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Feeding condition and the relative contribution of different dopamine receptor subtypes to the discriminative stimulus effects of cocaine in rats

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Abstract

Rationale—The contribution of dopamine receptor subtypes in mediating the discriminative stimulus effects of cocaine is not fully established. Many drug discrimination studies use food to maintain responding, necessitating food restriction, which can alter drug effects.

Objective—This study established stimulus control with cocaine (10 mg/kg) in free-feeding and food-restricted rats responding under a schedule of stimulus shock termination (SST) and in food-restricted rats responding under a schedule of food presentation to examine whether feeding condition or the reinforcer used to maintain responding impacts the effects of cocaine.

Method—Dopamine receptor agonists and antagonists were examined for their ability to mimic or attenuate, respectively, the effects of cocaine.

Result—Apomorphine, quinpirole, and lisuride occasioned >90% responding on the cocaine-associated lever in free-feeding rats responding under a schedule of SST; apomorphine, but not quinpirole or lisuride, occasioned >90% responding on the cocaine lever in food-restricted rats responding under a schedule of SST. In food-restricted rats responding for food these drugs occasioned little cocaine lever responding and were comparatively more potent in decreasing responding. In free-feeding rats, the effects of cocaine were attenuated by the D2/D3 receptor antagonist raclopride and the D3 receptor-selective antagonist PG01037. In food-restricted rats, raclopride and the D2 receptor-selective antagonist L-741,626 attenuated the effects of cocaine. Raclopride antagonized quinpirole in all groups while PG01037 antagonized quinpirole only in free-feeding rats.

Conclusion—These results demonstrate significant differences in the discriminative stimulus of cocaine that are due to feeding conditions and not to the use of different reinforcers across procedures.

Introduction

The abuse of cocaine is a worldwide health concern and affects more than 4.8 million people in the U.S. (National Survey on Drug Use and Health 2009). Cocaine binds to dopamine transporters and blocks the reuptake of dopamine (Heikkila et al. 1975; Koe 1976; Reith et al. 1986), thereby enhancing the concentration of extracellular dopamine (Kalivas and Duffy

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1990; Weiss et al. 1992) that binds to dopamine receptors. Drugs that inhibit the uptake or potentiate the release of dopamine, or drugs that bind to and have efficacy at dopamine receptors, can mimic many of the effects (e.g. discriminative stimulus) of cocaine. Moreover, dopamine receptor antagonists often attenuate the effects of cocaine and related drugs (Acri et al. 1995; Caine and Koob 1993; Spealman 1996; Witkin et al. 1991). It is clear that dopamine receptors mediate many of the effects of cocaine; the role of particular dopamine receptor subtypes is less clear, although D2 and D3 receptors are thought to play a role (Achat-Mendes et al. 2010; Acri et al. 1995; Caine and Koob 1993; Sinnott et al. 1999; Spealman 1996).

Drug discrimination procedures have proven valuable for elucidating the role of dopamine receptor subtypes mediating the discriminative stimulus effects of cocaine. For example, nonselective D2/D3 dopamine receptor agonists (e.g. quinpirole) often share discriminative stimulus effects with cocaine (Callahan and Cunningham 1993; Kantak et al. 1995; Witkin et al. 1991) and nonselective D2/D3 receptor antagonists often attenuate the discriminative stimulus effects of cocaine (Callahan et al. 1991; Costanza et al. 2001). However, the ability of dopamine receptor agonists to mimic and antagonists to attenuate the effects of cocaine varies among studies (Meert et al. 1996; Witkin et al. 1991). For example, quinpirole can engender as little as 40% and as much as 90% cocaine-lever responding (Barrett and Appel 1989; Callahan et al. 1991; Witkin et al. 1991) in rats trained to discriminate cocaine from saline. The reasons for such disparity are unclear and might include experimental variables such as drug history (Caine et al. 2000); however, feeding condition can also affect dopamine systems and sensitivity to drugs acting on those systems (Baladi et al. 2011; Collins et al. 2008; Sevak et al. 2008).

