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# Discriminative stimulus effects of esteratic local anesthetics in squirrel monkeys

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**Abstract**

A number of esteratic local anesthetics serve as positive reinforcers and produce cocaine-like discriminative stimulus effects in animals. It has been suggested that the affinity of these compounds for a site on the dopamine transporter, and not their local anesthetic actions, is responsible for these abuse-related behavioral effects. In the present study, three local anesthetics previously shown to be self-administered in animals were examined in squirrel monkeys trained to discriminate cocaine (0.3 mg/kg) from saline in a two-lever, food-reinforced procedure. Dimethocaine (0.1–3.0 mg/kg) fully and dose-dependently substituted for cocaine. Doses of dimethocaine (1.7 mg/kg) and cocaine (0.3 mg/kg) which produced full (> 80%) substitution for cocaine were administered in combination with the dopamine $D_1$ receptor antagonist SCH 39166 ((−)-*trans*-6,7,7a,8,9,13b-hexahydro-3-chloro-2-hydroxy-*N*-methyl-5*H*-benzo[*d*]naphtho-(2,1-b)azepine) and the dopamine $D_2$ receptor antagonist raclopride (both at 0.003–0.03 mg/kg). SCH 39166 fully blocked the cocaine-like discriminative stimulus effects of dimethocaine and cocaine, but raclopride produced only partial antagonism of cocaine-lever selection. In addition, there was some evidence that raclopride blocked cocaine-lever responding produced by a lower dose of dimethocaine. In substitution studies, neither procaine (1–10 mg/kg) nor chloroprocaine (1–30 mg/kg) produced cocaine-like effects. These results support a role for dopamine in the behavioral effects of some local anesthetics.

*Keywords:* Drug discrimination; Local anesthetic; Dopamine; Cocaine; Dimethocaine; Procaine; Chloroprocaine; SCH 39166; Raclopride; (Squirrel monkey)

## 1. Introduction

In addition to its well-known effects as a sympathomimetic stimulant, cocaine is also a highly effective topical anesthetic (Garfield and Gugino, 1987). While the pharmacological actions of cocaine at a site located on the dopamine transporter protein are generally considered to form the cellular basis for its abuse-related effects (Woolverton and Johnson, 1992), other local anesthetics have also been found to maintain intravenous self-administration in laboratory animals (Ford and Balster, 1977; Hammerbeck and Mitchell, 1978; Woolverton and Balster, 1979,1982; Johanson, 1980; De la Garza and Johanson, 1982). In particular, the esteratic local anesthetics dimethocaine, procaine and chloroprocaine all serve as reinforcers in monkeys. Of these, dimethocaine displays relatively high affinity for the dopamine transporter (Ritz et al., 1987) and produces other behavioral effects consistent with dopaminergic stimulation, such as ipsilateral turning in rats with unilateral lesions of the substantia nigra (Silverman, 1990) and full substitution for cocaine in animals trained to discriminate cocaine from vehicle (Graham and Balster, 1993). This evidence strongly suggests that the behavioral effects of dimethocaine can be ascribed to a cocaine-like dopaminergic stimulation.

Procaine and chloroprocaine, on the other hand, display comparatively low affinity for the dopamine transporter (Ritz et al., 1987) and their reinforcing effects are correspondingly less potent than those of dimethocaine. Neither procaine nor chloroprocaine in-

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duces ipsilateral rotation in rats (Silverman, 1990), and procaine only inconsistently substitutes for the cocaine discriminative stimulus in rats (Colpaert et al., 1979; McKenna and Ho, 1980; Huang and Wilson, 1982; Silverman and Schultz, 1989; Graham and Balster, 1993), pigeons (Jarbe, 1984; De la Garza and Johanson, 1985), and rhesus monkeys (De la Garza and Johanson, 1983). Moreover, the dopamine antagonist haloperidol was reported to be ineffective in blocking either the reinforcing (De la Garza and Johanson, 1982) or discriminative stimulus effects of procaine (Silverman and Schultz, 1989). Thus, there appear to be important pharmacological differences between cocaine and other local anesthetics which leave in question the cellular basis for their reinforcing effects in animals.

The purpose of the present experiment was to examine the cocaine-like discriminative stimulus effects of local anesthetics in squirrel monkeys, and to assess with site-selective antagonists whether the effects of compounds substituting for cocaine can be attributed to a dopaminergic mechanism, as might be predicted based on their documented effectiveness as reinforcers.

