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Pharmacological Regulation of Intravenous Cocaine and Heroin Self-Administration in Rats: A Variable Dose Paradigm

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GERBER, G. J. AND R. A. WISE. *Pharmacological regulation of intravenous cocaine and heroin self-administration in rats: A variable dose paradigm.* PHARMACOL BIOCHEM BEHAV 32(2) 527–531, 1989.—Rats were trained to intravenously self-administer unit doses of cocaine or heroin. Constant supplemental infusion of a portion of each rat's mean hourly intake increased the mean time between successive infusions, but the effect was not statistically reliable from the data of a small sample of animals. A variable dose per infusion (VDI) paradigm was developed which enabled testing of several unit doses of cocaine or heroin within single test sessions. Unit doses of 0.5, 1.0, and 2.0 mg/kg of cocaine or 0.025, 0.05, and 0.1 mg/kg of heroin were made available with equal frequency but in unpredictable sequence to independent groups of rats. The mean time between successive infusions was linearly related to the log dose of the preceding infusion in each case. Pimozide, a drug thought to attenuate the reinforcing effects of both cocaine and heroin, shifted the functions without disturbing the dose-response relations; pimozide reliably decreased the time between successive cocaine infusions across a 4-fold range of pimozide doses. The effect of pimozide on heroin self-administration was not statistically significant and disrupted responding at the highest dose tested. This paradigm thus offers a within-session assessment of the dose-dependent duration of reinforcing actions of cocaine and heroin, and this assessment is sensitive to at least one challenge of intravenous drug reinforcement.

Self-administration Cocaine Heroin Pimozide Rats

INTRAVENOUS amphetamine self-administration in rats is maintained across a wide range of unit doses and work requirements. Rats maintain relatively constant hourly drug intake despite a wide range of changes in unit dose and schedule of reinforcement (11–13, 19). The constancy of drug intake appears to be largely under pharmacological control, as rats initiate responding whenever the blood level of d-amphetamine falls to approximately 0.2 μl/ml (22), accelerating or decelerating responding if amphetamine metabolism is accelerated or retarded (4). Temporal conditioning can also influence rate of responding, however, particularly in the short run: the rate of responding in extinction, when no drug is given, is correlated with the rate of responding during previous training in paradigms where the training dose and the associated response rate was maintained at a constant level (23).

Intravenous opiate self-administration is much more irregular than amphetamine or cocaine self-administration, at least in rats tested under fixed unit doses and work requirements. While mean response rate is inversely related to unit doses over the meaningful (20) range of unit doses (6), the variability of individual response records suggests that opiate self-administration is not under the same degree of pharmacological control as is amphetamine (22) self-administration. Moreover, while high-dose neuroleptic treatment causes cessation of opiate self-administration, low and moderate doses do not cause the robust compensatory increases that are seen when the same drugs are used to challenge psychomotor stimulant self-administration (5). Thus, it appears possible that opiate self-administration is not under the same degree of pharmacological control as is stimulant self-administration.

One of the problems with studying pharmacological control of drug self-administration is the problem of day-to-day stability of response rate. Particularly in the case of heroin self-administration, variability of interresponse times makes it necessary to test animals for several days at each unit dose in order to establish a reliable dose-effect function. Inasmuch as heroin intake tends to increase from day to day (at least in the early weeks of testing), it is difficult to obtain dose-effect data that are not confounded by changes in baseline. Both the seemingly random variability of succes-

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sive interresponse times and the progressive changes in baseline are much greater in the case of heroin self-administration than in the case of cocaine self-administration in the rat (2).

The present paper reports three experiments designed to examine the extent and nature of pharmacological control of intravenous cocaine and heroin self-administration in the rat. First, cocaine and heroin self-administration were examined in animals given supplemental intravenous infusion of each self-administered drug. The question of interest was how accurately rats would compensate for unearned drug infusion. Second, cocaine and heroin self-administration were examined in animals given variable reinforcing doses within sessions. Three doses were tested with each training drug, and the dose per injection was varied irregularly from reinforcement to reinforcement. The relation between the duration of postinjection pauses in responding and the dose of the previous injection was determined and compared between the two classes of self-administered drugs. Finally, this relation was challenged with pimozide, a member of a drug class generally thought to reduce the reinforcing effects of amphetamine and cocaine (5, 21, 24, 25), and argued by some investigators to have similar, if less robust, effects on the reinforcing effects of opiates (1, 10, 15, 16).