Several studies have examined the impact of feeding condition on sensitivity (i.e. potency) to drugs acting at dopamine receptors (Baladi et al. 2011; Collins et al. 2008; Sevak et al. 2008), with one study demonstrating that different dopamine receptors mediate the discriminative stimulus effects of quinpirole depending on feeding condition (Baladi et al. 2010). Specifically, a number of studies have reported that the discriminative stimulus effects of nonselective D2/D3 dopamine receptor agonists, like quinpirole, are mediated by dopamine D2 receptors (Appel et al. 1988; Baker et al. 1999; Bristow et al. 1998; Christian et al. 2001; Katz and Alling 2000; Kleven and Koek 1997; Koffarnus et al. 2009; Millan et al. 2000, 2007). Those studies used food to maintain responding, thereby necessitating food restriction throughout the experiment. In contrast, discriminative stimulus effects of quinpirole in non-food restricted rats [responding under a schedule of stimulus shock termination (SST)], are mediated by D3, and not D2, receptors (Baladi et al. 2010). However, it is unclear whether feeding condition similarly impacts the relative contribution of dopamine receptor subtypes in the discriminative stimulus effects of indirect-acting dopamine receptor agonists (e.g. cocaine).

One aim of this study was to examine the discriminative stimulus effects of cocaine in free-feeding and food-restricted rats responding under the same schedule of reinforcement (SST). Because it is possible that differences in discriminative stimulus effects between free-feeding and food-restricted rats are influenced by the type of reinforcer that is used to maintain responding, the effects of cocaine were also evaluated in food-restricted rats responding under a schedule of food presentation. Direct- and indirect-acting dopamine receptor agonists were studied for their ability to mimic the effects of cocaine and dopamine receptor antagonists were studied for their ability to attenuate the effects of cocaine. Because quinpirole occasioned responding on the cocaine lever in some rats, selected doses of antagonists, based on their ability to attenuate either D3- or D2-receptor mediated effects in rats (Baladi et al. 2010; Collins et al. 2005, 2007), were examined for their ability to attenuate the cocaine-like discriminative stimulus effects of quinpirole. In light of results

from previous studies with direct-acting dopamine receptor agonists (e.g. quinpirole), it was expected that D3 receptors would play a more prominent role in mediating the effects of cocaine in free-feeding rats, as compared with food-restricted rats, and that the type of reinforcer used to maintain responding would not impact the role of different receptor subtypes.

Methods

Subjects

Eighteen male Sprague-Dawley rats (Harlan, Indianapolis, IN), weighing 250 to 300 g upon arrival, were housed individually in an environmentally controlled room ($24 \pm 1^\circ\text{C}$, $50 \pm 10\%$ relative humidity) under a 12-h light/dark cycle. Six rats had free access (mean body weight at end of study was 450 g) and 12 rats had restricted (body weight maintained at 320 g) access to standard laboratory chow (Harlan Teklad 7912). All rats had free access to water in the home cage. Rats were maintained and experiments were conducted in accordance with the Institutional Animal Care and Use Committee, the University of Texas Health Science Center at San Antonio, and with the *Guide for Care and Use of Laboratory Animals* (Institute of Laboratory Animal Resources, 1996).

Apparatus

Sessions were conducted in operant conditioning chambers located in sound-attenuating, ventilated enclosures and equipped with two levers and associated stimulus lights (models ENV-018ME, ENV-008CT, and ENV-022M; Med Associates Inc., St. Albans, VT). In experiments where rats responded under a schedule of SST, one side of the chamber was a stainless steel response panel equipped with two metal levers and stimulus lights located 11.5 cm apart and separated by a clear Plexiglas partition ($1.4 \times 5.2 \times 20.4$ cm high) that extended from the floor to the ceiling of the chamber. In all chambers, the grid floor comprised 19 stainless steel rods, 4.8 mm in diameter, spaced 1.6 cm apart, and oriented parallel to the response panel. A constant current generator (model ENV-414; Med Associates, Inc.) delivered a scrambled electric current to the grid floor of the chamber. In experiments where rats responded under a schedule of food presentation, the chambers were equipped with a food hopper. Data were collected using MED-PC IV software (Med Associates, Inc.) and a PC interface.

Single-Cycle Drug Discrimination Procedure

All 18 rats were trained to discriminate 10 mg/kg cocaine (intraperitoneal) from vehicle (i.e. saline). Six free-feeding (free-feeding/SST) and 6 food-restricted (food-restricted/SST) rats responded under a schedule of SST and 6 food-restricted rats responded under a schedule of food presentation (food-restricted/food). Discriminative control was first established with an acute-dosing, single-cycle procedure. Daily sessions began with a 10-min timeout period, during which stimulus lights were not illuminated and responding had no programmed consequence. The timeout period was followed by 21 trials during which illumination of a house light signaled the delivery of a brief (250 ms) shock stimulus (1.5 mA) every 10 s (i.e. 12 rats responding under a schedule of SST) or the availability of a food pellet (i.e. 6 rats responding under the schedule of food presentation). A response on the injection-appropriate (correct) lever or the passage of 50 s ended the trial (i.e. postponed shock or delivered a food pellet, turned off the house light, and initiated a 50-s timeout). Vehicle or 10 mg/kg of cocaine was administered immediately before the session. Stimulus control was considered adequate for testing when the following criteria were satisfied for four consecutive or five of six sessions: 1) the first response of the first trial was made on the correct lever; and 2) at least 80% of the trials were completed by a response on the correct lever. Test sessions were identical to training sessions except that a response on either lever was reinforced (i.e.

postponed shock or delivered food), ending the trial, and different doses of cocaine were administered before the session.

