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Drug-Induced Reinstatement of Extinguished Self-Administration Behavior in Monkeys[1,2,3]

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GERBER, G. J. AND R. STRETCH. *Drug-induced reinstatement of extinguished self-administration behavior in monkeys.* PHARMAC. BIOCHEM. BEHAV. 3(6) 1055–1061, 1975. – Responding was established in squirrel monkeys under a modified progressive ratio schedule of IV d-amphetamine or cocaine self-administration. Substitution of saline for the drug solutions resulted in extinction of the self-administration behavior. IV injections of certain doses of d-amphetamine or cocaine, immediately prior to test sessions in which response-contingent saline infusions were delivered, reinstated the rate and pattern of responding observed during sessions in which drug was self-administered. Presession IV injections of several doses of pentobarbital or chlorpromazine failed to consistently reinstate responding. These results were interpreted in terms of the discriminative control of drug self-administration behavior by the current drug state of the subject.

Drug dependence Self-administration Extinction d-Amphetamine Cocaine Pentobarbital Chlorpromazine

IN studies of intravenous (IV) self-administration of drugs in animals, investigators frequently substitute saline for drug solutions to demonstrate that self-administration behavior is maintained only when responding results in the delivery of drug infusions. Characteristically, the response-contingent delivery of saline results in cessation (extinction) of responding.

Experiments using squirrel monkeys trained to self-administer d-amphetamine under modified progressive ratio schedules of reinforcement have demonstrated that if the monkeys received an intramuscular injection of d-amphetamine prior to a session in which saline infusions alone were available, responding did not extinguish. The pattern of responding observed under these conditions was indistinguishable from that seen during amphetamine self-administration sessions [14]. If self-administration behavior was extinguished by substituting saline for the drug solution, administration of a presession IV injection of d-amphetamine resulted in consistent dose-dependent reinstatement of the characteristic pattern of drug self-administration behavior, even though only response-contingent saline infusions were delivered [13]. Reinstatement of responding for 10 consecutive sessions was reported in this study, but it had been observed to continue, undiminished, for more than 20 sessions.

In the present experiment, the pharmacological generality of the reinstatement of extinguished drug self-administration by presession drug injections was examined. Other classes of drugs (pentobarbital, chlorpromazine and cocaine) were tested for their capacity to reinstate responding. Monkeys with cocaine self-administration histories were also tested to determine whether reinstatement occurs in animals that have self-administered a drug other than d-amphetamine.

METHOD

Animals

Juvenile and adult male squirrel monkeys (*Saimiri sciureus*) were used; none had been exposed previously to any form of experimentation. Body weights ranged from 400 to 800 g. Employing the surgical procedures described in [12], an intravenous catheter was inserted into the external jugular vein of each monkey and connected to a catheter-protection system prior to the experiments.

Apparatus

Monkeys were tested daily in a small primate restraining chair (BRS/LVE). The response lever was located 8–10 cm in front of the seated monkey; each lever depression closed a microswitch, constituting a response for recording purposes. A cue lamp (BRS/LVE 111-05) was located directly above the response lever; provision also was made

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[3] Reprints may be obtained from G. Gerber, Department of Psychology, Sir George Williams University, 1455 deMaisonneuve Blvd. W., Montreal, Quebec H3G 1M8, Canada.

to control presentation of a houselight and masking noise (75 dB) within the ventilated cubicle. Experimental conditions were controlled automatically by standard relay, timing and counting equipment; responses and infusions were tabulated by digital counters and plotted by a Gerbrands cumulative response recorder.

Infusions were delivered by an adjustable displacement piston pump (Milton-Roy model 196–31 instrument minipump). Each infusion consisted of 100 mcg/kg of drug in 0.5 cc/.750 kg body weight, delivered over 30 sec. Drugs were prepared in sterile normal saline using sterile procedures; drug dosages are expressed in terms of the salt.

