REINSTATEMENT OF COCAINE-REINFORCED RESPONDING IN THE RAT

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ABSTRACT

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The reinitiation of drug-taking behavior after a drug-free period was studied in rats. A series of experiments are presented that were designed to examine the effect of non-contingent "priming" drug injections and conditioned stimuli associated with drug injections on the tendency to reinitiate responding during extinction. Rats implanted with intravenous catheters were trained to self-administer cocaine hydrochloride (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. The reinstatement of responding was measured by the latency to the first response and the total number of responses following the treatment. The first experiments demonstrated that cocaine injections between 0.25 and 4.0 mg/kg effectively restored responding during extinction, and that they did so regardless of the duration of the extinction period (between 10 minutes and

180 minutes) intervening since drug self-administration. Further experiments showed that amphetamine, apomorphine and morphine but not ethanol, heroin or methohexital produced reinstatement of previously cocaine-reinforced responding. These results with other drugs are interpretable in terms of the degree of similarity of the stimulus properties of the test drugs to the self-administered drug, cocaine. Neither amphetamine, cocaine, nor morphine increased 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. These experiments show that the stimulus properties of drugs can come to influence the animals' tendency to respond for these drugs as reinforcers, and that, to a lesser extent, conditioned stimuli associated with the drugs can also increase the likelihood of reinitiation of responding during extinction.

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Introduction

The widespread use of drugs for non-medical purposes has created serious social and medical problems. Our understanding of the factors involved in the initiation and maintenance of drug-taking remains poor, although various theoretical accounts have been postulated. The early theories (e.g., Lindesmith, 1947; Wikler, 1948; Weeks & Collins, 1964) stemmed from the fact that narcotic drugs produce aversive withdrawal effects upon discontinuation of use (Haertzen & Hooks, 1969). The idea is that these drugs, once consumed, produce physical dependence. After the initial ingestion the person "needs" further drug to relieve or avoid the considerable discomfort of withdrawal. This idea continues to influence thinking despite its repeated failure to gain support when submitted to experimental test (see, for example, a review by Grabowski & O'Brien, Note 1). While the avoidance of withdrawal may contribute to drug use, it fails to account for important features of drug-seeking behavior. A major problem for this view is that physical dependence is not necessary for drugs to be sought and ingested (Deneau, Yanagita & Seevers, 1969; Woods & Schuster, 1971; Pickens & Harris, 1968). One striking example of this is in the phenomenon of

relapse. Ex-drug users frequently revert to drug-taking after long periods of abstinence from the drug when the physical symptoms brought about by withdrawal are no longer present. Furthermore, while the model was originally proposed for opiate drugs which do produce aversive effects when withdrawn, it has been loosely applied to the use of other drugs, including stimulant drugs, which do not produce any appreciable withdrawal symptoms (Kalant, LeBlanc & Gibbins, 1971). Thus the avoidance of withdrawal model fails to explain both the relapse to the use of narcotics and the use of drugs that do not produce aversive withdrawal effects. An alternative account for drug-seeking behavior is that it is the euphoric effect of the psychoactive drugs that controls behavior. This idea is not inconsistent with clinical data on human drug-taking behavior, and has gained considerable experimental support from the study of the maintenance of drug self-administration by animals. A common sense view of this idea is that drugs, once experienced, are sought for their remembered pleasurable effects and when taken can, like food, act to "whet the appetite" for more. In addition it is thought that stimuli that predict the occurrence of drugs would gain positive properties through their association with them. These ideas would appear to be relevant to the

understanding of the phenomenon of relapse and of the initiation of craving, but have been neither precisely formulated nor put to experimental test.

This thesis represents an attempt to explore an aspect of these ideas by studying the reinitiation of drug-taking behavior in animals that have ceased to self-administer drugs. The effectiveness of unexpected non-response-contingent drug infusions and of unexpected presentations of drug-associated conditioned stimuli in eliciting the reinitiation of responding for cocaine hydrochloride was studied in rats. The data to be presented support the view that the stimulus properties produced by the direct pharmacological effect of drugs, as well as the environmental stimuli associated with them, have the power to re-instigate drug-seeking behavior as well as to maintain it in self-administration-experienced animals. The experiments demonstrate that quantitative relations exist between the dose of drugs and the "priming" effects they have on the initiation of previously learned drug-seeking behavior. Furthermore, these priming effects generalize to drugs other than the one originally self-administered in a way that might be predicted from what is known of their stimulus and pharmacological properties. It will be argued that

only through the investigation of these instigational properties of drugs and of the environmental stimuli associated with them will an understanding of the control of behavior by drugs be found.

Stimulant Drugs as Positive Reinforcers

Laboratory animals, including rats, cats, dogs, rabbits, rhesus and squirrel monkeys, and baboons self-administer a variety of stimulant drugs, such as d- and l-amphetamine, cocaine, phenmetrazine, and methylphenidate (see reviews by Spealman & Goldberg, 1978; Griffiths, Brady & Bradford, 1979). The acquisition and maintenance of the self-administration of these drugs appear to be the result of their positive reinforcing properties. When stimulant drugs are used as reinforcers the patterns of responding seen during acquisition, extinction, and under complex schedule control closely resemble the patterns of responding seen when conventional positive reinforcers such as food and water are used (Spealman & Goldberg, 1978). Moreover, injections of stimulant drugs share with conventional reinforcers the ability to establish conditioned reinforcers when they are repeatedly paired with initially neutral stimuli (Davis & Smith, 1974).

While the positive reinforcing property of stimulants does support patterns of behavior closely

resembling the patterns maintained by conventional reinforcers such as food and water, there remains an apparent difference in the pre-conditions under which the two types of reinforcer are effective. The ability of food (or water) to act as a reinforcer is generally believed to depend on the presence of a specific internal state, or condition of deprivation, that can be induced experimentally by withholding the appropriate reinforcer for some period of time. This deprivation induces a predictable change in the animal's physiological state over time, which, in turn, produces a specific predisposition in the animal to respond preferentially to those stimuli associated with the relevant reinforcer. While food deprivation is a technique routinely used to ensure reliable initiation of food-reinforced responding during operant sessions, such a simple experimental manipulation is not available with many other reinforcers, including stimulant drug reinforcement. The question of what factors control the initiation of responding in an animal in a "non-deprived" state can be asked in the context of stimulant drug reinforcement.

Self-Administration of Cocaine by Laboratory Animals

A brief description of the pattern of responding typically seen when cocaine injections are used as reinforcement will clarify some of the features of

stimulant drug self-administration. When rats are presented with a large intravenous dose (1 mg/kg/injection) of cocaine each time they respond on a lever, they typically respond at a very low rate (6 to 8 responses per hour) and at very regular intervals (Dougherty, 1973). At these doses there is an almost linear inverse relation between the dose of the drug self-administered and the rate of responding, such that, when the dose per injection is increased, the inter-response times are proportionately increased, and vice versa (Pickens & Thompson, 1968; Woods & Schuster, 1968; Dougherty & Pickens, 1976). The most parsimonious explanation for this widely spaced responding is to consider the animal drug "satiated" while its blood level of drug is above a certain point (Wilson, Hitomi & Schuster, 1971). That is, the high blood levels of drug inhibit responding without being either aversive or incapacitating; they simply make further drug deliveries non-reinforcing. When the metabolic breakdown of the drug brings the blood level below some critical point, the animal responds, restoring the level of drug in the blood. There is now considerable experimental support for this notion. Yokel and Pickens (1974) measured blood levels of d-amphetamine at the moment of response in self-administering rats, and found that the concentration of amphetamine in the blood was stable (0.18 µl/ml) at

the time of response across a range of self-administered doses per injection. When dose per injection is relatively small, rats typically show an initial burst of responding at the beginning of a session before the characteristic patterning with a dose-dependent regular post-reinforcement pause becomes evident. This initial burst is most pronounced with smaller doses per injection, as would be expected if a certain critical blood level of drug was to be reached and maintained (Dougherty & Pickens, 1976). Another line of evidence suggesting that blood level of drug is a critical factor comes from the report (Dougherty, 1973) that pretreatment with drugs that increase the rate of metabolic breakdown of amphetamine increases the rate of responding, and conversely, that drugs that slow down the catabolism of amphetamine correspondingly slow the rate of self-administration. Gerber and Wise (Note 2) have found that when rats are given variable doses of cocaine per infusion within a self-administration session on a continuous reinforcement schedule, their inter-response times vary directly with the magnitude of the preceding drug infusion. They also report that rates of responding are slowed proportionally when a continuous, low-dose infusion of cocaine is given in addition to the response-produced injections of cocaine during a

self-administration session, further suggesting that the blood level of drug determines the moment of response. The long pause after cocaine infusions might alternatively be attributed to a direct, debilitating effect of the drug that makes the animal unable to respond. This idea can be ruled out on the grounds that rats maintain high rates of responding during the inter-response times between stimulant drug infusions when brain stimulation reward is made available concurrently on a second lever. Normal drug-reinforced responding continues on the drug-associated lever and the animals respond at a high rate on the brain stimulation lever in the periods between drug infusions (Wise, Yokel, Hanssen & Gerber, 1977). It has also been suggested (Wilson, Hitomi & Schuster, 1971) that further responses after a large self-administered dose of stimulant drug may be inhibited by an aversive effect of the drug. While it seems reasonable to expect that sufficiently high doses of stimulants would produce aversive effects, there is little evidence to suggest that the doses of cocaine in the range typically self-administered produce appreciable aversive effects. If the long inter-response times were due to response-suppressant aversive effects, it might be expected that higher doses, which produce relatively longer inter-response times, would be relatively more

aversive than smaller doses. There is no evidence for such a relationship within the range of doses used here. Yokel (Note 3) gave rats a two-lever choice of two cocaine doses, and found no preference for lower (or higher) doses between 0.5 and 2.0 mg/kg/injection. In rhesus monkeys, reinforcement efficacy has actually been shown to increase with dose per injection of cocaine between 0.3 and 0.8 mg/kg/infusion as measured by the animals' preference on a two-lever concurrent variable interval schedule (Johanson, 1971; Llewllyn, Iglauer & Woods, 1976). Finally, Griffiths, Brady and Snell (1978) similarly found either no difference in reinforcement efficacy for different doses of cocaine, or a relative superiority for the higher doses when they tested baboons on a progressive ratio schedule. On this schedule progressively more responses are required of the animal for each successive reinforcement, and the point at which the animal stops responding is considered a measure of the reinforcer efficacy. Thus these alternative measures of the relative aversive or reinforcing effects of different doses of stimulant drugs provide no evidence that the blood levels of drug reached during drug self-administration are aversive. The long inter-response times seen during continuously available stimulant drug self-administration do not appear to be due to either

physically debilitating or aversive effects of the drug. Rather, as has been suggested by Yokel and Pickens (1974) and Yokel and Wise (1975) it appears to be due to the "satiating" effect of high blood levels of drug.

Reinitiation of Responding after Abstinence

The cycle of response suppression during drug satiation (immediately after a large dose infusion) followed by response enhancement some time later (as the blood level of drug falls) is somewhat analagous to the effects of food satiation and deprivation on responding for food reinforcement. However, this analogy fails to shed light on the factors controlling the initiation of drug-reinforced responding in the drug-free animal at a time when the effects of the previous drug injection cannot reasonably be said to be the controlling variable. Ordinary usage of the term deprivational state implies a change over time in the motivational state of the animal as a function of time without the reinforcer. This change in the animal's motivational state is characterized by an increased tendency to seek the withheld substance or to respond to stimuli associated with the reinforcer. It is particularly evident when responding is initiated in the absence of any external stimulus changes. Thus initiation of food-reinforced bar pressing in a rat some time after its last meal is an example of the development of a

specific motivational state, and similarly the reinitiation of drug-reinforced responding after a period of no responding during the post-reinforcement pause also indicates a specific disposition to respond for the drug reinforcer. With many traditional reinforcers such as food and water, continuing deprivation leads to an increasingly powerful motivational state. With other positive reinforcers, however, this relationship does not hold - it appears rather that the increased tendency to respond that is seen some time after the last reinforcement delivery dissipates with time in the absence of further reinforcement. Although experimental evidence for such a position is lacking, it seems likely that 'deprivation' of certain positive reinforcers such as saccharin solution or stimulant drugs produces only a transient change in the animal's motivational state, and that the alteration in the tendency to respond passes, making the notion of a long-term 'saccharin-deprived' or 'drug-deprived' animal meaningless. In the absence of an internal predisposing state (such as hunger or thirst), it seems likely that external environmental stimuli play the critical role in the control of the behavior. Indeed, the study of the initiation of responding for stimulant reinforcement provides a good model in which to study the control of behavior by conditioned environmental stimuli associated

with positive reinforcement, in the absence of a strong deprivational state. There is little question that environmental stimuli associated with food reinforcement can exert a strong influence on food-reinforced behaviors, even in apparently satiated animals, as documented by Morgan (1974) in his discussion of "resistance to satiation". However, certain definitional and methodological problems remain unresolved regarding the use of the concept of food satiation (Morgan, 1974) and it is difficult to examine the effects of conditioned stimuli independently of the animal's relative state of satiation or deprivation. Thus the study of the role of conditioned stimuli in the initiation of drug-reinforced responding in laboratory animals may further our understanding of the processes underlying the control of behavior by conditioned stimuli in general. It may also provide some insight into the role of environmental stimuli in the phenomenon of relapse to drug use in human ex-addicts.

A variety of informal techniques have been used in the drug self-administration laboratory to facilitate initiation of responding at the beginning of sessions. One technique commonly used is to give non-contingent "priming" injections of the self-administered drug to poorly responding rats. These priming injections

facilitate response initiation both during the initial acquisition of drug self-administration and subsequently at the beginning of daily self-administration sessions. Some of the parameters of the facilitation of responding after priming drug infusions will be examined in the present investigation. A second technique is to provide external cues correlated with the reinforcer, cues that may either signal the availability of the drug reinforcement contingent on a response (discriminative stimuli) or predict reinforcement delivery (Pavlovian conditioned stimuli). The final experiment reported here was designed to investigate the role of classically conditioned stimuli associated with reinforcement delivery in the reinitiation of drug-reinforced responding. A third technique that is used to facilitate response initiation is to food deprive the animals before the self-administration session (Carroll, France & Meisch, 1978). This effect will not be investigated in this thesis although it has interesting theoretical implications regarding the specificity of the response-enhancing effect of a deprivational state.

Priming Effects with Other Reinforcers

The enhancement of responding after non-contingent delivery of a reinforcer has been reported for several different reinforcers, including food and brain

stimulation rewards. Pavlov (1919) discussed the appetite-stimulating aftereffects of small quantities of food, pointing to the familiar phenomenon that "a person who at first displays indifference to his customary meal, afterwards begins to eat with gusto if his taste has been stimulated by something piquant" (p. 108). Konorski (1967) demonstrated the priming effect by offering a small portion of food to hungry dogs in an environment where they had never previously received food. While the dogs were initially impassive and calm before the presentation of food, they afterwards displayed a strong "hunger reflex" characterized by motor restlessness and increased attention to gustatory and olfactory stimuli. Konorski demonstrated the specificity of this priming effect by training dogs to perform two different movements, one for food reward and one for water reward. When the dogs were subsequently tested while both hungry and thirsty, a small quantity of food led to the food movement and water delivery led to the water movement. He suggested that there was a similar priming effect in humans, that of the so-called "peanut phenomenon" in which "one nut will arouse a selective appetite for eating another one" (Konorski, 1967, p. 20). Despite the familiarity of this phenomenon as illustrated by such anecdotal examples, surprisingly few experimental

studies have been undertaken to study it.

One laboratory example of such an effect is the local rate-enhancing effect of free food delivery in rats responding for food reinforcement (Deluty, 1976). Rats were trained to respond on a random interval (average of one minute) schedule for food pellets, and then additional food pellets were delivered non-contingently at fixed or random times. Immediately after non-contingent delivery of food there was an increase in response rate of 33% to 75% over baseline rates. One way to interpret these results might be in terms of the priming or response-enhancing aftereffects of free reinforcement delivery.

Another example of the response-facilitatory effect of free food delivery is the reinitiation of responding that is seen when free food pellets are given during extinction (Skinner, 1938; Reid, 1958; Eišerer, 1978). In Eiserer's (1978) experiment, rats were trained to bar press for food reinforcement under food deprivation conditions and allowed to feed freely before being tested in the extinction phase of the experiment. The animals were allowed to extinguish their bar pressing in the satiated condition, and when a period of two minutes occurred with no responses a free food pellet was delivered. Animals reinitiated responding within

one minute after the priming food delivery with a probability of .44 while the baseline probability of a response was only .19. Eiserer also scored the occurrence, following a free food delivery, of sub-threshold components of the bar-press response (e.g., rearing and orienting to the lever) in addition to counting successfully executed bar presses. Ninety percent of the priming food deliveries were followed by either a completed bar press or by a subthreshold component of the response, whereas the baseline occurrence of these responses was only 42%. It is noteworthy that the delivery of a food pellet retained its effectiveness in restoring responding even though the animals were tested while in a sated condition.

In another demonstration of the priming effect of free reinforcement during extinction, Panksepp and Trowill (1967) used intraorally-delivered chocolate milk as the reinforcer in rats that were either food deprived or not. Rats were prepared with fistulas to the mouth and were then trained to bar press for chocolate milk delivered intraorally. They were subsequently put under extinction conditions until their responding had ceased and then tested with two non-contingent reinforcement deliveries. Both the deprived and the non-deprived rats reinitiated responding after the priming delivery of

chocolate milk (83% and 71% of the animals in each group respectively responded).

While in each of these studies free reinforcement delivery resulted in an enhancement of responding, the basis of this priming effect is not clear. In both Eiserer's and Panksepp and Trowill's experiments, the schedule on which the animals had been trained was continuous reinforcement, in which a delivery of the reinforcer usually immediately precedes the next reinforced response. It has been argued (e.g., Reid, 1958) that under these circumstances each reinforcement delivery constitutes a discriminative stimulus that "sets the occasion" for the next response. The idea is that a stimulus in the presence of which behavior has been reinforced comes to directly evoke the motor response that led to the reinforcement. The existence of such a direct connection between stimulus and response has been questioned recently, and alternative conceptions that emphasize motivational changes in response to a predictive stimulus have been favoured (e.g., Bindra, 1969; Bolles, 1972). The increase in the vigour of responding that is seen after non-contingent food delivery may reflect a general phenomenon of motivational arousal that occurs after delivery of any reinforcer (Bindra, 1969). Stimuli that are associated with the

reinforcer can also acquire some of these motivationally arousing properties (Sheffield & Campbell, 1954; Bindra & Palfai, 1967). The question of whether the enhanced responding seen after free reinforcement delivery in the preceding experiments relates to the signalling function of the food delivery or rather to motivational changes following food delivery remains to be resolved by direct experimental test. (Such a test could be done, for instance, by training animals under conditions where food delivery does not consistently precede further reinforced responses, and hence cannot act as a discriminative stimulus for responding. Under these circumstances an enhancement of responding after a free reinforcement delivery would provide some support for the motivational interpretation.)

One of the most striking and the most thoroughly studied examples of the priming phenomenon is in the case of brain stimulation reward. Operant responding (e.g., bar pressing and runway running) for electrical stimulation of the brain is greatly facilitated by "priming" brain stimulation pulses delivered shortly before the opportunity to respond (Gallistel, 1973). Both the magnitude of the response facilitation and the rate of decay of the effect are directly related to the intensity of the priming stimulation. The brain

stimulation priming effect is so powerful that some theorists (e.g., Deutsch, 1960) have postulated that the initiation of self-stimulation behavior actually depends on the direct electrophysiological activation of a "drive" pathway by the priming (or immediately preceding) train of stimulation. A considerable amount of research has been undertaken concerning the question of whether the drive-inducing and reinforcing effects of brain stimulation reward are mediated by one or more neurophysiological systems. The resolution of this question may have important consequences for our understanding of the interactions between reward and motivation or drive in association with naturally-occurring reinforcers. From a strictly behavioral point of view, however, the data regarding the response-enhancing effects of non-contingent trains of brain stimulation are consistent with the data with conventional reinforcers and support the notion that non-contingent reinforcement delivery specifically enhances the tendency to respond to stimuli associated with that reinforcer at least for a short period of time.

