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Eating high fat chow increases the sensitivity of rats to quinpirole-induced discriminative stimulus effects and yawning

Michelle G Baladi^a and Charles P France^{a,b}

^a Department of Pharmacology, University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA

^b Department of Psychiatry, University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA

Abstract

Discriminative stimulus effects of directly-acting dopamine receptor agonists (e.g. quinpirole) appear to be mediated by D₃ receptors in free-feeding rats. Free access to high fat chow increases sensitivity to quinpirole-induced yawning and the current study examined whether eating high fat chow increases sensitivity to the discriminative stimulus effects of quinpirole. Five rats discriminated between 0.032 mg/kg quinpirole and vehicle while responding under a continuous reinforcement schedule of stimulus shock termination. When rats had free access to high fat chow (discrimination training was suspended), the quinpirole discrimination dose-response curve shifted leftward, possibly indicating enhanced sensitivity at D₃ receptors. In the same rats, both the ascending (mediated by D₃ receptors) and descending (mediated by D₂ receptors) limbs of the dose- response curve for quinpirole-induced yawning shifted leftward. When rats had free access to a standard chow (discrimination training was suspended), the quinpirole discrimination and yawning dose-response curves did not change. Together with published data showing that the discriminative stimulus effects of quinpirole in free- feeding rats are mediated by D₃ receptors and the insensitivity of this effect of quinpirole to food restriction (shown to increase sensitivity to D₂ but not D₃-mediated effects), these results suggest that the leftward shift of the discrimination dose-response curve when rats eat high fat chow is likely due to enhanced sensitivity at D₃ receptors. Thus, eating high fat food enhances drug effects in a manner that might impact clinical effects of drugs or vulnerability to drug abuse.

Keywords

Dopamine receptor; high fat chow; quinpirole; yawning; drug discrimination; rat

Introduction

Feeding conditions can impact the behavioral effects of directly-acting dopamine receptor agonists (Carr et al., 2003; Collins et al., 2008; Sevak et al., 2008; Baladi and France, 2009). For example, food restriction decreases the frequency of quinpirole-induced yawning in rats (Sevak et al., 2008; Baladi and France, 2009). Dopamine receptor agonist-induced yawning generates an inverted U-shaped dose-response curve with the induction of yawning (ascending limb) thought to be mediated by D₃ receptors and the decrease in yawning (descending limb) thought to be mediated by D₂ receptors (Collins et al., 2005; Baladi et al., 2010; although see Depoortère et al., 2009). Decreased agonist- induced yawning in food-restricted rats is restored

by the D₂ receptor-selective antagonist L-741,626, suggesting that food restriction increases sensitivity at D₂ receptors (Collins et al., 2008; also see Carr et al., 2003).

Drug discrimination procedures have been used to investigate many drugs, including dopamine receptor agonists. The discriminative stimulus effects of dopamine receptor agonists that bind to both D₃ and D₂ receptors are thought to be mediated predominantly, if not exclusively, through D₂ receptors (Appel et al., 1988; Kleven and Koek, 1997; Bristow et al., 1998; Katz and Alling, 2000; Millan et al., 2000, 2007; Christian et al., 2001; Koffarnus et al., 2009). Most discrimination studies on dopamine receptor agonists used food (or water) to maintain lever pressing, thereby necessitating that subjects be food (or water) restricted. However, in rats, food restriction modifies some effects (e.g., yawning) of dopamine receptor agonists and a recent study shows that, in free-feeding rats, the discriminative stimulus effects of quinpirole are mediated through D₃, and not D₂, receptors (Baladi et al., 2010). In that study, the discriminative stimulus effects of quinpirole are antagonized by the D₃ receptor-selective antagonist PG01037 and the nonselective D₃/D₂ receptor antagonist raclopride, but not by the D₂ receptor-selective antagonist L-741,626. Moreover, the potencies of PG01037 and raclopride to antagonize the discriminative stimulus effects of quinpirole parallel their potencies to antagonize the ascending limb (mediated by D₃ receptors) of the quinpirole yawning dose-response curve. Further evidence that this effect of quinpirole in free-feeding rats is mediated by D₃ and not D₂ receptors is that acute food restriction that attenuates quinpirole-induced yawning, presumably by increasing sensitivity at D₂ receptors, does not affect the discriminative stimulus effects of quinpirole (Baladi et al., 2010).

