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Effects of Cocaine and Related Drugs in Nonhuman Primates. III. Self-Administration by Squirrel Monkeys[1]

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ABSTRACT

The self-administration of cocaine was compared with that of bupropion, 1-{2-[bis(4-fluorophenyl)methoxy]ethyl}-4-(3-phenylpropyl)piperazine, mazindol, methylphenidate and nomifensine, drugs that displace [^{3}H]cocaine from its binding sites and have monoamine uptake inhibiting effects in common with those of cocaine. Squirrel monkeys responded under a second-order fixed-interval schedule of consequent i.v. drug injection, and dose-effect curves were established by determining stable rates of responding maintained by saline and a range of doses of each drug. Cocaine (0.01–0.56 mg/kg/injection), bupropion (0.1–3.0 mg/kg/injection), 1-{2-[bis(4-fluorophenyl)methoxy]ethyl}-4-(3-phenylpropyl)piperazine-(0.03–1.0 mg/kg/injection), methylphenidate (0.01–0.3 mg/kg/injection) and nomifensine (0.01–0.3 mg/kg) maintained comparable rates and patterns of responding in all subjects, whereas mazindol (0.03–0.3 mg/kg) maintained self-administration behavior in only half the monkeys studied. The present results in conjunction with those of previous studies in squirrel monkeys reveal a close correspondence between the relative potencies of cocaine and related drugs for maintaining i.v. self-administration and for increasing rates of schedule-controlled responding, suggesting that the reinforcing and psychomotor-stimulant effects of the drugs are mediated similarly. The potency relations observed in the present study also agree generally with those observed for displacement of specifically bound [^{3}H]cocaine in monkey caudate-putamen suggesting that the reinforcing effects of cocaine involve its actions at specific recognition sites in brain.

Cocaine is known to inhibit the uptake of dopamine in the central nervous system (Heikkila *et al.*, 1975, 1979; Reith *et al.*, 1986), and alterations in the activity of dopamine receptors consequent to this action have been implicated in its reinforcing and other behavioral effects. In this regard, the potencies of cocaine and structurally related drugs for maintaining i.v. self-administration in monkeys (Spealman and Kelleher, 1981; Ritz *et al.*, 1987) correspond well with their potencies for inhibiting accumulation of [^{3}H]dopamine into presynaptic terminals or for displacing [^{3}H]mazindol from binding sites associated with the uptake of dopamine (Heikkila *et al.*, 1981; Spealman and Kelleher, 1981; Ritz *et al.*, 1987). Moreover, reports of i.v. self-administration of drugs that directly activate dopamine receptors such as apomorphine or piribedil (Gill *et al.*, 1978; Yokel and Wise, 1978; Woolverton *et al.*, 1984) and of attenuation of self-administration of cocaine by dopamine receptor blockers including chlorpromazine, haloperidol, perphenazine and pimozide (Wilson and Schuster, 1972; Gill *et al.*, 1978; Johanson *et al.*, 1976; de la Garza and Johanson, 1982; Woolverton, 1986) are consistent with the view that the reinforcing effects of cocaine involve alterations in dopamine-mediated transmission consequent to uptake inhibition. Cocaine also inhibits the uptake of other monoamines including norepinephrine and serotonin (Heikkila *et al.*, 1975; Hyttel, 1982; Reith *et al.*, 1986), but the available evidence dose not support a primary role for these actions in the self-administration of cocaine. Unlike cocaine, for example, inhibitors of uptake of norepinephrine such as nisoxetine or of serotonin such as imipramine do not maintain self-administration behavior in monkeys (Hoffmeister and Goldberg, 1973; Woolverton, 1987).