Another reported phenomenon that bears a close resemblance to the priming effect is the "reactivation effect" discussed by Spear (1978) in the context of memory processes. This refers to the facilitation of performance of a previously learned task by presession

presentation of the unconditioned stimulus, usually after a retention interval of at least 24 hours. For example, the decrement in performance that is typically seen at the beginning of a daily session of operant responding ("warm-up decrement") can be largely eliminated by presentation of the reinforcer immediately prior to the session. This effect is particularly strong with aversive conditioning tasks such as avoidance or escape (Hoffman, Fleshler & Chorny, 1961), but has also been reported with appetitive conditioning (Spear, 1967; Reid, 1958). While it has been suggested that the reinforcer presentation facilitates performance by enhancing the animal's motivation (Hoffman, Fleshler & Chorny, 1961), Spear (1978) favours the view that the effect is due rather to the facilitation of the memory retrieval of the task, by the cueing properties of the reinforcer. A particularly striking example of the reactivation effect lends indirect support for this latter interpretation. Spear and Parsons (1976) showed that one presentation of the reinforcer (foot shock) given 24 hours prior to testing alleviated forgetting of an avoidance task that had been learned one month previously. A manipulation that maintains its effectiveness for as long as 24 hours is more likely to involve memory than motivational processes. Forgetting

can also be alleviated (or prevented) by occasional presentations of the stimuli associated with the learning task (conditioned stimuli or discriminative stimuli) over a long retention interval, despite the fact that such presentations constitute the procedure for extinction of the conditioned effects (Spear & Parsons, 1976). Whether the facilitation of performance after unconditioned (or conditioned stimulus) presentation can be accounted for by memory or motivational processes alone or some combination of these factors remains an open question.

The degree to which the response-enhancing effect of non-contingent reinforcement delivery is specific to responses previously established by the same reinforcer has not been systematically studied. Konorski (1967) addressed the question in a study referred to earlier in which two distinct operant responses were trained in dogs, one for food reinforcement and one for water reinforcement. He showed that a priming delivery of food led to the food-related response and water delivery led to the water response in animals deprived of both substances. Further studies of this kind are necessary to determine the specificity of the priming effect to responding that has been established by the same reinforcer used as the priming event. A general arousal effect would be indicated if all responding was

increased nonspecifically, regardless of the type of reinforcement originally used to establish the response.

Priming with Drugs as Reinforcers

Casual observations in the self-administration laboratory suggest that non-contingent infusions of the self-administered drug, presented at a time when the animal's blood level of drug is relatively low, produce a strong facilitation of responding. This effect has been documented (Stretch & Gerber, 1973; Gerber & Stretch, 1975) in monkeys trained to self-administer either cocaine or amphetamine. After self-administration training the monkeys were put on extinction conditions for several sessions until their rate of responding fell to low levels. Then test sessions were given in which the extinction conditions remained in effect, but prior to which the monkeys were given either intramuscular or intravenous injections of either the self-administered drug or another drug of the same or a different class. Presession injections of the self-administered drug resulted in a powerful reinstatement of responding, producing patterns of responding within the session that were indistinguishable from the drug-reinforced sessions. There was also a strong facilitation of responding after pretreatment with another drug of the same class (i.e., cocaine pretreatment for monkeys trained to self-administer

amphetamine, and amphetamine pretreatment for cocaine-trained animals), but only transient effects after pretreatment with drugs from another class (barbiturate or minor tranquilizer). The facilitatory effect of these non-contingent drug injections on responding after extinction was interpreted by the authors as an example of the discriminative stimulus control of responding by the drug. That is, the presession infusion of the self-administered drug reestablished the stimulus conditions that were present when responding was reinforced in the self-administration sessions. The other drugs tested produced responding only to the extent that their stimulus properties are known to resemble the self-administered drug (Colpaert, Niemegeers & Janssen, 1979; Ando & Yanagita, 1978).

The similarity between the stimulus properties of different drugs has been examined in drug discrimination experiments (Overton, 1971; Stewart, 1962; Thompson & Pickens, 1971) in which drugs are used as the discriminative stimulus for responding for a positive reinforcer or avoidance of an aversive stimulus. In these experiments animals are trained to make one response (usually a lever press) after a presession injection of a drug, and another response (on a second lever) after a saline injection. Then on test sessions, others drugs

are substituted for the training drug, and the animals' tendency to respond on the drug- or saline-lever is taken to indicate the degree of similarity or dissimilarity of the test drug to the training drug. Cocaine has been studied extensively in this paradigm (Colpaert, Niemegeers & Janssen, 1976; Colpaert, Niemegeers & Janssen, 1979; D'Mello & Stolerman, 1977; Ho & Silverman, 1978). When cocaine (injected intraperitoneally) is used as the discriminative stimulus in rats, other stimulants such as d-amphetamine and methylphenidate produce good generalization to the cocaine-associated lever (Colpaert et al., 1979). The dopamine agonist apomorphine, the narcotic analgesic fentanyl, and the psychotomimetic phencyclidine, also produce fairly good generalization to the cocaine-associated lever, whereas a wide variety of other centrally active substances, including morphine, produce little or no drug-lever responding. Recently, Ando and Yanagita (1978) tested the discriminative stimulus properties of intravenously-administered cocaine in rhesus monkeys. They reported substantial responding on the cocaine-associated lever when the animals were tested after morphine and d-amphetamine injections, but not after ethyl alcohol, chlorpromazine or pentobarbital. The inconsistency in the degree of generalization from cocaine to morphine in this and the Colpaert et al.

(1979) study can probably be accounted for by the different routes of administration. It is possible that the stimulus properties of intravenously-delivered morphine do resemble cocaine, whereas when morphine is delivered intraperitoneally it is sufficiently different to give a poor generalization response in this paradigm. Results from these drug discrimination experiments provide a useful profile of the similarity and dissimilarity of the stimulus properties of a wide range of substances in experimental animals.

The Gerber and Stretch experiments (Gerber & Streteh, 1975; Stretch & Gerber, 1973) suggested that, in monkeys, presession injections of the drug to be self-administered can reinstate responding after extinction. This may be due, as they suggested, to the discriminative stimulus control of responding by the drug. On the other hand, it may also be related to the more general phenomenon of enhancement of responding that occurs after non-contingent delivery of a reinforcer as is seen with other reinforcers. What these experiments do suggest, however, is that the presence of drug in the body enhances drug-related behavior in an animal returned to the environment where drug has in the past been available. It was the potential significance of this finding that led to the present investigation.

The Present Experiments

The experiments to be reported here further investigated the phenomenon of drug-induced reinstatement of self-administration responding in rats. Non-contingent, "priming", intravenous infusions of drug were given during extinction after a cocaine self-administration session. The experiments consisted of two phases: an initial training phase in which rats were trained to self-administer intravenously-delivered cocaine at a standard dose of 1 mg/kg/injection, and a second phase of daily testing sessions. Figure 1 illustrates the sequence of events on test sessions. Each test session consisted of a period of cocaine self-administration (1 - 2 hours) followed by extinction conditions for the remainder of the session. The experimental manipulation consisted of the delivery of a non-contingent infusion of a drug or saline (or in the last experiment a tone associated with drug infusions) during the extinction period. The animals' tendency to reinitiate responding immediately after the drug infusion was measured. Extinction conditions were introduced in one of two ways, either by disconnecting the power to the infusion pump or by substituting saline for the drug solution. Using the first method, responses during the extinction period had no consequences for the animal and thus there was a radical change in response consequences.

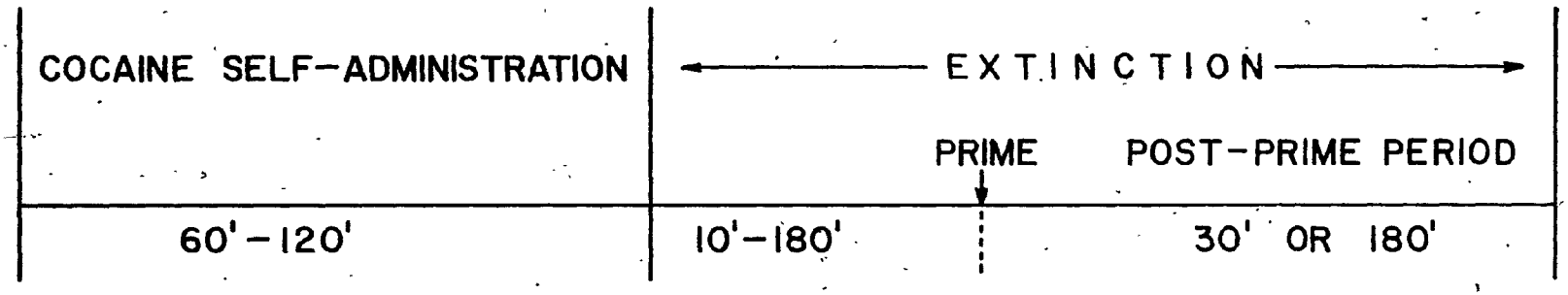


FIGURE 1

A schematic representation of the sequence of events during test sessions.

It did, however, make it possible to deliver the priming cocaine infusions automatically from the adjacent programming room. Using the second method, each response during extinction produced an infusion of saline, but the priming drug injections had to be delivered into the infusion system manually by the experimenter. Extinction by syringe pump disconnection was suitable for procedures in which the same cocaine solution was used for both self-administration and the priming injections; in these cases the drug solution could remain in the infusion and catheter tubing throughout the extinction period. Extinction by saline substitution, on the other hand, ensured that the infusion tubing and catheter contained only saline solution at the time of testing, and was therefore suitable for the experiments in which drug solutions other than the self-administered drug were to be infused through the system. The two extinction methods produced highly similar patterns of extinction responding. When syringe disconnection was used as the method of extinction the priming infusion was given at a fixed time after the self-administration period, regardless of the animal's responding, while with saline substitution a criterion period of 60 minutes without a response was allowed to pass before the non-contingent infusion was given. These methodological differences

did not appear to affect the magnitude of the response-enhancement after priming drug infusions.

The first experiments were designed to establish the effectiveness of non-contingent infusions of the self-administered drug in reinstating responding after extinction and to determine the effect of the dose of priming infusions on the magnitude of the effect (Experiment 1A and 1B). The second Experiment examined the relationship between the time since the last self-administration period and the amount of responding after the priming infusion. In Experiment 3 the generalizability of the prime-induced enhancement of responding to priming injections of other psychoactive drugs was examined. In the final experiment an attempt was made to demonstrate that a conditioned stimulus that had been associated with reinforcing drug infusions could also reinstate responding after extinction.

EXPERIMENT 1A

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. A further purpose of the experiment was to determine whether the magnitude of the response-enhancing effect was a function of the dose of cocaine administered. Priming doses that were half, double and equal to the self-administered dose (1 mg/kg) were tested. Extinction was introduced by disconnecting the syringe pump, and all priming injections were given at a fixed time, one hour after the introduction of the extinction conditions.

Method

Subjects

Five male Sprague-Dawley rats from Canadian Breeding Farms Limited, weighing 300 to 350 grams 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, but were dropped from the experiments either because of

catheter failure at an early stage or because of failure to acquire stable self-administration (see Appendix 2). Only the data from rats that reached the test phase of the experiments will be reported. Animals were housed in a temperature- and humidity-controlled animal room on a 12-hour 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 & 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. x 0.11 cm o.d., and 0.03 cm i.d. x 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 subcutaneously 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 pack consisting of a subcutaneously implanted plastic plate connected by two stainless steel screws to an aluminum 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 I.U./ml) physiological saline for the first week after catheterization to protect against the formation of emboliSms in the vein. When catheter failure occurred due to blockage or leakage during the course of the experiment, animals were recatheterized using the right vein.

Apparatus

Five operant chambers (30 cm x 20 cm x 20 cm) were used in this experiment, each with fittings above the box to suspend swivel (Brown, Amit & Weeks, 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 pack 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 decibel white noise was continuously present to mask extraneous noise.

Only one concentration of cocaine hydrochloride (B.D.H. Chemicals Ltd.) solution dissolved in physiological saline and 5 I.U./ml heparin added was used. Adjustments for dosages by weight were made by altering the volume of the solution infused: to deliver a 1 mg/kg infusion dose of cocaine to a 500 gram rat, a volume of 0.125 ml of solution was injected over 13 seconds. The injection time (and hence volume) was adjusted appropriately for rats whose weights deviated by 10 grams or more from 500 grams. The cocaine solution was made up weekly.

Procedure

Self-administration training began two days after surgery. The rats were connected to infusion tubing

in the test chambers for 2- to 3-hour 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. Non-contingent 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 three weeks of training were dropped from the experiment.

Daily test sessions began when an 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 to 2 hours 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 minutes 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 minutes following the priming injection were recorded. All animals were tested twice at each dose; the order of tests was counterbalanced.

Results

In Experiment 1A and all subsequent experiments two measures were taken, the latency to the first response after the drug or saline infusion and the total number of responses in the post-prime period. In most cases the data from these measures are presented graphically as both means and medians of treatment conditions. Because of the small number of animals and occasional extreme scores, the median values often reveal trends across treatments that are obscured when means are considered. This is particularly true in the latency measure, where, if an animal failed to respond on one trial its score was recorded as the entire duration of the post-prime period, a value that may disproportionately weight the mean.

Analysis of variance and post hoc trend analyses

were performed on both the latencies and total number of responses in each experiment. In those experiments where there was a saline control infusion, data from the saline test were included as a level of the main treatment effect (drug effect). Post hoc tests for linear trends across doses included data from the saline infusion as the 0.0 mg/kg dose in these experiments.

Extinction

Figure 2 shows the changes in responding over the 60-minute period of extinction. When extinction conditions were introduced responding increased initially, reaching a peak mean of 6.3 responses in the period between 10 and 20 minutes after the commencement of extinction. Responding subsequently declined to near-operant levels over the remainder of the 60-minute extinction period.

Responding after a Cocaine Priming Injection

At all three doses tested the cocaine priming injection given 1 hour after the commencement of extinction produced a marked increase in responding. Figure 3 shows that the mean latencies to the first response after the cocaine infusions were between 6 and 10 minutes, whereas the average latency when no infusion was given (0.0 mg/kg dose) was over 20 minutes. Figure 3 also shows that the mean number of responses in the

FIGURE 2

Mean number of responses per 10 minutes during self-administration (continuous reinforcement: CRF) and during extinction in Experiment 1A. Mean values are based on eight extinction sessions for each of five rats, and standard errors of the means are indicated.

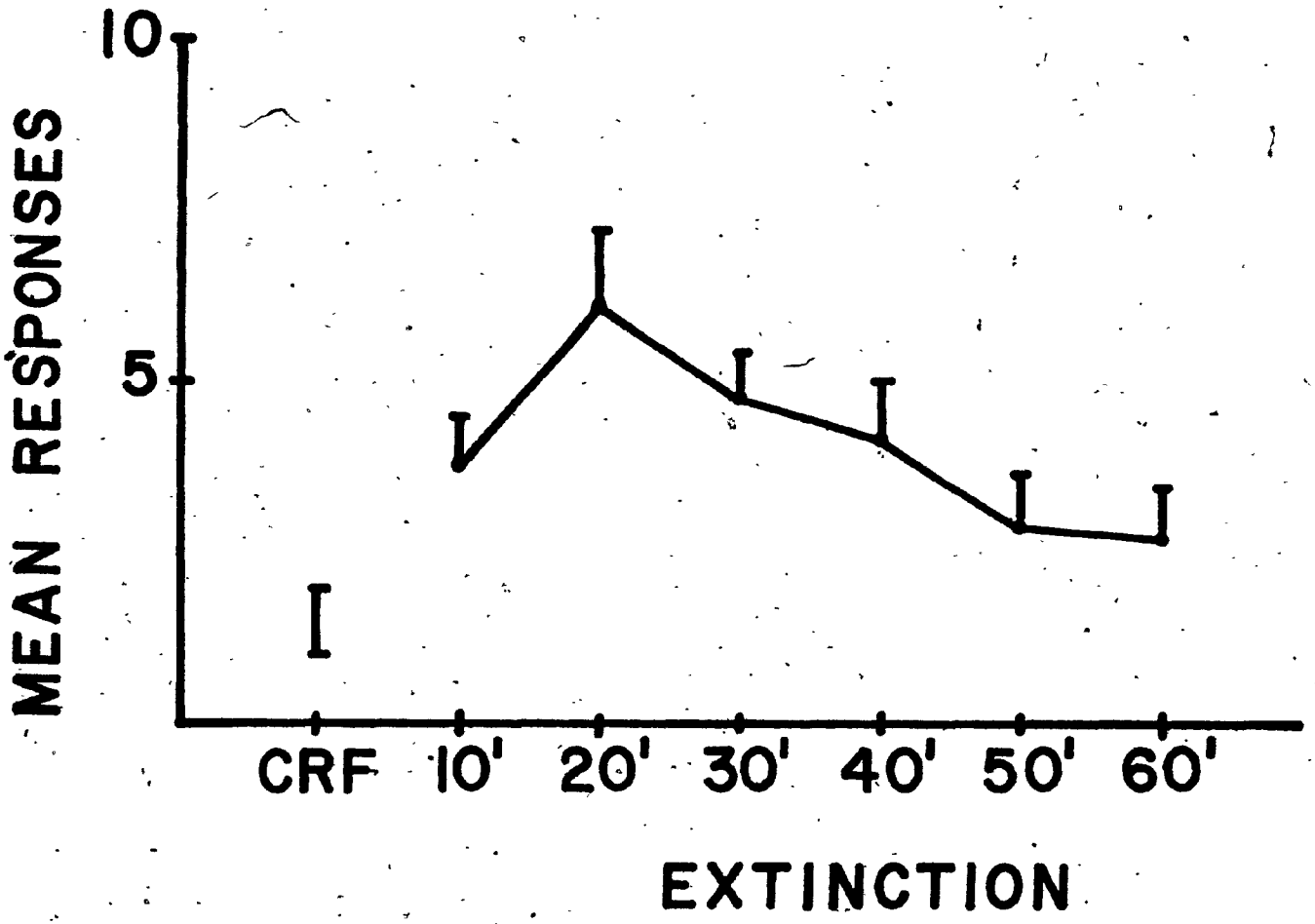
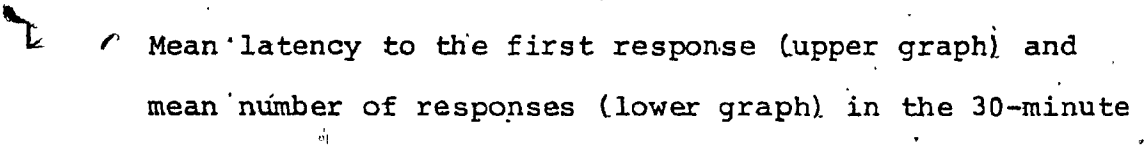
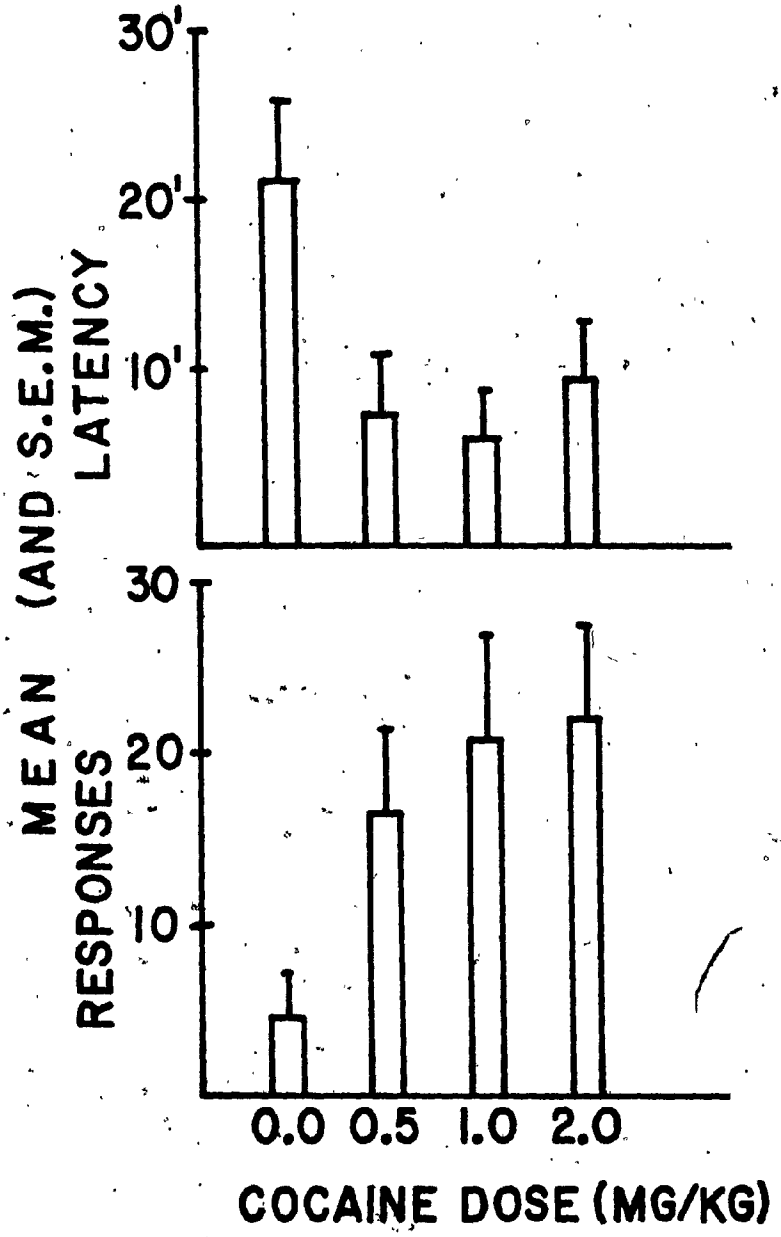

10
5
MEAN RESPONSES
CRF
10'
20'
30'
40'
50'
60'
EXTINCTION

FIGURE 3



Mean latency to the first response (upper graph) and mean number of responses (lower graph) in the 30-minute period after cocaine injections (0.5, 1.0 and 2.0 mg/kg) or "dummy trial" (0.0 mg/kg) given during extinction after a cocaine self-administration session. Mean values are based on two determinations per rat in each of five animals. Standard errors of the means are indicated.


