Pharmacology Biochemistry & Behavior, Vol. 4, pp. 427–433.

The Effects of Perphenazine on Self-Administration Behavior[1]

CHRIS E. JOHANSON, DAVID A. KANDEL[2] AND KATHRYN BONESE[3]

The University of Chicago, Pritzker School of Medicine, Department of Psychiatry
950 East 59th Street, Chicago IL 60637 USA

(Received 29 September 1975)

JOHANSON, C. E., D. A. KANDEL AND K. BONESE. *The effects of perphenazine on self-administration behavior.* PHARMAC. BIOCHEM. BEHAV. 4(4) 427–433, 1976. – In Experiment 1, 6 rhesus monkeys prepared with intravenous catheters responded on a fixed-ratio 10 schedule for either an injection of 0.2 mg/kg of cocaine or 0.5 mg/kg of pentobarbital during a daily 3 hr session. The substitution of saline or various doses of perphenazine resulted in very low rates of responding. These results indicate that perphenazine is not a positive reinforcer. Pretreating animals maintained on 0.1 mg/kg or 0.2 mg/kg of cocaine with perphenazine resulted in increases in rate of self-administration at some doses and a decrease in rate at higher doses. The dose of perphenazine which resulted in the maximal increase in cocaine self-administration was directly related to the dose of cocaine maintaining responding. Pretreating animals maintained on 0.5 mg/kg of pentobarbital with perphenazine had no effect at doses which increased cocaine self-administration but decreased rate of pentobarbital self-administration at higher doses. These results indicate that perphenazine is capable of antagonizing some of the effects of cocaine.

Perphenazine Cocaine Pentobarbital Antagonism Self-administration

RESEARCH conducted during the past 10 years has shown that rhesus monkeys repeatedly make responses which are followed by an intravenous infusion of a variety of centrally active drugs including psychomotor stimulants, opiates, barbiturates and alcohol [15]. Since any stimulus which increases the probability of a behavior which it follows is defined as a positive reinforcer [16], these drugs, like food and water, can be considered reinforcers. While many drugs have been tested for their reinforcing properties, one class that has been largely overlooked in this research is the phenothiazines.

The phenothiazines can be differentiated on the basis of chemical structure; pharmacological activity can be significantly altered by substitution at the nitrogen of the central ring structure [9]. One group of phenothiazines has an aliphatic group at this locus; a second group has a piperazine substitution. Drugs of the second group are more potent antipsychotics, have less sedative effects, but produce more extrapyramidal symptoms than the aliphatic-substituted compounds [9]. Several studies have shown that chlorpromazine (CPZ), a widely used phenothiazine of the first group, is unable to maintain lever press responding and function as a positive reinforcer [2, 7, 21]. Since the pharmacological activity of phenothiazines is related to changes in substitution at the nitrogen locus, it is necessary to test other phenothiazines to determine if the inability to serve as a positive reinforcer is a general property of the entire class. In the present series of experiments, perphenazine, a piperazine-substituted phenothiazine, was examined. In the first study, this phenothiazine was tested to determine whether it could function as a positive reinforcer in rhesus monkeys. Responding was initially established using drugs which have previously been shown to be positive reinforcers under a wide variety of experimental circumstances. For half of the animals, responding was maintained by cocaine and for the other half, the consequent event was pentobarbital. Both drugs were used since it has been shown that response frequency and patterning maintained by a test drug can be influenced by the type of drug originally maintaining responding [14].

In addition to investigating the reinforcing properties of perphenazine, a second study was conducted to determine its effects on responding maintained by cocaine or pentobarbital. If access to cocaine is limited to 3–4 hr per day, the total daily intake is approximately the same regardless of dose per infusion [18]. That is, as the infusion dose is increased, frequency of self-administration decreases. At present the mechanisms underlying this dose-dependent decrease are unclear since rate of self-administration may reflect the magnitude of the reinforcing properties of the dose or it may merely be a function of its ability to disrupt ongoing behavior, regardless of the stimulus maintaining responding [10, 15, 18, 20]. Chlorpromazine has been shown to antagonize a variety of the behavioral effects of psychomotor stimulant drugs [1, 4, 12, 13, 17]. Of particular interest is its ability to increase the frequency of

[1]This research was supported by NIDA Grants DA-00047 and DA-00250. We would like to thank Dr. S. Sathe and Schering Laboratories for partial support of the research and the supply of perphenazine. We would also like to thank Abbott Laboratories for furnishing the pentobarbital.

[2]Now at the Department of Psychology, University of Maryland, College Park, Maryland.
[3]Now at the Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut, 06510.

self-administration of cocaine at certain doses [20]. The second study was designed to determine whether perphenazine was also capable of antagonizing the effects of cocaine in this situation. In addition, its effects on responding maintained by pentobarbital were evaluated to determine the specificity of the antagonism.