## 2. Materials and methods

### 2.1. Subjects and apparatus

Eight adult male squirrel monkeys (Buckshire), weighing 700–900 g, served as subjects. Subjects were housed in a vivarium and provided continuous access to water. An initial period of food restriction was imposed in which animals' weights were reduced to 80% of their free-feeding weights. The post-restriction weights fell within the ranges shown above. Weights were maintained throughout the experiment by post-session supplemental feedings of Purina New World Monkey Chow.

For daily (Monday–Friday) behavioral sessions, monkeys were seated in Plexiglas restraint chairs (BRS/LVE, Laurel, MD, USA) equipped with a house light and a food dispenser which delivered 97-mg food pellets (Noyes, Frenchtown, NJ, USA). Sessions were controlled and data recorded by an IBM-compatible personal computer and electronic interface (MED Associates, St. Albans, VT, USA). All sessions were 30 min in length.

### 2.2. Procedure

The monkeys used in the present experiments had been previously trained to discriminate i.m. injections of cocaine from saline; the procedure is described elsewhere (Mansbach and Balster, 1993). Briefly, animals were injected 10 min before the session with either saline or cocaine (0.3 mg/kg i.m.). For each subject, one lever was designated correct after cocaine injections and the other as correct after saline injections. Behavior was maintained by food presentation under a fixed-ratio 32 (FR 32) schedule of reinforcement. Lever-presses produced food only when made on the injection-appropriate lever for that day; incorrect presses reset the response requirement on the correct lever.

Substitution or antagonism tests occurred on Tuesdays and Fridays provided that the subject met the following criteria on the day before testing: (1) 80% of total responses were made on the injection-appropriate lever and (2) the first 32 consecutive responses were completed on the injection-appropriate lever. For substitution tests, various drug doses were administered before sessions in which responding on either lever produced food. In antagonism tests, various doses of SCH 39166 ((−)-*trans*-6,7,7a,8,9,13b-hexahydro-3-chloro-2-hydroxy-*N*-methyl-5*H*-benzo[*d*]naphtho-(2,1-b)azepine) or raclopride were administered 10 min prior to administration of cocaine or dimethocaine. Although responding on either lever produced food, the ratio requirement on both levers was reset if the animal switched levers. Full substitution for cocaine was considered to have occurred when the mean percentage of cocaine-lever responding was 80% or greater. Overall response rates (in responses/s) were also collected for each session. On test days, the overall percentage of cocaine-lever selection was included in group averages only if the response rate for the session was 0.05 responses/s or greater. Therefore, lever-selection data presented for higher doses do not always reflect observations for the entire group, and lever selection data were not plotted unless at least 50% of the subjects responded at a rate greater than 0.05 responses/s. The response rate data are presented for all subjects tested. Each dose-response curve was followed by test days on which the training dose of cocaine or saline was administered (preceded by an additional vehicle injection for interaction studies with dopamine antagonists). These data, presented to the left of each dose-response curve in Figs. 1–5, served as a reference for the degree of stimulus control exerted by cocaine and saline under testing conditions. Doses were administered in a mixed order. $ED_{50}$ values were calculated for lever selection data by least-squares regression on the linear portions of the curve. Differences in mean response rates were assessed by dependent-means *t*-tests (Winer, 1971).

### 2.3. Drugs

Cocaine HCl (National Institute on Drug Abuse), raclopride tartrate (obtained from Astra Research Centre, Sodertalje, Sweden), dimethocaine HCl

(Roche, Nutley, NJ, USA), SCH 39166 HCl (obtained from Schering-Plough Research, Bloomfield, NJ, USA), procaine HCl (Sigma Chemical, St. Louis, MO, USA) and chloroprocaine HCl (Astra Pharmaceutical Products, Westboro, MA, USA) were dissolved in physiological saline. Dosages were calculated as the salts. All injections were administered intramuscularly. Pretreatment times were: cocaine, procaine, dimethocaine, chloroprocaine: 10 min; SCH 39166 and raclopride: 20 min.