Despite an increased appreciation of the involvement of the dopamine uptake system in the reinforcing effects of cocaine, the precise neurochemical actions that lead to its self-administration remain to be clarified. [^{3}H]Cocaine has been shown to bind with high affinity to saturable sites in brain tissue of rodents (Kennedy and Hanbauer, 1983; Reith *et al.*, 1986; Calligaro and Eldefrawi, 1987), humans (Schoemaker *et al.*, 1985) and monkeys (Madras *et al.*, 1989). Binding of cocaine and related drugs to these sites appears to be associated with

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ABBREVIATIONS: GBR 12909, 1-{2-[bis(4-fluorophenyl)methoxy]ethyl}-4-(3-phenylpropyl)piperazine; FI, fixed-interval; FR, fixed-ratio.

the inhibition of uptake of dopamine and its consequent behavioral effects. Indeed, there is a high degree of correspondence in the potencies of drugs for displacing specifically bound [^{3}H] cocaine, for inhibiting the uptake of dopamine and for producing stereotypy in mice or increasing schedule-controlled responding in monkeys (Reith *et al.*, 1986; Madras *et al.*, 1989; Spealman *et al.*, 1989).

The present studies were conducted to evaluate further the relationship between the behavioral effects of cocaine and its binding to specific recognition sites associated with dopamine uptake. Specifically, cocaine and several structurally distinct drugs that are known to inhibit uptake of dopamine and other monoamines (bupropion, GBR 12909, mazindol, methylphenidate and nomifensine) were compared directly for their capacity to maintain i.v. self-administration. In these experiments squirrel monkeys were studied under a second-order schedule of i.v. drug injections similar to the schedules used previously to evaluate the reinforcing effects of cocaine and other psychomotor-stimulant drugs (Goldberg *et al.*, 1981; Spealman and Goldberg, 1982; Bergman and Spealman, 1986). In conjunction with the findings of previous studies of self-administration of structural analogs of cocaine, the present results support the view that the reinforcing effects of cocaine-like drugs are associated with binding to specific cocaine recognition sites in brain.

Methods

Subjects. Five adult male squirrel monkeys (*Saimiri sciureus*), weighing 0.9 to 1.0 kg, were studied in daily experimental sessions (Monday–Friday). Between sessions the monkeys lived in individual home cages where they had access to water and a nutritionally balanced diet of Purina Monkey Chow, Teklad Monkey Diet, fresh fruit and vegetables. One monkey (S-93) was untrained at the beginning of the study; the other four monkeys had responded previously under second-order schedules of i.v. drug injection similar to the one described below. Each monkey was prepared with a chronic venous catheter using the general surgical procedure described by Herd *et al.* (1969). Under halothane anesthesia and in aseptic conditions, one end of a polyvinyl chloride catheter (inside diameter, 0.38 mm; outside diameter, 0.76 mm) was passed to the level of the right atrium by way of a jugular or femoral vein. The distal end of the catheter was passed s.c. and exited in the midscapular region. Catheters were flushed with 0.9% saline solution and were sealed with stainless-steel obturators when not in use. Monkeys wore nylon-mesh jackets at all times to protect the catheters.

Apparatus. Experimental sessions were conducted within a ventilated, sound-attenuating chamber provided with white noise to mask extraneous sounds. Monkeys were seated in a Plexiglas chair and faced a panel upon which were mounted a response lever (model 121-05, BRS/LVE, Beltsville, MD) and colored lamps. Each press of the lever with a minimal downward force of 0.25 N produced a click of a relay within the chamber and was recorded as a response. The colored lamps could be illuminated to serve as visual stimuli. Venous catheters were connected by polyvinyl chloride tubing to a motor-driven syringe located outside the chamber. The syringe could be operated by automatic programming equipment; each operation lasted 200 msec and delivered 0.2 ml into the catheter.

Schedule of self-administration. All monkeys were trained to respond under a second-order FI schedule of i.v. drug injection similar to the schedule described previously by Goldberg *et al.* (1981). In the presence of a white light, completion of every 10th response (FR10; monkey S-93) or 30th response (FR30; other monkeys) during the 10-min FI produced a 1-sec change in illumination from white to amber (brief stimulus). Completion of the first FR after the 10-min FI elapsed produced both the brief stimulus and an i.v. injection of drug or vehicle solution. A 60-sec timeout period, during which stimulus lights were off and responses had no programmed consequences, followed each injection. Sessions ended upon the completion of five cycles of the second-order schedule or 90-min, whichever occurred first.

