Published in final edited form as:

Synapse. 2011 May ; 65(5): 404–411. doi:10.1002/syn.20858.

Competitive dopamine receptor antagonists increase the equiactive cocaine concentration during self-administration

Andrew B Norman¹, Mantana K Norman¹, Michael R Tabet¹, Vladimir L Tsibulsky¹, and Amadeo J Pesce²

¹ Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA

² Department of Pathology and Laboratory Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA

Summary

Competitive dopamine receptor antagonists increase the rate of cocaine self-administration. As the rate of self-administration at a particular unit dose is determined by the satiety threshold and the elimination half-life ($t_{1/2}$) of cocaine, we investigated whether dopamine receptor antagonists altered these parameters. The plasma cocaine concentration at the time of each self-administration was constant during a session demonstrating that this satiety threshold concentration represents an equiactive cocaine concentration. The plasma cocaine concentration at the time of self-administration was increased by SCH23390, consistent with pharmacological theory. In rats trained to reliably self-administer cocaine, SCH23390 had no effect on the plasma steady-state cocaine concentration produced by constant infusions of cocaine. Therefore, this antagonist had no effect on cocaine $t_{1/2}$ at a dose that accelerated cocaine self-administration. A continuous cocaine infusion at a rate that maintained steady state concentrations above the satiety threshold stopped self-administration. SCH23390, or the D₂ dopamine receptor antagonist (–) eticlopride, reinstated self-administration in the presence of the constant cocaine infusion. This is consistent with SCH23390 and eticlopride raising the satiety threshold above the steady state level produced by the constant cocaine infusion. It is concluded that the antagonist-induced acceleration of cocaine self-administration is the result of a pharmacokinetic/pharmacodynamic interaction whereby the rate of cocaine elimination is faster at the higher concentrations, as dictated by first-order kinetics, so that cocaine levels decline more rapidly to the elevated satiety threshold. This results in the decreased inter-injection intervals.

Keywords

Compulsion zone; satiety threshold; pharmacokinetics; pharmacodynamics; equiactive agonist concentration; SCH23390; eticlopride; D₁ dopamine receptor; D₂ dopamine receptor

INTRODUCTION

When administered systemically in moderate doses, competitive D₁-like and D₂-like dopamine receptor antagonists increased the rate of cocaine self-administration (Koob et al., 1987; Britton et al., 1991; Corrigan and Coen, 1991; Hubner and Moreton, 1991; Mello and

Corresponding author: Andrew B. Norman, Ph.D., Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati, College of Medicine, 231 Albert Sabin Way, Cincinnati, OH 45267-0583, USA., andrew.norman@uc.edu, Tel: (513) 558-6654, Fax: (513) 558-0042.

Negus, 1996; Norman et al., 1999; Barrett et al., 2004). A pharmacological understanding of competitive antagonism is based on the principle of an increase in the equiactive concentration of an agonist (Schild, 1957; Rang, 2006; Colquhoun, 2007). Therefore, the application of this principle to the self-administration paradigm should represent a useful approach to identifying the mechanism by which competitive antagonists accelerate self-administration.

A pharmacological explanation of the regulation of drug self-administration hypothesizes that a constant magnitude of drug effect is maintained not only across different unit doses (Yokel and Pickens, 1974) but also in the presence of antagonists (Yokel and Wise, 1975; Gerber and Wise, 1989). Falling dopamine levels when they reach a certain level trigger successive responses in the intravenous cocaine self-administration paradigm (Wise et al., 1995). Therefore, after a self-administration of cocaine, the next self-administration will occur when cocaine levels once again fall back to this minimum maintained cocaine concentration that, by definition, is equiactive. An important assumption is that this equiactive concentration is constant throughout a session and the validity of this assumption was investigated in the present study.

This pharmacological model can be described mathematically by the equation: $T = \ln(1 + D_U / D_{ST}) / k$, where T is the time between successive injections, which is proportional to the cocaine unit dose (D_U). Furthermore, T is inversely proportional to the first-order elimination rate constant (k) of cocaine and to the minimum maintained cocaine concentration (D_{ST}). The parameter D_{ST} has been termed the satiety threshold (Tsibulsky and Norman, 1999) and in this pharmacological model represents the equiactive cocaine concentration. The magnitude of this parameter, therefore, should be increased in the presence of competitive dopamine receptor antagonists. We tested herein this hypothesis by investigating the effects of the D₁-like dopamine receptor antagonist SCH23390 and the D₂-like dopamine receptor antagonist eticlopride on the cocaine satiety threshold. In addition, the effect of SCH23390 on the cocaine elimination rate constant was determined by measuring the effect on the plasma cocaine steady state concentration.