## 3. Results

Fig. 1 illustrates the results of substitution tests with cocaine, dimethocaine, procaine and chloroprocaine. Control tests with saline and the cocaine training dose confirmed that the monkeys' behavior was under good stimulus control (upper panel, left side). Both cocaine

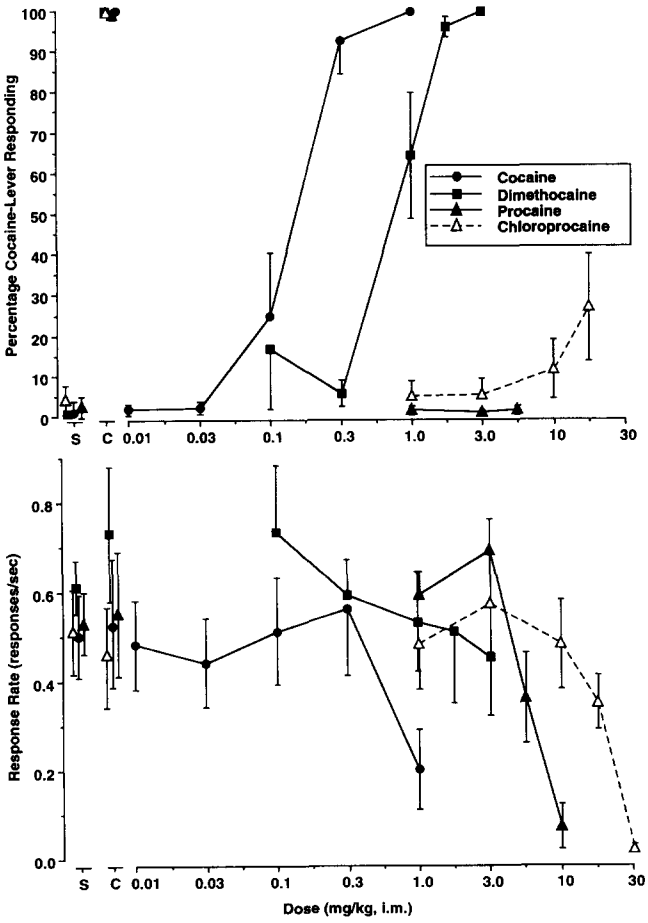


Fig. 1. Effects of local anesthetics in squirrel monkeys trained to discriminate i.m. injections of cocaine (0.3 mg/kg) from saline. The top panel presents lever-selection data; the bottom panel depicts session response rates. Symbols above S and C depict the results of control tests with saline vehicle (S) and the cocaine training dose (C). Shown are the means (±S.E.) of results in 6–8 monkeys. Lever selection data for 1.0 mg/kg cocaine represent 5 of 7 monkeys.

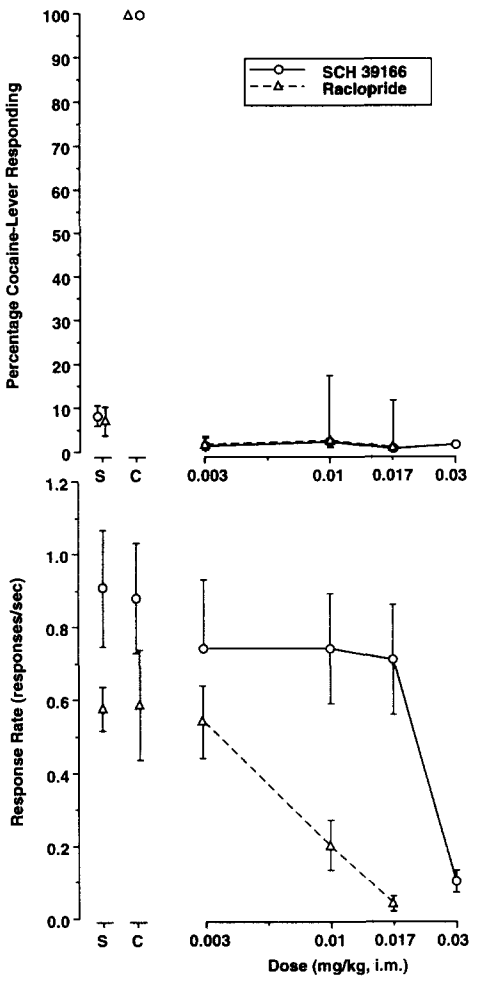


Fig. 2. Effects of SCH 39166 and raclopride in squirrel monkeys trained to discriminate injections of cocaine from saline. Details are as in Fig. 1. Shown are the means (±S.E.) of results in 7–8 monkeys. Lever selection data are depicted in 4 and 5 monkeys, respectively, for raclopride doses of 0.01 and 0.017 mg/kg.

