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Environmental and Pharmacological Factors in the Development of Noncontingent Tolerance to Cocaine in Pigeons

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Abstract

Previous research with rats and monkeys has shown that tolerance to behavioral effects of cocaine developed if the drug was administered before behavioral test sessions but not if it was administered after sessions, a finding known as *contingent tolerance*. In contrast, a recent experiment using pigeons found that they showed tolerance resulting from postsession drug administration (*noncontingent tolerance*). The 4 experiments reported in this article were conducted to examine that result more fully. Experiment 1 found that immediate presession administration of cocaine to pigeons reliably led to tolerance to effects on food-reinforced operant key pecking and that immediate postsession administration of cocaine also led to tolerance in half the subjects, those whose key pecking was not suppressed by postsession dosing. Experiment 2 showed that eating in the home cage under the effects of postsession cocaine was not necessary for tolerance to develop to effects of postsession cocaine and that the majority of subjects developed tolerance from postsession cocaine administration. Experiment 3 found that mere drug exposure in the home cage without exposure to an experimental session did not reliably produce tolerance during the behavioral session. Experiment 4 showed that tolerance from postsession cocaine administration could be observed even when daily dosing was discontinued during dose–response curve assessment. Therefore, the combined results showed that pigeons often developed tolerance to effects of cocaine during the behavioral session when cocaine was administered postsession and that this tolerance was not the result of feeding under effects of the drug.

Keywords

tolerance; cocaine; pigeon; contingent tolerance; key pecking

Drug tolerance, a loss of drug effect relative to initial impact, is a common outcome of repeated drug exposure (Carlton, 1983; Wolgin, 1989). Tolerance is often viewed as an adjustment to a disturbance caused by initial drug effects, and its development may depend on the original drug effect and the frequency of drug administration. Repeated, frequent administration of a drug often leads to the development of tolerance to its effects on behavior (cf. Stewart & Badiani, 1993).

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Contingent tolerance is a form of tolerance frequently associated with operant behavior. Specifically, contingent tolerance develops only when drug is administered before the behavioral session and not when drug is administered after the behavioral session or with no temporal association with the behavioral session (Carlton & Wolgin, 1971). Contingent tolerance is likely relevant to human drug taking, given the operant nature of much human behavior, and may explain some instances of the development of drug tolerance in humans.

Many past experiments have investigated whether contingent tolerance develops to effects of psychoactive drugs, including cocaine. Two studies found that contingent tolerance developed to effects of cocaine on a milk-drinking task in rats (Bowen, Fowler, & Kallman, 1993; Woolverton, Kandel, & Schuster, 1978). Contingent tolerance has also been found to effects of cocaine on a key-pressing task in squirrel monkeys (Branch & Sizemore, 1988) and to effects of cocaine on lever pressing on a fixed interval schedule of reinforcement and on nose poking on a fixed ratio (FR) schedule of reinforcement in rats (Smith, 1990).

Most past research on contingent tolerance has been conducted with rats (Bowen et al., 1993; Campbell & Seiden, 1973; Carlton & Wolgin, 1971; Chen, 1968; Poulos, Wilkinson, & Cappell, 1981; Wenger, Tiffany, Bombardier, Nicholls, & Woods, 1981; Woolverton et al., 1978), and one experiment used monkeys (Branch & Sizemore, 1988). Pinkston and Branch (2004) found non-contingent tolerance to effects of cocaine on key pecking in pigeons. Because it involved a within-subject design and used a more complicated behavioral procedure than past experiments investigating contingent tolerance to cocaine; however, the Pinkston and Branch study did not provide for a direct test of whether contingent tolerance had developed.

The purpose of the present experiments was to investigate whether tolerance to the effects of cocaine is contingent on the relationship between the time of drug administration and the experimental session in pigeons.

Experiment 1

Method

Subjects—Subjects were 12 male White Carneau pigeons (*Columba livia*; Double “T” Farm, Glenwood, IA). Six subjects (Cohort 1) were experimentally experienced and ranged in age from 5 months to 1 year 5 months at the beginning of the experiment. The remaining subjects (Cohort 2) were experimentally naïve and approximately 7 months old at the beginning of the experiment. Cohorts were run in succession. All were drug naïve. Subjects were housed in individual home cages in a windowless colony room on a 16.5: 7.5-hr light–dark cycle (lights on at 7 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% of their free-feeding body weight by postsession feeding (Purina ProGrains for Pigeons) delivered immediately after each session if needed. All experimental protocols were approved by the Institutional Animal Care and Use Committee at the University of Florida.

Apparatus—Experimental sessions for all experiments were conducted in similarly constructed BRS/LVE Inc. (Beltsville, MD; Model PIP-010-016) standard three-key operant test chambers (31.0 cm × 36.5 cm × 35.0 cm). The center key (2.5-cm diameter) in each chamber was located on the panel 8.7 cm from the ceiling, equidistant from both side-walls. To register a response, the keys required approximately 0.07–0.11 N. A 28-V DC houselight was centered 2.2 cm from the ceiling at the center of the panel and illuminated the chamber during the experimental session. Mixed grain could be made available through a 5.5 cm × 5.0 cm aperture centered near the base of the 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, Walter, & Chu, 1995) software on a computer located in another room. A cumulative recorder in another room recorded responses as a function of time during daily sessions.

Procedure

Training: All subjects in Cohort 1 had previous experience pecking a key, so they required one to three sessions of exposure to an FR 1 schedule of reinforcement to adjust to the new experimental chamber and white keylight. Key pecks were reinforced with 3-s access to mixed grain during training and baseline conditions. Throughout all experiments, the keylight and houselights were extinguished during food presentation.

Subjects in Cohort 2 and in all subsequent experiments were trained to peck a white keylight through reinforcement of successive approximations. This method was not successful for 1 subject (43) that was later trained to peck the key through autoshaping (Brown & Jenkins, 1968). Subjects were then put on an FR 1 for one to four 40-reinforcement sessions until subjects responded 40 times in the session with minimal pause. All subjects then underwent ratio training in which the ratio requirement was gradually incremented on the basis of individual subjects' behavior from FR 1 to FR 20 across two to four sessions.