MATERIALS AND METHODS

Cocaine self-administration training

Male Sprague-Dawley rats (from SASCO, Wilmington, MA, initial weight 180 – 200 g and 400 – 500 g over the duration of these studies) were housed individually on a 12 h light - dark cycle (lights on at 6:00 a.m.) and food and water were available ad libitum. All studies were conducted in accordance with the Guide for the Care and Use of Laboratory Animals. Rats were surgically implanted with an indwelling catheter into the right jugular vein under halothane anesthesia. Beginning six or seven days after the surgery, rats were trained to self-administer cocaine HCl using a fixed ratio (FR = 1) schedule with no time out period (TO = 0) after the injection of cocaine was completed. This schedule was used throughout the subsequent self-administration studies.

Test chambers (modified chambers from Lafayette Instrument Co., Lafayette, IN) were each equipped with an active and an inactive lever. Each chamber was situated inside of a laminated wooden compartment (43 × 61 × 35 cm) that provided sound attenuation and was equipped with a house light. Infusion pumps (model PHM-100, Med Associates Inc., Georgia, VT) were situated outside of the compartments. Computers controlled unconditioned stimuli (drug injection) using a program written in Medstate NotationR language (Med Associates, Inc., St. Albans, VT).

Training at the unit dose of 1.5 $\mu\text{mol/kg}$ cocaine continued until individual rats met the criterion for stable maintained self-administration. This criterion was no systematic change of the mean and standard deviation of the inter-injection intervals between five consecutive sessions.

Between sessions the unit doses of cocaine ranged from 0.75 to 12 $\mu\text{mol/kg}$ and were regulated by the duration of the injection, which ranged from 2 to 40 s. To optimize the time to reach satiety threshold levels the first four unit doses of cocaine were programmed to be 1.5 $\mu\text{mol/kg}$. After the self-administration of these initial doses the program switched subsequent doses to the required maintenance unit dose in random order between sessions. These data were used to calculate the magnitudes of the cocaine satiety threshold and $t_{1/2}$ for individual rats as described previously (Tsitulsky and Norman, 1999).

Collection of blood samples during cocaine self-administration

In order to test the hypothesis that the satiety threshold was constant during the maintenance phase of self-administration sessions, the plasma cocaine concentration at the time of lever presses was measured during this phase. Rats that reliably self-administered cocaine were implanted with a second catheter in the left femoral vein for blood sampling and self-administration sessions continued daily. During the sessions in which blood samples were collected these rats self-administered cocaine at a unit dose of 3 $\mu\text{mol/kg}$, which typically produced inter-injection intervals of approximately 5–6 min. After 90 min, when the inter-injection intervals were stable, rats were observed and after a self-injection of cocaine was complete the pump was manually switched off. The rats were then observed until they pressed the lever at which time they were removed from the chamber and a blood sample (approximately 200 – 400 μl) was rapidly collected. The first 50 μl of the sample was discarded to avoid dilution of the blood with the heparinized saline within the catheter. The catheter was flushed with heparinized saline (100 μl), the rats were returned to the chamber and the infusion pump was switched on. The times of the switching off and on of the pump, the time of lever press and the time to collect the blood sample were recorded. After rats were returned to the chamber self-administration resumed and at approximately 60 min intervals the blood collection procedure was repeated. Therefore, these values were representative of the minimum plasma cocaine concentrations during the maintenance phase of the session and were assumed to correspond to the cocaine satiety threshold.

In order to determine whether the injection of SCH23390 accelerated cocaine self-administration and produced an increase in the plasma cocaine concentration, at approximately 20 min following the collection of the third blood sample the rats were removed from the chamber and administered SCH23390 at a dose of 15 nmol/kg via the femoral catheter and immediately returned to the chamber. Approximately 20 min after the injection, when self-administration rates were maximally increased, another blood sample was collected as described above after which the self-administration session resumed uninterrupted. The total duration of the self-administration session was approximately 7 hours.

The blood samples were placed into cooled heparinized polypropylene centrifuge tubes and the samples were centrifuged for 3 min at 5,000 x g. The plasma was aspirated, placed into polypropylene storage vials and stored at -70°C until cocaine concentrations were assayed using gas chromatography/mass spectrometry (GC/MS).