(0.01–1.0 mg/kg) and dimethocaine (0.1–3.0 mg/kg) occasioned full (> 80%) and dose-dependent substitution for the cocaine training stimulus. The $ED_{50}$ for cocaine-lever selection was 0.37 μmol/kg for cocaine and 2.29 μmol/kg for dimethocaine. In contrast to the effects of dimethocaine, procaine occasioned little or no substitution for cocaine up to 10 mg/kg, a dose that reduced the mean response rate by 87% as compared with saline control. Chloroprocaine produced a maximum of 27% cocaine-lever responding at a dose of 17 mg/kg; nearly complete disruption of responding was observed when a higher dose of chloroprocaine was tested.

Fig. 2 illustrates the effects of the dopamine $D_1$ receptor antagonist SCH 39166 and the dopamine $D_2$ receptor antagonist raclopride in cocaine-trained monkeys. Neither drug substituted for cocaine, although both reduced rates of responding at higher doses. Various doses of SCH 39166 and raclopride were then

tested in combination with doses of cocaine (0.3 mg/kg) and dimethocaine (1.7 mg/kg) that produced full substitution (> 80%) for cocaine when given alone. As illustrated in Fig. 3, SCH 39166 dose-dependently decreased cocaine-lever selection occasioned by cocaine and by dimethocaine. The mean percentage of cocaine-lever responding occasioned by cocaine was decreased to 19.5% by a SCH 39166 dose of 0.03 mg/kg. The same dose of SCH 39166 completely blocked cocaine-lever responding occasioned by dimethocaine. In addition, the mean response rate following co-administration of 0.03 mg/kg SCH 39166 and 0.3 mg/kg cocaine was significantly higher than the rate observed when this dose of SCH 39166 was administered alone ($P < 0.01$) (Fig. 2). Dimethocaine also attenuated the rate-decreasing effects of SCH 39166, but this difference did not achieve statistical significance.

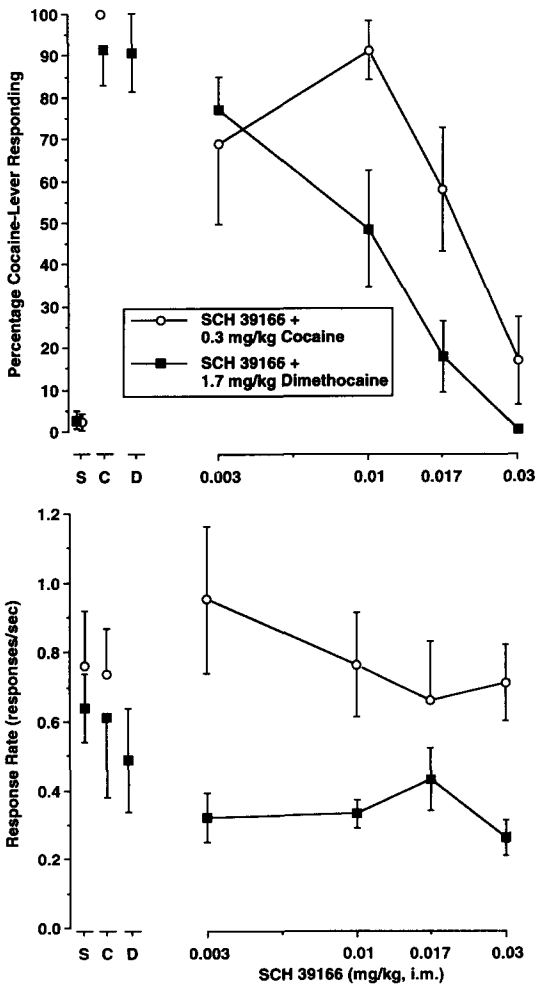


Fig. 3. Effects of cocaine-SCH 39166 and dimethocaine-SCH39166 combinations in squirrel monkeys trained to discriminate injections of cocaine from saline. Administration of SCH 39166 preceded doses of cocaine (C; 0.3 mg/kg) or dimethocaine (D; 1.7 mg/kg) which, when preceded by saline injections, produced > 80% cocaine-appropriate responding. Other details are as in Fig. 1. Shown are the means (±S.E.) of results in 5–7 monkeys.