Because D₃ receptors appear to mediate the discriminative stimulus effects of quinpirole in free-feeding rats, it might be expected that altering sensitivity at D₃ receptors will alter sensitivity to the discriminative stimulus effects of quinpirole. In rats with free access to high fat chow, both the ascending and descending limbs of the quinpirole yawning dose-response curve shift leftward, indicating an increase in sensitivity at D₃ and D₂ receptors (Baladi and France, 2009). The current study examined whether eating high fat chow also increases sensitivity to the discriminative stimulus effects of quinpirole under conditions where those effects are mediated by D₃ receptors.

Methods

Subjects

Five male Sprague-Dawley rats (Harlan, Indianapolis, Indiana, USA), weighing 250–300 g, were housed individually in an environmentally controlled room (24 ± 1°C, 50 ± 10% relative humidity) under a 12/12 h light/dark cycle. Rats had free access to a standard laboratory chow in the home cage except for a 22-day period when they had free access to a high fat chow in the home cage. Water was continuously available in the home cage. Animals 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 1996 *Guide for Care and Use of Laboratory Animals* (Institute of Laboratory Animal Resources on Life Sciences, the National Research Council, and the National Academy of Sciences).

Diet

Rats had free access to a standard laboratory chow (Harlan Teklad 7912; content by weight = 5.7% fat and 19.9% protein with a calculated gross energy content of 4.1 kcal/g) or a high fat chow (Harlan Teklad 06414; content by weight = 34.3% fat and 23.5% protein with a calculated gross energy content of 5.1 kcal/g).

Apparatus

Experimental sessions were conducted in operant chambers located in sound-attenuating, ventilated enclosures (Model ENV-018ME and ENV-008CT; MED Associates Inc., St. Albans, Vermont, USA). 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. The grid floor of the chamber was 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 (Med Associates, Inc.) delivered a scrambled electric current to the grid floor of the chamber. Data were collected using MED-PC IV software (MED Associates, Inc.) and a PC interface.

Drug Discrimination

Five rats were trained previously to discriminate 0.032 mg/kg quinpirole (i.p.) from saline, while responding under a continuous reinforcement schedule of stimulus shock termination (Baladi et al., 2010). The prior study used an acute-dosing, single-cycle procedure, whereas the current study used 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 the scheduled delivery of a brief (250 msec) electric stimulus (1.5 mA) every 10 s; a response on the injection-appropriate (correct) lever or the passage of 30 s turned off the house light, ended the trial, and initiated a 30-s timeout. If a rat failed to make the first response on the correct lever in more than 5 trials in one cycle, the session ended. For saline training sessions, animals received an i.p. injection of saline before one cycle followed by between one and three sham (handling but no injection) cycles. For drug training sessions, animals received an i.p. injection of 0.032 mg/kg quinpirole before one cycle followed by a single sham injection. The cycle during which quinpirole was administered was preceded by up to two cycles during which saline or sham injections were administered. Testing began after animals satisfied the following criteria for four consecutive or five out of six sessions under the multiple-cycle procedure: 1) the first response of all 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 the same criteria for two consecutive sessions. Multiple-cycle test sessions were identical to training sessions except that a response on either lever postponed shock and either saline or increasing doses of quinpirole were administered across cycles. Under all conditions, quinpirole was studied up to the training dose (0.032 mg/kg) and occasioned at least 80% responding on the quinpirole lever.

In order to test whether stimulus control was maintained in the absence of training, dose-response curves were determined for quinpirole the day before the temporary suspension of training and on days 7, 14, and 21 of the period when no training occurred (i.e., the only sessions were tests on the 3 designated days of a 21-day period); throughout this test rats had free access to standard chow in the home cage. Next, quinpirole discrimination dose-response curves were determined in the same fashion (i.e., prior to and 7, 14 and 21 days after discontinuation of training); however, throughout this test rats had free access to a high fat chow in the home cage. During both of these experiments (i.e., suspended training while eating either standard or high fat chow), dose-response curves for quinpirole-induced yawning were determined prior to, 15, and 22 days after the temporary discontinuation of training.

