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Effects of Local Anesthetics on Fixed-Interval Responding in Rhesus Monkeys[1]

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WOOLVERTON, W L AND R L BALSTER *Effects of local anesthetics on fixed-interval responding in rhesus monkeys* PHARMACOL BIOCHEM BEHAV **18**(3) 383–387, 1983 —Several local anesthetics of both the ester and amide type were administered IM to rhesus monkeys trained to respond on a fixed-interval 5 min schedule of food delivery With the exception of procainamide, all local anesthetics produced dose-related decreases in response rates Effects on pattern of responding varied between local anesthetics With some (cocaine, dimethocaine and lidocaine) rate-dependent effects were apparent When control rates were low, these compounds increased rates, when control rates were high, they decreased rates However, with others (procaine, chloroprocaine, tetracaine and propoxycaine) no rate-dependent effects were noted, i e , these compounds had little or no effect on the pattern of responding, even at doses that substantially reduced response rates Consistent with other experiments with these compounds cocaine was the most potent of the group In several instances, local anesthetics which had similar stimulus properties in other behavioral paradigms differed in terms of their effects on fixed-interval behavior

Local anesthetics Schedule-controlled behavior Rhesus monkey

RECENTLY, there has developed an interest in the behavioral pharmacology of local anesthetics Since the initial discovery [2,5] that procaine can function as a positive reinforcer when delivered intravenously to rhesus monkeys, a number of other local anesthetics have been found to function as positive reinforcers in this species [6, 15, 16] It has also been found that procaine can function as a discriminative stimulus in rats and that several other local anesthetics, including cocaine, produce procaine lever responding [16] Further, it has been reported [14] that lidocaine cannot be distinguished from cocaine in experienced human volunteers The possibility that local anesthetics share stimulus properties with drugs of abuse is clearly of interest

The present experiment was designed to further compare the behavioral effects of local anesthetics in rhesus monkeys The effects of each of the local anesthetics we have studied in self-administration and drug discrimination [15,16] were determined in rhesus monkeys trained to respond on a fixed-interval 5 min schedule of food delivery A number of local anesthetics that had stimulus properties in common with cocaine in other behavioral paradigms were distinctly different from cocaine in this experiment

METHOD

Animals and Apparatus

The animals were 4 adult male rhesus monkeys (*Macaca mulatta*) that weighed between 8 1 and 11 2 kg at the beginning of the experiment Two of the animals (B002 and B4115) had previous experience with acute injections of cannabinoids, phencyclidine, phencyclidine analogues and combinations of phencyclidine and pentobarbital Monkey 4156 had experience with intravenous self-administration of local anesthetics and injections of combinations of phencyclidine and pentobarbital The fourth animal (M-324) had a brief history of intravenous cocaine self-administration All animals were drug free for at least 1 month prior to the start of the present experiment The animals were individually housed in standard primate cages (0 6×0 7×0 8 m) where water was continuously available Food intake was restricted to food delivered in the experimental sessions (usually twenty 1 g banana-flavored pellets, P J Noyes, Lancaster, NH, Formula L) and supplemental post-session feedings of approximately 100 g/day Purina Monkey Chow with a chewable multivitamin tablet

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Experimental sessions were conducted in an upright refrigerator shell equipped with an exhaust fan The monkeys were seated for the duration of the experimental session in a primate chair which restricted movement by a waist stock and shoulder rings A response lever with three stimulus lights above it and a food trough were mounted on the inside of the door of the chamber Lever pressing resulted in the delivery of two food pellets by an automatic pellet dispenser (BRS/LVE, Beltsville, MD, PDC) mounted outside the chamber door Experimental contingencies were controlled by solid state programming equipment located in an adjacent room Data were recorded automatically in the form of response totals and cumulative response recordings

Procedure

The animals had been trained to lever press on a fixed-interval 5-min (FI 5) schedule of food presentation At the beginning of the session the lever lights were illuminated and the first lever press after 5 min resulted in food delivery If an animal did not respond within 1 min after the 5-min FI had elapsed (limited hold LH 1 min), the available food pellets were forfeited and the schedule advanced into a 1-min timeout (TO 1 min), during which the lever lights were extinguished and responding had no consequence The session automatically terminated after the end of the tenth TO period Experimental sessions were conducted 5 days/week, Monday through Friday

