Published in final edited form as:

Behav Pharmacol. 2010 October ; 21(7): 660–667. doi:10.1097/FBP.0b013e32833e7f16.

Response topography in behavioral tolerance to cocaine with rats

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Keywords

Rat; Cocaine; Operant; Tolerance; Behavioral Tolerance; Contingent Tolerance

INTRODUCTION

Tolerance to the behavioral effects of drugs is often characterized by two features: it occurs after repeated use and is revealed as an attenuation of the initial drug effect (Carlton 1983). Research has shown that the temporal relationship between drug administration and the onset of the experimental session can play a significant role in the development of tolerance (see Wolgin, 1989, for a review). Tolerance is more likely to develop when a drug is administered before, rather than after, an experimental session, an outcome known as contingent tolerance.

Contingent tolerance has been studied with a preparation known as the Before-After (B-A) test of tolerance (e.g., Branch and Sizemore 1988; Bowen et al. 1993; Campbell and Seiden 1973; Carlton and Wolgin, 1971; Chen 1968; Smith 1990; Tang and Falk 1978; Wenger, et al., 1981; Woolverton et al., 1978; for discussion see Carlton 1983 pp. 126-128 and 133-138). The B-A design entails response measurements and repeated drug administration for two groups: the 'Before' group receives a chronic dose of drug prior to the experimental session and the 'After' group receives the same dose following the session. An advantage of the B-A design is that the number of drug administrations and experience in the experimental session is held constant for both groups. Thus, group differences can be attributed to the relationship between time of drug administration and the behavior performed during the experimental session.

B-A tests of tolerance that have used rats and psychomotor stimulants have shown contingent tolerance (Bowen et al. 1993; Campbell and Seiden 1973; Carlton and Wolgin 1971; Smith 1990; Woolverton et al. 1978). Some of these experiments involved unconditioned consummatory responses (Bowen et al. 1993; Carlton and Wolgin 1971; Woolverton et al. 1978), whereas others used operantly conditioned responses (Campbell and Seiden 1973; Smith 1990). In contrast, relatively recent B-A tests of tolerance using operantly conditioned responses with pigeons showed that tolerance developed regardless of the temporal relationship

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between drug administration and the experimental session (Marusich and Branch 2009; Pinkston and Branch 2004). That is pigeons in both 'Before' and 'After' groups showed evidence of tolerance to the rate-decreasing effects of cocaine. Besides using pigeons, these studies used an operant response topography, key pecking, which was formally similar to the consummatory response occasioned by the reinforcer.

The purpose of this experiment was to determine if an operant response topography similar to consummatory responses occasioned by the reinforcer would lead contingent tolerance in rats. We employed a B-A test of tolerance that exposed rats to procedures similar to previous experimental arrangements with pigeons. Experiments using pigeons have employed conditioned key pecking maintained by access to grain, which pigeons subsequently pecked to consume (Marusich and Branch 2009; Pinkston and Branch 2004; see Ator 1991; Ferster and Skinner 1957, for details of method). The current experiment emulated this procedure by conditioning licking of an empty sipper tube, which was maintained by water presented in a separate tube.

Method

Subjects

Subjects were six experimentally naive male Long Evans rats (*Rattus norvegicus*). All subjects were 120 days old at the beginning of training conditions. Subjects were housed individually in home cages with pine shavings for bedding. The colony room was windowless, light illumination began at 6:00 a.m., and animals were exposed to a 12:12-h light-dark cycle. Subjects were maintained on a 21.5 h/day water deprivation regimen. Animals had unrestricted access to Rodent Lab Diet 5001 (PMI Nutrition International, Brentwood, MO) when in their home cage.

