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Discriminative Stimulus Properties of Local Anesthetics in *d*-Amphetamine- and Pentobarbital-Trained Pigeons

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ZACNY, J. P. AND W. L. WOOLVERTON. *Discriminative stimulus properties of local anesthetics in* d-*amphetamine- and pentobarbital-trained pigeons.* PHARMACOL BIOCHEM BEHAV **33**(3) 527–531, 1989.—Pigeons were trained to discriminate either *d*-amphetamine (1.7 mg/kg, IM) or pentobarbital (10 mg/kg, IM) from saline in a two-key, food-reinforced drug discrimination paradigm. Cocaine, procaine, and lidocaine were administered before test sessions to determine if these local anesthetics shared discriminative stimulus (DS) properties with either training drug. Cocaine (0.1–3.0 mg/kg) substituted for *d*-amphetamine in all 4 birds from the *d*-amphetamine-trained group. Procaine (3.0–56 mg/kg) substituted in 3 of the 4 birds from this group, and lidocaine (3.0–30 mg/kg) did not substitute in any bird. In contrast, cocaine, procaine, and lidocaine did not substitute for pentobarbital in any bird in the pentobarbital-trained group. These results suggest that the DS properties of some local anesthetics may be similar to those of psychomotor stimulants. Further, although some local anesthetics may have sedative-like actions, apparently these are not the basis of their DS effects.

Local anesthetics Discriminative stimulus Procaine Lidocaine Cocaine *d*-Amphetamine Pentobarbital Pigeons

THERE is current interest in the behavioral effects of local anesthetics, due in part to the widespread abuse of cocaine, itself a local anesthetic. Several local anesthetics, including cocaine, procaine, dimethylprocaine, dimethocaine, and chloroprocaine, have been shown to have reinforcing effects in animals (17, 28, 29). Not surprisingly, cocaine functions as a reinforcer in cocaine-experienced humans (6). A number of local anesthetics, including the ones mentioned above, and tetracaine, propoxycaine, and lidocaine, substituted for procaine in a drug discrimination paradigm utilizing rats (29), suggesting that these local anesthetics share DS properties.

The basis for these behavioral effects of local anesthetics has not been established. Some experiments suggest that local anesthetics have effects in common with psychomotor stimulants. For example, Woolverton and Balster (29) reported that *d*-amphetamine and cocaine substituted for procaine in rats. In other drug discrimination studies utilizing monkeys, rats, and pigeons, procaine partially substituted for cocaine (11, 12, 16, 19). There is also some overlap in the subjective effects of procaine and cocaine in cocaine-experienced humans (7). Local anesthetics also have effects in common with sedatives. It has been reported that local anesthetics may act as central nervous system depressants (18). Indeed, both lidocaine and procaine have been used to treat status epilepticus (1,10). Sedation and ataxia in rats have been reported with the local anesthetic, lidocaine (22). Procaine can produce general anesthesia in animals (27) and humans (21). In addition, procaine has been reported to potentiate the effects of other general anesthetics (9).

These commonalities in effects between local anesthetics and both psychomotor stimulants and sedatives raise the possibility that local anesthetics have DS effects in common with these two drug classes. It may be the case that some local anesthetics have stimulant-like DS properties while others have sedative-like DS properties. Indeed, there is evidence which suggests that differences do exist between the DS properties of cocaine, procaine and lidocaine [e.g., (11,12)]. Accordingly, the DS properties of cocaine, procaine, and lidocaine were examined in groups of pigeons trained to discriminate *d*-amphetamine or pentobarbital from saline. These training drugs were chosen because they are regarded as a prototypic stimulant and sedative, respectively. The

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local anesthetics procaine and lidocaine were chosen as representatives of the ester and amide types, respectively, of local anesthetics.