When responding was stable, dose-effect determinations were begun Drugs were administered on Tuesdays and Fridays, with Thursdays serving as control sessions The animals were injected intramuscularly 5 min before the session while seated in the primate chair Dose-effect determinations were done in the following order procaine (Pfaltz and Bauer, Stanford, CT), lidocaine (Pfaltz and Bauer, Stanford, CT), procainamide (Pfaltz and Bauer, Stanford, CT), piperocaine (Eli Lilly and Co , Indianapolis, IN), dimethocaine (Hoffmann-La Roche, Inc , Nutley, NJ), tetracaine (Pfaltz and Bauer, Stanford, CT), propoxycaine (Sterling-Winthrop Research Institute, Rensselaer, NY), cocaine (National Institute on Drug Abuse, Washington, DC) and chloroprocaine (Penwalt Corporation, Rochester, NY) Procaine was retested at the end of the series to assure that tolerance had not developed as a result of repeated testing with local anesthetics 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/10 kg Doses are expressed as μmoles/kg, and calculated for the salt For purposes of comparison, 1 0 μmole of each compound is equivalent to the following cocaine HCl-340 μg, chloroprocaine HCl-307 μg, procaine HCl-273 μg, dimethocaine HCl-315 μg, piperocaine HCl-298 μg, propoxycaine HCl-331 μg, procainamide, lidocaine HCl-271 μg, tetracaine HCl-300 μg

Data Analysis

Drug effects on overall response rate (responses/sec excluding TO) and pattern of responding (quarter-life) were calculated and group means and standard errors are presented Quarter-life is defined as that portion of the FI that had elapsed when one-fourth of the total responses had occurred [4] For rate-dependency analysis [7], the FI was divided into 5 one-min segments and drug effects on local response rates were determined as a function of average rates of responding in the corresponding segments of the FI under control conditions In all cases, control conditions were defined as mean response rates on the four control days (Thursdays) during each dose-effect determination on which no injection was given Control rates and drug rates were determined for individual animals

Potency comparisons were also made between local anesthetics for effects on response rate Since a measure of potency based upon overall response rate would be confounded by combining rate-increasing and rate-decreasing effects in one measure, calculations were based on effects on responding in bin 5 of the FI only Responding in bin 5 occurred at high rates under control conditions and only rate-decreasing effects were seen when drugs were administered The effects of each dose of each drug were calculated on an individual basis as percent of control Rates of responding on Thursdays during dose-effect determinations served as control data Dose-effect lines were then calculated by the method of least squares linear regression and ED_{50} values calculated for each drug

Local anesthetics were also compared in terms of relative durations of action by comparing cumulative response records To equate intensities, the lowest dose that completely suppressed responding in the first 5 min interval was used for this comparison The duration of complete response suppression was then measured from the response record

RESULTS

Under control conditions, rates and patterns of responding typical of a fixed-interval schedule of reinforcement were seen Control rates of responding in individual animals ranged between 0 5 (Monkey B4115) and 1 6 (also Monkey B4115) responses/sec over the course of the experiment Control values for quarter-life ranged between 0 56 (Monkey M-324) and 0 81 (Monkey B002) indicating a positively accelerated pattern of responding

Figure 1 shows response rate and quarter-life data for each drug, averaged over all four monkeys Sufficient doses of each drug, with the exception of procainamide, reduced overall response rates to near 0 levels With procainamide, solubility limitations precluded testing doses higher than 128 μmoles/kg However, 64 μmoles/kg administered intravenously reduced response rates to 0 43 response/sec, indicating that procainamide is active in sufficient concentrations in this preparation Although increases in overall response rate were occasionally seen with most of the local anesthetics only with tetracaine were increases noted in all animals In spite of these similarities in effects on overall response rate, effects on quarter-life varied between local anesthetics Decreases in quarter-life indicative of disruption of the pattern of fixed-interval responding were apparent with dimethocaine, lidocaine, cocaine and to some extent piperocaine However, for the other local anesthetics, quarter-life values were either increased or not affected

