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Self-Administration of Agonists Selective for Dopamine D₂, D₃, and D₄ Receptors by Rhesus Monkeys

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Abstract

Dopamine receptor mechanisms are thought to play a role in the reinforcing effects of cocaine and other abused drugs. The lack of receptor-selective agonists has made it difficult to determine the role of the individual dopamine receptors in mediating these reinforcing effects. In this study, rhesus monkeys with a history of intravenous cocaine self-administration were tested for the reinforcing effects of several D₃-preferring agonists, a D₂-preferring agonist, and a D₄ agonist. The D₂-preferring agonist did not maintain responding in any monkeys, and the D₄ agonist was self-administered at low rates, just above those maintained by saline in one monkey. The D₃-preferring agonists were self-administered by approximately half of the animals, although at lower rates than cocaine. These results indicate the apparent limited reinforcing effectiveness of D₂-like agonists requires activity at D₃ receptors. Previous data from this laboratory and others also suggest that these drugs may not serve as reinforcers directly; the behavior may be maintained by response-contingent delivery of stimuli previously paired with cocaine. The ability of drug-related stimuli to maintain responding apparently differs among monkeys and other organisms, and may be related to individual differences in drug-taking behavior in humans.

Keywords

D2-like agonists; reinforcing effects; rhesus monkeys; self-administration

Introduction

Although the importance of dopamine neurotransmission in brain reward pathways has been frequently acknowledged (e.g., Wise and Bozarth, 1985; Ritz and Kuhar, 1993), the role of each of the five subtypes of dopamine receptors in the reward process remains unclear. The

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D₂, D₃, and D₄ receptors are subtypes of the general category of D₂-like receptors, whereas the D₁ and D₅ receptors comprise the category of D₁-like receptors. Although considerable amounts of research have been directed toward evaluation of the behavioral effects of drugs that act specifically on the D₁-like vs the D₂-like receptors, further distinctions have been more difficult due to the structural homology among some of the subtypes of these receptors. Of the D₂-like receptors, which are the focus of the present manuscript, the D₂ and the D₃ receptors have especially high structural homology. Although D₂ and D₃ receptor ligands with relatively high *in vitro* selectivity, such as sumanirole (compound (R)-6 in Heier et al., 1997) and pramipexole (Newman-Tancredi et al., 2002) have been identified, all available compounds have activity at both receptors and seem to show less effective selectivity *in vivo* (Collins et al., 2007). Researchers have therefore been restricted to evaluating drugs that bind to the D₃ site with somewhat higher affinity than they bind to the D₂ site, and vice versa. These are referred to as D₃-preferring and D₂-preferring compounds in the present manuscript.

Two findings in particular have increased interest in D₃ receptors: the discovery that these receptors are expressed primarily in the mesocortical limbic reward pathway (Sokoloff et al., 1990; Levasque et al., 1992), and the observation that Parkinson's patients taking D₃-preferring agonists such as pramipexole or ropinirole occasionally show compulsive behavior such as excessive gambling, shopping, or sexual behavior (Aiken, 2007). The possibility that this receptor subtype is involved in disrupted reinforcement processes such as those observed in drug addiction were raised by these findings.

D₃-preferring agonists frequently have been shown to have properties in experimental animals, including non-human primates, that are similar to those of cocaine. For example, pre-session treatment with the D₃-preferring agonists quinelorane and 7-OH-DPAT produced leftward shifts in the cocaine dose-effect curves in rhesus monkeys. In fact, following administration of these drugs, the highest rates of responding occurred when responding produced only the stimuli previously paired with cocaine (Caine et al., 2000). Additionally, some D₃-preferring agonists (NPA and quinpirole), like cocaine itself, have been shown to reinstate cocaine-extinguished behavior in squirrel monkeys. Others (PD 128,907 and 7-OH-DPAT) did not have this ability, in part because the extremely variable effects of the drugs prevented statistically significant effects (Khroyan et al., 2000). In a study in which rhesus monkeys chose between cocaine and food, substitution of saline for cocaine led to selection of the food alternative. Pre-session administration of each of the D₃-preferring agonists quinelorane, R-(+)-NPA, (+) PHNO, and PD 128,907 produced decreased selection of the food alternative, and increased selection of the saline (previously cocaine) alternative. This was similar to effects produced by pre-session administration of cocaine. For each of the D₃-preferring agonists, however, the cocaine-like effect was marked in two of the four monkeys, and did not occur in the other two monkeys (Gasior et al., 2004).