Multiple-Cycle Drug Discrimination Procedure

After a cocaine dose-response curve was determined under the acute-dosing, single-cycle procedure, the experimental conditions were changed to a cumulative-dosing, multiple-cycle procedure consisting of one to four 20-min cycles. Each cycle consisted of 10 trials and began with a 10-min timeout period, during which stimulus lights were not illuminated and responding had no programmed consequence. The timeout period was followed by illumination of the house light signaling scheduled delivery of a brief electric stimulus every 10 s (12 rats) or the availability of a food pellet (6 rats). A response on the injection-appropriate (correct) lever or the passage of 30 s ended the trial (i.e. postponed shock or delivered a food pellet, turned off the house light, and initiated a 30-s timeout). If in any cycle fewer than five trials were completed by a response on the correct lever, the session ended. For vehicle training sessions, animals received an intraperitoneal injection of vehicle or a “sham” injection (i.e. no injection) before each of 1–4 cycles; only a response on the vehicle-associated lever was reinforced. For drug training sessions, animals received an intraperitoneal injection of 10 mg/kg cocaine before one cycle followed by a single “sham” injection before the next cycle; for both cycles, only a response on the drug-associated lever was reinforced. The cycle when cocaine was administered was preceded by 0–2 vehicle or “sham” injection cycles and for these cycles, only a response on the vehicle-associated lever was reinforced. Testing resumed under the multiple-cycle procedure after rats satisfied the following criteria for four consecutive or five of six sessions: 1) the first response of all completed cycles was on the correct lever; and 2) at least 80% of the trials were completed by a response on the correct lever. Thereafter, tests were conducted whenever animals satisfied these same criteria for two consecutive sessions. Multiple-cycle test sessions were identical to training sessions except that a response on either lever was reinforced and either vehicle or increasing doses of drug was administered across cycles. For substitution studies, vehicle was administered before the first cycle, followed by increasing doses of a drug before subsequent cycles, with the cumulative dose increasing by 0.5 log unit per cycle. Drugs were studied up to doses that either occasioned greater than 80% responding on the cocaine lever, markedly decreased responding (i.e. decreased the number of cycles completed by a response), or up to the largest doses that could be administered safely. For drug combination studies, a single dose of antagonist was administered subcutaneously (Baladi et al., 2010; Collins et al., 2005) 10 min before the first (saline) test cycle (i.e. 30 min before the first dose of agonist).

Data Analyses

Drug discrimination data are expressed as a percentage of the total responses made on the cocaine-associated lever, averaged across groups of 6 rats each ($\pm$ SEM), and are plotted as a function of cumulative dose. Also plotted as a function of cumulative dose is the average percentage of trials completed in a cycle ($\pm$ SEM). When a rat completed fewer than five trials in a cycle, discrimination data from that rat on that test were not included in the group average, although data for the percentage of trials completed were included in the group average. The average percentage of responses on the cocaine-associated lever were plotted for a cycle (dose) only when at least half of the rats (≥ 3) completed at least five trials each in that cycle (e.g., Koek et al. 2006). For each group, differences between cocaine dose-response curves in the presence and absence of antagonist were analyzed by simultaneously fitting straight lines to the linear portion of the dose-response curves by means of GraphPad Prism (GraphPad Software Inc., San Diego, CA). The linear portion included doses that spanned the 50% level of effect and included not more than one dose with greater than 75% effect and not more than one dose with less than 25% effect. Dose-response curves that did

not span the 50% effect level were not analyzed by linear curve fitting. Differences between slopes and intercepts of the curves were analyzed with the *F* ratio test (GraphPad Prism), as detailed elsewhere (Koek et al. 2006). ED₅₀ values were calculated for individual rats using linear regression when at least three appropriate data points were available and otherwise by interpolation. The 95% confidence limits (CLs) were calculated from ED₅₀ values averaged among rats. The potency of a drug was considered to be significantly different between groups if the 95% CLs of the ED₅₀ values did not overlap. When the 95% CLs of the dose ratio did not include 1, antagonists were considered to have significantly shifted the agonist dose-response curve to the right.

