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Reinforcing Properties of Some Local Anesthetics in Rhesus Monkeys

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WOOLVERTON, W. L. AND R. L. BALSTER. *Reinforcing properties of some local anesthetics in rhesus monkeys.* PHARMAC. BIOCHEM. BEHAV. 11(6) 669–672, 1979.—The reinforcing properties of several local anesthetics were determined in rhesus monkeys experienced in the intravenous self-injection of cocaine. Intravenous procaine and, occasionally, tetracaine maintained response rates higher than did vehicle injections in most monkeys. In contrast, lidocaine, procainamide and diethylaminoethanol (a metabolite of procaine) failed to maintain responding resulting in their intravenous delivery. These results demonstrate that not all local anesthetics are positive reinforcers in the rhesus monkey when delivered intravenously. Furthermore, the reinforcing properties of procaine probably cannot be attributed to its metabolite diethylaminoethanol. The data suggest that short-acting, esteratic local anesthetics are most likely to have reinforcing properties in the rhesus monkey.

Local anesthetics Procaine Lidocaine Tetracaine Procainamide Diethylaminoethanol Rhesus monkey Drug self-administration

ALTHOUGH local anesthetics are not typically used for their central nervous system effects, systemic administration of sufficient doses of these compounds can produce behavioral effects which are mediated by the CNS. In humans, euphoria and drowsiness have been reported following the intravenous administration of both lidocaine and procaine. Procaine has been studied as a geriatric antidepressant [1,14] and has been used as an intravenous general anesthetic [6,11]. Several local anesthetics have been shown to disrupt schedule-controlled performance in pigeons [9]. In addition, although local anesthetics are not commonly considered to be drugs of abuse, it has recently been found that procaine can function to maintain responding that leads to its intravenous delivery in rhesus monkeys [5,7]. Intravenous chloroprocaine has also been found to act as a positive reinforcer in rhesus monkeys (Johanson, personal communication). Furthermore, van Dyke *et al.* [12] reported that human volunteers found intranasal lidocaine indistinguishable from cocaine delivered by the same route.

This report describes the results of studies of the reinforcing properties of other local anesthetics and a related compound chosen to provide answers to specific questions concerning the generality of and mechanism for the reinforcing properties of procaine reported previously [5]. The following questions were addressed by this study. (1) Can other local anesthetics serve as positive reinforcers in rhesus monkeys? To answer this question, three additional local anesthetics, lidocaine, procainamide and tetracaine were compared to procaine. (2) Can the reinforcing properties of procaine be related to its metabolism as has been suggested [5]? Procaine (as well as chloroprocaine) is rapidly hydrolyzed to diethylaminoethanol (DEAE) and p-aminobenzoic acid. To test the hypothesis that DEAE mediates the reinforcing properties of procaine, equimolar doses of this metabolite were compared to procaine. (3) Can the longer acting amide-linked anesthetics also serve as positive reinforcers? Procainamide is the amide counterpart of the ester procaine and lidocaine is an amide-linked local anesthetic as well. The results presented with these compounds provide additional data relevant to the phenomenon of local anesthetics as positive reinforcers.

METHOD

The general methods for this study were similar to those used previously to study procaine self-administration [5].

Animals and Apparatus

The animals were five adult male rhesus monkeys that weighed between 5.5–7.7 kg at the beginning of the experiment. Monkey No. 3147 had a history of PCP self-administration. All other animals were drug naive. Each was fitted with a stainless steel restraint harness [3] 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) 24 hr/day for the duration of the experiment. Water was continuously available and each monkey received approximately 200 g of Purina Monkey Chow and a chewable multiple vitamin tablet each day.