Apparatus

All sessions occurred daily in one 30.5 cm × 24.1 cm × 29.2 cm operant conditioning chamber (ENV-007; Med Associates, St. Albans, VT). One of the chamber walls was stainless steel and included two retractable sipper tubes (ENV-252M, Med Associates, St. Albans, VT). The remaining chamber walls, ceiling, and door were made of translucent acrylic plastic. The chamber floor consisted of stainless steel rods positioned above a stainless steel waste pan. Retractable sipper tubes were made available through 2.5- x 1.2-cm holes, which were located approximately 1 cm from the rod floor. For the sake of clarity, the waterless sipper tube will be referred to as the "response sipper" and water-filled sipper tube will be called the "reinforcement sipper." The response sipper was located 19 cm from the chamber door and 3 cm from the wall opposite the door. To avoid recording non-lick responses, the response tube was permanently recessed 0.5 cm from its access hole. Licks on the response sipper were counted by a lick-o-meter (ENV-250, Med Associates, St. Albans, VT). The opening for the reinforcement sipper was located 3 cm from the chamber door. The reinforcement sipper was recessed by 2 cm until the animal completed the reinforcement schedule, then it was moved into the chamber via a motor driven platform (ENV-252M, Med Associates, St. Albans, VT). A 28-V white house light was centrally located 2 cm from the ceiling on the wall opposing the tubes. The chamber was enclosed in a 41 cm × 56 cm × 47 cm (internal dimensions) sound- and light-attenuating cubicle (Coulbourn Industries, Whitehall, PA). Extraneous sounds were masked by a fan located on the back wall of the cubicle and a second fan located within the surrounding room. Experimental events were arranged and recorded by Med-PC® software contained on a personal computer.

Procedure

Training—All subjects were experimentally naive and required training (i.e., magazine training) to lick the reinforcement tube. Magazine training consisted of repeated presentations of the reinforcement sipper for variable durations of time (3–20 s) until the subjects reliably approached it upon presentation. Following magazine training, sessions consisted of the opportunity to earn 9 s of water reinforcement for each lick. These sessions lasted for 40 water presentations or 20 minutes, whichever came first. Some subjects required no further training, but for some animals response-sipper licking was shaped via a method of differential reinforcement of successive approximations of the terminal response. Once response-sipper licking was established, within-session water access was systematically decreased from 9 to 2.5 s over five sessions. After this decrease in water duration, the response requirement was increased to 20 licks per water presentation (i.e., a Fixed Ratio, or FR, 20). The increase occurred over 14 sessions for all subjects, except number 290 who required 22 sessions.

Baseline—Licks on the response tube were reinforced with 2.5 s of water access under an FR 20 schedule. This schedule replicated parameters used in a previous study that included pigeons and key pecking (Marusich and Branch 2009). Sessions occurred once daily at approximately the same time. Experimental procedures began after a 10-min. blackout, which included no programmed stimuli. The duration of the blackout was chosen based on the reported maximal distribution time for i.p. injections of cocaine (Pan and Hedaya 1998). Sessions were terminated following 40 reinforcer presentations or after 25 min., whichever came first. Baseline conditions were in effect for 50 sessions.

Drug Regimen—The acute effects of cocaine on responding were determined by pre-session drug injections that occurred every five days. The initial range included doses of: 30.0, 17.0, 10.0, 3.0 and 0 mg/kg (Vehicle). This range of doses was administered twice in a fixed, descending order. The fixed-dosing order was used to facilitate detection of systematic effects of repeated drug administration (Sidman 1960). No systematic effects or trends were observed during the acute assessment. Some doses were repeated and doses of 1.0 and 0.1 mg/kg were administered, as needed, to complete the characterization of acute dose-response functions.