Procedure

Acquisition of control performance. Ten monkeys were trained to self-administer d-amphetamine sulfate and 14 trained to self-administer cocaine hydrochloride. In initial testing, monkeys were placed in the testing apparatus daily and given the opportunity to self-administer 10 100 mcg/kg drug infusions within a maximum 2 hr period. Monkeys self-administered under a CRF schedule in which each lever press made when an infusion was not occurring produced an infusion. Responses made during an infusion were without consequence. The houselight and masking noise (75 dB) were present in the test cubicle for the duration of test sessions, except during infusions when the houselight and noise were switched off and a green cue light was illuminated. The infusion correlated changes in exteroceptive stimuli were in effect throughout the course of the experiment.

Following stabilization of drug intake, the monkeys were transferred to a modified progressive ratio 1 schedule of reinforcement (PrR 1). Response requirements for the first 10 infusions were 1, 2, 3 . . . . 10 responses. Following the 10th infusion, or following the expiry of a 15 min period (pause parameter) during which no response was made, a 30 min time out (TO) period began. During TO, all lights and masking noise were absent, and responding was without programmed consequence, although it was recorded. After the expiry of TO, a second series of 10 infusions was available under the same response requirements necessary to produce the first set of infusions. Periods during which infusions were available are referred to as time in (TI) periods. A modified progressive ratio schedule of reinforcement [4] was used in the present investigation to enable comparison with earlier reports of the reinstatement effect. This schedule has been found to be particularly effective in producing stable self-administration of d-amphetamine in squirrel monkeys.

After several sessions in which responding was well maintained under this schedule, the pause parameter was reduced to 5 min. Previous experiments (Stretch and Gerber, unpublished observations) have demonstrated that reduction of the duration of the pause parameter results in less variability in day-to-day performance under the modified progressive ratio schedule. During the period in which performance was being stabilized, it was necessary to increase drug dosage per infusion in order to maintain intake approaching 10 infusions per TI. Doses of d-amphetamine were increased to 150 or 200 mcg/kg/infusion, and cocaine doses were increased to 150 mcg/kg/infusion. Failure to increase drug dosage during the stabilization period resulted in the self-administration of fewer than 10 infusions per TI period.

Reinstatement of extinguished responding by presession drug administration. Each observation consisted of three 3 session components:

Drug self-administration. Monkeys were tested for 3 sessions under the PrR 1 drug self-administration schedule; each session was preceded by a 2 cc IV saline injections.

Saline substitution. Sessions were run during which saline was substituted for the self-administered drug; each session was preceded by an IV saline injection. Monkeys were tested until the mean response rate for the 3 most recent sessions was less than 15 percent of the mean response rate during drug self-administration. This was accepted as a criterion for considering the behavior extinguished. Only the last 3 sessions are presented as data.

Reinstatement. Three sessions were run which were identical to saline substitution sessions except that 1 min before each session, monkeys received IV injections of a drug solution, rather than saline. Responding during these sessions resulted in the delivery of saline infusions. Reinstatement drugs were tested at three doses using independent groups of three monkeys for each drug. The order of administration of doses was determined by a Latin square, so that each monkey received an independent presentation of doses.

The drugs tested for reinstatement properties in monkeys with amphetamine self-administration histories were: cocaine hydrochloride in doses of 150, 300 and 1000 mcg/kg; pentobarbital sodium in doses of 1000, 3000 and 6000 mcg/kg and chlorpromazine hydrochloride in doses of 30, 100, and 300 mcg/kg. Monkeys with cocaine self-administration histories were tested with the same three drugs, as well as with d-amphetamine sulfate in doses of 150, 300, and 1000 mcg/kg. Reinstatement of d-amphetamine self-administration behavior by d-amphetamine pretreatment was demonstrated previously [13].

RESULTS

All results are expressed in terms of mean response rate per second and mean number of infusions per session. Data from all animals was used in calculating group means, although not all animals completed all parts of the experiment. Due to the large number of sessions necessary to extinguish responding of some cocaine self-administering animals, it was not possible to test all reinstatement doses indicated in the experimental design prior to catheter malfunction.