A more detailed analysis of pattern of responding based on local effects within the fixed-interval is shown for cocaine and procaine in Fig 2 As can be seen, cocaine produced rate-dependent effects, increasing low response rates seen early in the interval and decreasing high rates seen late in the interval Similar effects were seen with lidocaine and dimethocaine Rate-increasing and rate-decreasing effects were not as substantial with piperocaine In contrast, doses of procaine that had similar effects on overall response rates either uniformly decreased rates throughout the interval or decreased low rates proportionately more than high rates

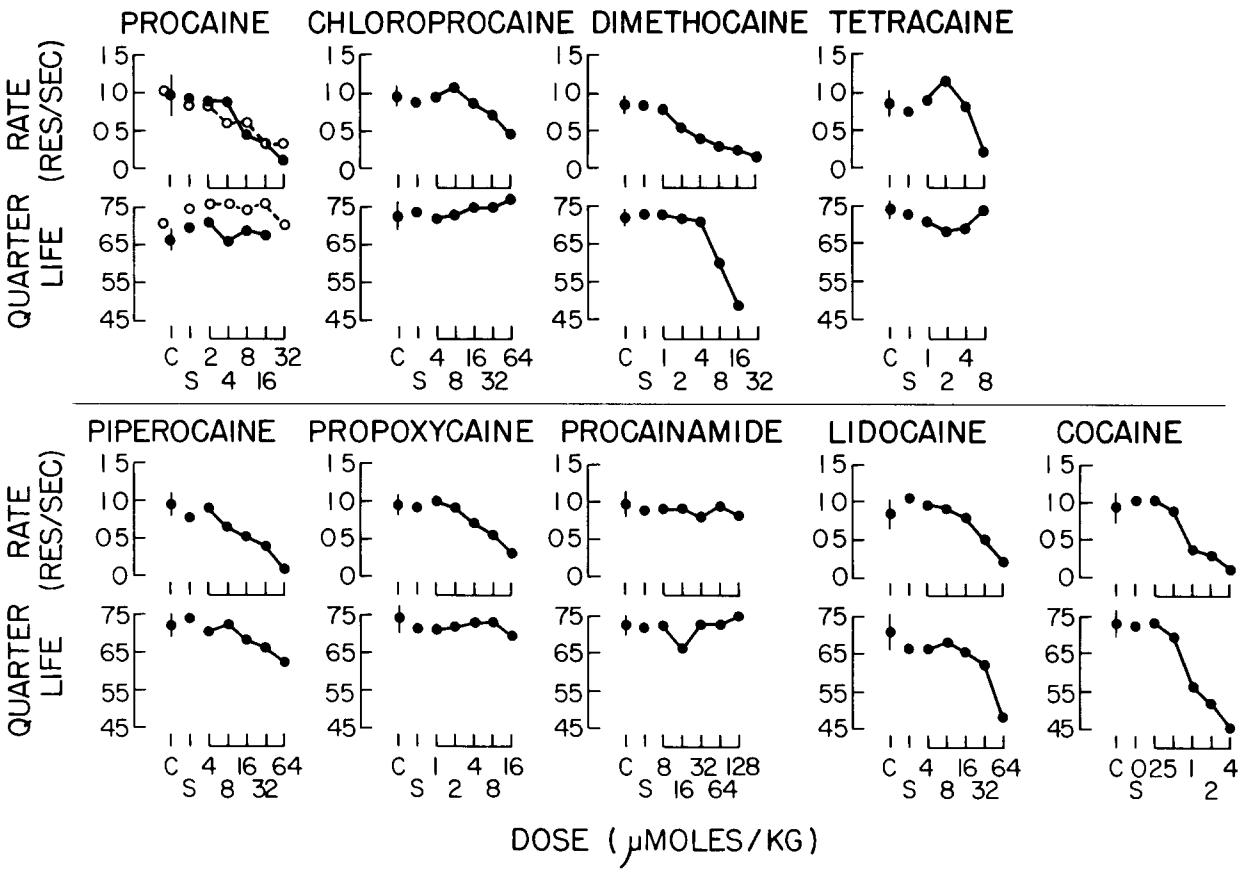

FIG 1 Effects of several local anesthetics on fixed-interval responding in rhesus monkeys Each point represents the mean value for four monkeys for control days (C), saline injection (S) and various doses of each local anesthetic The vertical lines around each control value are the standard errors of the means Standard errors for drug effects were generally less than 10% of the mean The open symbols for procaine are the data for the dose-response redetermination at the end of the series Injections were given IM 5 min before the session

