Psychopharmacology (1981) 75:134–143

Psychopharmacology

Reinstatement of Cocaine-Reinforced Responding in the Rat

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Abstract. Non-contingent "priming" drug injections and conditioned stimuli associated with drug injections led to reinstatement of responding after a period of extinction. Rats implanted with intravenous catheters were trained to self-administer cocaine (1 mg/kg/injection), and then given daily test sessions consisting of a period of self-administration followed by extinction conditions. Test drug injections or conditioned stimuli were presented during extinction and the latency to the first response and the total number of responses following the treatment were measured. Cocaine injections of 0.5, 1.0, and 2.0 mg/kg restored responding during extinction, regardless of the duration of the extinction period (between 10 min and 180 min) since drug self-administration. Amphetamine, apomorphine, and morphine but not ethanol, heroin, or methohexital reinstated previously cocaine-reinforced responding. Amphetamine, cocaine, and morphine did not increase responding in animals trained to bar press only for food reinforcement, suggesting that the reinstatement effect is specific to drug-reinforced responses. The final experiment showed that a tone that had been paired with drug infusions acquired a statistically significant tendency to facilitate responding when tested during extinction but this effect disappeared after the first test presentation of the tone.

Key words: Cocaine self-administration – Reinstatement – Priming – Conditioned drug effects

The reinforcing property of intravenously-delivered stimulant drugs has been well demonstrated (see reviews by Spealman and Goldberg 1978; Griffiths et al. 1979). Laboratory animals readily acquire and maintain a response when stimulants are given as reinforcement, and under intermittent schedules of reinforcement the animals show the characteristic patterns of responding that are seen with conventional reinforcers. One aspect of behavior maintained by drug reinforcers that has received relatively little experimental attention, however, is what factors underlie the reinitiation of responding in animals trained to self-administer but that are currently drug free. Little is known about the conditions predisposing animals to reinitiate drug-reinforced responding. The lack of attention to this question is surprising in view of its relevance to the persistent clinical problem of relapse in human drug use. The experiments presented here represent an attempt to examine two factors that facilitate response reinitiation during extinction in rats trained to self-administer cocaine: The presentation of non-contingent "priming" injections of the self-administered or other drugs, and the presentation of conditioned stimuli that have been associated with the drug.

Gerber and Stretch (1975) and Stretch and Gerber (1973) established that in rhesus monkeys pre-session injections of a self-administered drug led to the restoration of responding in animals whose rates had fallen to low levels over repeated extinction sessions. Moreover, the pattern of responding exhibited by these animals after pre-session drug treatment was in some cases indistinguishable from the patterns seen during self-administration under a progressive ratio schedule, even though on test sessions responding led only to saline infusions. Gerber and Stretch (1975) also reported that both cocaine and amphetamine led to a restoration of responding in animals that had been reinforced by either of these agents, whereas neither chlorpromazine nor pentobarbital produced a consistent facilitatory effect on stimulant-reinforced responding. Similarly, Davis and Smith (1976) found that pre-session injections of morphine restored previously morphine-reinforced bar pressing in rats after a period of extinction. Pickens and Harris reported in 1968 that a single non-contingent "priming" infusion was sufficient to terminate a self-imposed abstinence period in rats trained to self-administer *d*-amphetamine. These results can be understood in terms of the control of operant responding by the discriminative stimulus properties acquired by the drugs during self-administration training, and Gerber and Stretch's results suggest that drugs other than the previously self administration drug increase the tendency to respond to the extent that their stimulus properties resemble those of the self-administered drug. Thus the presence of drug in the body appears to enhance drug-related behavior in animals returned to the environment where drug has in the past been available. It was the potential significance of this finding to our understanding of factors leading to relapse in human ex-drug users that led us to examine the phenomenon more closely.

Experiment I

This experiment was designed to explore the effect of a priming cocaine injection given during extinction after a period of cocaine self-administration. The priming injection was given by the same intravenous route as the self-administered drug injections, and it was not accompanied by any changes in the external stimulus conditions. Dose-dependence of the response-enhancing effect was examined

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0033-3158/81/0075/0134/$02.00

by giving priming doses that were half, double, and equal to the self-administered dose (1 mg/kg). Extinction was introduced by disconnecting the syringe pump, and all priming injections were given at a fixed time, 1 h, after the introduction of the extinction conditions.

Materials and Methods

Subjects. Five male Sprague-Dawley rats from Canadian Breeding Farms Limited, weighing 300 – 350 g upon arrival in the laboratory were used. For this and all subsequent experiments, more animals than are reported were initially catheterized and started on self-administration training. Some were dropped from the experiments because of catheter failure at an early stage, others because of failure to acquire stable self-administration. Only the data from rats that reached the test phase of the experiments are reported. Animals were housed in a temperature- and humidity-controlled animal room on a 12 h day/night cycle. Food and water were continuously available except for occasional periods of food deprivation during the early stages of self-administration training.

Surgery. Intravenous catheters (Pickens and Thompson 1975) were implanted into the left jugular vein of the rats, under pentobarbital (Nembutal) anaesthesia. The catheters were constructed from two thicknesses of silastic tubing (0.06 cm i.d. × 0.11 cm o.d., and 0.03 cm i.d. × 0.06 cm o.d.) with an Elastomer silastic coating over the larger tubing. The smaller tubing was inserted into the vein and the catheter was anchored to muscle tissue near the point of entry into the vein. It was passed SC behind the left front leg to an exit point on the rat's back at the level of the shoulders. The catheter was joined externally to a back consisting of a SC implanted plastic plate connected by two stainless steel screws to an aluminium external plate. This plate in turn held a screw-type connector (guide cannula) to connect with the infusion system. The connector was covered with a cap ("dummy" cannula) when the animal was not connected to the infusion system. Catheters were flushed daily with heparinized (5 IU/ml) physiological saline for the first week after catheterization to protect against the formation of emboli in the vein. When catheter failure occurred due to blockage or leakage during the course of the experiment, animals were re-catheterized using the right vein.