EXPERIMENT 1

METHOD

Animals

The animals were 6 adult male rhesus monkeys (A043, A060, A069, A110, A113 and 4029) weighing between 3.9 and 8.5 kg. Two monkeys (A060 and 4029) were experimentally naive; the other 4 had prior drug self-administration experience with responding maintained by a variety of drugs. Each animal was anesthetized with sodium pentobarbital (30 mg/kg i.v.) and surgically prepared with an intravenous silicone catheter. The proximal end of the catheter was inserted into a major vein for a distance calculated to have it terminate in the superior vena cava; the other end of the catheter was threaded subcutaneously and exited the body through an incision in the back of the animal. It was not always possible to maintain a single catheter for the duration of the experiment. However, several veins can be used for chronic catheterization in the rhesus monkey; the most accessible are the internal jugulars, external jugulars, and femorals. In the present experiment, when a catheter was dislodged, the monkey was removed from the experiment for a minimum of 10 days. At this time a replacement catheter was surgically inserted as before and the animal returned to the experiment.

All animals had continuous access to water and were given 20 Purina Monkey Chow biscuits and a sugar cube covered with liquid vitamins every morning. In addition, their diet was frequently supplemented with fresh fruit. Occasionally antibiotics were administered intramuscularly to arrest a catheter tract infection.

Apparatus

Each animal was housed throughout the entire experiment in a chamber that served as both the experimental cubicle and home cage. For A110 and A113 these chambers were top-loading, open metal grid cages and for A043, A060, A069 and 4029 the chambers were front-loading, sound-attenuating wooden cubicles equipped with a ventilation fan. In the wooden cubicles, the monkeys were visually isolated but the door had a 1-way mirror for observation. On the inside front of all the chambers were 2 response levers (BRS/LVE, PRL 001/121-07) each with a stimulus light mounted 5 cm above it. A white and a red light were located on the ceiling in the wooden cubicles, while in the metal cages, a red light was located between the other 2 stimulus lights.

Each monkey wore a stainless steel harness and was restrained by a spring arm 45 cm in length and 1.5 cm in dia. which was attached to the wall at the back of the chamber. This arrangement allowed the monkey relatively unrestricted movement and provided protection for the catheter which was threaded through the arm to the outside of the cubicle and connected to a peristaltic infusion pump (Cole-Parmer 7540X) which delivered solutions at the rate of 6 ml/min.

Cables connected the experimental cubicles to electromechanical programming and recording equipment located in an adjacent room.

Procedure

Training. Since four of the animals had previously been employed in similar experiments, these animals were exposed immediately to the terminal schedule. However, training was necessary for A060 and 4029.

Initially each lever press on the right lever (lever 1) in the presence of a stimulus light was followed by an infusion of 0.2 mg/kg of cocaine. In general, this training was accomplished by merely placing the animal in the experimental situation in which one of the stimulus lights was illuminated. Occasionally it was necessary to tape a raisin on the lever to increase the probability of the response. Following the acquisition of the lever-pressing response, the number of responses required for cocaine delivery was gradually increased to 10 (fixed-ratio 10; FR 10). At that time, 2 animals (A069 and A113) were given access to 0.5 mg/kg pentobarbital rather than cocaine. No additional training was necessary.

Terminal Schedule. During each daily 3 hr session, the animals obtained intravenous infusions of 0.2 mg/kg of cocaine (A060, A043, A110 and 4029) or 0.5 mg/kg pentobarbital (A069 and A113) by pressing lever 1 on a fixed-ratio 10 schedule of reinforcement. The number of infusions delivered and the total number of responses on lever 1 were recorded every 30 min. Responses on the left lever (lever 2) were also recorded but had no other programmed consequence.

Drug or saline availability was associated with illuminated white stimulus lights above both levers; in the wooden cubicles, the white ceiling light was also illuminated during the 3 hr session. However, these stimulus lights were extinguished during infusions and a red light was illuminated. The infusion volume was 0.2 ml/kg of body weight.

Following the establishment of stable rates of responding during the baseline conditions (less than 10% variation in the total number of infusions per session for 3 consecutive sessions), saline was substituted for the drug maintaining responding for 6 sessions to determine the pattern of extinction performance. All animals were then returned to baseline conditions where responding was maintained on the FR 10 schedule of drug delivery. When an animal's performance again reached baseline criterion (less than 10% variation), a perphenazine solution was substituted for the baseline drug for 6 sessions for each dose. Five doses of perphenazine were tested in 3 of the animals (A060, A069, A110): 0.0001, 0.001, 0.01, and 0.1 and 1.0 mg/kg/infusion. The highest dose was omitted for A113. Sessions were conducted daily for these 4 animals. There was a return to baseline drug conditions between the substitution of each of the doses of perphenazine until responding maintained by cocaine or pentobarbital was stable; the order in which the animals received the doses was varied (see Table 1). After returning to the baseline drug conditions following the testing of all the doses of perphenazine, saline was substituted for the drug for 6 sessions. For A043 and 4029, only the dose of 0.01 mg/kg of perphenazine was tested for 6 sessions. However, each of these sessions was separated by at least 3 days and no sessions were conducted on the other days. Sessions were

TABLE 1

EXPERIMENT 1: ORDER OF TESTING

Animal	Perphenazine Dose (mg/kg) 0.0001	0.001	0.01	0.1	1.0
A060	5	2	3	1	4
A069	5	3	1	4	2
A110	4	1	5	2	3
A113	3	4	2	1	

thus separated by 3 days to control for cumulative drug effects.

