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Effects of Haloperidol and Physostigmine on Self-Administration of Local Anesthetics

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GARZA, R. DE LA AND C. E. JOHANSON. *Effects of haloperidol and physostigmine on self-administration of local anesthetics.* PHARMAC. BIOCHEM. BEHAV. 17(6) 1295–1299, 1982.—Four rhesus monkeys were maintained under a FR 10 schedule of cocaine (0.1 mg/kg) or procaine (0.4 or 1.6 mg/kg) delivery. Haloperidol (0.01–0.08 mg/kg), physostigmine (0.0125–0.1 mg/kg) or saline treatments were administered prior to sessions in which responding was maintained by each of these drugs. Haloperidol produced dose-related increases in the self-administration of cocaine and dose-related decreases in the self-administration of both doses of procaine. Physostigmine produced dose-related decreases in the self-administration of both cocaine and procaine. These results suggest that the reinforcing properties of cocaine are specifically modified by drugs which interact with catecholamines. On the other hand, it seems unlikely that the reinforcing properties of procaine are mediated by the same mechanism. While the results of this experiment indicate that cholinergic mechanisms may not play a major role in mediating the reinforcing properties of either drug, additional studies with other cholinergic agonists and particularly antagonists as well as additional procedures are needed.

Cocaine Procaine Haloperidol Physostigmine Self-administration Pretreatments

SEVERAL studies have shown that intravenous procaine can maintain responding that leads to its delivery under fixed-ratio schedules in rhesus monkeys [2, 4, 6]. Several other local anesthetics such as dimethocaine and chloroprocaine have also been shown to be positive reinforcers [6,18]. Although little is known about the central sites of action that mediate the reinforcing properties of local anesthetics, it is possible that these central mechanisms are similar to those of cocaine, a short-acting, esteratic local anesthetic with reinforcing properties.

The effects of cocaine in the brain are presumably mediated by the blockade of catecholamine reuptake mechanisms [11]. Treatment with haloperidol as well as other agents that block dopamine receptors [1] results in increases in the self-administration of cocaine [7, 13, 16]. Similar increases occur when the dose of cocaine maintaining responding is decreased [12] and it has been proposed that these two effects are equivalent, i.e., they represent a decrease in the reinforcing properties of cocaine. Therefore, it has been concluded that the reinforcing properties of cocaine are mediated by central catecholamines. More specifically, dopamine has been implicated as the brain neurotransmitter subserving cocaine reinforcement; this neurotransmitter has also been suggested as a mediator for other reward systems [15]. Although both cocaine and procaine are local anesthetics, procaine does not block reuptake of catecholamines. Nevertheless, catecholamines may be involved in procaine's reinforcing effects particularly since it is a monoamine oxidase inhibitor [5,9]. On the other hand, since procaine has also been shown to have both cholinergic agonist and antagonist properties, some of procaine's effects may be mediated by the cholinergic system [10].

The present experiment was designed to investigate the possible role of both the catecholaminergic and cholinergic systems in mediating the reinforcing properties of procaine. First, the effects of haloperidol on the self-administration of both cocaine and procaine were determined. If the central mechanisms of both drugs are similar, haloperidol should have the same effect on the self-administration of each drug. Second, the effects of physostigmine, a cholinesterase inhibitor, on cocaine- and procaine-maintained responding were also determined. Physostigmine has only been shown to produce decreases in cocaine self-administration which have been interpreted as non-specific [14]; however, the involvement of the cholinergic system in some of the effects of procaine [10] suggests that procaine self-administration might be specifically altered following physostigmine.

METHOD

Animals

One female (7061) and three male rhesus monkeys (7039, 0038, 8089) weighing between 5 and 8 kg were used in this study. Two of the monkeys (7061, 7039) had been used previously in self-administration studies with responding maintained by psychomotor stimulants, opiates or local anesthetics under similar schedules of drug delivery. The other two monkeys (0038, 8089) were experimentally naive at the

start of the study. The eyeballs of monkey 8089 had been removed for experimental purposes prior to purchase by this laboratory.

All monkeys received ad lib food and water throughout the course of the experiment. Vitamins were supplied as dietary supplements on a daily basis. In addition, diet was frequently supplemented with fruit.