Acquisition of Control Performance

A representative cumulative response record of drug self-administration performance under the PrR 1, 5 min pause schedule is shown in record A of Fig. 1. This record is for a monkey trained to self-administer d-amphetamine.

Mean responses per second and infusions per session data for each group of monkeys self-administering d-amphetamine or cocaine are shown in the left hand columns of Figs. 2, 3 and 4. Mean response rates for drug self-administration performances ranged from 0.30 to 0.69 responses per second, and mean infusions per session ranged from 17.6 to 20.0.

Saline Substitution Performance

Record B of Fig. 1 shows performance of Monkey G97 several sessions after saline had been substituted for

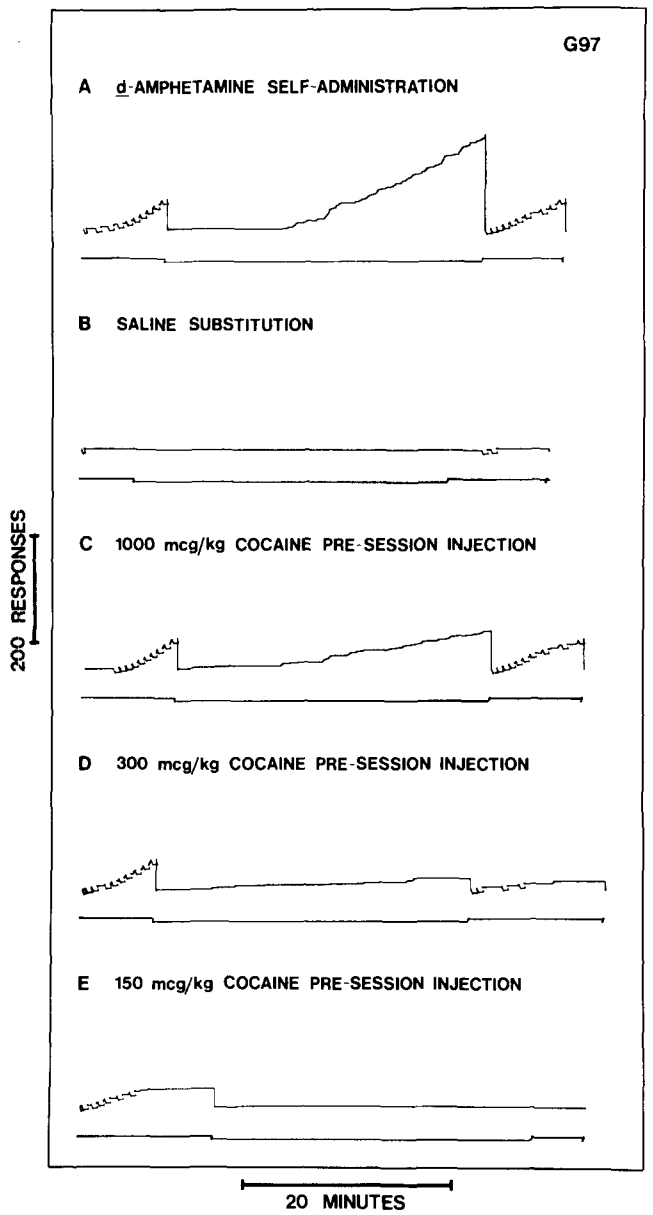

FIG. 1. Sample cumulative-response records showing performance under a modified progressive ratio (PrR) schedule of self-administration for monkey G97 during the three phases of the experiment. Record A shows performance under the PrR 1 5 min pause schedule of d-amphetamine self-administration (150 mcg/kg/infusion); the session was preceded by an IV saline injection. In Record B, saline was substituted for the drug, and the session was also preceded by a saline injection. Prior to the sessions shown in records C, D and E, the monkey received IV injections of cocaine at doses of 1000, 300 and 150 mcg/kg, respectively; however the sole consequence of responding was the delivery of saline infusions. Each record shows a complete session. The cumulative response pen is displaced in a downward direction to denote the duration of each 30 sec infusion; responses during infusions do not appear on the record. The response pen is reset at the beginning and end of the time out (TO) period, which is indicated by the displacement of the event pen beneath the response record. Responding during TO appears on the cumulative record, but was without any programmed consequence.

