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A novel choice method for studying drugs as punishers

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Abstract

In contrast to reinforcing effects, little is known about the neurobehavioral pharmacology of aversive effects of drugs that may limit their self-administration. The present study was designed to develop a novel choice method for studying drugs as punishers. Rhesus monkeys ($n=4$) were trained in a two-lever choice procedure. During a trial, completion of a variable-ratio 10 (VR10) schedule on one lever resulted in the simultaneous injection of a drug and delivery of two food pellets. Completion of an independent VR10 on the other lever resulted in simultaneous delivery of a saline injection and two food pellets. Reinforcer delivery ended a trial and began a time-out (TO) of 10 min. Sessions ended after approximately 4 h. When a preference was observed, injection/lever pairings were reversed to ensure reinforcer preference. When the drug injection was histamine (0.0015–0.006 mg/kg/injection), preference for the drug + food option decreased in a dose-related manner to near 0% in all monkeys. Effective doses of histamine were approximately 10-fold lower than in previously published experiments. In contrast, when the drug was cocaine (0.012–0.2 mg/kg/injection), preference for the drug + food option increased in a dose-related manner to near 100% in all monkeys. Choice may be a sensitive and selective method for studying aversive effects of drugs.

Keywords: Cocaine; Histamine; Reinforcement; Punishment; Self-administration; Rhesus monkey

1. Introduction

A stimulus serves as a positive reinforcer if the occurrence of a response that led to its presentation increases. Conversely, a stimulus serves as a punisher if the occurrence of a response that led to its presentation decreases (Morse and Kelleher, 1977). Some drugs can function as positive reinforcers to maintain self-administration under a broad range of conditions (e.g., Young and Herling, 1986). Other drugs usually fail to maintain self-administration. This latter category could include nonreinforcers and drugs that can function as punishers to suppress behavior that leads to their administration. Operant self-administration procedures that utilize simple schedules of reinforcement do not clearly differentiate drugs that are nonreinforcers from drugs that may function as punishers. Drugs of both types would be expected to maintain responding at or below the levels maintained by drug vehicle.

Distinctions between nonreinforcers and drugs that function as punishers can be drawn using other behavioral approaches. Punishment paradigms, for example, have been reported in which drug injections are simultaneously delivered with a positive reinforcer, typically food, and effectively punish food-maintained responding (Goldberg, 1980; Takada et al., 1986). Other procedures have been used to study the negative reinforcing effects of drugs (Hoffmeister, 1975; Takada et al., 1986). Methods developed outside of the traditional operant paradigm have been designed to study negative ‘‘affective’’ components of drug effects. The conditioned place preference/place aversion method has proven productive in this regard. In addition to the extensive literature on place preference, place aversions have been demonstrated for several drugs (see Tzschentke, 1998). The extent to which these effects may overlap punishing effects has not been established.

It is reasonable to suppose that a mixture of reinforcing and punishing effects determines the self-administration of some drugs. For example, the proposed negative modulatory effect of 5-HT actions on the self-administration of stimulants (Ritz and Kuhar, 1989; Roberts et al., 1999) may be a consequence of punishing effects of 5-HT uptake blockade.

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It has also been proposed that cocaine can have an aversive component of action when administered repeatedly and/or in high doses (Goeders, 1992; Goeders et al., 1993; Yang et al., 1992). Using another approach, Ettenberg and Geist (1991, 1993) reported that although rats would run down a runway to receive an injection of cocaine, they exhibited a pattern of "stop and retreat." The authors interpreted this to be approach–avoidance behavior that had to do with a combination of positive and negative components of cocaine's effects. This approach may be useful for broadening our understanding of mechanisms of behavioral control by drugs (Geist and Ettenberg, 1997; McFarland and Ettenberg, 1995). Schulteis et al. (1994) have used disruption of operant behavior as part of a behavioral battery designed to quantify the aversive effects of opioid withdrawal.

