walter,

1993) controlled experimental events and recorded data, and cumulative-response recorders provided live-time data collection.

Procedure

Training—After the pigeons reliably approached and ate from the raised hopper, responses to the center key (illuminated white) were shaped by reinforcing successive approximations. Once key pecking was established, the following session consisted of an FR 1 schedule with the center key illuminated white and lasted until the pigeon earned 60 reinforcers.

General procedure—To arrange a three-component multiple schedule, we introduced two additional key colors—red and green. A 5-min blackout occurred at the beginning of all sessions. Each component was selected randomly without replacement and remained in effect until the pigeon earned four reinforcers, after which the next component began immediately. If a pigeon failed to earn all four programmed reinforcers within an allotted time limit, then components ended after 90 (white), 300 (red), or 810 (green) s elapsed. The white, red, and green keys always signaled the small-, medium-, and large-ratio components, respectively. A sequence of all components comprised a block, and sessions ended after three blocks.

The FR response requirement in each component was increased gradually across sessions until the target FR in each component was achieved; the targeted terminal schedule was a multiple FR 5 FR 25 FR 125 schedule. Each FR increase (i.e., 2, 3, 5, 8, 12, 20, 25, 30, 36, 47, 55, 65, 75, 85, 95, 105, 125) occurred only if visual inspection of the cumulative-response records and overall response-rate data revealed that within-session responding in all components appeared stable. Typically, FR increases occurred each session; no pigeons were exposed to the same multiple-schedule parameters for more than two consecutive sessions.

Baseline—During baseline our aim was to obtain consistent responding in all components with differentially longer postreinforcement pause in the large-ratio component. In order to accomplish these outcomes, the details of the procedure were tailored to individual subjects. Pigeons 1082 and 1186 responded under FR 5 FR 25 FR 125 with 3-s access to grain. Pigeon 1166 responded under the same schedule, but his weight was increased from 85% to 98% of his free-feeding body weight, and his reinforcer access was increased to 4 s. Pigeon 1163 responded with 3-s access to grain, but his large-ratio performance deteriorated beyond FR 80, so this value ultimately was chosen for his large-ratio component. In order to maintain responding, pigeon 1859 required 6-s access to food and a reduction of the response requirements to FR 5, FR 15, and FR 45. The baseline conditions remained in effect until response rate and postreinforcement pause were stable for at least 30 sessions.

General pharmacological procedure—Cocaine hydrochloride obtained from National Institute on Drug Abuse was dissolved in 0.9% saline solution. Doses were delivered in mg/kg, expressed in terms of the salt, and administered intramuscularly (pectoral muscle) immediately prior to a session. Dose volume (in mL/kg) was determined by 0.1% of a subject's 85% weight (even if weight was adjusted later). For example, Pigeon 1859's 85% weight was 682 g and it always received a 0.68-mL injection.

Acute administration—Doses were administered every fifth session in either an ascending (Pigeons 1166 and 1186) or descending (Pigeons 1082, 1163, and 1859) series. The series of doses for Pigeons 1082, 1163, and 1186 included 0.0 mg/kg (i.e., saline), 1.0 mg/kg, 3.0 mg/kg, 5.6 mg/kg, and 10.0 mg/kg. The effects of this series of doses on response rate and postreinforcement pause were assessed twice. Pigeon 1859 received the

same series of doses, but after the two determinations, we administered an abbreviated series of 0.0 mg/kg, 3.0 mg/kg, and 5.6 mg/kg for two additional determinations of each dose. We altered the series of doses for Pigeon 1166 such that the 1.0 mg/kg was excluded and a 17.0 mg/kg dose, the largest dose permitted by the IACUC protocol, also was assessed. Table 1 shows the number of times a dose was administered for each pigeon.