Squirrel monkeys trained to discriminate the interoceptive effects of cocaine vs saline, showed a maximum of 73% cocaine-appropriate responses following administration of PD 128,907 (Achat-Mendes et al., 2010), and (+)-PHNO, quinpirole, and quinelorane on average also produced considerable, but less than 100%, selection of the cocaine-appropriate manipulandum (Spealman et al., 1991). Interestingly, Spealman et al. (1991) indicated that one of the four monkeys tested did show greater than 90% selection of the cocaine-appropriate lever, suggesting individual differences among the monkeys in detection of the cocaine-like stimulus effects of some D₃-preferring agonists.

Other findings also indicated that D₃-preferring agonists produced complete cocaine-like discriminative stimulus effects in a subset (3 of 4) of rhesus monkeys, and served as

reinforcers in monkeys with cocaine-self-administration histories (Sinnott et al., 1999; Nader and Mach, 1996). It was clear, however, that monkeys required a cocaine self-administration history in order to show orderly self-administration of either quinpirole (Sinnott et al., 1999) or 7-OH-DPAT (Nader and Mach, 1996).

A cocaine history has also been shown to be necessary for quinpirole self-administration in the rat (Collins and Woods, 2007). Remifentanyl history was also effective, although less so than a cocaine history, whereas experience with food or ketamine-maintained responding was ineffective in establishing quinpirole-maintained responding. It should be noted that the amounts of both quinpirole and 7-OH-DPAT that were self-administered in most of these studies were sufficient to produce *in vivo* effects that are mediated by both the D₂ and D₃ receptors (Collins et al., 2007).

Much less work has been published on the effects of the D₂-preferring agonist sumanirole on behavior of rhesus monkeys. Although a recent report suggests that sumanirole is capable of producing dose-dependent increases in cocaine-appropriate responses in both drug discrimination and reinstatement assays in squirrel monkeys (Achat-Mendes et al. 2010), to the best of our knowledge the ability of sumanirole to serve as a reinforcer in monkeys has not been reported. Similarly, although several D₄-selective agonists have been synthesized recently (Enguehard-Gueiffier and Gueiffier, 2006), no studies of D₄-selective agonists in monkeys have been published.

In the present study, agonists that are currently the most selective at each of the three D₂-like receptors were evaluated for reinforcing effects in rhesus monkeys with a history of cocaine self-administration (see Table 1). By comparing levels of self-administration of agonists selective for each of the D₂-like receptors under conditions that promote self-administration of D₃-preferring agonists, we sought to determine which D₂-like receptors were necessary or sufficient to support self-administration behavior. The monkeys were given access to 0.01 mg/kg/injection (mg/kg/inj) cocaine, saline or one of several D₂-like agonists during twice-daily sessions (see Table 2 for compounds, receptor binding affinities, and efficacy data). The selected D₂-preferring agonist was sumanirole (McCall et al., 2005). The D₄ agonist was ABT-724, a drug that has been found by some (e.g., Brioni et al., 2004), but not others (Collins et al., 2009; Depoortere et al., 2009), to mediate penile erection in rats. The D₃-preferring agonists were pramipexole, ropinirole, and quinpirole (Newman-Tancredi et al., 2002).

Method

Subjects

Seven male (DA, FI, LU, BO, KE, KO, and OZ) and three female (GI, TP, and MA) rhesus monkeys (*Macaca mulatta*) with varied experimental histories including drug self-administration served as subjects. At the start of the experiment, the median age of the subjects was 14 years (range 8 to 20 years) and the median weight was 9.4 kg (range 7.2 to 13.9 kg). Subjects were given fresh fruit and other edible treats each day and fed Purina® monkey chow to maintain healthy weights (determined by veterinary staff and somewhat less than *ad lib* weights). Water and environmental enrichment toys were continuously available, both in and out of session.

Apparatus

Monkeys were housed in stainless steel cages (83.3 cm high by 76.2 cm wide by 91.4 cm deep) in visual contact with other monkeys of the same species. Located on one side of the cage was an instrument panel containing two or three depressible levers (Model 121-07,

BRS-LVE) each requiring 10 to 15 g (0.10 to 0.15 N) of downward force to operate. The levers were separated by 0.3-cm thick stainless steel dividers extending 8 cm from the response panel. A stimulus light was positioned above each lever. An injection pump was located behind the cage. Experimental events were controlled by computers in an adjacent room running Med-PC IV® (Med-Associates, Georgia, VT, USA) software.