Collection of blood samples during the continuous infusion of cocaine

The hypothesis that SCH2390 altered the $t_{1/2}$ of cocaine was tested by measuring the effect of SCH23390 on the steady state plasma cocaine concentration. Rats trained to self-

administer cocaine and implanted with both a jugular and a femoral catheter were placed in a chamber and a continuous infusion of cocaine was initiated at rate of 0.18, 0.36 or 0.72 $\mu\text{mol/kg min}^{-1}$ via the jugular catheter. Lever pressing behavior had no consequence during these sessions and was not recorded. After 90 min the rats were removed from the chamber and a blood sample was rapidly collected via the femoral vein as described above. The infusion of cocaine was not interrupted during the sampling procedure. The procedure was repeated twice at 60 min intervals. After the third blood sample was obtained, the rats were removed from the chamber and injected with SCH23390 (15 nmol/kg) via the femoral catheter and replaced into the chamber. Blood samples were obtained at 20 min after the injection of SCH23390 and then hourly until the cocaine infusion was terminated after a total session time of approximately 7 hours.

The continuous infusion of cocaine during cocaine self-administration and the effects of SCH23390 and eticlopride

A Y-connector inserted into the catheter allowed cocaine to be administered either by self-administration or via an investigator-controlled variable rate infusion pump. After rats self-administered cocaine at a unit dose of 0.75 $\mu\text{mol/kg}$ for at least 90 min, the infusion pump was switched on and a constant infusion of cocaine was maintained as described previously (Tsibulsky and Norman, 1999). The rate of the infusion was adjusted for each individual animal to maintain steady state cocaine levels just above the satiety threshold where self-administration stopped or was very infrequent. The mean $\pm$ SEM final rates of cocaine infusion for the vehicle, SCH23390 and eticlopride sessions were 0.56 ± 0.04 , 0.56 ± 0.03 and 0.40 ± 0.02 $\mu\text{mol/kg min}^{-1}$, respectively. During the continuous cocaine infusion animals could self-administer cocaine at any time.

At approximately 90 min after the start of the continuous infusion of cocaine, the rats were removed from the chamber, disconnected and injected with vehicle (0.4% ethanol v/v in saline, 0.5 ml/kg), SCH23390 (20 nmol/kg) or eticlopride (30 nmol/kg) via the jugular catheter. The tubing was then reattached to the catheter and rats were placed back into the chamber. The total time required to complete this procedure was approximately 30 – 40 s. The mean durations of the continuous infusion after the injections were 191 min, 226 min and 299 min for vehicle, SCH23390 or eticlopride, respectively. The continuous infusion of cocaine was then terminated and after an additional 60 min the self-administration pump was also switched off. Lever pressing behavior was recorded until the behavior extinguished, which was defined as 30 min without any presses.

Preparation of plasma samples

Blood (400 μl) was collected in a 1.5 ml polypropylene microcentrifuge tubes containing 5.6 μl heparin (1.0 unit/ μl) and NaF (8 mg per 0.4 ml of blood) to inhibit, respectively blood coagulation and enzymatic hydrolysis of cocaine (Warner and Norman, 2000). The blood samples were centrifuged at 5000 x g for 3 min, then the plasma (200 μl) was carefully separated from packed red blood cells, placed into sterile 1.5 ml Eppendorf microcentrifuge tubes, rapidly frozen on dry ice and then stored at -80°C until analysis.

Analysis of plasma cocaine concentrations

The procedure has been described elsewhere (Norman et al., 2007). Briefly, cocaine concentrations were measured in samples of heparinized and NaF-treated plasma obtained from cocaine treated rats using cocaine- D_3 as an internal standard. Cocaine concentrations were determined by comparison to a standard curve from 50 – 5000 ng/ml of cocaine, samples of which also included cocaine- D_3 . The gas chromatograph/mass spectrometer (GC/MS) consisted of a Varian 3800 gas chromatograph, a Saturn 2000 ion trap spectrometer

operating in full scan mode with electron impact ionization. The lower limit of detection of cocaine was 10 ng/ml and the assay was linear within the range of 50–5000 ng/ml.

Materials

Cocaine HCl was obtained from Research Triangle Institute (Research Triangle Park, NC) under the National Institute on Drug Abuse drug supply program. Cocaine HCl (40 µmol/ml) was dissolved in normal saline solution containing one unit per ml of heparin and then passed through a sterile 0.2 µm acetate filter immediately prior to use in the self-administration studies. Heparin sodium was obtained from American Pharmaceutical Partners, Inc. (Schaumburg, IL). Streptokinase, R(+)-SCH23390 HCl and S(-)-eticlopride HCl were purchased from Sigma (St. Louis, MO). SCH23390 and eticlopride were prepared daily in sterile normal saline from stock solutions (each 10 µmol/ml in absolute ethanol and stored at -20°C). Methohexital sodium (Brevital) was manufactured by King Pharmaceuticals (Bristol, TN). Cocaine used as an external standard (1 mg/ml) and internal standard (cocaine-D₃) (0.1 mg/ml) in methanol or acetonitrile were purchased from Radian International LLC, (Austin, TX). Rat plasma with heparin was obtained from Harlan Bioproducts for Science (Indianapolis, IN). All chemicals were purchased from Sigma-Aldrich (St. Louis, MO) or Pierce chemicals (Rockford, IL). All chemicals were purchased in the highest available purity and used without any further purification.