Drug Solutions

All the drugs used in this experiment were dissolved in 0.9% physiological saline. Doses refer to the salt. Cocaine HCl and sodium pentobarbitol solutions were changed at least once a week, whereas the perphenazine solutions were changed at least once every 48 hr.

RESULTS

Figure 1 shows the mean number of infusions of perphenazine self-administered by the 4 animals tested with 4 or more doses as a function of dose per infusion. These means were calculated from the last 3 sessions of each substitution. The mean and range of saline infusions are also shown and the mean and standard error of baseline drug infusions are indicated to the right of each curve. On the last 3 days of substitution, animals A043 and 4029, whose sessions were separated by 3 days, self-administered a mean of 11 and 4 infusions of 0.01 mg/kg perphenazine, respectively. For each animal, no dose of perphenazine maintained more responding than that maintained by saline. Table 2 indicates mean perphenazine intake for each dose tested. While intake increased as a function of dose, the number of infusions taken was small and they occurred in the first few minutes of the session.

Pentobarbital and cocaine infusions (Fig. 2) were distributed equally between the first and second halves of the session although the distribution of interreinforcement times was different for the 2 drugs. Cocaine was self-administered at regular inter-infusion intervals whereas several infusions of pentobarbital were taken rapidly with long pauses between bursts. Nevertheless, these bursts of infusions were evenly distributed throughout the session. Saline, however, tended to be self-administered almost exclusively in the beginning of the session with an occasional burst later in the session. As shown in Fig. 2, the pattern of perphenazine responding tended to be similar to that of saline in that all the infusions were taken in the initial part of the session. However, responding rarely occurred later in the session.

Figure 3 shows the number of infusions self-administered by A110 on each of the 6 sessions of saline extinction as well as the substitution of 0.001 mg/kg of perphenazine. In both cases, response frequency was relatively high on the first session but gradually declined to low rates. Such a pattern is typical of extinction and is representative of the pattern of responding maintained by perphenazine for all animals.

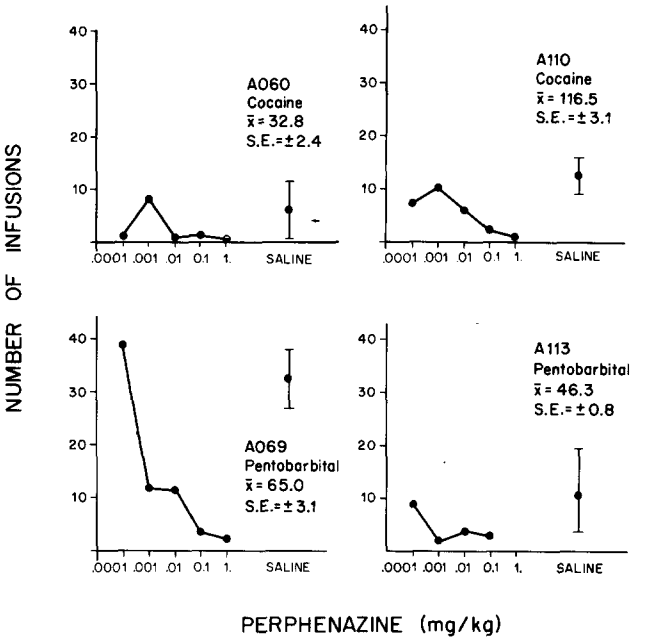

FIG. 1. Mean number of infusions of perphenazine self-administered each session at several doses shown separately for animals A060, A069, A110 and A113. The mean and range of saline infusions is shown on the right of each graph. The mean and standard error of the number of infusions of 0.2 mg/kg cocaine (A060, A110) or 0.5 mg/kg pentobarbital (A069, A113) are indicated in the right of each graph. Means are calculated from the last 3 sessions of each condition.

TABLE 2

EXPERIMENT 1: MEAN PERPHENAZINE INTAKE (MG/KG) FOR EACH ANIMAL AS A FUNCTION OF DOSE, CALCULATED FROM THE LAST THREE DAYS OF SUBSTITUTION

Animal	Dose (mg/kg/inf) 0.0001	0.001	0.01	0.1	1.0
A043	NT*	NT*	0.11	NT*	NT*
A060	0.0001	0.008	0.01	0.1	0
A069†	0.0039	0.012	0.11	0.3	2.0
A110	0.0007	0.01	0.06	0.2	1.0
A113†	0.0009	0.002	0.04	0.3	NT*
4029	NT*	NT*	0.04	NT*	NT*

*Dose not tested.
†Baseline drug of pentobarbital.