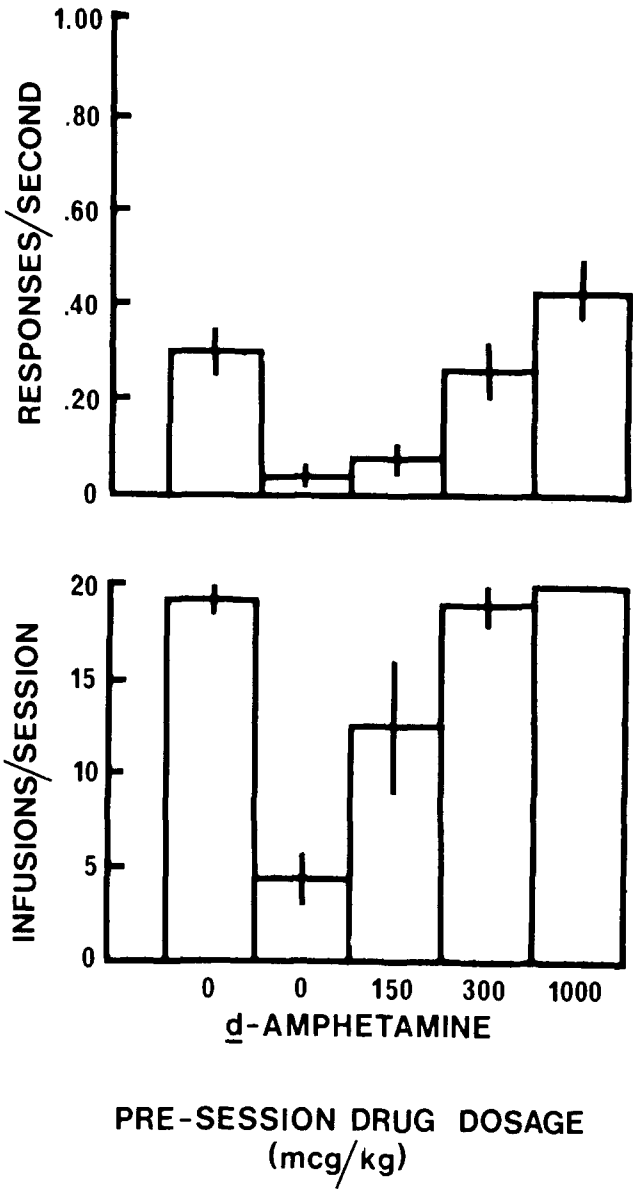

FIG. 2. Histograms summarizing results for the group of monkeys which was trained to self-administer cocaine, subsequently had saline substituted for the drug, and then received presession injections of 3 doses of d-amphetamine. The upper group of histograms shows mean responses per sec under time-in conditions; the lower histograms show mean number of infusions obtained during a test session; standard errors of the mean are also shown for each column. Presession drug dosages are indicated. From left to right, the first set of columns refers to cocaine self-administration performance; the second set refers to performance when saline was substituted for cocaine; the next 3 sets of columns refer to sessions when saline was self-administered, but presession injections of d-amphetamine, at the dosages indicated, were given.

