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# Effects of delivery rate and non-contingent infusion of cocaine on cocaine self-administration in rhesus monkeys

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**Abstract** The goal of this study was to determine whether slowly infused, response-independent cocaine would reduce cocaine self-administration in an animal model of drug abuse. Seven male rhesus monkeys self-administered IV cocaine on a fixed-ratio 30 schedule (5-min time-out). With unit dose (0.056 mg/kg per infusion for one monkey and 0.032 mg/kg per infusion for the rest) and infusion volume (0.5 ml) held constant, the rate of delivery was manipulated (0.125, 0.1875, 0.375, 0.75 and 3 ml/min, with infusions lasting 240, 160, 80, 40, and 10 s, respectively). Response rates increased monotonically as a function of delivery rate. Responding for cocaine at the slowest delivery rate did not differ from saline. The effects of infusing additional cocaine (starting 30 min prior to the session) at this non-reinforcing rate (0.125 ml/min) were then determined. Delivery rate of the self-administered infusion was manipulated as before. Non-contingent cocaine significantly increased responding for cocaine (at the fastest delivery rate) and for saline. While non-contingent cocaine reduced responding for cocaine in two of the seven monkeys, it also significantly reduced responding in three monkeys that responded for food on the same schedule. Plasma levels of cocaine delivered at rates of 0.125 and 3 ml/min were compared in five other monkeys. While a higher peak was reached with the faster infusion, levels did not differ after 5 min. Thus, when an infusion became available (after the 5-min time-out) in the self-administration experiments, plasma levels should not have differed regardless of the delivery rate. These results suggest that a low-dose, slow-delivery treatment with cocaine might prime or reinstate drug seeking rather than decrease it.

**Key words** Substitution therapy · Self-administration · Cocaine · Rhesus monkey

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## Introduction

Substitution therapy is one of the most effective strategies for treating drug dependence. Methadone substitution has long been an effective treatment for heroin dependence (Dole and Nyswander 1965; Simpson et al. 1987), and systems for the slow delivery of nicotine have become popular in recent years for reducing tobacco smoking (Henningfield 1995). The ultimate goal of substitution therapy is to reduce the dose of the substituted drug over time until the person is no longer dependent and abstinence can be maintained without severe withdrawal symptoms or craving. In practice, methadone treatment does not consistently lead to abstinence (O'Brien 1996), but it may still be valuable because it eliminates the excessive behavioral patterns and risks involved in obtaining and self-administering illicit drugs (Ball et al. 1988).

A common feature of these successful substitution treatments is that there is a slow onset and long duration of action. This can be achieved by altering the way the drug is delivered (e.g., nicotine delivered in chewing gum or a patch), or by treating with a drug from the same class, but with different pharmacokinetic properties (e.g., orally-administered methadone). It is possible that cocaine, delivered in a form that provides a slow onset and long duration of action, might reduce drug seeking and serve as an intermediate step towards abstinence. However, the administration of cocaine itself as a substitution therapy for cocaine abuse has not been applied in clinical practice (Mendelson and Mello 1996; O'Brien 1996), nor has it been studied extensively in the laboratory (Nestler 1994; Mello and Negus 1996). Therefore, the purpose of the present study was to determine wheth-

er slowly delivered, response-independent cocaine would reduce the amount of cocaine self-administered by rhesus monkeys.

The abuse liability of cocaine is largely dependent on the rapidity with which the drug enters the bloodstream, and consequently the brain. For example, Balster and Schuster (1973) demonstrated that rhesus monkeys' self-administration of IV cocaine varied as a direct function of the rate at which the drug was infused. With the unit dose held constant, rates of self-administration were reduced by up to 80% when the drug was delivered slowly. A procedure like that of Balster and Schuster (1973) was used in the present experiment to determine the fastest delivery rate that would not maintain self-administration. Cocaine was then infused at this delivery rate while the monkey was allowed to self-administer additional cocaine. The obtained effects were compared to those of a similar slow infusion of cocaine administered to monkeys that responded for food. In addition, plasma levels of cocaine were analyzed to compare the pharmacokinetic profiles of cocaine administered under slow and fast delivery rates.