This effect on local rates was also seen with chloroprocaine while tetracaine and propoxycaine did not differentially alter local response rates

Potency comparisons among local anesthetics for effects on high rate responding are shown in Table 1 Cocaine was the most potent of these with an ED_{50} of 1 1 μmole/kg (0 36 mg/kg) Dimethocaine and tetracaine were approximately 1/3 and 1/6 as potent as cocaine, respectively With the exception of chloroprocaine and procainamide, the remainder of the local anesthetics tested were $^1/_{10}$–$^1/_{15}$ as potent as cocaine Chloroprocaine was approximately $^1/_{60}$ as potent as cocaine while an ED_{50} could not be calculated for procainamide Differences in potency could not be accounted for by changes in sensitivity to the effects of local anesthetics since, allowing for shifts in pattern of responding under control conditions, the effects of procaine were the same after the series as they had been before (Fig 1) The drugs could be ranked in the following order in terms of duration of action procaine = chloroprocaine<dimethocaine = propoxycaine< cocaine<piperocaine<tetracaine=lidocaine

TABLE 1

POTENCY COMPARISONS AMONG LOCAL ANESTHETICS IN RHESUS MONKEYS FOR FIXED INTERVAL RESPONDING

Compound	ED_{50} (μmoles/kg)	Ratio to Cocaine	ED_{50} (mg/kg)	Ratio to Cocaine
Cocaine	1 1	1 0	0 36	1 0
Dimethocaine	3 7	3 4	1 2	3 3
Tetracaine	6 9	6 4	2 1	5 7
Propoxycaine	11 0	10 3	3 6	10 0
Procaine	13 2	12 3	3 6	10 0
Lidocaine	14 1	13 2	3 8	10 6
Piperocaine	17 8	16 6	5 3	14 7
Chloroprocaine	74 1	69 0	22 8	63 0

DISCUSSION

Similarities between the effects of local anesthetics and those of the local anesthetic-psychomotor stimulant cocaine have been noted in several behavioral paradigms Procaine, chloroprocaine, dimethylprocaine, dimethocaine and cocaine were all self-administered IV by rhesus monkeys [2, 5, 6, 15, 16] In rats trained to discriminate procaine from saline,