EXPERIMENT 1: SUPPLEMENTAL INTRAVENOUS DRUG INFUSION

In the first experiment, a period of constant supplemental drug infusion was examined for its effects on intravenous cocaine and heroin self-administration rates.

METHOD

Animals

Eleven male Sprague-Dawley rats weighing 350 to 400 g at the time of surgery were used. They were food deprived and trained to lever press for food (45-mg Noyes food pellets). Two weeks later, a chronic catheter was surgically implanted in the jugular vein and led out through a pedestal affixed to the skull (17).

Apparatus

One week after surgery, rats were trained to lever press for intravenous infusions of 1 mg/kg cocaine hydrochloride delivered in a volume of 0.25 ml over 1.43 sec, by a syringe pump (Razel Scientific Instruments, Stanford, CT, Model A). The output from the syringe was connected to the rat by polyethylene tubing with a fluid swivel.

Rats were tested for 3 hours per day in a 26×26×28 cm box containing a response lever (Ralph Gerbrands G6312) mounted 10 cm above the grid floor. A cue light was located directly above the lever and a house light was illuminated during test sessions, except for the duration of each infusion. Each lever press initiated delivery of a cocaine infusion, unless the press was made during an infusion. Rats were returned to their home cage between test sessions.

Procedure

Five rats were continued on cocaine at a unit dose of 1 mg/kg in 2-hour sessions, and six rats were switched to heroin reinforcement at a unit dose of 50 μg/kg in 4-hour sessions. Testing continued until drug intake was within 20% of the mean of the previous four days. For the next five days, 20% of each rat's mean hourly intake was delivered during a portion of the test sessions by connecting a second syringe pump that infused drug at a constant rate (Razel, Model A-99H). Rats receiving cocaine were given a constant infusion of cocaine for 30 min, commencing 1 hour after the start of the test session (total volume was 0.225 ml in 30 min, with dose being dependent on each rat's baseline intake). Rats receiving heroin were given a constant infusion of heroin for 60 min, also commencing 1 hour after the start of the test session (total volume was, again, 0.225 ml in 60 min). In this way, rats in both groups received the constant infusion for 25% of the test session. Each rat was tested once in this experiment.

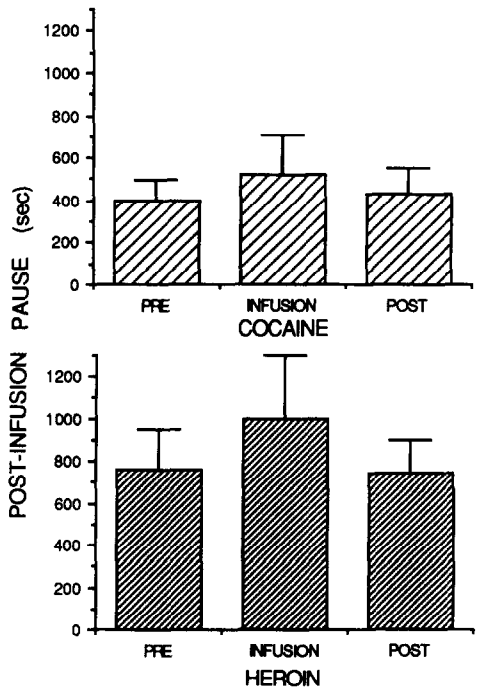

FIG. 1. Mean (±SEM) duration of postinfusion pauses before (PRE), during (INFUSION), and after (POST) periods of constant drug infusions equivalent to 20% of each rat's mean hourly self-administered drug intake.

Preparation of Drugs

Cocaine hydrochloride (May & Baker) and heroin hydrochloride (Health and Welfare, Canada) were prepared in normal saline containing 0.3% sodium meta-bisulfite and sterilized by filtration.

