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Behavioral Pharmacology of Local Anesthetics: Reinforcing and Discriminative Stimulus Effects[1]

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WOOLVERTON, W L AND R L BALSTER *Behavioral pharmacology of local anesthetics Reinforcing and discriminative stimulus effects* PHARMAC BIOCHEM BEHAV **16**(3) 491–500, 1982 —The reinforcing properties of several short-acting esteratic local anesthetics were determined in rhesus monkeys experienced in the IV self-administration of cocaine In addition, the discriminative stimulus properties of these and several other local anesthetics of both the ester and amide class were determined in rats trained to discriminate procaine from saline in a 2-lever operant task IV delivery of chloroprocaine, dimethylprocaine or dimethocaine maintained responding above vehicle levels in most monkeys while propoxycaine, piperocaine and dimethylaminoethanol (Deanol) failed to maintain self-administration behavior Thus some, but not all, short-acting esteratic local anesthetics are positive reinforcers in rhesus monkeys In addition, it is unlikely that the reinforcing effects of dimethylprocaine are mediated by its metabolite dimethylaminoethanol In rats, all local anesthetics tested except piperocaine and procainamide resulted in responding on the procaine-appropriate lever indicating procaine-like discriminative stimulus effects for these compounds In addition, injections of *d*-amphetamine resulted in principally procaine lever responding All local anesthetics that were self-administered by rhesus monkeys had discriminative stimulus effects in rats that were similar to those of procaine However, not all local anesthetics that were procaine-like in rats were self-administered by rhesus monkeys These data may represent a separation of these two stimulus properties for local anesthetics although other variables such as species differences may play a role

Local anesthetics Drug discrimination Self-administration Rhesus monkey Rat Procaine Lidocaine Tetracaine Procainamide Propoxycaine Piperocaine Chloroprocaine Dimethylprocaine Dimethocaine Cocaine Deanol

THE surprising finding that IV procaine can function as a positive reinforcer in rhesus monkeys [6,7] has led to speculation that other local anesthetics might also have reinforcing effects which could contribute to their abuse One member of this group, cocaine, is clearly self-administered by both laboratory animals and humans In addition, Van Dyke *et al* [18], using human volunteers, found that intranasal lidocaine was indistinguishable from cocaine administered by the same route Further research with animals has revealed that other local anesthetics have reinforcing effects in rhesus monkeys [9,20], though this is not a property of all members of this class, and has allowed the tentative conclusion that short-acting esteratic local anesthetics are most likely to have this effect

The first purpose of the present research was to further evaluate the hypothesis that short-acting, esteratic local anesthetics are more likely to be self-administered than other types of local anesthetics, and whether this was a property of esteratic local anesthetics in general It was also of interest to evaluate the reinforcing effects of dimethylaminoethanol (DMAE, Deanol) since this drug is a metabolite of several local anesthetics that are reinforcers, and as well has psychotropic effects in its own right [2,12] A second purpose of this research was to determine whether procaine could function as a discriminative stimulus and whether other local anesthetics had stimulus properties in common with procaine [15] The results presented demonstrate reinforcing effects in monkeys for several additional local anesthetics although not all esters were reinforcers In addition, most of the local anesthetics tested had discriminative stimulus effects that were similar to those of procaine in rats

EXPERIMENT 1 SELF-ADMINISTRATION STUDIES

METHOD

The general methods for this study were similar to those used previously to study the self-administration of procaine and other local anesthetics [6,20]

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Animals and Apparatus

The animals were six adult male rhesus monkeys (*Macaca mulatta*) that weighed between 7 9 and 11 7 kg at the beginning of the experiment All animals had experience in the self-administration of various psychoactive drugs including local anesthetics and phencyclidine Each was fitted with a stainless steel restraint harness [4] and spring arm which attached to the rear of the experimental cubicle The animal lived in the experimental cubicle (0 8 × 0 8 × 1 0 m) for the duration of the experiment Water was continuously available and each monkey received approximately 150 g of Purina Monkey Chow and a chewable multiple vitamin tablet each day, after the experimental session

On the inside front of each experimental cubicle two response levers were mounted on the transparent Plexiglas door 30 cm above the floor and a food dish was mounted between them Three jewelled stimulus lights were mounted directly above each lever Drug infusions were delivered via peristaltic infusion pumps (Cole-Parmer Co , Chicago IL) All programming and recording was accomplished by solid state equipment located in an adjacent room

Procedure

Surgery Following adaptation to the cubicle and restraint system, each animal was removed from the cubicle and injected with a combination of phencyclidine hydrochloride (1 mg/kg, IM) and atropine sulfate (0 04 mg/kg, IM) followed in 20–30 min by sodium pentobarbital (10–20 mg/kg IV) When anesthesia was adequate, a silicone catheter (0 08 cm ID, Ronsil Rubber Products, Bell Mead, NJ) was surgically implanted into a major vein Internal and external jugular and femoral veins could be catheterized The catheter was threaded through the spring arm to the back of the cubicle and connected to the infusion pump which delivered drug solutions at a rate of 1 ml/10 sec If a catheter became nonfunctional during the experiment, a new catheter was implanted as before following a 1–2 week period to allow any infection to clear Following surgery, the animal was returned to the cubicle

Training Initially, each animal was trained in the presence of the two white lights above the left lever to press the left lever for a 10-sec injection of 0 1 mg/kg cocaine hydrochloride During an injection the white lever lights were extinguished and the center red lever light was illuminated Responses occuring on the left lever during the injection as well as those occurring on the right lever had no programmed consequence Following acquisition of the lever press response, the number of responses required for drug delivery was increased to 10 over the period of one 2-hr session (fixed ratio 10 FR 10) After responding during daily 2-hr sessions stabilized (2-3 days), a dose of 0 1 μmole/kg/inj cocaine hydrochloride (34 μg/kg/inj) was used to maintain responding in all animals