METHOD

Subjects

Eight white Carneaux pigeons served as subjects. All eight birds had previously served in drug discrimination experiments. Four (1486, 1548, 3106, 7255) had been trained to discriminate pentobarbital (10 mg/kg) from saline, and were tested with antihistamine compounds. These birds comprised the pentobarbital-saline discrimination group in the present study. The other four (252, 3048, 4129, 4485) had been trained to discriminate *d*-amphetamine (1.7 mg/kg) from saline, and had been tested with combinations of *d*-amphetamine and nisoxetine or phenmetrazine. These four birds comprised the *d*-amphetamine-saline discrimination group in the present study. Body weight in the present study was reduced to 80% of free-feeding weight. When necessary, Purina Pigeon Checkers were given following an experimental session to maintain stable body weight.

Apparatus

Two custom-made chambers (inside dimensions $32 \times 28 \times 32$ cm) were used in the experiment, and have been described in detail elsewhere (5). Briefly, the boxes contained two illuminated pigeon keys located on a metal panel. Purina Pigeon Checkers were made available from a food magazine centered between and below the keys. The magazine was illuminated during food delivery. A houselight, mounted behind a back metal panel, provided illumination during sessions. The experiment was controlled by a Rockville AIM 65 microcomputer located in an adjacent room.

Procedure

Training. All birds had been trained to discriminate the training drug dose from saline prior to this experiment, and the initial training procedure has been described in detail elsewhere (5). During training sessions, drug or saline injections were given 10 min prior to every session. Injections were given IM in a 1.0 ml/kg volume. After an injection of drug, responding under a fixed-ratio (FR) 30 schedule of reinforcement on the appropriate key was followed by 3-sec access to grain, and, after an injection of saline, responding on the other key under the same schedule was followed by 3-sec access to grain. Incorrect responses reset the response requirement on the correct key. Each session lasted until 50 reinforcers were delivered or until 15 min had elapsed, whichever occurred first. Maintenance of the discrimination between drug and saline was defined as responding on the correct key at or above 90% of the total number of responses in a session, and responding less than 30 times on the incorrect key prior to the first reinforcer of the session. The injection preceding each session was selected from a semirandom sequence with the restriction that no condition would occur for three consecutive sessions.

Testing. The stimulus properties of all compounds were evaluated during test sessions. Test sessions differed from training sessions in that food was delivered following the completion of 30 responses on either key. Drug and saline training sessions were intermixed with test sessions in the following 10-day sequence: DTSDTSTDST (D = drug training session, S = saline training session, T = test session). A test session was conducted only if the two preceding training sessions met the criteria for stimulus control. If the criteria established for stimulus control were not maintained, test sessions were discontinued. At this time, the injection preceding each session was selected from a semirandom sequence, with the restriction that no condition occurred 3 consecutive times. When the criteria for stimulus control were met again, the 10-session testing sequence was reinstated.

Each group of pigeons was initially tested with several doses of its training drug. Dose-response functions of procaine, lidocaine and cocaine were determined once across birds in a counterbalanced order. Three or four doses of each test compound were tested in a mixed order. In most cases, a compound was tested until a dose was given that resulted in at least 80% of the responses on the training-drug key or until a dose was reached which reduced response rate to at least 50% of the rate for the training drug. For each pigeon, the dose-response function for each drug was completed before another compound was tested. After completion of each dose-response function, the effects of either the training dose or saline were determined in test sessions.

Data analyses. The percent of drug-key responding that occurred during the overall session was used as a measure of the ability of a drug to substitute for the training drug. A drug was considered to completely substitute for the training drug if it produced at least 80% drug-key responding. The overall session response rate (responses/sec) was also calculated. If no reinforcers were obtained during the test session, the data were not included in the analysis of drug-key responding, but were included in the analysis of drug-induced response rate alterations.

Drugs. *d*-Amphetamine HCl and cocaine HCl were obtained from the National Institute on Drug Abuse. Sodium pentobarbital was obtained from Abbott Laboratories (North Chicago, IL). Procaine HCl and lidocaine HCl were obtained commercially. All drugs were dissolved in 0.9% saline and the doses were calculated as the salt.