Each monkey was surgically prepared with a single lumen silicone catheter (Rodhelm Reiss Co., Belle Mead, NJ). The surgical procedure was performed under sodium pentobarbital anesthesia (up to 30 mg/kg, IV) under aseptic conditions. One end of the catheter was inserted into a major vein and threaded until it reached the right atrium of the heart. The other end was threaded subcutaneously to the back of the animal, exiting the skin through a small incision between the scapulae. The subjects were treated with a broad spectrum antibiotic (Keflin®, Lilly Co., Indianapolis, IN) when there was evidence of a catheter tract infection.

Apparatus

Each monkey was housed in a sound attenuating wooden cubicle (inside dimensions: 70×80×70 cm) that served as the experimental space. Each cubicle was equipped with a fan for ventilation and masking of extraneous sounds. A convex lens inserted into the door allowed visual inspection of the monkey. Mounted on the inside of the front door of the cubicle were two metal boxes (12.5×15×10 cm) located 23 cm apart. For monkeys 7039 and 8089, each box contained a response lever (PRL-001, BRS/LVE, Beltsville, MD) and four stimulus lights. Two of these lights were covered with red lens caps and two were covered with white lens caps. For monkeys 7061 and 0038, the right lever box contained a response lever and lights as described above but the left box was covered with a solid metal plate. The cubicles could be illuminated by either a red or white overhead light.

Each monkey wore a stainless steel harness connected to a spring arm 42 to 47 cm long (E & H Engineering, Chicago, IL). The spring arm was attached to the back of the cubicle allowing the monkey relatively unrestricted movement within the cubicle and provided protection for the catheter which was threaded through the arm. Outside the cubicle the catheter was connected to a peristaltic infusion pump (7540X, Cole-Parmer Instrument Co., Chicago, IL) which delivered solutions at the rate of 6 ml/min. Cables connected the experimental cubicle to solid state programming and recording equipment located in an adjacent room.

Procedure

For all monkeys, lever press training was accomplished by baiting the lever with food. They were trained to respond under a fixed ratio 10 schedule of drug delivery (10 responses per drug infusion; FR 10) in the presence of the white overhead light and the white stimulus lights above the lever(s). Responding on the left lever (monkeys 7039 and 8089) had no programmed consequences. Responding was initially maintained by an infusion of 0.1 mg/kg cocaine. During drug delivery the white lights were extinguished and the red lever and overhead lights were illuminated for the duration of the 10 sec infusion. Each experimental session was 3 hr in duration.

Although monkey 8089 was blind, the lights in the cubicle continued to operate as described above. An auditory cue (masking noise) was produced at the same time as the white overhead light was illuminated. The sound of the pump during drug delivery most likely served as a discriminative stimulus signalling reinforcer delivery. Because each session began with the illumination of the white ceiling light, the auditory cue signalled its onset. For clarity, the onset of the auditory cue is not included in the description of the procedure below. It should be assumed that every time the white overhead light went on, the speaker was also activated in the cubicle of monkey 8089. This monkey was trained to lever-press in a manner similar to the other monkeys except that initially his movement was restricted to the front of the cubicle near the lever. Training time was within the normal range.

After training was completed, responding was maintained by 0.4 mg/kg procaine, 1.6 mg/kg procaine or 0.1 mg/kg cocaine as the baseline drug. The doses of procaine were selected on the basis of a previous study that showed that the 0.4 mg/kg dose of procaine maintained relatively high rates of self-administration and the 1.6 mg/kg dose of procaine maintained low rates of self-administration [6]. Three of the monkeys were tested under all three baseline conditions; for monkey 8089, responding was maintained only by 0.1 mg/kg cocaine because procaine failed to maintain responding above saline levels at any dose.

When responding became stable, each monkey was treated with saline or several doses of haloperidol (0.01–0.08 mg/kg) or physostigmine (0.0125–0.1 mg/kg) under each baseline drug condition. Two to three successive sessions of stable responding (the number of infusions within ±10% of their mean) were required before a treatment was scheduled. Therefore a minimum of two sessions separated successive drug pretreatments. Table 1 shows the order of testing of the drugs for each monkey. The doses of haloperidol and physostigmine were given in mixed order. All doses of one drug were tested under a baseline condition before the other treatment drug was tested under the same baseline or the baseline drug maintaining responding was changed. Haloperidol and physostigmine treatments were given IM 5 min before a session in a 1 ml volume. At least once under each baseline condition when responding was stable, saline was substituted for the baseline drug for 6–10 sessions to determine the pattern of extinction.

Data Analysis

During each session, the number of infusions and the total number of responses were recorded every 30 min. The results from a treatment session are expressed as a percent of the mean of the immediately preceding 2 or 3 control sessions. Percent change rather than absolute values were used to express the results to facilitate comparisons because control rates of responding differed across monkeys and baseline drugs.