Substitution procedure Daily sessions were signaled by the illumination of the white lights over the left lever During baseline sessions, the animals received IV injections of 0 1 μmole/kg/inj cocaine contingent upon left lever responding on an FR10 schedule The number of injections delivered was recorded every 30 min and the total left lever responses were recorded for the session Following the establishment of stable rates of responding under baseline conditions (less than 10% variation in total numbers of injections per session for 3 consecutive sessions), 0 9% saline or a dose of one of the test compounds, was substituted for 6 consecutive sessions after which the animal was returned to baseline conditions

Several local anesthetics were substituted for cocaine in a counterbalanced order using this procedure At least three doses of each drug were tested in an unsystematic order in each animal, and all doses of one drug were completed before testing another drug Doses were initially selected in a range comparable to known reinforcing doses of procaine (1 0–3 0 μmoles/kg/inj) and were tested over a 30 to 100-fold range until doses high enough to suppress lever pressing in the first session of a substitution period were achieved In addition, saline was substituted for six sessions at the beginning of the dose series for each drug DMAE was also tested in one of the subjects (No 4173) used for the testing local anesthetics as well as two additional subjects

Drugs

The hydrochloride salts of the following local anesthetics were used chloroprocaine (Penwalt Corporation, Rochester, NY), dimethylprocaine (Abbott Laboratories N Chicago, IL), dimethocaine (Hoffman-LaRoche, Nutley NJ), piperocaine (Eli Lilly and Co , Indianapolis, IN), and propoxycaine (Sterling-Winthrop Research Institute, Rensselaer, NY) In addition, liquid dimethylaminoethanol (DMAE) was used (Pfaltz and Bauer, Stanford, CN) Each compound was dissolved in 0 9% saline for injection with concentrations adjusted so that injections were administered in a volume of 1 0 ml over a 10-sec period Doses were expressed as μmoles/kg/injection For purposes of comparison, 1 0 μmole of each compound is equivalent to the following cocaine HCl-340 μg, chloroprocaine HCl-307 μg, dimethylprocaine HCl-244 μg, dimethocaine HCl-315 μg, piperocaine HCl-298 μg, dimethylprocaine HCl-244 μg, dimethocaine HCl-315 μg, piperocaine HCl-298 μg, propoxycaine HCl-331 μg, and DMAE-89 μg The chemical structure of each local anesthetic is shown in Fig 1

Data Analysis

The number and distribution of injections over the last three sessions of a test drug substitution period were used in data analysis For each drug these values were compared to the same values for the last three sessions of the corresponding saline substitution period A drug was considered to be a positive reinforcer in a particular subject if the mean number of injections for the last three sessions of a test period exceeded the mean value for the corresponding saline substitution, and the ranges did not overlap

RESULTS

Under the baseline conditions, cocaine maintained stable responding that was above the range of saline values for each subject (values above C and S in Fig 2) There was, however, considerable variability between subjects in cocaine intake per session, with mean values ranging between 35 (No M263) and 118 (No 7623) inj/session When saline was substituted for cocaine, low rates of responding (<10 inj/session) were usually observed by the sixth session

When chloroprocaine, dimethocaine or dimethylprocaine were substituted for cocaine, self-administration was maintained above saline levels at least at one dose in all animals tested, and was often in excess of 100 inj/session (Figs 2 and 3) Although rates of responding were often not as high for

