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Self-administration of cocaine on a progressive ratio schedule in rats: dose-response relationship and effect of haloperidol pretreatment

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Abstract. Intravenous cocaine self-administration behavior in rats was investigated using a progressive ratio (PR) schedule of reinforcement. The first response on the lever each day produced a drug infusion, whereupon the requirements of the schedule escalated with each reinforcement until the behavior extinguished. The final ratio completed each day was found to be relatively stable, sensitive to changes in dose, and drastically reduced by pretreatment with haloperidol (0.05 mg/kg). We conclude that self-administration behavior of rats reinforced on a progressive ratio schedule can provide useful information about changes in the reinforcing efficacy of specific drugs.

Key words: Cocaine – Drug self-administration – Progressive ratio schedule – Haloperidol – Reinforcement

Intravenous self-administration procedures have been used with some success to investigate the neural substrates of drug reinforcement. Typically, investigators have attempted to assess the involvement of particular neurotransmitters or brain regions based on whether various neurotoxic lesions or pharmacological pretreatments produce a change in the rate of drug intake under simple schedules of reinforcement. For example, it has been argued that dopaminergic mechanisms are critical for psychomotor stimulant reward because prior administration of a dopamine receptor antagonist produces an increase in stimulant self-administration rate (Johanson et al. 1976; Risner and Jones 1976; Yokel and Wise 1976; de Wit and Wise 1977; Roberts and Vickers 1984). This increase has been interpreted as a compensatory response to a partial blockade of the reinforcing effects (Yokel and Wise 1976); this phenomenon is similar to the increased rate of drug intake observed following a reduction in the unit injection dose.

Unfortunately, rate of responding is an ambiguous measure of the rewarding effect of a drug injection. Wilson and Schuster (1973) point out that an increase in drug intake could be interpreted as either an increase or decrease in reinforcement efficacy and, indeed, others have interpreted reduced drug intake following specific lesions as a disruption of reinforcement mechanisms (Roberts et al. 1977). In an effort to find a useful method for evaluating the reinforcing strength of a drug in rats, we have applied a progressive ratio (PR) schedule to cocaine self-administration behavior. The effect of pretreatment with a dopamine receptor antagonist and manipulation of injection dose were examined.

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Methods

Male Wistar rats (Woodlyn Farms, Guleph, Ontario; 350–400 g) were initially trained to press a lever for food reinforcement and subsequently implanted under pentobarbital anaesthesia with permanently indwelling jugular cannulae (see Roberts and Goeders 1987). The cannulae travelled subcutaneously to the point of exit in the back at the mid-scapular level and were attached through a protective spring to a counter-balance/swivel assembly. Animals were housed in individual plexiglas testing chambers equipped with house lights, a removable lever, stimulus lights, and water bottle. Food was freely available.

Two days following surgery, animals were trained on a fixed ratio 1 (FR 1) schedule of reinforcement. During daily 4-h sessions a lever was introduced into the cage which, when depressed, produced an intravenous injection of cocaine (0.6 mg/injection in 0.1 ml saline delivered over 5 s). Coincident with the onset of the injection, a stimulus light was turned on for 20 s. Responding during this 20-s interval had no programmed consequence.

Animals that demonstrated a consistent pattern of cocaine self-administration over the course of 3–5 days were selected for testing on a PR schedule. Daily PR sessions lasted 5 h and began with a "priming" injection. The first response during each daily session produced an injection and, with each succeeding reinforcement, the response requirements to earn an injection escalated according to the following series: 2, 3, 5, 7, 9, 12, 15, 18, 23, 28, 33, 41, 49, 57, 70, 83, 96, 117, 138, 156, 200, 225, 275, 300, 325, 350, 375, 425. The series is approximately logarithmic. It was found in pilot experiments that, with this series, animals would self-administer during the 1st hour or two, but would not continue into the 5th hour of the session. Thus, self-administration behavior extinguished in each animal each day.

In the first experiment, 13 animals were tested for at least 5 consecutive days on the initial dose of 0.6 mg/injection, followed by testing with a dose of either 0.3 or 0.9 mg/injection.

In a separate series of experiments, rats were trained on a similar PR schedule, with the exception that a true

logarithmic function was selected as follows: 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 178, 219, 268, 328, 402, 492, 603, 737, 901. Following at least 4 days of baseline self-administration (0.6 mg/injection), animals were pretreated with a saline injection (1 ml/kg, IP) in order to habituate the animals to the injection procedure. The following day, rats were pretreated with either 0.025 or 0.05 mg/kg haloperidol (IP) 1 h prior to the test session. Eight animals were tested at each dose.

The breaking point was defined as the value of the final ratio completed during the session. Due to the escalating nature of the schedule, a log transform was performed on the breaking point values before submitting the data to a paired Student's *t*-test. This analysis yielded essentially the same statistic as an analysis of the number of injections taken.