30'
20'
10'
MEAN (AND S.E.M.) LATENCY
30
20
10
RESPONSES
0.0 0.5 1.0 2.0
COCAINE DOSE (MG/KG)

30-minute test period was between 16 and 22 responses following the drug infusions, compared to less than 5 responses after the "dummy" trial (no infusion). Analyses of variance showed a significant drug effect for both the latency-to-the-first-response measure ($F(3,12) = 4.34$, $p<.05$) and the number of responses ($F(3,12) = 4.10$, $p<.05$). Post hoc tests for linearity between the levels of the main effect (no infusion and three doses of cocaine) were significant for both latency ($F(1,12) = 5.7$, $p<.05$) and the number of responses ($F(1,12) = 29.4$, $p<.01$). Visual inspection of the means indicates that the linear trend was due to the overall drug versus no-drug difference rather than dose-dependent effects of cocaine.

Only the median scores for both latencies and number of responses revealed any indication of dose-dependent effects of cocaine. The highest dose of priming injection was associated with a slightly longer median latency and a somewhat larger median total number of responses (Figure 4). These trends are also evident when the mean number of responses per 10-minute period after the priming infusions are examined (Figure 5). At the lowest dose (0.5 mg/kg) the rate increased immediately after the priming injection but fell sharply to a low level after the first 10 minutes. At the

FIGURE 4

Median latency to the first response (upper graph) and median number of responses (lower graph) after cocaine injections (0.5, 1.0, or 2.0 mg/kg) or a "dummy trial" (0.0 mg/kg) in Experiment 1A. Medians are derived from ten values: two determinations per rat for each of five rats.

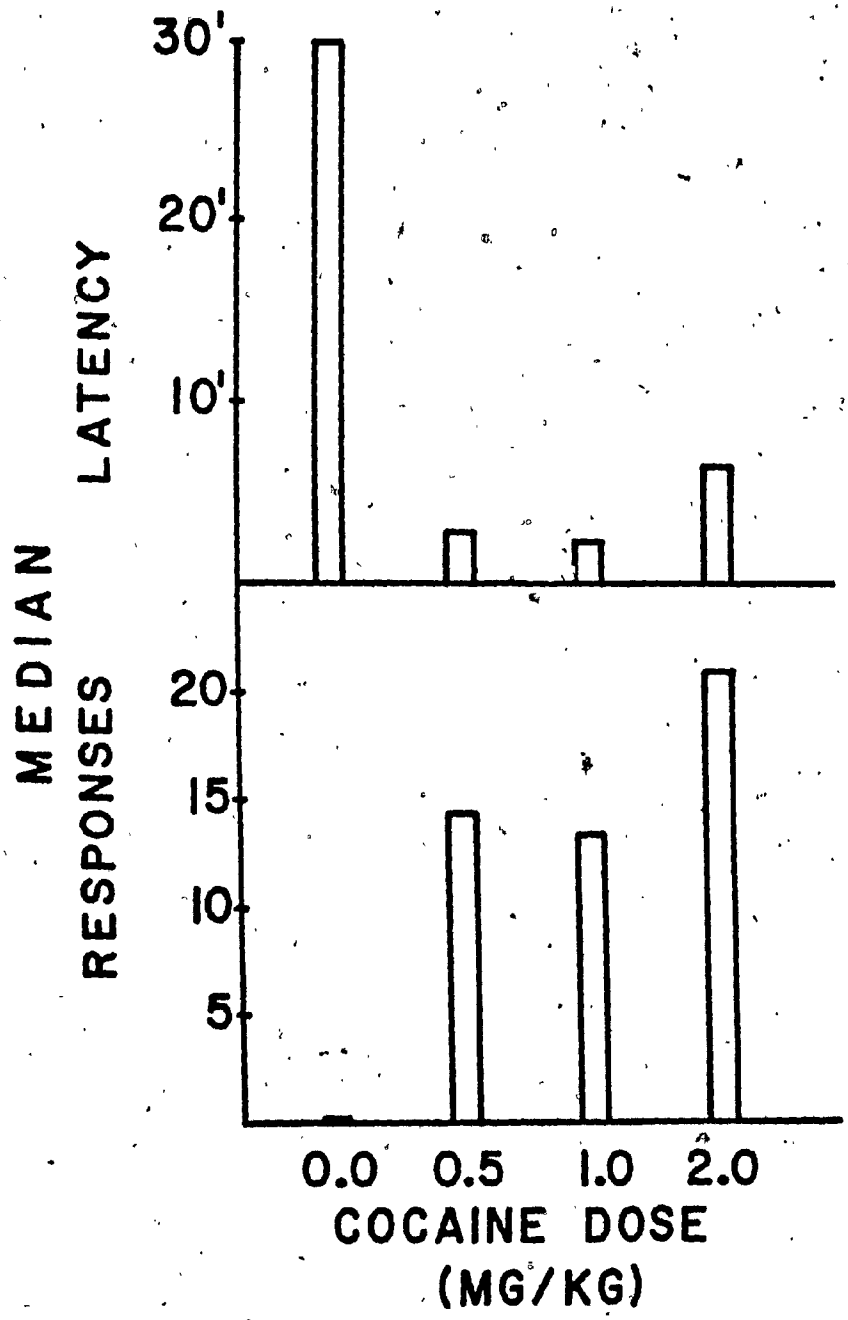
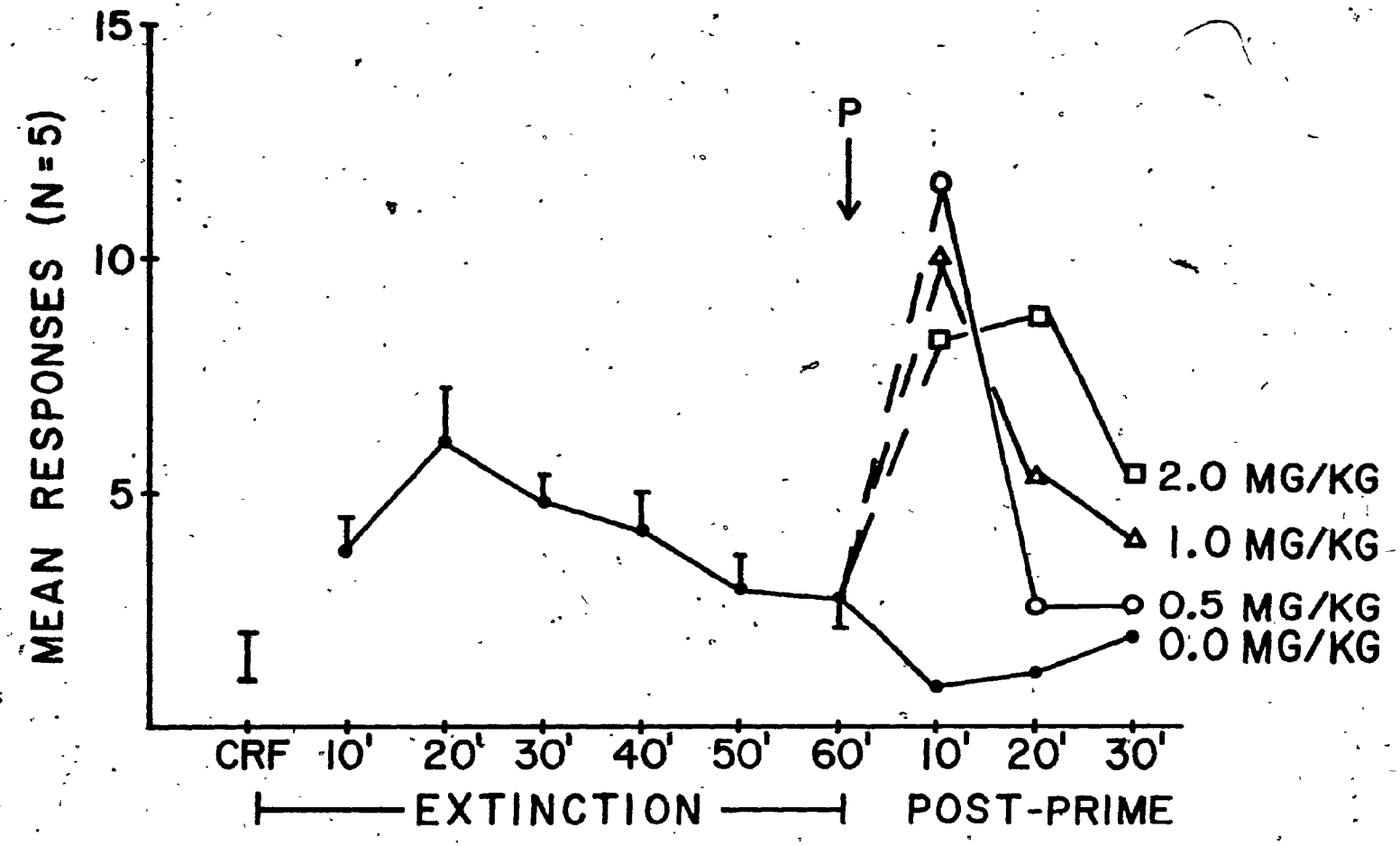

MEDIAN RESPONSES
LATENCY
30'
20'
10'
20
15
10
5
0.0
0.5
1.0
2.0
COCAINE DOSE
(MG/KG)

FIGURE 5

Mean number of responses per 10 minutes 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 1A. "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.


MEAN RESPONSES (N=5)
15
10
5
P
2.0 MG/KG
1.0 MG/KG
0.5 MG/KG
0.0 MG/KG
CRF
10'
20'
30'
40'
50'
60'
10'
20'
30'
EXTINCTION
POST-PRIME

1.0 mg/kg dose the rate also rose sharply but the return to baseline rate was not as rapid as for the lowest dose. In contrast to these, the highest dose produced its greatest increase in rate only in the second 10-minute period and an elevated rate was maintained throughout the 30-minute test period.

In summary, the results from Experiment 1A show clearly that non-contingent infusions of cocaine reinstate responding during extinction. There was also a tendency, although statistically non-significant, for the larger dose of cocaine to produce a longer latency to respond as well as a slower return to baseline rates.

Discussion

This experiment clearly demonstrated the response-enhancing effects of non-contingent infusions of cocaine delivered to rats following one hour of extinction after a self-administration session. At a time during extinction when responding had fallen to near-operant levels, priming infusions of cocaine at each of three doses resulted in a reinitiation of responding within 6 to 10 minutes. When no drug infusion was given at this time no responding occurred in the 30-minute test period.

The two lower doses of cocaine, 0.5 and 1.0 mg/kg,

produced highly similar latencies to the first response and total number of responses, and in both cases most of the responding occurred within the first 10 minutes of the 30-minute test period (Figure 5). In contrast to these, after the highest dose the latency was slightly longer and the responding was prolonged throughout the 30-minute test period. One interpretation of these results is in terms of the control of responding by the animal's current blood level of drug. By this account, the two lower doses of cocaine produced discriminable drug effects that reinstated responding by re-establishing the internal stimulus conditions that would have been present when drug was being self-administered. Responding abated as the drug from the priming infusion was metabolized and the drug stimulus faded. After administration of the highest priming dose, it is hypothesized that the higher blood levels suppressed responding for a short period of time (just as responding is suppressed in the long inter-response times during self-administration), and then responding was restored when the blood levels fell below a certain level. Responding apparently continued as long as there was enough drug circulating in the blood to produce a discriminable stimulus. After the highest dose the drug would have been expected to remain in the circulation

for a longer duration than after the lower doses, and thus responding was expected to be sustained for a longer period of time.

It is unlikely that the occasional non-contingent infusions of cocaine given as "primes" during self-administration training developed any appreciable signalling, or discriminative stimulus function "setting the occasion" for initiation of responding. Not all animals received such priming injections, and there was no relationship between the tendency to reinitiate responding after priming injections during tests and the number of primes given during training. Furthermore, a stimulus usually becomes established as a discriminative stimulus (S+) only against a background of another stimulus (S-) in whose presence responses are not reinforced; there were no times during self-administration training during which responses were not reinforced. Finally, it is notable that over repeated test sessions the priming drug infusions during extinction continued to elicit responding for as many as 80 test sessions in some animals, in spite of the fact that no further reinforcements were ever delivered after the initial self-administration period. Any initial discriminative stimulus properties of the priming injections that might have developed during the early drug self-administration

training would be expected to extinguish with such extensive experience with the drug stimulus followed by non-reinforcement.

EXPERIMENT 1B

The results from Experiment 1A established that priming injections of the self-administered drug can reinstate responding during extinction, and suggested that higher doses of the drug are associated with increased latency to the first response and prolonged responding after the priming injection. In Experiment 1B the relation between response reinitiation and dose of priming injection was examined further using a wider range of priming doses. In addition several minor procedural differences were introduced in Experiment 1B. Extinction was introduced by substituting saline for the cocaine solution rather than, as in Experiment 1A, by disconnecting the syringe pump. When one hour with no responses had elapsed during extinction a cocaine injection of either 0.125, 0.25, 0.5, 1.0, 2.0, or 4.0 mg/kg or a saline injection was delivered through the intravenous catheter by the experimenter.

Method

Subjects

Five male Sprague-Dawley rats were used, weighing 300 to 350 grams at the beginning of the experiment. They were food-deprived to 85% of free-feeding body weight

during the initial phase of the experiment.

Apparatus

The apparatus for self-administration was the same as in Experiment 1A. In addition, one one-lever Gerbrands operant chamber for delivery of food reinforcement was used.

Procedure

In order to facilitate subsequent acquisition of self-administration, animals were initially food deprived and trained to lever press for food reinforcement (Noyes pellets) on a variable ratio (VR6) schedule. They were allowed to feed freely again for at least three days before surgery. Catheterization proceeded as in Experiment 1A.

After recovery from surgery, rats were trained to self-administer 1 mg/kg cocaine hydrochloride as in Experiment 1A. When responding was reliable, daily test sessions commenced; they consisted of 1 to 2 hours of self-administration followed by extinction conditions for the remainder of the session. The extinction condition was introduced by substituting saline for the cocaine solution. At the beginning of the extinction period, the syringe containing cocaine solution was replaced by a syringe containing physiological saline. The 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 2 or 3 response-produced infusions after saline substitution, and following this all responses produced only saline infusions. When extinction responding had ceased for 30 minutes 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 after the saline injection the rats were given a cocaine injection of either 0.125, 0.25, 0.5, 1.0, 2.0, or 4.0 mg/kg in a volume of 0.1 to 0.4 ml followed by a saline solution (0.3 ml) to flush the drug through the system, or a second saline injection. These second injections were also delivered manually into the infusion system at the top of the swivel. The latency to the first response and the number of responses over the next 30-minute period were recorded. All rats were tested once at each dose, and the order of testing at different doses was counterbalanced.

Results

Extinction

The pattern of responding over the period of extinction in this experiment was similar to the pattern seen in Experiment 1A, despite the methodological differences (Figure 6). The onset of the increase in responding after the introduction of extinction conditions was slightly delayed in comparison with Experiment 1A, but reached a comparable peak rate ($\bar{x}$ = 6.2 responses per 10-minute period). The delay can probably be accounted for by the fact that in this experiment the first 2 or 3 responses after saline substitution delivered the cocaine solution remaining in the infusion system.

Responding after Cocaine Primes

Animals reinitiated responding after cocaine injections of between 0.25 and 4.0 mg/kg, but not after the lowest dose tested (0.125 mg/kg) or after saline injections (Figure 7). While the analyses of variance on both the latencies and the number of responses indicated that the differences between doses of drug and saline did not reach significant levels ($F(6,24) = 1.73$, $p>.10$ and $F(6,24) = 2.0$, $p>.10$ respectively), post hoc trend analyses did yield significant results, showing a linear trend for both latencies ($F(1,24) = 5.9$, $p<.05$)

FIGURE 6

Mean number of responses per 10 minutes during extinction after saline substitution (solid line) in Experiment 1B and after turning the power off on the syringe pump (broken line) in Experiment 1A. Determination of the means for Experiment 1A are based on eight extinction sessions in five rats, and for Experiment 1B the means are based on seven extinction sessions in a different group of five rats. Standard errors of the means are shown.

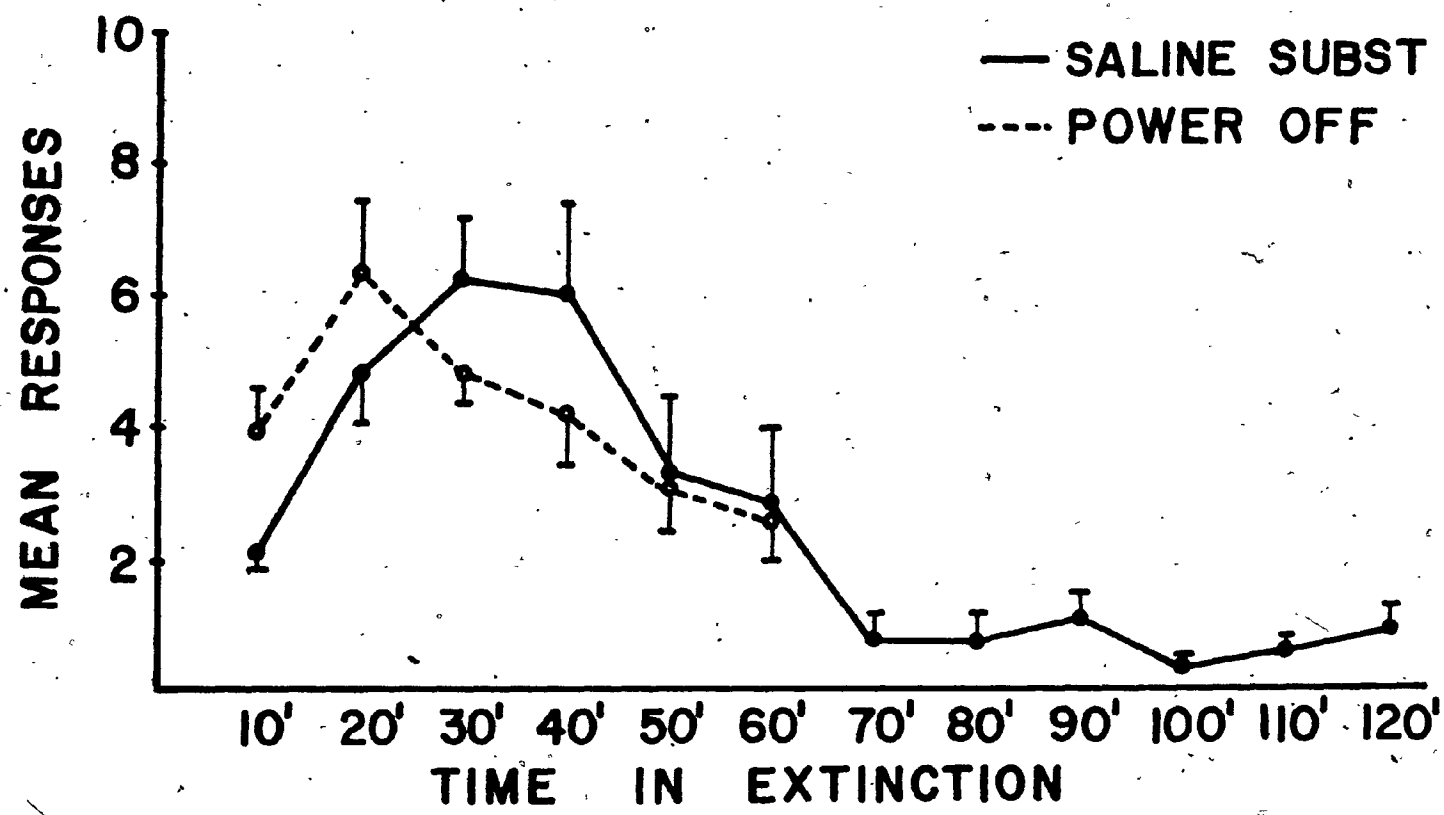

10
8
6
4
2
MEAN RESPONSES
SALINE SUBST
POWER OFF
10' 20' 30' 40' 50' 60' 70' 80' 90' 100' 110' 120'
TIME IN EXTINCTION

FIGURE 7

Mean latencies to the first response (upper graph) and mean number of responses (lower graph) after cocaine in doses of 0.125 mg/kg (labelled 0.1), 0.25 (labelled 0.2), 0.5 mg/kg, 1.0 mg/kg, 2.0 mg/kg, or 4.0 mg/kg or after a saline infusion. Means are based on one determination per rat in five rats. Standard errors of the means are indicated.