Baseline: Experimental sessions began with a 5-min blackout during which key pecking had no consequence, followed by an FR 20 schedule of reinforcement for 20 min or until 40 reinforcers were obtained, whichever came first. Responding was determined to be stable by visual inspection of graphs of daily sessionwide response rates after 30–40 sessions. Sessions for all experiments were conducted 7 days a week at approximately the same time each day.

Drug regimen: After responding was judged to be stable both within and across sessions, acute effects of cocaine were assessed by administration of the drug once per week. Saline and cocaine doses of 10.0 mg/kg, 5.6 mg/kg, 3.0 mg/kg, and 1.0 mg/kg were administered in descending order, and then each dose was given a second time, also in descending order. Following the first two administrations of each dose, any dose that produced effects judged to be too variable across two assessments was repeated until the mean effect was judged to be representative (doses were administered up to a maximum of six times throughout all experiments). Some subjects were also administered 4.2 mg/kg or 7.4 mg/kg cocaine if none of the doses in the original set produced an approximately 50% decrease in rate of responding.

Subjects were then divided into two groups on the basis of each subject's initial dose–response curve, with an attempt to produce two groups each containing subjects with similar drug effects. Three subjects from each cohort were assigned to each group. Each subject was then administered a dose of cocaine, which originally produced an approximately 50% decrease in rate on FR responding, chronically (i.e., once per day) for 30 sessions. The presession–postsession group was administered cocaine immediately before the session and saline immediately after the session. The postsession–presession group was administered saline immediately before the session and cocaine immediately after the session. All subjects in Cohort 1 were administered 5.6 mg/kg chronically. Chronic doses for subjects in Cohort 2 included 5.6 mg/kg, 7.4 mg/kg, and 10.0 mg/kg cocaine.

Dose–response curves were then redetermined. Specifically, subjects continued to be administered their chronic dose every day except once weekly when they were administered one of their initial acute doses of cocaine or saline presession. All test doses were followed by postsession saline administration. Some subjects were administered 13.0 mg/kg or 17.0 mg/kg if none of the original series of doses produced complete suppression of responding. Doses that produced variable effects were repeated for up to five administrations. One subject in the presession–postsession group (4991) pecked very little during chronic presession administration and during dose–response curve redetermination. This subject was then administered saline presession once every four sessions, with presession cocaine administered before intervening sessions (cf. Miller & Branch, 2004). This regimen continued until key pecking resumed on days when cocaine was administered presession (approximately 50 sessions). The dose–response curve was then redetermined for this subject, with data excluded from when key pecking was suppressed.

Following dose–response redetermination, subjects in the postsession–presession group were switched to the presession drug administration regimen for 30 sessions. Subjects in the presession–postsession group were switched to the postsession administration regimen for 30 sessions. The dose–response curve was then redetermined as described earlier.

Drug procedure: Cocaine hydrochloride (obtained from the National Institute on Drug Abuse) was dissolved in sterile 0.9% sodium chloride solution. Doses were determined by the weight of the salt, and the injection volume was 1 mL/kg. Drug was administered via intramuscular injections in the breast muscle. During daily administration, injections alternated sides of the breast.

Results and Discussion

Figure 1 displays the average key-pecking response rate within a session for the presession–postsession group in Experiment 1, calculated as the percentage of saline vehicle rate of responding, plotted as a function of dose of cocaine. Average response rates following saline administration are shown in Table 1 for all subjects and all phases of the experiment. Cocaine resulted in dose-dependent decreases in rate of key pecking.

Dose–response curves following chronic administration were determined by averaging the response rate following each administration of each dose and dividing this value by the average saline (no-drug) response rate during dose–response curve redetermination.

Following 30 sessions of pre-session administration of cocaine, the dose–response assessments showed that all subjects in the pre-session–post-session group showed tolerance, as predicted, to the rate-decreasing effects of cocaine, as indicated by higher response rates under effects of larger doses of cocaine as compared with those during acute administration.

We used the z approximation to the binomial probability distribution to compare the descending portions of the dose–response curve for acute administration versus chronic administration for the group. More specifically, this test took into account each individual administration. We did not include doses that were assessed only during chronic administration, and we used only the highest value from acute administration. For each dose on the descending limb of the acute dose–response function, we subtracted the highest value of each acute dose from the effects of each administration of that dose during chronic administration. If the effects of a dose were not changed by chronic administration, the differences should have been evenly split between positive and negative instances. The binomial probability test showed statistically significant tolerance ($z = 17.1$, $p < .001$; 342 positive and 17 negative instances).

After chronic dosing was switched from pre-session to post-session, 3 subjects (754, 36, and 4991) continued to show varying degrees of tolerance to the effects of cocaine, and 1 subject showed a loss of tolerance (40). For those subjects (49 and 592) administered a larger chronic dose (7.4 mg/kg or 10.0 mg/kg), post-session administration produced a substantial decrease in rate of responding following saline vehicle to near zero. That is, responding occurred only at very low rates in every session. This suppression of responding made it impossible to determine whether these subjects were still tolerant to the rate-decreasing effects of cocaine. Overall, the switch from pre-session to post-session administration did not produce additional tolerance for any subject ($z = 1.4$, $p > .05$; 113 positive and 92 negative instances) and was associated with an apparent slight loss of tolerance for some subjects (36, 4991, and 40) as indicated by a shift in the post-session dose–response curves to the left of the pre-session curves.