## Materials and methods

### Subjects

Ten adult, male, rhesus monkeys were individually housed in a colony room where lights were on from 8:00 a.m. to 8:00 p.m. All of these monkeys were jacketed and tethered and had chronic IV catheters (Silastic). Three monkeys were trained only with food. When training sessions were not being conducted, saline solution was slowly infused (0.03 ml/min) to maintain catheter patency. Five other monkeys, used in the pharmacokinetics experiment, were housed untethered in a similar, separate room. These monkeys did not have chronic catheters at the time of testing, and had not received cocaine for at least 30 days. All monkeys had previously been exposed to a second-order schedule of cocaine self-administration. None of the monkeys were food deprived. Fresh fruit and environmental enrichment were provided daily.

Animals used in this study were maintained in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC), and all procedures were conducted in accordance with the guidelines of the Institutional Care and Use Committee of the Addiction Research Center and the National Research Council (1996).

### Apparatus

An operant panel, attached to the front of each monkey's home cage, included two response levers (BRS/LVE PRL-001) with cue lights (BRS/LVE QUE-003) above each lever. Cocaine was delivered by a peristaltic pump (Harvard 55-7766). Saline was slowly infused by a second pump when sessions were not being conducted. During treatment sessions, non-contingent cocaine was delivered by a third pump, using the same concentration of drug used for self-administration. For monkeys trained with food, a dispenser between the levers dispensed 1-g banana pellets (Bio-Serv), which maintained responding without requiring food deprivation. Experimental events were controlled with a MED Associates computer interface in an adjoining room.

### Procedure

Under baseline conditions, seven monkeys self-administered IV cocaine (unit dose: 0.032 mg/kg for six monkeys, 0.056 mg/kg for monkey 892; volume: 0.5 ml; pump rate: 3 ml/min) at an infusion duration of 10 s on a fixed-ratio 30 schedule. When a blue stimulus light above the active lever was turned on, the 30th response on that lever turned off the light and produced an infusion of cocaine (or saline during certain phases of the experiment). Response rates were calculated during the time the blue light was present. The infusion was signaled by a 2-s illumination of a yellow light over the lever. Responses on the other (inactive) lever were recorded but had no programmed effect. The side (left versus right) of the active lever was counterbalanced across subjects. Following a reinforced response (i.e., starting from the beginning of each infusion), there was a 5-min time-out period, during which the stimulus lights were turned off and responding had no scheduled consequences. Sessions lasted 1 h, during which a maximum of 12 infusions could be self-administered. If each fixed ratio was satisfied soon after the blue light was presented, all 12 reinforcers were received and the session ended during the final time-out period. If the fixed ratio was not satisfied promptly, and the total amount of time that the light was on during the session exceeded 5 min, the session ended before the 12th reinforcer could be made available. Thus, the response rate in the presence of the light and the number of reinforcers per session were related, but not perfectly correlated. Response rates could increase or decrease without affecting the number of reinforcers per session unless the total amount of time spent with the light on was altered by an increment of 5 min.

Sessions were conducted daily at 6:00 a.m., 12:00 p.m., and 6:00 p.m. Monkeys 832, 836, and 892 had three sessions/day. Monkeys that did not respond consistently with three daily sessions were switched to two daily sessions (nos 862, 865, 876, 891). Three other monkeys (nos 827, 895, 897) lever-pressed for food pellets under the same fixed-ratio 30, time-out 5-min schedule, with a single pellet delivered in place of the infusion during two daily sessions.