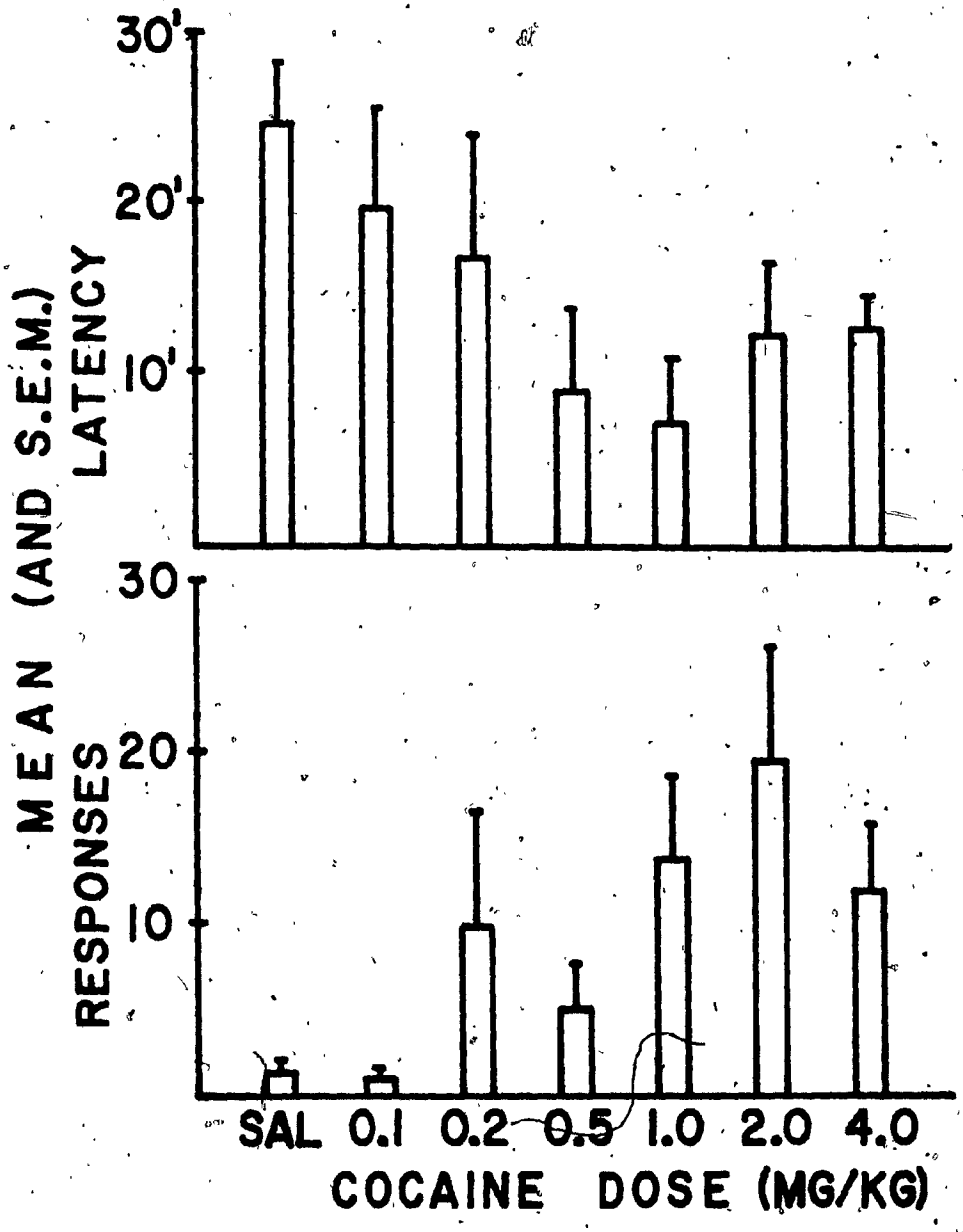
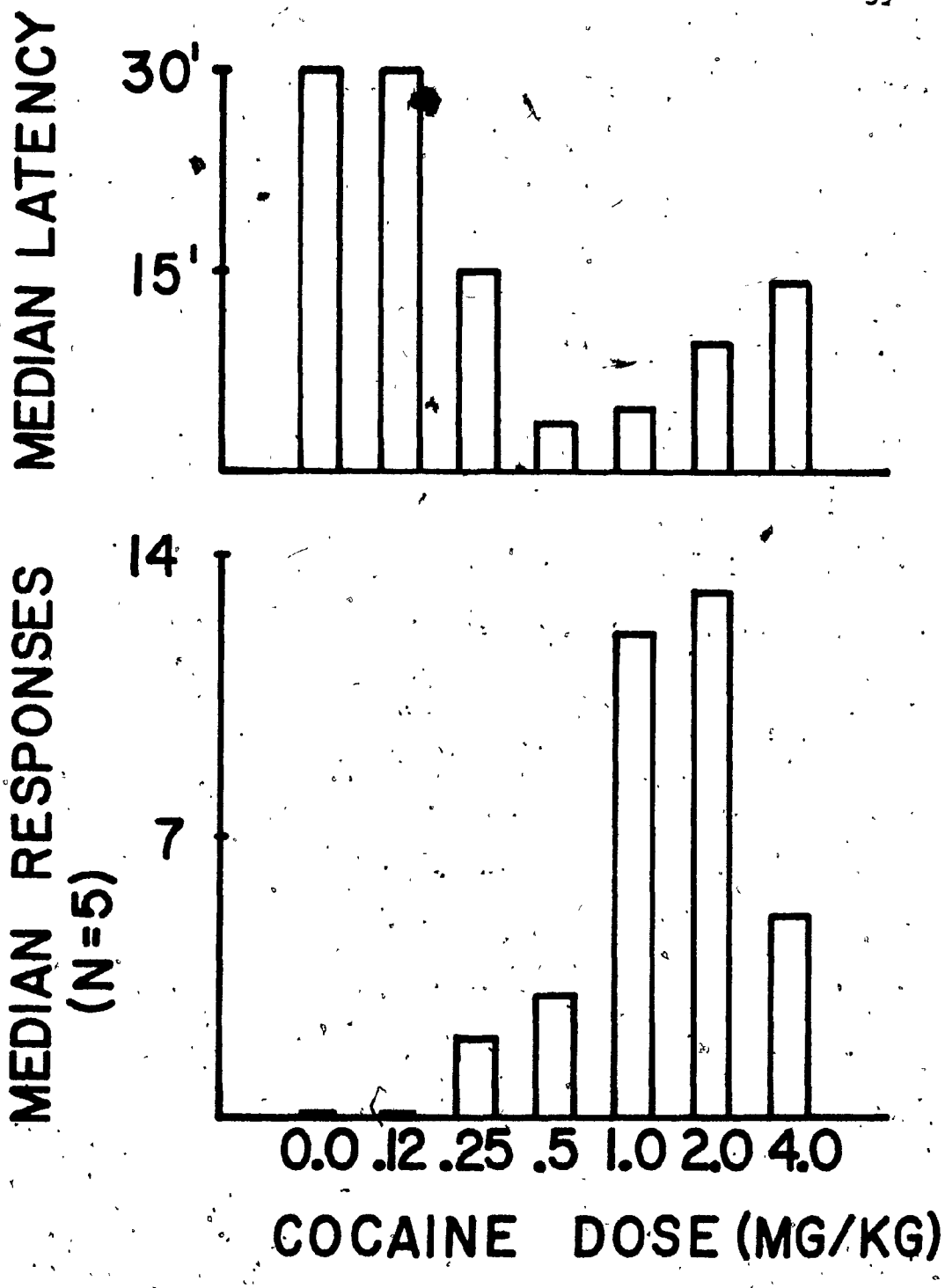

30'
20'
10'
MEAN (AND S.E.M.) LATENCY
30
20
10
RESPONSES
SAL 0.1 0.2 0.5 1.0 2.0 4.0
COCAINE DOSE (MG/KG)

FIGURE 8

Median latencies to the first response (upper graph) and median number of responses (lower graph) after cocaine (0.125 (labelled .12), 0.25, 0.5, 1.0, 2.0 and 4.0 mg/kg) or saline (labelled 0.0 mg/kg). Median values are based on one test at each dose from five animals.

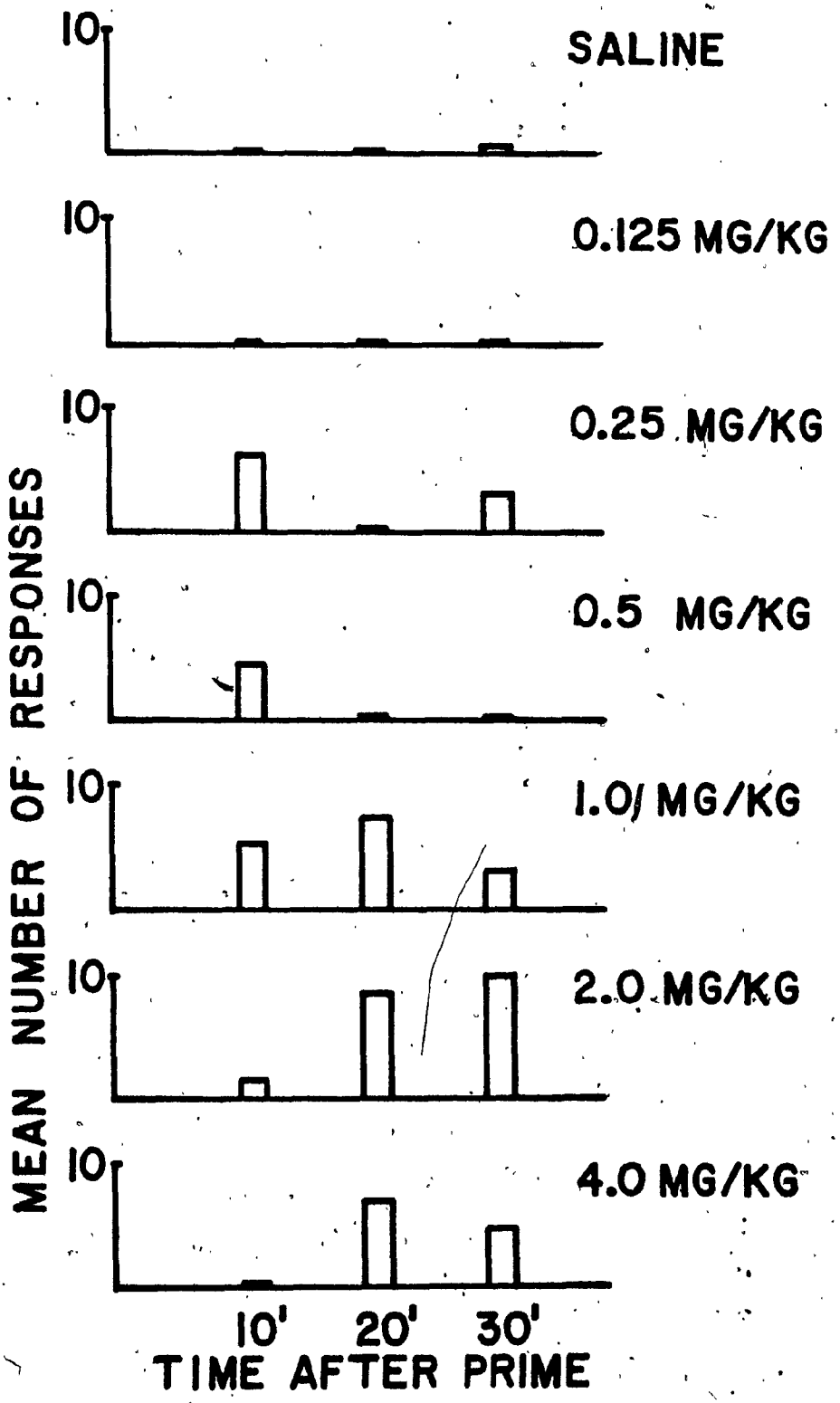

MEDIAN LATENCY
30'
15'
MEDIAN RESPONSES (N=5)
14
7
0.0 .12 .25 .5 1.0 2.0 4.0
COCAINE DOSE (MG/KG)

and responses ($F(1,24) = 21.5$, $p<.01$). Thus while the individual means did not differ greatly they did form an orderly, dose-related pattern. Inspection of the median latencies and the median number of responses for the different doses suggests the same dose-dependent pattern that was seen in the median scores in Experiment 1A (Figure 8). The median latency to respond decreased as the dose of priming injection increased between 0.5 and 4.0 mg/kg. In addition, when the number of responses after priming injections are separated into three successive 10-minute periods (Figure 9) it can be seen that higher doses tended to produce slightly prolonged responding relative to the lower doses. Any dose-dependent differences in the mean latencies were probably masked by the fact that in some instances animals did not respond within the 30-minute period.

The results of Experiment 1B show that cocaine priming injections between 0.25 and 4.0 mg/kg given after 60 minutes of no responding during extinction produced reliable reinstatement of responding. As in Experiment 1A there was also a non-significant tendency for higher doses of cocaine to produce both longer latencies to respond and a greater number of responses.

FIGURE 9

Mean number of responses per 10 minutes after priming cocaine infusions at each of the doses indicated or after saline infusion in Experiment 1B. Mean values are based on one determination per rat for five animals.


10
SALINE
10
0.125 MG/KG
10
0.25 MG/KG
10
0.5 MG/KG
10
1.0 MG/KG
10
2.0 MG/KG
10
4.0 MG/KG
MEAN NUMBER OF RESPONSES
10'
20'
30'
TIME AFTER PRIME

Discussion

In this experiment priming doses of cocaine between 0.25 and 4.0 mg/kg given during extinction restored responding whereas the lowest dose (0.125 mg/kg) was no more effective than a saline infusion. These results confirm and extend the results from Experiment 1A. Although the variability of scores for each dosage was large, there was some indication that higher doses resulted in a longer latency to respond and prolonged responding, as was seen in Experiment 1A. This pattern is consistent with an interpretation in terms of the control of responding by the amount of drug in the blood. Such an account would predict that the animals should respond when, and as long as there was either enough drug to produce a discriminable effect, or enough to reestablish the stimulus conditions of the self-administration period. However, when blood levels exceed a certain level, as after the higher priming doses, a response-suppressant effect should be observed, similar to that seen between infusions during normal self-administration. The results of this experiment are consistent with such an account.

The saline control infusion in this experiment did not produce a reinstatement of responding. It might

have been expected that the interoceptive stimulus produced by the infusion of a fluid into the vein would acquire some conditioned properties by virtue of its repeated pairing with the drug stimulus, and thus affect responding in its own right. Any conditioned properties this stimulus might have acquired, however, were probably extinguished during the repeated saline infusions during the extinction period, as well as the daily experimenter-delivered saline infusions given before the cocaine test priming injections. The patterns of responding during extinction in Experiment 1A, in which no saline infusions were given during extinction, and the pattern in Experiment 1B, in which responses during extinction did produce saline infusions can be compared but with the caution necessary in making comparisons between different experiments. It can be noted that in Experiment 1B the duration of responding was somewhat longer than in Experiment 1A, a result that would be expected if the saline infusions had acquired some conditioned reinforcing properties. There are, however, too many minor differences between these two experiments to be able to conclude that conditioning is the source of the differences in duration of responding.

EXPERIMENT 2

The first experiments established that the priming effect was real, and there was some suggestion 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. Was the power of the priming infusion to enhance responding limited to the period shortly after the self-administration session, or did it retain its effectiveness well after cessation of responding? It will be remembered that while within Experiment 1A and 1B the conditions for presentation of the priming infusions were constant, the two experiments differed in terms of the duration of the extinction period that passed before the priming injection was given. In Experiment 1A the extinction period was always 1 hour regardless of whether or not responding had ceased, whereas in Experiment 1B the priming infusion was only given one hour after the cessation of responding during extinction. While the results from these two experiments suggested that the tendency to respond did not vary as a function of time since the last self-administration period, a more systematic investigation was needed to confirm this.

A standard dose of 1 mg/kg of cocaine was given as prime in this experiment after an extinction period of 10, 30, 60, 120, or 180 minutes. Extinction in this experiment was introduced by syringe pump disconnection.

Method

Subjects

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

Apparatus

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

Procedure

Self-administration training proceeded as in Experiment 1A. Test sessions consisted of a 1- to 2-hour period 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 1A. A 1 mg/kg cocaine injection was given at either 10, 30, 60, 120, or 180 minutes after the commencement of extinction. The latency to the first response and the number of responses in the 30-minute 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

Animals responded to the cocaine priming injections after all of the extinction durations tested. Figure 10 shows that 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 ($F(4,16) = 0.63$, $p>.25$). It should be noted, however, that when median latencies were calculated (Figure 11), the latency to respond after the 10-minute extinction duration was almost double the latency after the other extinction durations. Relatively small differences in latencies between treatments may have been obscured by the large contribution to the variance of those animals that did not respond within the 30-minute criterion.

Both the mean (Figure 10) and the median (Figure 11) 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 of the effect of extinction duration on number of responses was significant

FIGURE 10

Mean latencies to the first response (upper graph) and mean number of responses (lower graph) in the 30-minute period following a cocaine priming infusion (1 mg/kg) following extinction periods of 10, 30, 60, 120 and 180 minutes in duration. Means represent data from five animals, with two determinations for each animal at each extinction duration.