Although the intake of perphenazine on the last three sessions of substitution was relatively small, at the 3 high doses the amount self-administered on the first session of the substitution was large enough to produce typical phenothiazine behavioral effects including immobility, tremors, ptosis, and failure to react to external stimuli (Table 3).

EXPERIMENT 2

METHOD

Animals and Apparatus

The animals were 4 rhesus monkeys previously used in

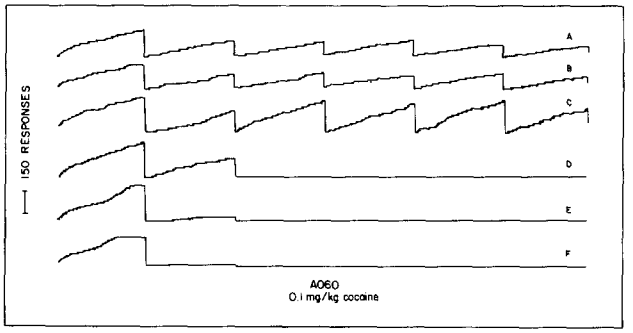

FIG. 2. Cumulative records of the pattern of intake of cocaine, pentobarbital, saline and perphenazine during a 3 hr daily session. Ordinate: cumulative responses; abscissa: time. The completion of the FR is indicated by a downward deflection of the pen. The response pen resets every 30 min.

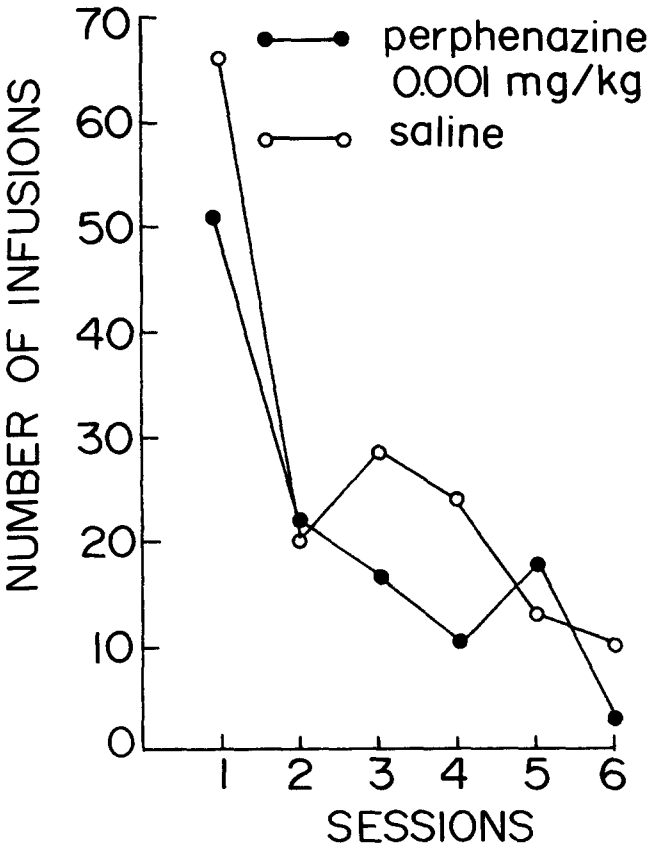

FIG. 3. The number of saline (open circles) and perphenazine (filled circles) infusions taken by A110 during each of 6 consecutive sessions following sessions when 0.2 mg/kg of cocaine was available.

Experiment 1 (A060, A069, A110 and A113). The apparatus was the same as in Experiment 1.

Procedure

The procedure was identical to Experiment 1 with responding maintained by 0.2 mg/kg of cocaine for 2 of the animals (A060 and A110) and maintained by 0.5 mg/kg of pentobarbital for the other 2 animals (A069 and A113).

TABLE 3

EXPERIMENT 1: INTAKE (MG/KG) DURING FIRST SESSION OF PERPHENAZINE SUBSTITUTION

Animal	0.0001 mg/kg	0.001 mg/kg	0.01 mg/kg	0.1 mg/kg	1.0 mg/kg
A060	0.002	0.012	0.14	1.2	5.0
A069	0.016	0.016	0.17	0.7	9.0
A110	0.004	0.051	0.21	2.0	8.0
A113	0.002	0.014	0.16	0.7	—

When rates of responding maintained by these drugs were stable according to the criterion described in Experiment 1, a dose of perphenazine dissolved in 1 ml of 0.9% physiological saline was given intramuscularly immediately prior to the experimental session. Perphenazine solutions were prepared on the day the pretreatment was to be administered.