Figure 2 shows average key-pecking rate as a function of dose of cocaine in the post-session–pre-session group. Acute administration of cocaine produced dose-related decreases in key pecking for all subjects that were of similar magnitude to the rate decreases seen for subjects in the pre-session–post-session group. After cocaine was administered post-session for 30 sessions, 3 of 6 subjects (45, 35, and 43) surprisingly showed notable tolerance to the rate-decreasing effects of cocaine (see Table 1). Subjects 727 and 752 showed little change in drug effects. Data accumulated from these 5 subjects showed statistically significant tolerance ($z = 3.38$, $p < .001$; 58 positive and 26 negative instances). Subject 596, which was administered 10.0 mg/kg cocaine post-session, showed near-zero response rates following either cocaine or saline administration, an effect similar to that seen when subjects in the pre-session–post-session group were given large doses of cocaine post-session. Subjects 35 and 752 also occasionally showed response suppression.

Following the first 30 sessions after the switch from post-session to pre-session administration of cocaine, some of the subjects in the post-session–pre-session group that had previously developed tolerance (45 and 43) continued to show varying degrees of tolerance as

displayed in Figure 2. Subject 35 showed an apparent loss of tolerance, and Subject 727 showed little change in drug effects compared with the postsession condition. Subject 596 continued to have a very low saline vehicle control rate and occasionally pecked at a slow rate when cocaine was administered. Subject 752, which did not develop notable tolerance following postsession dosing, did show substantial tolerance following pre-session administration of cocaine. Overall, the aggregated group data showed no significant change from postsession to pre-session administration ($z = -0.96, p > .05$; 85 positive and 99 negative instances).

To provide ancillary analyses about the magnitude of tolerance, we calculated the effective dose 50 (ED50; the dose that produced a 50% decrease in response rate) for each subject for each drug regimen on the basis of a straight-line fit to the dose–response curve for each individual pigeon. If the largest dose of cocaine did not completely suppress responding, we added an additional point, set to a value of zero, for a dose that was one-eighth of a log unit larger than the largest dose used. We did not calculate ED50s when subjects showed response suppression. ED50s are shown in Table 2. For the pre-session–postsession group, all subjects showed an increase in ED50 from acute administration to pre-session administration. Similarly, subjects in the postsession–pre-session group all showed an increase in ED50 from acute administration (Column 2) to postsession administration (Column 4), except for the subject that showed response suppression. Notably, the proportional increase in the ED50 was similar, on average, for the two groups. Most subjects from the pre-session–postsession group that did not show response suppression when drug administration was moved to postsession continued to show an ED50 that was larger than that from acute administration. Most subjects in the postsession–pre-session group that did not show response suppression also had a larger ED50 when switched to pre-session administration compared with acute administration.

Experiment 2

The results of Experiment 1 were not consistent with past research on contingent tolerance to cocaine that found contingent tolerance (Bowen et al., 1993; Branch & Sizemore, 1988; Smith, 1990; Woolverton et al., 1978), except for one experiment conducted using pigeons (Pinkston & Branch, 2004) that found noncontingent tolerance. Although there are many procedural differences in the experiments conducted with pigeons compared with those conducted with other species, one particular procedural aspect of Experiment 1 potentially contributed to the noncontingent tolerance seen in that experiment and to the intersubject variability in effects for the postsession–pre-session group. Subjects in the postsession–pre-session group were fed in their home cage immediately after the session and immediately after postsession cocaine administration if they weighed less than their 80% free-feeding body weight. Some subjects were consistently fed after the session because their weight was low, and some were rarely fed after the session because they were at or above their 80% free-feeding body weight. Those that were consistently fed after the session were also those that developed tolerance to effects of cocaine during the session when cocaine was administered postsession. Subjects that were not regularly fed after the session did not show tolerance to effects of cocaine following postsession administration.

This correlation suggested that eating under effects of cocaine in the home cage might have contributed to the development of tolerance to effects of cocaine during the session. Eating in the home cage, that is, pecking at grain, involves behavior similar to key pecking in the operant chamber. Therefore, subjects who often eat under effects of cocaine in the home cage might develop tolerance to effects of cocaine on eating, and this tolerance might generalize to behavior associated with key pecking during the behavioral session. Hence, the purpose of Experiment 2 was to investigate whether eating under effects of cocaine in the home cage can contribute to the development of tolerance to key pecking during the behavioral session.

Method

Subjects—Subjects were 12 adult male White Carneau pigeons (*Columba livia*). All subjects were experimentally and drug naïve and approximately 7 months old. Subjects were housed and maintained as in Experiment 1.

Procedure

Baseline: The baseline program was identical to that used in Experiment 1. After 34–42 sessions, responding was determined to be stable by visual inspection of graphs of daily sessionwide response rates and of cumulative records. Pecks were initially reinforced with 3-s access to mixed grain, a duration that was then titrated to shorter times until a duration was found for each subject such that postsession body weights were approximately 10–15 g less than 80% free-feeding body weight every day. The final grain access durations ranged from 1.2 s to 2.5 s.

Drug regimen: After responding was determined to be stable with the final hopper-access durations in place, we assessed acute effects of cocaine as described in Experiment 1, except that injections occurred every 4 days (cf. Marusich & Branch, 2006). Doses of 13.0 mg/kg and 17.0 mg/kg cocaine were also assessed for some subjects when no dose in the initial range of doses produced complete suppression of responding. One subject died at the beginning of the acute dosing phase from an unknown cause.

Following acute dosing, subjects were divided into two matched groups on the basis of initial dose–response curves. Each subject was then administered, chronically for 30 consecutive sessions, a dose of cocaine that originally produced a moderate rate-decreasing effect on FR responding. We chose this dose on the basis of the same criteria used to select a chronic dose in Experiment 1. Subjects in both groups were administered saline immediately before each session during the chronic drug regimen. The immediate-drug group was administered cocaine immediately after the session, and the delayed-drug group was administered cocaine 60 min after the session (cf. Marusich & Branch, 2008). Both groups were fed their postsession ration of food in the home cage within 5 min of session termination. We calculated postsession rations as the difference between the subject's postsession weight and the subject's 80% free-feeding body weight, with a minimum of 5 g fed if the subject was near or above its 80% weight. Therefore, the immediate-drug group was administered drug and then given its postsession ration, and the delayed-drug group was given its postsession ration and then administered drug 60 min later.