Data analysis and statistical procedures

Changes in plasma cocaine concentrations as a function of time over the duration of the self-administration sessions and the continuous cocaine infusions were assessed using a one-way ANOVA with repeated measures followed with post-hoc Tukey's test. Linear regression analysis of inter-injection intervals as a function of time was used to demonstrate the constant rate of self-administration during the maintenance phase of sessions. Paired t-tests were used to assess the effects of a continuous cocaine infusion and the injection of antagonists on the rate of cocaine self-administration.

RESULTS

Minimum plasma cocaine concentrations during the maintained self-administration of cocaine

As shown in the representative session in Fig. 1A, the rates of cocaine self-administration were relatively constant. This was evidenced by a lack of systematic deviation of the inter-injection intervals from the linear regression line. The group mean $\pm$ SEM inter-injection interval was 363 ± 25 s ($n = 7$ rats) at a unit dose of 3 µmol/kg. The mean $\pm$ SEM plasma concentrations of cocaine measured at the time of lever press at the indicated session times were 3.3 ± 0.2 , 3.0 ± 0.2 and 3.1 ± 0.3 µmol/l, respectively (Fig. 1B). There were no significant differences ($p > 0.1$, one-way ANOVA with repeated measures) between these first three measures of the minimum plasma cocaine concentrations.

SCH23390 increased the rate of cocaine self-administration

As shown in Fig. 1A, within minutes after the injection of SCH23390 (15 nmol/kg) the rate of cocaine self-administration increased. By 20–30 min after the injection of SCH23390, the rate of cocaine self-administration began to decline and a blood sample was taken at the time of a lever press. The mean $\pm$ SEM time between the injection of SCH23390 and taking the blood sample was 23.0 ± 1.5 min. At this time the group mean $\pm$ SEM inter-injection interval of cocaine self-administration was 197 ± 11 s ($n = 7$ rats), significantly shorter ($P < 0.01$, paired t-test) than the mean interval prior to the administration of SCH23390. The plasma cocaine concentration at this time was increased to a mean $\pm$ SEM of 4.2 ± 0.4 µmol/

l, significantly higher ($P < 0.01$, one-way ANOVA with repeated measures and post-hoc Tukey's test) than the concentrations observed prior to the injection of SCH23390 (Fig. 1B).

SCH23390 had no effect on the steady state plasma concentration of cocaine during a constant infusion

The steady state concentration of a drug (C_{ss}) during a continuous i.v. infusion (bioavailability = 1) is determined according to the equation $C_{ss} = r/k$, where r is the rate of the constant infusion of drug and k is the elimination rate constant of the drug. As $k = \ln(2)/t_{1/2}$, C_{ss} is directly proportional to the drug $t_{1/2}$. To determine whether SCH23390 altered the $t_{1/2}$ of cocaine the ability to influence the steady state concentration of cocaine was investigated. As shown in Fig. 2, after 180 min the plasma cocaine concentrations were stable at all infusion rates, indicating that cocaine concentrations were at or near steady state. Across this range of infusion rates the steady state concentration of cocaine was proportional to the rate of infusion. Importantly, after the injection of SCH23390 (15 nmol/kg) there was no significant change ($p > 0.1$, one-way ANOVA with repeated measures) in the steady state plasma cocaine concentration at any rate of infusion of cocaine.

Antagonists reinstated self-administration during the constant infusion of cocaine

As shown in Fig. 3, after the initial loading phase of the session, rats self-administered cocaine at a relatively constant rate with mean inter-injection intervals of between 134–173 s (Table 1). After the start of a constant infusion of cocaine, self-administration stopped. Consequently, the mean rate of self-administration prior to the antagonist or vehicle treatment was negligible (Table 1, period 1). After the i.v. injection of vehicle the rate of self-administration was negligible and was not significantly different ($p > 0.5$, paired t-test) from the very low rates observed prior to the injection (Fig. 3A; Table 1, period 2). In contrast, shortly after the injection of SCH23390 (Fig. 3B) or eticlopride (Fig. 3C) high rates of self-administration were reinstated. The mean inter-injection intervals during the 30 min after the reinstatement produced by SCH23390 and eticlopride were 90 and 135 s, respectively (Table 1, period 2). The rate of cocaine self-administration gradually declined (Figs. 3B and 3C) and typically returned towards baseline values in the presence of the constant infusion of cocaine by 180 min after the injection of SCH23390 (Fig. 3B) or eticlopride (Fig. 3C). After the constant non-contingent infusion of cocaine was terminated rats resumed the self-administration of cocaine (Figs. 3A, 3B and 3C; Table 1). In the sessions in which rats were injected with SCH23390 there was no significant difference in the rate of self-administration before and after the cocaine infusion (Table 1). However, in the sessions in which rats were injected with eticlopride the rate of self-administration after the termination of the constant infusion was significantly higher, ($p < 0.01$, paired t-test) than the rate of self-administration observed prior to the constant infusion of cocaine (Table 1). When access to self-administered cocaine was terminated there was the typical abrupt increase in the rate of lever pressing behavior that gradually declined until responding was extinguished (Fig. 3).