Chronic administration—Based on visual analysis of the acute dose-response functions and corresponding cumulative-response records, we selected the largest dose that failed to suppress rates or elevate postreinforcement pause during acute administration. We chose 1.0 mg/kg for Pigeon 1859, 3.0 mg/kg for Pigeons 1163, 1166, and 1186, and 5.6 mg/kg for Pigeon 1082. The dose then was administered immediately prior to 30 consecutive sessions. Rarely, during chronic administration (at most twice for any individual pigeon and never successive sessions), an apparatus failure prevented us from conducting a daily session. Under these circumstances, the pigeon still received administration of its chronic dose and was returned to its home cage.

During-chronic assessment—To determine whether and the extent to which tolerance developed, we reassessed the effect of the series of doses on rate and pause by administering a probe dose from the series every fifth session. On days intervening probes, pigeons received their chronic dose. After two determinations of each dose from the series, we replicated doses at the critical points in the curve and probed for tolerance to higher doses if necessary. Table 1 shows the number of times a dose was administered for each pigeon.

Postchronic saline administration and assessment—Pigeons received saline immediately prior to 30 consecutive sessions. To determine whether tolerance was reversible or attenuated, we reassessed the effect of the series of doses a final time by administering a probe from the series every fifth session. On days intervening probes, pigeons received a saline injection. After two determinations of each dose from the series, we replicated doses at the critical points in the curve if necessary. Table 1 shows the number of times a dose was administered for each pigeon.

Data analysis—The primary dependent variables were overall response rate and postreinforcement pause. Both measures were plotted as a function of cocaine dose to obtain dose-response functions, from which area-under-the-curve (AUC) measures could be derived and used to quantify the degree of tolerance. Because the chronically administered dose was one without detected effect on rate or pause, the AUC was calculated using only data points corresponding to the chronic dose and those greater than the chronic dose. In order to normalize the values for absolute rates that differed across components and pigeons, AUC measures were expressed as a proportion of the “maximum” possible tolerance in each condition. To calculate the maximum possible, all values (i.e., across doses) were set equal to the value for the chronic dose in each phase. That is, hypothetical points that revealed no change at all in drug effect were used to set the maximum. The areas under the obtained curves then were divided by this “maximum” area. Therefore, a proportion at or near 1.0 indicates no change in rates or pause upon administration of doses higher than the chronic dose, that is, complete tolerance across the doses tested. For response rate, then, larger proportions indicate more tolerance. Because acute cocaine dose-dependently increased pause, smaller proportions indicate more tolerance. Thus, values greater than 1.0, indicate less tolerance, with 1.0 again the value that would indicate complete tolerance.

Results

Figure 1 shows the overall response rate and postreinforcement pause in each component of the multiple schedule as a function of session across the baseline, during-acute assessment, and chronic administration phases for individual pigeons. During baseline, rates and pause were stable across components, with more across-session variability evident in the large-ratio component. Data paths in the acute phase exclude sessions on which a probe dose was administered. During acute administration, rates and pause remained stable and within the range of baseline response rates. The highest dose that failed to have a substantial effect on responding acutely did not substantially alter pigeons' performance when it was administered chronically, either. Some across-subject variability was noted. For example, Pigeon 1082's large-ratio rates increased and large-ratio pause decreased somewhat, but there appeared to be trends in those directions at the conclusion of acute administration. A change in performance during low-dose chronic administration was most evident in Pigeon 1163's large-ratio rates and pause. Pigeon 1186's large-ratio performance appeared to be affected during the first session of chronic administration, but rates and pause immediately returned to levels comparable to the previous phase in the subsequent sessions.

Figure 2 shows overall response rates for individual pigeons in each component as a function of cocaine dose. For all pigeons, acute cocaine administration dose-dependently decreased response rates. Following chronic administration, across-subject and across-component variability was evident with respect to the degree of tolerance that developed. Overall, doses of cocaine—those larger than the chronically administered dose—that acutely produced large decreases in rates, subsequently had less of an effect when they were administered during the chronic-assessment phase.