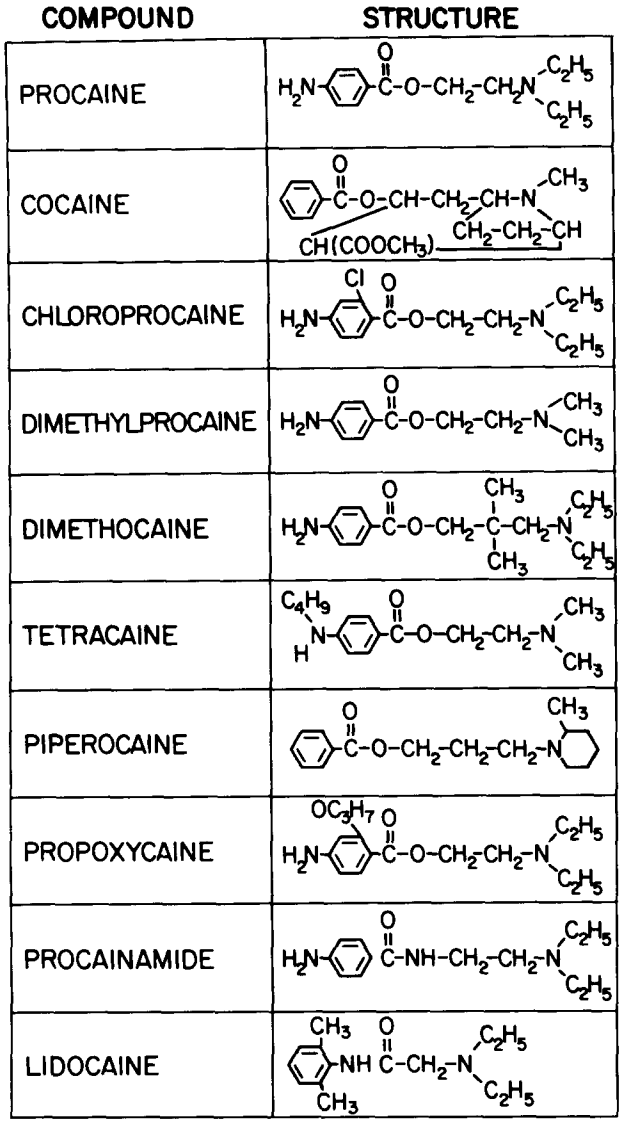

FIG 1 Chemical structures of local anesthetics

chloroprocaine and dimethylprocaine as for dimethocaine, dose-response relationships for all three of these compounds were generally of the inverted "U" shape frequently described for drugs that are positive reinforcers [19] Of these three, dimethocaine was the most potent with responding consistently maintained in the range of 0 1 to 1 0 μmoles/kg/inj as compared to the 1 0–3 0 μmoles/kg/inj doses of chloroprocaine and dimethylprocaine that were usually required to maintain self-administration In addition, the range of doses of dimethocaine that supported self-administration behavior was relatively wide In contrast, when piperocaine or propoxycaine were substituted for cocaine, responding at or below saline levels was consistently observed (Figs 2 and 3) Furthermore, there was no systematic dose-response relationship for these compounds until doses high enough to suppress responding were achieved In this regard, propoxycaine and piperocaine were approximately equipotent, with 3 μmoles/kg/inj usually suppressing responding to below saline levels DMAE, which was tested in two additional animals not shown in Fig 2 (No 3018, M-269), also failed to maintain response rates above vehicle control values (Table 1)

Comparisons are made between drugs in terms of pattern of responding over the experimental session in Figs 3 and 4 and Table 1 Consistent with the findings of others [1, 5, 20], responding for cocaine was relatively evenly distributed over the session, with slightly more than 25% of the toal number of injections taken in the first 1/4 of the session In contrast, when saline was substituted for cocaine, a typical extinction pattern of responding was observed with approximately 75% of the total number of injections taken in the first 1/4 of the session Responding for chloroprocaine and dimethylprocaine was evenly spaced over the session in animals that reliably self-administered these drugs at high rates (Fig 3) However, low rates of responding in later segments of the session by M263 and 7623 account for the irregular pattern seen in the group data in Fig 4 At doses that were self-administered, dimethocaine maintained a pattern of evenly spaced responding that was similar to that seen with cocaine (Figs 3 and 4) Responding for piperocaine, propoxycaine and DMAE occurred with a saline-like pattern in all cases at all doses tested (Figs 3, 4 and Table 1)

TABLE 1

SELF-ADMINISTRATION OF DIMETHYLAMINOETHANOL (DMAE) BY RHESUS MONKEYS*

Compound	Dose (μmoles/kg/injection)	Injections/Session Mean	Injections/Session Range	Percent of Total per 30 Minutes First	Second	Third	Fourth
Cocaine	0 1	73	47–96	31	25	22	22
Saline	—	8 9	3–12	67	20	8	5
DMAE	1 0	4	3–5	78	9	13	0
DMAE	3 0	3 9	2–5	77	7	0	16
DMAE	10	5 7	3–8	83	3	8	6
DMAE	30	4	3–8	78	8	14	0

*Injection data are means for three rhesus monkeys (Nos 4173, 3018 and M269) Ranges include all three monkeys