RESULTS AND DISCUSSION

Periods of response-independent supplemental drug infusion increased the duration of postinfusion pauses in both cocaine and heroin self-administration (Fig. 1). In each case, mean response rate returned to normal when response-independent infusions were terminated. There was approximately a 25% adjustment of response rate during the period of response-independent infusions. Since the response-independent infusions were adjusted to 20% of the normal rate of drug intake, the overall responding for heroin compensated with reasonably similar accuracy to the overall re-

TABLE 1

MEAN (±SEM) POSTINFUSION PAUSE AS A FUNCTION OF INFUSION DOSE (IN SECONDS)

	Cocaine Unit Dose (mg/kg)				Heroin Unit Dose (μg/kg)		
Rat	0.5	1.0	2.0	Rat	25	50	100
117	142 ± 14	280 ± 10	699 ± 41	223	439 ± 105	748 ± 113	1113 ± 115
144	219 ± 19	424 ± 13	555 ± 18	227	423 ± 125	1174 ± 370	1372 ± 289
145	302 ± 50	399 ± 32	664 ± 76	228	458 ± 65	730 ± 75	933 ± 100
170	251 ± 43	640 ± 47	876 ± 32	264	313 ± 70	1221 ± 189	1954 ± 273
191	208 ± 22	332 ± 19	452 ± 42	267	298 ± 43	425 ± 53	776 ± 89
226	206 ± 24	389 ± 19	462 ± 39	282	155 ± 40	1178 ± 302	1570 ± 202

sponding for cocaine. However, while the degree of decrease in response rate was consistent with the hypothesis that the animals were compensating for supplemental infusions, there was considerable variability in the interresponse times, and the changes in response rate were not statistically reliable. Thus, while the data appear interesting and deserving of further analysis, this experiment does not by itself provide convincing evidence of pharmacological regulation of drug intake. If a more effective procedure had not been devised (see next experiment), additional animals or additional replications would have been required.

It is, nonetheless, interesting to consider these data more closely (particularly because convincing evidence of pharmacological regulation of drug intake is provided in the next experiment). While variability in *mean* response rate was similar between the cocaine-trained and the heroin-trained animals—standard errors of the means were about 20% of baseline intake in each case—variability in the *individual* interresponse times were not. There was great within-subjects variability of heroin interinfusion pauses and much less within-subjects variability of cocaine interinfusion pauses. Examination of individual records indicates how mean performance for a given animal could be highly predictable while individual interinfusion pauses were variable; there was a great tendency for long interinfusion pauses to follow short ones and for short ones to follow long ones. In other words, sequential interinfusion pauses were not independent; each animal's pauses compensated, to a considerable degree, for any irregularity of the previous pause.

EXPERIMENT 2: VARIABLE DOSE PER INFUSION (VDI)

In order to establish statistically reliable dose-effect data within single sessions, a variable dose per infusion (VDI) paradigm was developed. In this paradigm, the relations were determined between self-administered cocaine or heroin dose and duration of the subsequent postinfusion pause in responding.

METHOD

Animals and Apparatus

Twelve male rats were surgically prepared as described in Experiment 1. Six rats were trained to self-administer cocaine infusions using routines described above. Initial training continued until daily drug intake did not vary by more than 20% of the mean of the previous 4 three-hour sessions. At this time, these animals were started on the variable dose paradigm described below. The other six rats were trained to self-administer heroin hydrochloride at a dose of 50 μg/kg/infusion until daily drug intake did not vary by more than 20% of the mean of the previous 4 three-hour sessions. These rats were then started on the variable dose paradigm with heroin reinforcement.

Procedure

Three infusion times (0.72, 1.43, and 2.86 sec) were programmed in a repeating irregular sequence. This resulted in cocaine dosage of 0.5, 1.0, and 2.0 mg/kg/infusion, and heroin dosage of 25, 50, and 100 μg/kg/infusion. The paradigm thus involved a four-fold range of doses within each testing session. Three-hour test sessions were run daily until the total number of infusions each day was within 20% of the mean of the previous four days. The time elapsed between each earned infusion and the subsequent lever-press (postinfusion pause) was recorded. Rats were prevented from obtaining two infusions in rapid succession (before drug from the first infusion could be distributed in the animals' blood circulation), by making response ineffective if it occurred within 14 sec after the last reinforced response. A total of approximately six weeks of training was required for rats to reach the 20% stability criterion.

RESULTS AND DISCUSSION

The mean postinfusion pause depended on the dose of the preceding infusion. This is shown for individual rats tested under the variable dose paradigm in Table 1. Means and standard errors of postinfusion pauses were calculated on the basis of five baseline sessions for each rat. Postinfusion pauses were proportional to the dose of drug received, and did not depend on sequential position. Postinfusion pauses were briefer for cocaine than for heroin within the range of doses tested. The correlation between dose and mean postinfusion pause was $r=.81$ ($n=6$; $p<0.001$) for cocaine, and $r=.76$ ($n=6$; $p<0.001$) for heroin. Mean postinfusion pause was linearly related to the log dose of the previous injection of either heroin or cocaine (Fig. 2). Again, standard errors for the session means were comparable, but within-session variability was greater in the heroin condition.