The two pigeons for which the most dramatic instances of tolerance occurred were Pigeons 1082 and 1186. During acute dosing, 10.0 mg/kg of cocaine eliminated responding in the medium- and large-ratio components and nearly eliminated responding in the small-ratio component. During-chronic assessment of tolerance revealed that the effect of 10.0 mg/kg on response rate was greatly attenuated, with tolerance most evident in the small-ratio component. Note as well, that the during-chronic assessment included a dose, 13.0 mg/kg, which was larger than any dose tested acutely. When this dose was administered, tolerance was evident in the small-ratio component, but less so in the medium- and large-ratio components. Interestingly, even in the medium-ratio component (and large-ratio component for Pigeon 1082), some degree of tolerance occurred because response rates were not eliminated when 13.0 mg/kg were administered, and this dose was larger than the dose that eliminated responding entirely during acute administration. Following postchronic saline administration, the effects of cocaine appeared to be more similar to the effects during acute than chronic assessment, indicating that tolerance mostly was reversible for Pigeon 1082. For Pigeon 1186, tolerance was reversed only at the 13.0 mg/kg dose.

For Pigeon 1163, the range bars are wide at the 3.0 mg/kg and 5.6 mg/kg doses for the postchronic assessment because responding appeared to be bimodal. That is, for three of six determinations responding was eliminated, but for three of six determinations responding was comparable to that at lower doses. The order of the determinations was not predictive of the degree of responding that occurred. The wide range bars somewhat inhibited clarity with respect to evidence of tolerance, but by comparing the open squares to the closed circles, one can see that mean responding shifted in a direction that indicates tolerance did develop. In other words, Pigeon 1163 was tolerant to the effects of 5.6 mg/kg for two of two during-chronic administrations. Some tolerance also was evident when 10.0 mg/kg were administered. When administered acutely, 10.0 mg/kg eliminated responding in all three

components, but in during-chronic assessment, some responding occurred in the small- and medium-ratio components.

For Pigeon 1166 responding was maintained in the small- and medium-ratio components when 17.0 mg/kg (i.e., the largest dose that the IACUC protocol permitted us to administer) were administered acutely. Towards this end of the curves, it was difficult to ascertain the degree to which tolerance developed in the small-ratio component due to that fact that the 17.0 mg/kg dose reduced responding by only 50% relative to control levels. In order to obtain even this reduction, it was necessary to decrease the deprivation such that this pigeon maintained at 98% of his free-feeding weight. All the mean values from the during-chronic assessment, nevertheless, are above those from acute determinations. In the medium-ratio component, tolerance developed to the effects of 17.0 mg/kg. Response rates were higher after chronic administration of 3.0 mg/kg than they were when 17.0 mg/kg were administered acutely. Tolerance to the effects of this dose failed to develop in the large-ratio component. After postchronic saline administration, the effects of the 17.0 mg/kg in the medium-ratio component provided evidence that tolerance was reversed.

For Pigeon 1859, the range of effects for 5.6 mg/kg was wide for the acute administrations and during-chronic assessments. This dose was administered four times in each phase. This dose either reduced responding substantially or not at all in the small- and medium-ratio components, and the order of determinations was not predictive of the degree of responding that occurred. After chronic administration of 1.0 mg/kg, however, the mean and range of 5.6 mg/kg effects shifted up in both the small- and medium-ratio components; no tolerance was evident in the large-ratio component. After postchronic saline administration, the effects of 5.6 mg/kg tended to shift towards the direction of acute effects, but did not reverse fully in the small-ratio component. Effects in the medium-ratio component remained at chronic levels following postchronic saline administration, and no change across phases seemed to occur in the large-ratio component.

Figure 3 shows total postreinforcement pause for individual pigeons in each component as a function of cocaine dose. Overall, these data show that for all pigeons the pause tended to be shorter for the during-chronic determinations relative to the effects obtained during acute administration. Similar to the response rate data shown in Figure 2, across-subject-and-component variability was observed.