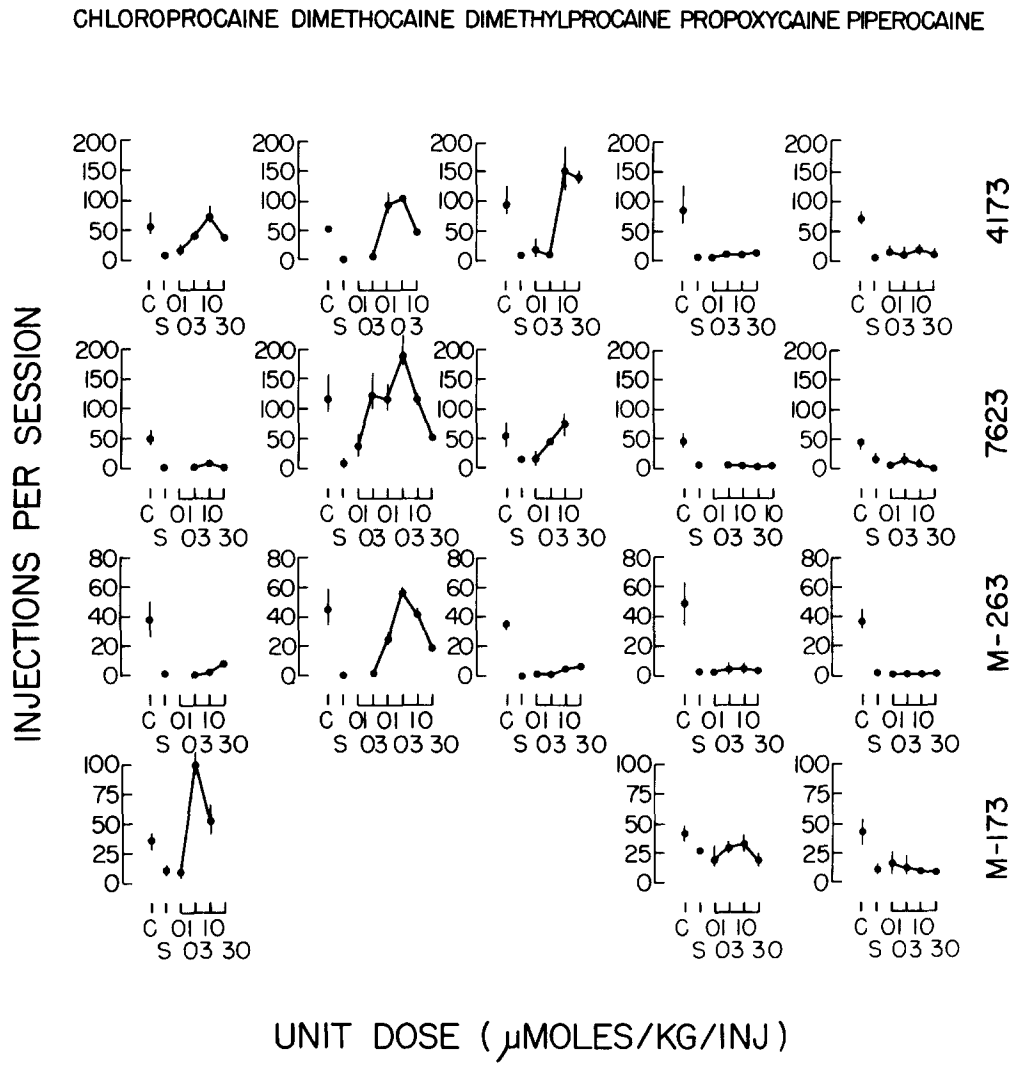

FIG 2 Self-administration of esteratic local anesthetics by rhesus monkeys Each point represents the mean number of injections of each compound for each animal during the last three sessions of a substitution period, and vertical bars represent the range Occasionally the range is smaller than the point The points above S represent responding over the corresponding period of saline substitution during each dose-response determination The points above C represent the average number of injections of cocaine (0 1 μmoles/kg/inj) taken during the last three sessions preceding each dose of that test drug, usually a total of 12 cocaine sessions

EXPERIMENT 2 DRUG DISCRIMINATION STUDIES

METHOD

Animals and Apparatus

The animals were 10 drug-naive male albino Sprague-Dawley derived DUB rats (Flow Laboratories, Dublin, VA) that weighed between 180 and 260 g at the beginning of the experiment During the course of the experiment, several animals died either from an overdose of a local anesthetic or from an unspecified illness Because of the extended duration of the experiments, body weights were allowed to increase gradually and the animals weighed between 260 and 325 grams at the end of the experiment They were individually housed in ceiling suspended steel cages (18 × 19 × 25 cm) in a room with a 12 hour light-dark cycle Experimental sessions were conducted during the light cycle Water was available at all times except during experimental sessions, and food availability was restricted to that delivered in the experimental sessions in the form of 45 mg food pellets (Formula

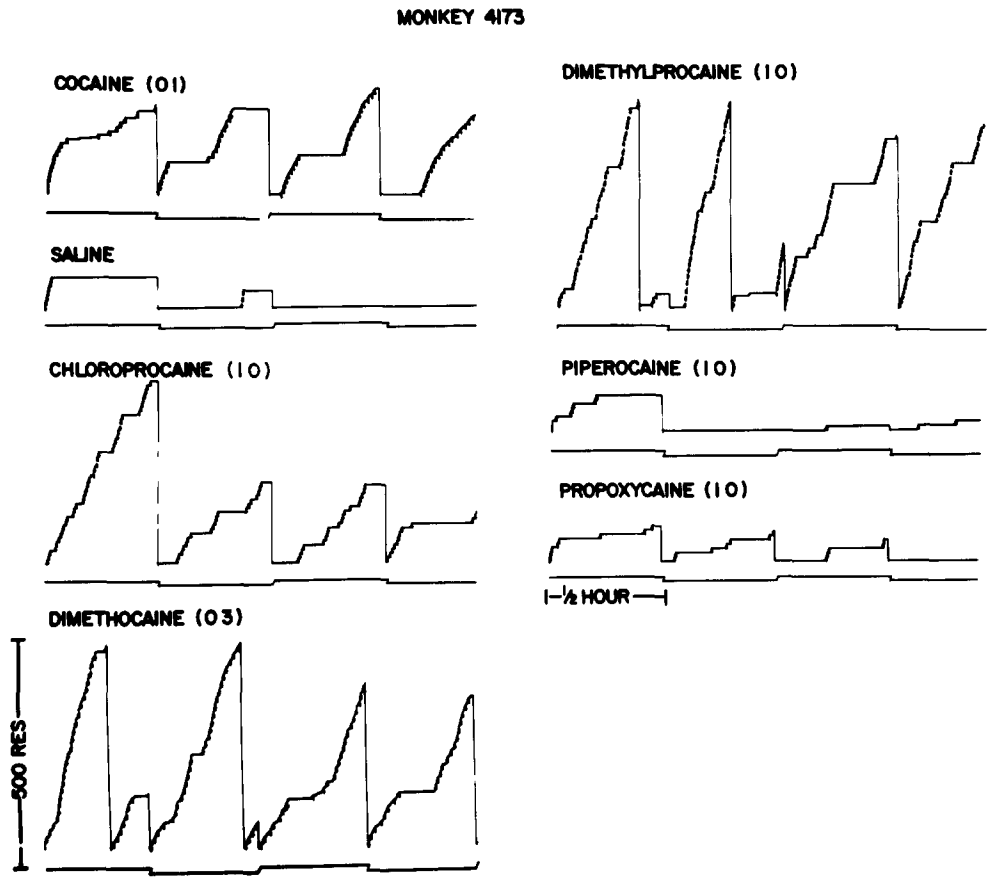

FIG 3 Cumulative response records of local anesthetic self-administration by a single animal (Monkey 4173) Records were selected from one of the last three sessions of a six-session substitution period Each diagonal mark of the response pen represents an injection, and vertical marks of the event pen denote 30 min segments of the session In addition, the response pen reset each 1/2 hour For reinforcing drugs, the dose that maintained the highest response rates was selected For non-reinforcing drugs, the highest dose that did not suppress responding was selected Drug doses (μmoles/kg/inj) are in parentheses