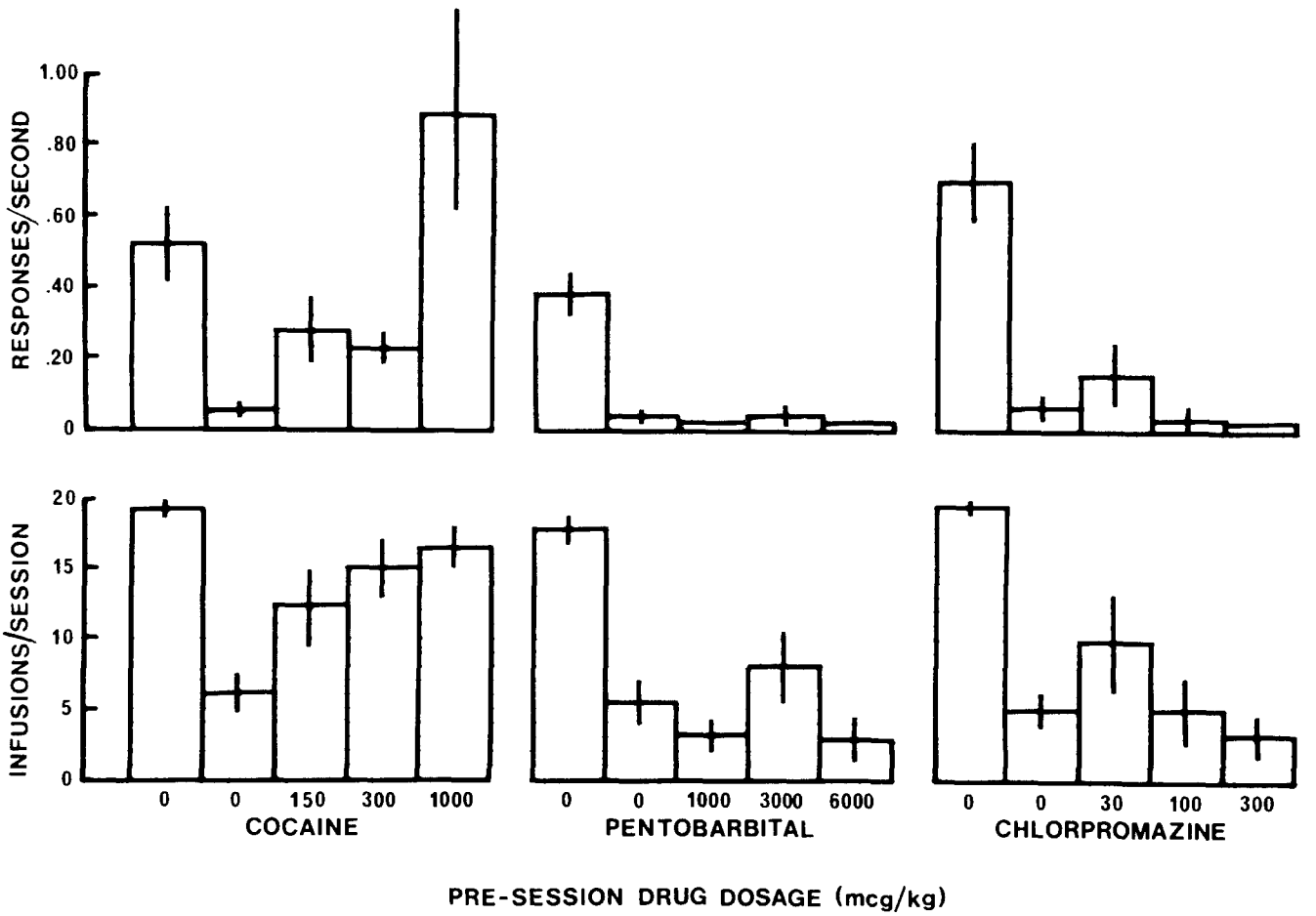

FIG. 3. Histograms summarizing results for groups of monkeys which were trained to self-administer d-amphetamine. subsequently had saline substituted for the drug, and then received presession injection of 3 doses of either cocaine, pentobarbital or chlorpromazine. The upper group of histograms shows mean responses per sec under time-in conditions; the lower histograms show mean number of infusions obtained during a test session; standard errors of the mean are also shown for each column. Presession drug dosages are indicated. For each drug pretreatment group, beginning at the left, the first set of columns refers to d-amphetamine self-administration performance; the second set refers to performance when saline was substituted for d-amphetamine; the next 3 sets of columns refer to sessions when saline was self-administered, but presession injections of cocaine, pentobarbital or chlorpromazine, at the dosage indicated, were administered.

d-amphetamine. While responding decreased to low rates, resulting in the delivery of few saline infusions for most monkeys with d-amphetamine self-administration histories, several monkeys with cocaine self-administration histories maintained responding at rates sufficient to obtain a greater number of saline infusions. As shown in the second set of columns for each group of histograms in Figs. 2, 3 and 4, mean response rates ranged from 0.03 to 0.05 responses per second, and from 0.02 to 0.08 responses per second for monkeys with histories of self-administering d-amphetamine and cocaine, respectively. Mean saline infusions obtained in this phase ranged from 5.1 to 6.1, and from 4.3 to 13.6 for the two groups, respectively.