For Pigeons 1082 and 1186, acute 10.0 mg/kg cocaine administration maximized pausing in all three components. In the chronic-assessment phase, pausing was decreased substantially, with the greatest degree of decrease appearing in the small-ratio component. For Pigeon 1082, tolerance was reversible in the medium- and large-ratio components, and it was attenuated in the small-ratio component. For Pigeon 1186, tolerance was attenuated only in the small- and medium-ratio components and only at the 13.0 mg/kg dose. For Pigeon 1163, wide range bars at the 3.0 mg/kg and 5.6 mg/kg doses in the postchronic phase make the comparison between the acute and during-chronic assessments more challenging. Nonetheless, tolerance appeared to develop to the effects of 5.6 mg/kg, as pausing was noticeably shorter in the chronic-assessment phase (i.e., open squares were below closed circles in all three components). Although tolerance to the effects of 10.0 mg/kg was less than that observed for 5.6 mg/kg, tolerance to 10.0 mg/kg was most evident in the small-ratio component and did not develop in the large-ratio component. Furthermore, Pigeon 1163 was more sensitive to cocaine's pause-increasing effects following postchronic saline administration (relative to both the acute and during-chronic effects) in all three components. For Pigeon 1166, some tolerance was evident at the 5.6 mg/kg and 17.0 mg/kg doses in the small-ratio component, but the most convincing evidence of tolerance for this pigeon occurred at the 17.0 mg/kg dose in the medium-ratio component. Tolerance to the

effects of this dose failed to occur in the large-ratio component. After postchronic saline administration, tolerance was not attenuated in the small-ratio component, but the effects of the 17.0 mg/kg dose in the medium-ratio component provided evidence that tolerance was reversed. For Pigeon 1859, the range of acute effects for 5.6 mg/kg was wide because the effects seemed to be bimodal. Several determinations revealed that pausing either was increased greatly or not at all by this dose. After chronic administration of 1.0 mg/kg, the mean and the range of 5.6 mg/kg effects shifted down for pause in both the small- and medium-ratio components, indicating that some degree of tolerance had developed. Tolerance to 10.0 mg/kg was not evident nor was tolerance observed at any dose in the large-ratio component. In the large-ratio component the range of effects for both 3.0 mg/kg and 5.6 mg/kg became narrower for the chronic assessment relative to the acute range. After postchronic saline administration, the effects of 5.6 mg/kg tended to shift towards the direction of acute effects in the small-ratio component, but did not reverse fully. Effects in the medium-ratio component remained at chronic levels, and no change across phases occurred in the large-ratio component.

Figure 4 shows the AUC data for response rates (upper panels) and pause (lower panels) in each ratio component across phases for all pigeons. With respect to the rate data, the AUC-based measure for the chronic-assessment phase was generally greater than that for the acute-administration phase for all pigeons, indicating that tolerance to the effects of higher doses occurred following chronic administration. An exception was that tolerance did not develop for Pigeon 1859 in the large-ratio component. For Pigeons 1082 and 1186, the extent to which tolerance developed appeared greatest in the small-ratio component relative to the other two components. For Pigeon 1163, tolerance occurred comparably across components. The somewhat lesser AUC shift evident in Pigeon 1166's small-ratio component relative to the other components likely is explained by the fact that in acute administration, substantial responding was maintained even at the largest dose administered. The AUC-based measure for the chronic-assessment phase also was greater than that for the postchronic assessment in several instances, indicating that tolerance was reversible, or at least attenuated, following postchronic saline administration. For example, for Pigeons 1082 and 1163 in all three components, postchronic dose-response functions were more similar to those obtained under acute administration, rather than chronic assessment. Furthermore, Pigeon 1163 was more sensitive to the rate-decreasing effects of cocaine following postchronic saline administration, as the AUC-based measure for this phase was less than that for acute administration.