Following 30 days of this chronic drug regimen, the dose–response curve was redetermined as described in Experiment 1 except that test doses were administered once every 4 days. All test doses were followed by postsession saline administered at the same time each subject was normally injected drug on the basis of group assignment. Some subjects were also given doses of 13.0 mg/kg and 17.0 mg/kg cocaine when no dose in the initial range of doses produced a consistent decrease in rate of responding.

Results and Discussion

Figure 3 displays the average key-pecking response rate for the immediate-drug group in Experiment 2, calculated as the percentage of saline vehicle rate of responding, plotted as a function of dose of cocaine. During acute cocaine administration, all subjects showed dose-dependent decreases in rate of key pecking. Following 30 sessions of cocaine administered immediately after the session, 2 of 5 subjects (648 and 244) showed tolerance to the rate-decreasing effects of cocaine as indicated by the dose–response curve shifted to the right, and notably the saline rates for these 2 subjects were comparable to those seen before chronic dosing. Table 3 shows the average rate of responding following saline administration for each subject during each phase of the experiment. Subject 634 showed little change in drug effects. Data from these 3 subjects combined showed no statistically significant tolerance ($z = 1.09$, $p > .05$; 39 positive and 29 negative instances). Subjects 2173 and 606, which were administered 10.0 mg/kg cocaine immediately postsession, showed near-zero saline vehicle control rates and pecked little following pre-session drug administration. Overall, effects in this group replicate the pattern of effects seen with Experiment 1's postsession–pre-session group in that subjects that were not administered a high dose of cocaine chronically developed tolerance from postsession dosing, and those that were administered a high dose of cocaine chronically often showed response suppression.

Figure 4 shows dose–response functions for the delayed-drug group. Acute administration of cocaine produced dose-related decreases in key pecking for all subjects. Thirty sessions of cocaine administered 60 min after the session produced shifts to the right in the dose–response function for all subjects in the delayed-drug group. This tolerance was statistically significant for the aggregated group data ($z = 4.62$, $p < .001$; 87 positive and 35 negative instances). The administration of 10.0 mg/kg cocaine (to 3 of the pigeons) 60 min after the session ended did not produce the response suppression that was seen in the immediate-drug group and in Experiment 1 when large doses of cocaine were administered immediately after the session.

All subjects in the immediate-drug group that did not commonly show response suppression had a larger ED50 following chronic administration (see Table 4). Similarly, all subjects in the delayed-drug group showed an increase in ED50 following chronic administration. Thus, all subjects in both groups that did not show response suppression developed tolerance.

Experiment 3

The results of Experiments 1 and 2 suggest that pigeons often develop tolerance to effects of cocaine during a behavioral session when cocaine is repeatedly administered after the

session. Tolerance developed for most subjects administered cocaine postsession except those administered a large dose (e.g., 7.4 mg/kg or 10.0 mg/kg) immediately after the session, a result similar to the findings of Pinkston and Branch (2004). Key pecking or eating under effects of cocaine was not necessary for tolerance to develop to the rate-decreasing effects of cocaine during the session. It was also not necessary for cocaine to be closely temporally related or contextually related to the behavioral session. These results implicate two potential factors, drug exposure and exposure to the experimental contingencies, although these need not occur simultaneously. Therefore, the purpose of Experiment 3 was to examine whether mere drug exposure in the home cage without exposure to experimental contingencies would lead to the development of tolerance to effects of cocaine during the behavioral session.

Method

Subjects—Subjects were 6 adult male White Carneau pigeons (*Columba livia*). All subjects were experimentally and drug naïve and approximately 8 months old. All were maintained at 83% of their free-feeding body weight (the local Institutional Animal Care and Use Committee mandated the change in this fixed parameter from the 80% level of the previous experiments) by postsession feeding. Subjects were housed and maintained as in Experiment 1.

Baseline: The baseline program was identical to that used in Experiment 1. After 50–53 sessions, responding was determined to be stable by visual inspection of graphs of daily sessionwide response rates. One subject died from unknown causes during baseline conditions.

Drug regimen: After responding was determined to be stable, we assessed acute effects of cocaine as described in Experiment 2. We also assessed doses of 13.0 mg/kg cocaine for some subjects when no dose in the initial range produced complete suppression of responding.

Following acute dosing, all subjects were exposed to 30 daily administrations of saline, with no exposure to the experimental chamber. Subjects were weighed and fed up to 83% of their free-feeding body weight between 10:00 a.m. and 10:30 a.m. and were injected with saline between 11:30 a.m. and 12:00 p.m. The purpose of this phase was to examine whether prolonged time away from the experimental chamber had any effect. Then daily sessions resumed, and the dose–response curve was redetermined. In the second phase, all subjects were exposed to 30 daily administrations of 5.6 mg/kg cocaine, with no exposure to the experimental chamber. Subjects were fed and administered drugs at the times specified in the previous phase, but otherwise remained in their home cages. Exposure to the FR schedule was then reinitiated, and the dose–response curve was redetermined. No injections occurred on days between acute doses to minimize the amount of pairing of the drug and the experimental context and to minimize the amount of exposure to the experimental contingencies while under effects of the drug.

The third phase of the experiment was identical to the second, except that chronic dosing continued for 60 days. The same chronic dose was used for this phase. Exposure to the FR schedule then recommenced, and the dose–response curve was again redetermined.

During the fourth and final phase of the experiment, subjects were exposed to daily sessions and daily administration of 5.6 mg/kg cocaine immediately before the behavioral session for 30 days. Then the dose–response curve was redetermined, and 5.6 mg/kg cocaine continued to be administered on days between test doses.