A, P J Noyes Co , Lancaster, NH) and adjusted supplemental feedings of 10–15 g of laboratory rat chow (Rodent Lab Chow, Ralston Purina Co , St Louis, MO) given after each session

Experimental sessions were conducted in two identical two-lever modular operant chambers (Model E10-10, Coulbourn Instruments, LeHigh Valley, PA) Both levers were mounted on one wall 60 cm above the floor, and a food trough was centered between them A white light illuminated the chamber during experimental sessions The chamber was enclosed in a sound attenuating cubicle equipped with an exhaust fan Solid state programming equipment located in an adjacent room controlled the contingencies and recorded behavior

Procedure

Training sessions Animals were trained in a two-lever food-reinforced drug discrimination paradigm The rats were divided into 2 groups of 5 rats each, food deprived to 75–80% of their free-feeding weights, and assigned to one of the two experimental chambers For the group of animals in one experimental chamber, the right lever was designated the drug lever and the left lever was designated the saline or non-drug lever This condition was reversed for the second group of animals Initial training was carried out in the non-drug condition, with each animal in each group trained to press the non-drug lever on a FR-1 schedule for the delivery of a single pellet After responding occurred reliably on the non-drug lever, animals were injected (1 0 ml/kg, IP) 10 min before some experimental sessions with 200 μmoles/kg procaine HCl (54 6 mg/kg), and only responding on the drug lever was reinforced during the experimental session On non-drug days, each animal received a saline injection (1 ml/kg, IP) 10 min before the experimental session Procaine (P) or saline

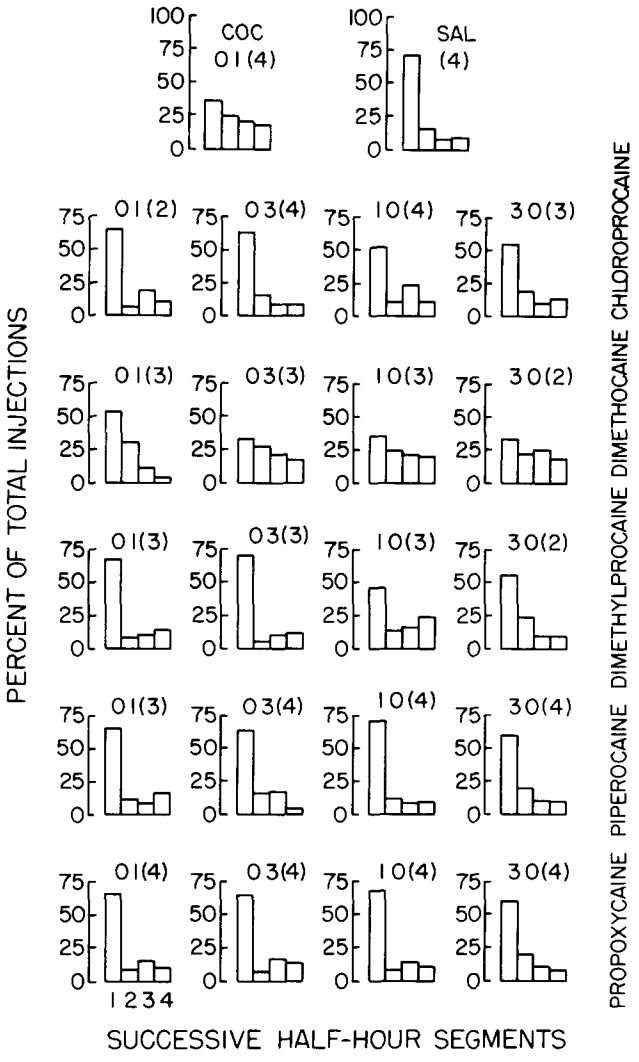

FIG 4 Pattern of responding for local anesthetics Each bar represents the median percent of the total number of injections taken in each 1/2 hour segment of the experimental session The data are from the last three sessions at each test dose for all the subjects Numbers above each histogram are the drug dose in μmoles/kg/inj and parentheses are the total number of animals tested at that dose

(S) pretreatments were given on a double alternation schedule in which two consecutive sessions with drug pretreatment followed two consecutive sessions with saline pretreatment Over about 10 sessions the response requirement on both levers was gradually increased to 32 responses per food pellet (FR-32) Sessions were conducted Sundays through Fridays and lasted 30 min

Test sessions When responding was stable (less than 10% variation in overall response rate from day to day) and under good stimulus control (90% correct) test sessions were begun Test sessions were conducted on Tuesdays and Fridays An IP injection of saline or a test drug was given 10 min before the test session, during which food was available for responding on either lever on a FR 32 schedule Generally, a test session lasted 100 sec If the subjects did not complete a fixed ratio during the 100 sec, the test session was extended up to 10 min until the first reinforcer was delivered The same dose of a test compound was administered before both test sessions in a week so that each dose was tested with each training condition in effect on the preceding day to correct for any tendency to respond on the lever that had been reinforced on the preceding day Doses that ranged from one that had no effect on responding to a dose that suppressed rates of responding to less than 50% of control levels were tested in a non-systematic order The effects of all doses of one drug were determined before testing another drug, and saline was tested as part of the dose-response function of each drug The order of drug testing was procaine, lidocaine, tetracaine, procainamide, piperocaine, dimethocaine, chloroprocaine, dimethylprocaine, cocaine, propoxycaine