On the inside front of each experimental cubicle two response levers were mounted on the transparent Plexiglas door 30 cm above the floor with a food dish between them and three jewelled stimulus lights 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 (10–30 mg/kg, IV). When anesthesia was adequate, a silicone catheter (0.08 cm ID, Ronsil Rubber Products, Belle 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 hollow arm to the back of the cubicle and connected to the infusion pump which could deliver drug solutions at a rate of 1 ml/10 seconds. If a catheter became non-functional 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 2 white left lever lights to press the left lever for a 10 sec infusion of 0.1 mg/kg cocaine hydrochloride. During an infusion the white lever lights were extinguished and the center red lever light was illuminated. Responses occurring during the infusion 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 over the period of one 2 hr session to 10 (fixed ratio 10: FR 10). After responding during daily 2 hr sessions stabilized (2–3 days) a dose of 0.1 μmole/kg/infusion cocaine hydrochloride (34 μg/kg/infusion) was used to maintain responding in all animals.

Baseline conditions. Daily 2 hr sessions were signaled by the illumination of the white lever lights over the left lever. During each session, the animals received IV infusions of 0.1 μmole/kg cocaine contingent upon left lever responding under an FR 10 schedule. The number of infusions delivered was recorded every 30 minutes, and total left lever responses were recorded for the session.

Test drug substitution procedure. Following the establishment of stable rates of responding under baseline conditions (less than 10% variation in total number of infusions 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.

The test compounds were procaine, diethylaminoethanol (DEAE), lidocaine, tetracaine and procainamide. At least two doses of each drug were tested in an unsystematic order on an individual basis. Usually, all doses of one drug were tested before testing another drug. The exceptions were No. 4173 and No. 4156 where the 2 highest doses of each drug were tested in an initial series, followed by a series of 2 lower doses of each drug. The rationale for selection of drug doses was as follows. Initially, doses were selected in a range that was comparable to known reinforcing doses of procaine (3 and 10 μmoles/kg/infusion), and were compared on an equimolar basis. Since procaine is hydrolyzed to DEAE and p-aminobenzoic acid, only these doses of DEAE were tested. However, for procainamide and lidocaine, it was apparent that these doses were sufficiently high to suppress responding in some animals. Therefore, for these compounds, lower doses were tested that did not suppress responding and were comparable to known reinforcing doses of cocaine (0.1 and 0.3 μmole/kg/infusion). In addition, since tetracaine is a more potent local anesthetic (by about 10 fold) than the other compounds, test doses were lower for tetracaine. Saline was substituted at least twice for six days in each animal irregularly in the series. After the entire series had been tested, at least one dose of procaine was retested in animals Nos. 3147, 4173, and 4156 to determine whether any change in effect of the drug had resulted from repeated testing with similar compounds.

Drugs. Procaine hydrochloride, lidocaine hydrochloride, tetracaine hydrochloride, procainamide hydrochloride and 2-diethylaminoethanol (DEAE) were purchased commercially (Pfaltz and Bauer, Stanford, Conn.). Cocaine hydrochloride was obtained from the National Institute on Drug Abuse. Drugs were dissolved in 0.9% saline for injection, with concentrations adjusted so that infusions were administered in a volume of 1 ml. Doses are expressed as μmoles/kg/infusion. For purposes of comparison 1 μmole of each test compound is equivalent to the following: cocaine HCl—340 μg; procaine HCl—273 μg; lidocaine HCl—271 μg; procainamide HCl—272 μg; tetracaine HCl—300 μg and DEAE—117 μg.

Data analysis. The number and distribution of infusions over the last 3 sessions of a test drug substitution period were used in data analyses. These values were compared to the same values for the last 3 sessions of a saline substitution period. A drug was considered to be a positive reinforcer if the mean number of infusions for the last 3 sessions of a test period (infusion rate) exceeded the mean number for the corresponding value for a saline substitution and the ranges of these values did not overlap.

RESULTS

Under baseline conditions cocaine maintained stable infusion rates above the range of saline values for each subject (values above C and S in Fig. 1). There was, however, considerable variability between subjects in cocaine intake per session, with mean values ranging between 41.7 (M327) and 236.7 (No. 4173) infusions per session. When saline was substituted for cocaine, low infusion rates (<20 infusions/session) were usually observed by the sixth session. The exceptions were animal No. 4163 and the second saline substitution in animal No. 3147.