Four delivery rates (0.75, 0.375, 0.1875, and 0.125 ml/min, with durations of 40, 80, 160, and 240 s, respectively) were compared to the baseline (3 ml/min for 10 s) in a non-systematic order. Unit dose was constant across all conditions. The time-out still lasted 5 min from the beginning of the infusion. Each infusion-duration condition was maintained for at least six consecutive sessions until rates of responding and reinforcement stabilized (i.e., showed no consistent upward or downward trend for three consecutive sessions). Data points were taken from the last three sessions under the condition. Baseline conditions (10-s infusion) were maintained between test conditions for at least five sessions, until response and reinforcement rates restabilized. This rarely required more than five sessions. Before and after the phase where infusion duration was manipulated, it was verified that responding decreased when saline was substituted for cocaine.

Once the effects of delivery rate had been determined, a delivery rate that did not reliably maintain self-administration was chosen to serve as a treatment in the next phase of the experiment. During treatment sessions, cocaine was administered independently of the monkey's behavior at a continuous rate of 0.125 ml/min (0.008 mg/kg per min) starting 30 min before each self-administration session and continuing throughout the session. During this treatment phase, the rate and duration of the self-administered infusion was manipulated as before. The effects of substituting saline for self-administered cocaine were also examined under non-contingent cocaine infusion. Behavior of food-trained monkeys was studied under the 0.125 ml/min treatment condition, as well as a 0.1875 ml/min treatment condition that was intended to produce intake levels similar to those of the monkeys that self-administered cocaine in addition to the non-contingent treatment.

Plasma levels of cocaine produced by 10- and 240-s infusion durations were determined in five other monkeys. To increase plasma levels and thus detectability, the unit dose from the self-ad-

ministration studies was increased ten-fold in the plasma study. The effects of the lower dose can be extrapolated from the higher dose because distribution and clearance of the drug are proportional to concentration (as long as enzymatic processes are not saturated, which would not occur within this range of doses). Monkeys were anesthetized with ketamine and isoflurane, and two temporary IV lines were inserted. A single IV infusion of cocaine (0.32 mg/kg in a volume of 0.5 ml) was administered over 10 s on one day and over 240 s on another day. Blood (0.5–1.0 ml) was drawn from the second IV line 0, 1, 2.5, 5, 7.5, 10, 12.5, 15, 20, 30, 45, and 60 min following the infusion. Samples were stored at −70º C in heparinized Vaccutainers containing 25 µl NaF and 25 µl AcOH. Cocaine levels in the samples were analyzed by GC/MS. Plasma concentrations obtained 5 min after the start of the infusion (this point was actually 5 min and 10 s after the 240-s infusion) were compared. Peak concentrations produced by the two infusion rates were also compared. While samples were not drawn during the course of the infusions, it is unlikely that a peak could have occurred during this time. With a steady infusion delivered over a period considerably shorter than the half-life of the drug, the peak concentration should not have occurred until the entire dose had been delivered.

### Statistical analysis

Because response and reinforcement rates were not independent, and because the response rate measure was more sensitive (as described above), a univariate, repeated-measures ANOVA was performed on response rate data. Planned contrasts were used to compare response rates under the baseline (10-s) infusion duration to the rates under each of the other infusion durations 1) during the no-treatment and 2) during the non-contingent-cocaine treatment conditions. In addition, the response rate under each infusion duration during the no-treatment condition was compared to the rate under the same infusion duration during non-contingent cocaine treatment. Each of these three sets of contrasts maintained an overall significance level of 0.05.

## Results

As infusion duration was increased, response rates (Fig. 1) and reinforcement rates (Fig. 2) decreased. The main effect of infusion duration on response rate (see Fig. 3) was statistically significant [$F(5,30)=14.1$, $P<0.0001$]. Contrasts revealed that responding for the 160-s [$F(1,29)=4.55$, $P<0.042$], and 240-s [$F(1,29)=12.32$, $P<0.002$] infusions was significantly lower than for the 10-s, baseline duration. The 240-s infusion maintained response rates about equal to those maintained by saline. Response rates were very low under saline substitution, while the number of infusions per session was typically about 25% of baseline.