Drugs and testing procedures. Responding was maintained initially in all monkeys by i.v. injections of cocaine (0.1 mg/kg). Next, responding was extinguished by substituting saline for cocaine. Subsequently, the effects of the following drugs were determined: bupropion HCl, 0.1 to 3.0 mg/kg/injection (0.36–10.9 μmol/kg/injection); (−)-cocaine HCl, 0.01 to 0.56 mg/kg/injection (0.03–1.65 μmol/kg/injection); GBR 12909, 0.03 to 1.0 mg/kg/injection (0.06–1.91 μmol/kg/injection); mazindol, 0.03 to 0.3 mg/kg/injection (0.11–1.05 μmol/kg/injection); methylphenidate HCl, 0.01 to 0.3 mg/kg/injection (0.040–1.19 μmol/kg/injection); and nomifensine maleate, 0.01 to 0.3 mg/kg/injection (0.03–0.84 μmol/kg/injection). Mazindol was dissolved in a small volume of 8.5% lactic acid and diluted to the desired concentrations with 0.9% saline; other drugs were dissolved directly in distilled water or 0.9% saline.

Each drug was studied over at least a 10-fold range of doses in each of three to five monkeys. The drugs were studied in different orders with different monkeys and experiments with one drug usually were completed before another drug was studied. The effects of 0.9% saline were determined on two or more occasions in each monkey. Except where noted, saline and each dose of drug was studied for at least five consecutive sessions (range, 5–15 sessions) and until there were no systematic trends in rates of responding for at least three consecutive sessions.

Analysis of responding. Rates of responding were computed for each session by dividing total responses by elapsed time (excluding responses and time during timeout periods). A dose of drug was considered to maintain responding when the mean rate of responding over the last three sessions was at least two S.D. above the mean rate determined during the substitution of saline. The number of responses in successive 2-min periods of each 10-min FI was recorded and used to compute quarter-life values (Herrnstein and Morse, 1957; Gollub, 1964). The quarter-life is the percentage of time taken to complete the first quarter of the responses in the interval and provides a measure of the temporal patterning of responding that is relatively independent of response rate.

For comparisons of potency, ED_{50} values were calculated for each drug. In individual monkeys, half the difference between the mean response rate observed for vehicle and for the dose that maintained maximal responding was subtracted from that maximal rate of responding. The dose of drug that maintained responding at the resulting half-maximal rate (ED_{50}) was then determined by linear interpolation using the ascending portion of the log dose-response curve.

Results

Effects of cocaine. Cocaine maintained self-administration under the second-order FI schedule in all five monkeys (fig. 1). Performances were similar to those reported previously using comparable schedules of cocaine self-administration and generally were characterized by a pause at the beginning of the 10-min FI followed by sustained responding as the interval progressed (fig. 2, top left). Except for monkey S-93, average rates of responding maintained by cocaine increased and then decreased as the dose per injection was increased from 0.01 to 0.3 or 0.56 mg/kg per injection. For monkey S-93, average rates of responding increased as a function of dose up to 0.3 mg/kg per injection. At the highest dose, tremors were evident after the session and, therefore, doses greater than 0.3 mg/kg were not studied in this monkey.