The pretreatment doses were selected for each animal in an attempt to generate a dose-response curve such that the lowest dose of perphenazine given had no effect, and the highest dose suppressed self-administration behavior by 50% or more. Doses used ranged from 0.001 mg/kg to 0.1 mg/kg. Between pretreatments, animals were maintained on the baseline drug until responding again became stable.

After the complete dose-response curve was completed for the animals maintained on 0.2 mg/kg/infusion of cocaine (A060 and A110), the dose of this baseline drug was decreased to 0.1 mg/kg/infusion and a second series of perphenazine pretreatments were conducted as before.

RESULTS

Figure 4 presents the percent change in the number of cocaine infusions delivered as a function of increasing doses of perphenazine for animals A060 and A110. A dose of 0.001 mg/kg of perphenazine had little effect on the self-administration of either 0.1 mg/kg or 0.2 mg/kg of cocaine. However, as the dose of perphenazine increased, the number of infusions delivered increased above baseline levels. Further increases in perphenazine pretreatment dose finally resulted in a decrease in cocaine intake in both animals. Perphenazine at a dose of 0.01 mg/kg resulted in the maximum increase in responding maintained by the lower dose of cocaine. Doses higher than 0.02 mg/kg of perphenazine resulted in decreased intake. When the dose of cocaine maintaining responding was 0.2 mg/kg, 0.01 mg/kg of perphenazine also resulted in an increase in rate of responding although a dose of 0.05 mg/kg of perphenazine resulted in the maximal increase for both animals. As with the lower cocaine dose, 0.1 mg/kg of perphenazine resulted in a decrease in intake.

Figures 5 and 6 show cumulative records of each of the daily sessions on which A060 was pretreated with perphenazine with both 0.1 mg/kg (Fig. 5) and 0.2 mg/kg cocaine (Fig. 6) as the baseline dose. As can be seen, when no perphenazine was given prior to the session (Fig. 5a and 6a), A060 self-administered cocaine at regular intervals throughout the session except for a burst of infusions at the beginning. Following each infusion there was a dose-dependent post-reinforcement pause terminated by a high rate of responding typical of ratio performance. This

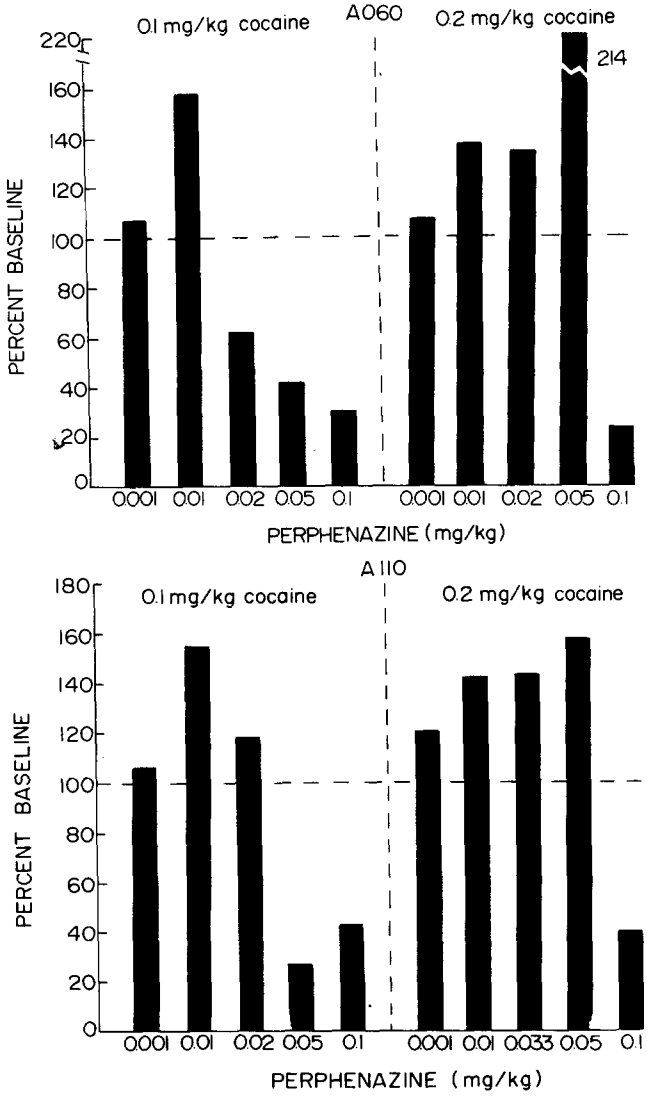

FIG. 4. Percent change in responding maintained by 0.1 or 0.2 mg/kg of cocaine following pretreatment with various doses of perphenazine for animals A060 and A110. The horizontal dotted line indicates no change.