Rats were paired according to acute dose-response functions. Each pair had functions with similar response rate ranges and drug sensitivities. The pairs were divided prior to the assessment of chronic-cocaine effects. One pair-mate was randomly assigned to the 'Before' group, and the other was assigned to the 'After' group. Subjects in the 'Before' group received an injection of cocaine (17.0 mg/kg) immediately prior to the session. Following the session, they were returned to the home cage and received a 0 mg/kg (Vehicle) injection after 25 minutes. After 10 more minutes, they were given 1 h access to water via a licking tube. Subjects in the 'After' group received an injection of vehicle immediately before the session and were returned to their home cages directly after the session. After 25 min. they received an injection of cocaine (17.0 mg/kg). The delay to post-session injections helped prevent within-session response suppression, which has accompanied post-session drug administration that occurred directly after a session (Branch and Sizemore 1988; Glowa and Barrett 1983; Pinkston and Branch 2004). The chronic dose (17.0 mg/kg) was chosen because acute administration decreased responding by more than 60%, but did not completely suppress responding. The 'After' group received 1 h of water access 10 min. after drug injection. Introduction of water into the home cage was delayed to allow for the distribution of i.p. injected cocaine (Pan and Hedaya 1998). Access to water was provided by stainless steel water tubes measuring between 3 and 4 cm long, 0.8 cm wide, and had an opening of 0.4 cm. The tubes were positioned in the ceiling of the home cages, and required a licking response similar to the one used during experimental sessions.

The effects of cocaine were reassessed following the 30th consecutive day of exposure to the chronic dose. The reassessment, or chronic assessment, was conducted in the same manner as the acute assessment, except that the chronic dose was administered on the four days between probe doses (i.e., 30.0, 17.0, 10.0, 3.0mg/kg and Vehicle). In addition, doses of 42.0 mg/kg were necessary to complete the characterization of the dose-response functions. The experiment was completed after the chronic drug assessment and lasted for 276 consecutive sessions.

Drug Procedure—Cocaine Hydrochloride (obtained from the National Institute on Drug Abuse) was dissolved in 0.9% saline for the first 184 sessions of drug administration. After the 184th session, cocaine hydrochloride was dissolved in 0.1 molar solution of sodium phosphate. The change was made because some injections of 30.0 mg/kg were followed by skin abscesses at the site of injection. The abscesses only occurred during the chronic assessment. No further abscesses were observed following the change to sodium phosphate vehicle. Daily doses were determined by the weight of cocaine salt and injection volume was 1.0 ml/kg. Doses were administered via an i.p. injection. The site of injection was alternated between the two sides of the stomach.

Data Analysis—The main dependent variable was rate of response-sipper licking for each session. More specifically, the total number of responses that occurred in one session was divided by the time needed to complete the session, minus time of water access. Points in the dose-response function were determined by averaging response rates for all sessions that were preceded by cocaine or vehicle, with the exception of control points. The control point values were determined by averaging response rates from sessions that occurred the day before an injection of cocaine or vehicle.

For some analyses, estimates of the dose that decreased response rates by fifty percent, the Effective-Dose 50 (ED₅₀), were used to quantify the difference between acute and chronic dose-response curves. ED₅₀ values were estimated by fitting a negative-sigmoid logistic function to the dose-response data (GraphPad Prism 5.0):

$$Y = \frac{100}{1 + (10^{\log ED_{50} - X})^{Hill Slope}} \quad (1)$$

In Equation 1, Y represents percent of vehicle response rate and X represents cocaine dose. The *Hill Slope* is the steepness of the dose-response function. $\log ED_{50}$ represents the logarithm of drug dose that produces fifty percent of vehicle response rates. The use of vehicle-normalized response rates allowed the numerator to be 100%, representing vehicle responding.

Model comparisons using Akaike's Corrected Information Criterion (AIC_C; Motulsky and Christopoulos 2004) were also performed for some measures. The AIC_C compared a local and global model. Equation 1 was fit separately to the data from the individual treatment phases (local) and a second model, using Equation 1, was fit to data combined from all treatment phases (global). The AIC_C determined the likelihood that each model correctly accounted for the data by comparing the goodness-of-fit, while correcting for the number of free parameters in the respective models. The AIC_C for each model was determined by the following equation:

$$AIC_c = N \times \ln \left(\frac{SS}{N} \right) + \frac{2K(K+1)}{N-K-1} \quad (2)$$

In Equation 2, N is the number of observations, K is the number of parameters plus 1, and SS refers to the sum-of-squared residuals.