Apparatus. Five operant chambers (30 cm × 20 cm × 20 cm) were used in this experiment, each with fittings above the box to suspend a swivel (Brown et al. 1976) and the infusion tubing. Each box contained a lever (3 cm wide, protruding 3 cm into the box and having a thickness of 0.7 cm) mounted on a side wall 2 cm from the floor of the chamber. The infusion tubing leading from the rat's back pack to the swivel was enclosed in a coil of stainless steel wire that twisted the swivel as the animal moved and afforded some protection to the plastic tubing. This coil of wire encasing the tubing was attached to the screws in the back and to the moving part of the swivel. Further tubing led from the swivel to an infusion pump (Razel Syringe Pump Model A) outside the chamber. Each depression of the lever started a timer that activated the infusion pump for the number of seconds needed to deliver the appropriate volume of drug solution. Bar presses during an infusion were counted but did not reset the timer and had no further experimental consequences. All bar presses were recorded on event recorders and counters. Electromechanical equipment for the control of infusion duration and the recording of data was situated in an adjacent room. The experimental room was dimly lit and 60 db white noise was continuously present to mask extraneous noise.

A single concentration solution (4 mg/ml) of cocaine HCl (B.D.H. Chemicals Ltd., Toronto, Canada) was made up in physiological saline with 5 IU/ml heparin added. The solution was infused at a rate of 0.01 ml/s. Adjustments for dose and body weight were made by changing the infusion duration. The cocaine solution was made up weekly.

Procedure. Self-administration training began 2 days after surgery. The rats were connected to infusion tubing in the test chambers for 2- to 3-h daily sessions during which cocaine (1.0 mg/kg/injection) was available for each bar press. Animals were occasionally food deprived overnight to facilitate responding the following day during the training phase. Noncontingent priming injections of 1 mg/kg were occasionally given although an effort was made to keep these to a minimum. Animals that failed to acquire stable responding for the drug after 3 weeks of training were dropped from the experiment.

Daily test sessions began when a animal reliably initiated responding at the beginning of the session and responded regularly throughout the session. Stable responding was reached after an average of 14 sessions. Each test session consisted of 1 – 2 h of stable self-administration, followed by extinction conditions for the remainder of the session. The period of self-administration was varied slightly from day to day to maintain a degree of unexpectedness in the onset of extinction conditions. The extinction condition in this experiment was programmed by disconnecting the power to the syringe pump. Lever presses during the extinction period resulted only in the click of the lever microswitch for the animal. After 60 min of extinction the rats were given either a non-contingent priming injection of 0.5, 1.0, or 2.0 mg/kg of cocaine or no injection ("dummy" trial). Priming injections were controlled from the adjacent programming room. The latency to the first response after the priming injection and the total number of responses in the 30 min following the priming injection were recorded. All animals were tested twice at each dose; the order of tests was counterbalanced.

Results and Discussion

It can be seen from Fig. 1 that when extinction conditions were introduced responding increased initially, reaching a peak in the period between 10 and 20 min after the commencement of extinction, and subsequently declining over the remainder of the 60-min extinction period. Following the priming injection of cocaine there was a marked increase in responding at all doses tested. Higher doses were associated with longer latencies to respond [$F(3,12) = 4.34$, $P < 0.05$], and, in spite of this, with higher total numbers of responses in the 30-min post-prime period [$F(3,12) = 4.10$, $P < 0.05$]. The relation between dose and effectiveness of priming injection over the 30-min test period is shown in greater detail in Fig. 1. At the lowest dose (0.5 mg/kg) the greatest number of responses was made in the first 10 min following the priming injection; few responses were made after that. At the 1.0 mg/kg dose responding increased sharply in the first 10 min and returned to baseline more slowly than at the lowest dose. At the highest dose once responding began it remained elevated throughout the 30-min test period.

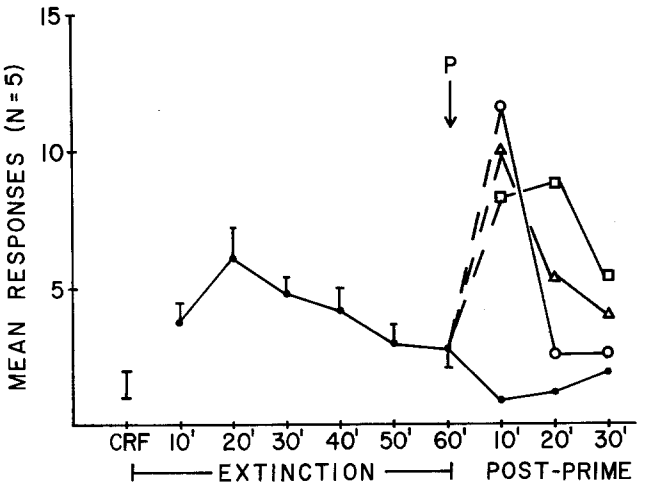

Fig. 1. Mean number of responses per 10 min during self-administration (continuous reinforcement: CRF), during extinction, and after cocaine priming injections of 2.0, 1.0, and 0.5 mg/kg or after a "dummy trial" (0.0 mg/kg) in Experiment 1. "P" indicates the point at which the priming injection was given. The mean values during extinction are based on eight determinations for each of five rats; the means after the priming infusions are based on two determinations per rat for each of five rats. Standard errors of the mean are indicated for the mean values during extinction. ●, 0.0 mg/kg; ○, 0.5 mg/kg; △, 1.0 mg/kg; □, 2.0 mg/kg

The effects of a wider range of priming doses of cocaine (0.125, 0.25, 0.5, 1.0, 2.0, or 4.0 mg/kg) were tested in another five animals. In these animals extinction was introduced by substituting saline for the cocaine solution rather than by disconnecting the syringe pump. When 1 h with no responses had elapsed during extinction a priming injection of either cocaine or saline was delivered through the intravenous catheter by the experimenter. The pattern of responding during extinction in these animals was similar to that seen in the initial study despite the methodological differences. Animals reinitiated responding after all but the lowest dose of cocaine. The same relation between dose and effectiveness of the priming injection over time was observed; higher doses resulted in a longer latency to respond and more prolonged responding.