Thus under terminal conditions animals responded on a FR 32 schedule food delivery with the weekly sequence of sessions for all animals being P,S, Test, S,P, Test Animals were fed but experimental sessions were not conducted on Saturdays

Drugs

In addition to the local anesthetics used in the self-administration experiment (cocaine, chloroprocaine, dimethocaine, dimethylprocaine, propoxycaine and piperocaine), procaine, procainamide, lidocaine and tetracaine (Pfaltz and Bauer) were tested In addition, the effects of selected doses of *d*-amphetamine (City Chemical Corp , NY) were determined in these rats All drugs were dissolved in 0 9% saline to an injection volume of 1 0 ml/kg Doses are expressed in μmoles/kg For purposes of comparison, 1 0 μmole of each compound is equivalent to procaine HCl-273 μg, procainamide HCl-272 μg, lidocaine HCl-271 μg, tetracaine HCl-300 μg and *d*-amphetamine SO_4-116 5 μg (233 μg/2 μmole)

Data Analysis

Data from test sessions were analysed in terms of drug effects on overall response rate (responses/sec) and the percent of total responses that occurred on the drug lever Data were calculated for individual animals and the mean and standard error of the mean were calculated for the group A test drug was considered to have procaine-like discriminative effects if at some dose an average of 75% of the responding in a session occurred on the drug lever For potency comparisons, response rate data were converted to percent of control response rates using the rates during the saline test sessions from that dose-response determination as control rates, again individually calculated Dose-response lines were calculated for response rate and percent drug lever responding by the method of least squares linear regression using the sensibly linear portion of each dose-response function ED_{50} values were calculated from these lines For overall response rate, the data for all animals tested were included in the analysis For percent drug lever responding, the constraint was added that at least 50% of the animals tested complete at least 32 total responses for those data to be included in the analysis

RESULTS

The procaine-saline discrimination was acquired over a

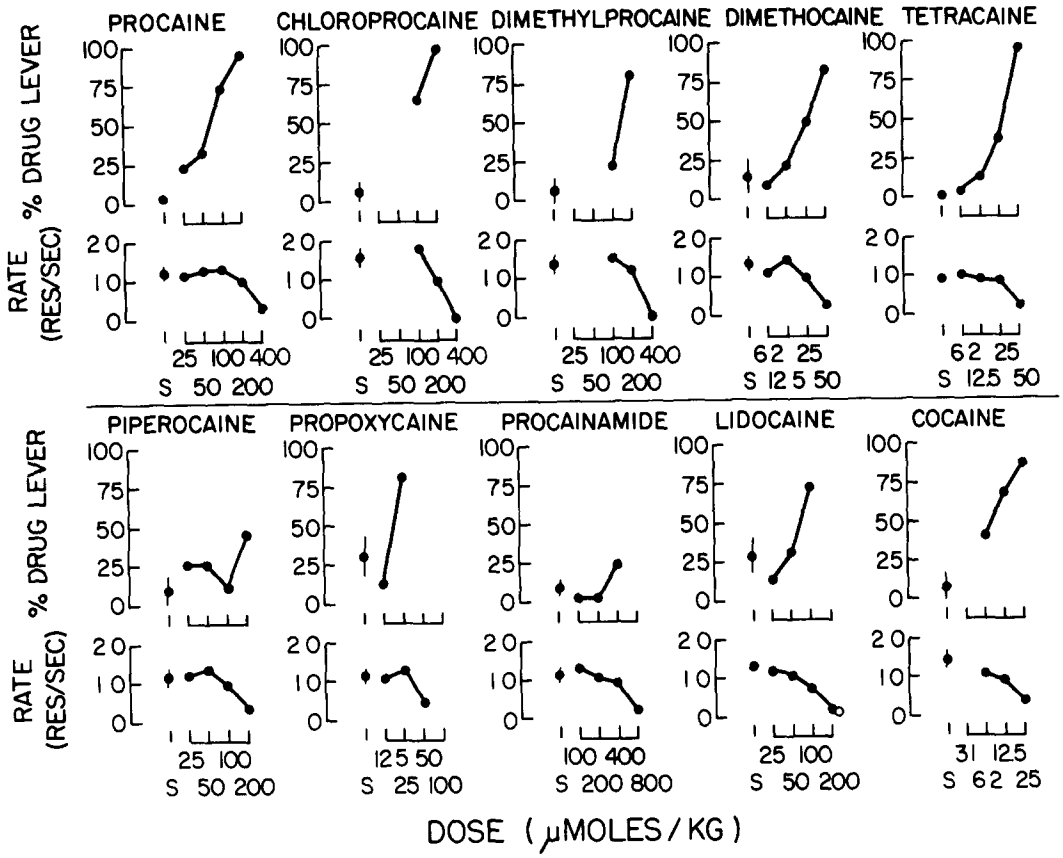

FIG 5 The discriminative stimulus properties of local anesthetics in rats There are two dependent measures for each local anesthetic—percent drug lever responding and effects on overall response rate Each point is the mean of two determinations in 6–10 subjects Standard errors are represented for saline test values (S) For other points the standard errors ranged between ±10% of the mean Two of three animals tested died following injections of 400 μmoles/kg chloroprocaine so others were not tested The open circle at 200 μmoles/kg lidocaine represents a retest of this dose Values for % drug-lever responding are not presented when response rates were low, i e , most animals did not respond (see text)

period of about 40 training sessions By the 20th double-alternation, rates of responding under the FR 32 schedule were stable and 90–100% of the total responses occurred on the appropriate lever