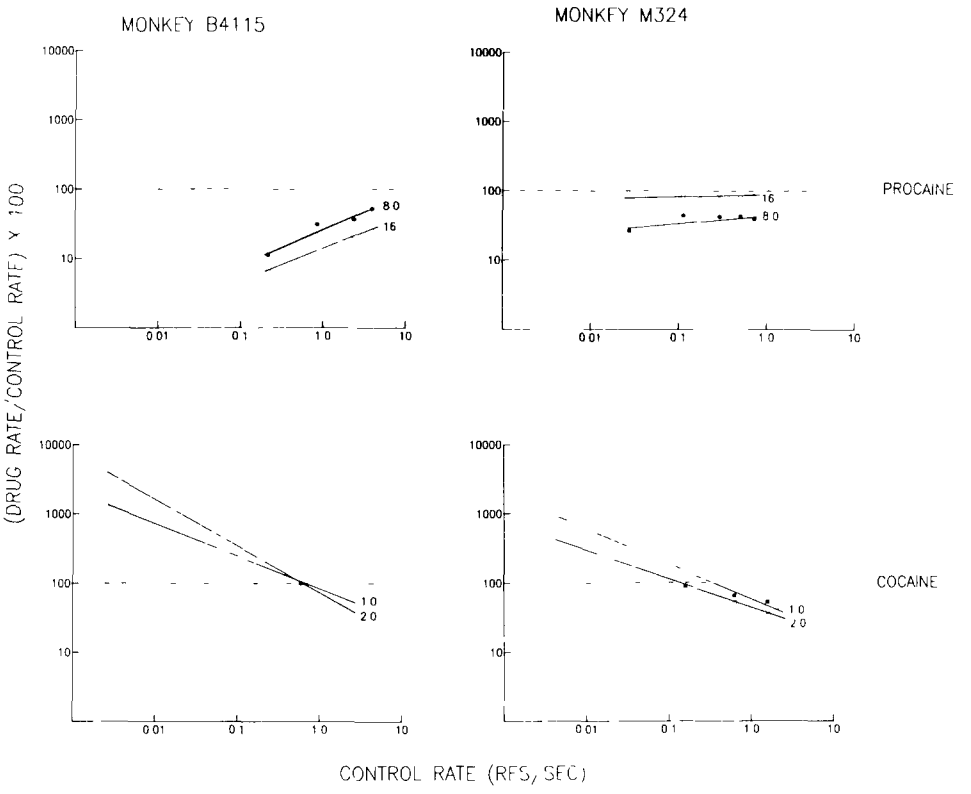

FIG 2 Effects of selected doses of local anesthetics as a function of control response rate for two rhesus monkeys Abscissae Control rate in responses/sec ordinates (drug rate/control rate) × 100 Each point represents the control rate and drug rate for a single 1 min bin of the fixed-interval Points were not plotted when control rates were less than 0 001 responses/sec

all of the local anesthetics tested in the present study except piperocaine and procainamide produced at least 75% drug lever responding [16] In the present study, all of these local anesthetics produced dose-related decreases in fixed-interval responding However there were distinct differences between local anesthetics in terms of their effects on pattern of responding Cocaine, lidocaine, dimethocaine and to some extent piperocaine all disrupted the pattern of responding in a typical rate-dependent fashion Where rates had been low under control conditions, each of these compounds increased rates Where rates had been high, each decreased rates On the other hand, procaine, chloroprocaine, tetracaine and propoxycaine all had more atypical effects on fixed-interval responding Responding was either not affected or decreased by these compounds, regardless of control rate It should be noted that similar effects on the pattern of fixed-interval responding have been found with other psychoactive drugs including tetrahydrocannabinols [1,3] some antipsychotic compounds [8] and physostigmine [9,13] Whether these similarities in behavioral effects reflect some common mechanism of action is unclear at this time

Differences between the effects of cocaine and those of other local anesthetics on fixed-interval responding have been noted previously In pigeons, some doses of cocaine increased overall response rates while procaine and lidocaine did not [10] In that experiment differences were also noted in the effects of these drugs on the pattern of FI responding, although a detailed analysis of these differences was not undertaken In addition, the potency relationship between procaine and cocaine was similar to that found in monkeys However, while lidocaine was slightly more potent than procaine in pigeons, the two were equipotent in monkeys

Differences were also noted in terms of durations of action of the various local anesthetics Although the comparisons made here must be considered approximate, several facts should be mentioned Procaine and chloroprocaine were the shortest acting of the local anesthetics This observation is consistent with the known short half-life of procaine [12] and may account for the high rate of responding maintained by these compounds in self-administration experiments [2, 6, 15, 16] It should also be noted that the only amide local anesthetic to have behavioral effects, lidocaine, was one of the longest acting compounds This finding is also consistent with the known differences in metabolism of esteratic and amide local anesthetics Esters are rapidly hydrolyzed by serum esterases while amides are more slowly degraded by the liver [11] The potency relationships discussed above were at least partially determined by these differences in duration of action Procaine would be expected to be more potent relative to tetracaine were the experimental session shorter

Similarities between local anesthetics in this behavioral paradigm were not consistent with similarities noted in other experiments Of the compounds that function as positive reinforcers in rhesus monkeys, two (cocaine and dimethocaine) reduced quarter-life values while two (procaine and chloroprocaine) did not Among the compounds that were not positive reinforcers in monkeys lidocaine reduced quarter-life values while propoxycaine did not and piperocaine had intermediate effects Similarly, compounds that had procaine-like discriminative stimulus properties in rats both did (cocaine, lidocaine, dimethocaine) and did not (procaine, chloroprocaine, tetracaine, propoxycaine) reduce quarter-life values In addition, effects on fixed-interval responding are not consistent with chemical class Of the local anesthetics that are esters, four (procaine, chloroprocaine, tetracaine, propoxycaine) failed to reduce quarter-life values while two (cocaine, dimethocaine) did Of the two amides tested, lidocaine reduced quarter-life values while procainamide had no behavioral effects in this situation Thus, although there are notable similarities between the reinforcing and discriminative stimulus properties of local anesthetics, particularly of the esteratic class [6, 15, 16], the present experiment suggests significant differences in the behavioral effects of these compounds

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