DISCUSSION

The lack of any SCH23390-induced change in the steady-state plasma cocaine concentration during a constant cocaine infusion demonstrates that SCH23390 did not change the first-order elimination rate constant of cocaine. Therefore, changes in cocaine clearance cannot account for the SCH23390-induced acceleration of cocaine self-administration.

The stable plasma concentrations of cocaine measured at the time of lever presses sampled throughout the maintenance phase of self-administration sessions demonstrate that the satiety threshold remained constant. This verifies a major assumption of the satiety threshold

model of maintained self-administration and is consistent with the hypothesis that the satiety threshold represents an equiactive agonist concentration. The minimum plasma drug concentrations during the self-administration amphetamine (Yokel and Pickens, 1974), phenethylamine (Cone et al., 1978), and in the yoked control group of cocaine self-administration (Lau and Sun, 2002) were also constant. Therefore, the concentration of cocaine and other stimulants appears to be fundamental to the regulation of self-administration behavior.

The mean satiety threshold value is typically presented in units of dose (Tsibulsky and Norman, 1999). This operational value should differ from the actual plasma concentration by the apparent volume of distribution (V_d). As the satiety threshold in rats typically ranged from 4.0–5.8 $\mu\text{mol/kg}$ (see Norman and Tsibulsky, 2006) and the mean plasma cocaine concentration was approximately 3.1 $\mu\text{mol/l}$, the cocaine V_d in our rats ranged from approximately 1.3–1.9 l/kg, consistent with literature values (Booze et al., 1997).

The SCH23390-induced increase in the plasma concentration of cocaine at the time of lever press is consistent with a SCH23390-induced increase in the cocaine satiety threshold, i.e. in the equiactive concentration of cocaine. Further evidence of antagonist-induced increases in the satiety threshold is provided by the ability of SCH23390 to reinstate self-administration that has ceased in the presence of a continuous infusion of cocaine. The compulsion zone theory of the regulation of cocaine self-administration states that cocaine-induced lever pressing occurs only when cocaine levels are between the level at which lever pressing behavior is reinstated (priming threshold) and the satiety threshold (Norman and Tsibulsky, 2006). The theory predicts that the continuous infusion of cocaine at a rate that maintains steady-state concentrations above the satiety threshold prevents self-administration (Tsibulsky and Norman, 1999). The theory further predicts that if the satiety threshold was increased above the level of cocaine produced by the constant infusion, then these cocaine levels would be within the compulsion zone and self-administration should be reinstated. The SCH23390-induced reinstatement of cocaine self-administration under these conditions is consistent with this hypothesis.

Based on the ability of receptor subtype selective antagonists to accelerate cocaine self-administration, it was suggested that both D_1 -like and D_2 -like dopamine receptors mediate cocaine self-administration (Corrigall and Coen, 1991; Hubner and Moreton, 1991; Barrett et al., 2004). Similarly, the SCH23390- and eticlopride-induced elevation of the satiety threshold is consistent with a role for both D_1 -like and D_2 -like dopamine receptors in the regulation of this key pharmacodynamic parameter.

It is well documented that cocaine is eliminated from rodents (Misra et al., 1977; Benuck et al., 1987; Booze et al., 1997; Warner and Norman, 2000; Norman et al., 2007) and humans (Harris et al., 2003; Evans and Foltin, 2004) by first-order kinetics. Therefore, at the higher cocaine concentrations occurring in the presence of antagonists the rate of cocaine elimination must be faster as dictated by first-order kinetics. The concentration of cocaine after administration will decline back to the satiety threshold sooner resulting in a shorter inter-injection interval. This pharmacokinetic/pharmacodynamic interaction is illustrated in Fig. 4 and provides an explanation for the antagonist-induced acceleration of cocaine self-administration in vivo.