Maximal rates of responding in individual monkeys (1.07–1.48 responses/sec) were maintained by doses of cocaine ranging from 0.03 to 0.3 mg/kg. At these doses, patterns of respond-

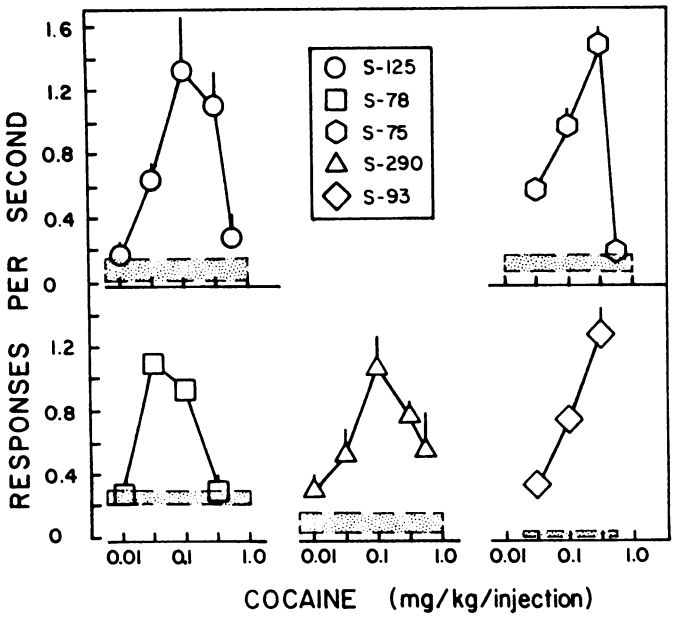

Fig. 1. Effects of dose per injection on responding maintained by i.v. injections of cocaine under the second-order 10-min FI schedule. Abscissae: dose, log scale; ordinates: rates of responding. Points are means based on the last three sessions at each dose of drug and vertical lines show ± S.D.; ± S.D. is omitted if it is within the diameter of the symbol. Horizontal stippled bar represent the mean ± S.D. values averaged for all periods of saline substitution in the individual subject.

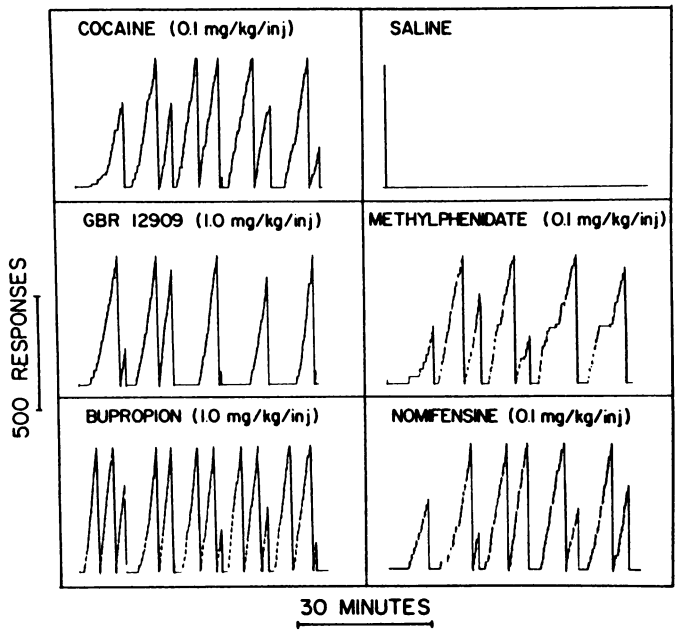

Fig. 2. Representative performances maintained by i.v. injections of cocaine, GBR 12909, bupropion, nomifensine, methylphenidate and saline under the second-order FI schedule (monkey S-75). Abscissae: time; ordinates: cumulative responses. Diagonal marks show presentations of the 1-sec visual stimulus. The recorder reset after 550 responses or after each injection. Each panel shows a complete record at the doses specified or when saline was substituted for the drugs.

ing generally were similar in successive FIs of the daily session, although average quarter-life values tended to decline somewhat over the course of the session (table 1). For the group of monkeys, the average dose of cocaine that maintained half-maximal rates of responding (ED_{50}) was 0.05 mg/kg (0.14 μmol/kg) per injection (table 2). When saline was substituted for cocaine, responding occurred irregularly and at low rates throughout the session for all monkeys.