The model with the lower AIC_C is more likely to be correct. In addition, the absolute difference between the two scores conveys a measure of the confidence in the appropriateness of one model over the other. This distance can be expressed as an evidence ratio, which is defined by:

$$Evidence\ ratio = \frac{1}{e^{-0.5 \cdot \Delta AIC_C}} \quad (3)$$

In Equation 3, ΔAIC_C refers to the difference between the two AIC_C scores.

An AIC_C evidence ratio that favored the local model would mean that two independent functions fit to the individual treatment phases would be more likely to account for the data. On the other hand, an AIC_C evidence ratio that favored the global model would mean that one function using all data, regardless of treatment, would be more appropriate for the data. In terms of the current experiment, an evidence ratio that favored the local model would support an argument for tolerance. Alternatively, an evidence ratio that favored the global model would mean that tolerance had not developed and that differences between treatment phases were negligible.

Results

Individual and group averaged dose-response functions generally exhibited dose-dependent decreases in response-sipper licking (Figures 1- 4). Acute administrations of 30.0 mg/kg decreased response rates to less than 5 % of vehicle responding in the After group (Fig. 1) and to less than 20% in the Before group (Fig. 2). Response rates in both groups rarely increased above vehicle levels, and never outside the range of variation. The lowest dose (3.0 mg/kg) resulted in less responding than the vehicle mean, but the vehicle range overlapped with low dose ranges of subjects 289, 290, 291, and 292.

Comparisons of the 'Before' and 'After' group acute dose-response functions did not reveal systematic differences. The form and range of the acute dose-response functions were consistent across individuals and groups (Fig. 1, 2, and 3). Additionally, a comparison of group averaged data did not show between-group variations (Fig. 4). An AIC_C model comparison between the group averaged dose-response functions revealed an evidence ratio of 6.18 in favor of the global model. It is therefore unlikely that group differences existed prior to the chronic dosing regimen.

The chronic dosing regimen revealed evidence of tolerance to the rate-decreasing effects of cocaine for all subjects (Fig. 1 and 2) and groups (Fig. 3). The dose-response functions for the chronic assessment (open squares in Fig. 1, 2, and 3) fall to the right of the dose-response functions from the acute assessment (closed circles in Fig. 1, 2, 3). Chronic ED_{50} values were greater than acute ED_{50} values for all subjects (Table 1). On average, chronic ED_{50} values represented a three-fold increase over acute estimates. An AIC_C comparison of group averaged dose-response functions found that the local model was preferred, with the evidence ratio equaling 22.04 for the 'After' group and >9999 (the limit of the statistical program) for the 'Before' group (Fig. 3). AIC_C comparisons conducted for individual subjects were consistent with the overall group comparisons (Table 2).

Comparisons of 'Before' and 'After' group chronic dose-response functions did not reveal systematic differences. The form of the dose-response functions and range of response rates were consistent across individuals and groups (Fig. 1, 2, and 3). A comparison of group

averages did not show between group variations (Fig. 4). An AIC_C model comparison between the group averaged dose-response functions revealed that the global model was 3.596 times more likely to be correct than the local models. It is therefore unlikely that there were differences between chronic dose-response functions associated with the Before and After groups.

Discussion

The current experiment was designed to determine if operantly-reinforced consummatory responses would reveal contingent tolerance to the rate-decreasing effects of cocaine. This was examined using a B-A test of tolerance using rats in procedures that paralleled conditions used in earlier experiments with pigeons (Marusich and Branch 2009; Pinkston and Branch 2004). The present experiment resulted in tolerance in both the 'Before' and 'After' groups, and thus showed that tolerance to the rate-decreasing effects of cocaine on operantly-reinforced sipper licking was not contingent on drug experience during the behavioral tests. Simply put, we found "non-contingent" tolerance, which replicates previous results involving pigeons (Marusich and Branch 2009; Pinkston and Branch 2004), but the current finding is unlike those of most studies conducted with rats (cf. Bowen et al. 1993; Campbell and Seiden 1973; Carlton and Wolgin 1971; Chen 1968; Smith 1990; Wenger et al. 1981; Woolverton, et al., 1978). Furthermore, the current pattern of results is not consistent with those of previous rat experiments that included unconditioned consummatory licking to measure tolerance (Bowen et al. 1993; Carlton and Wolgin 1971; Woolverton et al. 1978). The current results support the hypothesis that operantly-reinforced consummatory responses are less likely to reveal contingent tolerance.