Results and Discussion

Figure 5 displays cocaine dose–response curves for Experiment 3, with rate calculated as the percentage of saline vehicle rate of responding. Table 5 shows the average rate of responding following saline administration for each subject during each phase of the experiment. During acute administration, all subjects showed dose-dependent decreases in rate of key pecking. Thirty sessions in the home cage with saline administration were followed by a slight but relatively consistent shift in the dose–response curve to the right, suggesting that time off from experimental sessions was itself associated with modest changes in the dose–response function ($z = 2.39$, $p < .01$; 63 positive and 38 negative instances). Although there was some variability in key pecking, the variability during dose–response curve determinations was constant and did not represent a shift in behavior over time. Because of the slight shift in the dose–response curves following 30 days off with saline administered in the home cage, we used the data from 30 days off with saline administered in the home cage as a comparison for the subsequent drug regimens.

When cocaine was administered daily in the home cage for 30 consecutive sessions, that regimen produced a variety of drug effects across subjects compared with the drug effects during 30 days of saline administration in the home cage shown in Figure 6. Subjects 740 and 945 developed tolerance following this regimen, whereas Subject 965 developed sensitization. Subject 881 showed little effect of this drug regimen, and Subject 808 skipped this drug regimen because of illness. When we analyzed the data across the group, no statistically significant tolerance was shown ($z = -0.44$, $p > .05$; 38 positive and 43 negative instances). Because tolerance did not develop in all subjects following 30 administrations of cocaine in the home cage, subjects were given an additional 60 daily administrations of cocaine in the home cage with no exposure to experimental sessions (see Figure 6). This drug regimen had little effect on most subjects and did not produce additional tolerance for subjects that previously showed tolerance (Subjects 945 and 740). Subject 965 continued to show sensitization. A binomial probability calculation showed there was a significant change at the group aggregate level when dose–response curves were compared for acute administration of cocaine and following 60 administrations of cocaine in the home cage in the direction of sensitization rather than tolerance ($z = -4.01$, $p < .001$; 20 positive and 56 negative instances).

Cocaine was then administered pre-session for 30 days to see whether any additional tolerance would develop for those subjects already showing tolerance and to see whether those that did not previously show tolerance would develop it (see Figure 6). Daily pre-session cocaine administration led to additional tolerance in Subjects 740 and 945 and the

emergence of modest tolerance for Subject 881. Subject 965 continued to show sensitization to effects of large doses of cocaine and showed increases in rate of responding under effects of small doses of cocaine. The group aggregate showed no significant tolerance from chronic pre-session administration compared with acute administration ($z = -1.56$, $p > .05$; 57 positive and 76 negative instances).

Visual inspection of the graphs was supported by an analysis of ED50s, with all subjects showing an increase in ED50 from initial acute administration to following 30 sessions of saline administration in the home cage (see Table 6). Following 30 days of cocaine administered in the home cage with no exposure to the experimental session, ED50s decreased for most subjects, and the increase for 1 subject was relatively small. Most subjects had a slightly lower ED50 following 60 days of cocaine administration than following 30 days of saline administration. When cocaine was administered pre-session with daily experimental sessions, only 2 subjects (740 and 945) showed a large increase in ED50 following pre-session administration compared with that following 30 days of saline administration. The other 3 subjects showed a slight decrease in ED50 compared with that following 30 days of saline administration.

Experiment 4

The results of Experiment 3 showed that mere drug exposure in the home cage without exposure to the behavioral session was not sufficient to produce consistent tolerance to effects of cocaine during the behavioral session. Nevertheless, it is possible that tolerance had developed during the chronic drug regimen but that it was diminished or not expressed during dose–response curve redetermination because daily cocaine administration was discontinued. Therefore, the purpose of Experiment 4 was to determine whether daily cocaine administration during dose–response curve redetermination would reveal tolerance.

Method

Subjects—Subjects were 6 adult male White Carneaux pigeons (*Columba livia*). All subjects were experimentally and drug naïve and approximately 7 months old. Subjects were housed and maintained as in Experiment 3.

Procedure

Baseline: The baseline program was identical to that used in Experiment 1. After 51–64 sessions, responding was determined to be stable by visual inspection of graphs of daily sessionwide response rates. One subject died from unknown causes during baseline conditions.

Drug regimen: After responding was determined to be stable, we assessed acute effects of cocaine as described in Experiment 2. Following acute dosing, each subject was administered 5.6 mg/kg cocaine 60 min after the session ended for 60 consecutive sessions. Subjects were administered saline every day immediately before the session during the chronic drug regimen and were fed their postsession ration within 5 min after the session if needed.

Following this chronic drug regimen, the dose–response curve was redetermined as described in Experiment 2. On intervening days, subjects were administered saline before the session. Postsession saline was administered 60 min after the session on acute dosing days and intervening days. The dose of 13.0 mg/kg cocaine was also assessed for all subjects.

Once dose–response curve redetermination was complete, the curve was assessed again as described earlier except that rather than saline, 5.6 mg/kg cocaine was administered 60 min postsession on intervening days. Saline was administered before the session on intervening days and 60 min postsession on test-dose days.

Finally, subjects were administered 5.6 mg/kg cocaine immediately before each session, with saline administered 60 min after the session for 30 consecutive sessions. The dose–response curve was then redetermined as described earlier, with 5.6 mg/kg cocaine administered pre-session on intervening days. Saline was administered 60 min postsession on acute dosing days and intervening days.

Results and Discussion

Figure 7 displays cocaine dose–response functions for average key-pecking rate calculated as the percentage of saline vehicle rate of responding. Table 7 shows the average response rate following saline administration for each subject during each phase of the experiment. During acute cocaine administration, all subjects showed dose-dependent decreases in rate of key pecking. Sixty sessions of daily cocaine administrations 60 min after the session ended followed by dose–response curve redetermination with saline administered on intervening days produced slight tolerance for all subjects that was especially consistent at the larger doses. This tolerance, however, was not statistically significant at the group aggregate level ($z = 0.48$, $p > .05$; 111 positive and 103 negative instances).