This pattern is consistent with an interpretation in terms of the control of responding by the current level of drug in the blood (Yokel and Pickens, 1974). Such an account predicts that the animal should respond when, and as long as, there is enough drug to produce a discriminable effect and thereby reestablish the stimulus conditions of the self-administration period. Following the priming infusion of a high dose of the drug, responding might be expected to be suppressed for a period, just as it is between infusions during regular self-administration. As the blood level of drug decreases below a critical level, however, responding should be initiated and would be expected to be maintained until such time as the drug stimulus is no longer discriminable. The results of this experiment are consistent with such an account.

Experiment 2

The first experiment established that the priming effect was real and that it was sensitive to drug dose. The next question asked was whether the time since the last self-administered drug injection was an important variable in determining the magnitude of the response-enhancing effect of the priming cocaine infusion. A standard dose of 1 mg/kg of cocaine was given as the priming injection in this experiment after an extinction period of 10, 30, 60, 120, or 180 min. Extinction in this experiment was introduced by syringe pump disconnection.

Materials and Methods

Subjects. Five male Sprague-Dawley rats served as subjects. Two of these had served as subjects in Experiment 1 prior to testing in Experiment 2.

Apparatus. The apparatus was the same as that used in Experiment 1.

Procedure. Self-administration training proceeded as in Experiment 1. Test sessions consisted of 1–2 h periods of self-administration followed by extinction conditions for the remainder of the session. The extinction condition was introduced by disconnecting the syringe pump as in Experiment 1. A 1 mg/kg cocaine injection was given at either 10, 30, 60, 120, or 180 min after the commencement of extinction. The latency to the first response and the number of responses in the 30-min period following the priming injection were recorded. Each animal was tested twice at each extinction time (on different days) and the order of test presentation was counterbalanced.

Results and Discussion

Priming drug infusions given during extinction between 30 min and 3 h after the self-administration period were all effective in reinstating responding. The mean latency to the first response after the priming injection was not affected by the extinction duration preceding it. This was confirmed by a non-significant treatment effect in an analysis of variance [$F(4,16) = 0.63$, $P > 0.25$]. The mean number of responses following cocaine priming infusions reflect a downward trend in the total number of responses as the extinction duration increased. Analysis of variance on the effect of extinction duration on number of responses was significant [$F(12,48) = 2.03$, $P < 0.05$] and there was a significant linear trend between levels [$F(1,48) = 23.5$, $P < 0.01$]. Examination of the number of responses per 10 min after the priming infusions (Fig. 2) shows that for all extinction durations, except the 10-min one, the peak of the increase in response rates occurred within the first 10 min after the injection; after that, rates fell quickly to low levels. In contrast to this, the responses after the injection following only 10 min of extinction were distributed across the entire 30-min post-prime period.

It should be noted in regard to this that because the typical inter-response time during self-administration is about 10 min, and because the extinction period was introduced regardless of the animal's responses, some animals had made no non-reinforced responses at the time of the priming injection. The priming infusion in these animals thus effectively took the place of the next response-produced infusion, and delayed the next response by a further 10 min. The responding that occurred after this delay was, in effect, the animal's first experience with extinction on that test day.

Experiment 3

Experiment 3 was designed to test the effectiveness of drugs other than the self-administered drug (cocaine) in the rein-

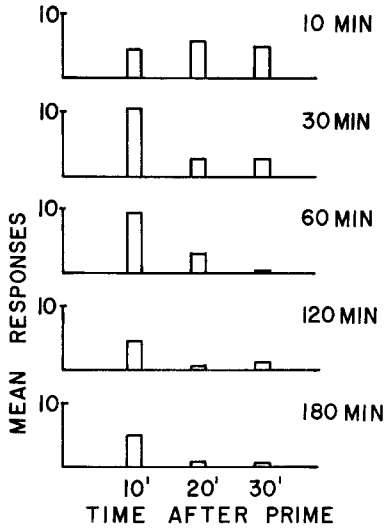

Fig. 2. Mean number of responses per 10 min after a 1 mg/kg cocaine priming infusion given 10, 30, 60, 120, or 180 min after the end of the self-administration period. Each mean is based on two determinations for each of five rats

statement of responding during extinction. As Gerber and Stretch (1975) argued, it is possible that the self-administered drug comes to act as a discriminative stimulus for reinforced responding and that subsequently the presence of the drug reinstates responding by re-establishing those stimulus conditions. If this interpretation is correct then it would be expected that priming infusions of drugs with stimulus properties similar to those of cocaine would also effectively reinstate responding.

The stimulus properties of different drugs have been extensively studied in the drug discrimination paradigm (Colpaert et al. 1979). Amphetamine has been shown to have stimulus properties that are highly similar to cocaine (Silverman and Ho 1977). Both of these drugs are known to increase dopaminergic activity in the brain, although they do so by different mechanisms (Randrup and Munkvad 1966; Glowinski and Baldessarini 1966; Carr and Moore 1969; Ross and Renyi 1967). The dopamine receptor agonist apomorphine also leads to cocaine controlled responding in the drug discrimination paradigm (Ho and Silverman 1978; Colpaert et al. 1979). Thus, on the basis of both the similarity of the stimulus properties of these three drugs and the similarity in their sites of central action (insofar as they act on the dopaminergic system) it was expected that both amphetamine and apomorphine would be effective in the reinstatement of previously cocaine-reinforced responding in the present experiment.