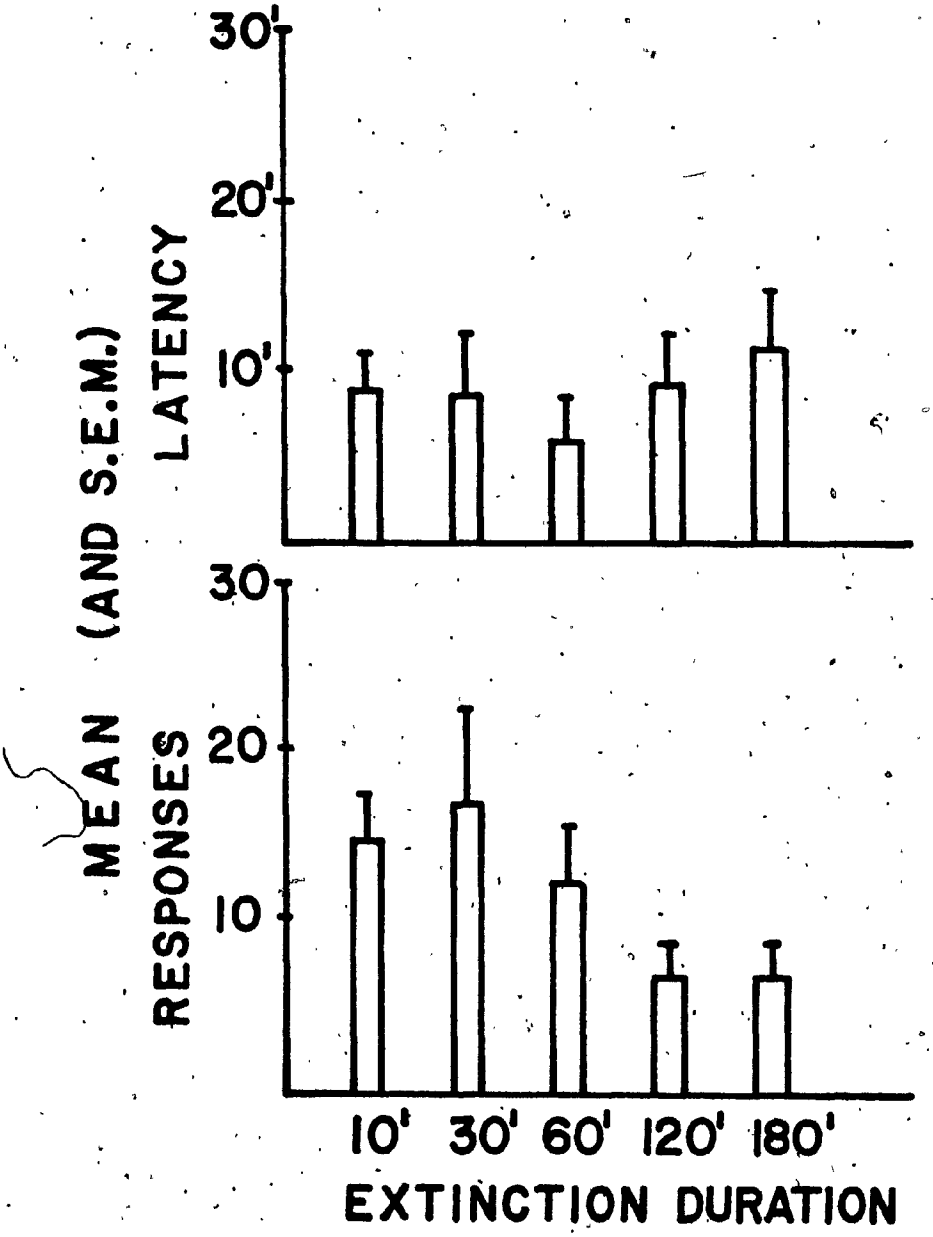
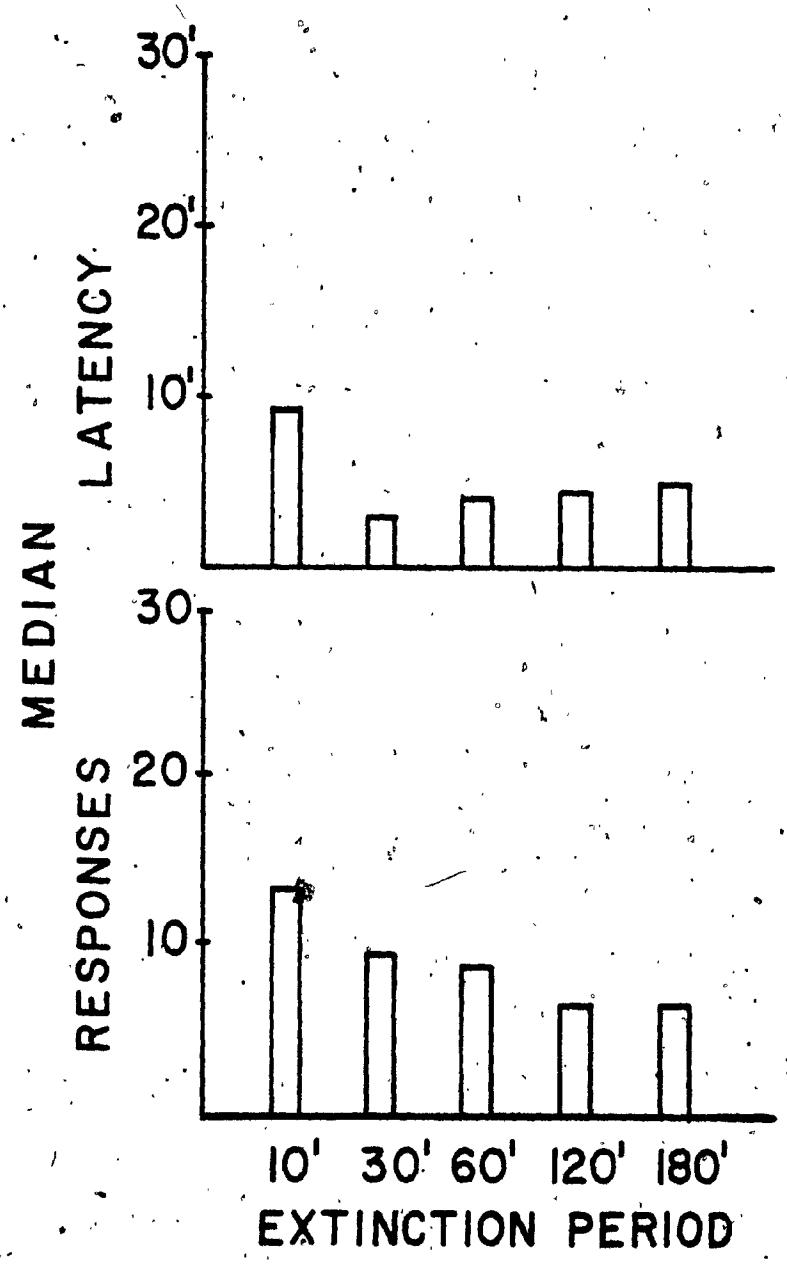

30'
20'
10'
LATENCY
MEAN (AND S.E.M.)
30
20
10
RESPONSES
10' 30' 60' 120' 180'
EXTINCTION DURATION

FIGURE 11

Median latencies to the first response (upper graph) and number of responses (lower graph) after cocaine priming infusions (1.0 mg/kg) following extinction periods of 10, 30, 60, 120 and 180 minutes. Medians are based on ten values; two determinations per rat for each of five rats.


30'
20'
10'
MEDIAN LATENCY
30
20
10
RESPONSES
10' 30' 60' 120' 180'
EXTINCTION PERIOD

($F(12,48) = 2.03$, $p<.05$) and there was a significant linear trend between levels ($F(1,48) = 23.5$, $p<.01$). Examination of the number of responses per 10 minutes after the priming infusions (Figure 12) shows that for all extinction durations, except the 10-minute one, the peak of the increase in response rates occurred within the first 10 minutes after the injection; after that, rates fell quickly to low levels. In contrast to this, the responses after the injection following only 10 minutes of extinction were distributed across the entire 30-minute post-prime period.

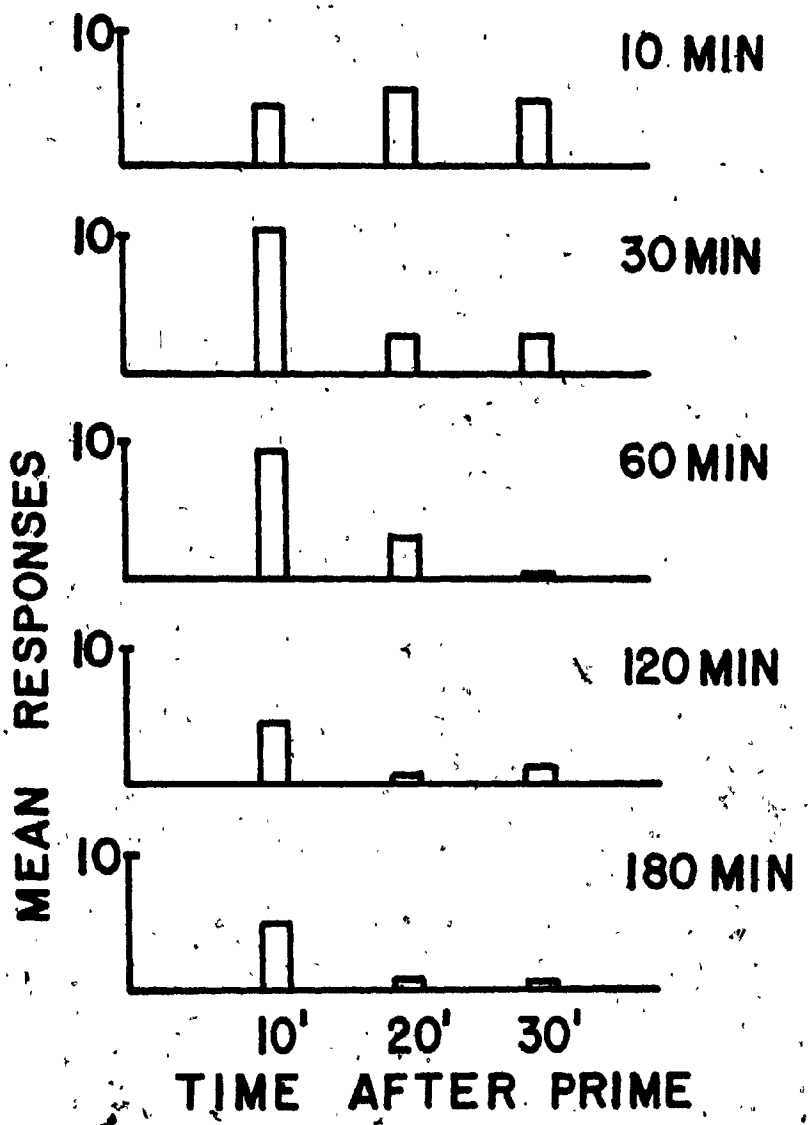
In summary, the results of this experiment showed that the 1 mg/kg cocaine priming infusion elicited responding in animals regardless of the duration of the extinction period. Furthermore, there was no statistically significant difference in the latency to respond as a function of extinction duration, but there was a significant trend for fewer responses to be made after longer periods of extinction.

Discussion

Priming drug infusions given during extinction, between 30 minutes to 3 hours after the self-administration period were all effective in reinstating responding. While the latencies to

FIGURE 12

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


10
10 MIN
10
30 MIN
10
60 MIN
10
120 MIN
10
180 MIN
MEAN RESPONSES
10'
20'
30'
TIME AFTER PRIME

respond were not appreciably different at the four time intervals tested within this range, the total number of responses was slightly lower after the longer extinction durations. It might be argued that when the priming injections were given after shorter extinction periods there was still some drug left in the blood from the self-administration period, and that therefore the actual level reached by the priming infusion was somewhat higher. The tendency for higher blood levels of drug to elicit slightly more responding is consistent with trends observed in Experiments 1A and 1B. It would be necessary, however, to have data on the rate of elimination of drug and the actual blood levels at the time of the priming infusion in order to make such a case.

The pattern of responding after only 10 minutes of extinction was different from the pattern seen after the other test times; responses were distributed throughout the 30-minute post-prime period, rather than being concentrated in the 10 minutes after the priming infusion. It should be noted, however, that because the typical inter-response time during self-administration is about 10 to 15 minutes, and because the extinction period was introduced regardless of the animals' 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 to 15 minutes. The responding that occurred after this delay was, in effect, the animal's first experience with extinction on that test day. The data from individual animals (Appendix I) lend support to this explanation. On the four occasions when animals had made zero or only one unreinforced response prior to the priming injection, latencies to respond to the priming injection were 12, 17, 15 and 16 minutes. On the four occasions when six or more non-reinforced responses had been made prior to the priming injection the latencies to the first response were 0.5, 0.5, 0.5 and 7 minutes.

EXPERIMENT 3A

Experiment 3A was designed to test the effectiveness of drugs other than the self-administered drug (cocaine) in the reinstatement 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 might 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 (Colpaerts et al., 1979) and results from these studies provide a good basis for inferences about the similarities and dissimilarities of the subjective effects of different drugs in rats. Not unexpectedly, amphetamine has been shown to have stimulus properties that are highly similar to cocaine (Silverman & Ho, 1977). There is evidence that the discriminative stimuli provided by both amphetamine and cocaine are both central in origin and mediated by dopaminergic systems (Ho & Silverman,

1978). Both of these drugs are known to increase dopaminergic activity in the brain, although they do so by different mechanisms (Randrup & Munkvad, 1966; Glowinski & Baldessarini, 1966; Carr & Moore, 1969; Ross & Renyi, 1967). Similarly, apomorphine produces stimulus properties resembling cocaine in the drug discrimination paradigm (Ho & Silverman, 1978; Colpaerts, Niemegeers & Janssen, 1979), and it is also known to be an effective dopamine receptor agonist (Colpaert, Van Bever & Leysen, 1976). Thus, on the basis of both the similarity of the stimulus properties of these three drugs as evidenced in the drug discrimination paradigm, 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 produces 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, Gianutsos & Puri,

1975) and agonists (Colpaert et al., 1976). 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 & Fraser, 1961). Heroin and morphine are believed to share the same central mechanism, as heroin is rapidly hydrolized to morphine in the body (Goodman & 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 & Gilman, 1975, p. 101) have a clear effect on dopaminergic activity. These drugs have not been specifically tested in rats trained with cocaine cue, but neither animals trained on ethanol-saline discriminations nor animals trained on pentobarbital-saline discriminations show generalization to amphetamine (Silverman & Ho, 1977). The stimulus properties of drugs from these diverse classes (barbiturate, stimulant, depressant and narcotic) 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 (heroin: Gerber & Wise, Note 2;

van Ree & de Wied, 1977; Oei, Singer & Jefferys, 1980; methohexital: Collins, Weeks & Good, 1978; Pickens, Muchow & DeNoble, 1980; ethanol: Smith, Werner & Davis, 1975; DeNoble & Begleiter, 1978). The interesting possibility existed that it was the reinforcing property rather than the similarity in discriminable stimulus properties in general 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.

Method

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. Four animals had been tested in Experiment 1A and 2, four had served in Experiment 1B, and four had served in Experiment 4 before being tested in this experiment.

Apparatus

The five operant chambers described in Experiment 1A were used. In addition, four other boxes of slightly different design were also used. They were non-commercially-made boxes (25 cm x 25 cm x 30 cm) two

of which were constructed from aluminum and two from plywood, all with a plexiglass front and top. The boxes were fitted with infusion systems as described in Experiment 1A, 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 Ltd.), apomorphine hydrochloride (F.E. Cornell and Co. Ltd.), diacetylmorphine hydrochloride (heroin) (Health and Welfare Canada), morphine sulphate (BDH Chemicals Ltd.) and the short-acting barbiturate methohexital sodium (Eli Lilly Co. Ltd.). Amphetamine, morphine and heroin were dissolved in physiological saline with 5 I.U./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 to 2 hours of stable cocaine self-administration followed by extinction introduced by saline substitution, as described in Experiment 1B. Thirty minutes after responding had ceased under extinction conditions, a saline injection (0.3 ml) was delivered manually into the top of the swivel to ensure that all cocaine solution was out of the infusion tubing and the catheter. Thirty minutes later, rats were given either a second saline injection or an infusion of one of the following drugs:

Apomorphine (0.0625, 0.125, 0.25 or 0.5 mg/kg)

Amphetamine (0.1, 0.3, 1.0 or 2.0 mg/kg)

Ethanol (1, 3 or 10 mg/kg by volume)

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 to 0.4 ml over a 5 second 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 determinations 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 Golpaert & Rosecrans, 1978).

Results

Amphetamine

Amphetamine produced a clear reinstatement of responding at three of the four doses tested. The median scores, illustrated in Figure 13, indicate that whereas neither saline nor the lowest dose (0.1 mg/kg) of amphetamine elicited responding, the three higher doses did produce a reinitiation of bar pressing. The mean latencies to the first response and the mean total number of responses after different doses of amphetamine are given in Table 1. Analysis of variance performed on these data (excluding the highest dose, see Method) showed that there was a significant effect of drug treatment on latency to respond ($F(3,12) = 12.07$, $p<.01$), but not on the total number of responses ($F(3,12) = 2.72$, $p>.05$). There were significant linear trends across drug doses (including the 0.0 mg/kg dose and excluding the 2.0 mg/kg dose) as measured by the post hoc trend analysis for both the latency ($F(1,12) = 434.7$, $p<.01$) and response ($F(1,12) = 41.8$, $p<.01$) measures.

The pattern of responding over the 3-hour test period is illustrated in Figure 14. At the 0.3 mg/kg dose, there was a small increase in responding during the first hour of the 3-hour test period. The rate peaked at 60 minutes

Table 1

Mean latencies to the first response (in minutes) and mean number of responses after infusions of amphetamine, apomorphine and morphine during extinction in Experiment 3A. The number (N) of animals tested at each dose is given, and the duration (in minutes) of the test period during which responses were counted is indicated. The last column shows the number of animals that made at least one response at that dose. Standard errors of the means are given in parentheses after each mean value.

Drug	Dose	N	Test Period	Mean (& s.e.m.) Latency (Mins.)	Mean (& s.e.m.) Responses	Number of Animals Responding
Amphetamine	0.0 (sal)	9	180	165 (8.4)	1.1 (0.5)	3/9
Amphetamine	0.1 mg/kg	5	180	124 (28.3)	2.4 (1.2)	3/5
Amphetamine	0.3 mg/kg	5	180	55 (30.0)	7.2 (3.4)	4/5
Amphetamine	1.0 mg/kg	5	180	27.6 (16.8)	88.2 (51.7)	5/5
Amphetamine	2.0 mg/kg	4	180	55.5 (23.3)	55.5 (11.0)	4/4
Apomorphine	0.0 (sal)	8	60	60 (-)	0 (-)	0/8
Apomorphine	0.0625 mg/kg	8	60	27.8 (8.9)	7.1 (3.5)	5/8
Apomorphine	0.125 mg/kg	8	60	23.8 (7.4)	4.7 (1.8)	6/8
Apomorphine	0.25 mg/kg	8	60	26 (7.3)	6.3 (3.2)	6/8
Apomorphine	0.5 mg/kg	8	60	25.3 (8.2)	4.3 (2.0)	6/8
Morphine	0.0 (sal)	9	180	145 (16.1)	0.7 (0.3)	4/9
Morphine	0.3 mg/kg	9	180	138.3 (19.9)	1.1 (0.53)	3/9
Morphine	1.0 mg/kg	9	180	80 (16.0)	6.7 (2.4)	8/9
Morphine	3.0 mg/kg	9	180	114.5 (15.8)	4.2 (1.3)	7/9

FIGURE 13

Median latencies to respond (upper graph) and median number of responses (lower graph) in the 180 minutes following amphetamine injection (0.1, 0.3, 1.0 and 2.0 mg/kg) or saline injection. Data for the lowest three doses were gathered from five animals, one determination per rat. A separate group of rats (N = 4) was tested at the 2.0 mg/kg dose. The medians presented for saline are based on all nine animals.