Yawning

Yawning was defined as an opening of the mouth such that the lower incisors were completely visible (Kurashima et al., 1995; Sevak et al., 2008; Baladi and France, 2009). On the day of testing, rats were transferred from their home cage to a test cage (same dimensions as home

cage but with no food, water, or bedding) and allowed to habituate for 15 min. Cumulative dose-response curves were generated for quinpirole (0.0032–0.32 mg/kg i.p.) with increasing doses administered every 30 min. Beginning 20 min after each injection, the total number of yawns was recorded for 10 min. The five rats in the discrimination study were studied when they had free access to a standard chow and when they had free access to a high fat chow (see above).

Data Analyses

Drug discrimination data are expressed as a percentage of the total responses made on the quinpirole-associated lever averaged among five rats ($\pm$ SEM) and plotted as a function of dose. When a rat completed fewer than 5 trials, discrimination data from that test were not included in the average. Yawning data are expressed as the average ($\pm$ SEM) number of yawns during the 10-min observation period and plotted as a function of dose.

For each feeding condition, differences between quinpirole dose-response curves were analyzed by simultaneously fitting straight lines to the linear portion of the dose-response curves by means of GraphPad Prism (GraphPad Software, San Diego, California, USA). 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. 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, otherwise by interpolation. To calculate ED₅₀ values for quinpirole-induced yawning, a common maximum effect was selected for individual rats. The 95% confidence limits were calculated from ED₅₀ values averaged among rats. To evaluate changes in potency as a result of feeding condition, a dose ratio was calculated for each rat by dividing the ED₅₀ obtained before access to a high fat chow (when rats had access to a standard chow) by the ED₅₀ value obtained during access to a high fat chow. When the 95% confidence limits of the dose ratio did not include one, eating high fat chow was considered to significantly change the potency of the drug relative to its potency when rats ate standard chow.

Drugs

Quinpirole [(–)-quinpirole [*trans*-(–)-(4*aR*)-4,4*a*,5,6,7,8,8*a*,9-octahydro-5-propyl-1*H*-pyrazolo[3,4-*g*]quinoline HCl]] was purchased from Sigma-Aldrich (St. Louis, Missouri, USA). Quinpirole was dissolved in sterile 0.9% saline and administered i.p. in a volume of 1 ml/kg.

Results

Vehicle and small doses of quinpirole occasioned responding predominantly on the vehicle-associated lever, whereas larger doses of quinpirole increased responding on the quinpirole-associated lever (Fig. 1, upper panels, filled circles). Temporary suspension of training did not significantly affect stimulus control with quinpirole when rats had free access to standard chow, as indicated by the similarity in ED₅₀ values calculated from the four dose-response curves that were obtained during the period of suspended training (mean [95% confidence limit] = 0.016 [0.012–0.019] mg/kg before; 0.018 [0.017–0.019] mg/kg after 1 week; 0.018 [0.017–0.020] mg/kg after 2 weeks; and 0.016 [0.013–0.020] mg/kg after 3 weeks; Fig. 1, upper left panel). In the same rats, small doses of quinpirole increased and larger doses decreased yawning, resulting in an inverted U-shaped dose-response curve (Fig. 1, lower panels, filled circles). Sensitivity to this effect of quinpirole was not different among dose-response curves determined during a period of access to standard chow (i.e., when discrimination training was suspended; Fig. 1, lower left panel; Table 1). In fact, ED₅₀ values calculated for the ascending

limb (mean ED_{50} = 0.017 [0.011–0.022] mg/kg before; 0.029 [0.011–0.047] mg/kg after 2 weeks; 0.026 [0.009–0.044] mg/kg after 3 weeks) and the descending limb (mean ED_{50} = 0.159 [0.132–0.185] mg/kg before; 0.126 [0.063–0.190] mg/kg after 2 weeks; 0.142 [0.099–0.184] mg/kg after 3 weeks) of the yawning dose-response curves were not different from each other (Fig. 1, lower left panel).