Drugs

Physostigmine was obtained as the sulfate salt from Sigma Chemical Co. (St. Louis, MO). Procaine was obtained as the hydrochloride salt from J. T. Baker Chemical Co. (Phillipsburg, NJ). Cocaine was obtained as the hydrochloride salt from the National Institute on Drug Abuse. These three drugs were dissolved in saline and the doses were calculated as the salt. Haloperidol was obtained as the Haldol preparation from McNeil Pharmaceutical (Spring House, PA) and was diluted in saline to the required concentrations. Haloperidol doses are expressed as the base.

TABLE 1

ORDER OF TESTING

Order		Monkey 0038	7039	7061	8089
1	B	0.4 mg/kg Pro	0.4 mg/kg Pro	0.1 mg/kg Coc	0.1 mg/kg Coc
	T	Hal	Physo	Physo	Physo
2	B	0.4 mg/kg Pro	1.6 mg/kg Pro	0.4 mg/kg Pro	0.1 mg/kg Coc
	T	Physo	Physo	Physo	Hal
3	B	1.6 mg/kg Pro	0.1 mg/kg Coc	1.6 mg/kg Pro	
	T	Hal	Physo	Physo	
4	B	1.6 mg/kg Pro	0.1 mg/kg Coc	0.1 mg/kg Coc	
	T	Physo	Hal	Hal	
5	B	0.1 mg/kg Coc	0.4 mg/kg Pro	0.4 mg/kg Pro	
	T	Hal	Hal	Hal	
6	B	0.1 mg/kg Coc	1.6 mg/kg Pro	1.6 mg/kg Pro	
	T	Physo	Hal	Hal	

Abbreviations: B=baseline drug; T=treatment drug; Pro=procaine; Coc=cocaine; Physo=physostigmine; Hal=haloperidol.

TABLE 2

MEAN NUMBER OF INFUSIONS SELF-ADMINISTERED UNDER EACH BASELINE CONDITION AND DURING SALINE SUBSTITUTION*

	0.1 mg/kg Cocaine (mean±S.E.)	0.4 mg/kg Procaine (mean±S.E.)	1.6 mg/kg Procaine (mean±S.E.)	Saline† (mean±Range)
0038	29.3 ± 1.9	156.9 ± 6.0	62.5 ± 2.7	3.5 1–6
7039	53.1 ± 3.7	154.1 ± 6.9	82.7 ± 5.1	6.3 1–11
7061	48.7 ± 3.4	67.6 ± 2.9	36.2 ± 1.3	6.7 2–15
8089	43.0 ± 2.0			2.7 0–7

*The means were calculated from the control means obtained prior to every treatment with both physostigmine and haloperidol as described in the text.

†Mean number of infusions during last 2–3 sessions of saline substitution.

RESULTS

Control Performance

The pattern of responding maintained by cocaine or procaine was typical of fixed-ratio performance maintained by drugs. Following each drug delivery, there was a pause followed by a high rate of responding until the delivery of the next infusion. Cocaine infusions were evenly spaced over the three hour session, but the pattern of procaine self-administration was more irregular. Generally, two or three infusions of procaine occurred within a short interval of each other and this burst of infusions was followed by a pause until the next group of infusions occurred. The pause after a burst of infusions was longer following the high dose of procaine than after the low dose of procaine.

Table 2 shows the mean number of infusions under each baseline condition as well as the results of saline substitution for each monkey. For all drugs, there were noticeable differences in intake across monkeys. These differences in sensitivity were not correlated for procaine and cocaine. For instance, although monkey 0038 self-administered the least cocaine, his intake of 0.4 mg/kg procaine was higher than the other monkeys. For all monkeys, saline rates were low and the pattern was erratic across the session.

Haloperidol Treatments

In Fig. 1 the effects of haloperidol treatments on the self-administration of cocaine and both doses of procaine are shown. When cocaine was the baseline drug, haloperidol produced increases in the self-administration of cocaine in all monkeys. As haloperidol dose was increased up to 0.04 mg/kg, cocaine self-administration increased to at least 200% of control in 3 of the monkeys. Higher haloperidol doses decreased self-administration. For monkey 7039, there were also increases in cocaine self-administration following treatment with 0.01 and 0.02 mg/kg haloperidol.

Prior to testing the 0.04 mg/kg dose of haloperidol, baseline cocaine self-administration increased dramatically for no apparent reason and the animal was moderately stimulated during the sessions. When 0.04 mg/kg of haloperidol was administered, monkey 7039 began responding almost continuously. Since the monkey appeared extremely agitated, the session was terminated.