With respect to the pause data, the proportion for the chronic-assessment phase was less than that for the acute-administration phase, confirming that tolerance developed for all pigeons across components. The only exception was Pigeon 1166 in the small-ratio component, in which not much tolerance developed to cocaine's pause-increasing effects. For all pigeons, the extent to which tolerance developed seemed to be greatest in either the small- or medium-ratio components relative to the large-ratio component. Following postchronic saline administration, the AUC proportion was greater than that for the chronic-assessment phase for Pigeons 1082, 1166, and 1859, but only for the medium- and large-ratio components. Tolerance to the pause-increasing effects of cocaine neither was reversible nor attenuated in the small-ratio component.

Figure 5 shows an alternative way to ascertain whether and the degree to which tolerance developed in each component. Consumption, the number of reinforcers earned out of 12 available, is shown as a function of cocaine dose. Because cocaine increased pause and decreased rates, consumption decreased due to the time-limit contingency in each component.

When administered acutely, 10.0 mg/kg was a large enough dose either to reduce markedly or to eliminate consumption in all components for three pigeons (1082, 1163, and 1186). For these pigeons tolerance to cocaine after chronic administration was evidenced by increased consumption. The greatest degree of tolerance occurred at the smallest FR requirement. For Pigeons 1082 and 1186, tolerance in the small-ratio component was substantial—they never failed to earn an available reinforcer even at a dose that was higher than a dose that interrupted consumption acutely.

For Pigeon 1166 in the small-ratio component, even the largest dose of cocaine did not interrupt consumption acutely; therefore we were unable to examine any increases in consumption after chronic administration in this pigeon. Tolerance to 17.0 mg/kg in the medium-ratio component was maximal, with all 12 reinforcers earned after chronic administration of 3.0 mg/kg compared to only 9 earned during acute administration. Some tolerance also was evident in the large-ratio component, but to a lesser extent than that observed in the medium-ratio component, therefore showing schedule parameter specificity similar to that of Pigeons 1082, 1163, and 1186.

For Pigeon 1859, modest tolerance occurred to effects of 5.6 mg/kg in the small- and medium- ratio components and to 3.0 mg/kg in the large ratio component. At these doses, the number of reinforcers earned always was greater after chronic administration. During acute administration the range of consumption at these doses was much wider. Although mean consumption for 10.0 mg/kg in the chronic-assessment phase was lower than mean consumption for 10.0 mg/kg in the acute-administration phase in the small- and medium-ratio components, the range of effects extended beyond the mean of acute effects. In the large-ratio component both the acute and chronic range of effects at 5.6 mg/kg were wide. Acutely, the bottom of the range reaches zero, but Pigeon 1859 always earned at least some reinforcers and sometimes earned all reinforcers at 5.6 mg/kg after chronic administration of 1.0 mg/kg. Additionally, there seemed to be slight tolerance in the large-ratio component even at 10.0 mg/kg; acutely 10.0 mg/kg caused Pigeon 1859's consumption to plummet to zero in this component, but after chronic administration he earned a reinforcer.

Discussion

The purpose of the present experiment was to determine whether, when a dose that produced no measured change in performance was given repeatedly, tolerance would develop to cocaine's rate-decreasing and pause-increasing effects and, if it did, whether the degree of tolerance developed differentially across FR parameters. To do so, we arranged a three-component multiple FR schedule of food reinforcement, and the effects (on response rate and pause) of a series of doses of cocaine were assessed before, during, and after chronic pre-session administration of a low dose that produced no changes in rate or pausing, a dose hereafter called subthreshold. Following chronic administration, for all pigeons, sensitivity was decreased to doses of cocaine that acutely diminished, and even eliminated, responding. Following postchronic saline administration, for three of five pigeons, tolerance was reversed entirely or attenuated. For one pigeon the extent to which tolerance developed was markedly less pronounced relative to the other pigeons. Nonetheless, an overall pattern revealed that the degree of tolerance was inversely related to the FR requirement, with tolerance generally being greater as the FR requirement decreased for all pigeons.