Effects of bupropion, GBR 12909, methylphenidate and nomifensine. Bupropion, GBR 12909, methylphenidate and nomifensine maintained i.v. self-administration behavior with rates and patterns of responding similar to those maintained by cocaine (figs. 2 and 3; table 1). Maximal rates of responding for individual monkeys were maintained by 0.56 to 1.0 mg/kg of bupropion (1.04–1.60 responses/sec), 0.3 to 1.0 mg/kg of GBR 12909 (0.98–1.15 responses/sec), 0.03 to 0.1 mg/kg of methylphenidate (0.73–1.40 responses/sec) and 0.03 to 0.1 mg/kg of nomifensine (0.83–1.39 responses/sec). Higher doses of each drug either maintained lower rates of responding or did not maintain responding above values observed with saline. The highest doses of GBR 12909 (0.56–1.0 mg/kg per injection) or bupropion (3.0 mg/kg per injection) occasionally produced tremors in individual monkeys (fig. 3) that were observed in the home cage immediately after the session. Average ED_{50} values for the four drugs were 0.04 mg/kg (0.18 μmol/kg) for methylphenidate, 0.05 mg/kg (0.14 μmol/kg) for nomifensine, 0.23 mg/kg (0.45 μmol/kg) for GBR 12909 and 0.4 mg/kg (1.45 μmol/kg) for bupropion. Based on individual ED_{50} values, the rank order of potency for cocaine, GBR 12909 and bupropion was the same in each monkey. The potency of methylphenidate and nomifensine relative to cocaine, however, differed somewhat from monkey to monkey. Methylphenidate and nomifensine were either equipotent or somewhat more potent than cocaine in three monkeys, but less potent than cocaine in the fourth monkey (S-78; table 2).

Effects of mazindol. Mazindol (0.03–0.3 mg/kg per injection) maintained self-administration in only two of the four monkeys studied (fig. 4). Response rates and quarter-life values (table 1) comparable to those observed for cocaine were maintained by injections of 0.1 and 0.3 mg/kg in monkey S-93. Injections of 0.3 mg/kg, however, produced profuse salivation, self-mutilation and vocalizations characteristic of distress calls in squirrel monkeys (Newman, 1985). Consequently, experiments with higher doses of mazindol were not conducted. Rates of responding significantly above values for saline also were maintained by injections of 0.03 and 0.1 mg/kg of mazindol in a second monkey (S-290). The maximal rates of responding, however, were only 60 to 70% of those maintained by cocaine or bupropion. Based on ED_{50} values, mazindol was approximately 3 to 5 times more potent than cocaine in monkeys S-93 and S-290. In the remaining two monkeys, S-75 and S-78, only erratic responding at low rates were observed with mazindol over the entire range of doses studied (0.03–0.3 mg/kg per injection).

Discussion

The present results confirm previous findings in studies of self-administration of cocaine under second-order schedules (cf. Goldberg *et al.*, 1981; Bergman and Spealman, 1986) and extend those findings to include bupropion, GBR 12909, methylphenidate and nomifensine. Each of the four drugs maintained comparable rates and patterns of responding under the second-order schedule in all monkeys studied. Low doses did not maintain responding above rates observed with saline and, as the dose per injection was increased, overall rates of responding maintained by each drug generally increased to a maximum and then decreased.

TABLE 1

Quarter-life values (means and ranges for three to five monkeys) in successive 10-min FIs under the second-order FI schedule of drug self-administration

The values for each drug represent the effects of doses that maintained maximal overall rates of responding in individual monkeys. The quarter-life value for a drug in each monkey represents the mean of the values for the last three sessions during which the optimum dose of that drug was studied.