Non-contingent cocaine consistently decreased responding in only two of the seven monkeys (nos 862 and 876). In contrast, five monkeys showed increased responding during non-contingent cocaine treatment under at least

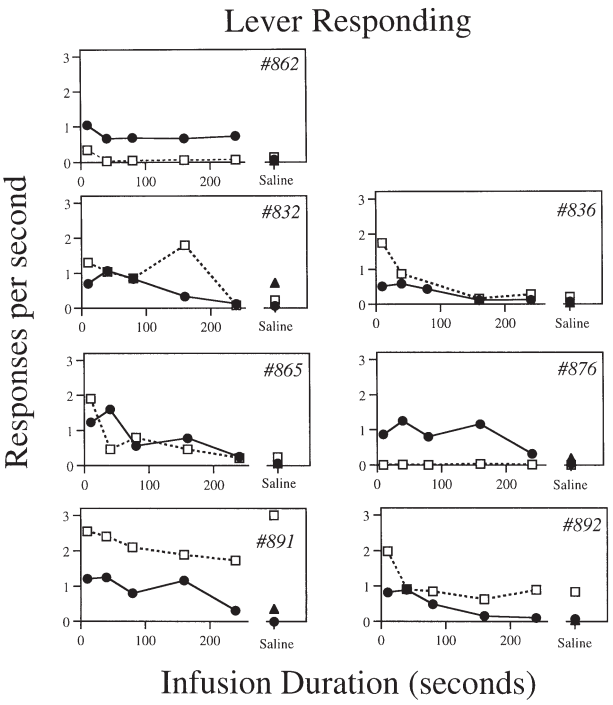


**Fig. 1** Lever-response rates (responses/s) for each monkey in the cocaine self-administration group. Rates are presented as a function of the duration of the self-administered infusion (in s) with non-contingent cocaine (“Cocaine Treatment”) and without additional cocaine (“No Treatment”) Rates are also presented during saline substitution in the No Treatment and Cocaine Treatment phases, as well as following the treatment phase (“Saline Redetermination”). ● No treatment, □ cocaine treatment, ▲ redetermined saline

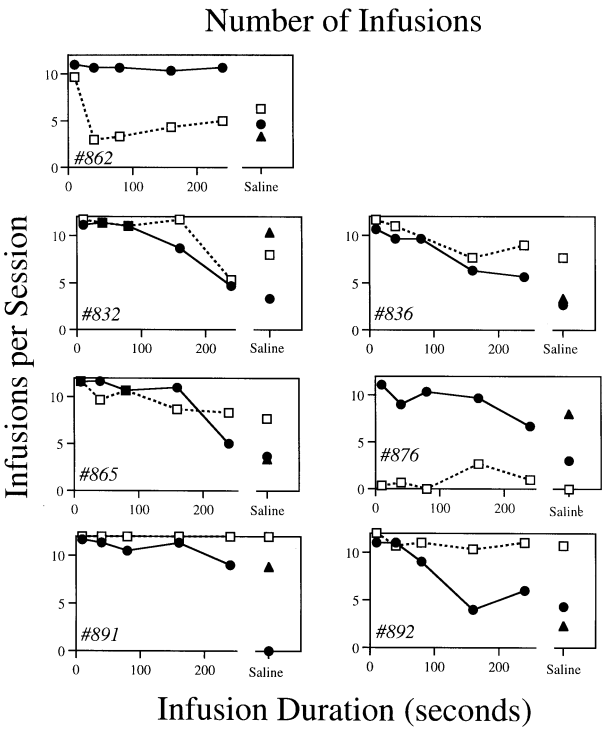


**Fig. 2** Rates of cocaine self-administration (infusions per session) for each monkey in the cocaine self-administration group. Rates are presented as a function of the duration of the self-administered infusion (in s) with non-contingent cocaine (“Cocaine Treatment”) and without additional cocaine (“No Treatment”). Rates are also presented during saline substitution in the No Treatment and Cocaine Treatment phases, as well as following the treatment phase (“Saline Redetermination”). ● No treatment, □ cocaine treatment, ▲ redetermined saline