An understanding of the behavioral neuropharmacology of aversive effects of drugs would improve our understanding of drug self-administration. The literature on drugs as punishers includes studies with histamine (Goldberg, 1980; Katz and Goldberg, 1986), nicotine (Goldberg and Spealman, 1983), and β-carboline (Takada et al., 1986; 1992). Opioid antagonists have been shown to be effective for conditioning place aversions in dependent animals, as has lithium chloride in nondependent animals (Kelsey and Arnold, 1994; Kosten, 1994; Shippenberg et al., 1988). Kappa opioid agonists may also have aversive effects (Sante et al., 2000). However, it is difficult to make any general statements about the behavioral neuropharmacology of aversive effects from the relatively limited collection of studies. In a more applied sense, it may also be useful for the development of medications to develop behavioral procedures that allow us to specify a more precise combination of reinforcing and punishing effects.

The major goal of the present experiment was to develop and provide an initial validation of a novel operant choice method for studying drugs as punishers. Choice procedures have proven very useful in the study of drugs as reinforcers (see Woolverton and Nader, 1990; Young and Herling, 1986). It seems reasonable to suggest that the simultaneous availability of an alternative reinforcer in a choice situation would increase sensitivity to punishing effects. That is, the dose at which a drug can effectively punish a behavior may be lower when a viable behavioral alternative is offered. Indeed, previous behavioral research suggests that punishment has a greater effect on responding maintained under concurrent as opposed to single operant situations (Azrin and Holz, 1966; Rachlin, 1967). A sensitive method would be predicted to have enhanced pharmacological selectivity and allow separation of punishing effects from nonspecific suppression of responding.

To this end, monkeys were allowed to choose between two options, both of which delivered food pellets and an intravenous injection simultaneously. To establish the effects of a known punisher, a histamine injection was delivered with food as one of the options, while the other option delivered a saline injection with food. Punishment would be evident in the development of a preference for the option paired with a saline injection. For comparison to a known positive reinforcer, a cocaine injection was delivered with food as one of the options, while the other option delivered a saline injection with food.

2. Methods

The Institutional Animal Care and Use Committee of the University of Mississippi Medical Center approved the experimental protocol. All procedures were in compliance with the NIH Guide for the Care and Use of Laboratory Animals.

2.1. Animals and apparatus

Subjects were four male rhesus monkeys (*Macaca mulatta*) weighing between 8.9 and 13.1 kg at the beginning of the study. Three were experimentally naïve and the fourth, 9127, had an extensive history of responding in choice experiments (see Anderson and Woolverton, 2003).

Each monkey was housed in a ventilated cubicle (Plas-Labs, 1 m^3) that served as the experimental chamber. The door of the cubicle was clear plastic. Two metal boxes were mounted on the door, 33 cm apart. Each contained a lever (PRL-001, BRS/LVE, Beltsville, MD) and four lights, two white and two red. A stainless steel harness restrained each monkey and a spring tether (E&H Engineering, Chicago, IL) was attached to the rear of the cubicle. This allowed the monkey relatively unrestricted movement and protected the catheter, which was threaded through the spring. Outside the cubicle, the catheter was connected to two infusion pumps (7540X, Cole-Parmer Instrument, Chicago, IL) that injected solutions (approximately 1.0 ml/10 s). In addition, 1 g banana-flavored pellets (P.J. Noyes, Lancaster, NH) could be delivered to the food dish on the front of the cubicle by pellet dispensers (Ralph Gerbrands, Model G5310). Macintosh computers controlled experimental events and recorded data.

2.2. Procedure

Each monkey was surgically prepared with a double lumen, silicone intravenous catheter (Reiss Manufacturing, Blackstone, VA, 0.076 cm ID × 0.236 cm OD), implanted under ketamine and isoflurane anesthesia. The proximal end was inserted into a major vein for a distance calculated to terminate in the vena cava. The distal end was threaded subcutaneously to the back of the monkey, exiting the body through a small incision in the skin. When a catheter failed, the monkey was removed from the experiment for at least a week and given antibiotics. A new catheter was implanted and the monkey was returned to the experiment. Each lumen of the catheter was filled immediately after the session with

a solution of 20 units/ml heparin to help prevent clotting at the catheter tip.