Acute cocaine administration dose-dependently decreased responding across all three components of the multiple schedule, a finding that is consistent with those obtained in other studies employing FR schedules either as a component of a multiple schedule or a single schedule (e.g., Hoffman et al., 1987; Hughes & Branch, 1991; Pinkston & Branch, 2004; Schaal, Miller, & Odum, 1995; Stafford & Branch, 1996). Within- and across-session

responding remained stable even throughout repeated administration of the subthreshold dose, which further supported the decision made during acute administration (consisting of just two determinations of this dose) to characterize it as “subthreshold” (1.0 mg/kg for Pigeon 1859, 3.0 for Pigeons 1163, 1166, and 1186, and 5.6 mg/kg for Pigeon 1082).

Pigeon 1859 showed, at best, only very modest tolerance. It is possible that this result was related to the dose selected for repeated administration. Specifically, the dose might have been functionally smaller than those tested with the other pigeons in that it was 0.5 log unit smaller than the lowest dose at which an effect was observed. For the other pigeons, the so-called subthreshold dose was 0.25 log unit smaller than the lowest dose that resulted in a measureable change. Had we assessed the effects of doses between 1.0 and 3.0 mg/kg for Pigeon 1859 during acute administration, we might have been able to identify a subthreshold dose greater than 1.0 mg/kg.

To our knowledge, this is the first demonstration of tolerance to behavioral effects of larger doses of cocaine following chronic presession administration of a subthreshold dose. Bowen et al. (1993) assessed tolerance to the suppressive effect of cocaine on a milk-drinking task in rats using a low, moderate, or high dose. They found that dose-specific tolerance developed to effects of the low dose, but it failed to generalize during administration of higher probe doses. Note that because tolerance developed with the low dose, it could not have been subthreshold initially. Furthermore, the tolerance observed in our experiment compellingly was not dose-specific, but instead reflected a shift to the right of the entire dose-response curve. That is, when we probed for tolerance by occasionally substituting higher doses for the chronic dose, tolerance was evident at a range of higher doses, inconsistent with Bowen et al.’s findings.

Our findings confirm and extend the results reported by both Stafford and Branch (1996) and Pinkston and Branch (2004). Whereas Stafford and Branch demonstrated that chronic presession administration of a low dose engendered tolerance to cocaine’s disruptive effects on responding maintained by an FR 30 schedule of reinforcement, Pinkston and Branch arranged a multiple FR 5 FR 100 schedule and demonstrated that tolerance developed following chronic presession administration of a low dose. The effect reported by Pinkston and Branch occurred only for three of six pigeons, all of which previously had been exposed to a chronic postsession administration condition. Their pigeons not only had a history of drug administration, but also the low dose was selected for presession administration because it had no effect on within-session response when postsession administrations were administered acutely. By the end of chronic postsession administration of the low dose, within- and across- session response rates no longer were identical to control response rates. Response rates had decreased in either the small- or large-ratio component for four of seven pigeons. Thus, the changes observed as a result of chronic postsession administration indicate that the dose may have had some behavioral action that became apparent only during repeated administration. In our experiment we were able to demonstrate that presession administration of a subthreshold dose did not affect response rates across chronic-administration sessions. When administration of the chronic dose was discontinued, and saline was administered repeatedly, response rates persisted at relatively stable levels (i.e., did not change).

Additionally, we found that the degree of tolerance often depended on the FR parameter, consistent with previous studies showing that the response requirement can be a key determinant of the development of tolerance. That is, tolerance generally is more substantial for responding under small-ratio components, and not under large-ratio components, of a multiple schedule (Branch, 1990; Hoffman et al., 1987; Hughes & Branch, 1991; Nickel & Poling, 1990; Nickel et al., 1993; Pinkston & Branch, 2004; Van Haaren & Anderson, 1994;

Yoon & Branch, 2004). A noteworthy feature of the present data was that for four of five pigeons, some degree of tolerance developed in the large-ratio component. For example, for Pigeons 1082, 1163, and 1186 moderate tolerance developed in that component to the effects of 10.0 mg/kg—evidenced by response rate means, upper ranges, or both that are comparable to control and saline levels of responding. Similarly, for Pigeon 1163 some tolerance to the effects of 5.6 mg/kg but not 10.0 mg/kg was evident in the large-ratio component, even though tolerance occurred to the effects of 10.0 mg/kg in the small-ratio component.