The four other psychoactive drugs tested in this experiment were chosen partly because of their dissimilarity to cocaine. The narcotic drug morphine produced poor generalization when tested in rats trained on a cocaine-saline discrimination (Colpaert et al. 1979). The action of narcotic analgesics on the dopaminergic system is not understood; they have been labelled as both antagonists (Lal 1977) and agonists (Colpaert et al. 1976), or both (Joyce and Iverson 1979). Heroin has not been specifically tested in the drug discrimination paradigm with rats but its subjective effects in humans are known to be highly similar to the effects of morphine (Martin and Fraser 1961) and its central mechanism of action is thought to be the same as morphine (Goodman and Gilman 1975, p 249). Good reinstatement of responding in the present experiment was not expected with either morphine or heroin. Finally, neither ethanol (Rawat 1976) nor the short-acting barbiturate methohexital (Goodman and Gilman 1975, p 101) have a direct effect on dopaminergic activity. These drugs have not been specifically tested in rats trained with a cocaine cue, but neither animals trained on ethanol-saline discriminations nor animals trained on pentobarbital-saline discriminations show generalization to amphetamine (Silverman and Ho 1977). The stimulus properties of drugs from these diverse classes appear to be dissimilar.

While the stimulus properties of morphine, heroin, ethanol, and methohexital do not appear to resemble the stimulus properties of cocaine, all these drugs do have in common the property of being self-administered by laboratory animals (e.g., van Ree and de Wied 1977; Collins et al. 1978; Smith et al. 1975). The interesting possibility existed that it was the reinforcing property, in particular, rather than the similarity in any other discriminable stimulus properties that was importantly involved in the drug-induced reinstatement of responding after extinction. This possibility was addressed by testing these drugs that are self-administered but whose stimulus properties are different from cocaine.

Materials and Methods

Subjects. Fifteen male Sprague-Dawley rats were used in this experiment of which all but four had been trained to lever press for food reinforcement before catheterization. Twelve animals had been tested in earlier experiments described here before being tested in this experiment.

Apparatus. The five operant chambers described in Experiment 1 were used. In addition, four other boxes of slightly different design were also used. These were noncommercially-made boxes (25 cm × 25 cm × 30 cm) two of which were constructed from aluminium and two from plywood, all with a plexiglass front and top. The boxes were fitted with infusion systems as described in Experiment 1, and Gerbrands levers (4.5 cm long and 1 cm wide) mounted in the center of the back wall, 7 cm from the grid floor. For sound attenuation purposes the boxes were housed in individual refrigerator cases; each was equipped with a ventilating fan and each had a 7.5 cm speaker mounted on an inside wall of the refrigerator above the rat chamber.

Drugs. The drugs used were *d*-amphetamine sulphate (Smith, Kline and French Canada, Mississauga, Ontario), apomorphine HCl (F.E. Cornell, Montreal), diacetylmorphine HCl (heroin) (Health and Welfare Canada), morphine sulphate (BDH Chemicals, Toronto), and the short-acting barbiturate methohexital sodium (Eli Lilly, Scarborough, Ontario). Amphetamine, morphine, and heroin were dissolved in physiological saline with 5 IU/ml heparin and used within 1 week of preparation; apomorphine was freshly prepared on each day of use, and methohexital was commercially prepared in solution form.

Procedure. Animals were trained to self-administer cocaine as in previous experiments. Test sessions began when responding was stable and reliable. Each test session consisted of 1 – 2 h of stable cocaine self-administration followed by extinction introduced by saline substitution. At the beginning of the extinction period, the syringe containing cocaine solution was replaced by a syringe containing physiological saline. The

Table 1. Median latency and median number of responses made after each of the test drugs used in Experiment 3

Drug	Dose	Animals	Duration of post-prime period (s)	Median latency (s)	Median responses
Amphetamine	0.1 mg/kg	5	180	150	1
	0.3 mg/kg	5	180	15	5
	1.0 mg/kg	5	180	8	35
	2.0 mg/kg	4	180	47	56
Saline	–	9	180	180	0
Apomorphine	0.0625 mg/kg	9	60	15	2
	0.125 mg/kg	9	60	12	6
	0.25	9	60	20	2
	0.5 mg/kg	9	60	30	2
Saline	–	9	60	60	0
Morphine	0.3 mg/kg	9	180	180	0
	1.0 mg/kg	9	180	65	2
	3.0 mg/kg	9	180	100	2
Saline	–	9	180	180	0
Heroin	50 μg/kg	2	180	180	0
	100 μg/kg	2	180	180	0
	200 μg/kg	6	180	108	4.3
Saline	–	6	180	135	1.5
ETOH	1.0 mg/kg	5	30	30	0
	3.0 mg/kg	5	30	30	0
	10.0 mg/kg	5	30	30	0
Methohexital	1.0 mg/kg	2	60	60	0
	2.0 mg/kg	2	60	60	0

infusion tubing was flushed with saline from the syringe to the top of the swivel, leaving cocaine solution in the infusion tubing from the top of the swivel to the point of entry into the rat's vein. The remaining cocaine solution was delivered to the rat with the first two or three response-produced infusions after saline substitution, and following this all responses produced only saline infusions. When extinction responding had ceased for 30 min a saline injection was slowly infused manually into the system from the top of the swivel. This saline injection ensured that the drug solution was thoroughly cleared from the infusion tubing and catheter. Thirty minutes later, rats were given either a second saline injection or an infusion of one of the following drugs:

Amphetamine (0.1, 0.3, 1.0 or 2.0 mg/kg)
Apomorphine (0.0625, 0.125, 0.25 or 0.5 mg/kg)
Ethanol (1, 3 or 10 mg/kg)
Heroin (50, 100 or 200 μg/kg)
Methohexital (1 or 2 mg/kg)
Morphine (0.3, 1.0 or 3.0 mg/kg).