Monkeys were maintained at 90% of their original weights by feeding between 130 and 150 g/day of food, individually determined to maintain stable body weight. Diets included food pellets delivered during sessions and supplemental monkey chow (Teklad 25% Monkey Diet, Harlan/Teklad, Madison, WI). Monkey chow was given after the session, between 16:30 and 17:00 each day. In addition, each monkey was given fresh fruit and a chewable vitamin tablet daily. All monkeys were weighed regularly and feeding was adjusted to correct for any changes in body weight over the course of the experiment. Water was available continuously.

Sessions began at 12:00 each day, 7 days/week. To start the session, a sampling period was programmed during which subjects could sample the consequences of pressing each lever. The white lights were illuminated above one lever, randomly determined. Lever pressing under a variable-ratio 10 (VR10) schedule of reinforcement resulted in the delivery of the consequence associated with that lever. VR values were calculated according the algorithm of Fleshler and Hoffman (1962), but counting responses rather than time. After reinforcer delivery, a time-out period of 1 min (TO 1′) began during which lights were extinguished and responses had no consequence. At the completion of the TO, the white lights were illuminated above the other lever and the monkey could sample that consequence by pressing the illuminated lever under the identical VR schedule of reinforcement. After reinforcer delivery, the TO began again. Each consequence could be sampled in this manner five times in an alternating sequence. Completion of the sampling component was required before continuing the session.

When all sampling cycles were complete, choice trials began. For choice trials, the white lights were illuminated over both levers and both consequences were available under VR10 schedules that were identical and identical to the schedule in effect in the sampling period. That is, a concurrent VR10 VR10 (conc VR10 VR10) schedule of reinforcement was in effect. The VRs were independent, i.e., the availability or delivery of reinforcement as a consequence of responding on one lever had no effect on the schedule maintaining responding on the other lever. A response on one lever that followed a response on the other lever (a changeover response) was not reinforced but started a change-over-delay (COD) of 4 s during which additional responses on the first lever were not reinforced. Responses during the COD were recorded and counted toward the completion of the VR but were not reinforced. If the response requirement was met during the COD, the first response after the COD ended was reinforced. The COD contingency was included to prevent superstitious switching between levers.

When the response requirement was fulfilled for one of the levers, the consequence associated with that lever was delivered. Consequences could be food only (two food pellets, used for training), pump 1 + food (two food pellets), or pump 2 + food (two food pellets), delivered over a reinforcement period of 10 s. Food pellets were delivered at a rate of 1/s, beginning at the onset of the reinforcement period. During the reinforcement period, white lights over the lever associated with reinforcement were extinguished and red lights were illuminated. After the delivery of an injection + food, there was a TO of 5 min, during which lever lights were extinguished and responses were counted but had no other consequence. Responses during the reinforcer period were included in the TO responses. Sessions ended after 500 lever presses had been emitted (excluding lever pressing during TO) or when 4 h had elapsed, whichever came first. A particular consequence was paired with a lever for at least four consecutive sessions and until behavior was stable. Stability was defined as at least three consecutive sessions in which the total number of trials completed and the total number of drug injections was within 15% of the running mean and there were no upward or downward trends in the data. When less than 10 drug injections were taken, the stability criterion was ± 2 injections. If a monkey exhibited $\geq 75\%$ choice of one of the consequences, the position of the consequences was reversed to determine whether a reinforcer preference or a position preference was controlling behavior.

Initially, responding was established in naive monkeys by delivering food as a consequence of responding on either lever. For a period of at least 1 month, VR values were manipulated to ensure a history of responding on both levers and to establish experience with switching from one lever to the other. After responding was well established, the double-lumen catheter was implanted and baseline was reestablished with a saline injection delivered simultaneously with food for both options. After responding was again well maintained, the saline solution delivered by one pump was replaced with a drug solution, while the other pump continued to deliver a saline solution. In short, under terminal conditions, monkeys chose between the simultaneous delivery of an active drug + food or saline + food under conc VR10 schedules.