RESULTS

d-*Amphetamine-Trained Group*

The training dose of *d*-amphetamine (1.7 mg/kg) administered during test sessions engendered 100% *d*-amphetamine-key responding, and saline administered during test sessions engendered no *d*-amphetamine-key responding in all 4 birds (Fig. 1). Response rates were reduced by *d*-amphetamine in a dose-related manner in 3 out of 4 birds. Cocaine substituted completely for *d*-amphetamine in all 4 birds. Cocaine substituted at a dose which did not appreciably reduce response rate in 2 of the 4 birds (pigeons 252 and 4129). Cocaine was similar in potency to *d*-amphetamine both in terms of producing *d*-amphetamine-key responding and response rate decrements. Procaine substituted for *d*-amphetamine (i.e., >80% *d*-amphetamine-key responding) in 3 of 4 birds (pigeons 4485, 252, 4129) at doses which did not substantially reduce response rate. Procaine was approximately 1/10th as potent as *d*-amphetamine. In bird 3048, procaine did not engender any *d*-amphetamine-key responding up to doses that completely suppressed responding. In contrast, lidocaine did not engender any *d*-amphetamine-key responding in any of the birds tested up to a dose of 30 mg/kg. Doses beyond 30 mg/kg were not tested because 56 mg/kg caused loss of the righting reflex in several untrained test birds.

Pentobarbital-Trained Group

The training dose of pentobarbital (10 mg/kg) and saline administered during test sessions engendered 100% and 0% pentobarbital-key responding, respectively, in all 4 birds (Fig. 2). Pentobarbital produced a dose-related increase in the percentage of responses emitted on the pentobarbital-key in all 4 birds. Pentobarbital had little, if any, effect on response rate. Cocaine did not substitute for pentobarbital up to doses that reduced or suppressed responding in all 4 birds. Likewise, procaine did not substitute for pentobarbital up to doses that markedly reduced or suppressed