When daily postsession administration continued and dose–response curve redetermination was accomplished with the drug being administered on intervening days, all subjects continued to show tolerance compared with the acute effects of cocaine (see Figure 7). One subject, 961, showed tolerance at the largest dose when daily cocaine administration resumed, and 2 other subjects, 811 and 286, showed a slight shift of the function back to the left. The dose–response curve following this regimen was significantly different from that during acute administration at the group aggregate level ($z = 3.49$, $p < .001$; 128 positive and 77 negative instances). When cocaine was then administered daily pre-session for 30 sessions before dose–response assessments were conducted again, with daily administration of 5.6 mg/kg on days intervening between tests with other doses, the tolerance produced by postsession administration was maintained for 2 subjects (811 and 286) and increased for the 3 other subjects (279, 961, and 109; see Figure 7). This produced statistically significant tolerance compared with acute administration at the group level ($z = 7.55$, $p < .001$; 289 positive and 133 negative instances).

Visual inspection of the graphs was supported by an analysis of ED50s (see Table 8). Following postsession administration, all subjects showed an increase in ED50 from acute administration to postsession administration with saline administered on intervening days.

When cocaine was administered (postsession) on intervening days during the dose–response assessment, all subjects had a larger ED50 compared with that during acute administration. Of 5 subjects, 3 (109, 279, and 961) showed a larger ED50 for pre-session administration compared with postsession administration regimens, and the other 2 subjects (811 and 286) showed ED50s that were similar to that during acute administration.

General Discussion

The main conclusion of these experiments was that non-contingent tolerance was observed in pigeons. Most subjects in all experiments administered postsession cocaine showed rightward shifts in the normalized dose–response curve, which were consistently observed when the drug was given 1 hr after sessions. Experiment 1 found that immediate postsession administration of cocaine in pigeons could result in tolerance to effects of cocaine during the behavioral session. Experiment 2 also examined effects of postsession drug administration. Eating under the effects of cocaine was controlled, and most subjects showed rightward shifts in the normalized dose–response curve regardless of whether they ate under the effects of the drug. The only exceptions were subjects that received a relatively large dose immediately postsession, which resulted in response suppression during sessions. Subjects in Experiment 4 also consistently developed tolerance following postsession administration of cocaine. In Experiments 1, 2, and 4, all subjects that never showed postsession drug-induced response suppression showed notable rightward shifts in the normalized dose–response curve following chronic postsession cocaine administration. A paired *t* test comparing the ED50 from acute administration and the ED50 from the first postsession dosing regimen across subjects in all experiments was significant, $t(16) = 5.02$, $p < .001$ (average acute ED50 = 4.58; average postsession ED50 = 8.61).

The results of this research are not consistent with much past research on contingent tolerance, except the small amount of research conducted with pigeons. Pinkston and Branch (2004) found noncontingent tolerance to cocaine in pigeons, but Bowen et al. (1993), Branch and Sizemore (1988), Smith (1990), and Woolverton et al. (1978) all found contingent tolerance to cocaine when squirrel monkeys or rats were used as subjects. Therefore, most research conducted using cocaine has found that postsession cocaine administration does not lead to tolerance (Bowen et al., 1993; Branch & Sizemore, 1988; Smith, 1990; Woolverton et al., 1978), and some has even found that postsession administration of cocaine leads to sensitization (Bowen et al., 1993; Woolverton et al., 1978). Although the contrast between the current findings and examinations of contingent tolerance with other species may appear to be evidence of a species difference in contingent tolerance to cocaine, it remains possible that experimental differences rather than a species difference produced the differences in outcomes.

It is possible that tolerance from postsession dosing may take longer to develop than tolerance from pre-session administration. No experiments have examined this directly by systematically using different lengths of chronic regimens. The present experiments used chronic regimens of similar length but longer than the average of those that have found contingent tolerance. Within the first 18 days of chronic administration, 4 of 6 subjects (36, 40, 592, and 752) in the pre-session–postsession group in Experiment 1 developed tolerance,

indicating that tolerance often develops quickly when cocaine is administered pre-session. The chronic dosing regimens of previous experiments that found contingent tolerance to cocaine may not have been long enough to capture the tolerance that may have developed had post-session dosing continued.

A comparison of the results of Experiments 1, 2, and 4 with those of Experiment 3 shows that some factor (or factors) associated with behavioral sessions or the experimental context was (or were) important in the development of tolerance. Subjects in Experiments 1, 2, and 4 usually developed tolerance when exposed daily to the experimental session (in the experimental context) even when given their chronic dose after the daily session, the administration of which was well separated from the experimental context for the delayed-drug group in Experiment 2 and all subjects in Experiment 4. Experiment 3 found that not exposing subjects to the experimental session or the experimental context during the chronic dosing regimen produced little tolerance. Therefore, exposure to the experimental session or experimental context may have been a key factor in the development of tolerance. Although these experiments did not explicitly examine drug-paired cues in the context (e.g., the room in which injections were administered or the experimental context in which the drug was experienced), past research has shown that drug-paired cues play a large role in determining whether tolerance will develop (Siegel, 1989).

In summary, these experiments suggest that under the conditions arranged, tolerance to effects of cocaine during the behavioral session in pigeons was not dependent on drug administration before the behavioral session or on feeding while under effects of the drug. The majority of subjects administered drug immediately after or 60 min after the session still showed rightward shifts in the normalized dose–response curve, indicating that it is not necessary for subjects to engage in the target behavior while under effects of the drug for them to develop tolerance to effects of the drug on the target behavior. Although contingent tolerance to cocaine previously appeared to be a reliable finding (Bowen et al., 1993; Branch & Sizemore, 1988; Smith, 1990; Woolverton et al., 1978), results of these experiments combined with those of Pinkston and Branch (2004) suggest that noncontingent tolerance to cocaine may be common in pigeons.

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Figure 1.