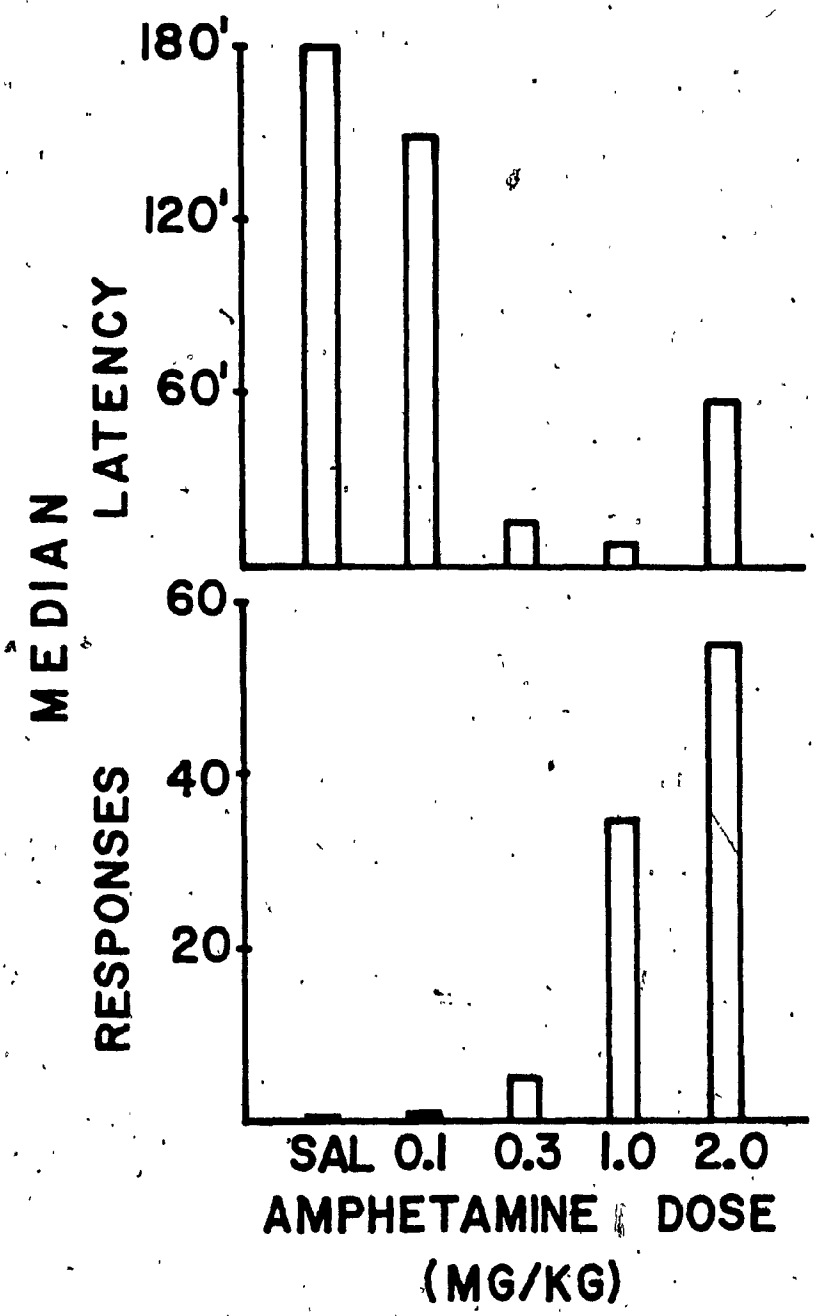
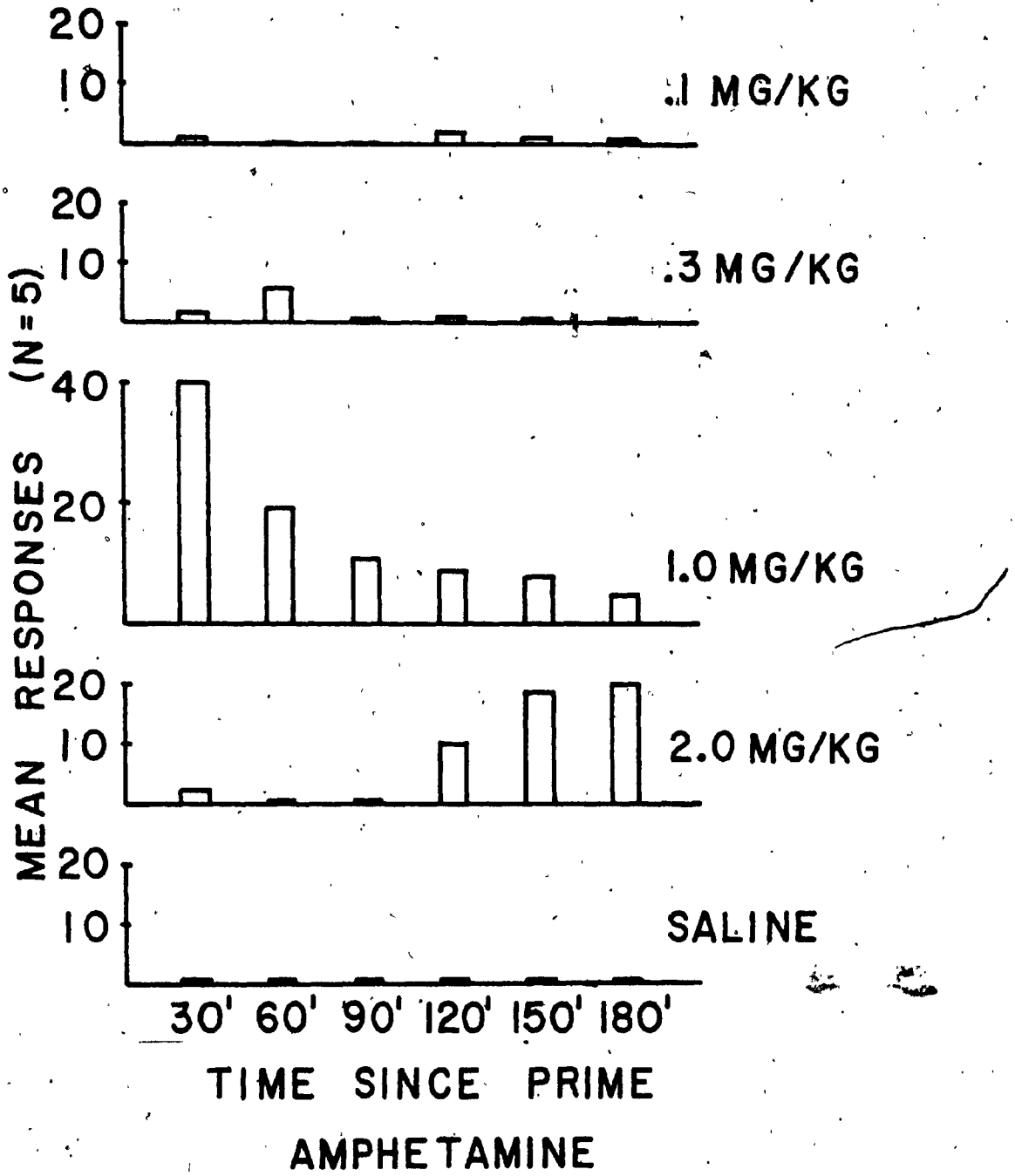

180'
120'
60'
MEDIAN LATENCY
60
40
20
RESPONSES
SAL 0.1 0.3 1.0 2.0
AMPHETAMINE DOSE
(MG/KG)

FIGURE 14

Mean number of responses per 30-minute period after amphetamine injections (0.1, 0.3, 1.0, or 2.0 mg/kg) or saline given during extinction after a cocaine self-administration session. Mean values for the 0.1, 0.3 and 1.0 mg/kg doses are based on one determination per rat for each of five animals. A separate group of animals (N = 4) was tested at the 2.0 mg/kg dose, and data from all nine animals are incorporated in the saline means.


20
10
.1 MG/KG
20
10
.3 MG/KG
MEAN RESPONSES (N=5)
40
20
1.0 MG/KG
20
10
2.0 MG/KG
20
10
SALINE
30' 60' 90' 120' 150' 180'
TIME SINCE PRIME
AMPHETAMINE

($\bar{x}$ = 5.4 responses per 30 minutes), and thereafter rates fell to control levels. At the 1.0 mg/kg dose there was a large increase in rate ($\bar{x}$ = 40.2 responses) in the first 30 minutes, followed by a gradual decline in responding throughout the 3-hour test period. At the highest dose tested (2.0 mg/kg) there was some responding in the first 30 minutes, but the large increase in rate did not occur until between 2 and 3 hours after the drug infusion. The mean peak in response rate (19.5 responses per 30 minutes) occurred in the final 30-minute period of the test period. When the number of responses after different doses of amphetamine were analysed across the six consecutive 30-minute time periods in an analysis of variance, there was a significant time effect ($F(5,20) = 3.36$, $p<.05$) and a significant interaction between drug dose and time ($F(15,60) = 2.17$, $p<.05$). Observation of the animals after the highest doses of amphetamine revealed that a great deal of stereotyped behavior (vigourous sniffing and vertical head movements) occurred during the period between 60 and 90 minutes, a time when few bar presses were made.

In summary, priming injections of amphetamine were effective in reinstating responding during extinction in doses between 0.3 and 2.0 mg/kg but not at 0.1 mg/kg. The time course of the enhancement of responding for

the three effective doses changed as a function of the dose (Figure 14). At the lowest dose, responding occurred soon after the infusion; as the dose was increased, the peak of the increase in responding occurred later in the 3-hour test period.

Apomorphine

Figure 15 shows the median latencies to respond and the median number of responses made after each of the four doses of apomorphine. It can be seen that there was some reinstatement of responding at all doses. An analysis of variance carried out on the latency scores shows that there was a significant drug effect ($F(4,28) = 5.33$, $p<.01$); the analysis carried out on the response measure yielded a non-significant result ($F(4,28) = 1.67$, $p>.05$). Post hoc analyses showed a significant linear trend for latencies ($F(1,28) = 9.5$, $p<.01$), but not for number of responses ($F(1,28) = 4.0$, $p>.05$). Visual inspection of the median latencies (and the mean values presented in Table 1) suggest that the significant linear trend was due to the difference between saline and all the drug doses rather than between different doses of the drug. When the mean number of responses made in each 10 minutes after the prime is considered (Figure 16), it can be seen that there was a clear effect of dose on the time course of responding. At the lowest doses the

FIGURE 15

Median latencies to respond (upper graph) and median number of responses (lower graph) in the 60-minute period following apomorphine injection (0.0625 mg/kg (labelled .06), 0.125 mg/kg (labelled .12), 0.25 mg/kg and 0.5 mg/kg) or saline injection. Eight animals were tested once at each dose.

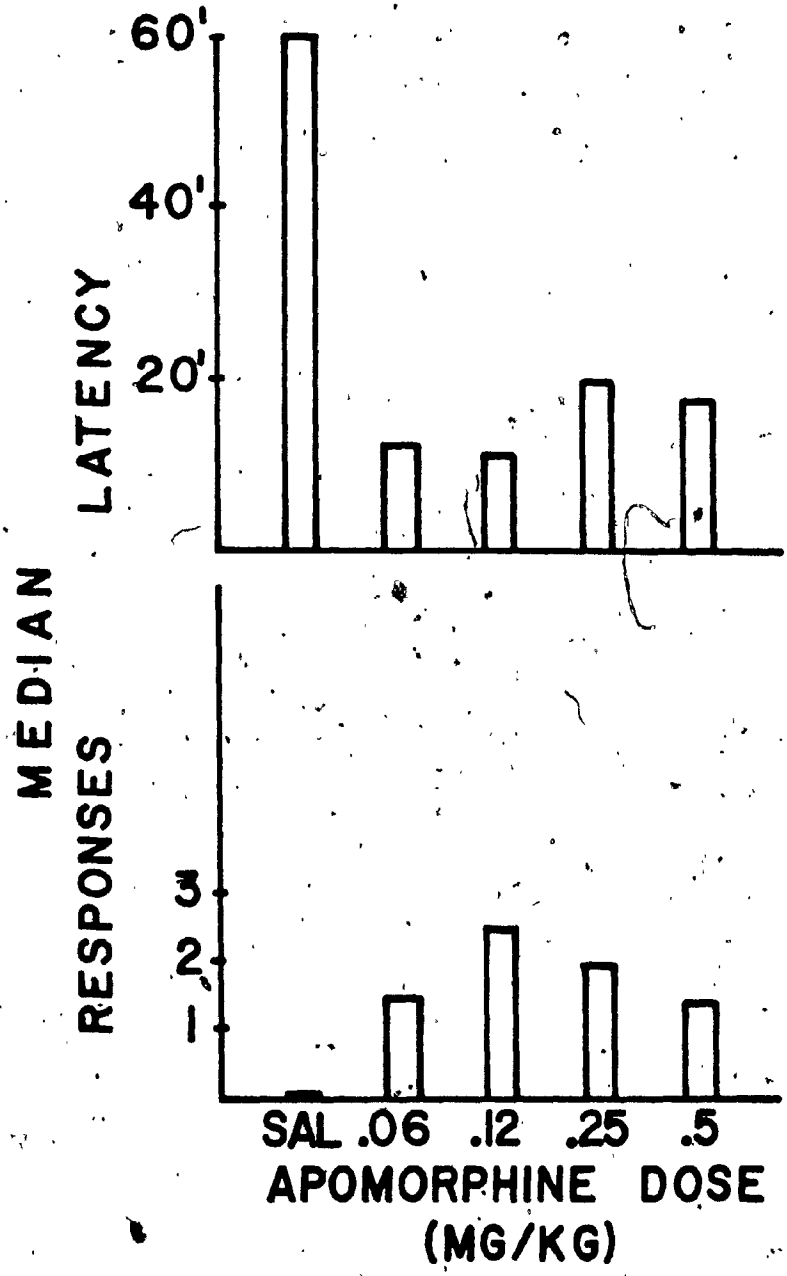
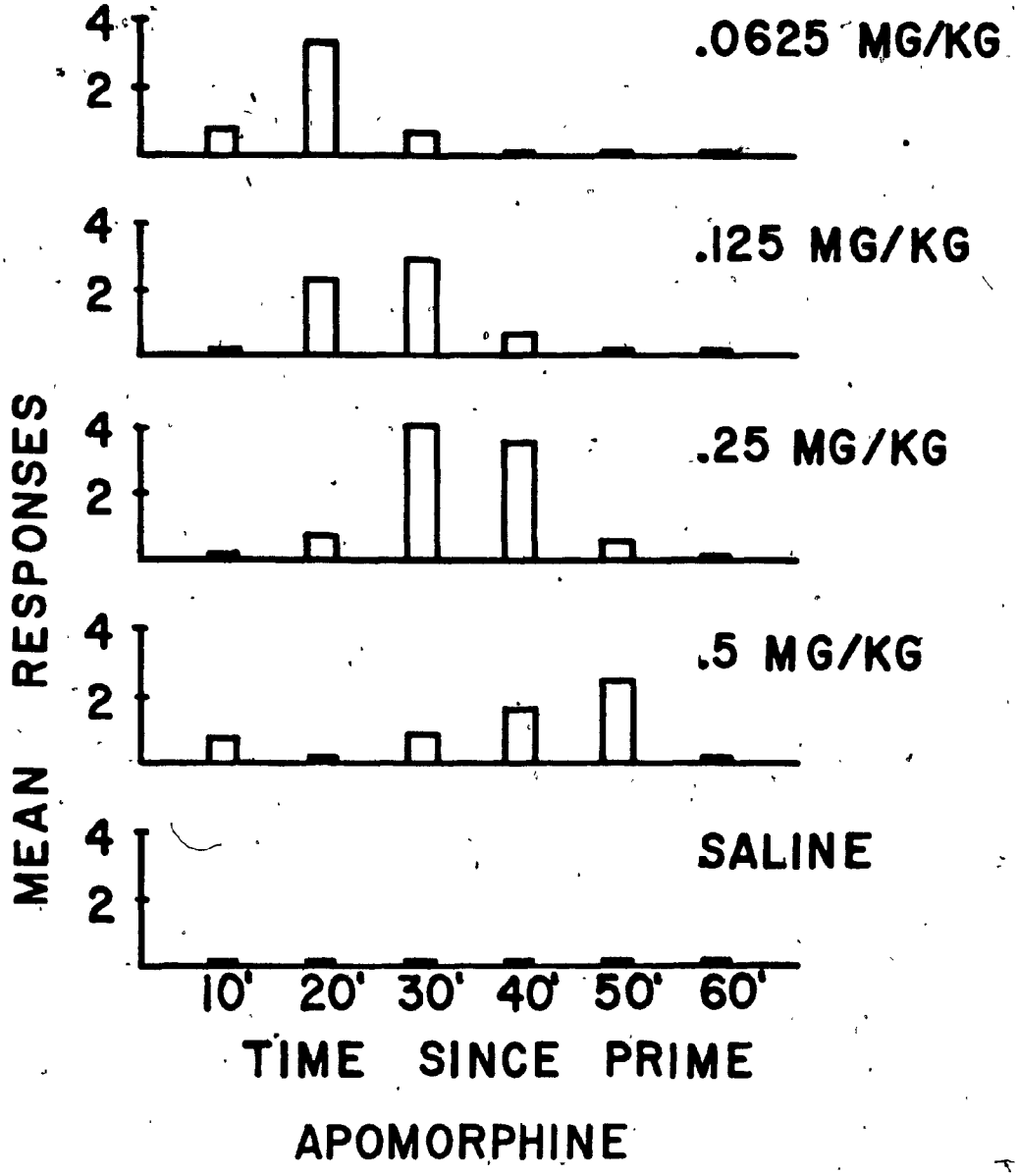

60'
40'
20'
MEDIAN LATENCY
RESPONSES
3
2
1
SAL .06 .12 .25 .5
APOMORPHINE DOSE
(MG/KG)

FIGURE 16

Mean number of responses per 10-minute period after an injection of apomorphine (0.0625, 0.125, 0.25, or 0.5 mg/kg) or saline given during extinction after a cocaine self-administration session. Each mean is based on one determination from each of eight rats.


.0625 MG/KG
.125 MG/KG
.25 MG/KG
.5 MG/KG
SALINE
4
2
MEAN RESPONSES
10' 20' 30' 40' 50' 60'
TIME SINCE PRIME
APOMORPHINE

increase in responding occurred immediately after the drug infusion; as the dose was increased, responding occurred later in the test period. Stereotyped behavior was observed at the three highest doses tested during the period of low responding that followed the drug infusion.

Morphine

The two highest doses of morphine tested produced some reinstatement of responding during extinction (Figure 17). Analyses of variance of the effect of drug carried out on both latency ($F(3,24) = 3.63$, $p<.05$) and response ($F(3,24) = 3.65$, $p<.05$) scores were significant. Post hoc trend analyses showed a significant linear trend for responses ($F(1,24) = 20$, $p<.01$) but not for latency ($F(1,24) = 4.2$, $p>.05$). As with the apomorphine results, visual inspection of the means suggests that the significant linear trend is due to the presence or absence of any effect of the drug rather than to orderly morphine dose-effects. Both the time course and the magnitude of the response-enhancing effect varied with the dose of morphine administered (Figure 18). At the lowest dose (0.3 mg/kg) there was only a slight increase in responding which occurred at 60 minutes after the infusion. The response enhancement at the highest doses (1.0 and 3.0 mg/kg) was both greater ($\bar{x}$ = 6.75 and 4.2

FIGURE 17

Median latencies to respond (upper graph) and median number of responses (lower graph) following morphine injections (0.3, 1.0 and 3.0 mg/kg) or saline injections. Nine animals were tested once at each dose.