When procaine was substituted for cocaine, the number of infusions per session was normally above saline levels at least at one dose (3 μmoles/kg/infusion). The exceptions were No. 4163, who took an unusually high number of saline infusions, and No. 3147, whose responding for saline in the second saline substitution period was considerably higher than that observed when saline was tested initially. In this case saline and procaine infusion rates overlapped. In the range of doses tested, infusion rates for procaine were inversely related to dose per infusion. When tetracaine was substituted for cocaine the number of infusions was above saline levels at a single dose in three of four animals tested. In the fourth animal infusion rates were fairly high though not above this subject's high saline rates. Although rates were not as high as those maintained by procaine or cocaine, the dose-response relationship for tetracaine in two of the four animals was an inverted "U" shape frequently described for drugs that are positive reinforcers [4,13].

In contrast, when DEAE, lidocaine and procainamide were substituted for cocaine, responding at or below saline levels was consistently observed (Fig. 1). Although the mean infusion rate was occasionally slightly higher than saline for these drugs, the ranges of these values overlapped with

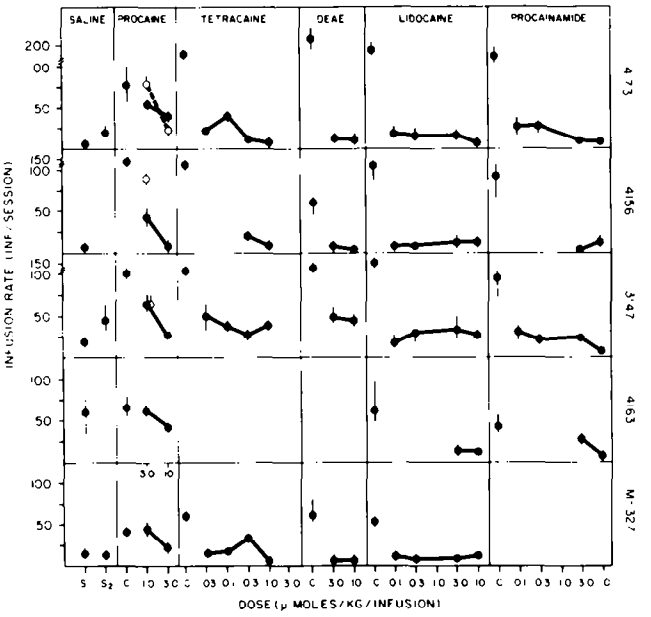

FIG. 1. Mean number of infusions of the test compounds for each animal during the last three sessions of each substitution period (vertical bars represent the range of infusions). The points above S_1 and S_2 represent the mean number of infusions of saline during the first and second saline substitution. The points above C represent the mean number of infusions of cocaine (0.1 μmoles/kg/infusion, 34 μg/kg/infusion) taken during the last three sessions before each substitution period. Open circles (procaine No. 4173, No. 4156, No. 3147) represent redeterminations of the effects of these doses following completion of the entire series.

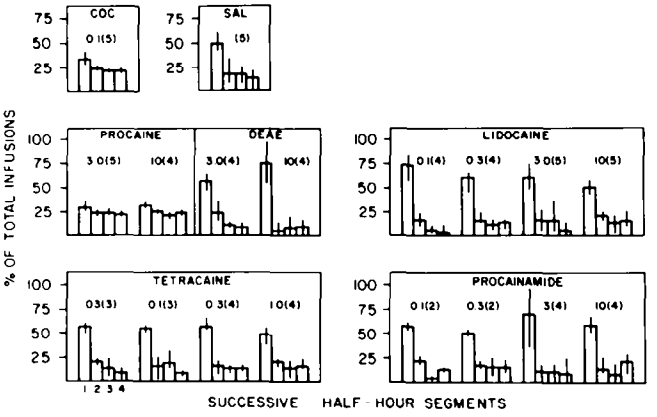

FIG. 2. Percent of total taken in each 30 minute segment of the experimental session. Values were averaged for all animals tested and vertical lines represent the range of effects. Numbers above each histogram are the drug dose, in μmoles/kg, and in parentheses are the total numbers of animals tested at that dose.

saline and so probably represent random variability in responding for a non-reinforcing compound. Furthermore, there was no systematic dose-response relationship for any of these compounds until doses high enough to suppress responding were reached. For animal No. 4163, the mean number of saline infusions per session was exceptionally high, making interpretation of his data difficult. However, these data are of interest for at least two reasons. The rates (as well as patterns) of responding for lidocaine and procainamide are comparable to those of the other animals tested with these compounds. In addition, the fact that infusion rates for these compounds were below saline levels likely indicates that behaviorally active doses were being tested.