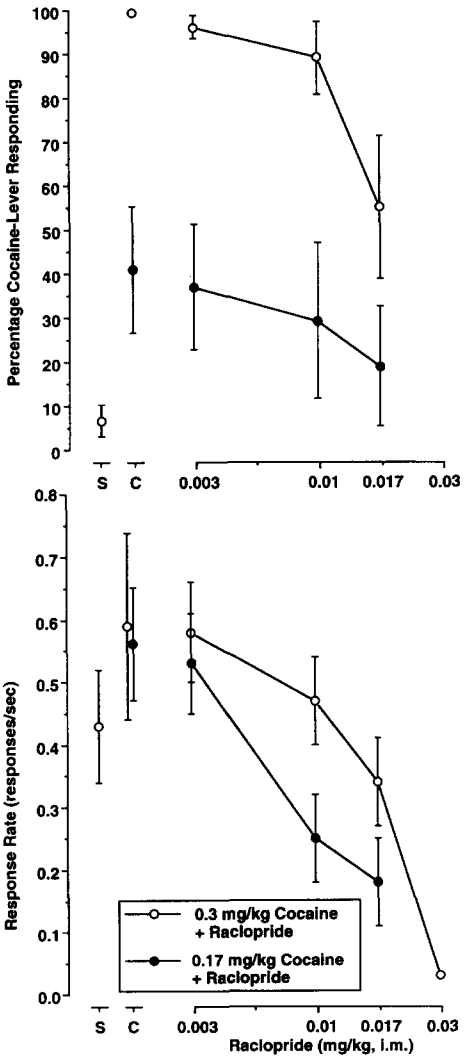


Fig. 4. Effects of cocaine-raclopride combinations in monkeys trained to discriminate cocaine from saline. Injections of the cocaine training dose (0.3 mg/kg) or a lower cocaine dose (0.17 mg/kg) were preceded by administration of saline or raclopride. Other details are as in Fig. 1. Shown are the means (±S.E.) of results in 7–8 monkeys. Lever selection data are presented for 6 monkeys in tests with 0.01 mg/kg and 0.017 mg/kg raclopride in combination with cocaine.

Figs. 4 and 5 present the results of interaction experiments with raclopride. Raclopride produced only a partial reversal of cocaine-lever selection induced by the cocaine training dose (0.3 mg/kg), with the greatest decrease observed at 0.017 mg/kg raclopride (55% cocaine-lever responding). There was evidence, however, that cocaine blocked the rate-decreasing effects of 0.017 mg/kg raclopride ($P < 0.05$). Effects of a higher raclopride dose (0.03 mg/kg) on lever selection data could not be evaluated because at this dose the mean response rate was decreased to 7% of saline control.