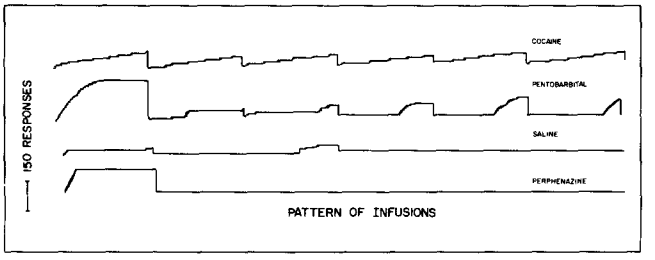

FIG. 5. Cumulative records of the effects of perphenazine pretreatment just before the session on responding maintained by 0.1 mg/kg of cocaine for animal A060 over a 3 hr session. Record A: no pretreatment; Record B: pretreatment with 0.001 mg/kg of perphenazine; Record C: pretreatment with 0.01 mg/kg of perphenazine; Record D: pretreatment with 0.02 mg/kg of perphenazine; Record E: pretreatment with 0.05 mg/kg of perphenazine; Record F: pretreatment with 0.1 mg/kg of perphenazine. Ordinate: cumulative responses; abscissa: time. The completion of the FR is indicated by a downward deflection of the pen. The response pen resets every 30 min.

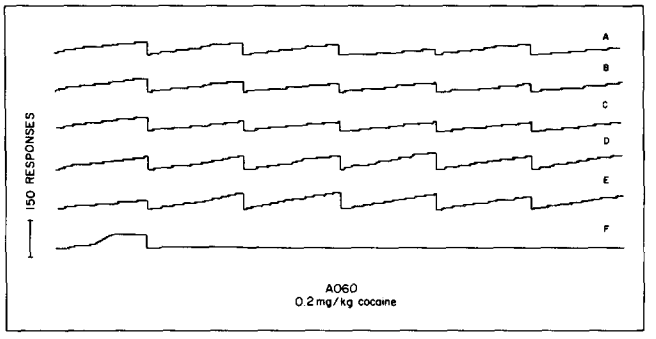

FIG. 6. Cumulative records of the effects of perphenazine pretreatment just before the session on responding maintained by 0.2 mg/kg of cocaine for animal A060 over a 3 hr session. Record A: no pretreatment; Record B: pretreatment with 0.001 mg/kg of perphenazine; Record C: pretreatment with 0.01 mg/kg of perphenazine; Record D: pretreatment with 0.02 mg/kg of perphanazine; Record E: pretreatment with 0.05 mg/kg of perphenazine; Record F: pretreatment with 0.1 mg/kg of perphenazine. Ordinate: cumulative responses; abscissa: time. The completion of the FR is indicated by a downward deflection of the pen. The response pen resets every 30 min.

responding occurred at the same rate for both doses but the post-reinforcement pause was longer at the higher baseline dose, resulting in a lower frequency of self-administration. At the lowest pretreatment dose of perphenazine (Fig. 5b and 6b), there was little change in responding maintained by either dose of cocaine. A dose of 0.01 mg/kg of perphenazine, however, resulted in an increased frequency of self-administration maintained by both doses of cocaine (Fig. 5c and 6c). The effect was characterized by a decrease in the post-reinforcement pause but had little effect on the terminal rate of responding. That is, the ratio pattern was not disrupted and sudden bursts of responding were not seen. Higher doses of perphenazine resulted in a decrease in rate of self-administration for A060 when responding was maintained by 0.1 mg/kg of cocaine (Fig. 5d,e,f). The onset of this effect, which was characterized by a cessation in responding lasting the remainder of the session, was a direct function of dose. Prior to the sudden suppression, responding was unaffected in pattern but increased in frequency relative to baseline responding.

At 0.2 mg/kg/infusion of cocaine, 0.02 and 0.05 mg/kg of perphenazine resulted, not in suppression, but in even greater increases in intake (Fig. 6d,6e). The onset of this effect was gradual. Again, there were no bursts in responding but instead a shortening of the post-reinforcement pause. The highest dose of perphenazine, 0.1 mg/kg, again resulted in an abrupt termination in responding as was seen with the lower dose of cocaine. The results for A110 were similar.

Figure 7 shows the results of perphenazine pretreatment for animals whose responding was maintained by 0.5 mg/kg of pentobarbital. For animal A069, 0.001, 0.01 and 0.02 mg/kg perphenazine had little effect on rate or pattern of pentobarbital self-administration compared to baseline.