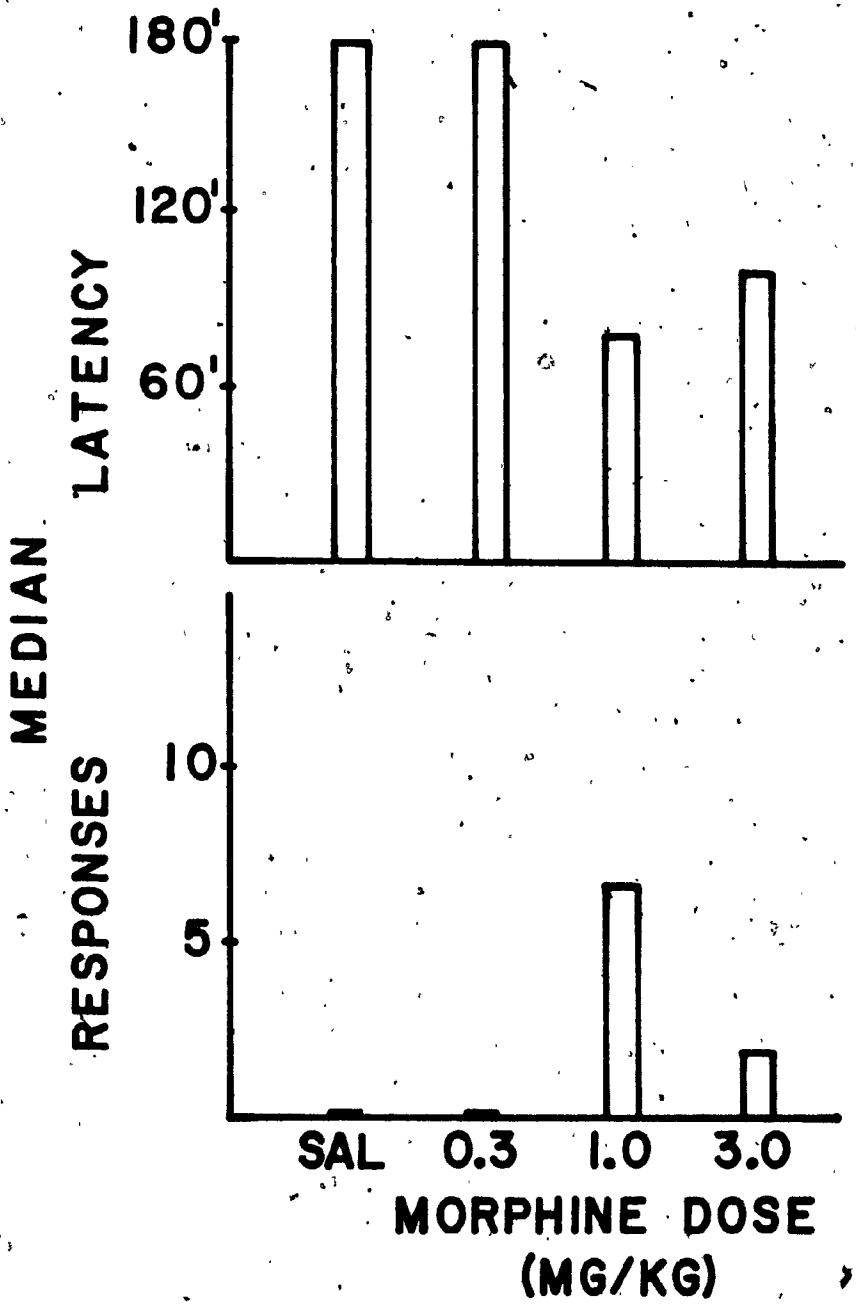
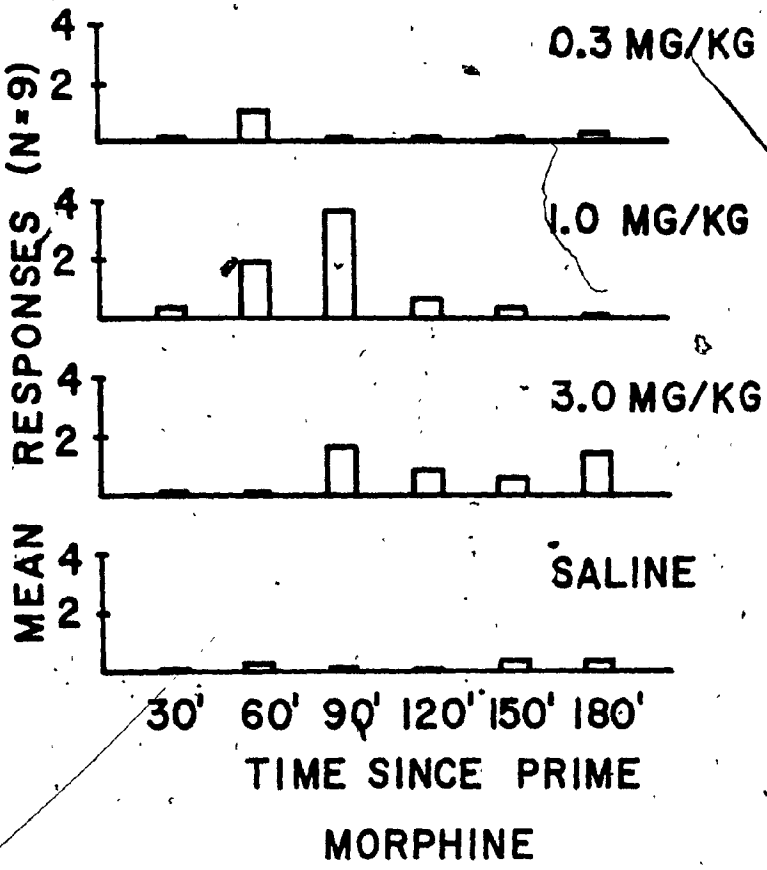

180'
120'
60'
MEDIAN LATENCY
10
5
RESPONSES
SAL
0.3
1.0
3.0
MORPHINE DOSE
(MG/KG)

FIGURE 18

Mean number of responses per 30-minute period after a morphine injection (0.3, 1.0, or 3.0 mg/kg) or a saline injection given during extinction after a period of cocaine self-administration. Means are based on data from nine rats.


0.3 MG/KG
1.0 MG/KG
3.0 MG/KG
SALINE
MEAN RESPONSES (N=9)
4
2
30' 60' 90' 120' 150' 180'
TIME SINCE PRIME
MORPHINE

responses over the 3 hours for the two doses respectively) and occurred later in the test period when compared to the 0.3 mg/kg dose. The dose-dependent effects of morphine are also evident when the number of animals affected (responding at least once) by the three doses are examined (Table 1). It can be seen that at the two highest doses most of the animals (eight and seven out of nine animals) had responded by the end of the 3-hour test period, and that the higher of the two doses was associated with a slightly later onset of the effect.

Ethanol, Heroin and Methohexital

Table 2 summarizes the results from the tests with drugs that had little or no effect on responding during extinction. Ethanol was tested at three doses, and out of the five animals tested one responded at both 1 and 3 mg/kg, and none responded after 10 mg/kg ethanol. Heroin was tested at three doses, and with three different durations of test period following the infusion. Seven animals were tested at the two lower doses, with varying test periods for different animals. Only one animal out of seven responded after the 50 µg/kg dose, and two out of seven responded after the 100 µg/kg dose of heroin. On the two saline control sessions (with test periods of equivalent durations) only one animal responded after the saline injection on one of its tests. Six

Table 2

The proportion of animals making at least one response after injections of ethanol, heroin and methohexital delivered during extinction. The number of animals tested at each dose is indicated (N) and the duration (in minutes) of the test period is given. For all drugs except ethanol, each animal was given a saline test on a separate day, and the number of animals responding after saline are indicated. The individual animals' numbers are given in the last column; the animals that made at least one response are underlined.

Drug	Dose	N	Test Period (Mins)	Animals Responding at Least Once			
				Saline Test		Drug Test	(Animals #)
Ethanol	1 mg/kg	5	30	-		1/5	(2,3,5,6,R6)
Ethanol	3 mg/kg	5	30	-		1/5	(2,3,5,6,R6)
Ethanol	10 mg/kg	5	30	-		0/5	(2,3,5,6,R6)
Heroin	50 µg/kg	3	30	0/3		0/3	(B3,B4,B5)
Heroin	50 µg/kg	2	60	0/2		1/2	(B9,B10)
Heroin	50 µg/kg	2	180	0/2		0/2	(R6,5)
Heroin	100 µg/kg	2	30	0/2		1/2	(B5,B4)
Heroin	100 µg/kg	3	60	1/3	(B2)	1/3	(B2,B3,B10)
Heroin	100 µg/kg	2	180	0/2		0/2	(5,R6)
Heroin	200 µg/kg	6	180	3/6	(Y3,B10,Y6)	4/6	(Y2,Y3,Y6,Y5,B10,A6)
Methohexital	1 mg/kg	2	60	0/2		0/2	(B4,B2)
Methohexital	2 mg/kg	2	60	0/2		0/2	(B4,B2)

additional animals were tested with either 200 µg/kg heroin or saline for a 180-minute test period. Four out of these six animals responded after the heroin injection but a similar number of animals, though not the same animals, responded after saline. The number of responses made per 30-minute interval after heroin (200 µg/kg) and after saline are presented in Table 3; as can be seen there is no clear trend in the distribution of responses over the 3-hour test period. Methohexital, at 1 and 2 mg/kg, produced no responding within a 60-minute period in the two animals tested.

Discussion

Amphetamine injections given during extinction produced a clear reinstatement of responding at all but the lowest dose tested. While neither saline injections nor the 0.1 mg/kg dose restored responding, the two highest doses (1.0 and 2.0 mg/kg) produced a great deal of responding and the intermediate dose (0.3 mg/kg) had a small effect. The 1.0 and 2.0 mg/kg doses were each associated with a distinctive time course of effect: The 1.0 mg/kg dose produced its strongest increase soon after the injection whereas the 2.0 mg/kg dose affected rates only toward the latter half of the 3-hour test period. This temporal distribution of responding over the test

Table 3

Individual animals' responses per 30 minutes after saline and after 200 µg/kg heroin, delivered during extinction following a cocaine self-administration session.

	Time After Infusion					
Saline:						
Rat	30'	60'	90'	120'	150'	180'
A6	0	0	0	0	0	0
Y3	0	0	0	2	13	0
Y6	0	0	17	3	0	0
B10	0	0	0	0	0	5
Y5	0	0	0	0	0	0
Y2	0	0	0	0	0	0
Heroin 200 µg/kg:						
Rat						
A6	0	2	3	1	0	0
Y3	0	0	0	0	0	0
Y6	0	0	0	1	1	0
B10	0	0	0	0	0	0
Y2	0	0	1	13	1	0
Y5	0	0	3	0	0	0

period resembled the pattern seen after different doses of cocaine, although the time course of the amphetamine effects was considerably extended.

These results were expected on the basis of the similarity of the stimulus properties of amphetamine and cocaine (Colpaert et al., 1976), and they are consistent with the notion that drugs reinstate responding during extinction by re-establishing the stimulus conditions that were present during drug self-administration. It is notable that the two highest doses of amphetamine produced considerably more responding overall than even cocaine injections: This is probably attributable to the considerably longer duration of the effect of amphetamine than of cocaine. It appears that responding occurs when, and as long as, the drug stimulus is present.

The absence of responding during the first 2 hours after the highest dose of amphetamine is probably related to the same factors that led to low levels of responding observed after the highest cocaine priming dose in Experiments 1A and 1B, and that determine the response suppression observed between infusions during drug self-administration. It would appear that after sufficiently high doses of these drugs, the animals begin to respond only as the blood level of drug falls below a critical level. Thus not only did priming

injections of amphetamine effectively reinstate responding after extinction following a session of cocaine self-administration, but many of the dose-dependent effects observed were similar to those seen with reinstatement by cocaine injections.

Apomorphine had a response-enhancing effect at each of the four doses tested. The temporal distribution of responding after the injection varied with the dose of apomorphine in a manner consistent with the dose-effects seen with cocaine and amphetamine: Low doses increased responding early in the test period whereas higher doses increased responding toward the middle or latter half of the test period. This pattern is consistent with the idea that circulating drug provides the stimulus that leads to responding in these animals. The magnitude of the response-enhancement after apomorphine at these doses was smaller than after either amphetamine or cocaine, and the absence of a direct relationship between size of apomorphine dose and number of responses suggests that higher doses than those tested would not have produced appreciably more responding. It might therefore be concluded that there is only a limited similarity in the stimulus properties of cocaine and apomorphine. This conclusion is supported by the results from drug generalization tests in rats trained with cocaine as

the cue (Colpaert et al., 1979). While amphetamine produced responding on the drug lever 100% of the time, apomorphine injections produced a maximum of only 75% drug-lever responding below doses that severely suppressed responding.

In the present experiment morphine led to a small but reliable increase in responding, and the same dose-dependent temporal distributions seen with other drugs were evident here. That is, low doses produced rate increases sooner after the drug injection than larger doses. The latencies to the first response at all doses of morphine tested were considerably longer, however, than with the other drugs. The long latencies to respond after morphine in this paradigm suggest a possible explanation for some otherwise discrepant findings. While morphine is generally considered to have a depressant effect (as a narcotic drug), there is evidence that it produces a biphasic effect, consisting of initial depressant effect followed by a subsequent excitatory effect (Kumar, Mitchell & Stolerman, 1971; Holtzman, 1976; Oka & Hosoya, 1976). It might be this latter phase that resembles the cocaine stimulus, thereby eliciting responding in this paradigm. The failures to show generalization between cocaine and morphine in the drug discrimination paradigm in rats might be explained by this time course of

morphine's effects. The typical drug discrimination experiments give intraperitoneal injections of the test drug 30 minutes before testing, and are therefore tested when the depressant effects of morphine predominate. It seems likely that it is only during the later excitatory phase of morphine's effect that this drug produces a stimulus sufficiently similar to cocaine to reinstate previously cocaine-reinforced responding. 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 aspects of the stimulus properties of intravenously-administered morphine resemble cocaine's effect.

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 & 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 & Fraser, 1961). It may be that some other aspect of the heroin stimulus such as its novelty suppressed

responding in the present experiment.

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. It should be noted that the animals did not lose the tendency to respond to cocaine priming infusions after these repeated tests with ineffective substances. Animals whose catheters remained patent were given a final reinstatement test with cocaine and showed good reinitiation of responding at this time.

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 and heroin 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. Intravenous ethanol self-administration has been demonstrated (DeNoble & Begleiter, 1978; Smith et al., 1975), and yet produced no tendency to respond in the present experiment.

It can be concluded from Experiment 3A that other psychoactive drugs reinstate cocaine-reinforced

responding after extinction if their stimulus properties resemble those of cocaine as determined in tests of drug discrimination. This supports the hypothesis that priming infusions given during extinction elicit responding to the extent that they re-establish 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), 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 will be addressed in the next experiment.

EXPERIMENT 3B

Experiment 3A showed that injections of amphetamine, apomorphine, and, to a lesser extent, morphine were effective in reinstating responding after extinction of cocaine-reinforced responding. Ethanol, heroin, and methohexital had no effect. Amphetamine, apomorphine and morphine are all known to have locomotor stimulant effects, and therefore the possibility existed that the lever pressing observed after priming injections was due to increased general activity. Animals were tested in enclosed chambers with easily pressed levers that could have been hit at random by highly excited animals. While direct observations made of the animals during test sessions did not support the view that the lever was being hit by accident, it was felt that some kind of a control experiment to test for the possibility should be made. In addition, the situation is made somewhat more complicated by Hill's (1970) demonstration that stimulant drugs can potentiate the effectiveness of conditioned stimuli in general. Thus the further possibility existed that the infusions of the test drugs in Experiment 3A did not specifically affect drug-reinforced responses but rather enhanced the likelihood of all behaviors controlled by

environmental conditioned stimuli. These alternative explanations were addressed in the present experiment. A group of rats was trained to bar press for food reinforcement. They 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 3A, these animals were given infusions of cocaine, amphetamine or morphine. Reinstatement of responding after the drug infusions in these animals would point to a general activity effect or a general enhancement of the effectiveness of conditioned stimuli by these drugs.

Method

Subjects

Eleven male Sprague-Dawley rats weighing 300 to 350 grams upon arrival in the laboratory were used. They were food-deprived to 85% of their free-feeding body weight during the initial phase of the experiment.

Apparatus

The operant chamber equipped for food reinforcement and the nine self-administration boxes described in previous experiments were used.

Procedure

The rats were food deprived and trained to lever press for food (45 mg Noyes pellets) reinforcement on a variable ratio six schedule. They were then allowed to feed freely for one week and to regain the pre-deprivation weight before catheterization. They were implanted with intravenous catheters as in previous experiments. Beginning two days after catheterization the animals were given three daily 3-hour extinction sessions in the self-administration boxes without being connected to the infusion system. These extinction sessions were found to be necessary to allow previously food-reinforced responding to extinguish to meet the criterion periods of 30 minutes with no responses. After this period of extinction, test sessions with drug infusions were begun. On test sessions rats were connected to the infusion system in the self-administration boxes, and each bar press resulted in an infusion (0.125 ml) of physiological saline. After at least 1 hour and a criterion period of 30 minutes had passed with no responses, a drug infusion of either cocaine (1.0 mg/kg, N=7; or 2.0 mg/kg, N=3), amphetamine (1.0 mg/kg, N=3), or morphine (1.0 mg/kg, N=8), or a saline infusion was given through the infusion system and then flushed with saline. The latency to respond and the number of responses in the period

following the drug infusion were recorded. The duration of the post-infusion observation period for each drug was the same as that used in Experiment 3A.

Results

Table 4 summarizes the number of drug-naive but food-trained animals that made at least one response after an intravenous infusion of either cocaine, amphetamine, morphine, or saline. Neither cocaine nor amphetamine enhanced responding in these animals. Unfortunately, as can be seen from the number of animals responding after the saline infusion, responding during extinction persisted in these animals, in spite of a minimum of six days after extinction conditions in the self-administration boxes. While the relatively large number of responses after saline makes interpretation of the results with morphine injections difficult, inspection of individual animal data shows little evidence of a drug effect (Table 5). Of the five animals that did not respond after saline, only two responded after morphine. A t-test for related samples on the number of responses made after saline and after morphine yielded non-significant results ($t = -0.31$, $p > .50$); similarly there was no significant difference between the treatments when the latency

Table 4

Proportion of animals making at least one response after infusions of cocaine, amphetamine, morphine or saline in Experiment 3B. These animals had been trained to bar press for food reinforcement only.

Drug	Dose	N	Test Period (min)	Number of animals responding at least once
Cocaine	1 mg/kg	7	60	2/7
Cocaine	2 mg/kg	3	60	0/3
Amphetamine	1 mg/kg	3	180	1/3
Morphine	1 mg/kg	8	180	4/8
Saline	-	10	180	4/10

Table 5

Individual animals' latencies to the first response (in minutes) and number of responses after cocaine, amphetamine morphine and saline infusions in Experiment 3B. The test period was 60 minutes after cocaine and 180 minutes in all other cases. Animals in this experiments had been trained with food reinforcement only.

	Rat	Latency (Mins.)	Responses
Cocaine (1 mg/kg)	B5	60	0
	B6	60	0
	B7	60	0
	B8	60	0
	Y1	60	0
	Y2	55	1
	Y4	55	2
Cocaine (2 mg/kg)	Y1	60	0
	Y2	60	0
	Y4	60	0
Amphetamine (1 mg/kg)	B8	95	3
	B9	180	0
	Y4	180	0
Morphine (1 mg/kg)	B5	32	5
	B6	180	0
	B7	180	0
	B8	110	4
	Y4	180	0
	A1	60	1
	A3	110	9
	A4	180	0
Saline	B5	180	0
	B6	32	7
	B7	180	0
	B8	180	0
	Y1	180	0
	Y2	120	11
	Y4	180	0
	A3	5	2
	A1	6	5
	A4	180	0

measure was used ($t = -0.32$, $p>.50$). There was therefore no evidence for a general response enhancement after cocaine, amphetamine, or morphine injections in these animals.

Discussion

It was found that none of the three drugs tested (cocaine, amphetamine and morphine) led to a reinstatement of food-reinforced bar-pressing after extinction. In the previous experiments the same doses of these drugs led to a strong reinstatement of responding in animals that had a history of cocaine self-administration. Thus, this experiment provided no evidence for either a general enhancement of previously reinforced responses (or an increased effectiveness of environmental conditioned stimuli), or a general motor excitation leading to many "accidental" bar presses. Rather, the response-enhancing effect observed in previous experiments seems to be specific to responses previously reinforced by cocaine injections.

There were, however, many methodological differences between this "control" experiment and the experiments showing reinstatement, and firm conclusions ruling out these alternative explanations must await more rigorous control tests. Four major aspects in which the

food-reinforced animals in this experiment differed from drug-reinforced animals at the time of testing were: 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. For food-reinforced animals, the test drug injection was their first experience with drugs, whereas the drug-reinforced animals had considerable previous experience with cocaine. Animals' responses to drugs are very much influenced by previous exposure to the same and different drugs (Schuster and Johanson, 1974). The acquisition period for self-administration consisted of an average of 20 daily 2- to 3-hour sessions, whereas the food-trained animals had an average of 7 30-minute sessions. It is difficult to equate operant experience with such different reinforcers. The rates of responding during these acquisition phases also differed radically - 1 response per 10 minutes is typical for self-administration while 50 responses per minute is characteristic for food-reinforced responding on a variable ratio schedule. Finally, while the extinction procedure for self-administration-experienced animals was carried out immediately after the session of drug self-administration in the same experimental chamber,

food-reinforced animals were trained in one box and underwent extinction in the slightly different self-administration boxes. It is important to note, however, that the self-administration boxes elicited high levels of food-related responding. Several daily 2- to 3-hour sessions were needed before the previously food-reinforced animals ceased to respond for the criterion period of one hour required before a drug infusion was given. This was so in spite of the fact that animals were allowed ad libitum access to food during this period. Thus, while it might be argued that any one 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. A more adequately controlled procedure with a two-lever chamber (one lever associated with drug reinforcement and the other either with nothing or with food reinforcement) would allow for firmer conclusions.

EXPERIMENT 4

Attention has been given recently to the importance of conditioning factors in the phenomenon of relapse in human drug users (see review Grabowski & O'Brien, Note 1). Ex-heroin addicts, during the course of treatment or incarceration, usually undergo detoxification and even extended periods of abstinence from the formerly abused drug in an environment other than the drug abuse-associated environment. Upon return to the environment associated with drug use, these ex-addicts report strong feelings of craving for the drug as well as physiological symptoms resembling withdrawal illness (O'Brien, 1975). It has been suggested (Wikler, 1965; O'Brien, 1975) that these effects are the result of classical conditioning; that environmental stimuli can, by virtue of their association with drug reinforcement, subsequently elicit responses that affect the behavior of the organism in their own right. The present experiment sought to examine this effect in rats, that is whether stimuli associated with reinforcing cocaine infusions would in themselves increase the tendency to reinitiate responding during extinction. Just as in the previous experiments non-contingent drug infusions resulted in a reinstatement of extinguished

self-administration responding, so might conditioned stimuli in the present experiment also increase the tendency to respond during extinction. Two groups of animals were trained to self-administer cocaine on a variable interval schedule: one group received a tone simultaneously with each drug reinforcement 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.