Reinstatement of Extinguished Responding by Drug Pretreatment

Cumulative response records illustrating dose-dependent reinstatement of self-administration behavior that had been extinguished by saline substitution are shown in records C, D and E of Fig. 1. This monkey had been trained to self-administer d-amphetamine and, following saline substitution, dosages of cocaine were administered prior to sessions during which the sole consequence of responding was the delivery of saline infusions.

Results of administering presession drug injections to monkeys following the extinction of responding by saline substitution are shown in Fig. 2, 3 and 4. Drug dosages are labelled beneath the histograms. The clearest result of this treatment is that significant reinstatement of extinguished responding was obtained with several presession d-amphetamine and cocaine doses, but no consistent pattern of reinstatement was observed with either pentobarbital or chlorpromazine. Similar results were obtained with groups of monkeys having either d-amphetamine or cocaine self-administration histories. While response rates were not increased substantially by any presession dosages of pentobarbital or chlorpromazine tested, certain dosages of these drugs did increase the mean number of saline infusions obtained during these sessions. Due to the contingencies of the modified progressive ratio schedule of reinforcement used in this experiment, a monkey emitting a steady low

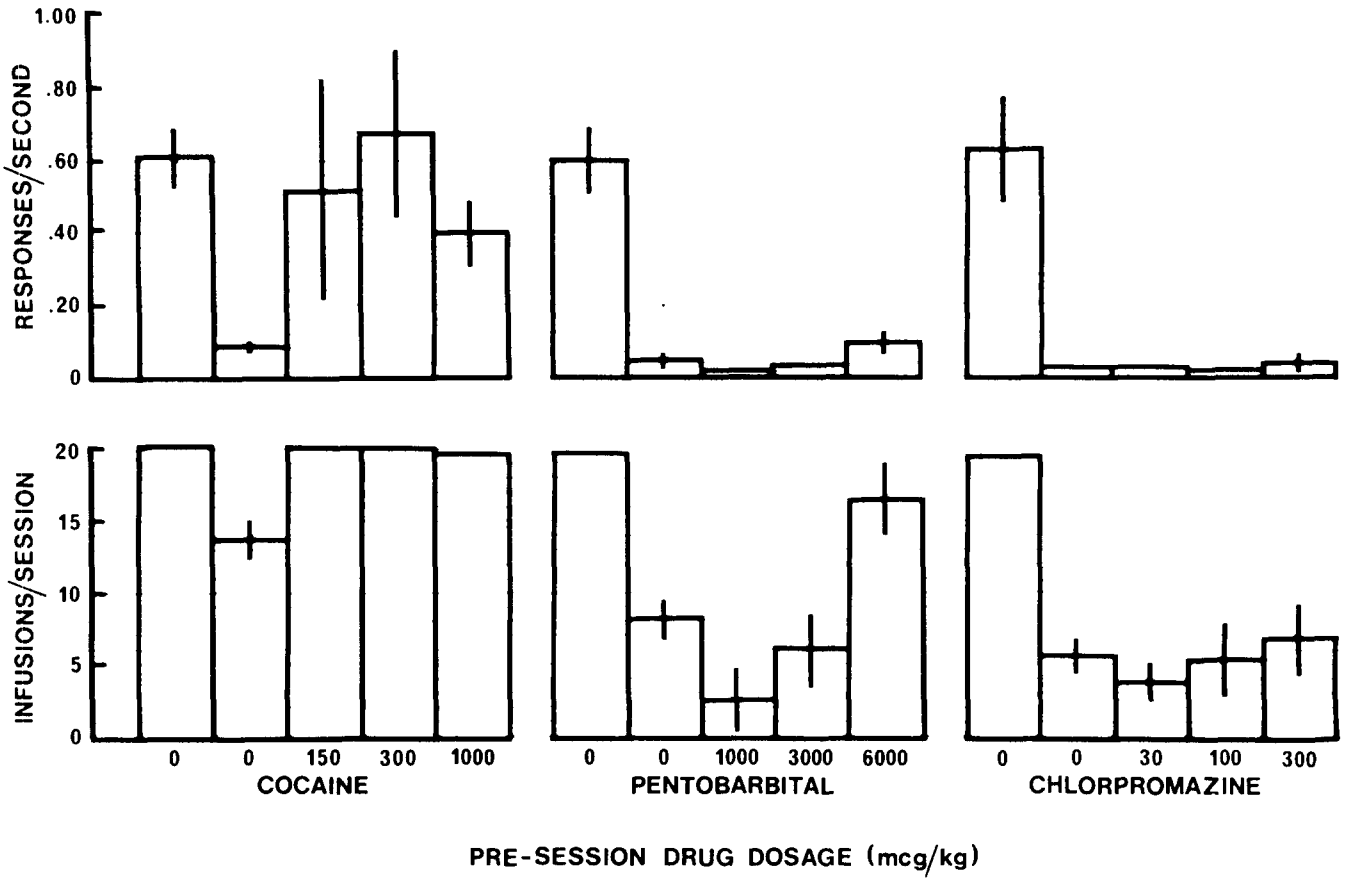

FIG. 4. Histograms summarizing results for groups of monkeys which were trained to self-administer cocaine, subsequently had saline substituted for the drug, and then received presession injections of 3 doses of either cocaine, pentobarbital or chlorpromazine. Conventions for this figure are the same as those for Fig. 3.

rate of responding could obtain the total number of infusions permitted under this schedule. It was only necessary for a monkey to emit one response every 5 min in order to obtain all available infusions. Thus, some disparity is evident between the rate of responding and the number of infusions obtained under certain drug pretreatment conditions.