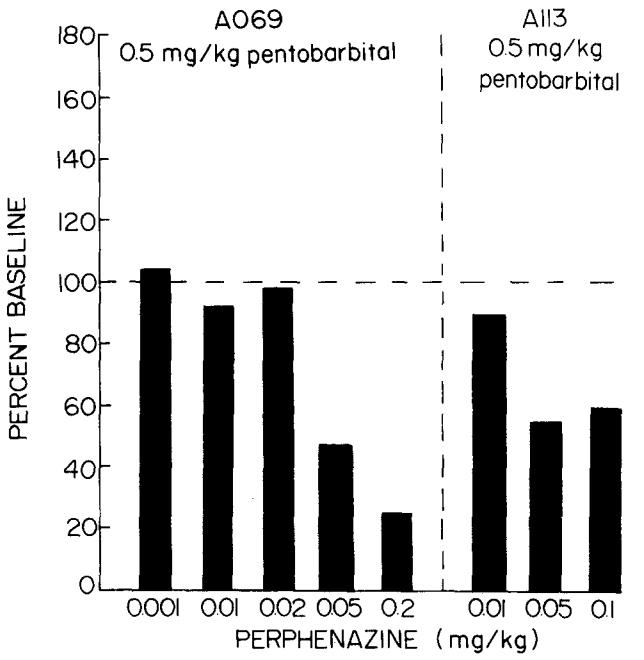

FIG. 7. Percent change in responding maintained by 0.5 mg/kg/inf of pentobarbital following pretreatment with various doses of perphenazine for animals A069 and A113. The horizontal dotted line indicates no change.

However, higher doses resulted in a decrease in overall intake due to an abrupt cessation in responding. The onset of the disruption was dose-dependent and behavior prior to the suppression appeared unaffected in rate and pattern. The data of A113 were similar although the dose-response curve was not completed due to catheter loss.

DISCUSSION

For all animals tested in Experiment 1, rates of responding maintained by perphenazine did not exceed rates of responding maintained by saline and were well below those maintained by cocaine or pentobarbital. Therefore, in this procedure, perphenazine did not function as a positive reinforcer. Since similar results have been found in studies using chlorpromazine, whose chemical structure is different from perphenazine, these data suggest that this is a property of the entire class of phenothiazines [2, 7, 21].

It is possible that the failure of perphenazine to maintain responding was because all the doses tested were too low. This explanation is unlikely given the extensive range of doses tested. In addition, the high doses tested produced observable behavioral effects in Experiment 1 and totally suppressed responding in Experiment 2. The ability of perphenazine to suppress lever responding could as well occur when its reinforcing effects were being tested. The rate modifying effects could mask any reinforcing properties the drug may have. While this possibility cannot be ruled out completely, it is unlikely since the lower doses produced no grossly observable behavioral effects at the rates they were self-administered on the last 3 days of testing. Nevertheless, on the first day of substitution of these lower doses, intake was high enough to produce observable behavioral effects. Therefore, it cannot be argued that these lower doses were not self-administered because the animal lacked sufficient exposure to their possible effects. Another factor entering into the assessment of a drug's reinforcing properties is its duration of action. A reinforcing compound with a very long duration of action might be self-administered at a very low rate. However, animals allowed to self-administer perphenazine every third day showed comparable rates of responding to those given daily access.

In summary, the data from Experiment 1 demonstrate that perphenazine is not a positive reinforcer. However, they cannot indicate whether this drug has no effect on responding producing it (i.e., is neutral) or whether it has negative reinforcing properties. There are some indications in the data that perphenazine is like saline. For instance, the pattern of intake for both saline and perphenazine across the 6 days of substitution were similar; rates of responding were high on the first day but subsequently declined. In addition, perphenazine and saline sessions were characterized by an initial burst of infusions followed by a cessation in responding. However, for perphenazine, this cessation was complete. As a result, total infusions per session were often considerably lower for perphenazine than for saline. This, coupled with the obvious effects of perphenazine on responding in Experiment 2, indicate that perphenazine may not be similar to saline. It is very likely instead that perphenazine has aversive properties capable of decreasing responding which produced it.

Recent studies [3, 5, 6] have demonstrated that certain drugs, including chlorpromazine [5], can function as negative reinforcers in that animals will respond to avoid or escape injections. Pilot research in this laboratory indicates that perphenazine will be escaped. If this is true, it is likely that the low rates of self-administration generated by perphenazine were a result of its negative reinforcing properties.

In Experiment 2, the doses of cocaine and pentobarbital self-administered maintained similar baseline responding. However, the effects of perphenazine pretreatment on responding for the 2 drugs differed markedly. No significant increase in pentobarbital self-administration was produced at any perphenazine pretreatment dose, while there were increases in cocaine self-administration greater than 50% of baseline.

The dose of perphenazine which produced the maximal increase in cocaine self-administration was directly related to the dose of cocaine maintaining responding. However, since the 2 doses of cocaine used maintain different rates of responding, the differential effect may not have been due to simply differences in reinforcer magnitude [11].