Results

All animals showed a consistent pattern of responding that was apparent from the 1st day of testing. Figure 1 A illustrates cocaine self-administration behavior on the PR schedule. During the early part of the test session, infusions were regularly spaced. Each drug injection was followed by a remarkably consistent post-infusion pause in responding, after which the animal would again begin to press the lever until the requirement for the next injection had been met. The animals would complete the ratio requirements quickly, typically within 1–2 min. At some point in the session, the requirements of the schedule exceeded the reinforcing efficacy of the drug dose and the lever pressing response extinguished.

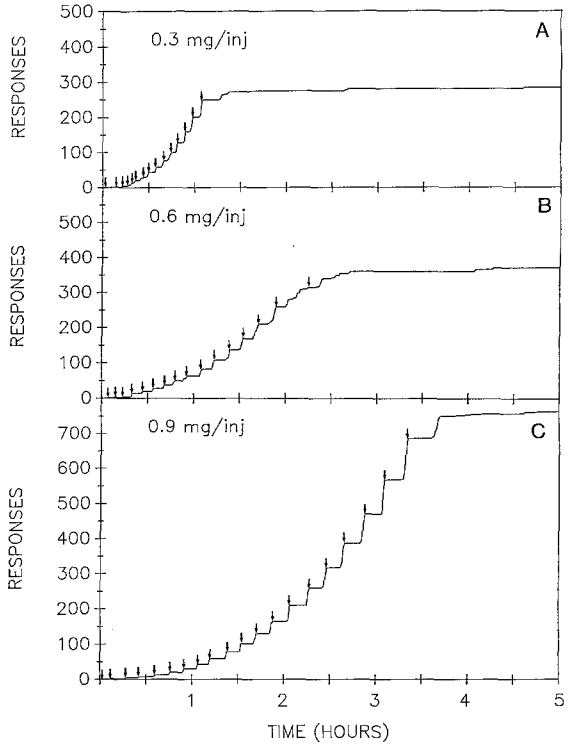

Fig. 1. Cummulative records of a rat responding under a progressive ratio schedule for three doses of cocaine reward. *Vertical increments* represent lever responses. *Arrows* indicate the time of the cocaine injection

Table 1 shows the breaking points (median of 5 days) for the three doses of cocaine. Eight of the nine animals tested at 0.3 and 0.6 mg/injection showed an increase in breaking point at the higher dose, a difference that proved to be statistically significant (paired $t=2.92$, $df=8$, $P<0.02$). No statistically significant difference was found between the breaking points determined for the higher doses of 0.6 and 0.9 mg/injection. The higher dose (0.9 mg/injection) produced increased breaking points in five animals tested, no consistent change in two animals tested and a decreased breaking point in one animal.

Table 2 shows the mean (±SEM) values for haloperidol pretreatment on cocaine self-administration behavior under the PR schedule of reinforcement. Haloperidol pretreatment produced a dose-dependent effect (see Table 2). The 0.05 dose was found to decrease the breaking point by an average of 35% compared to the saline pretreatment day ($t=2.03$, $df=7$, $P<0.05$) and to decrease the total responses made by an average of 45% ($t=2.56$, $df=7$, $P<0.05$). The rate at which the total number of injections were delivered was increased significantly after 0.05 mg/kg haloperidol ($t=4.43$, $df=7$, $P<0.01$). The 0.025 mg/kg dose of haloper-

Table 1. Responding on a progressive ratio schedule reinforced by various doses of cocaine. Data represent the median breaking point for 5 days of testing at each dose. Breaking point was defined as the final ratio completed

Subject no.	Cocaine (dose mg/inj)		
	0.3	0.6	0.9
633	33	83	
634	18	33	
643	15	15	
647	33	41	41
649	33	57	
651	41	57	57
652	57	70	117
653		96	117
655	57	156	83
657		96	138
661	57	138	
675		83	117
683		41	70
Mean	38.2	74.3	92.5
SD	16.1	40.7	34.6

Table 2. The effect of haloperidol pretreatment on rate of responding and breaking point on a progressive ratio schedule. Breaking point was defined as the final ratio completed. The time between the first and final injection was divided by the number of injections to yield "Injection rate". Data represent the mean±SEM ($N=8$). Asterisk (*) indicates significant difference between scores on Baseline day compared to Haloperidol day ($P<0.05$). Animals were injected with haloperidol 1 h prior to test. On baseline days, animals were injected with saline (1 ml/kg IP)

	Breaking point	Injection rate (injections/h)
Baseline	88.6±27.5	6.75±0.88
Haloperidol (0.025 mg/kg)	78.7±21.2	7.25±0.93
Baseline	74.8±18.1	7.60±0.72
Haloperidol (0.05 mg/kg)	*49.1±16.0	*10.06±1.08

idol had no significant effect on breaking point, total responses, or injection rate.