Monkeys were implanted with intravenous catheters in an internal jugular, external jugular, femoral, or brachial vein. Catheters were routed subcutaneously out the back of the monkey and through a flexible stainless steel tether held in place by a Teflon mesh jacket (Lomir, Quebec, Canada). Catheters were implanted under ketamine (10 mg/kg, intramuscular) and xylazine (2 mg/kg, intramuscular) anesthesia.

Procedure

Sessions were conducted twice daily (6:00 AM and 12:15 PM), seven days per week. Drugs were delivered according to a simple fixed-ratio (FR) 10 schedule of reinforcement with a limit of 60 injections in each session and a timeout period of 30 sec between response opportunities. The drugs were available for responding on the right lever and their availability was signaled by a red stimulus light above that lever. Responses on the other lever(s) had no scheduled consequences, but were recorded. Ten responses in the presence of the red light resulted in the activation of the injection pump, the red light was turned off, and a green light above the right lever was turned on. A volume of 1 ml of fluid was injected over 5 sec. After each injection, there was a timeout of 30 sec during which no lights were illuminated and responses had no scheduled consequences. Sessions ended after two hours or 60 injections, whichever occurred first.

Cocaine was used as the reference drug, and saline or different doses of the test compounds were substituted for cocaine on a regular basis in either the AM or PM session, no more often than once every fourth session (every other day).

Drugs

All drugs were dissolved in sterile saline and reported doses refer to the salts. Cocaine was obtained from National Institute on Drug Abuse, quinpirole was purchased from Sigma-Aldrich (St. Louis, MO), and ropinirole was purchased from Helix and Bond (Shanghai, China). Suppliers of the other drugs are indicated in the Source of Funding section.

Data Analysis

Cocaine and saline reference data were taken from sessions just preceding substitutions of each of the dopamine agonists. Data from the last three of these sessions of cocaine and saline were averaged to obtain the reference data for each test compound. "Self-administration" was operationally defined as responding at levels sufficient to obtain 40 or more injections in a single session, a value that differentiated all saline from all cocaine sessions. Averages of the three sessions of tests with each dose of each test drug are presented in the graphs and form the basis for the statistical tests. One-way repeated-measures ANOVAs and Pearson product-moment correlations were conducted with Prism 5 (GraphPad, Inc., La Jolla, CA, USA) and Wilcoxon signed rank tests were conducted in SPSS 17 (IBM Corporation, Armonk, NY, USA). Response rates were log transformed when compared statistically so they more closely approximated a normal distribution.

Results

All subjects received the maximum of 60 injections of 0.01 mg/kg/inj cocaine whenever it was available, such that the number of injections across control sessions when cocaine was

available was significantly greater than the number of injections when saline was available (top panels of figures 1, 2, 3, 4 and 5; Wilcoxon signed rank test, $z = -2.80$, $p < 0.01$). Response rates maintained by cocaine varied markedly among subjects (bottom panels of figures 1, 2, 3, 4 and 5), but were consistently and significantly higher than rates maintained by saline ($z = -2.80$, $p < 0.01$).

Substantial individual differences were seen in responding maintained by the D₃-preferring agonists quinpirole (Fig. 1), pramipexole (Fig. 2), and ropinirole (Fig. 3). For each drug, about half the subjects self-administered at least one dose at greater rates than saline (Table 3), but none of the effects on injections or response rate were statistically significant at a group level. Half of the ten tested monkeys self-administered quinpirole above saline levels (closed symbols, Fig. 1), and the remaining subjects did not self-administer quinpirole (open symbols, Fig. 1). Similarly with pramipexole, the same two of the seven monkeys that showed a clear pattern of quinpirole self-administration were also responsive to the apparent reinforcing effects of pramipexole (Fig. 2). Four of the remaining five monkeys were not, while one monkey (OZ) appeared to self-administer pramipexole but not quinpirole. Only three monkeys were evaluated using ropinirole. Two of these animals self-administered ropinirole at one or more doses (Fig. 3). These monkeys had also self-administered quinpirole and pramipexole. The third monkey, which had not self-administered quinpirole or pramipexole, also did not demonstrate an apparent reinforcing effect of ropinirole (Fig. 3).