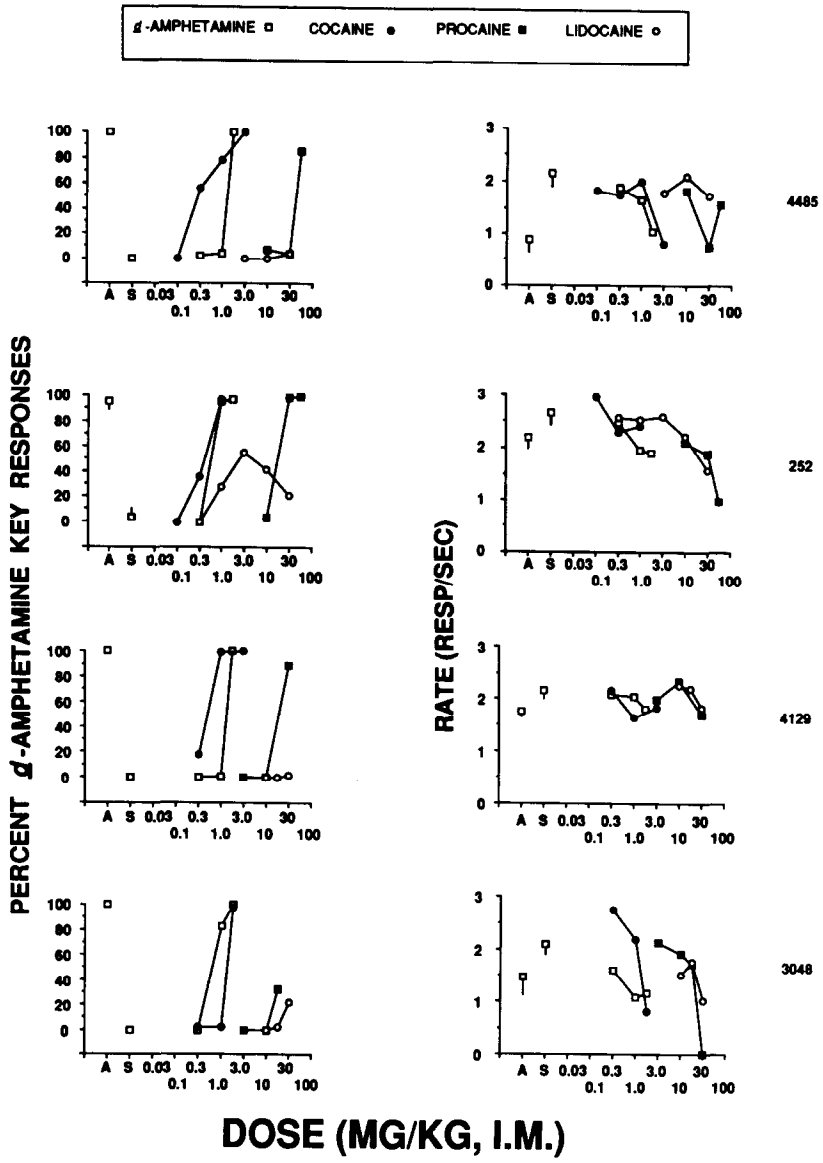

FIG. 1. For each of 4 pigeons, the percentage of *d*-amphetamine-appropriate responding (left frames) and response rate (right frames) as a function of dose for each test compound. Response rate refers to responses per second. The points above *d*-amphetamine (A) and saline (S) refer to means (and SD) from the two *d*-amphetamine and two saline test sessions obtained during determination of the dose-response functions.

responding in all 4 birds. In 3 of 4 birds, lidocaine did not engender any pentobarbital-key responding. In the fourth bird, 30 mg/kg of lidocaine produced 53% pentobarbital-key responding, and a substantial reduction in response rate.

DISCUSSION

Cocaine (4 of 4 birds) and procaine (3 of 4 birds) substituted for *d*-amphetamine, a prototypic psychomotor stimulant. Lidocaine, an amide type of local anesthetics, did not substitute for *d*-amphetamine. None of the local anesthetics substituted for pentobarbital, a prototypic sedative. The finding that cocaine substituted for *d*-amphetamine is in agreement with previous studies in which cross-generalization of the DS properties of cocaine and *d*-amphetamine has been observed (13,14). Both compounds are catecholamine agonists and share DS properties with other catecholamine agonists [e.g., (3,26)]. The finding that procaine substituted for *d*-amphetamine in 3 out of 4 birds is consistent with known biochemical similarities between the two compounds. Both compounds can block catecholamine uptake and both are monoamine oxidase (MAO) inhibitors (4, 20, 24, 25). This finding is also consistent with a study in which *d*-amphetamine substituted for procaine in rats (29). The present results in conjunction with the Woolverton and Balster study (29) suggest that there is cross-generalization between the DS properties of *d*-amphetamine and procaine.

It is apparent that the DS properties of lidocaine are not *d*-amphetamine-like. This result is not entirely surprising, given that lidocaine appears to have minimal impact on catecholamines