An obvious difference between the present study and earlier reports of contingent tolerance using consummatory behavior is that the present experiment measured a response that was similar in form to a consummatory response, but did not result in consumption. The reinforcer was delivered at a second location. This procedure is analogous to the situation when pigeons peck response keys under the control of food reinforcement: they peck at keys and then peck at grain, which is available in a separate location from the key. Here the rats licked at an empty tube, then licked to consume water from another. Perhaps divorcing the response from its usual (consummatory) function is what is necessary to make contingent tolerance less likely to occur.

Although the results of the current experiment support our hypothesis, the failure to observe contingent tolerance may be due to experimental procedures unrelated to response topography. This is suggested by the results of other experiments using consummatory behavior itself as the dependent measure, which have shown contingent tolerance (e.g., Bowen et al. 1993; Carlton and Wolgin 1971; Woolverton et al., 1978). First, it is possible that the acute assessment of cocaine effects on response rate produced tolerance in the 'After' group. Animals were exposed to various cocaine doses between 11 and 18 times, which could have been sufficient for tolerance to develop. This argument, however, is inconsistent with previous examples of contingent tolerance that included similar acute assessments (Branch and Sizemore, 1987; Smith, 1990; Woolverton, et al., 1978). Notably, Sizemore and Branch (1987) exposed nonhuman primates to various doses of cocaine up to 48 times during an acute assessment and found tolerance to be contingent on chronic pre-session drug administration. Additionally, visual inspection of the current data revealed no systematic trends, including tolerance, during the acute assessment. When combined with the previously mentioned data the current outcome supports the notion that acute drug exposure did not affect the current outcome.

Overlearning could be a second alternative account for the current results. Overlearning of the operant response, during the relatively lengthy course of this study, could have countered behavioral disruptions caused by the chronic pre-session cocaine administration. This process

would lead to a pattern of results that would merely resemble tolerance (attenuation of the drug effect). Again, previous examples of contingent tolerance do not support this alternative hypothesis. The number of baseline, acute, and chronic sessions in the current experiment paralleled previous experimental procedures that resulted in contingent tolerance. More specifically, previous examples of contingent tolerance involved acute phases that ranged from 14 to 228 sessions, and chronic phases from 24 to 45 sessions (Branch and Sizemore, 1987; Carlton and Wolgin, 1971; Smith, 1990; Woolverton et al., 1978). The number of acute (11-18) and chronic (30) sessions for the current experiment fell within those ranges. Additionally, the previous experiments employed operantly-conditioned responses that were not similar to consummatory responses (Branch and Sizemore, 1987; Smith, 1990) or unconditioned consummatory responses (Carlton and Wolgin, 1971; Woolverton, et al., 1978).

Another possibility is that rats in the 'After' group had the opportunity to develop tolerance to the rate-decreasing effects of cocaine while in their home cages and that this tolerance generalized to the experimental setting. This could have occurred when animals were injected with drug after the session, but 10 min. prior to availability of water in the home cage. Home-cage water was available through a tube positioned in the ceiling and a licking response, similar to the experimental response, was required for water to be consumed. A previous experiment with pigeons was designed to address this possibility of home-cage tolerance generalizing to the experimental setting. The authors found grain pecking in the home cage while under the influence of cocaine was not necessary for tolerance to develop (Marusich and Branch, 2009). This result suggests that tolerance is unlikely to generalize from the home cage to experimental session in the current experiment. Because that study was conducted with pigeons, however, it remains possible that the 'After' group tolerance with rats of the present study reflected effects of licking while drugged in the home cage. Further experimentation can determine if that was the case.