Each graph shows data from an individual subject, except for the bottom panel, which shows data from the group average. Response rate is plotted as a function of dose (log scale) of cocaine for the pre-session–post-session (pre–post) group in Experiment 1. Data are plotted as percentage of values obtained after administration of saline vehicle. Black circles display the effects of cocaine during acute administration, white triangles show the effects after 30 days of pre-session cocaine administration, and gray squares show the effects after 30 sessions of post-session cocaine administration. Points are means from all determinations. The points above S1, S2, and S3 indicate the average effects of saline vehicle control, with error bars displaying the range of effects of saline vehicle. Numbers centered above each graph identify the subjects. Numbers to the right of the y-axis identify the dose of cocaine administered chronically for each subject. Data from the second chronic regimen from Subjects 592 and 49 are not shown on individual subject plots and are not included in the group average because of response suppression.

Figure 2.

Each graph shows data from an individual subject, except for the bottom panel, which shows the group average. Response rate as a percentage of control is plotted as a function of dose of cocaine for the postsession–presession (post–pre) group in Experiment 1. Black circles display the effects of cocaine during acute administration, white triangles show the effects after 30 days of postsession cocaine administration, and gray squares show the effects after 30 days of presession cocaine administration. Points are means from all determinations. The points above S1, S2, and S3 indicate the average effects of saline vehicle control, with error bars displaying the range of effects of saline vehicle. Numbers centered above each graph identify the subjects. Numbers to the right of the y-axes identify the dose of cocaine administered chronically for each subject. Data from the first and second chronic regimens from Subjects 596 are not shown on the individual subject plot and are not included in the group average because of response suppression.

Figure 3.

Each graph shows data from an individual subject, except for the bottom panel, which shows data from the group average. Response rate is plotted as a function of dose of cocaine for the immediate-drug group in Experiment 2. Data are plotted as percentage of values obtained after administration of saline vehicle. Black circles display the effects of cocaine during acute administration, and white triangles show the effects after 30 days of cocaine administered immediately after the session. Points are means from all determinations. The points above S1, S2, and S3 indicate the average effects of saline vehicle control, with error bars displaying the range of effects of saline vehicle. Numbers centered above each graph identify the subjects. Numbers to the right of the y-axes identify the dose of cocaine administered chronically for each subject. Data from Subjects 2173 and 606 are not included in the group average from the chronic regimen.

Figure 4.

Each graph shows data from an individual subject, except for the bottom panel, which shows the group average. Response rate is plotted as a function of dose of cocaine for the delayed-drug group in Experiment 2. Data are plotted as percentage of values obtained after administration of saline vehicle. Black circles display the effects of cocaine during acute administration, and white triangles show the effects after 30 days of cocaine administered 60 min after the session ended. Points are means from all determinations. The points above S1, S2, and S3 indicate the average effects of saline vehicle control, with error bars displaying the range of effects of saline vehicle. Numbers centered above each graph identify the subjects. Numbers to the right of the y-axis identify the dose of cocaine administered chronically for each subject.

Figure 5.

Each graph shows data from an individual subject, except for the bottom right panel, which shows the group average. Response rate is plotted as a function of dose (log scale) of cocaine for Experiment 3. Data are plotted as percentage of values obtained after administration of saline vehicle. Black circles display the effects of cocaine during acute administration, and white triangles show the effects after 30 days of saline administration with no exposure to the session. Points are means from all determinations. The points above S1, S2, and S3 indicate the average effects of saline vehicle control, with error bars displaying the range of effects of saline vehicle. Numbers centered above each graph identify the subjects. Numbers to the right of the y-axes identify the dose of cocaine administered chronically for each subject.

Figure 6.

Each graph shows data from an individual subject, except for the bottom right panel, which shows the group average. Response rate is plotted as a function of dose (log scale) of cocaine for Experiment 3. Data are plotted as percentage of values obtained after administration of saline vehicle. Black circles display the effects of cocaine after 30 days of saline administration in the home cage, white squares show effects after 30 days of cocaine administration with no exposure to the session, light gray diamonds show effects after 60 days of cocaine administration with no exposure to the session, and dark gray triangles show effects after 30 days of presession cocaine with daily experimental sessions. Points are means from all determinations. The points above S1, S2, and S3 indicate the average effects of saline vehicle control, with error bars displaying the range of effects of saline vehicle. Numbers centered above each graph identify the subjects. Numbers to the right of the y-axes identify the dose of cocaine administered chronically for each subject.

Figure 7.

Each graph shows data from an individual subject, except for the bottom right panel, which shows the group average. Response rate is plotted as a function of dose of cocaine for Experiment 4. Data are plotted as percentage of values obtained after administration of saline vehicle. Black circles display the effects of cocaine during acute administration, white triangles show the effects after 60 days of cocaine administered 60 min after the session ended with saline administered on intervening days, light gray squares show the effects of cocaine administered 60 min after the session ended with cocaine administered on intervening days, and dark gray diamonds show effects after 30 days of presession cocaine administration. Points are means from all determinations. The points above S1, S2, and S3 indicate the average effects of saline vehicle control, with error bars displaying the range of effects of saline vehicle. Numbers centered above each graph identify the subjects. Numbers to the right of the y-axis identify the dose of cocaine administered chronically for each subject.

Table 1

Mean Number of Key Pecks per Minute Following Saline Vehicle Administration for Each Phase of Experiment 1

Phase	Subject					
	592	49	4991	754	36	40
Acute	144.6 (16.9)	139.3 (19.4)	156.9 (4.7)	222.3 (29.5)	150.3 (8.5)	180.0 (10.3)
Chronic 1	36.6 (38.4)	108.8 (16.0)	140.1 (4.1)	209.7 (4.1)	148.15 (3.6)	133.9 (66.8)
Chronic 2	14.6 (27.5)	12.6 (27.9)	153.6 (13.0)	201.9 (17.6)	157.3 (5.3)	199.8 (21.5)
	45	35	43	727	596	752
Acute	61.3 (12.1)	109.8 (8.2)	140.8 (33.3)	158.45 (6.6)	192.3 (21.2)	179.6 (5.7)
Chronic 1	90.0 (10.8)	75.5 (62.5)	128.8 (9.3)	158.8 (7.8)	0.3 (0.7)	161.5 (59.9)
Chronic 2	62.1 (6.3)	92.3 (25.1)	50.1 (24.0)	150.65 (6.0)	4.3 (5.9)	156.7 (73.2)

Note. Data were used to calculate percentage of saline values for figures 1 and 2. Standard deviations appear in parentheses.