Sumanitrole was not self-administered on an FR 10 schedule above saline levels at any dose tested by any of the five subjects exposed to this D₂-preferring agonist (Fig. 4, Table 3). Two of these monkeys had self-administered each of the D₃-preferring agonists. No main effect of sumanitrole dose was observed on either response rates or injections. One of five monkeys self-administered ABT-724 (Fig. 5, Table 3). Rates and intake were well below that shown by cocaine for this monkey, but above that shown for saline. As with the other drugs, there was no main effect of ABT-724 dose on injections or response rates.

There was a significant correlation between the maximum rate obtained at any dose of quinpirole and the rate of responding for cocaine ($r = .71$, $p < 0.025$). While the correlation between maximum pramipexole rate and cocaine rate was moderately high ($r = .48$, n.s.), this, along with the analogous correlations with the other drugs, was not statistically significant.

Discussion

In the current set of experiments, none of the D₂-like agonists, acting with some selectivity on the D₂, D₃, or D₄ receptors, maintained rates of self-administration behavior that approximated those maintained by cocaine. The only D₂-like agonists that appeared to be self-administered above saline levels in some subjects were those that bind preferentially to D₃ receptors, although it is important to acknowledge that the amounts of D₃-preferring agonists that were taken by these monkeys were likely sufficient to bind to the D₂ as well as to the D₃ receptor. It appears that D₃ agonism is necessary for D₂/D₃ agonists to support self-administration, but the current results cannot distinguish whether D₃ agonist activity in the absence of D₂ agonist activity is sufficient. Nevertheless, these data indicate that of the three D₂-like receptors, only D₃-preferring agonists support appreciable self-administration, and that cocaine appears to engender much more robust responding by preventing uptake of monoamines than do agonists that preferentially activate any of the D₂-like dopamine receptors.

Interestingly, even though the D₃-preferring agonists were self-administered more readily than were the D₂-preferring and the D₄ receptor agonists, they did not serve an apparent reinforcing function in all animals. Only five of ten monkeys showed levels of quinpirole self-administration that were above those produced by saline. Furthermore, monkeys that showed substantial levels of quinpirole intake also showed greater levels of intake of ropinirole and pramipexole than monkeys that showed low levels of quinpirole intake.

The finding that quinpirole, pramipexole, and ropinirole maintained substantial intake in some of the monkeys might be offered as evidence that there are individual differences in sensitivity to the reinforcing effects of D₃-preferring agonists. There are, however, alternative explanations of these data. All of these animals had ongoing experience with cocaine self-administration, but the duration or amount of previous access did not appear to correlate with propensity to self-administer the D₃ compounds (see Table 1). As shown by Nader and Mach (1996) in rhesus monkeys and by Collins and Woods (2007) in rats, a history of cocaine self-administration is required for D₃-preferring agonists to demonstrate apparent reinforcing effectiveness. Further studies in rats indicated that non-contingent administration of quinpirole or pramipexole produced increases in responding if, and only if, the response produced a stimulus previously paired with contingent cocaine administration (Collins and Woods, 2009; Collins et al., 2012). It is therefore possible that quinpirole, ropinirole, and pramipexole were not serving as primary reinforcers in any monkeys in the current study, but rather were serving to enhance motivational effects of the stimulus conditions that were associated with cocaine administration. If this was the case, this enhancement was sufficient to produce relatively high rates of responding in half of the monkeys. While this explanation cannot be confirmed solely on the basis of the current experiment, it is supported by findings that D₃-preferring agonists increase responding followed by cocaine-paired stimuli (Caine et al., 2000; Khroyan et al., 2000).

Rather than increasing stimulus control exerted by cocaine-paired stimuli, an alternative explanation that should be considered is that D₃-preferring agonists actually decrease stimulus control in general. This could account for the variability in reporting a cocaine-like discriminative stimulus effect following administration of D₃-preferring agonists (Achat-Mendes et al., 2010; Spealman et al. 1991), and for the increase in timeout responding and the increase in switching between cocaine-associated and food-associated manipulanda (Gasior et al., 2004).