Drug	FI of Session				
	1	2	3	4	5
Cocaine	0.59 (0.46–0.67)	0.46 (0.42–0.48)	0.40 (0.28–0.52)	0.43 (0.29–0.65)	0.38 (0.24–0.58)
Bupropion	0.54 (0.50–0.59)	0.39 (0.26–0.52)	0.56 (0.44–0.67)	0.55 (0.42–0.86)	0.70 (0.58–0.90)
GBR 12909	0.69 (0.49–0.86)	0.54 (0.48–0.59)	0.62 (0.58–0.69)	0.55 (0.54–0.57)	0.50 (0.39–0.59)
Methylphenidate	0.60 (0.52–0.64)	0.46 (0.27–0.58)	0.43 (0.25–0.58)	0.52 (0.24–0.72)	0.40 (0.24–0.50)
Nomifensine	0.71 (0.55–0.93)	0.75 (0.46–0.92)	0.43 (0.29–0.57)	0.52 (0.25–0.81)	0.62 (0.26–0.93)
Mazindol*	0.71 (0.51, 0.91)	0.40 (0.33, 0.46)	0.31 (0.28, 0.34)	0.36 (0.40, 0.31)	0.44 (0.33, 0.54)

* Data for mazindol represent the average quarter-life values for the two monkeys (S-93 and S-290) in which self-administration responding was maintained.

TABLE 2

Doses (nanomoles per kilogram) producing half-maximal rates of drug-maintained responding (ED_{50}) for individual monkeys

Monkey	Cocaine	Methylphenidate	GBR 12909	Bupropion	Nomifensine	Mazindol
S-125	85	40	527	2267	37	
S-78	58	316	132		169	Ineffective
S-75	207	80	873	1847	169	Ineffective
S-290	111		402	536		20
S-93	238	277			169	70

The present results are consistent with previous reports that bupropion, methylphenidate and nomifensine effectively maintain i.v. self-administration in rhesus monkeys [Johanson and Schuster, 1975; UM 1239 (bupropion) in Woods *et al.*, 1983; Winger and Woods, 1985]. These drugs also have psychomotor-stimulant effects comparable to those of cocaine in squirrel monkeys (McKearney, 1982; Bergman and Spealman, 1988; Spealman *et al.*, 1989) and have cocaine-like interoceptive stimulus effects in both rats and monkeys (Jones *et al.*, 1980; Melia *et al.*, 1989). Moreover, clinical reports and laboratory evaluations of the subjective effects of psychomotor stimulants in human subjects have indicated that high doses of methylphenidate and nomifensine may have considerable abuse liability (Martin *et al.*, 1971; Siegfried and Taeuber, 1984; Boning and Fuchs, 1986). Of interest, bupropion, in p.o. doses up to 400 mg, does not have stimulant-like subjective effects in humans and usually is considered to have low abuse liability (Griffith *et al.*, 1983; Miller and Griffith, 1983). The reasons for the apparently dissimilar effects of bupropion in monkeys and humans are unclear, but might be accounted for partly by differences in biodisposition after administration by different routes (p.o. *vs.* i.v.). In this regard, Butz *et al.* (1982) have shown that peak concentrations of bupropion in brain tissue of mice and rats after p.o. administration of 10.0 mg/kg are approximately 10% of concentrations measured after i.v. administration of the same dose. Findings such as these suggest that clinically relevant doses of p.o. bupropion do not result in concentrations in brain that are sufficient to produce psychomotor-stimulant effects.

Based on average ED_{50} values, cocaine, methylphenidate and nomifensine were approximately equipotent in the present study, whereas GBR 12909 and bupropion were, respectively, 4 and 12 times less potent than cocaine. Despite differences in