Drugs were injected in a volume of 0.1 – 0.4 ml over a 5-s infusion duration, and were followed immediately by a 0.3 ml saline infusion to flush the drug through the infusion system and catheter. All animals were tested only once at each dose of each drug. The order of doses tested was counterbalanced for all the drugs except for morphine, in which case the tests were in order of ascending doses (to minimize the possibility of residual drug effects on the subsequent test day). Different doses of each drug were tested on consecutive days whenever possible, and a saline control test day was always given between tests with different drugs. Each animal was tested on as many drugs as catheter life allowed, and the order of drugs tested varied from animal to animal. Individual animals were tested on all doses of a particular drug as well as the appropriate saline control test. The only exception was the case of the 2.0 mg/kg amphetamine test, for which a separate group of four animals was used. (These animals were tested after completion of the initial dose-response determination in order to extend the dose range.) Saline control data were also collected on these four animals. The duration of the post-injection test period varied with the different drugs tested. The actual test periods chosen were determined by observation of the animals during pilot tests and by consideration of the duration of pharmacological action of the test drug. Drug doses were selected so that a dose known to be self-administered by rats (when applicable) fell roughly in the middle of the range of doses tested. The self-administered dose was in all cases well above the dose producing discriminable stimulus effects in drug discrimination experiments (see Colpaert and Rosecrans 1978).

Results and Discussion

Median latencies to the first response and median number of responses in the period following the priming infusions for all drugs tested are presented in Table 1.

Amphetamine produced a clear reinstatement of responding at three of the four doses tested. Analysis of variance performed on the latencies to the first response (excluding the highest dose, see Method) yielded a significant effect of drug treatment [$F(3,12) = 12.07$, $P < 0.01$].

The patterns of responding over the 3-h test period for the 1.0 and 2.0 mg/kg doses are illustrated in Fig. 3. At the 1.0 mg/kg dose there was a large increase in rate in the first 30 min, followed by a gradual decline in responding throughout the 3-h test period. At the highest dose tested (2.0 mg/kg) there was some responding in the first 30 min, but the peak in response rate occurred only in the final 30-min period of the

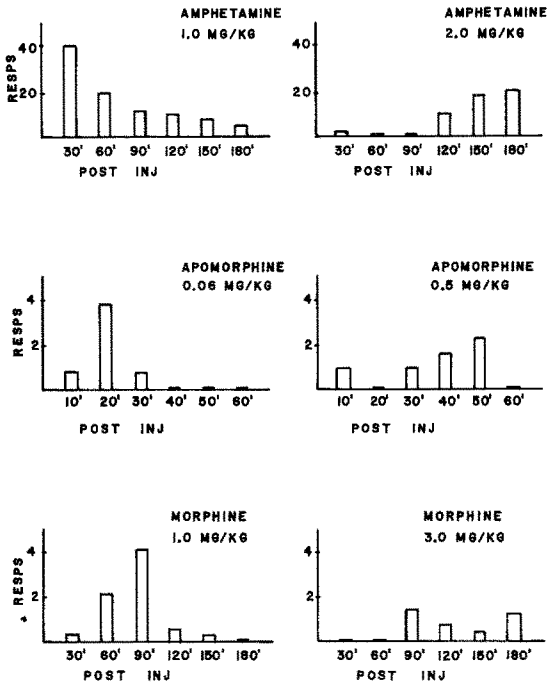

Fig. 3. Mean number of responses after infusions of a low and a higher dose of amphetamine, apomorphine, and morphine, given during extinction after a period of cocaine self-administration. Responding after lower doses occurred sooner after the priming infusion than the responding produced by higher doses

test period, almost 3 h after the drug infusion. When the number of responses after different doses of amphetamine was analyzed across the six consecutive 30-min time periods in an analysis of variance, there was a significant time effect [$F(5,20) = 3.36$, $P < 0.05$] and a significant interaction between drug dose and time [$F(15,60) = 2.17$, $P < 0.05$]. Observation of the animals after the highest doses of amphetamine revealed that a great deal of stereotyped behavior (vigorous sniffing and vertical head movements) occurred during the period of low responding 60 – 90 min after the infusion.

Apomorphine produced some reinstatement of responding at all doses tested (Table 1). It can be seen from Fig. 3 that there was an effect of dose on the time course of responding. At the 0.0625 mg/kg dose, the highest response rate occurred shortly after the drug infusion, whereas at the 0.5 mg/kg dose the highest rate occurred later in the test period. At the three highest doses, stereotyped behavior was observed during the period of low responding that followed the drug infusion. An analysis of variance carried out on the latency scores yielded a significant drug effect [$F(4,28) = 5.33$, $P < 0.01$]; in the case of the response frequency measure, the drug effect was not significant [$F(4,28) = 1.67$, $P > 0.10$].

The two highest doses of morphine tested produced some reinstatement of responding during extinction (Table 1). Analyses of variance carried out on the latency scores and the number of responses yielded significant drug effects [$F(3,24) = 3.63$, $P < 0.05$ and $F(3,24) = 3.65$, $P < 0.05$, respectively]. It can be seen from Fig. 3 that the time course of the response-enhancing effect varied with the dose of morphine administered. At the 1.0 mg/kg dose the increase in responding occurred at 60 min after the infusion, whereas at the highest dose (3.0 mg/kg) the increased responding occurred later in the test period.

Thus, with all three of these test drugs, amphetamine, apomorphine and morphine, there was a dose-related enhancement of responding after priming infusions. In all three cases the lowest effective dose of the drug produced responding with a shorter latency than the higher doses of the drug. While the overall time-course of the response-enhancing effects varied with the drugs, the dose-dependent temporal distribution of responding was the same. This pattern was the same as that seen across a range of cocaine doses tested in earlier experiments. After low dose infusions, the drug has an immediate effect on responding, whereas after higher priming doses there is a period of low responding immediately after the drug infusion, just as there is a period of low responding after a high dose of self-administered drug. It is as though responding is suppressed by high blood levels of drug and is then initiated as levels fall below a certain point.

The particularly long latencies seen after morphine in this paradigm also suggest a possible explanation for some conflicting results in drug discrimination generalization tests between morphine and stimulant drugs (see Colpaert et al. 1979; Ando and Yanagita 1978). While morphine is usually thought to have a predominantly depressant effect, there is also evidence that it has a later excitatory effect (Kumar et al. 1971; Holtzman 1976; Oka and Hosoya 1976). It might be during this latter excitatory phase that the stimulus properties of morphine resemble those of cocaine, thereby eliciting responding in this paradigm. In the typical drug discrimination experiments, the test drug is injected intraperitoneally 30 min before testing, and, therefore, animals are tested when the depressant effects of morphine predominate. It seems likely that it is only during the later excitatory phase that morphine produces a stimulus that is similar to cocaine. Ando and Yanagita (1978) have recently reported that monkeys trained on a cocaine/saline discrimination do show generalization to morphine when the drugs are administered by the intravenous route. Their results, taken together with the results from the present experiment, suggest that at least some aspect of the stimulus properties of intravenously-administered morphine resembles the effects of cocaine.