In summary, the current experiment illustrated that tolerance to the rate-decreasing effects of cocaine was not affected by the time of drug administration. This atypical result for rats may have been due to the fact that the reinforced response was similar in topography to behavior involved in consuming the reinforcer. The results and procedures of the current study closely resemble those of prior experiments with pigeons (Marusich and Branch 2009; Pinkston and Branch 2004), which have also shown non-contingent tolerance. Notably, in those experiments the forms of the operant response and the behavior necessary to consumer the reinforcer have been similar. Further investigation, however, is needed to examine the mechanisms responsible for this outcome and its generalizability.

Acknowledgments

This research was supported by NIH grant DA004074-21 from the National Institute on Drug Abuse. We would like to thank members of the Branch and Dallery Labs at the University of Florida for their assistance on this project.

Source Funding: This research was supported by NIH grant DA004074.

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Figure 1.

Session response rates are presented as percent of vehicle response rates as a function of cocaine dose. Acute and chronic dose-response functions are present for all members of the 'After' group. Each panel presents data from an individual subject. The subject number is identified in the top-right portion of the panel. Black circles represent data collected during the acute assessment and white squares represent data collected during the chronic assessment. The points and range bars above "A" and "C" correspond to the average responses rates that occurred following pre-session vehicle administrations for the acute and chronic assessments respectively. Error bars represent the standard error of the mean. Please note that the first point after the x-axis break is 1.0 mg/kg.

Figure. 2.

Session response rate are presented as percent of vehicle response rate as a function of cocaine dose. Acute and chronic dose-response functions are present for all members of the 'Before' group. Each panel presents data from an individual subject. The subject number is identified in the top-right portion of the panel. Black circles represent data collected during the acute assessment and white squares represent data collected during the chronic assessment. The points and range bars above "A" and "C" correspond to the average responses rates that occurred following pre-session vehicle administrations for the acute and chronic assessments respectively. Error bars represent the standard error of the mean. Please note that the first point after the x-axis break is 0.1 mg/kg and the undefined tick corresponds to 30.0 mg/kg.

Figure 3.

Mean group dose-response functions for both the Before and After groups. Group means were derived from individual-subject means. All response rates are presented as a percentage of the response rates observed in sessions following vehicle injections. Black circles represent data collected during the acute assessment and white squares represent data collected during the chronic assessment. The points and range bars above "A" and "C" correspond to the average responses rates that occurred following pre-session vehicle administrations for the acute and chronic assessments respectively. Error bars represent the standard error of the mean. Please note that the first point after the x-axis break is 0.1 mg/kg and the undefined tick corresponds to 30.0 mg/kg.

Figure 4.

'Before' and 'After' group average response rates as a function of cocaine dose. Panels present data according to treatment phase, which is identified in the top-right corner of the panel. Filled Triangles represent 'Before' group response rates and open hexagons represent 'After' group response rates. All response rates are presented as a percentage of the response rates observed in sessions following vehicle injections. Points and error bars above "V" correspond to the average responses rates that occurred following pre-session vehicle administrations for the 'Before' and 'After' groups. Error bars represent the standard error of the mean. Please note that the first point after the x-axis break is 0.1 mg/kg and the undefined tick corresponds to 30.0 mg/kg.

Table 1

Estimated Effective Dose 50 (mg/kg)

Group	Subject	Acute	Chronic
After	289	8.284	28.58
	290	6.428	30.72
	291	15.20	35.49
	292	9.552	17.40
	Mean	12.74	30.79
Before	292	14.85	31.45
	296	12.10	38.02
	Mean	12.88	37.13

Table 2

Model comparisons using Akaike's Corrected Information Criterion

Group	Subject	Preferred Model	ΔAIC_C	Evidence ratio
After	289	Local	5.18	13.33
	290	Local	11.27	280.03
	291	Local	9.68	126.47
	293	Local	12.45	505.00
	Mean	Local	6.19	22.04
Before	292	Local	18.09	8493.94
	296	Local	40.94	>9999.99
	Mean	Local	24.34	>9999.99