Drugs

The following compounds were purchased from Sigma-Aldrich (St. Louis, MO): (–)-quinpirole [*trans*-(–)-(4*aR*)-4,4*a*,5,6,7,8,8*a*,9-octahydro-5-propyl-1*H*-pyrazolo[3,4-*g*]quinolone HCl]; *S*-(–)-raclopride (+)-tartrate salt [3,5-dichloro-*N*-(1-ethylpyrrolidin-2-ylmethyl)-2-hydroxy-6-methoxybenzamide]; and *S*-(+)-apomorphine hydrochloride. Lisuride hydrogen maleate was purchased from Alfarma Research and Development (Prague, Czech Republic), and L-741,626 was purchased from Tocris Bioscience (Ellisville, MO). Cocaine hydrochloride, morphine sulfate, and *d*-amphetamine sulfate were provided by the Research Technology Branch, National Institute of Drug Abuse (Rockville, MD). PG01037 (*N*-{4-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-*trans*-but-2-enyl}-4-pyridine-2-ylbenzamide HCl) was synthesized by Jianjing Cao (Medicinal Chemistry Section, National Institute on Drug Abuse, Baltimore, MD) using methods reported previously (Grundt et al. 2005). With the exception of L-741,626 (base), doses are expressed in terms of the salt forms shown above. L-741,626 was dissolved in a solution of 1% 1 M HCl, 5% ethanol, and 94% sterile physiological (0.9%) saline. PG01037 was dissolved in sterile 0.9% saline and 10% β-cyclodextrin. Other drugs were dissolved in 0.9% saline. L-741,626, PG01037, and raclopride were administered subcutaneously, typically in a volume of 1 ml/kg; other drugs were administered intraperitoneally in a volume of 1 ml/kg.

Results

Free-feeding/SST rats (*n*=6) and food-restricted/SST rats (*n*=6) satisfied the testing criteria under the single-cycle procedure after an average of 42 (range 27–50) and 32 (range 17–63) training sessions, respectively. Food-restricted/food rats satisfied the testing criteria after an average of 38 (range 21–58) training sessions. In all groups, administration of saline or the smallest dose (1.0 mg/kg) of cocaine occasioned responding predominantly on the saline-associated lever and administration of the training dose of cocaine (10.0 mg/kg) occasioned responding predominantly on the cocaine-associated lever; an intermediate dose of cocaine (3.2 mg/kg) occasioned partial responding on the cocaine-associated lever (data not shown).

Experimental conditions were then changed to a multiple-cycle procedure; free-feeding/SST rats and food-restricted/SST rats satisfied the testing criteria again after an average of 8 (range 4–14) and 12 (range 4–29) training sessions, respectively; food-restricted/food rats satisfied the testing criteria again after an average of 10 (range 6–13) training sessions. For all three groups of rats, cocaine dose-response curves determined under the multiple-cycle, cumulative-dosing procedure (Fig 1) were similar to those determined under the single-cycle, acute-dosing procedures (data not shown). For free-feeding/SST rats ED₅₀ values were 2.26 (95% CL = 1.27–4.02) and 2.51 mg/kg (1.12–5.61) for the single- and multiple-cycle procedures, respectively. For food-restricted/SST rats ED₅₀ values were 3.60 (2.03–6.39) and 4.90 mg/kg (3.59–6.68) for the single- and multiple-cycle procedures, respectively. And for food-restricted/food rats ED₅₀ values were 3.38 (1.83–6.22) and 3.61 mg/kg (1.68–7.75) for the single- and multiple-cycle procedures, respectively. Thus,

regardless of the type of reinforcer used to maintain responding or the feeding condition (food restricted or free feeding), cocaine occasioned responding on the drug-associated lever at similar doses (Fig 1). Amphetamine also increased responding on the cocaine-associated lever with the largest dose (1.0 mg/kg) occasioning more than 80% drug-lever responding in all groups (free-feeding/SST ED_{50} = 0.48 mg/kg [0.27–0.85]; food-restricted/SST ED_{50} = 0.58 mg/kg [0.50–0.66]; and food-restricted/food ED_{50} = 0.43 mg/kg [0.25–0.76]; Fig 1, upper panel B). Cocaine and amphetamine did not affect the percentage of trials completed in any group (Fig. 1, lower panels A and B).