Table 1 shows that ethanol, heroin, and methohexital had little or no effect on responding during extinction.

While the highest dose of heroin tested (200 µg/kg) appeared to elicit some responding, the rates were comparable to rates seen after saline control tests in those animals. More importantly, the responding that did occur was distributed across the entire 180 min post-prime period suggesting that responding was not drug-induced. In view of the results with morphine reinstatement just described, the negative results with heroin injections are puzzling. Morphine and heroin are believed to act by the same mechanism (Goodman and Gilman 1975, p 249), and at least in humans, the subjective effects of heroin and morphine are reportedly so similar as to be often difficult to discriminate (Martin and Fraser 1961). One possible reason for the failure to find reinstatement with heroin is that the doses tried were simply too small. The lack of reinstatement after injections of ethanol and methohexital was expected on the basis of the demonstrated dissimilarity between these drugs and stimulant drugs in tests of drug discrimination, and the absence of shared central mechanisms of action.

The possibility that all self-administered drugs share some common positively reinforcing property that would be sufficiently similar to reinstate previously drug-reinforced responding based on any one of them is made unlikely by these

results. Methohexital (Pickens et al. 1981) and heroin (Van Ree and de Wied 1977), are both readily self-administered by rats at the doses tested in this paradigm, and yet they were ineffective in restoring responding in this experiment. Ethanol is also self-administered intravenously (Smith et al. 1975), and yet did not influence the tendency to respond in the present experiment.

It can be concluded from Experiment 3 that other psychoactive drugs reinstate cocaine-reinforced responding after extinction if their stimulus properties resemble those of cocaine. This supports the hypothesis that priming infusions given during extinction elicit responding to the extent that they reestablish the stimulus conditions that are present during drug self-administration.

Finally, it should be noted that one of the primary pharmacological effects of cocaine is its stimulant or excitatory effect on the animal. It might be argued, therefore, that general excitation of the animal is accompanied by an indiscriminate increase of all prepotent behaviors (including previously reinforced bar pressing) (see Hill 1970), or that it may simply increase "accidental" bar presses resulting from greater physical activity in the chamber. The facilitation of responding observed in the foregoing experiments may thus have been unrelated to the discriminable stimulus properties of the drug stimulus per se, but rather to these more general effects. This alternative explanation of the priming effects was addressed in a control experiment.

A group of rats was trained to bar press for food reinforcement. The animals were subsequently catheterized so that intravenous drug injections could be given them while they were bar pressing for food. After a period of no food-related responding, comparable to the period used in Experiment 3, these animals were given infusions of cocaine, amphetamine, or morphine. Reinstatement of responding after the drug infusions in these animals would have pointed to a general activity effect or a general enhancement of the effectiveness of conditioned stimuli by these drugs. None of these drugs produced any more responding in these animals than saline control infusions.

There were several methodological differences between this "control" experiment and the experiment showing reinstatement. The animals' drug histories at the time of test, the durations of their acquisition and extinction periods, their baseline rates of responding during acquisition, and the environments in which acquisition and extinction took place all differed in this experiment. While it might be argued that any of these methodological differences could account for the failure of the drugs to enhance responding in these food-trained animals, the present experiment was considered at least a preliminary test of the specificity of the drug-induced reinstatement phenomenon to animals trained to bar press with drugs as reinforcers. As a further control for general activity effects, a number of animals were tested in chambers with a second, inoperative, lever. Responding on this second lever consistently remained at low levels after priming drug infusions.

Experiment 4

This experiment was designed to determine whether stimuli associated with reinforcing cocaine infusions would in themselves increase the tendency to reinitiate responding during extinction. Two groups of animals were trained to self-administer cocaine on a variable ratio (VR6) schedule: one group received a tone simultaneously with each reinforcing drug infusion throughout training, while the other group received the tone but not specifically related to drug reinforcement delivery. On test sessions the tone was presented after a period of extinction, and the group that had had correlated presentations of the tone and drug was expected to be more likely to return to bar pressing than the group for which tone and drug presentation were uncorrelated.

Materials and Methods

Subjects. Nineteen male Sprague-Dawley rats weighing 300–350 g upon arrival were used. They were food deprived to 85% of their free-feeding body weight during the initial food-reinforcement training phase of the experiment.

Apparatus. The four operant chambers housed in the refrigerators (described in Experiment 3) were used in this experiment. The tone to be used as conditioned stimulus in this experiment was an intermittent (1 s on, 1 s off), 60 db, 6000 cps tone operated by the timer that controlled the drugs infusion.

Procedure. The animals were first trained to lever press for food reinforcement on a variable ratio (VR6) schedule of reinforcement, and were then allowed to return to free-feeding weight before being implanted with intravenous catheters. After recovery from surgery, self-administration training began. The first 2 days of self-administration training, during which animals received a 1 mg/kg cocaine infusion for each lever press, proceeded without presentation of any tones. After this, 12 of the animals (correlated group) received a tone concurrently with every response-produced drug infusion. The duration of the infusion and the tone was between 11 and 13 s depending on the animal's weight. There was a 2–3-s delay between the time the syringe pump was turned on and the time the animal experienced the drug effect as judged by observable orienting and startle responses. This delay was due in part to the inertia in the infusion system and possibly also to the time required for the drug to be carried in the blood circulation from the point of entry in the vein to the brain. Thus it was assumed that the tone preceded the perceptible drug stimulus by 2–3 s. The other seven animals (uncorrelated group) received the tone at times not related to their drug infusions; the tones for these animals were "yoked" to the infusions of another rat. All animals were given seven daily 2–3-h sessions of self-administration training during which each press delivered a drug infusion followed by a further 14 sessions on a variable ratio (VR6) schedule of reinforcement.