Effects of cocaine and histamine on choice were determined in the present experiment. Cocaine was selected because of its well-established effectiveness as a positive reinforcer. Histamine was studied because injections of histamine previously have been shown to punish lever pressing in monkeys (Goldberg, 1980; Katz and Goldberg, 1986). Doses were tested in an irregular order, one immediately after another, and ranged between a dose high enough to establish clear preference for one or the other option, relative to saline, and one low enough that no preference was apparent.

2.3. Data analysis

Dependent variables recorded in sessions included total responses emitted on each lever, time spent responding on

each lever, and total reinforcers delivered for each option. For time, a recording timer started with the first response on a lever and stopped with the first response on the other lever. Changeover responses were also recorded. A changeover response is a response that followed a response on the opposite lever and provides a measure of lever switching. Mean values were calculated for individual subjects over the last three stable sessions of a condition and its reversal (total of six sessions). Because of variable drug sensitivity across subjects, data are presented individually and the range of the original condition and its reversal is presented as a measure of variability.

3. Results

Sessions virtually always ended by expiration of the session timer, i.e., completion of the total number of responses available rarely ended the session. When saline or low drug doses were delivered with food, monkeys generally completed 40 or more trials during a session (Table 1). The number of trials completed was not systematically affected by histamine dose but was decreased as cocaine dose increased.

When saline + food was the consequence of responding on either lever, monkeys chose pump 1 + food on approximately 50% of the trials (Fig. 1). In three of the four monkeys, this was the result of choosing the lever associated with pump 1 + food exclusively when it was paired with one lever and continuing to respond on that lever when the lever/pump pairing was reversed (asterisks in Fig. 1). That is, when the consequence of pressing either lever was the same, a position preference appeared to control behavior. The exception to this rule was monkey AV27, who responded approximately equally on both levers under this condition. When low doses of histamine were delivered with food, responding was similar to that seen with saline (Fig. 1). When histamine dose was increased, monkeys chose the saline + food option virtually exclusively. Preferences developed over a 1- to 2-week period in both the initial condition and the reversal. The lowest effective dose of histamine ranged between 0.0015 mg/kg/injection (L35, 9127) and 0.006 mg/kg/injection (M381). Occasionally, responding on both levers was reduced in the first 2–3 days of histamine availability and a saline + food preference developed over the next several days.

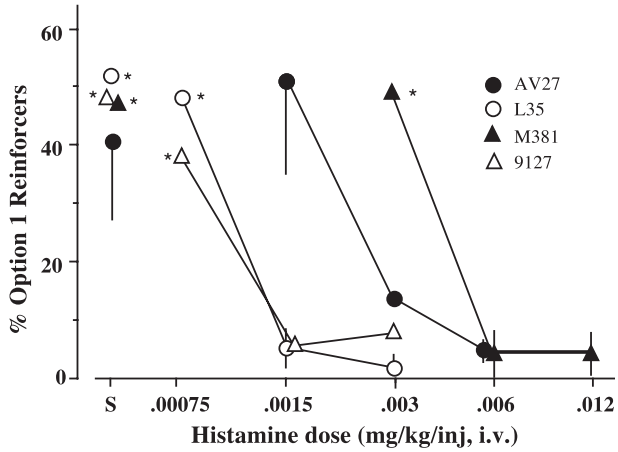

Fig. 1. The percentage of choice trials on which monkeys chose Option 1. Choosing Option 1 simultaneously delivered an injection of saline or the indicated dose of histamine and two food pellets. Choosing Option 2 simultaneously delivered an injection of saline and two food pellets. Symbols and numbers in the legend represent data from different monkeys. Points are the mean of two 3-session conditions: one when Option 1 was available for pressing the right lever, and the second when Option 1 was available for pressing the left lever. Vertical lines are the range of the two conditions. Where vertical lines do not appear, the range is contained within the point, except that asterisks indicate points where values for the two conditions ranged between at least $\leq 25\%$ and $\geq 75\%$.