In contrast, the nonselective D2/D3 receptor agonist apomorphine was slightly more potent to occasion responding on the cocaine-associated lever in free-feeding/SST rats (ED_{50} = 0.28 mg/kg [0.13–0.62]) as compared with food-restricted/SST rats (ED_{50} = 0.70 mg/kg [0.30–1.64]; Fig 1, upper panel C). Whereas apomorphine occasioned more than 80% responding on the cocaine-associated lever in both groups of rats responding under a schedule of SST, in rats responding for food apomorphine occasioned only partial (maximum 24%) responding on the cocaine-associated lever, up to a dose (1.0 mg/kg) that markedly decreased the number of trials completed (Fig 1, lower panel C). With the exception of a modest decrease in the number of trials completed after the administration of 1.0 mg/kg of apomorphine in free-feeding rats, apomorphine did not markedly alter the percentage of trials completed in rats responding under a schedule of SST (Fig 1, lower panel C, circles and triangles).

In free-feeding/SST rats, the D3-preferring agonist quinpirole and the nonselective D2/D3 agonist lisuride increased responding on the cocaine-associated lever in a dose-related manner (Fig 1, upper panels D and E) with the largest dose of each occasioning more than 80% drug-lever responding (quinpirole ED_{50} = 0.16 [0.06–0.43]; lisuride ED_{50} = 0.15 mg/kg [0.06–0.36]). In contrast, in food-restricted/SST rats, the largest doses of quinpirole and lisuride occasioned an average of 60% and 51% drug-lever responding, respectively (Fig 1, upper panels D and E). Quinpirole and lisuride occasioned little to no drug-lever responding in food-restricted/food rats; however, larger doses could not be studied because of the behavioral suppressant effects of quinpirole and lisuride in these rats (i.e., decreased number of trials completed; Fig 1, lower panels D and E). Morphine did not occasion responding on the cocaine-associated lever in any group of rats; moreover, a dose of 10 mg/kg markedly decreased the number of trials completed in free-feeding/SST rats and in food-restricted/food rats, but not in food-restricted/SST rats (data not shown).

In all three groups of rats, the nonselective D2/D3 receptor antagonist raclopride (0.056 mg/kg) shifted the cocaine discrimination dose-response curve significantly to the right (Fig 2, left panels, compare closed circles to open squares; Table 1). In free-feeding rats, doses of 1.0 and 3.2 mg/kg of the D2 receptor selective antagonist L-741,626 did not significantly alter the discriminative stimulus effects of cocaine (Fig 3, upper middle panel); however, in food-restricted/SST rats and food-restricted/food rats, a dose of 3.2 mg/kg of L-741,626 shifted the cocaine discrimination dose-response curve significantly to the right (Fig 2, lower middle panels, compare closed circles to open squares; Table 1). In free-feeding/SST rats, the largest dose tested of the D3 receptor selective antagonist PG01037 (56 mg/kg) shifted the cocaine dose-response curve to the right; this dose of PG01037 did not significantly alter the cocaine discrimination dose-response curve in food-restricted rats (Fig 2, right panels, compare closed circles to open squares; Table 1). When administered alone, none of the antagonists occasioned responding on the cocaine-associated lever (Fig 2, data above V) or decreased the number of trials completed (data not shown).

A final experiment examined whether a dose of 0.056 mg/kg raclopride, 1.0 mg/kg L-741,626, or 56 mg/kg PG01037 attenuated the discriminative stimulus effects of

quinpirole in all ($n = 6$) free-feeding/SST rats or in the subset ($n = 3$) of food-restricted/SST rats that responded on the cocaine-associated lever after receiving quinpirole (i.e., Fig 1, panel D). In free-feeding/SST rats, the nonselective D2/D3 receptor antagonist raclopride (0.056 mg/kg) and the D3 receptor selective antagonist PG01037 (56 mg/kg), but not the D2 receptor selective antagonist L-741,626, shifted the quinpirole discrimination dose-response curves significantly to the right (Fig 3, upper panels; Table 2). However, in food-restricted/SST rats, raclopride (0.056 mg/kg), but not L-741,626 or PG01037, shifted the quinpirole discrimination dose-response curve significantly to the right (Fig 3, lower panels; Table 2). When administered alone, none of the antagonists occasioned responding on the cocaine-associated lever (Fig 2, data above V) or decreased the percentage of trials completed (data not shown).