After 2 weeks of stable responding, three consecutive daily test sessions were given, each consisting of a 1–2-h self-administration period followed by a period of extinction (by syringe pump disconnection) with no tone presentations. When responding during extinction had ceased, a criterion period of 30 min with no responses was allowed to pass before one of the following three events was presented: a 1 mg/kg cocaine infusion, the tone, or no event. The latency to respond and the number of responses in the subsequent 30-min period were recorded. After a further period of 30 min with no responses, one of the remaining events was presented and the latency and the number of responses in the following 30 min were recorded. Finally, after another 30 min of no responses the third event was tested. The order of presentation of these events was counterbalanced.

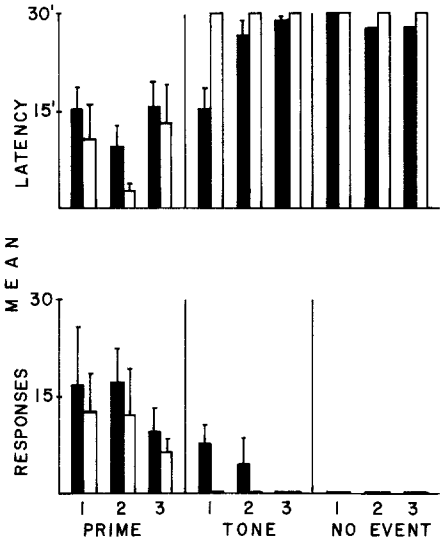

Fig. 4. Mean latencies to first response (upper graph) and mean number of responses (lower graph) after each of three tests (on 3 separate days) with the priming cocaine injection (1 mg/kg), the tone, and no event, presented during extinction after a cocaine self-administration session. Responses were recorded for the 30-min period following each of these events, and a period of 30 min with no responses was allowed to pass before another event was presented. These means are based on only those animals meeting the criterion of making a response on at least one of the priming tests and responding after not more than one of the no event tests. Filled bars refer to the correlated group ($N = 10$) and open bars refer to the uncorrelated group ($N = 4$); standard errors of the means are indicated

Results and Discussion

Animals from both the correlated and the uncorrelated groups responded after the priming injection on most occasions across the three tests (72% and 66% of the priming drug injections were followed by at least one response for the correlated and uncorrelated groups respectively). Following presentation of the tone, 66% of the animals in the correlated condition responded on the first trial, whereas only 28% of the uncorrelated group responded after the first presentation of the tone. However, on the subsequent two presentations of the tone, very few animals from either group responded (correlated group: 16% and uncorrelated group: 14%). Few animals from either group responded after no event (13% correlated and 19% of the uncorrelated). Inspection of results from individual animals revealed that some animals from both groups responded repeatedly after no event, and certain other animals did not respond at all after the priming infusions. Because the results from these animals are difficult to interpret, the data from only those animals making a response on at least one of the priming tests and responding on no more than one of the no event tests were included in the calculation of the group means (Fig. 4). For the animals from the correlated group that met these criteria ($N = 10$), there was a significant difference between the mean number of responses after the tone and after no event on the first day of testing ($\bar{x} = 7.3$ and 0 responses, respectively; $t(9) = 2.35$, $P < 0.05$). Four animals from the uncorrelated group met these criteria, and of these none responded on the first test day after either the tone or no event. Thus at least on the first test day, the tone elicited responding in the animals in the correlated group and did not alter responding in the animals with uncorrelated experience with the tone and drug infusions.

Experiment 4 showed that a stimulus that had been associated with cocaine infusions transiently increased the tendency to reinitiate responding during extinction; on the first but not the subsequent two tests, there was a greater tendency to respond after tone presentations than after no event. This was true only for the group that had had experience with correlated presentations of the tone and drug infusions. The results therefore partially confirmed the experimental hypothesis in that the effect occurred, but it was not anticipated that the effect would appear only on the first of the three test trials.

It is possible that only minimal conditioning occurred in this experiment because of some aspect of the conditioning situation such as the perceptual modality of the conditioned stimulus or the temporal parameters of the onset and offset of the conditioned stimulus relative to the drug stimulus onset and decay. Ideally a more easily measured conditioned response should be monitored concurrently during training to confirm the development of conditioning. Another possible reason for the precipitous extinction of the conditioned response is that the overall stimulus conditions during the test sessions differed radically from the conditions on training days due to the introduction of extinction conditions during operant responding. This might be avoided in future experiments by giving the animals previous experience with extinction conditions.

These results contribute in two ways to our understanding of how conditioned stimuli can affect drug-seeking behavior. One of these concerns the use of a stimulant drug as the reinforcer. Much of the research and discussion about the role of conditioned drug effects in relapse has involved the use of withdrawal-producing opiate drugs. As a result of this, one of the major points of issue has been whether the conditioned response to drug-related stimuli is an opponent, withdrawal-like response that leads the animal to seek drug to escape from an aversive state, or whether it is rather a positive drug-like conditioned effect (O'Brien 1976; Wikler 1965). Leaving aside the question of whether animals respond even for opiates in order to avoid withdrawal, the idea of a conditioned withdrawal-like effect with stimulant drugs is unlikely because of the notable absence of any aversive after effects of stimulant drugs. Rather, it seems more likely that the conditioned stimulus, at least in these experiments, acquires some of the positively reinforcing properties of the unconditioned stimulus, and elicits responding more by acting as a "reminder".