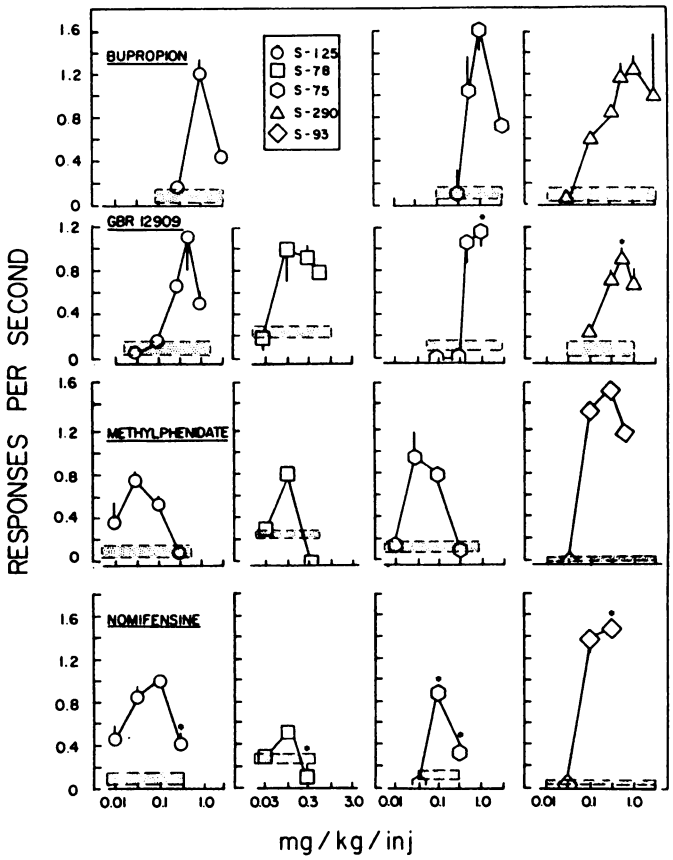

Fig. 3. Effects of dose per injection on responding maintained by i.v. injections of GBR 12909, bupropion, methylphenidate and nomifensine under the second-order 10-min FI schedule. Asterisks mark doses at which tremor or profuse salivation was occasionally evident after the experimental session. Other details are as in figure 1.

species (squirrel monkey *vs.* rhesus monkey) and in the schedule of self-administration (second-order FI *vs.* FR) under which they were studied, doses of bupropion and nomifensine that maintained responding in the present study are comparable to doses that maintained self-administration in previous experiments (Winger and Woods, 1985; Woods *et al.*, 1983). The comparable potencies of cocaine and methylphenidate also are consistent with previous findings. For example, similar doses

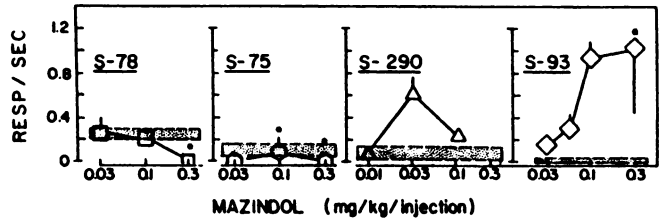

Fig. 4. Effects of dose per injection on responding maintained by i.v. injections of mazindol under the second-order 10-min FI schedule. Asterisks mark doses at which self-mutilation and distress vocalization (S-93 only) or profuse salivation were evident after the experimental session. Other details are as in figure 1. RESP, responses.

of the two drugs have been found to maintain comparable rates of self-administration in drug-choice experiments in rhesus monkeys (Johanson and Schuster, 1975). GBR 12909 previously has not been studied in self-administration experiments; however, its potency relative to cocaine in the present study is similar to its potency for increasing schedule-controlled responding in squirrel monkeys (Spealman *et al.*, 1989).

In contrast to the consistent effects of cocaine, mazindol had different effects in different monkeys. The self-administration of mazindol has been reported previously in both rhesus monkeys and dogs (Wilson and Schuster, 1976; Risner and Silcox, 1981; Corwin *et al.*, 1987). The present findings with mazindol confirm the results of Corwin *et al.* (1987) showing that the reinforcing effects of mazindol can vary among individual subjects. They also are consistent with results of studies in human subjects allowed to choose between p.o. doses of mazindol and placebo (Chait *et al.*, 1986, 1987). In those studies, clinically relevant doses of mazindol were less preferred than placebo and produced reportedly noxious side-effects. In the present study mazindol produced apparently noxious effects such as self-mutilation, distress vocalizations and excessive salivation. These effects were not evident with the other drugs that were studied and may have deterred the self-administration of mazindol in individual monkeys.