Discussion

This study demonstrates that the relative contribution of different dopamine receptor subtypes to the discriminative stimulus effects of cocaine varies across feeding conditions and that the type of reinforcer used to maintain responding does not appear to contribute to these differences. Consistent with studies that examined the discriminative stimulus effects of direct-acting dopamine receptor agonists across different feeding conditions (Appel et al. 1988; Baker et al. 1999; Baladi et al. 2010; Bristow et al. 1998; Christian et al. 2001; Katz and Alling 2000; Kleven and Koek 1997; Koffarnus et al. 2009; Millan et al. 2000, 2007), it appears as though D3 receptors have a predominant role in mediating the discriminative stimulus effects of the indirect-acting dopamine receptor agonist cocaine in free-feeding rats whereas both D2 and D3 (and perhaps other) receptors mediate the discriminative stimulus effects of cocaine in food-restricted rats (also see Achat-Mendes et al. 2010).

The discriminative stimulus effects of the indirect-acting dopamine receptor agonists cocaine and amphetamine were not different among rats maintained under different feeding conditions. These similarities do not necessarily indicate similarities in the qualitative or quantitative features of the cocaine discriminative stimulus since the apparent potency of cocaine (i.e., position of the cocaine dose-response curve) in drug discrimination procedures is determined by the dose used for training (for review, see Comer et al. 1991) which was the same for all groups. Although cocaine and amphetamine have different mechanisms of action, both increase extracellular concentrations of dopamine that act on various receptors.

In contrast, the discriminative stimulus effects of direct-acting dopamine receptor agonists were different between free-feeding and food-restricted rats responding under a schedule of SST. For example, although apomorphine occasioned more than 90% responding on the cocaine-associated lever in both groups, it was 3-fold more potent in free-feeding/SST rats compared with food-restricted/SST rats. The direct-acting agonists quinpirole and lisuride also occasioned more than 90% responding on the cocaine-associated lever in free-feeding/SST rats. In contrast, quinpirole and lisuride occasioned maxima of 60 and 51% responding on the cocaine-associated lever, respectively, in food-restricted/SST rats. It is unlikely that the failure of quinpirole and lisuride to occasion more responding on the cocaine-associated lever was due to the ranges of doses studied because the doses of quinpirole (10 mg/kg) and lisuride (1.0 mg/kg) tested were larger than doses that decreased responding for food in other studies (0.02 mg/kg lisuride; Cunningham et al. 1987; 0.1 mg/kg quinpirole; Katz and Alling 2000). The selectivity of direct-acting agonists for dopamine receptor subtypes likely impacts their ability to mimic the effects of cocaine. Binding affinity estimates for dopamine receptor agonists vary among studies. Nevertheless, apomorphine has similar affinities for D2 ($K_i = 24$ nM) and D3 ($K_i = 20$ nM; Sokoloff et al. 1990) receptors and lower affinity for D1 receptors ($K_i = 87$ nM; Anderson et al. 1985). Quinpirole is 113-fold more selective for D3 ($K_i = 5.1$ nM) than D2 ($K_i = 576$ nM) receptors (Sokoloff et al. 1990) with negligible

affinity for D1 receptors (Mottola et al. 2002). In vivo, apomorphine is estimated to be 3-fold, and quinpirole 10-fold, more selective for D3 over D2 receptors (Collins et al. 2007). In vitro, lisuride has high affinity for D2 ($K_i = 0.95$ nM), D3 ($K_i = 1.08$ nM), and serotonin receptors (Gerlach et al. 2003; Markstein et al. 1986; Marona-Lewicka et al. 2002). Because the role of D3 receptors in mediating drug effects appears to be reduced by food restriction, the selectivity of some direct-acting dopamine receptor agonists for D3 over D2 receptors might contribute to their reduced or lack of cocaine-like discriminative stimulus effects in food-restricted rats. Consistent with the notion that food restriction increases the relative contribution of D2 receptors in the actions of drugs acting at dopamine receptors, food restriction has been shown to increase D2 receptor binding (Thanos et al. 2008) as well as coupling between D2 receptors and G proteins (Carr, 2002).

In food-restricted/food rats, direct-acting dopamine receptor agonists occasioned little responding on the cocaine lever, perhaps related to the marked effects these drugs had on the percentage of trials completed. Given the greater sensitivity of food-restricted/food rats (as compared to rats responding under a schedule of SST) to the rate-decreasing effects of direct-acting dopamine receptor agonists, it is difficult to assess possible cocaine-like discriminative stimulus effects of these agonists. It seems likely, therefore, that differences among studies (that used food to maintain responding) in the extent to which direct-acting dopamine receptor agonists share discriminative stimulus effects with cocaine are due, in part, to the relative sensitivity of subjects to the rate-decreasing effects of drugs. Responding maintained under a schedule of food presentation is more sensitive than responding maintained under a schedule of SST to the rate-decreasing effects of many (Katz and Barrett 1978; McMahon et al. 2005) but not all (McMahon and France 2002) drugs. Food-restricted/SST rats were less sensitive than free-feeding/SST rats and food-restricted/food rats to the behavioral suppressant effects of morphine. It might be that food restriction and shock intensity interact such that food restriction facilitates an insensitivity to electric shock (Griffiths 1962; Blanchard and Blanchard 1966).