Interestingly, after the rapid increase in the rate of cocaine self-administration in response to the injection of SCH23390, the gradual decline in this rate is consistent with the time-course of the elimination of this antagonist in rats (Hietala et al., 1992). If so, the self-administration paradigm could represent a useful assay system for measuring both the

pharmacodynamic potencies of dopamine receptor antagonists (Roberts and Vickers, 1984) and for measuring the pharmacokinetics of these antagonists.

In summary, the dopamine receptor antagonists SCH23390 and eticlopride elevated the cocaine satiety threshold. Even though there was no evidence for a SCH23390-induced change in the cocaine $t_{1/2}$, the absolute rate of elimination of cocaine at the higher concentrations increased as dictated by first-order kinetics. This resulted in cocaine levels falling more rapidly to the elevated satiety threshold. Therefore, the antagonist-induced acceleration of drug self-administration is explained by a pharmacokinetic/pharmacodynamic interaction within the framework of the compulsion zone theory.

Acknowledgments

Supported by United States PHS grant DA018538 from the National Institute on Drug Abuse. We thank Dr. William J. Ball for helpful discussions and William Buesing, Matthew Sperling and Charles Perkins for excellent technical assistance. We are also grateful to Nora E. Stevenson for providing program coordination.

References

- Barrett AC, Miller JR, Dohrmann JM, Caine SB. Effects of dopamine indirect agonists and selective D1-like and D2-like agonists and antagonists on cocaine self-administration and food maintained responding in rats. *Neuropharmacology* 2004;47:256–273. [PubMed: 15464142]
- Benuck M, Lajtha A, Reith MEA. Pharmacokinetics of systemically administered cocaine and locomotor stimulation in mice. *J Pharmacol Exp Ther* 1987;243:144–149. [PubMed: 3668848]
- Booze RM, Lehner AF, Wallace DR, Welch MA, Mactutus CF. Dose-response cocaine pharmacokinetics and metabolite profile following intravenous administration and arterial sampling in unanesthetized, freely moving male rats. *Neurotoxicol Teratol* 1997;19:7–15. [PubMed: 9088006]
- Britton DR, Curzon P, Mackenzie RG, Keabian JW, Williams JEG, Kerkman D. Evidence for involvement of both D1 and D2 receptors in maintaining cocaine self-administration. *Pharmacol Biochem Behav* 1991;39:911–915. [PubMed: 1684870]
- Caine SB, Koob GF. Effects of dopamine D-1 and D-2 antagonists on cocaine self-administration under different schedules of reinforcement in the rat. *J Pharmacol Exp Ther* 1994;270:209–218. [PubMed: 8035317]
- Colquhoun D. Why the Schild method is better than Schild realised. *Trends Pharmacol Sci* 2007;28:608–614. [PubMed: 18023486]
- Cone EJ, Risner ME, Niedert GL. Concentrations of phenethylamine in dog following single doses and during intravenous self-administration. *Res Commun Chem Pathol Pharmacol* 1978;22:211–232. [PubMed: 734213]
- Corrigall WA, Coen KM. Cocaine self-administration is increased by both D1 and D2 dopamine antagonists. *Pharmacol Biochem Behav* 1991;39:799–802. [PubMed: 1838414]
- Evans SM, Foltin RW. Pharmacokinetics of intravenous cocaine across the menstrual cycle in rhesus monkeys. *Neuropsychopharmacology* 2004;29:1889–1900. [PubMed: 15138443]
- Gerber GJ, Wise RA. Pharmacological regulation of intravenous cocaine and heroin self-administration in rats: A variable dose paradigm. *Pharmacol Biochem Behav* 1989;32:527–531. [PubMed: 2727015]
- Harris DS, Everhart ET, Mendelson J, Jones RT. The pharmacology of cocaethylene in humans following cocaine and ethanol administration. *Drug Alcohol Depend* 2003;72:169–182.
- Hietala J, Seppala T, Lappalainen J, Syvalahti E. Quantification of SCH 39166, a novel D1 dopamine receptor antagonist, in rat brain and blood. *Psychopharmacology* 1992;106:455–458. [PubMed: 1349751]
- Hubner CB, Moreton JE. Effects of selective D1 and D2 dopamine antagonists on cocaine self-administration in the rat. *Psychopharmacology* 1991;105:151–156. [PubMed: 1839063]