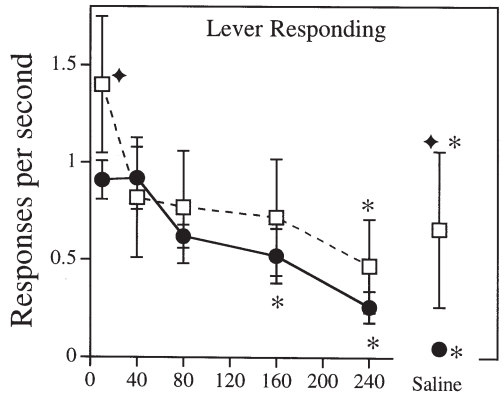


**Fig. 3** Mean response rates (±SEM) for the cocaine self-administration group. Rates are presented as a function of the duration of the self-administered infusion (in s) with non-contingent cocaine ("Cocaine Treatment") and without additional cocaine ("No Treatment") An *asterisk* indicates a significant difference compared to the baseline condition (10-s infusion with no treatment), $P>0.05$, and a *cross symbol* indicates a significant difference under cocaine treatment compared to the same infusion duration with no treatment, $P<0.05$. ● No treatment, □ cocaine treatment

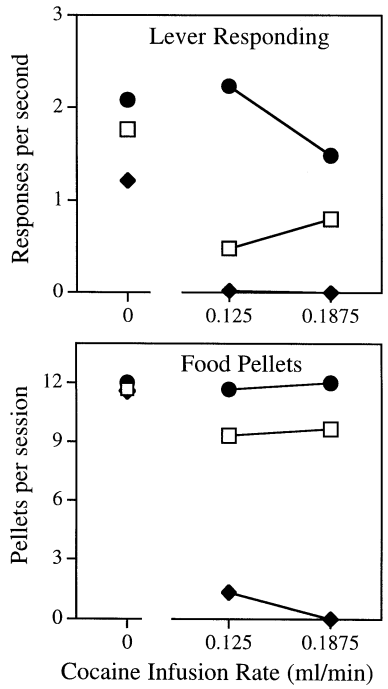


**Fig. 4** Rates of responding (*upper panel*) and food intake (*lower panel*) by individual monkeys trained with the food schedule. Rates are presented as a function of the rate of infusion (in ml/min) of cocaine solution. The 0.125 ml/min treatment was the same as the non-contingent cocaine treatment given to monkeys in the self-administration group. The 0.1875 ml/min treatment was intended to be comparable to non-contingent cocaine treatment with the addition of self-administered cocaine. □ Monkey 827, ◆ monkey 895, ● monkey 897

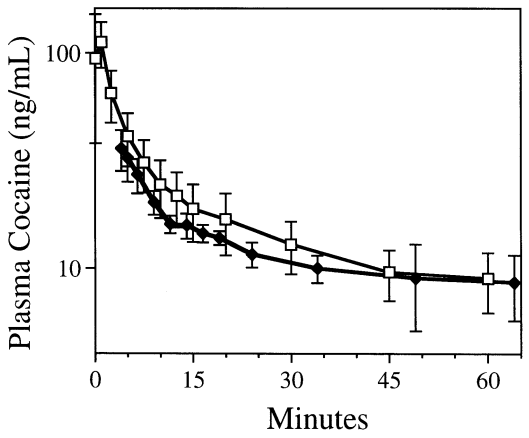


**Fig. 5** Mean concentration (±SEM) of cocaine in plasma following infusion of 0.32 mg/kg cocaine at the rates used for the 10- and 240-s infusion conditions in the self-administration study. Concentrations are expressed as a function of time elapsed since the start of the infusion. □ 10-s infusion, ◆ 240-s infusion

one infusion duration, and two (nos 891 and 892) showed increases across the range of delivery rates. Under the 10-s infusion duration, non-contingent cocaine significantly increased responding [$F(1,29)=7.05$, $P<0.013$]. Responding was also increased significantly by non-contingent treatment during saline substitution [$F(1,29)=10.75$, $P<0.003$]. In three monkeys (nos 832, 876, and 891; see filled triangles, Fig. 2), when all cocaine was discontinued following the non-contingent treatment phase of the study, intake decreased less than it had during saline substitution prior to the treatment phase.