The potential relevance of D₃ receptor activation in mediating behavioral aspects of conditional reinforcing stimuli has been suggested earlier (Beninger and Banasikowski, 2008; LeFoll et al., 2005; Pilla et al., 1999). Much of this research focused on the demonstration that D₃-selective, low efficacy agonists and antagonists are capable of reducing behavior maintained by cues associated with cocaine. In addition to these effects, work from our laboratory has demonstrated that D₃-preferring agonists (e.g., quinpirole, pramipexole, ropinirole) are not only capable of maintaining responding in rats with a history of cocaine self-administration (Collins and Woods, 2007), but also inducing dose-dependent increases in responding when these responses resulted in the presentation of cocaine-associated stimuli, effects that are absent when stimuli presentations are omitted (Collins and Woods, 2009; Collins et al., 2012). It is also known that individual differences exist in approach behavior to stimuli associated with food reinforcers in rats (Flagel et al., 2011). Some rats are prone to approaching the food reinforcers themselves while some rats approach the stimuli associated with these reinforcers. If similar individual differences exist in approach behavior in rhesus monkeys, this could explain why D₃-preferring agonists increase responding maintained by cocaine-paired stimuli in only some subjects. Perhaps it is only those subjects that preferentially attend to the stimuli associated with cocaine that

also show increases in apparent reinforcing effectiveness of D₃-preferring agonists. This notion is currently untested, but should be the focus of future experiments.

The finding that direct D₂ receptor agonism with sumanirole does not appear to be sufficient to maintain self-administration behavior in cocaine-experienced monkeys is puzzling, especially since sumanirole was recently found to have discriminative stimulus effects that were much like those of cocaine in squirrel monkeys (Achat-Mendes et al., 2010). Other investigators have found that D₂-like agonists do serve as reinforcers in rhesus monkeys (Ranaldi, et al., 2001; Woolverton, 1986; Woolverton, et al., 1984; Woolverton and Ranaldi, 2002), but the contribution of D₃ receptors to these limited reinforcing effects is not known. The lack of reinforcing effects of sumanirole could be attributed to pharmacokinetic aspects, such as slow onset of action. However, given its fairly rapid onset of hypothermic effect in rats (Collins et al., 2007), this is unlikely. More likely is the possibility that insufficiently large doses of sumanirole were tested in this study. It may be that apparent reinforcing effects require activation of both D₃ and D₂ receptors, and larger doses of this D₂-preferring agonist are necessary to produce activity at D₃ sites.

The D₄ agonist ABT-724 was self-administered by just one of five monkeys tested (LU), and at rates only slightly more than saline in that one monkey. No previous studies have evaluated selective D₄ compounds for reinforcing properties, and relatively little research has examined how D₄ receptors are involved in the reinforcing properties of cocaine and other stimulants. The current result showing little reinforcing effect of ABT-724 is consistent with studies in mice lacking the D₄ receptor that show no alteration in responding for food or cocaine (Thanos et al., 2010b) and no systematic change in the ability of methylphenidate, amphetamine, and cocaine to elicit a conditioned place preference (Thanos et al., 2010a). ABT-724 has lower intrinsic efficacy at the D₄ receptor than dopamine (Brioni et al., 2004), however, leaving open the possibilities that a lack of reinforcing effectiveness may be due to the partial agonist profile of this drug and that a full agonist might maintain more responding. A slow onset of action might also mitigate against an observation of self-administration of ABT-724, but this drug does not appear to have particularly slow absorption (Maron-Lewicka et al., 2008). From these data, it does not appear that D₄ receptor activation alone is sufficient to maintain robust self-administration behavior.

The data presented here could be taken as evidence that action at any one of the D₂-like receptor subtypes is not responsible for the reinforcing effects of cocaine. This is in contradiction to studies that show that D₂ antagonists are much more able than D₃ antagonists to suppress cocaine self-administration in squirrel monkeys (Achat-Mendes et al., 2010). Although this could be a species distinction, clearly further work with more selective agonists and antagonists is necessary and may help clarify this issue, which appears to be quite complex.

These data, along with published information, have several implications with respect to the contribution of dopamine D₂-like receptors in the underlying mechanism of cocaine's reinforcing effects, assuming these are mediated by dopamine reuptake blockade. It appears, using the most selective D₂, D₃, and D₄ receptor agonists available, that D₃/D₂ activation, possibly in concert, is required to maintain responding. It is important to note, however, that these effects are not observed in all animals, which may represent individual differences among the monkeys with regard to the motivational properties of the stimuli that were paired with cocaine rather than the direct reinforcing effect of the drugs themselves.