Similarly, when saline + food was the consequence of responding on either lever, monkeys allocated an average of approximately 50% of their response time to the pump 1 + food option (Fig. 2). In contrast to reinforcer data, however, this time average was based upon averaging values of approximately 50% for both lever/pump pairings in all but L35. The percentage of time spent responding on the pump 1 + food option decreased with histamine dose (Fig. 2). For two of the monkeys (L35, AV27), this measure approached zero. For the other two, there was more variability in this measure.

As with histamine, when low doses of cocaine were delivered with food, responding was similar to that seen with saline (Fig. 3). When cocaine dose was increased beyond this low dose, responding occurred virtually exclusively on the cocaine-associated lever. Preferences developed over a 1- to 2-week period. The lowest effective dose

Table 1
The mean number of trials completed over the last three sessions of a condition and its reversal

		Histamine (mg/kg/injection)					Cocaine (mg/kg/injection)					
Monkey	Saline	0.00075	0.0015	0.003	0.006	0.012	0.006	0.012	0.025	0.05	0.1	0.2
AV27	33.8		41.7	42.8	42.5			43.2	43.7	42.7	40.5	25.3
L35	41.2	30.8	42	27						44	36	15.8
M381	41.8			42.8	43.3	43	43.8	45.8	44.5	40.3	25.2	
9127	41.2	41	42	34				41.2	41.8	28.8	22.7	12.8

Empty cells are conditions that were not studied in individual monkeys.

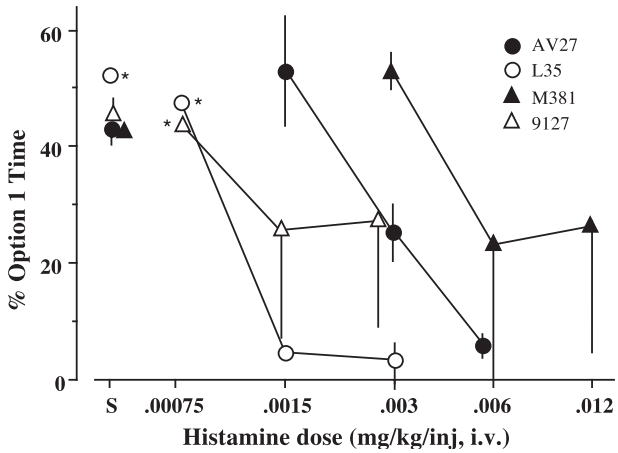

Fig. 2. The percentage of time in choice trials that monkeys spent responding for Option 1. Other details are as in Fig. 1.

of cocaine ranged between 0.012 mg/kg/injection (M381) and 0.1 mg/kg/injection (L35). Time spent responding on the lever associated with the pump 1 + food option increased with cocaine dose to an asymptote for two of the monkeys, L35 and M381 (Fig. 4). For the other two, this measure was a biphasic function of dose. For AV27, the majority of the response time between 0.05 and 0.2 mg/kg/injection cocaine was on the cocaine-associated lever, but there was variability in this effect. At higher doses of cocaine, monkey 9127 tended to spend more time responding on the lever initially paired with the cocaine injection even when that pairing was reversed.

In all cases, the percentage of responses that were emitted on a given lever was within 5% of the percentage of reinforcers delivered (data not shown). In AV27 and 9127, changeover responses were always less than 15, virtually always less than 10. In L35 and M381, they were always less than 10. Changeover responses did not systematically vary with drug or dose in any monkey (data not shown).