The effects of each local anesthetic on overall response rate and percent of drug lever responding in a test session are presented in Fig 5 Under control conditions (saline pretreatment), average response rates ranged between 0 9 and 1 6 responses/second Each of the test compounds decreased response rates in a dose-related manner In addition, with the exceptions of piperocaine and procainamide, each of the compounds produced at least 75% procaine lever responding at some dose In contrast to what was found with procaine, it was often necessary to use doses that decreased overall response rates to achieve this effect Only chloroprocaine and tetracaine produced procaine lever responding at a level that was comparable to that produced by the training dose of procaine The remaining compounds resulted in 75–90% procaine lever responding or less than 50% procaine-lever responding (procainamide and piperocaine)

The data in Table 2 compare the ED50's of the various local anesthetics for producing procaine lever responding and for decreasing overall response rate The compounds are arranged in the order of decreasing potency for discriminative stimulus effects Cocaine was the most potent and dimethylprocaine the least potent in producing procaine lever responding Piperocaine and procainamide never resulted in the 50% drug lever responding necessary for an ED50 determination Propoxycaine, dimethocaine and tetracaine were 1/2 to 1/3 as potent as cocaine in producing procaine lever responding In contrast, lidocaine, chloroprocaine and procaine were approximately 1/9 as potent as cocaine in this regard Potency relationships were in roughly the same order for response rate-decreasing effects, except for procaine and chloroprocaine potencies were reduced in this measure Procainamide was the least potent local anesthetic in reducing response rates

In the final column of Table 2, the ratios of the ED50 for response rate disruption to the ED50 for producing procaine-lever responding are presented for each compound The ratios are all higher than 1 0, indicating the sensitivity of the drug discrimination method in detecting a pharmacologi-

TABLE 2

POTENCIES OF LOCAL ANESTHETICS FOR GENERALIZATION TO PROCAINE AND FOR DISRUPTION OF RESPONDING DURING TEST SESSIONS IN RATS

Compound	% Procaine-Lever Responding (G) ED50 (μmoles/kg)	Ratio to Cocaine	Response Rate Disruption (R) ED50 (μmoles/kg)	Ratio to Cocaine	R/G
Cocaine	8	1 0	15	1 0	1 9
Propoxycaine	18	2 2	43	2 9	2 4
Dimethocaine	25	3 1	36	2 4	1 4
Tetracaine	26	3 2	43	2 9	1 7
Lidocaine	71	8 9	105	7 0	1 5
Chloroprocaine	73	9 1	224	15	3 1
Procaine	74	9 2	309	21	4 2
Dimethylprocaine	138	17 2	282	19	2 0
Piperocaine	—	—	148	10	—
Procainamide	—	—	538	36	—

cal effect The highest ratios were for procaine and chloroprocaine, indicating a good separation of stimulus effects from non-specific behavioral effects The ratio was also relatively high for propoxycaine, largely because of a very steep dose-response relationship for discriminability For the majority of the other compounds, the ED50 for rate-decreasing effects was about 1 5-2 times the ED50 for procaine-like discriminative stimulus effects

At the end of the experiment, selected doses of *d*-amphetamine were tested A dose of 5 0 μmoles/kg resulted in 88 5% drug lever responding (11 of 12 animals responding) and 10 μmoles/kg resulted in 99 8% drug lever responding (5 of 12 animals responding) Average response rates for these doses were 1 2 (±0 2 S E M) and 0 5 (±0 2 S E M) response/second respectively Thus, *d*-amphetamine generalized to procaine at a dose (5 0 μmoles/kg) that did not decrease response rates Though exact potency relations were not established *d*-amphetamine was considerably more potent than any other compound tested

DISCUSSION

Based on the results of the present experiment as well as reports by other investigators [6, 7, 9, 20], cocaine, procaine, chloroprocaine, dimethocaine and dimethylprocaine are all local anesthetics that can clearly function as positive reinforcers when delivered IV to rhesus monkeys Other local anesthetics such as tetracaine [20] and proparacaine [9] are occasionally self-administered at low rates and might be termed "marginal" reinforcers Furthermore, procaine can function as a discriminative stimulus in rats, and several local anesthetics have discriminative stimulus effects that are similar to those of procaine in this species On the other hand, under these conditions lidocaine and procainamide (shown in a previous study) [20], and piperocaine and propoxycaine (shown in this study) are not positive reinforcers in monkeys and piperocaine and procainamide do not have procaine-like discriminative stimulus effects in rats To the extent that the procedures used in these experiments are predictive of these stimulus properties in humans, the implication is that some but not all local anesthetics would be expected to have abuse potential in humans In this regard, it was particularly provocative to find that cocaine and *d*-amphetamine, drugs with well known abuse potential, produced procaine-appropiate responding in rats The results are in contrast to the findings of Colpaert *et al* [3] that procaine and lidocaine failed to produce drug lever responding in rats trained to discriminate 10 mg/kg cocaine from saline However, these authors tested only a single dose (10 mg/kg) of each of these drugs The potency differences reported in the present experiment make it likely that these doses of procaine and lidocaine were too low to produce cocaine lever responding Alternatively, generalization between local anesthetics may depend upon the training drug used In addition, it should be noted that lidocaine, a drug that was not self-administered by rhesus monkeys [20], had procaine-like discriminative effects in rats, and has been reported to be indistinguishable from cocaine in experienced human volunteers [18] In many respects, the method used by Van Dyke *et al* [18] is more like a drug discrimination procedure than self-administration Clearly, the possibility that local anesthetics have stimulus properties in common with drugs of the psychomotor stimulant class deserves further research