Table 2

Effective Dose 50s (Mg/Kg) for Each Subject for Each Phase of Experiment 1

	Phase		
	Acute	Presession	Postsession
Subject			
592	3.45	13.02	—
49	8.01	11.44	—
4991	3.53	15.63	11.51
754	3.91	6.11	5.71
36	4.63	11.79	9.36
40	5.18	8.22	4.86
Presession–postsession mean (<i>SD</i>)	4.79 (1.71)	11.04 (3.40)	7.86 (3.12)
45	5.08	14.42	14.30
35	5.07	4.41	7.89
43	2.43	7.31	12.90
727	2.50	2.69	3.35
596	10.26	—	—
752	4.08	8.76	4.29
Postsession–presession mean (<i>SD</i>)	3.83 (2.87)	12.64 (4.94)	8.55 (4.53)

Table 3

Mean Number of Key Pecks per Minute Following Saline Vehicle Administration for Each Phase of Experiment 2

	Subject					
Phase	648	634	2173	244	606	
Acute	196.3 (18.9)	176.5 (4.3)	259.6 (3.8)	60.2 (21.5)	178.3 (6.6)	
Chronic	177.6 (13.6)	109.8 (50.7)	0.0 (0.0)	66.1 (10.5)	0.1 (0.2)	
	582	21	604	544	6110	653
Acute	212.2 (4.3)	169.4 (25.6)	149.0 (36.6)	187.2 (5.9)	117.7 (22.5)	182.2 (19.1)
Chronic	224.7 (13.6)	164.2 (20.8)	111.9 (16.7)	174.8 (6.3)	192.3 (10.3)	200.5 (12.5)

Note. Data were used to calculate percentage of saline values for Figures 3 and 4. Standard deviations appear in parentheses.

Table 4

Effective Dose 50s (Mg/Kg) for Each Subject for Each Phase of Experiment 2

	Phase	
	Acute	Chronic
Subject		
648	3.96	14.38
634	3.28	4.01
2173	12.42	—
244	2.12	5.91
606	5.28	—
Immediate-drug group mean (<i>SD</i>)	5.41 (4.08)	8.10 (5.52)
582	12.86	15.99
21	4.94	11.81
604	2.58	6.68
544	3.37	6.23
6110	4.48	7.36
653	3.75	7.54
Delayed-drug group mean (<i>SD</i>)	5.33 (3.78)	9.27 (3.85)

Table 5

Mean Number of Key Pecks per Minute Following Saline Vehicle Administration for Each Phase of Experiment 3

Phase	Subject				
	740	945	881	808	965
Acute	171.0 (5.9)	145.8 (9.5)	121.3 (3.7)	201.1 (7.2)	134.0 (14.6)
30 days saline	195.1 (11.4)	133.1 (7.9)	120.0 (9.0)	202.7 (2.4)	94.4 (4.6)
30 days cocaine	182.1 (0.9)	116.5 (22.0)	127.0 (19.2)	—	126.4 (7.1)
60 days cocaine	195.5 (15.3)	123.6 (3.5)	109.2 (21.9)	196.8 (5.3)	141.9 (25.5)
Presession	162.4 (12.1)	103.6 (11.8)	105.3 (4.0)	191.4 (26.5)	111.6 (14.8)

Note. Data were used to calculate percentage of saline values for Figures 5 and 6. Standard deviations appear in parentheses.

Table 6

Effective Dose 50s (Mg/Kg) for Each Subject for Each Phase of Experiment 3

	Phase				
	Acute	30 days saline	30 days cocaine	60 days cocaine	Presession
Subject					
740	4.47	8.25	7.26	8.18	23.79
945	3.53	4.22	6.90	7.07	14.06
881	3.88	6.93	4.59	4.27	4.14
808	4.41	8.95	—	4.44	7.11
965	9.48	9.82	5.14	3.78	4.04
<i>M (SD)</i>	5.15 (2.45)	7.63 (2.18)	5.97 (1.31)	5.55 (1.95)	10.63 (8.41)

Table 7

Mean Number of Key Pecks per Minute Following Saline Vehicle Administration for Each Phase of Experiment 4

Phase	Subject				
	811	286	109	279	961
Acute	146.7 (16.1)	142.8 (61.1)	139.1 (7.8)	105.7 (8.5)	183.8 (11.4)
Postsession, saline-saline	172.8 (12.5)	173.5 (13.6)	159.6 (6.1)	105.4 (15.1)	195.1 (7.9)
Postsession, saline-cocaine	158.9 (39.0)	170.2 (24.8)	157.3 (11.3)	98.1 (27.2)	181.1 (50.9)
Presession	166.4 (7.4)	177.8 (0.4)	119.9 (24.5)	83.2 (24.5)	193.2 (3.0)

Note. Data were used to calculate percentage of saline values for Figure 7. Standard deviations appear in parentheses.

Table 8

Effective Dose 50s (Mg/Kg) for Each Subject for Each Phase of Experiment 4

	Phase			
	Acute	Postsession, saline– saline	Postsession, saline– cocaine	Presession
Subject				
811	5.99	6.60	6.53	5.92
286	5.86	8.82	6.93	5.69
109	3.74	5.48	5.50	10.44
279	3.41	5.73	8.45	8.97
961	5.13	6.46	6.37	13.29
<i>M (SD)</i>	4.83 (1.19)	6.62 (1.41)	6.76 (1.08)	8.86 (3.19)