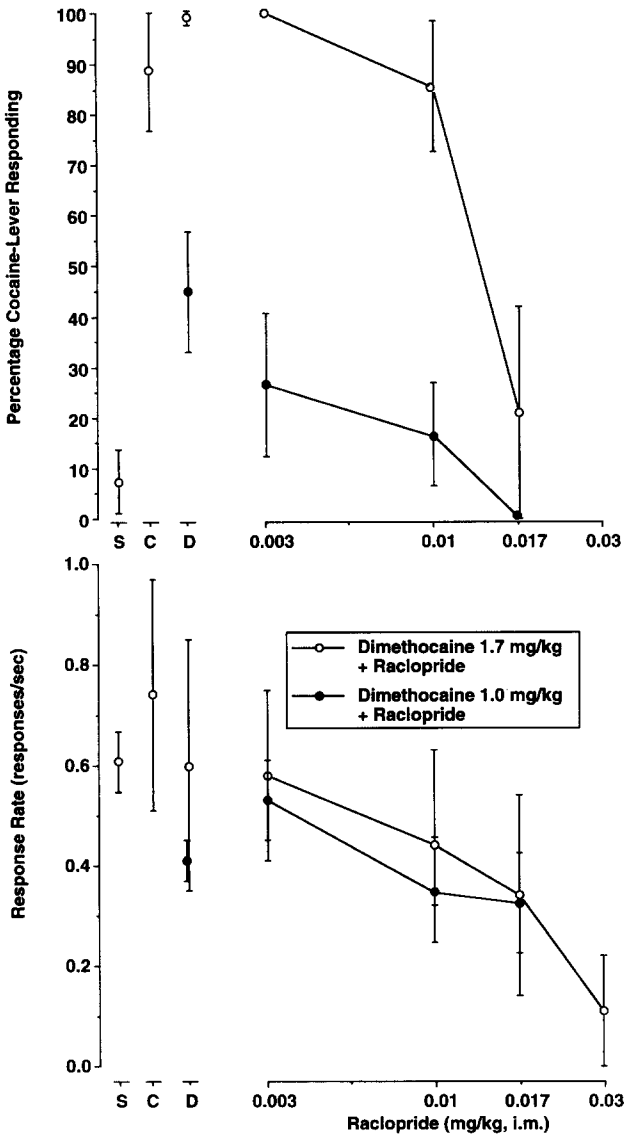


Fig. 5. Effects of dimethocaine-raclopride combinations in monkeys trained to discriminate cocaine from saline. Injections of 1.7 mg/kg or 1.0 mg/kg dimethocaine (D) were preceded by administration of saline or raclopride. Other details are as in Fig. 1. Shown are the means (±S.E.) of results in 5–6 monkeys. Lever selection data for tests with 0.01 and 0.017 mg/kg raclopride in combination with 1.7 mg/kg dimethocaine are presented for 3 and 4 monkeys, respectively. Lever selection data for 0.017 mg/kg raclopride in combination with 1.0 mg/kg dimethocaine are presented for 5 monkeys.

Because the antagonism of cocaine's effects by raclopride was equivocal, raclopride was tested again in the presence of a lower dose of cocaine (0.17 mg/kg). This dose of cocaine occasioned 41% drug-lever responding when given alone (Fig. 4, top panel). Raclopride partially blocked the drug-lever responding elicited by this dose of cocaine, reducing cocaine-lever selection to 19% at a raclopride dose of 0.017 mg/kg. At this lower dose of cocaine, the antagonism of the rate-decreasing effects of raclopride was not significant.

When raclopride was administered in conjunction with 1.7 mg/kg dimethocaine, a partial antagonism of dimethocaine's cocaine-like effect was observed (Fig. 5). Although mean cocaine-lever responding was reduced to 21% by 0.017 mg/kg raclopride, 2 of the 5 monkeys tested with this dose combination failed to emit any responses. However, in 2 of the remaining 3 monkeys, cocaine-lever responding was completely blocked. When tested in combination with a lower dose of dimethocaine (1.0 mg/kg), cocaine lever responding was dose-dependently decreased from 45% (dimethocaine alone) to 0% (raclopride 0.017 mg/kg). At this raclopride-dimethocaine dose combination, 1 of 6 monkeys failed to respond, but the mean response rate was found to be significantly higher than when raclopride was administered alone ($P < 0.05$).

## 4. Discussion

Dimethocaine produced full substitution for cocaine in the squirrel monkey, as has been reported in rats (Graham and Balster, 1993). The observed 6.2-fold potency difference in monkeys between cocaine and dimethocaine corresponds roughly to the 4-fold difference reported in the rat (Graham and Balster, 1993), but is somewhat greater than the 2-fold difference in affinity between the two compounds in binding to the dopamine transporter in rat brain (Ritz et al., 1987). In contrast, neither procaine nor chloroprocaine substituted for cocaine, up to doses which produced considerable decreases in overall response rate. These results are consistent with the higher affinity of dimethocaine in binding to the dopamine transporter (Ritz et al., 1987) and its greater potency in blocking dopamine uptake in rat synaptosomes (J. Woodward, personal communication). In the study by Graham and Balster (1993), rats were trained to discriminate between cocaine and procaine or saline; under this baseline both procaine and lidocaine were less effective in producing cocaine-appropriate responding than they were when animals simply discriminated cocaine from saline. These findings suggest that certain discriminable effects of local anesthetics are separable from their cocaine-like dopaminergic effects. Thus, it is possible that the expression of cocaine-like effects under the present conditions may have been masked by the disruptive, noncocaine-like effects of local anesthetics at higher doses, as has been suggested (De la Garza and Johanson, 1983).