When the baseline drug maintaining responding was changed to 0.4 mg/kg procaine, haloperidol produced dose-dependent decreases in the number of infusions taken during the session relative to baseline levels for monkeys 0038 and 7061. In the third monkey (7039), 0.005 and 0.01 mg/kg halo-

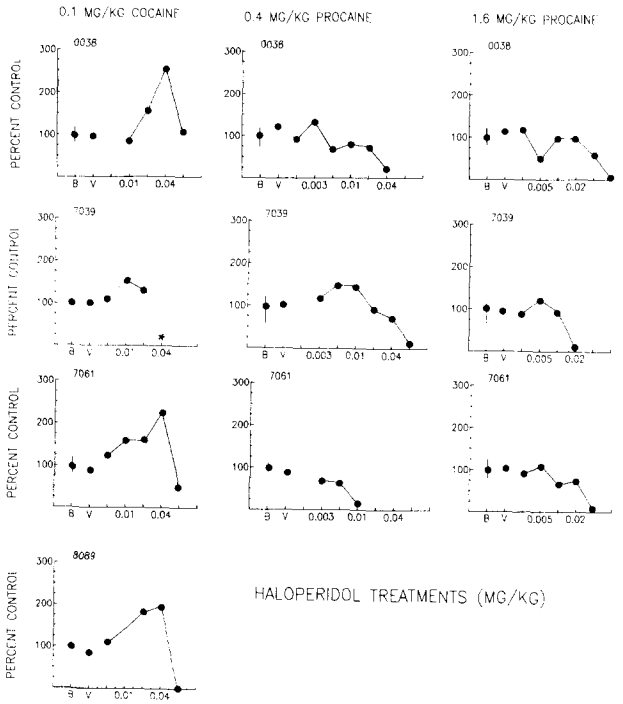

FIG. 1. The effects of haloperidol treatment given 5 min prior to a session on responding maintained by 0.1 mg/kg cocaine (left column), 0.4 mg/kg procaine (center column) or 1.6 mg/kg procaine (right column) under a FR 10 schedule in each monkey tested. The doses of haloperidol are indicated on the abscissae on a log scale. The results are represented on the ordinate as a percent of the mean number of infusions self-administered during the 2–3 baseline sessions immediately preceding each treatment session. The point above "V" represents the effects of saline treatment. The range of baseline means expressed as percentages of an overall mean are shown above "B." The asterisk indicates that the session was terminated (see Results, Haloperidol Treatment).

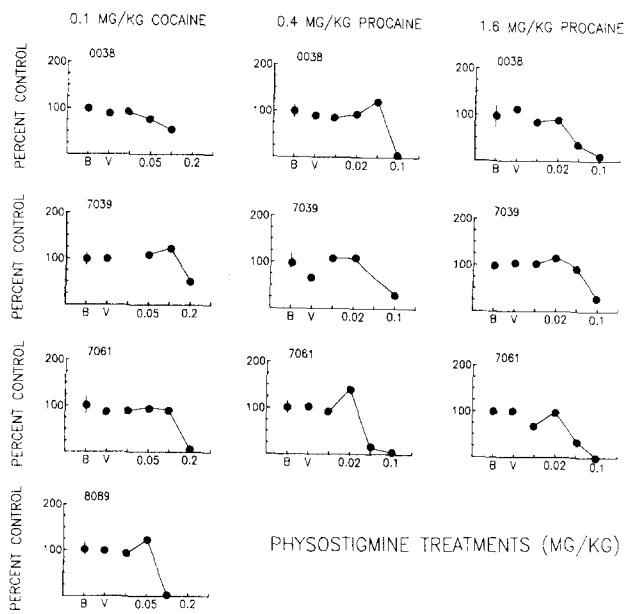

FIG. 2. The effects of physostigmine treatment given 5 min prior to a session on responding maintained by 0.1 mg/kg cocaine (left column), 0.4 mg/kg procaine (center column) or 1.6 mg/kg procaine (right column) under a FR 10 schedule in each monkey tested. The doses of physostigmine are indicated on the abscissae on a log scale. The results are represented on the ordinate as a percent of the mean number of infusions self-administered during the 2–3 baseline sessions immediately preceding each treatment session. The point above "V" represents the effects of saline treatment. The range of baseline means expressed as percentages of an overall mean are shown above "B."

peridol produced small increases in the number of infusions but higher doses produced dose-dependent decreases. When the dose of procaine maintaining responding was increased to 1.6 mg/kg procaine, haloperidol produced dose-dependent decreases in the number of infusions taken during the session in all monkeys. In two of the monkeys, a higher dose of haloperidol was required to suppress responding.