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References

- Achat-Mendes C, Grundt P, Cao J, Platt DM, Newman AH, Spealman RD. Dopamine D₃ and D₂ receptor mechanism in the abuse-related behavioral effects of cocaine: Studies with preferential antagonists in squirrel monkeys. *J Pharmacol Exp Ther*. 2010; 334:556–565. [PubMed: 20494958]
- Aiken CB. Pramipexole in psychiatry: A systematic review of the literature. *J Clin Psychiatry*. 2007; 68:1230–1236. [PubMed: 17854248]
- Beninger RJ, Banasikowski TJ. Dopaminergic mechanism of reward-related incentive learning: focus on the dopamine D₃ receptor. *Neurotox Res*. 2008; 14:57–70. [PubMed: 18790725]
- Brioni JD, Moreland RB, Cowart M, Hsieh GC, Stewart AO, Hedlund P, et al. Activation of dopamine D₄ receptors by ABT-724 induces penile erection in rats. *Proc Natl Acad Sci U S A*. 2004; 101:6758–6763. [PubMed: 15087502]
- Caine SB, Negus SS, Mello NK. Effects of dopamine D1-like and D2-like agonists on cocaine self-administration in rhesus monkeys: rapid assessment of cocaine dose-effect functions. *Psychopharmacology*. 2000; 148:41–51. [PubMed: 10663416]
- Collins GT, Woods JH. Drug and reinforcement history as determinants of the response-rate maintaining effects of quinpirole in the rat. *J Pharmacol Exp Ther*. 2007; 323:599–605. [PubMed: 17675585]
- Collins GT, Woods JH. Influence of conditioned reinforcement on the response-maintaining effects of quinpirole in rats. *Behav Pharmacol*. 2009; 20:492–504. [PubMed: 19696656]
- Collins GT, Newman AH, Grundt P, Rice KC, Husbands SM, Chauvignac C, et al. Yawning and hypothermia in rats: effects of dopamine D₃ and D₂ agonists and antagonists. *Psychopharmacology*. 2007; 193:159–170. [PubMed: 17393143]
- Collins GT, Truccone A, Haji-Abdi F, Newman AH, Grundt P, Rice KC, et al. Proerectile effects of dopamine D2-like agonists are mediated by the D₃ receptor in rats and mice. *J Pharmacol Exp Ther*. 2009; 329:210–227. [PubMed: 19136638]
- Collins GT, Cunningham AR, Chen J, Wang S, Newman AH, Woods JH. Effects of pramipexole on the reinforcing effectiveness of stimuli that were previously paired with cocaine reinforcement in rats. *Psychopharmacology*. 2012; 219:123–135. [PubMed: 21701814]
- Depoortere R, Bardin L, Rodrigues M, Abrial E, Aliaga M, Newman-Tancredi A. Penile erection and yawning induced by dopamine D2-like receptor agonists in rats: influence of strain and contribution of dopamine D₂, but not D₃ and D₄ receptors. *Behav Pharmacol*. 2009; 20:303–311. [PubMed: 19584712]
- Enguehard-Gueiffier C, Gueiffier A. Recent progress in medicinal chemistry of D₄ agonists. *Cur Medicinal Chem*. 2006; 13:2981–2993.
- Flagel SB, Clark JJ, Robinson TE, Mayo L, Czuj A, Willuhn I, et al. A selective role for dopamine in stimulus-reward learning. *Nature*. 2011; 469:53–57. [PubMed: 21150898]
- Gasior M, Paronis CA, Bergman J. Modification by dopaminergic drugs of choice behavior under concurrent schedules of intravenous saline and food delivery in monkeys. *J Pharmacol Exp Ther*. 2004; 308:249–259. [PubMed: 14563783]
- Heier RF, Dolak LA, Duncan JN, Hyslop DK, Lipton MF, Martin IJ, Mauragis MA, Piercey MF, Nichols NF, Schreur PJ, Smith MW, Moon MW. Synthesis and biological activities of (R)-5,6-dihydro-N,N-dimethyl-4H-imidazo[4,5,1-ij]quinolin-5-amine and its metabolites. *J Med Chem*. 1997; 40:639–646. [PubMed: 9057850]