Rats learned to respond predictably despite unreliable unit doses. Thus, when unit dose is unpredictable, responding for each drug is under major control of pharmacological factors. Reliable dose-response relations were determined for single animals within single sessions, and orderly, low-variance dose-response relations were demonstrated across small groups ($n=6$) of rats. Thus, this paradigm would appear to be useful for drug self-administration studies in the rat.

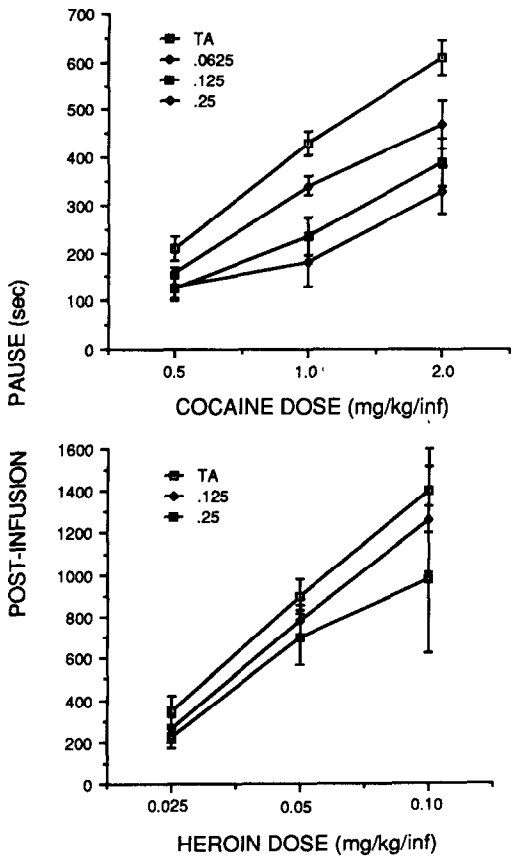

FIG. 2. Mean (±SEM) duration of postinfusion pauses as a function of self-administered injection dose and pimozide treatment for rats in the VDI paradigm. Pimozide doses in mg/kg; TA indicates the tartaric acid vehicle condition.

EXPERIMENT 3: PIMOZIDE TREATMENT

This experiment assessed the ability of pimozide to shift the dose-effect relations obtained using the VDI paradigm for cocaine and heroin self-administration.

METHOD

Procedure

The animals from Experiment 2 were used. Pimozide (Janssen Pharmaceuticals, Beerse, Belgium) or its vehicle (tartaric acid solution) was injected IP 4 hours before the start of selected test sessions. Pimozide was given at doses of 0.0625, 0.125, and 0.25 mg/kg in rats receiving cocaine, and at doses of 0.125, 0.25, and 0.5 mg/kg in rats receiving heroin. Each dose of pimozide was tested three times in each rat, in random order. Tartaric acid injections were given for five sessions prior to the start of pimozide testing and for three sessions between each pimozide session. Pimozide was dissolved in 0.3% tartaric acid solution in distilled water. Drug dosages are expressed in terms of the salt.

Data Analysis

The mean postinfusion pause duration was calculated for each dose of cocaine and heroin delivered under baseline, tartaric acid, and pimozide treatment conditions for each subject. Analyses of variance were performed on postreinforcement pause durations to compare effects of pimozide on cocaine and heroin self-administration. The mean of three determinations for each dose for each rat was used for the analyses.

RESULTS

Pimozide displaced the log dose-effect curves to the right for both cocaine and heroin self-administration (Fig. 2), but the effect was statistically reliable only in the case of cocaine self-administration. Mean postinfusion pause duration for five cocaine-reinforced rats (one catheter failed and could not be replaced) pretreated with tartaric acid or pimozide are shown in Fig. 2 (top panel). Increasing doses of pimozide produced decreases in duration of postinfusion pauses across all self-administered doses of cocaine, but did not change the slope of the relationship between unit doses and postinfusion puase duration. The effects of pimozide treatment were analyzed using a repeated measures two-way analysis of variance (self-administered drug dose × pimozide dose). Significant effects were found for the cocaine dose, $F(3,12)=82.54$, $p<0.0001$, for the pimozide dose, $F(3,12)=5.69$, $p<0.05$, and for the interaction, $F(6,24)=4.7$, $p<0.01$, reflecting the clustering of points at the low dose of cocaine (see Fig. 2).