Antagonism of cocaine by the nonselective antagonist raclopride, the D2-receptor selective antagonist L-741,626, and the D3-receptor selective antagonist PG01037 varied between free-feeding and food-restricted rats, supporting the view that the contribution of different dopamine receptor subtypes to the discriminative stimulus effects of dopamine receptor agonists varies across feeding conditions. In free-feeding rats raclopride (0.056 mg/kg) and PG01037 (56 mg/kg), but not L-741,626, significantly antagonized the discriminative stimulus effects of cocaine. However, in food-restricted rats, raclopride (0.032 and 0.056 mg/kg) and L-741,626 (3.2 mg/kg), but not PG01037, significantly antagonized the effects of cocaine, regardless of whether rats responded under a schedule of food presentation or SST. Raclopride has approximately equal affinity for D2 ($K_i = 1.8$ nM) and D3 ($K_i = 3.5$ nM) receptors (Sokoloff et al., 1990), L-741,626 is 15-fold more selective for D2 over D3 receptors (Grundt et al., 2007a), and PG01037 is 133-fold more selective for D3 over D2 receptors (Grundt et al., 2005, 2007b). In rats, a dose of 1.0 mg/kg L-741,626 acts selectively at D2 receptors while a larger dose of 3.2 mg/kg acts at both D2 and D3 receptors (Baladi et al. 2010). In addition, doses of 32 and 56 mg/kg PG01037 act selectively at D3 receptors (Baladi et al. 2010; Collins et al. 2005). A larger dose of raclopride (0.1 mg/kg; data not shown) was tested but had marked behavioral suppressant effects (i.e. no rat completed a trial), perhaps related to the catalepsy that occurs with this dose of raclopride (Sevak et al. 2006). Larger doses of L-741,626 were not tested due to a loss of selectivity for D2 over D3 receptors. Although L-741,626 (3.2 mg/kg) showed a trend to antagonize the effects of cocaine in free-feeding rats, the lack of significant antagonism might be due to actions of cocaine at other dopamine receptor subtypes or at non-dopamine (e.g. serotonin) receptors (Filip et al. 2006). However, the fact that PG01037 significantly antagonized the effects of cocaine in free-feeding, but not food-restricted, rats,

suggests that D3 receptors have a greater contribution to the discriminative stimulus effects of cocaine under free-feeding conditions. Furthermore, because a larger dose of L-741,626 (3.2 mg/kg), that presumably has actions at both D3 and D2 receptors, was necessary to antagonize cocaine in food-restricted rats, it is likely that D3 and D2 receptors contribute to the discriminative stimulus effects of cocaine under conditions of food restriction. These results are consistent with a role for D3 and D2 receptors in the discriminative stimulus effects of cocaine in food-restricted squirrel monkeys (Achat-Mendes et al. 2010).

Selective doses of antagonists that attenuated the effects of cocaine were examined for their ability to attenuate the effects of quinpirole. The nonselective antagonist raclopride attenuated the effects of quinpirole in free-feeding and food-restricted rats; however, the D3-selective antagonist PG01037 attenuated the effects of quinpirole in free-feeding but not food-restricted rats. These results provide further support for the view that the discriminative stimulus effects of quinpirole are mediated predominantly by D3 receptors in free-feeding rats and likely by D2 and D3 receptors in food-restricted rats.

Results from this study suggest that the discriminative stimulus effects of cocaine are not identical between free-feeding and food-restricted rats. This study focused on the contribution of dopamine D2 and D3 receptors to the discriminative stimulus effects of cocaine, as indicated by the ability of antagonists to attenuate the effects of cocaine. Consistent with studies on the discriminative stimulus effects of direct-acting dopamine receptor agonists (Baladi et al. 2010), the relative contribution of D3 receptors to the discriminative stimulus effects of cocaine appears to be greater in free-feeding as compared with food-restricted rats. Comparisons across different feeding conditions are potentially confounded by the fact that lever pressing is often maintained by different reinforcers in free-feeding and food-restricted rats. This study compared free-feeding and food-restricted rats that discriminated the same dose of cocaine while responding under the same schedule of SST. Together with data from food-restricted rats responding under a schedule of food presentation, it is clear that the contribution of different receptor subtypes to the discriminative stimulus effects of cocaine is not impacted by the type of reinforcer.