A second mechanism that has been proposed for the control of responding by environmental stimuli is that the stimuli come to act as discriminative stimuli that "set the occasion" for an operant response. This account requires, however, that the stimulus has consistently preceded the operant response and has acted as a signal to make a response. This was not the case in this experiment, for the correlated group the tone came on only after emission of the response that produced the reinforcement. In fact, the conditions were optimal for the tone to act as a stimulus not to respond because when the tone came on no further responses were necessary and reinforcement was imminent. A record was kept during self-administration training of the number of responses emitted during the tone and infusion, and most well-trained animals stopped responding when the tone began. It is often ignored that embedded in the procedure for

the establishment of a discriminative stimulus are the conditions necessary for the establishment of a classically conditioned effect. Both classically conditioned stimuli and, in the well-trained animal, discriminative stimuli, predict reinforcement delivery. Although in this experiment the tone-drug pairings were response-produced, the tone was a better predictor of reinforcement than the animals' response; on the average only one response in six was followed by drug on the partial reinforcement schedule, VR6, used, whereas the tone was consistently followed by drug. Thus the conditions were optimal for the development of the tone as a classically conditioned stimulus. It is likely, therefore, that in this experiment the tone elicited responding during extinction because it had acquired positive incentive properties by the processes of classical conditioning.

General Discussion

The question of how, in terms of mechanisms of learning and performance, the priming infusion of a drug exerts its control over responding in self-administration-experienced animals is not resolved by these experiments. Nevertheless, several aspects of the results may be relevant. One possible account of the reinstatement of responding is that the drug stimulus acquires "discriminative stimulus control" over responding. By this account a stimulus that has been present when responses are reinforced subsequently "evokes" the response. While on first glance this notion constitutes a satisfactory explanation, it has been argued (e.g., Bindra 1974) that the notion of a direct connection between a stimulus and the emission of a motor response is an oversimplification and is not supported by existing data. The absence of a direct connection between stimulus and response was apparent in these experiments. During normal drug self-administration there are long periods of time between responses during which the drug stimulus is present and no responses are emitted. It could be argued that only one critical blood level of drug (the level that immediately precedes the next response during self-administration) provides the cue for a response. This still leaves the problem, however, of accounting for the continued emission of responses during extinction and after priming infusions; animals continue to respond throughout a range of blood levels of drug that they have probably never experienced during self-administration. Thus there does not appear to be a direct connection between the stimulus produced by a particular blood level of drug and the emission of a motor response.

A further aspect of the data from the priming experiments argues against the interpretation of the discriminative stimulus control over behavior. A number of animals in these experiments had been subjects in several of the experiments, and were consequently exposed to up to 80 daily test sessions, each involving the same sequence of a period of self-administration followed by extinction conditions and a priming drug infusion some time during extinction. In spite of the fact that after the initial self-administration period no further responses were reinforced, and in particular responses after priming infusions were never reinforced, these animals continued to show strong response facilitation after priming infusions over repeated test sessions. On the basis of purely informational value of the priming drug infusions given during extinction, it would have been expected that these animals would learn to discriminate the drug stimulus when it occurred during self-administration from the drug when it was given during extinction (priming infusion), and would cease to respond after the priming infusion after a number of test sessions. Rather, their persistence of responding argues for a motivational interpretation of the facilitation of responding.

The finding that priming injections of both the self-administered drug and other drugs with similar stimulus properties could instigate or facilitate responding during extinction in rats trained to self-administer can be related to the phenomenon of relapse in human ex-addicts. The idea that ingestion of a formerly abused drug induces a strong motivational state or "craving" for the drug and that it retains the ability to do this over an indefinite period of abstinence from the drug is not new. It has been incorporated as one of the basic tenets of Alcoholics Anonymous (Anonymous 1939) that people who have at one time shown uncontrolled drinking and physical dependence are permanently unable to drink moderately; one drink is said to elicit an urge to have another. While this principle has been seriously questioned (Sobell and Sobell 1978) there is some experimental evidence for such a phenomenon in humans (Hodgson et al. 1979).

An interesting example of the "priming" effect in human drug use comes from a recent study (Meyer and Mirin 1979) of patterns of heroin self-administration in hospitalized ex-heroin addicts. Ratings of craving for the drug were taken before and after heroin intake in subjects free to self-administer a fixed dose of heroin when they wanted it. Surprisingly, the subjects reported only a very modest decrease in craving from immediately before to after heroin ingestion, and levels of craving during heroin self-administration never fell to levels as low as in drug-free periods (Meyer and Mirin 1979, p 73). It is possible that drug circulating in the blood acted as a "priming" stimulus maintaining the desire for more drug. We have recently completed a series of "priming" experiments in rats trained to self-administer heroin. The results parallel to a remarkable degree those reported with cocaine in the present paper. The fact that priming injections of opiates reinstate opiate self-administration just as priming injections of stimulants reinstate stimulant self-administration is, we feel, of significance for an understanding of relapse behavior.

The last experiment in the present investigation provided some experimental support for the idea that classically conditioned environmental stimuli associated with drug injections might facilitate the reinitiation of drug-taking behavior. This idea has been considered in the context of relapse to drug use in the human ex-addicts but has not received systematic experimental attention. One of the findings of the Meyer and Mirin (1979) study that relates to the role of environmental stimuli in drug-taking behavior was that the most powerful stimulus for eliciting craving in their subjects was the signal that drug was available. Subjects maintained reasonably low interest in drugs and low levels of reported craving as long as drug was unavailable, or in some cases, when the effectiveness of heroin was blocked by an opiate antagonist, naltrexone. As soon as the drug became available and for as long as it remained available the ratings of cravings were high. This finding suggests that craving and drug-seeking behavior are related to stimuli (or events) associated with drug availability. Our understanding of exactly how these stimuli initiate these feelings and gain control over behavior awaits further research. The exact nature of classically conditioned drug effects in both animals

and humans is being examined in several research laboratories (e.g., O'Brien 1976; Sideroff and Jarvik 1977; Eikelboom and Stewart 1979), and their possible role in drug-taking behavior, in particular in relapse, may soon be elucidated.

Acknowledgements. This research was supported by a grant from the Medical Research Council of Canada (MA 6678) awarded to Jane Stewart. Harriet de Wit was supported by a pre-doctoral fellowship from the Ministère de l'Education du Québec. The authors wish to acknowledge the expert technical assistance of Carol Washer and the helpful suggestions of Gary Gerber.

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Received November 3, 1980; Final version May 25, 1981