The effects of a selective dopamine $D_1$ (SCH 39166) and a $D_2$ (raclopride) receptor antagonist were examined in combination with doses of cocaine and dimethocaine which occasioned full (> 80%) substitution for cocaine. SCH 39166 dose-dependently blocked cocaine-lever selection induced by both drugs, but

raclopride was less effective, even at dose combinations which resulted in large response rate decreases. The best antagonism by raclopride (0.017 mg/kg) in combination with a fully cocaine-like dose of dimethocaine (1.7 mg/kg) reduced cocaine-lever selection to 21%, but in this case 2 of the 5 monkeys tested failed to respond. Because the antagonistic effects of raclopride only occurred at disruptive dose combinations, tests of raclopride were also conducted in conjunction with lower doses of cocaine and dimethocaine. These lower doses occasioned less than complete substitution for the cocaine training dose (see Figs. 4 and 5). Antagonism tests resulted in incomplete blockade of drug-lever responding occasioned by cocaine, but the partial substitution occasioned by dimethocaine was completely blocked. There was also some evidence that cocaine and dimethocaine attenuated the rate-decreasing effects of raclopride at some dose combinations. These findings confirm that at least some of the observed behavioral effects observed with both cocaine and dimethocaine were the result of dopamine $D_1$ and $D_2$ receptor stimulation.

The substitution and antagonism experiments suggest that dopamine receptor stimulation is an important component of the cocaine-like discriminative stimulus effects of dimethocaine in squirrel monkeys, and that its actions at the dopamine transporter probably underlie its reinforcing effect in rhesus monkeys. In contrast, procaine and chloroprocaine were devoid of cocaine-like effects. Because the two drugs did not substitute for cocaine, it was not possible in the present study to evaluate whether their discriminative effects might be dopaminergically mediated. These findings are unusual in that most self-administered dopaminergic agonists have been shown to substitute for cocaine or amphetamine in drug discrimination studies (Kamien and Woolverton, 1989; Kleven et al., 1990; Witkin et al., 1991). Thus, procaine and chloroprocaine can be readily distinguished from cocaine-like drug reinforcers by their lack of robust sympathomimetic effects. It is possible that lower potency in inhibiting dopamine reuptake is sufficient for the expression of reinforcing effects, while cocaine-like discriminative stimulus effects and other classical stimulant effects require higher potency. It may also be that species differences between rats, squirrel monkeys and rhesus monkeys in the dopaminergic effects of procaine and chloroprocaine will be found to be important. It has been reported, for example, that the discriminative stimulus effects of cocaine are readily blocked by dopamine antagonists in monkeys (Kleven et al., 1988, 1990; Mansbach and Balster, 1993) but only inconsistently in rats (Witkin et al., 1991; Baker et al., 1993).

There is some indirect evidence that cocaine-like cellular effects may be responsible for the reinforcing effects of esteratic local anesthetics other than cocaine and dimethocaine. The amide-linked local anesthetics, lidocaine and procainamide, are not reinforcers in rhesus monkeys (Woolverton and Balster, 1979) and are essentially inactive at cocaine-sensitive dopamine transporter binding sites (Ritz et al., 1987). However, other evidence casts doubt on a dopaminergic mechanism for reinforcing effects of local anesthetics other than cocaine. For example, lidocaine has been reported to be reinforcing in human subjects (Van Dyke et al., 1979). In addition, the reinforcing effects of procaine in rhesus monkeys and its discriminative stimulus effects in rats were not blocked by the dopamine antagonist haloperidol (De la Garza and Johanson, 1982; Silverman and Schultz, 1989). Moreover, cocaine self-administration in rhesus monkeys was not modified by dimethocaine, given as bolus i.v. injections in doses as high as 3 mg/kg (Mansbach and Balster, unpublished). Under such conditions, dopamine agonists known to be reinforcers usually produce a decrease in self-administration (Mansbach and Balster, 1991, 1993). Although the mechanism underlying the reinforcing effects of several local anesthetics remains unclear, the present results with dimethocaine help to define those properties of local anesthetics indicative of abuse potential. It is notable in this regard that procaine and lidocaine are not considered to be abused substances despite their reinforcing effects in humans and widespread exposure to the public as licensed medications.

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