The results from Experiment 2 are not surprising since a variety of the effects produced by psychomotor stimulant drugs are antagonized by the phenothiazines [4, 12, 17]. In addition, both of these classes of drugs are thought to exert their actions on a central dopaminergic system [8,17]. It has also been shown that certain doses of chlorpromazine increase the rate of cocaine self-administration [19]. The present study extends the generality of this antagonism to a second phenothiazine. Since responding maintained by pentobarbital is not increased, the effect seems to be drug specific. However, the mechanism of action of the increase in rate is not known. Perphenazine could be decreasing the duration of action of cocaine and thereby decreasing inter-reinforcement time. On the other hand, perphenazine may be interacting with cocaine's reinforcing properties. The major obstacle in separating these 2 possibilities is the

use of a fixed-ratio schedule of reinforcement. This schedule generates rates of responding for cocaine which are inversely related to dose. Other studies indicate this dose response curve is determined by both reinforcing efficacy and other rate-modifying properties of the drug [10]. In order to delineate the mechanism of action underlying the antagonism between psychomotor stimulants and the phenothiazines, behavioral procedures which measure only 1 effect are needed.

REFERENCES

1. Benesova, O. and Trinerova, I. The effects of psychotropic drugs on the cholinergic and adrenergic system. *Int. J. Neuropharm.* **3:** 473–478, 1964.
2. Deneau, G., T. Yanagita and M. H. Seevers. Self-administration of psychoactive substances by the monkey: measure of psychological dependence. *Psychopharmacologia* **16:** 30–48, 1969.
3. Downs, D. A. and J. H. Woods. Fixed-ratio escape and avoidance-escape from naloxone in morphine-dependent monkeys: effects of naloxone dose and morphine pretreatment. *J. exp. Analysis Behav.* **23:** 415–427, 1975.
4. Espelin, D. and A. Done Amphetamine poisoning. *New Engl. J. Med.* **278:** 1361–1365, 1968.
5. Goldberg, S. R., F. Hoffmeister, U. Schlicting and W. Wuttke. Aversive properties of nalorphine and naloxone in morphine-dependent rhesus monkeys. *J. Pharmac. exp. Ther.* **179:** 268–276, 1971.
6. Hoffmeister, F. Negative reinforcing properties of some psychotropic drugs in drug-naive monkeys. *J. Pharmac. exp. Ther.* **192:** 468, 1975.
7. Hoffmeister, F., S. R. Goldberg, U. Schlichting and W. Wuttke. Self-administration of *d*-amphetamine, morphine and chlorpromazine by cocaine "dependent" rhesus monkeys. *Naunyn-Schmiedelbergs Arch Pharmak.* **266:** 359–360, 1970.
8. Iversen, Leslie L. Dopamine receptors in the brain. *Science* **188:** 1084–1089, 1975.
9. Jarvik, M. E. Drugs used in the treatment of psychiatric disorders. In: *The Pharmacological Basis of Therapeutics,* edited by L. S. Goodman and A. Gilman. New York: The Macmillan Company, 1971, pp. 151–203.
10. Johanson, C. E. and C. R. Schuster. A choice procedure for drug reinforcers: cocaine and methylphenidate in the rhesus monkey. *J. Pharmac. exp. Ther.* **193:** 676–688, 1975.
11. Kelleher, R. T. and W. H. Morse. Determinants of the specificity of behavioral effects of drugs. *Ergebnisse der Physiologie* **60:** 1–56, 1968.
12. Maickel, R. Diverse central effects of chlorpromazine. *Int. J. Neuropharm.* **7:** 23–27, 1968.
13. Reid, A. Pharmacological antagonism between chlorpromazine and phenmetrazine in mental hospital patients. *Med. J. Aust.* **25:** 187–188, 1964.
14. Schlicting, U. U., S. R. Goldberg, W. Wuttke and F. Hoffmeister. *D*-amphetamine self-administration by rhesus monkeys with different self-administration histories. *Excerpta med. Int. Congr. Ser.* **220:** 62–69, 1971.
15. Schuster, C. R. and C. E. Johanson. The use of animal models for the study of drug abuse. In: *Research Advances in Alcohol and Drug Problems, Volume 1,* edited by R. J. Gibbons. et al. New York: John Wiley and Sons, 1974, pp. 1–31.
16. Skinner, B. F. *The Behavior of Organisms.* New York: Appleton-Century-Crofts, 1938.
17. Snyder, S. H., S. P. Bancerjee, H. I. Yamamura and D. Greenberg. Drugs, neurotransmitters, and schizophrenia. *Science* **184:** 1243–1253, 1974.
18. Wilson, M. C., M. Hitomi and C. R. Schuster. Psychomotor stimulant self-administration as a function of dosage per injection in the rhesus monkey. *Psychopharmacologia* **22:** 271–281, 1971.
19. Wilson, M. C. and C. R. Schuster. The effects of chlorpromazine on psychomotor stimulant self-administration in the rhesus monkey. *Psychopharmacologia* **26:** 115–126, 1972.
20. Wilson, M. C. and C. R. Schuster. Interactions between atropine, chlorpromazine and cocaine on food reinforced behavior. *Pharmac. Biochem. Behav.* **3:** 363–375, 1975.
21. Yanagita, T., M. A. Ando and S. Takahashi. A testing method for psychological dependence liability of drugs in monkeys. Committee on Problems of Drug Dependence, NAS-NRC, 1970, pp. 6583-6591.