Method

Subjects

Nineteen male Sprague-Dawley rats weighing 300 to 350 grams 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 3A) were used in this experiment. The tone to be used as conditioned stimulus in this

experiment was an intermittent (one second on, one second off), 60 decibel, 6000 hertz tone operated by the timer that controlled the drug 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 two 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 seconds depending on the animal's weight. There was a 2- to 3-second 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 to 3 seconds. 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- to 3-hour 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. Priming injections during this training phase were kept to a minimum and, when they were given, they were not accompanied by the tone. This was done in order to reduce the possibility that the tone should acquire discriminative stimulus properties by regularly preceding reinforced responses. After two weeks of stable responding, three consecutive daily test sessions were given, each consisting of a 1- to 2-hour 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 minutes 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-minute period were recorded. After a further period of 30 minutes

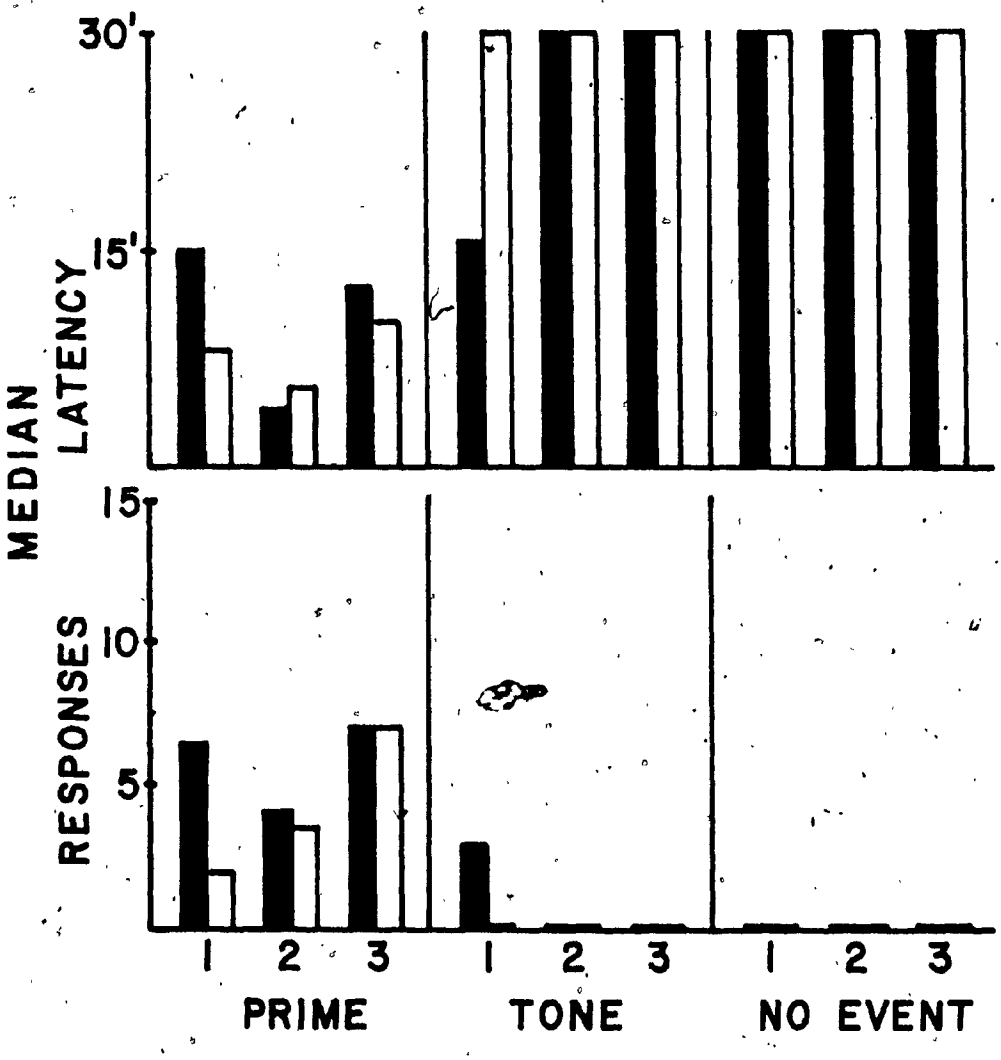
with no responses, one of the remaining events was presented and the latency and the number of responses in the following 30 minutes were recorded. Finally, after another 30 minutes of no responses the third event was tested. The order of presentation of these events was counterbalanced.

Results

The median latencies to respond and the median number of responses made by all the animals in the correlated and the uncorrelated conditions following the prime, the tone and no event are presented in Figure 19. It can be seen from these data that animals from both the correlated and the uncorrelated conditions responded following the priming infusion of cocaine on each of the three tests. Following the presentation of the tone, most of the animals in the correlated group responded on the first test day only, giving a median latency score of 15.5 minutes and a median of three responses for that day. Less than half the animals in this condition responded after the tone on the subsequent two test days. Of the seven animals tested in the uncorrelated condition only two responded after the tone on the first test and one on subsequent tests. Few animals responded on any occasion after no event in either condition.

FIGURE 19

Median latencies to the first response (upper graph) and median total number of responses (lower graph) in the 30-minute period following a priming infusion of cocaine (1 mg/kg), the tone or no event, each presented on three separate test days. Data from all animals are included in the calculation of these median values. Filled bars represent the medians for the correlated group (N = 12) and open bars refer to the uncorrelated group (N = 7).


30'
15'
MEDIAN LATENCY
15
10
5
RESPONSES
1 2 3 1 2 3 1 2 3
PRIME
TONE
NO EVENT

Data from individual animals are presented in Tables 6 and 7. It can be seen that some animals 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 are presented separately (Figure 20). For animals from the correlated group that met these criteria, there was a significant difference between the mean number of responses after the tone and after no event ($\bar{x}$ = 7.3 and 0 respectively) on the first day of testing ($t = 2.35$, $p<.05$, $df = 9$). 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 infusion.

Discussion

Experiment 4 showed that a stimulus that had been associated with cocaine infusions transiently increased

Table 6

Individual animals' latencies to respond (in minutes) in Experiment 4, after a prime (P), the tone (CS) and no event (NE). Each animal was tested with all three events on three separate test days. Animals that made no responses in the 30-minute test period are indicated with a dash (-).

Group	Rat	P			CS			NE		
		1	2	3	1	2	3	1	2	3
CORR	B1	0.5	0.5	-	5	-	-	-	-	-
CORR	B2	15	3	7	-	-	-	-	-	-
CORR	B3	-	-	-	-	-	-	-	-	-
CORR	B9	8	4	15	7	-	-	-	-	-
CORR	B10	20	17	2	15	-	-	-	-	-
CORR	R3	4	2	0.5	7	-	-	-	-	-
CORR	R5	20	-	-	-	-	-	-	-	-
CORR	1	-	3	10	-	-	-	-	-	-
CORR	3	12	4	-	5	20	-	-	-	-
CORR	7	15	27	28	12	-	17	-	-	-
CORR	10	-	3	5	13	3	-	-	2	
CORR	R1	5	-	7	16	7	-	7	12	20
UNCORR	R2	1	1	2	-	-	-	-	-	-
UNCORR	R6	2	-	7	15	0.5	10	12	-	10
UNCORR	4	8	5	8	-	-	-	-	-	-
UNCORR	2	-	9	12	17	-	-	20	25	-
UNCORR	12	-	-	-	-	-	-	-	-	-
UNCORR	Y5	-	2	-	-	-	-	-	-	-
UNCORR	Y2	4	6	15	-	-	-	-	-	-

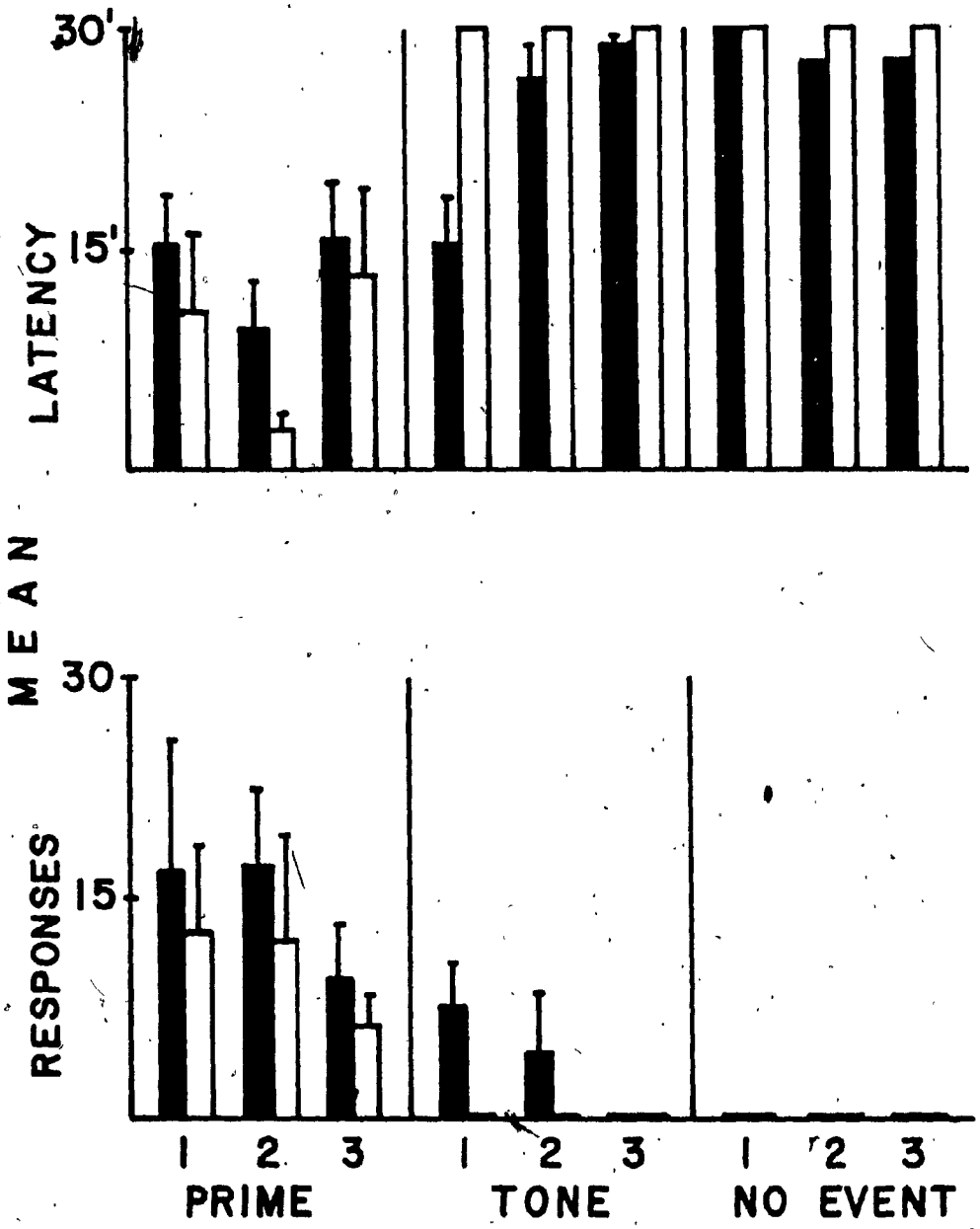
Table 7

Individual animals' number of responses after a prime (P), the tone (CS) or no event (NE) in Experiment 4, after each of three tests.

Group	Rat	P			CS			NE		
		1	2	3	1	2	3	1	2	3
CORR	B1	26	28	0	2	0	0	0	0	0
CORR	B2	2	41	30	0	0	0	0	0	0
CORR	B3	0	0	0	0	0	0	0	0	0
CORR	B9	7	14	6	4	0	0	0	0	0
CORR	B10	7	3	8	4	0	0	0	0	0
CORR	R3	17	42	27	1	0	0	0	0	3
CORR	R5	1	0	0	0	0	0	0	0	0
CORR	1	0	5	12	0	0	0	0	0	0
CORR	3	100	32	0	28	41	0	0	0	0
CORR	7	6	1	2	18	0	1	0	0	0
CORR	10	0	3	20	16	5	0	0	2	0
CORR	R1	32	0	22	11	2	0	10	2	5
UNCORR	R2	21	5	9	0	0	0	0	0	0
UNCORR	R6	36	0	12	1	3	6	1	0	12
UNCORR	2	0	25	10	48	0	0	24	1	0
UNCORR	4	27	36	5	0	0	0	0	0	0
UNCORR	12	0	0	0	0	0	0	0	0	0
UNCORR	Y5	0	3	0	0	0	0	0	0	0
UNCORR	Y2	2	4	11	0	0	0	0	0	0

FIGURE 20

Mean latencies to first response (upper graph) and mean number of responses (lower graph) after each of three tests (on three 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-minute period following each of these events, and a period of 30 minutes 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.


30'
15'
LATENCY
MEAN
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RESPONSES
1 2 3 1 2 3 1 2 3
PRIME
TONE
NO EVENT

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. Certainly the effectiveness of the conditioned stimulus in these animals is not comparable to the reported effectiveness of drug-associated stimuli in controlling relapse behavior in human ex-addicts.

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 could 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 (Wikler, 1965; Grabowski & O'Brien, Note 1). 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 aftereffects 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 animal's 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 process of classical conditioning.

General Discussion

These experiments showed 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. This finding 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 "uncontrollable urge" to have another. While this principle has been seriously questioned in recent years (Sobell & Sobell, 1978), the widespread acceptance of this notion attests to its veracity in many cases. The question of whether one drink "primes" or induces a craving for further drinks in alcoholics has been examined experimentally by Hodgson, Rankin and Stockwell (1979). In their study moderate or severely dependent alcoholics who had been

abstinent for at least one day were given a priming drink of low, high, or no alcohol content in the morning. Three hours later they were asked to rate their craving for a second drink ("I have a desire for a drink", rated from "not at all" to "very strong" on the five point scale) and, in addition, their rate of consumption of the afternoon drink was recorded as a behavioral measure of craving (Rankin, Hodgson & Stockwell, 1979). There was a significant correlation between "desire for a drink" and speed of consumption, and the severely dependent (although not the moderately dependent) subjects showed a tendency to consume their afternoon drink faster after a higher morning priming dose.

Another example of the "priming" effect in human drug use comes from a recent study (Meyer & Mirin, 1979) of patterns of heroin self-administration in hospitalized ex-heroin addicts. Ratings of craving for the drug (on a 100 mm line from strong to weak craving) were taken before and after heroin intake in subjects free to self-administer a fixed dose of heroin when they wanted it. Surprisingly, they found 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 & Mirin, 1979, p. 73). It is

possible that drug circulating in the blood acted as a "priming" stimulus maintaining the desire for more drug.

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, naloxone. As soon as the drug became available and for as long as it remained available the ratings of craving were high. This finding suggests that craving and drug-seeking behavior is 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 in being examined in several research laboratories (e.g., O'Brien, 1975; Sideroff & Jarvik, Note 4; Eikelboom & Stewart, 1979), and their possible role in drug-taking behavior, in particular in relapse, may soon be elucidated.

The reinstatement of drug-reinforced responding by experimenter-delivered infusions of a drug constitutes an experimental paradigm that has not previously been employed. In these experiments the principle function of the design was to investigate the conditions under which animals would reinitiate drug-taking after some drug-free period. The demonstration of response reinstatement after priming drug infusions has implications for both the understanding of relapse in human ex-addicts as well as for more theoretical questions of the role of learning and motivational processes in the control of behavior. In addition to being useful for the present purposes, the design of these experiments provides a novel and efficient method of testing other related experimental questions. The traditional drug discrimination experiments using a drug stimulus as a discriminative cue for food-reinforced responding have often been used as a test for abuse liability of new drugs. That is, if animals that have

been trained with a drug with known reinforcing properties show generalization to a test drug, that is taken to indicate a high probability of abuse potential with the new drug (Lal, 1977). It should be kept in mind, however, that the basis of the similarity in the stimulus properties of the two drugs may or may not involve their reinforcing properties. Evidence of the reinforcing efficacy of the training drug comes from an altogether different paradigm, usually involving a different route of administration. In the drug discrimination experiments the drugs are given in a context where their reinforcing properties are not necessarily relevant. The question of similarity of stimulus properties of drugs with possible reference to abuse liability can also be addressed in the reinstatement paradigm. In this case, evidence of the reinforcing efficacy of the training drug is readily apparent (during the self-administration period), and the test drug can be tested in a situation where drugs are acting as reinforcers. The results of Experiment 3A indicated that the reinforcing property of a drug is not in itself sufficient to produce reinstatement of previously drug-reinforced behavior, particularly when the training and test drugs are very dissimilar (e.g., in the case of stimulants and barbiturates). However, in cases where the drugs share at least some common

stimulus properties, the reinstatement paradigm may show whether these common properties are related in any way to the reinforcing properties. Thus, while this design shares some of the same interpretative problems regarding the particular aspects of the drug stimulus being used by the animals, it can be argued that in the context of a self-administration situation the animals would be more likely to focus on the reinforcing properties of the drugs.

A second advantage of the reinstatement paradigm for the investigation the stimulus properties of drugs, is that the time course of the effects of the test drug can be conveniently monitored. In conventional drug discrimination experiments, the similarity of the drugs can only be evaluated in the first few moments when the animal is put in the test situation. In many cases drugs have multiple effects that change over time, and because in the reinstatement paradigm the animals can remain in the test situation indefinitely from the moment of drug infusion, fluctuations in response tendency over time can be recorded continuously. Investigation of the time course of response-enhancement after a test drug may tell us which aspects of a drug stimulus are important in its effectiveness as a reinforcer. Furthermore, when considered together with the time course of other

behavioral and physiological effects of a drug, the data from reinstatement experiments might allow speculation regarding the neurochemical basis of the reinforcing and other properties of drugs.

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 "disciminative stimulus control" over responding. By this account a stimulus that has been present when responses are reinforced subsequently "evokes" the response. While on the 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. This suggests that the "control" that the drug stimulus

exerts over behavior is not complete, and further elaboration would be required to explain why in some cases the drug stimulus leads to a response (i.e., after a priming infusion) and in others it does not (i.e., in the 10 - 15 minutes between responses during self-administration). 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. However, this still leaves the problem of accounting for the continued emission of responses during extinction and after primes; the 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 presence of the drug stimulus and the emission of a motor response (bar press in this case).

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 were 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

sometime 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 cease to respond after the priming infusion after a number of test sessions. Rather, their persistence of responding argues for a more motivational interpretation of the facilitation of responding.

Bindra (1969) has argued for the existence of motivational aftereffects following the delivery of a reinforcer, and some of the evidence for the specific response-enhancing effects of reinforcement delivery was reviewed in the Introduction. The results of the present experiments are not inconsistent with this idea; unexpected presentations of the drug reinforcer resulted in a reinitiation of responding during extinction. The processes underlying this effect remain to be

investigated: How does a stimulus associated with positive reinforcement, in this case the reinforcing stimulus itself, control the animal's behavior? Does it do so simply by "reminding" the animals of the pleasurable stimulus, or does it actually have a direct arousing or activating role? Is the response-enhancement seen after priming infusions a direct (unconditioned) effect of the drug stimulus or does the drug stimulus produced by the priming infusion act as a conditioned stimulus which controls behavior by virtue of its previous association with larger, reinforcing drug infusions. These questions may be resolved by future investigation of the conditioned and unconditioned effects of self-administered drugs.

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Appendix 1

Individual animals' responses during extinction and latency to respond (minutes) after a cocaine injection given 10 minutes following onset of extinction condition, in Experiment 2.

Rat No.	Responses in Extn.	Latency (Mins.)
2	9	0.5
2	1	12
3	0	17
3	0	15
5	14	0.5
5	6	0.5
6	5	16
6	2	3
8	0	16
8	22	7

Appendix 2

Breakdown of number of implanted animals used or rejected.

Out of 46 rats catheterized:

31 reached testing stage

9 were rejected due to catheter failure or other equipment failure

6 were rejected because of failure to acquire stable self-administration responding

Appendix 3

Mean (and standard deviation) of number of responses during the first three days of extinction after continuous continuous reinforcement or variable ratio (VR6), correlated and uncorrelated groups.

	Day 1		Day 2		Day 3	
CRF	49	(47)	39	(17.2)	33	(20.3)
VR (all)	118	(87)	56	(37)	73	(49.3)
VR (Cor)	79	(54)	53	(37)	78	(50.3)
VR (Unc)	173.8	(94)	60.5	(36.6)	66.8	(47)