Reinstatement of extinguished cocaine self-administration responding by presession injections of d-amphetamine, shown in Fig. 2, closely resembles the pattern of dose-dependent reinstatement of extinguished d-amphetamine self-administration responding by presession injections of d-amphetamine previously reported [13].

Presession cocaine injections were effective in reinstating extinguished responding in groups with either d-amphetamine or cocaine self-administration histories. It can be noted in Fig. 4 that while response rates during the saline substitution phase were low (0.08 responses/sec), a mean of 13.6 saline infusions was obtained. Presession cocaine injections produced an inverted U shaped dose-dependent effect on response rates, but all doses increased the number of saline infusions obtained to the maximum (20).

Neither pentobarbital nor chlorpromazine presession injections restored response rates to those observed during the drug self-administration phase, but the shape of the dose-response relationship produced by presession injections of these drugs differed for monkeys with d-amphetamine, as compared to cocaine self-administration histories. For those monkeys with a d-amphetamine self-administration history, pentobarbital (3000 mcg/kg) and chlorpromazine (30 mcg/kg) produced the most pronounced increases in both response rates and the numbers of saline infusions obtained. For the monkeys with a cocaine self-administration history, the 6000 mcg/kg pentobarbital and the 300 mcg/kg chlorpromazine dosages produced the most pronounced increases in response rate and saline infusions obtained. Of particular note is the effect of 6000 mcg/kg presession pentobarbital injections on the group with a cocaine self-administration history. This dose doubled response rates and numbers of saline infusions obtained, when compared with saline substitution performance.

DISCUSSION

Once responding has been established by the response-contingent delivery of IV d-amphetamine or cocaine infusions, and has been extinguished subsequently by saline substitution, presession IV injections of certain doses of either d-amphetamine or cocaine reinstate responding for the duration of a testing session. During reinstatement test sessions, only response-contingent infusions of saline were delivered; yet, rates and patterns of responding, and the

numbers of infusions obtained were very similar to those observed when discrete infusions of the drug could be obtained by responding.