It is important to note that reinforcing effects in the monkey and procaine-like discriminative effects in the rat were not perfectly correlated All of the compounds that were self-administered by rhesus monkeys had discriminative effects in the rat that were similar to those of procaine However, not all drugs that had procaine-like discriminative effects in rats were self-administered by monkeys (i e, lidocaine and propoxycaine) It should be emphasized, therefore, that these two procedures may not be measuring the same pharmacological effects, i e , that discriminative stimulus properties that are similar to those of a reinforcing drug are not necessarily predictive of reinforcing properties Alternatively, differences such as species or route of administration may play a role in this divergence of stimulus properties Further research with rats using self-administration or rhesus monkeys using drug discrimination techniques would help clarify this issue

The mechanism for the behavioral effects of local anesthetics is unclear, although previous research has implicated

cholinergic systems in the mediation of some of the effects of local anesthetics in other preparations A local anesthetic binding site has been associated with the cholinergic receptor in *Torpedo* electric tissue [14] and several local anesthetics have been shown to act as cholinergic agonists [8] or antagonists [13] Moreover, it is interesting to note the structural similarites between esteratic local anesthetics and acetylcholine, as well as the fact that both can be hydrolyzed by cholinesterase [11,16] The results of this and earlier experiments that all local anesthetics that have been found to be reinforcers in monkeys are esters, and that all of the esteratic local anesthetics had procaine-like discriminative stimulus effects in rats are consistent with this possibility However, several factors argue against a cholinergic mechanism of action Drugs that interact with cholinegic systems as agonists or antagonists, e g , arecoline, nicotine and scopolamine, are not self-administered by rhesus monkeys under conditions similar to those used here [10] In addition, cocaine and *d*-amphetamine are positive reinforcers and have procaine-like discriminative effects in rats, though these are drugs which are not usually thought of in terms of their effects on cholinergic systems Indeed, the reinforcing and discriminative stimulus properties of these compounds are generally though to involve dopaminergic systems [3,21] In spite of general structural similarities in common with acetylcholine, there are clearly additional structural requirements among esteratic local anesthetics for these behavioral effects For instance, although propoxycaine and piperocaine are both esteratic local anesthetics, they were not self-administered by rhesus monkeys and piperocaine did not have procaine-like discriminative effects in rats It is possible that steric factors influence the ability of these compounds to interact with the receptor necessary to produce these behavioral effects In addition, the amide class of local anesthetics has not been tested extensively using these procedures and it would be premature to conclude that this type of local anesthetic is devoid of reinforcing properties Indeed, lidocaine is an amide with some procaine-like discriminative stimulus effects in rats Systematic structure-activity comparisons between behavioral tests and *in vitro* cholinergic assays as well as interaction studies with other cholinergic drugs could help clarify this issue

It can be said that it is unlikely that a metabolite of local anesthetics plays a role in mediating their reinforcing effects since neither DMAE nor diethylaminoethanol (DEAE) [20] maintained responding in any monkey tested With the exceptions of cocaine and piperocaine, all of the esteratic local anesthetics that have been investigated to date would be expected to have one of these compounds as a metabolite as a result of hydrolysis by serum esterases [16] In addition, propoxycaine which would be expected to have DEAE as a metabolite, was not self-administered It is possible, however, that systemic administration of DMAE and DEAE may not result in their reaching sites of action due to pharmocokinetic factors Local anesthetics, then, may be prodrugs carrying these metabolites to sites of actions

In light of these data, it may be considered somewhat surprising that there is little or no apparent abuse of local anesthetics among humans In this regard, several points deserve comment First, there may be a relatively high level of local anesthetic aubse that is now documented as cocaine abuse Most local anesthetics could substitute for cocaine on the basis of peripheral effects and taste [18], making it possible that local anesthetics are being used as an inexpensive substitute or adulterant for the more desirable cocaine Furthermore, potency differences might be expected to mitigate against abuse of compounds such as procaine and chloroprocaine Although direct dose-response comparisons were not made in this experiment, the dose range that maintains responding for IV cocaine that is above saline levels in rhesus monkeys using this procedure is 0 1 to 1 0 μmole/kg/inj (approximately 0 03 to 0 3 mg/kg/inj) compared to a dose range of 1 0 to 10 μmole/kg/inj (roughly 0 3–3 0 mg/kg/inj) necessary to maintain responding for procaine or chloroprocaine [9,20] In rats, cocaine was nine times more potent as a discriminative stimulus and 15–20 times more potent than these compounds in decreasing response rates Considering the 7 7 min half-life of IV procaine in humans [17], frequent injections (or insufflation) of large amounts of procaine would be necessary in order to maintain intoxication The constant, high rate of self-administration of these compounds by monkeys (Fig 3) is consistent with this notion Thus, the total mg weight of procaine comparable to recreational doses of cocaine would make it impractical to use Implicit in this argument is the possibility that more potent local anesthetics that are positive reinforcers in monkeys (e g , dimethocaine) could have more significant abuse potential in humans

It is also possible that the stimulus properties of local anesthetics in monkeys and rats are not related to their abuse potential in humans The demonstration of reliable IV self-administration of these drugs in rhesus monkeys using a procedure commonly used in preclinical assessment of abuse potential may therefore represent a false positive finding

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