- Khroyan TV, Barrett-Larimore RL, Rowlett JK, Spealman RD. Dopamine D1- and D2-like receptor mechanisms in relapse to cocaine-seeking behavior: effects of selective antagonists and agonists. *J Pharmacol Exp Ther.* 2000; 294:680–687. [PubMed: 10900248]
- Lévesque D, Diaz J, Pilon C, Martres MP, Giros B, Souil E, et al. Identification, characterization, and localization of the dopamine D₃ receptor in rat brain using 7-[3H]hydroxy-N,N-di-n-propyl-2-aminotetralin. *Proc Natl Acad Sci U S A.* 1992; 89:8155–8159. [PubMed: 1518841]
- LeFoll B, Goldberg SR, Sokoloff P. The dopamine D₃ receptor and drug dependence: effects on reward or beyond? *Neuropharmacology.* 2005; 49:525–541. [PubMed: 15963538]
- Marona-Lewicka D, Chemel BR, Nichols DE. Dopamine D₄ receptor involvement in the discriminative stimulus effects in rats of LSD, but not the phenethylamine hallucinogen DOI. *Psychopharmacology.* 2008; 203:265–277. [PubMed: 18604600]
- McCall RB, Lookingland KJ, Bedard PJ, Huff RM. Sumanitrole, a highly dopamine D₂-selective receptor agonist: in vitro and in vivo pharmacological characterization and efficacy in animal models of Parkinson's disease. *J Pharmacol Exp Ther.* 2005; 314:1248–1256. [PubMed: 15980060]
- Nader MA, Mach RH. Self-administration of the dopamine D₃ agonist 7-OH-DPAT in rhesus monkeys is modified by prior cocaine exposure. *Psychopharmacology.* 1996; 125:13–22. [PubMed: 8724444]
- Newman-Tancredi A, Cussac D, Audinot V, Nicolas JP, DeCeuninck F, Boutin JA, Millan MJ. Differential actions of antiparkinson agents at multiple classes of monoaminergic receptor. II. Agonist and antagonist properties at subtypes of dopamine D(2)-like receptor and alpha(1)/alpha(2)-adrenoceptor. *J Pharmacol Exp Ther.* 2002; 303:805–814. [PubMed: 12388667]
- Panlilio LV, Weiss SJ, Schindler CW. Motivational effects of compounding discriminative stimuli associated with food and cocaine. *Psychopharmacology.* 1998; 136:70–74. [PubMed: 9537684]
- Pilla M, Perachon S, Sautel F, Garrido F, Mann A, Wermuth CG, et al. Selective inhibition of cocaine-seeking behavior by a partial dopamine D₃ receptor agonist. *Nature.* 1999; 400:371–375. [PubMed: 10432116]
- Ranaldi R, Wang Z, Woolverton WL. Reinforcing effects of D₂ dopamine receptor agonists and partial agonists in rhesus monkeys. *Drug Alc Depend.* 2001; 64:209–217.
- Ritz MC, Kuhar MJ. Psychostimulant drugs and a dopamine hypothesis regarding addiction: update on recent research. *Biochem Soc Symp.* 1993; 59:51–64. [PubMed: 7910741]
- Sinnott RS, Mach RH, Nader MA. Dopamine D₂/D₃ receptors modulate cocaine's reinforcing and discriminative stimulus effects in rhesus monkeys. *Drug Alc Depend.* 1999; 54:97–110.
- Sokoloff P, Giros B, Martres MP, Bouthenet ML, Schwartz JC. Molecular cloning and characterization of a novel dopamine receptor (D₃) as a target for neuroleptics. *Nature.* 1990; 347:146–151. [PubMed: 1975644]
- Spealman RD, Bergman J, Madras BK, Melia KF. Discriminative stimulus effects of cocaine in squirrel monkeys: involvement of dopamine receptor subtypes. *J Pharmacol Exp Ther.* 1991; 258:945–953. [PubMed: 1679852]
- Thanos PK, Bermeo C, Rubinstein M, Suchland KL, Wang GJ, Grandy DK, Volkow ND. Conditioned place preference and locomotor activity in response to methylphenidate, amphetamine, and cocaine in mice lacking dopamine D₄ receptors. *J Psychopharmacol.* 2010a; 24:897–904. [PubMed: 19282420]
- Thanos PK, Habibi R, Michaelides M, Patel UB, Suchland K, Anderson BJ, et al. Dopamine D₄ receptor (D₄R) deletion in mice does not affect operant responding for food or cocaine. *Beh Brain Res.* 2010b; 207:508–511.
- Wise RA, Bozarth MA. Brain mechanisms of drug reward and euphoria. *Psychiatr Med.* 1985; 3:445–460. [PubMed: 2893431]
- Woolverton WL. Effects of a D₁ and D₂ dopamine antagonist on the self-administration of cocaine and pibedil by rhesus monkeys. *Pharmacol Biochem Behav.* 1986; 24:531–535. [PubMed: 2871561]
- Woolverton WL, Goldberg LI, Ginos JZ. Intravenous self-administration of dopamine receptor agonists by rhesus monkeys. *J Pharmacol Exp Ther.* 1984; 230:678–683. [PubMed: 6332190]