The neurochemical basis for the presumably noxious effects of mazindol is unclear. Mazindol is at least 10 times more potent in inhibiting the uptake of norepinephrine than the uptake of dopamine *in vitro* (Heikkila *et al.*, 1977; Hyttel, 1982), and its prominent actions at uptake sites for norepinephrine may limit its self-administration. However, methylphenidate and nomifensine also are approximately 10-fold more potent in inhibiting the uptake of norepinephrine compared to dopamine (Hyttel, 1982; Patrick *et al.*, 1987), yet both drugs consistently maintained self-administration behavior without producing noxious side-effects.

The doses of drugs that maintained self-administration behavior in the present study are similar to those shown to increase rates of schedule-controlled responding in squirrel monkeys (Spealman *et al.*, 1989). The correspondence between doses that increase rates of responding and maintain self-administration behavior (table 3) agrees with findings in previous studies of cocaine and structurally related compounds (*e.g.*, Spealman and Kelleher, 1979, 1981) and extends those findings to include drugs that are structurally different from cocaine. Taken together, these findings support the view that the reinforcing and psychomotor-stimulant effects of cocaine-like drugs may involve similar neurochemical actions (cf., Spealman and Kelleher, 1979).

The potency relations for cocaine and other comparably self-administered drugs in the present study and in previous studies in monkeys (Spealman and Kelleher, 1981; Ritz *et al.*, 1987) also correspond generally with their relative potencies for displacing [^{3}H]cocaine from caudate-putamen membranes of monkeys (table 3; Madras *et al.*, 1989) or for inhibiting the uptake of [^{3}H]dopamine in striatal tissue of rodents (Heikkila and Manzino, 1984; Janowsky *et al.*, 1986; Andersen, 1987). Of interest, however, GBR 12909 is less potent than cocaine in maintaining self-administration behavior, but has been shown to be more potent than cocaine in displacing [^{3}H]cocaine from binding sites in monkey caudate-putamen or inhibiting the uptake of dopamine *in vitro*. The reasons for such differences in relative potency are unknown but may be due to pharmacokinetic factors. Assessment of the bioavailability of GBR 12909 *in vivo* will be necessary to evaluate how factors of absorption, sequestration into different tissue compartments or metabolic degradation may limit concentrations that can be achieved at the presumed central nervous system sites of action. These considerations notwithstanding, the overall correspondence between their behavioral and neurochemical effects supports the view that the reinforcing effects of cocaine and related drugs involve their binding to specific recognition sites for cocaine associated with the uptake of dopamine in the central nervous system.

TABLE 3

Relative potencies of cocaine and related drugs in maintaining self-administration behavior, increasing rates of FI responding and displacing [^{3}H]cocaine from its binding sites in monkey caudate-putamen

Relative potency is defined as the mean ED_{50} or, in binding studies, IC_{50} for a particular drug divided by the mean ED_{50} or IC_{50} for cocaine.

	Relative Potency		
	Self-administration	Stimulant effect[a]	[^{3}H]Cocaine binding[b]
(−)-WIN 35,065-2	0.2[c]	0.3	0.6
Nomifensine	0.9	1.7	0.3
(−)-Cocaine	1.0	1.0	1.0
WIN 35,981	1.0[c]	0.6	1.3
Methylphenidate	1.2	1.6	0.5
(−)-Norcocaine	3.4[c]	3.0	6.1
GBR 12909	4.2	3.6	0.5
Bupropion	12	11	23
(+)-WIN 35,065-3	Ineffective[c]	56	

[a] From Spealman *et al.* (1989).
[b] From Madras *et al.* (1989).
[c] From Spealman and Kelleher (1981).

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