In contrast, when rats had free access to a high fat chow, there was a progressive leftward shift in the quinpirole discrimination dose-response curve (Fig. 1, upper right panel, open symbols). During this period of suspended training, the ED_{50} values for quinpirole decreased in a time-related manner as follows: mean ED_{50} = 0.017 (0.016–0.018) mg/kg before; 0.016 (0.010–0.023) mg/kg after 1 week; 0.014 (0.006–0.022) mg/kg after 2 weeks; and 0.005 (0.005–0.006) mg/kg after 3 weeks. In the same 3-week period of access to high fat chow, both the ascending and descending limbs of the yawning dose-response curve shifted leftward (Fig. 1, lower right panel, open symbols). The ED_{50} values calculated for the ascending limb (mean ED_{50} = 0.019 [0.012–0.025] mg/kg before; 0.019 [0.011–0.027] mg/kg after 2 weeks; 0.006 [0.001–0.011] mg/kg after 3 weeks) and the descending limb (mean ED_{50} = 0.153 [0.134–0.182] mg/kg before; 0.115 [0.064–0.166] mg/kg after 2 weeks; 0.057 [0.057–0.059] mg/kg after 3 weeks) of the yawning dose-response curves reflect an increased sensitivity to quinpirole across time (Fig. 1, lower right panel). Body weight increased an average ($\pm$ SEM) of 4.4 g ($\pm$ 1.9) during 3 weeks of free access to standard chow and 64.6 g ($\pm$ 10.9) during 3 weeks of access to high fat chow.

The same data shown in Fig. 1 are presented in Table 1 as dose ratios expressing the magnitude of shift in the quinpirole discrimination and yawning dose-response curves. Free access to standard chow did not significantly affect the discriminative stimulus effects of quinpirole or quinpirole-induced yawning (i.e., 95% confidence limits of the dose ratios include 1). However, 3 weeks of free access to high fat chow shifted the discrimination and yawning dose-response curves significantly to the left (i.e., 95% confidence limits of the dose ratios do not include 1). For example, the discrimination dose-response curve shifted 3.3-fold to the left while the ascending and descending limbs of the yawning dose-response curve shifted 4.2- and 2.8-fold, respectively, to the left (Table 1).

Discussion

Dopamine receptors are the primary site of action for many therapeutic drugs as well as many drugs that are abused. The current study shows that eating high fat chow increases sensitivity to some behavioral effects of the dopamine receptor agonist quinpirole. When rats ate high fat chow, the quinpirole dose-response curves for discrimination and yawning shifted leftward in a time-dependent manner. Together with other studies on the relationship between feeding conditions and drug effects, these results suggest that relatively modest changes in food intake (amount or content) can profoundly affect the behavioral effects of drugs acting on dopamine systems.

Two-lever drug discrimination procedures often use food to maintain responding, thereby necessitating that animals be food restricted. Based on studies from a number of laboratories (Appel et al., 1988; Bristow et al., 1998; Kleven and Koek, 1997; Katz and Alling, 2000; Millan et al., 2000, 2007; Christian et al., 2001; Koffarnus et al., 2009), it appears that, in food-restricted rats, the discriminative stimulus effects of agonists acting at both D_3 and D_2 receptors are mediated, predominantly if not exclusively, by D_2 receptors. However, a recent study (Baladi et al., 2010) indicates that in free-feeding rats responding under a schedule of stimulus shock termination, the discriminative stimulus effects of quinpirole are mediated by D_3 receptors. That study showed that, in free-feeding rats, the discriminative stimulus effects of quinpirole are attenuated by a D_3 -selective but not by a D_2 -selective dopamine receptor

antagonist. In addition, acute food restriction (i.e., 10 g/day for 7 days), which markedly alters quinpirole-induced yawning (thought to reflect increased sensitivity at D₂ receptors), had no effect on the quinpirole discriminative stimulus (Baladi et al., 2010), providing further evidence that the quinpirole discrimination in free-feeding rats is mediated by D₃ receptors. In contrast to food restriction increasing sensitivity at D₂ receptors, eating high fat chow appears to increase sensitivity at both D₃ and D₂ receptors, as indicated by leftward shifts in both limbs of the quinpirole yawning dose-response curve (Baladi and France, 2009; current study). Thus, it might be expected that eating high fat chow would also increase sensitivity to the D₃ receptor-mediated discriminative stimulus effects of quinpirole. Indeed, and in contrast to the lack of effect of food restriction on the quinpirole discriminative stimulus, the quinpirole discrimination dose-response curve shifted leftward in rats eating high fat chow. Taken together, these results suggest that the leftward shift of the quinpirole discrimination dose-response curve is due to increased sensitivity at D₃, and not D₂, receptors. Increased sensitivity to the discriminative stimulus effects of quinpirole appears to be due to eating high fat chow and not, for example, to the suspension of training because sensitivity to quinpirole did not change when training was suspended and rats ate a standard chow. It is possible that the particular reinforcers used among studies (stimulus shock termination in the current study, food or water in other studies) contribute to different results, although that possibility seems unlikely in light of the striking consistency in discriminative stimulus effects of other drugs (e.g., morphine) across different procedures using different reinforcers (Shannon and Holtzman, 1976; France et al., 1984; Li et al., 2008).