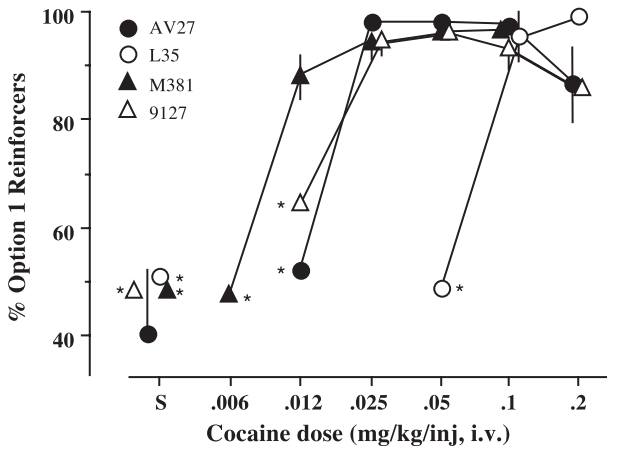

Fig. 3. The percentage of choice trials on which monkeys chose Option 1. Choosing Option 1 simultaneously delivered an injection of saline or the indicated dose of cocaine and two food pellets. Other details are as in Fig. 1.

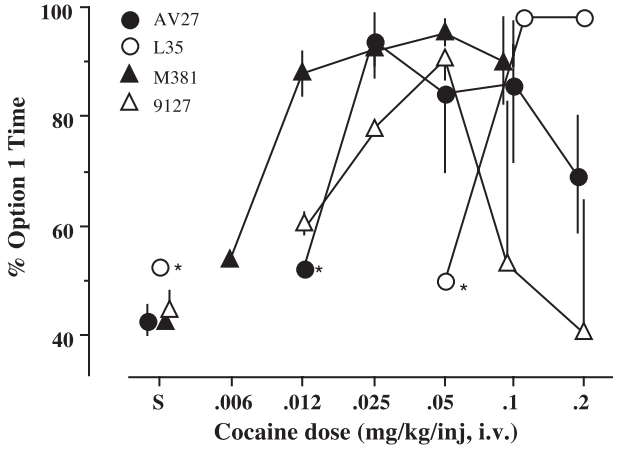

Fig. 4. The percentages of time in choice trials that monkeys spent responding for Option 1. Choosing Option 1 simultaneously delivered an injection of saline or the indicated dose of cocaine and two food pellets. Other details are as in Fig. 1.

This was true both over the first few sessions of a condition and at the end of a condition.

4. Discussion

The main finding of the present study is that the frequency of histamine + food choice decreased with dose. That is, histamine functioned as a punisher under the present conditions. This result confirms and extends previous reports of the punishing effects of histamine (Goldberg, 1980; Katz and Goldberg, 1986). One potential advantage of the present method is increased sensitivity to histamine relative to previously published methods. In studies of histamine as a punisher (Goldberg, 1980; Katz and Goldberg, 1986; Takada et al., 1992), histamine had little or no effect at 0.01 mg/kg/injection and responding was largely suppressed at 0.03–0.3 mg/kg/injection. In the present study, the effective dose range for histamine was 0.0015–0.006 mg/kg/injection. The dose of 0.012 mg/kg/injection was fully effective in the one monkey that was tested at this dose. Species could be a determinant of this potency difference: squirrel monkeys were used in previous studies with histamine punishment. In a study that examined histamine as a negative reinforcer in rhesus monkeys (Takada et al., 1986), histamine delivered at a rate of 7 μg/kg/s functioned as a negative reinforcer. In the present experiment, with 10-s infusions, punishing doses of histamine were infused at rates of 0.15–0.6 μg/kg/s. Although the experiments involve different methods, this comparison gives a sense of the sensitivity of the present procedure within a species. Enhanced sensitivity should offer advantages in terms of pharmacological selectivity for the study of punishing effects of drugs. Additional research is required to establish the generality of these conclusions.

In contrast to results with histamine, the frequency of cocaine + food choice increased with dose. This observation demonstrates pharmacological selectivity of the punishing effect. In addition, this result suggests that either these doses of cocaine lacked a punishing effect or that any punishing effect was overridden by the reinforcing effect. Dose–response functions were qualitatively and quantitatively similar to those that have been previously published for the cocaine/food choice in monkeys (e.g., Nader and Woolverton, 1991, 1992), demonstrating that the method is functionally similar to other choice methods using drugs as reinforcers.