Over the tested range of doses presession injections of pentobarbital or chlorpromazine did not reinstate response rates to the extent recorded during d-amphetamine or cocaine self-administration sessions. However, some doses of pentobarbital or chlorpromazine did increase the number of infusions obtained during reinstatement tests by engendering low rates of responding for prolonged periods. Under the conditions specified by the modified progressive ratio schedule used in these experiments, animals continued to obtain infusions, despite low rates of responding.

These findings can be interpreted within the framework of the discriminative control of behavior by drug states. When drugs with similar pharmacological properties, known to exert discriminative control over behavior, are administered in equally effective doses, they have been found to produce drug states which are relatively indistinguishable from one another [7,8]. Presession injections of d-amphetamine or cocaine for monkeys with histories of self-administering one of these two drugs, are likely to produce drug effects that are indistinguishable from the effects these drugs produced when they were self-administered. This account is compatible with the report that amphetamine and cocaine have similar subjective effects in humans when administered intravenously [6].

Drugs which exert discriminative control over behavior but have different pharmacological properties, can be readily distinguished from one another [7,8]. The failure of presession injections of pentobarbital or chlorpromazine to reinstate comparable response rates and patterns of d-amphetamine or cocaine self-administration behavior, is in keeping with these findings. Since pentobarbital and chlorpromazine have pharmacological properties very different from d-amphetamine or cocaine, it might be expected that drug effects produced by pentobarbital or chlorpromazine would be readily distinguishable from the effects of either d-amphetamine or cocaine [8]. This interpretation suggests that pentobarbital or chlorpromazine did not reinstate similar response rates and patterns of d-amphetamine or cocaine self-administration behavior since the effects produced by presession injections of either chlorpromazine or pentobarbital were distinguishable from the effects produced by psychomotor stimulant self-administration.

A phenomenon similar to the reinstatement effect has been reported [11]. Discriminative stimuli associated with response-contingent morphine injections exerted behavioral control under extinction conditions, only when the session was preceded by an injection of morphine. The reinstatement of extinguished responding has also been observed in monkeys with histories of self-administering methohexital when they received a presession injection of pentobarbital (R. N. Grove, personal communication).

The demonstration of drug-induced increases of extinguished responding by psychomotor stimulants, seen in the present experiments, is methodologically similar to procedures used in other experiments. When exteroceptive stimuli previously associated with the availability of food reinforcement were present during extinction, pipradrol [3] and amphetamine [10] have both been shown to increase response rates of rats. However in the experiment using pipradrol [3], rats received the drug each day after food reinforcement was discontinued, whereas in the present experiments responding was extinguished before presession drug injections were begun. In Skinner and Herons' experiment [10], the description of their procedure was too brief to determine whether exteroceptive stimulus conditions were the same during reinforcement and extinction phases of the experiment. Furthermore, it is difficult to extrapolate from this experiment since each animal received the drug on only one occasion at a single dose level. Animals in the present experiments received repeated administrations of 3 dosages of each drug studied.

In view of important differences between the procedures used to demonstrate the reinstatement of extinguished drug self-administration behavior, and other behavioral effects of psychomotor stimulant drugs described in the experiments noted above, the reinstatement effect merits consideration as a separate phenomenon.

The present results suggest that the reinstatement effects may be useful in predicting the outcome of other procedures designed to assess the reinforcing properties of drugs, in which a test drug is substituted for one which monkeys reliably self-administer. The finding that cocaine or d-amphetamine will reinstate extinguished responding in monkeys that have been trained to self-administer either of the drugs, agrees with the finding that d-amphetamine will be self-administered when substituted for cocaine in monkeys with cocaine self-administration histories [1, 2, 5, 9]. The finding that pentobarbital or chlorpromazine did not reinstate responding in the present experiment corresponds to findings from separate experiments that these drugs do not maintain responding when substituted for cocaine or other psychomotor stimulant drugs (Yanagita, Ando and Takahashi, personal communication and [5]).

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