Slow, non-contingent infusion of cocaine tended to reduce responding for food (Fig. 4). Like two of the monkeys that responded for cocaine, one monkey essentially stopped responding for food when cocaine was administered non-contingently. At the higher delivery rate, responding was significantly reduced [$t(2)=5.26$, $P<0.04$].

Figure 5 shows that the peak plasma level of cocaine produced by the faster infusion was significantly higher than that produced by the slower infusion [$t(4)=3.02$, $P<0.04$]. The peak plasma level produced by the 240-s infusion (immediately following the infusion, at the first point of the 240-s curve) was substantially lower than the peak reached with the faster infusion (1 min after the infusion). Five minutes after the start of the infusion (which corresponds to the duration of the post-infusion time-out period under the self-administration schedule), plasma levels produced by the two infusions did not differ [$t(4)=0.66$, $P>0.55$]. Thus, by the time the next infusion became available under the self-administration schedule, plasma levels should have been similar across all delivery-rate conditions.

## Discussion

The demonstration of a positive relationship between responding for cocaine and the speed with which the

drug is delivered represents a systematic replication of the results of Balster and Schuster (1973). At the slowest delivery rate, self-administration dropped to saline levels, indicating that cocaine delivered at this rate was not reinforcing. The pharmacokinetic profiles obtained here indicate that: 1) the peak plasma concentration of cocaine would have been higher after a fast infusion, but 2) levels after the 5-min time-out period would not have differed regardless of the delivery rate. Thus, faster infusions were more reinforcing because they produced a sharp increase in plasma concentration, making more drug available to the brain shortly after the reinforced response. The similarity between plasma levels following time-out (when the next infusion became available) makes it unlikely that slower infusions were self-administered less frequently as a result of longer-lasting effects (i.e., satiation). The half-life of cocaine under these conditions (21–31.5 min) agrees with the 24-min half-life obtained with a higher dose (1 mg/kg) infused over 40–60 s in non-anesthetized rhesus monkeys (Saady et al. 1995). This consistency confirms that the pharmacokinetics were not altered by the use of anesthesia and should have been similar across this range of doses, allowing the pharmacokinetic data obtained here to be extrapolated to the self-administration situation.

Non-contingent treatment with cocaine clearly reduced self-administration in only two of the seven monkeys. Although this suggests that substitution treatment might be effective for some individuals, similar reductions in food-maintained responding indicate that this effect was not specific to self-administration or due to "substitution". In general, non-contingent cocaine had the opposite effect: two monkeys showed increased responding across the range of delivery rates, and the other three increased responding under at least one condition. Pre-session treatment with slowly infused cocaine apparently primed or reinstated (Gerber and Stretch 1975; Stewart and deWit 1987) responding here, enhancing responding at the beginning of a session, when the self-administered infusion was too slow to be reinforcing, or when saline was substituted for self-administered cocaine.

In earlier studies, IV cocaine was administered non-contingently to rhesus monkeys as a bolus prior to self-administration sessions (Mansbach and Balster 1993; Skjoldager et al. 1993). High pre-session doses reduced responding only for a brief time, apparently as a direct effect of the drug rather than substitution (Skjoldager et al. 1993). Pre-session cocaine decreased food responding and cocaine responding non-selectively (Mansbach and Balster 1993), even with IM administration, which should have produced a longer duration of action (Herling et al. 1979).