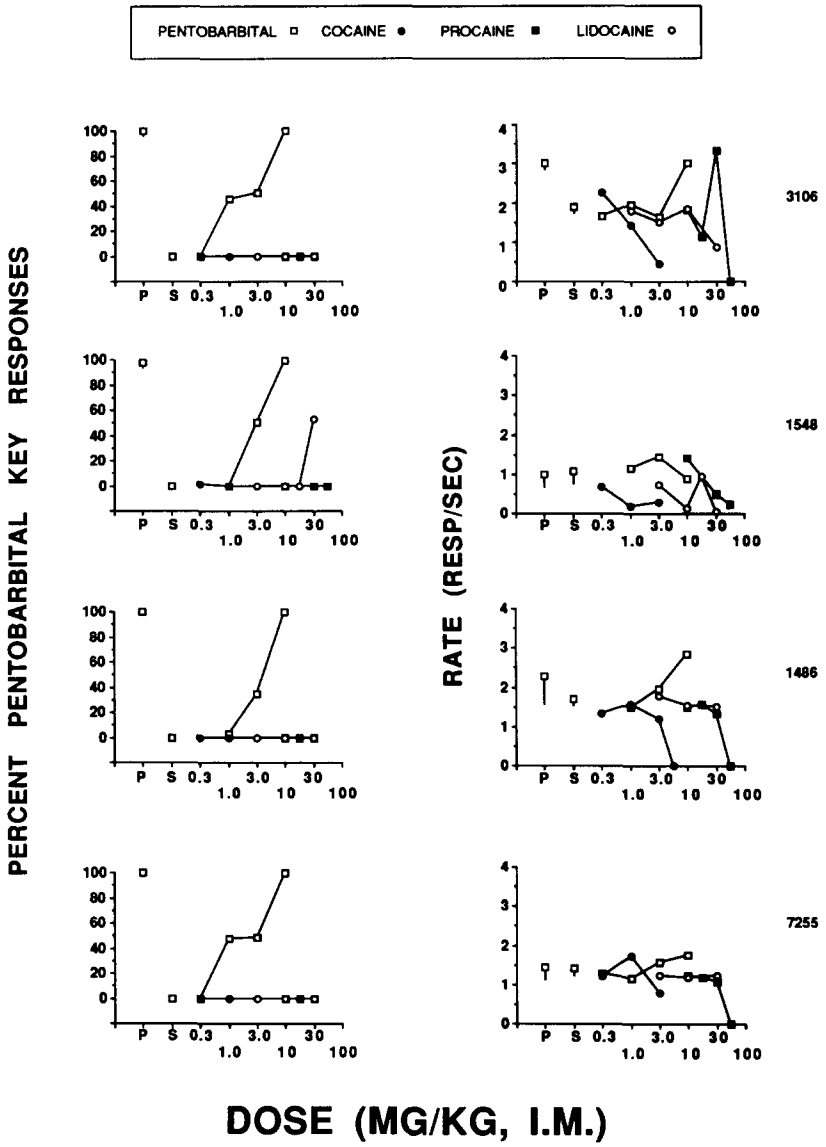

FIG. 2. For each of 4 pigeons, the percentage of pentobarbital-appropriate responding (left frames) and response rate (right frames) as a function of dose for each test compound. Response rate refers to responses per second. The points above pentobarbital (P) and saline (S) refer to means (and SD) from the two pentobarbital and two saline test sessions obtained during determination of the dose-response functions.

(23,24) and has been reported not to share DS properties with cocaine (12,15). Further, lidocaine did not have a spectrum of subjective effects in humans which are typically observed with *d*-amphetamine, cocaine and other psychomotor stimulants (2,8). Taken together with the effects of procaine in these animals, these results support the notion that there are important behavioral differences between esteratic and amide local anesthetics (29).

None of the local anesthetics substituted for pentobarbital. It was not entirely surprising that cocaine did not substitute for pentobarbital, given that in previous studies, pentobarbital did not substitute for cocaine (11,12). However, procaine, like pentobarbital, has been used as a general anesthetic (21,27), and lidocaine, like pentobarbital, has sedative properties (22). The present results suggest that the sedative-like properties of these local anesthetics are not involved in mediating their DS effects.

In conclusion, cocaine and procaine share DS properties with a prototypic psychomotor stimulant, *d*-amphetamine. The differences in the ability of cocaine, procaine, and lidocaine to substitute for *d*-amphetamine are consistent with the pharmacologic and behavioral profile of these local anesthetics. These results support the notion that esteratic local anesthetics have some behavioral similarities to psychomotor stimulants. Further, the sedative-like properties associated with at least procaine and lidocaine do not appear to be involved in mediating their DS effects, since they did not substitute for a prototypic sedative.

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