- Koob GF, Le HT, Creese I. The D₁ dopamine receptor antagonist SCH 23390 increases cocaine self-administration in the rat. *Neurosci Lett* 1987;79:315–320. [PubMed: 2958724]
- Lau CE, Sun L. The pharmacokinetic determinants of the frequency and pattern of intravenous cocaine self-administration in rats by pharmacokinetic modeling. *Drug Metab Dispos* 2002;30:254–261. [PubMed: 11854142]
- Mello NK, Negus SS. Preclinical evaluation of pharmacotherapies for treatment of cocaine and opioid abuse using drug self-administration procedures. *Neuropsychopharmacology* 1996;14:375–424. [PubMed: 8726752]
- Misra AL, Giri VV, Patel MN, Alluri VR, Mule SJ. Disposition and metabolism of [³H] cocaine in acutely and chronically treated monkeys. *Drug Alcohol Depend* 1977;2:261–272. [PubMed: 560292]
- Norman AB, Norman MK, Hall JF, Tsibulsky VL. Priming threshold: A novel quantitative measure of the reinstatement of cocaine self-administration. *Brain Res* 1999;831:165–174. [PubMed: 10411996]
- Norman AB, Tsibulsky VL. The compulsion zone: A pharmacological theory of acquired cocaine self-administration. *Brain Res* 2006;1116:143–152. [PubMed: 16942754]
- Norman AB, Tabet MR, Norman MK, Buesing WR, Pesce AJ, Ball WJ. A chimeric human/murine anticocaine monoclonal antibody inhibits the distribution of cocaine to the brain in mice. *J Pharmacol Exp Ther* 2007;320:145–153. [PubMed: 17023573]
- Rang HP. The receptor concept: Pharmacology's big idea. *Br J Pharmacol* 2006;147:S9–S16. [PubMed: 16402126]
- Roberts DCS, Vickers G. Atypical neuroleptics increase self-administration of cocaine: An evaluation of a behavioural screen for antipsychotic activity. *Psychopharmacology* 1984;82:135–139. [PubMed: 6141584]
- Schild HO. Drug antagonism and pAx. *Pharmacol Rev* 1957;9:242–246. [PubMed: 13465304]
- Tsibulsky VL, Norman AB. Satiety threshold: A quantitative model of maintained cocaine self-administration. *Brain Res* 1999;839:85–93. [PubMed: 10482802]
- Warner A, Norman AB. Mechanisms of cocaine hydrolysis and metabolism in vitro and in vivo: A clarification. *Ther Drug Monit* 2000;22:266–270. [PubMed: 10850392]
- Wise, RA. Intravenous self-administration: a special case of positive reinforcement. In: Bozarth, MA., editor. *Methods of assessing the reinforcing properties of abused drugs*. Springer-Verlag; New York: 1987. p. 117-141.
- Wise RA. Cognitive factors in addiction and nucleus accumbens function: some hints from rodent models. *Psychobiology* 1999;27:300–310.
- Wise RA, Newton P, Leeb K, Burnette B, Pocock D, Justice JB. Fluctuations in nucleus accumbens dopamine concentration during intravenous cocaine self-administration in rats. *Psychopharmacology* 1995;120:10–20. [PubMed: 7480530]
- Yokel RA, Pickens R. Drug level of d- and l-amphetamine during intravenous self-administration. *Psychopharmacologia* 1974;34:255–264. [PubMed: 4819978]
- Yokel RA, Wise RA. Increased lever pressing for amphetamine after pimozide in rats: Implications for a dopamine theory of reward. *Science* 1975;187:547–549. [PubMed: 1114313]

Figure 1.

Cumulative event record of a cocaine self-administration session (A) and the plasma cocaine concentrations at the time of lever press (B). In this cumulative record from a representative session each vertical increment represents a self-administration of cocaine or a lever press that resulted in no cocaine injection. The horizontal distance between increments represents the inter-injection interval. The ascending arrows indicate where blood samples were taken (immediately after a lever press that resulted in no cocaine injection) for the measurement of plasma cocaine concentrations. The descending arrow indicates the time of injection of SCH23390 (15 nmol/kg). The mean $\pm$ SEM inter-injection interval during the maintenance phase of the session and prior to the injection of SCH23390 was 329 ± 15 s ($n = 35$ cocaine self-injections). The straight line represents the best fit regression through these inter-injection intervals indicated by the squares. The mean $\pm$ SEM inter-injection interval for the

4 self-administrations after the injection of SCH23390 was 168 ± 11 s. In Panel B symbols represent the mean $\pm$ SEM plasma cocaine concentrations from 7 rats. The arrow indicates the time of injection of SCH23390 (15 nmol/kg). There was no significant difference between any of the first 3 mean values ($p > 0.1$, one-way ANOVA with repeated measures). The mean plasma cocaine concentration 20 min after the injection of SCH23390 was significantly higher than the plasma cocaine concentrations prior to the injection of SCH23390 (* $P < 0.05$, one-way ANOVA with repeated measures and post-hoc Tukey's test).

Figure 2.