Comparisons between the patterns of responding for each of the test compounds are made in Fig. 2. Consistent with the findings of others [2, 4, 5], responding for cocaine was relatively evenly distributed over the experimental session, with slightly more than 30% of the infusions taken in the first 1/2 hour of the session. In contrast, when saline was substituted for cocaine a typical extinction pattern of responding was observed with approximately 50% of the total number of infusions being taken in the first 1/2 hour of the session. When procaine was tested, the pattern of responding was similar to that observed for cocaine, both test doses resulting in evenly spaced responding throughout the session in all animals. In contrast, the pattern of responding for all other test compounds was essentially identical to that for saline, with usually more than 50% of the infusions being taken in the first 1/2 hour of the experimental session.

DISCUSSION

The results presented here confirm the findings of others [5,7] that intravenous procaine has reinforcing properties in rhesus monkeys. That these effects of procaine are probably not mediated by the metabolite DEAE, is indicated by the fact that DEAE, tested in equimolar doses, maintained rates and patterns similar to those maintained by saline in all animals. However, the possibility that DEAE fails to pass biological membranes in a manner similar to procaine cannot be eliminated by the present experiment. Another local anesthetic, tetracaine, maintained rates above saline levels at one dose each in 3 of 4 animals tested, although the dose range for these effects was narrow. The pattern of responding for tetracaine was similar to the pattern of responding for saline. However, since tetracaine is a potent and long-acting local anesthetic, this pattern of responding may be due to suppression of responding late in the session by drug self-injected in the early segments. Similar patterns of responding have been observed for other long-acting drugs that are positive reinforcers tested under similar conditions [2]. It is also of interest to note that one of the metabolites of tetracaine is dimethylaminoethanol (Deanol), itself a CNS stimulant [8]. Though the data are suggestive, the conclusion that tetracaine is a positive reinforcer is tenuous and must await further research.

The data presented here fail to support the hypothesis that all local anesthetics have positively reinforcing properties. Neither procainamide nor lidocaine maintained rates above saline levels at any dose tested. In addition, the pattern of responding for these compounds was an extinction pattern of responding. The results with lidocaine are of particular interest as well since van Dyke *et al.* [12] reported that lidocaine was indistinguishable from cocaine and produced euphoria in experienced human volunteers. Our data do not suggest that lidocaine is a reinforcer in rhesus monkeys.

Structurally, most local anesthetics can be classified in one of two groups, ester-linked and amide-linked compounds [10]. One way these two groups differ is in the route of metabolism: esteratic local anesthetics are broken down rapidly by serum esterase whereas the amide compounds are

more slowly broken down in the liver. Procaine, chloroprocaine and cocaine are all short-acting esteratic local anesthetics as well as positive reinforcers, whereas tetracaine is a longer acting esteratic compound which may have reinforcing properties. In contrast, procainamide and lidocaine are long-acting amide-linked local anesthetics and are not positive reinforcers. The results with procainamide are of particular interest since, except for this linkage, procainamide is structurally identical to procaine. These facts, taken together, suggest that short-acting ester-linked local anesthetics are most likely to have reinforcing properties in the rhesus monkey. Whether the important factor is the duration of action or the metabolic pathway could be evaluated by testing the reinforcing properties of a short-acting amide-linked compound or additional long-acting esters. Studies of possible qualitative differences between the central nervous system effects of procaine, chloroprocaine, tetracaine, lidocaine and procainamide may also reveal a basis for the differences seen between the reinforcing effects of these compounds.

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