Mean postinfusion pause duration for four heroin-reinforced rats (two catheter failures) pretreated with tartaric acid or pimozide are shown in Fig. 2 (bottom panel). The 0.5 mg/kg dose of pimozide completely suppressed responding in most rats; data for this dose are not shown in the graph and were not included in the analysis of variance. There was no statistically reliable effect of the analysed doses of pimozide (0.0625 to 0.25 mg/kg) on the heroin dose-response curve; a repeated measures two-way analysis of variance (self-administered drug dose × pimozide dose), that excluded the 0.5 mg/kg dose of pimozide, showed no significant effect for pimozide, $F(2,6)=1.69$, a significant effect for heroin dose, $F(2,6)=30.41$, $p<0.001$, and no significant interaction.

DISCUSSION

Pimozide caused orderly shifts in the cocaine dose-effect curves across a 4-fold range of pimozide doses; the effect was to decrease the duration of postreinforcement pauses, thus increasing response rates. This parallels the well-known effects of neuroleptics in constant-dose stimulant self-administration studies (3, 5, 18, 24, 25). Lower doses of pimozide (data not shown) were ineffective and higher doses caused cessation of responding.

Pimozide also caused shifts in the heroin dose-effect curve, but these shifts were not statistically reliable and were seen with a narrower range of pimozide doses. Again, this parallels what is seen in fixed dose paradigms. Small, statistically unreliable increases in opiate self-administration have been consistently reported (5, 10, 15), though their interpretation, because of the absence of statistical reliability, has been neglected. Since statistically reliable increases are caused by the selective D-1 antagonist SCH 23390, and since the D-1 antagonist is thought to alter behavior by gating D-2 receptor functions which are blocked by pimozide (8,21), it would appear that the small effects of the D-2 antagonists on heroin self-administration are biologically significant. It is important to note that the present paradigm shows a degree of sensitivity to these effects which is similar to that of the constant dose paradigms. The explanation for the narrow range of neuroleptic doses that produce compensatory increases in heroin self-administration and the small compen-

satory increases that are repeatedly seen as a result of neuroleptic challenge [this study; (5, 10, 15)] may be attributable to differences in the "side" effects of D-1 and D-2 antagonists. The side effect of most obvious interest in this regard is the ability of D-2 antagonists to interact with opiates to produce depolarization inactivation of the dopamine system (14). The D-1 antagonist SCH 23390 does not accelerate dopamine cell firing (7), and thus should not augment the ability of opiates (9) to cause depolarization inactivation. Whether or not this explanation for the differences in the effects of neuroleptics on cocaine and heroin self-administration proves viable, the VDI paradigm reflects the same profiles as are reflected in fixed-dose paradigms (5, 10, 15).

GENERAL DISCUSSION

The present data suggest that heroin self-administration, like cocaine self-administration, is under important, though not exclusive, control of blood or tissue levels of the self-administered drug. It seems clear that the moment-to-moment control of heroin self-administration is less closely regulated than that of cocaine self-administration, but that cumulative effects of irregular responding have important consequences for subsequent responding for each drug. While the supplemental infusion paradigm is interesting, reliable data are not readily obtained from small groups of animals and single days of testing; several replications would seem to be required for statistically significant data with small samples. The variable dose paradigm, on the other hand, seems to give reliable dose-response data with small groups of animals and single days of testing. The dose-response relations established with this paradigm are robust enough to survive displacement of the dose-response relations by pharmacological treatment with pimozide, a drug suggested to alter reinforcement efficacy for both opiates and psychomotor stimulants. The VDI paradigm should be particularly useful when the number of available testing days is limited, as in the case of brain lesion studies or studies involving drug challenges in which tolerance or receptor supersensitivity might develop. This paradigm also seems ideally suited for determination of tolerance to the reinforcing properties of the self-administered drugs themselves, since it allows tracking of day-to-day changes in the dose-effect curve while maintaining a counterbalanced sequence of doses both within and between test sessions.

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