The lack of effect of SCH23390 on plasma steady-state cocaine concentrations. Non-contingent continuous infusions of cocaine were administered to the rats via a jugular catheter. In separate sessions, the rates of cocaine infusions were 0.18, 0.36 or 0.72 μmol/kg min⁻¹. Symbols represent the mean ± SEM plasma cocaine concentrations from 5 rats. The steady-state level of cocaine was proportional to the rate of infusion. The asterisk indicates a plasma concentration of cocaine significantly lower (**p* < 0.05, one-way ANOVA with repeated measures and post-hoc Tukey's test) than subsequent concentrations. The time of injection of SCH23390 (15 nmol/kg) is indicated by the arrow. There was no significant increase (*p* > 0.1, one-way ANOVA) in the mean plasma cocaine concentration 20 min after the injection of SCH23390 compared to the level of cocaine measured immediately prior to the injection of SCH23390 at any infusion rate of cocaine.

Figure 3.

The reinstatement of cocaine self-administration by dopamine receptor antagonists. Intravenous catheters were connected via a Y connector to a pump through which cocaine was self-administered and to an investigator controlled infusion pump. Rats self-administered cocaine at a unit dose of $0.75 \mu\text{mol/kg}$ for approximately 90 min. Then a continuous non-contingent infusion of cocaine was started and rats could still self-administer cocaine at any time. The rates of the continuous infusions were between 0.36 and $0.84 \mu\text{mol/kg min}^{-1}$ (mean = $0.51 \mu\text{mol/kg min}^{-1}$) and were sufficient to maintain steady state levels above the satiety threshold and consequently stop self-administration. After approximately 90 min the rats were removed from the chamber, administered either SCH23390 (20 nmol/kg), eticlopride (30 nmol/kg) or 10% ethanol/saline vehicle at a volume of 0.5 ml/kg and quickly returned to the chamber. The non-contingent infusion continued until the rate of self-administration approached zero. The infusion pump was then switched off and self-administration resumed until access to cocaine was terminated. Lever presses that occurred after access to cocaine was terminated are indicated by the smaller filled circles. The session ended when lever-pressing behavior extinguished. The horizontal bars labeled 1 or 2 represent the 30 min periods from which intervals were measured and reported in Table 1.

Figure 4.

A pharmacokinetic/pharmacodynamic model of the antagonist-induced increase in the rate of cocaine self-administration. The descending lines represent the cocaine level after a self-administration of $3.0 \mu\text{mol/kg}$ during the maintenance phase of a self-administration session. The horizontal lines represent the minimum cocaine levels (satiety threshold) in the absence and presence of an antagonist. The antagonist-induced increase in the satiety threshold results in an increase in the cocaine concentration. First-order elimination kinetics dictates a faster rate of cocaine elimination at the higher concentrations of cocaine even if the cocaine elimination $t_{1/2}$ does not change in the presence of antagonist (for example SCH23390 as demonstrated in Fig. 2). Consequently, the cocaine levels decline to the satiety threshold more rapidly, resulting in a shorter inter-injection interval. In this model it is assumed that: 1) the cocaine $t_{1/2}$ is 9 min, 2) the injection and subsequent distribution of cocaine is instantaneous and 3) a single compartment pharmacokinetic model applies to the distribution and elimination of cocaine.

Table 1

The effect of SCH23390 and eticlopride on the rate of cocaine self-administration during the constant infusion of cocaine.

	Inter-injection intervals (s)			
	Pre cocaine infusion	Period 1	Period 2	Post cocaine infusion
Vehicle (n = 9)	135 ± 9	>1800	1711 ± 91	153 ± 13
SCH23390 (n = 7)	134 ± 9	1710 ± 90	90 ± 8***	117 ± 7
Eticlopride (n = 7)	173 ± 10	>1800	135 ± 20***	123 ± 8**

Values represent the mean ± SEM inter-injection intervals from the number of rats shown in parentheses during the indicated periods of the sessions. The horizontal bars labeled 1 or 2 that are shown in Fig. 3 represent the 1800 s periods from which the inter-injection intervals reported in this table were taken. "Pre cocaine infusion" represents the inter-injection intervals after the initial loading phase was complete and when the rate of self-administration was constant. Period 1 is representative of the effect of the constant infusion of cocaine. Period 2 is representative of the effect of the i.v. injection of antagonist or vehicle during the constant infusion of cocaine. "Post cocaine infusion" represents the inter-injection intervals after the termination of the constant infusion of cocaine. Significantly different from the maintenance phase of the session for the corresponding antagonist,

**
p < 0.01, paired t-test. Significantly different from cocaine infusion,

p < 0.001, paired t-test.