It would be premature to conclude that lesser tolerance observed in the large-ratio components implicates FR 125 (for Pigeons 1082, 1166, and 1186), FR 80 (for Pigeon 1163), and FR 45 (for Pigeon 1859) as upper limits of response requirements beyond which tolerance becomes increasingly unlikely to occur. Rather, it is possible that tolerance was least evident in the large-ratio components due the presence of smaller ratios as components of the multiple schedule. Smith (1986) clearly demonstrated that multiple-schedule context on tolerance can influence whether tolerance is observed under a particular schedule of reinforcement. Therefore, it is unknown whether and the degree to which tolerance would have occurred to cocaine's rate-decreasing effects on responding under a single FR 125, FR 80, or FR 45 schedule following chronic administration of a subthreshold dose.

Perhaps the most striking feature of the present findings is that tolerance developed despite no apparent loss, or even reduction, of reinforcement rate in any of the FR components during chronic administration of the small dose. Such a finding cannot be accounted for by the long-standing, widely supported explanation for behavioral tolerance known as the reinforcement-loss hypothesis (Schuster et al., 1966), which asserts that tolerance is an adaptive mechanism allowing an organism to adjust its behavior to compensate for the decreased rate of reinforcement in the presence of drug effects. The reinforcement-loss hypothesis is silent with respect to the development of tolerance when there is no evidence of disruption during chronic administration.

One could argue that pigeons in the present experiment rapidly adjusted to the loss of reinforcement during acute administration of larger doses. Such a position would suggest that upon repeated tests with a particular dose during acute administration, second and subsequent administrations should reveal effects consistent with the development of tolerance. No such effects were observed.

Although the chronic dose never disrupted behavior such that rate of reinforcement was altered (i.e., responding under the chronic dose was indistinguishable from control responding), we cannot dismiss entirely the role of reinforcement rate. At least in some senses, reinforcement rate still may be relevant in an interpretation of the present data. Because FR schedules were employed, reinforcement rate in a given component depended on response rates: Increased response rates proportionally increase the reinforcement rate. Across components, even if response rates were equivalent, reinforcement rates differed because of the differences in response requirement (e.g., completing an FR 125 normally requires more time than does completing an FR 5). Under baseline conditions, response rate was highest in the medium-ratio component and lowest in the large-ratio component. Responding under ratio schedules is known to increase and then decrease with increases in response requirement (e.g., Baum, 1993). If baseline response rates are conceptualized as strength of the response, and acute cocaine administration disrupts responding, then we should have observed the greatest and least relative reduction in rates to occur in the large- and medium-ratio components, respectively. Behavioral momentum theory (Nevin, 1974), however, asserts that behavior in the context of higher reinforcement rates, by virtue of stimulus-reinforcer pairings, will be more resistant to change upon subsequent presentation

of disruptor variables, independent of baseline response rates (i.e., response–reinforcer pairings). This perspective seems to provide a better account for the present data in that the obtained reinforcement rate was greatest in the small-ratio component and responding under this component also was least sensitive to cocaine’s acute effects for most (three of five) pigeons. Perhaps it is the case that the greatest degree of tolerance will occur in contexts that engender the least initial disruption of responding. That is, behavioral momentum may be predictive of subsequent tolerance. Nevertheless, two caveats are noteworthy here. First, both Branch (1990) and Schama and Branch (1989), using interval schedules in which reinforcement rate is relatively independent of response rate, did not find a systematic relationship between differential reinforcement rates and the degree to which tolerance developed across components of multiple schedules. Second, response strength indexed using pharmacological disruptors often produces different effects than when traditional disruptors, such as extinction and prefeeding, are employed (Cohen, 1986).