The paucity of promising candidates for treating cocaine abuse continues to stimulate research on the mechanisms mediating the behavioral effects of cocaine including the contribution of different dopamine receptor subtypes to those effects. There is an abundance of data supporting a role for D2 receptors in mediating some effects of cocaine; however, the role of D3 receptors is less clear, in part because of a lack of compounds that act selectively at D3 receptors. One major difference between D2 and D3 receptor subtypes is their brain distribution; specifically, the restricted limbic pattern of distribution of D3 receptors (Levesque et al. 1992) has prompted the suggestion that these receptors might provide a target for treating cocaine abuse without inducing extrapyramidal side effects that commonly occur with D2 receptor antagonists (Xi and Gardner 2007). Thus, understanding how the roles of these receptors change as a consequence of feeding condition could facilitate development of effective medications for cocaine abuse and other psychiatric disorders.

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Fig. 1.

Discriminative stimulus effects and the percentage of trials completed for cocaine, amphetamine, apomorphine (nonselective D2/D3 receptor agonist), quinpirole (D3-preferring agonist), and lisuride (nonselective D2/D3 receptor agonist) in free-feeding/SST rats, food-restricted/SST rats, and food-restricted/food rats. Ordinates: upper panels, mean ($\pm$ SEM) percentage of responses on the cocaine-associated lever; lower panels, mean ($\pm$ SEM) percentage of trials completed. Abscissa: dose in milligrams per kilogram of body weight; V = vehicle.

Fig. 2.

Discriminative stimulus effects of cocaine administered alone and in combination with different doses of raclopride (nonselective D2/D3 receptor antagonist; left), L-741,626 (selective D2 receptor antagonist; middle), and PG01037 (selective D3 receptor antagonist; right) in free-feeding/SST rats (upper), food-restricted/SST rats (middle), and food-restricted/food rats (lower). Dashed lines indicate that the antagonist shifted the cocaine dose-response curve significantly to the right. See Figure 1 for other details.

Fig. 3.

Discriminative stimulus effects of quinpirole administered alone and in combination with selected doses of raclopride (left), L-741,626 (middle), and PG01037 (right) in 6 free-feeding/SST rats (upper) and 3 food-restricted/SST rats (middle). Dashed lines indicate that the antagonist shifted the quinpirole dose-response curve significantly to the right. See Figure 1 for other details.

Table 1ED₅₀ values for cocaine in combination with dopamine receptor antagonists

	Potency ratio ^a (95% Confidence Interval)		
	Free-feeding/SST	Food-restricted/SST	Food-restricted/food
Cocaine +			
Raclopride (mg/kg)			
0.032	1.46 (0.57–2.36)	2.36 (1.31–3.42) ^b	1.81 (1.26–2.37) ^b
0.056	2.77 (1.92–3.61) ^b	3.60 (2.08–5.12) ^b	2.36 (1.42–3.29) ^b
L-741,626 (mg/kg)			
1	0.99 (0.52–1.46)	1.65 (0.64–2.67)	1.64 (0.01–3.27)
3.2	2.38 (–1.39–6.15)	2.52 (1.54–3.51) ^b	2.34 (1.45–3.23) ^b
PG01037 (mg/kg)			
32	2.52 (–0.47–5.51)	1.17 (0.88–1.46)	1.96 (0.48–3.45)
56	3.40 (1.42–5.38) ^b	2.10 (0.11–4.10)	2.22 (–2.08–6.51)

^aRatio of cocaine ED₅₀ with antagonist/ cocaine ED₅₀ without antagonist^b95% Confidence Interval of the potency ratio did not include 1

Table 2ED₅₀ values for quinpirole in combination with dopamine receptor antagonists

	Potency ratio ^a (95% Confidence Interval)	
	Free-feeding/SST	Food-restricted/SST
Quinpirole +		
Raclopride (mg/kg)		
0.056	3.52 (1.86–5.18) ^b	2.93 (2.27–3.59) ^b
L-741,626 (mg/kg)		
1	1.24 (0.61–1.87)	1.36 (–0.10–2.80)
PG01037 (mg/kg)		
56	3.08 (1.46–4.70) ^b	1.24 (0.12–2.37)

^aRatio of quinpirole ED₅₀ with antagonist/ quinpirole ED₅₀ without antagonist^b95% Confidence Interval of the potency ratio did not include 1