Another result that deserves comment is that responding tended to be all-or-none for one of the options. This was manifest in both the indifference seen when both injections were saline, or when low doses were delivered with food, and in the preference seen with higher doses. Mean data when saline + food was delivered as both consequences indicated an indifference that was based upon a position preference. That is, when there was no clear preference between reinforcers, monkeys showed a position preference that resulted in exclusive choice of one reinforcer when it was associated with, for example, the right lever and exclusive preference for the other reinforcer when it was associated with the right lever. Considered across position reversals, essentially half of the responses and half of the choices were for each reinforcer, while within a condition, choice was all-or-none. Although this is a measure of indifference between the reinforcers, a consistent position preference has the potential to influence choice data. As dose was increased, full preference developed abruptly rather than being graded with an increase in dose. Quantitative analysis of two-point dose–response functions can be problematic. It seems likely that all-or-none responding is a function of the use of a ratio schedule of reinforcement. For example, position preferences with fixed ratio schedules of reinforcement have been reported previously in the cocaine self-administration choice literature (Johanson and Schuster, 1975). Position preferences can be avoided by the use of a switching procedure to study drug choice (Aigner and Balster, 1978; Woolverton and Johanson, 1984). In previous studies of cocaine/food choice in monkeys using a switching procedure, choice was generally more graded than in the present experiment (Nader and Woolverton, 1991, 1992). All-or-none responding has also been an issue in the drug discrimination literature. The use of response-based schedules (FR and VR) is associated with all-or-none dose–response functions with drugs as discriminative stimuli. Graded dose–response functions are often a consequence of averaging all-or-none effects both within and across subjects. On the other hand, the use of time-based schedules has led to more graded dose–response function both within and across subjects (McMillan and Hardwick, 1996; Stolerman, 1989). It seems probable that methodological modifications such as these may enhance the measurement of punishing effects of drugs.

Since it has been suggested that choice may be better represented by time allocation than response allocation (Baum, 1979; Brownstein and Pliskoff, 1968), time spent responding on each lever was measured in the present experiment. This measure was both qualitatively and quantitatively highly variable across monkeys and may not be a useful indicator of preference under the current conditions. Since changeover performance often provides a measure of indifference between options and may suggest response chaining between options (Davison and McCarthy, 1988), we measured this behavior as well. Consistent with the relatively quantal nature of the choice data, there was little evidence of changeover responding between the options.

Considering the present data, as well as previous experiments with drugs as punishers, it is interesting to speculate on the nature of the punishing effect. Since histamine does not cross the blood-brain barrier (Hershowitz, 1979), the punishing effect of histamine must be based upon a primary peripheral site of action. In this sense, histamine would seem similar to electric shock and, e.g., volatile alkyl nitrites, compounds that apparently function as positive reinforcers based upon an action that is also initiated outside the CNS (Balster, 1998). Although one would assume that perception of these effects involves the CNS, it seems unlikely that punishment by histamine involves direct stimulation of CNS histamine receptors. In the present experiment, there was considerable individual variation in sensitivity to both cocaine and histamine. It is unclear whether this is somehow related to the method. Interestingly, however, the monkey that was the most sensitive to cocaine (M381) was the least sensitive to histamine. Conversely, the monkey that was the least sensitive to cocaine (L35) was one of the two most sensitive to histamine. It is interesting to speculate that individual differences in self-administration may be related to individual differences in relative sensitivity to reinforcing and punishing effects of drugs. Clearly, this is too small a sample on which to base firm conclusions. Nevertheless, since the reinforcing effect of cocaine and the punishing effect of histamine appear to be initiated at divergent sites of action, this finding suggests a differential behavioral sensitivity among individuals to reinforcing and punishing effects of drugs. Such individual differences could contribute to individual differences in drug abuse. It remains for future research to address these intriguing issues.

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