Overall, tolerance generally was greatest in the components with smaller ratios, and following postchronic saline administration, tolerance was usually diminished. These results confirmed those obtained in previous studies suggesting tolerance to cocaine’s effects could occur by chronic low-dose administration. Moreover, our results demonstrate that under these conditions, repeated exposure to the disruptive effects of cocaine on food-maintained responding is not a necessary factor in the development of tolerance. At first glance, it is tempting to explain the tolerance obtained in the present study by pointing to physiological and pharmacological mechanisms given that we were unable to track the emergence of tolerance across sessions during chronic administration. The use of a subthreshold dose obstructed observable changes in behavior during chronic administration, and we only were able to determine that tolerance had occurred via occasional probing with higher doses. The use of the multiple schedule allowed us to demonstrate that tolerance was not equal across components, therefore, metabolic or physiological changes alone cannot fully explain our results. Identification and parametric assessment of other conditions under which the reinforcement-loss hypothesis fails to account for behavioral tolerance should be a focus of future research. A question that was not addressed by the present data was whether an injection of the subthreshold dose was discriminable from an injection of saline under these conditions or if it would be behaviorally active under other conditions. Empirically addressing questions of this nature could prove fruitful in contributing to and enhancing the understanding interactions between physiological and behavioral mechanisms of drug tolerance.

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Fig. 1.

Overall response rate (left column) and postreinforcement pause (right column) as a function of session across the baseline, during-acute assessment, and chronic-administration phases in each ratio component for individual pigeons (shown by row). Thickness of the data paths corresponds to the size of the FR parameter in each component. Note the individually scaled y-axes for rate data and logged y-axes for pause data.

Fig. 2.

Overall response rates for individual pigeons (shown by row) in each component (shown by column) as a function of cocaine dose. The C and S on the x-axis represent Control and Saline, respectively. Closed circles, open squares, and closed triangles represent data obtained from the acute, chronic, and postchronic phases, respectively. Data points are the average of at least two determinations per dose, but the exact numbers of doses that individual pigeons received during each phase of dose-effect determinations are reported in Table 1. Error bars indicate the range of effects. Note the individually scaled y-axes.

Fig. 3. Total postreinforcement pause for individual pigeons (shown by row) in each component (shown by column) as a function of cocaine dose. Note the logged y-axes. Details are the same as those for Figure 2.

Fig. 4.

Area-under-the-curve (AUC) data, expressed as a proportion of complete tolerance (see text for explanation), for response rates and pause in each ratio component across phases for all pigeons (shown by column). White, black, and grey bars represent the acute, chronic, and postchronic phases, respectively. Note the individually scaled y-axes.

Fig. 5.

The number of reinforcers per session earned out of the 12 possible as a function of cocaine dose for individual pigeons across the three FR parameters. Each row shows data for a single pigeon, and each panel is for a single component of the multiple schedule. Each data point is the mean of at least two probe determinations, and error bars denote the range of values. Filled circles represent data obtained in the acute phase, open squares represent data obtained in the chronic phase, and filled triangles represent data obtained in the postchronic phase.

Table 1

For all pigeons, the number of determinations for each probe dose across phases. See text for details.

Pigeon	Phase	Number of Probes									
		Saline	1.0	3.0	5.6	10.0	13.0	17.0			
1082	Acute	2	2	2	2	2	-	-			
	Chronic	2	2	2	2	2	3	-			
	Post chronic	2	2	2	2	2	-	-			
1163	Acute	2	2	2	2	2	-	-			
	Chronic	2	2	2	2	2	-	-			
	Post chronic	3	3	6	6	3	-	-			
1166	Acute	2	-	2	2	2	-	2			
	Chronic	2	-	2	2	2	-	2			
	Post chronic	2	-	2	2	2	-	2			
1186	Acute	2	2	2	2	2	-	-			
	Chronic	2	2	2	4	4	2	-			
	Post chronic	2	2	2	2	2	2	-			
1859	Acute	4	2	2	4	4	-	-			
	Chronic	2	2	4	4	3	-	-			
	Post chronic	2	2	2	2	2	-	-			