Woolverton WL, Ranaldi R. Comparison of the reinforcing efficacy of two dopamine D2-like receptor agonists in rhesus monkeys using a progressive-ratio schedule of reinforcement. *Pharmacol Biochem Behav.* 2002; 72:803–809. [PubMed: 12062569]

Figure 1. Self-administered injections (top) and response rates (bottom) maintained by saline, 0.01 mg/kg/inj cocaine, and quinpirole on a fixed ratio 10 schedule of reinforcement. Symbols represent the individual subject mean data from three or more single-session substitutions on a 0.01 mg/kg/inj cocaine baseline.

Figure 2. Self-administered injections (top) and response rates (bottom) maintained by saline, 0.01 mg/kg/inj cocaine, and pramipexole on a fixed ratio 10 schedule of reinforcement. Symbols represent the individual subject mean data from three or more single-session substitutions on a 0.01 mg/kg/inj cocaine baseline.

Figure 3. Self-administered injections (top) and response rates (bottom) maintained by saline, 0.01 mg/kg/inj cocaine, and ropinirole on a fixed ratio 10 schedule of reinforcement. Symbols represent the individual subject mean data from three or more single-session substitutions on a 0.01 mg/kg/inj cocaine baseline.

Figure 4. Self-administered injections (top) and response rates (bottom) maintained by saline, 0.01 mg/kg/inj cocaine, and sumanirole on a fixed ratio 10 schedule of reinforcement. Symbols represent the individual subject mean data from three or more single-session substitutions on a 0.01 mg/kg/inj cocaine baseline.

Figure 5. Self-administered injections (top) and response rates (bottom) maintained by saline, 0.01 mg/kg/inj cocaine, and ABT-724 on a fixed ratio 10 schedule of reinforcement. Symbols represent the individual subject mean data from three or more single-session substitutions on a 0.01 mg/kg/inj cocaine baseline.

Table 1

Histories of cocaine intake across subjects.

	Days of cocaine access	Average daily dose (mg/kg)	Total cocaine (mg/kg)
DA	723	0.55	395
FI	583 ^a	1.16	591
LU	716	0.35	254
GI	37	1.40	52
TP	56	1.37	77
OZ	71	1.32	94
KO	415	0.55	226
BO	131 ^a	1.17	94
KE	253	0.94	238
MA	56	1.00	56

^aIn some cases, detailed cocaine intake data were not retrievable for a portion of days when cocaine was available. Those cases are not included in the total cocaine and average daily dose calculations, but are included in the days of access figures.

Table 2

Binding affinities and efficacies relative to dopamine for each of the compounds tested.

	Binding Affinity (nM)			Efficacy	Reference
	D₂	D₃	D₄		
Quinpirole	692	6.8	62	67% (D ₃)	Newman-Tancredi et al., 2002
Pramipexole	380	2.2	129	70% (D ₃)	Newman-Tancredi et al., 2002
Ropinirole	525	28	2884	59% (D ₃)	Newman-Tancredi et al., 2002
Sumanitrole	9.0	1940	>2190	~100% (D ₂) ^a	McCall et al., 2005
ABT-724	>10,000	not tested	56	61% (D ₄)	Brioni et al., 2004

Note: When affinities for multiple variants of one receptor were reported, the mean value appears on this table.

^aMcCall et al. (2005) states that sumanitrole is as efficacious as dopamine without providing precise figures.

Table 3

Summary of compounds that were (+) or were not (–) self-administered at any dose by each subject.

	Quinpirole	Pramipexole	Ropinirole	Sumanirole	ABT-724
DA	+	+	+	–	–
FI	+				
LU	+	+	+	–	+
GI	+				
TP	+				
OZ	–	+			
KO	–	–			
BO	–	–		–	–
KE	–	–		–	–
MA	–	–	–	–	–