Discussion

The PR schedule appears to elicit a consistent pattern of responding in rats that is relatively stable from session to session. Surprising to us was the fact that the breaking point established on the 1st day of testing on the PR schedule was a good predictor of the breaking point on subsequent days; that is, an extended "acquisition period" was not necessary. The breaking point on the 1st day accurately reflected the breaking point for the following days.

The rate of drug intake during the 1st hour or two was approximately equal to the rate of drug intake during the baseline training period on an FR 1 schedule of reward. Animals learned to depress the lever until an infusion was delivered. At high ratios, this was accomplished with a burst of responses made within 1–2 min but, as the response requirements of the schedule increased, the self-administration behavior eventually extinguished.

With regard to the schedule of reinforcement used, Hodos (1961) suggested that the PR schedule could be employed to assess the relative strength of food reward. This method has been applied subsequently to the study of drug reinforcement in rhesus monkeys (Hoffmeister 1979) baboons (Griffiths et al. 1975, 1978, 1979) and dogs (Risner and Silcox 1981; Risner and Goldberg 1983; Riser and Cone 1986). In these later studies, a fixed ratio was imposed during the daily session, and if the animal performed to some criterion, the ratio was increased the following day. By contrast, in the schedule reported here, the response requirements increased after each reinforcement, as originally suggested by Hodos (1961). Bedford et al. (1978) have used a similar procedure with rhesus monkeys. However, their procedure differs from the present study in that the ratio series continued on the following day where the animal had left off, whereas in the present study the break point was established each day, with the PR schedule being reset at the beginning of the session.

In general, higher doses of cocaine produced higher breaking points, although it should be emphasized that this was not necessarily true for all animals. Some rats peaked at the middle dose (e.g., no. 655, Table 1). Others showed a flat dose/response curve (e.g., no. 647). The PR data suggest that there is variability from animal to animal in the dose of cocaine that sustains maximal responding. For some, the optimum dose was 0.6 mg/injection, whereas for others it was higher. This is consistent with the data of Bedford et al. (1978), who found that each rhesus monkey tested showed a variable, often U-shaped, dose/response curve. Presumably, there is an optimal dose for each subject, whether monkey or rat, past which performance on the PR schedule will decline.

In order to evaluate whether cocaine self-administration on a PR schedule of reinforcement is sensitive to pharmacological manipulation, we investigated the effect of haloperidol pretreatment. On simple schedules, it has been repeatedly demonstrated that prior administration of a dopamine antagonist produces an increase in stimulant self-administration rate. (Johanson et al. 1976; Risner and Jones 1976; Yokel and Wise 1976; de Wit and Wise 1977). We have previously shown that a dose of 0.05 mg/kg haloperidol is the minimum dose necessary to produce an increase in response rate on an FR 1 schedule (Roberts and Vickers 1984). In the present study, we found that 0.05 mg/kg haloperidol caused a significant increase in the injection rate, a finding consistent with the literature. However, this same dose caused a significant decrease in breaking point on the PR schedule. These data indicate that animals will compensate for the dopamine receptor blockade by increasing their drug intake when the drug injections can be "earned" with little effort, but at higher ratios the reponse extinguishes.

It might be argued that the decrease in breaking point is a result of some motor impairment caused by the DA antagonist and not a specific attenuation of the rewarding efficacy. This hypothesis is difficult to dismiss; however, it should be noted that 0.05 mg/kg is an extremely small dose of haloperidol and would not be expected to disrupt operant responding for food (see Rastogi and McMillan 1985). Furthermore, an *increase* in rate of self-administration was observed at the same time as the the decreased breaking points. Not withstanding some future demonstration of a motor impairment, we interpret the lowered breaking points after haloperidol pretreatment to indicate a reduced reinforcing efficacy of cocaine, consistent with the hypothesis that stimulation of dopamine receptors mediate the reinforcing effects of cocaine (Roberts et al. 1980).

It appears feasible to apply the PR schedule to the study of drug self-administration in rats. It has recently been employed to demonstrate decreased breaking points for cocaine reinforcement following 6-hydroxy-dopamine (6-OHDA) lesions of the nucleus accumbens (Koob et al. 1987). Of critical importance has been the observation that changes in breaking point are not necessarily accompanied by alterations in rate of drug intake. For example, 6-OHDA lesions of the nucleus accumbens do not change the rate of apomorphine intake (Roberts et al. 1977), yet produce substantial increases in breaking points (Roberts 1988). Similarly, Roberts et al. (1988) have shown that the PR schedule provides evidence that estrous fluctuations influence the reinforcing efficacy of cocaine even though rate of self-administration is not affected. These and the present data demonstrate that the PR schedule provides essential information in the study of drug reinforcement not provided by simpler schedules of reinforcement.

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