Glowa and Fantegrossi (1997) recently suggested that non-contingent cocaine may be more likely to decrease self-administration when the unit dose is low (making the behavior more susceptible to change) and the treatment is continuous (overcoming the rapid metabolism of cocaine). When they administered non-contingent cocaine to rhesus monkeys as a continuous, slow infusion during the session in addition to a pre-session bolus, cocaine responding (as opposed to food) was selectively reduced with a 0.01 mg/kg unit dose of cocaine, but not 0.056 mg/kg. Self-administration was decreased when the total non-contingent dose was 2–3 times the amount usually self-administered during a session. In the present study, self-administration was not consistently decreased, even though the total non-contingent dose was approximately double the amount usually self-administered. While these studies differed procedurally in a number of ways, it is notable that the pre-session treatment in the present study consisted of a slow infusion starting 30 min prior to the session, while Glowa and Fantegrossi (1997) administered their pre-session treatment as a bolus immediately prior to the session. This suggests that the high peak levels of cocaine produced by a bolus pre-treatment (supplemented by a slow, continuous infusion) may reduce responding, while the lower peak produced by a slowly-infused pre-treatment may prime responding. If so, a slow-delivery system of cocaine that produces low blood levels would probably not be a widely effective treatment for cocaine abuse, and might even increase drug seeking.

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## References

Ball JC, Myers CP, Friedman SR (1988) Reducing the risk of AIDS through methadone maintenance treatment. J Health Soc Behav 29: 214–226

Balster RL, Schuster CR (1973) Fixed-interval schedule of cocaine reinforcement: effect of dose and infusion duration. J Exp Anal Behav 20: 119–129

Dole VP, Nyswander ME (1965) A medical treatment for diacetylmorphine (heroin) addiction. JAMA 193: 646–650

Gerber GJ, Stretch R (1975) Drug-induced reinstatement of extinguished self-administration behavior in monkeys. Pharmacol Biochem Behav 3: 1055–1061

Glowa JR, Fantegrossi W E (1997) Effects of dopaminergic drugs on food- and cocaine-maintained responding IV. Continuous cocaine infusions. Drug Alcohol Depend 45:71–79

Henningfield JE (1995) Nicotine medications for smoking cessation. N Engl J Med 333: 1196–1203

Herling S, Downs DA, Woods JH (1979) Cocaine, *d*-amphetamine, and pentobarbital effects on responding maintained by food or cocaine in rhesus monkeys. Psychopharmacology 64: 261–269

Mansbach RS, Balster RL (1993) Effects of mazindol on behavior maintained or occasioned by cocaine. Drug Alcohol Depend 31: 183–191

Mello NK, Negus SS (1996) Preclinical evaluation of pharmacotherapies for treatment of cocaine and opioid abuse using drug self-administration procedures. Neuropsychopharmacology 14: 375–424

Mendelson JH, Mello, NK (1996) Management of cocaine abuse and dependence. N Engl J Med 334: 965–972

National Research Council (1996) Guide for care and use of laboratory animals. National Academy Press, Washington

Nestler EJ (1994) Molecular mechanisms of drug addiction. J Neurosci 12: 2439–2450

O'Brien CP (1996) Recent developments in the pharmacotherapy of substance abuse. J Consult Clin Psychol 64: 677–686

Saady JJ, Bowman ER, Aceto MD (1995) Cocaine, ecgonine methyl ester, and benzoylecgonine plasma profiles in rhesus monkeys. J Anal Toxicol 19: 571–575

Simpson DD, Joe DW, Bracy SA (1987) Six-year follow-up of opioid addicts after admission to treatment. Arch Gen Psychiatry 39: 1318–1326

Skjoldager P, Winger G, Woods JH (1993) Effects of GBR 12909 and cocaine on cocaine-maintained behavior in rhesus monkeys. Drug Alcohol Depend 33: 31–39

Stewart J, de Wit H (1987) Reinstatement of drug-taking behavior as a method of assessing incentive motivational properties of drugs. In: Bozarth MA (ed) Methods of assessing the reinforcing properties of drugs. Springer, New York, pp 211–228