Physostigmine Treatments

In Fig. 2, the effects of physostigmine treatments on the self-administration of cocaine and both doses of procaine are shown. Lower doses of physostigmine had little effect on responding maintained by cocaine. At the highest dose tested in each monkey, responding decreased and in two cases was almost totally suppressed. When responding was maintained by either dose of procaine, there was a dose-dependent decrease in the number of infusions. However, with each monkey, one dose of physostigmine produced small increases in procaine intake relative to control sessions under one of the two procaine baseline conditions. The dose required to almost completely suppress responding was the same for both doses of procaine but somewhat higher with cocaine.

DISCUSSION

Several studies have demonstrated that procaine is capable of maintaining responding leading to its delivery in rhesus monkeys [2, 4, 6]. Although little is known about the central mechanism of action of procaine, this drug is similar in some respects to another local anesthetic, cocaine, whose reinforcing properties may be mediated in some way by catecholamines [13]. Although procaine is not a catecholaminergic uptake blocker, both drugs are local anesthetics, and at high doses produce convulsions that can be terminated by diazepam [8]. Furthermore, both cocaine and procaine as well as other local anesthetics which maintain responding are ester-linked molecules that are rapidly metabolized; on the other hand, amide-linked local anesthetics and esterase local anesthetics with long durations of action have minimal reinforcing properties [6, 17, 18]. Therefore, it is possible that cocaine and procaine share a similar central mechanism of action mediating their reinforcing properties which does no involve reuptake.

The results of the present study do not support the hypothesis of a similar mechanism. Haloperidol is a dopaminergic receptor blocker [1] which has been shown to increase cocaine self-administration [3]. Other drugs such as the phenothiazines which also block catecholaminergic receptors have similar rate-increasing effects [7,13]. In the present study, haloperidol increased cocaine self-

administration as expected. The self-administration of procaine was not increased in any consistent manner by haloperidol. As the dose of the treatment drug increased, there were only dose-dependent decreases in responding. This finding suggests that dopamine is not a mediator of procaine's reinforcing properties. However, since few studies have been done in this area, further studies are clearly essential to completely rule out any involvement of the dopaminergic system. For example, in a study in rats where responding was maintained by apomorphine, a dopamine antagonist, butaclamol, did not produce rate increases [19]. Furthermore, the results obtained in the present study may have depended on the specific parameters of the procedure (e.g. treatment time, dose of procaine). In addition, the combination of haloperidol and procaine may have produced unique direct effects on response rates which prevented the observation of increases. In 2 animals there was some indication that the rate decreases were not merely a non-specific effect since higher haloperidol doses were required to suppress responding maintained by the higher dose of procaine. However, since this could have been due to differences in baseline rates of responding, further studies with additional procaine doses and rate-independent procedures are essential.

Dose-dependent decreases were also found following treatment with physostigmine in animals self-administering cocaine, suggesting that its reinforcing properties are not modified by increasing receptor levels of acetylcholine. Similar rate decreases of cocaine-maintained responding with physostigmine have been shown previously but with a higher dose of cocaine [14]. Although it is difficult to compare across studies, the dose of physostigmine which suppressed responding of this higher dose (0.2 mg/kg) was similar to the dose which suppressed responding of the lower dose in the present study. This failure to show a cocaine dose-related effect suggests a non-specific interaction. However, since atropine, a cholinergic receptor antagonist has been shown to increase cocaine self-administration [14], the cholinergic system may play some role in cocaine's effects. Physostigmine also produced rate decreases for procaine-maintained responding and the dose which suppressed responding was the same for both doses of procaine. Although additional studies may be necessary, these results suggest that the reinforcing properties of procaine are not affected by increased levels of acetylcholine. However, since procaine has been shown to have cholinergic agonist as well as antagonist properties, additional studies using cholinergic antagonists such as atropine are needed.

In summary, the results of the present study which replicate many previous findings suggest that the reinforcing properties of cocaine are mediated by dopamine. The dose-dependent decreases of responding following treatment with haloperidol when procaine maintained responding and following treatment with physostigmine with both baseline drugs suggest non-specific drug interactions in these cases. However, these results should only be considered preliminary since further studies under other experimental conditions are necessary to eliminate alternate conclusions.

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