Previous studies examining the impact of eating high fat chow on D₂ receptors have shown both increases (South and Huang, 2008) and decreases (Johnson and Kenny, 2010); it is unknown whether feeding conditions used in the current study modify D₂ or D₃ receptor number or function. The D₃ receptor shares significant sequence homology with the D₂ receptor, but in rats displays a much more restricted, limbic pattern of distribution compared with that of the D₂ receptor (Levesque et al., 1992). Based in part on this restricted distribution, D₃ receptors are thought to be potentially important targets for treating psychoses, Parkinson's disease, and substance abuse (for reviews, see Joyce, 2001; Newman et al., 2005). Whereas agonist-induced yawning is thought to be mediated by dopamine receptors in the paraventricular nucleus (Argiolas and Melis, 1998), it is less clear which brain region(s) mediates the discriminative stimulus effects of dopamine receptor agonists. Because sensitivity increases to quinpirole discriminative stimulus effects and quinpirole-induced yawning in rats eating high fat food, it appears as though increases in dopamine receptor sensitivity reflect general, not regional, receptor changes.

It is known that eating high fat chow can increase sensitivity to some effects of quinpirole (e.g., yawning) and this study extends that finding to the discriminative stimulus effects of quinpirole. This change in discriminative stimulus effects appears to reflect an increased sensitivity at D₃ receptors which are thought to mediate some of the behavioral effects of drugs of abuse (e.g., cocaine; Caine and Koob, 1993; Acri et al., 1995; Spealman, 1996). To the extent that the discriminative stimulus effects of drugs are predictive of subjective effects in humans (Schuster and Johanson, 1988), these results suggest that eating high fat food might affect abuse-related effects of drugs. Understanding the relationship between consumption of high fat food, particularly in light of the worldwide obesity epidemic (Ogden et al., 2007), and the effects of drugs acting on dopamine systems could provide insights with regard to individual differences in sensitivity and vulnerability to therapeutic and abused drugs.

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Fig. 1.

Discriminative stimulus effects of quinpirole (upper panels) and quinpirole-induced yawning (lower panels), determined before (filled circles) and 1, 2, and 3 weeks after (open symbols) suspension of training, during which time rats ($n=5$) had free access to either standard (left panels) or high fat (right panels) chow in the home cage. Horizontal axes: dose in milligrams per kilogram of body weight; "V", vehicle. Vertical axes: mean ($\pm$ SEM) percentage of responses on the quinpirole-appropriate lever (upper) and mean ($\pm$ SEM) number of yawns in 10 min (lower) for the same 5 rats.

Table 1

The effect of feeding condition on the discriminative stimulus effects and of yawning by quinpirole: dose ratios

Feeding condition	Dose Ratio		
	Discrimination	Yawning (ascending)	Yawning (descending)
<u>Standard chow</u>			
After 1 week	0.88 (0.67–1.09)	-	-
After 2 weeks	0.86 (0.67–1.04) ^a	0.78 (0.28–1.28) ^b	1.55 (0.78–2.31) ^c
After 3 weeks	1.06 (0.62–1.51)	0.88 (0.34–1.43)	1.16 (0.98–1.34)
<u>High fat chow</u>			
After 1 week	1.29 (0.46–2.13)	-	-
After 2 weeks	2.90 (–0.94–6.75)	1.08 (0.23–1.92)	1.08 (0.61–1.55)
After 3 weeks	3.27* (2.75–3.78)	4.15* (2.24–6.06)	2.80* (2.34–3.27)

^aDose ratio (95% confidence limits) for the effects of feeding condition on the discriminative stimulus effects of quinpirole in 5 rats

^bDose ratio (95% confidence limits) for the effects of feeding condition on the ascending limb of the quinpirole dose-response curve for yawning in 5 rats

^cDose ratio (95% confidence limits) for the effects of feeding condition on the descending limb of the quinpirole dose-response curve in 5 rats

* 95% confidence limits do not include 1