European Journal of Pharmacology 610 (2009) 55–60

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Behavioural Pharmacology

High fat diet and food restriction differentially modify the behavioral effects of quinpirole and raclopride in rats

Michelle G. Baladi, Charles P. France *

Departments of Pharmacology (MGB, CPF) and Psychiatry (CPF), University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA

ARTICLE INFO

Article history:
Received 24 January 2009
Received in revised form 4 March 2009
Accepted 18 March 2009
Available online 25 March 2009

Keywords:
Dopamine receptor
Food restriction
High fat diet
Quinpirole
Raclopride
Yawning

ABSTRACT

Nutritional status can impact dopamine systems in a manner that might be important to understanding possible common neurobiological mechanisms that mediate abnormal compulsive food (e.g., obesity) and drug taking. Limiting food intake, for example, can increase sensitivity to the behavioral effects of indirect-acting dopamine receptor agonists. Much less is known regarding possible diet-induced changes in sensitivity to direct-acting dopamine receptor drugs. The present study investigated the effects of a high fat diet and of food restriction on sensitivity of rats to the behavioral effects of a direct-acting dopamine receptor agonist and a dopamine receptor antagonist. Free access to high fat chow increased sensitivity to quinpirole-induced yawning without changing sensitivity to raclopride-induced catalepsy or quinpirole-induced hypothermia. Food restriction (10 g/day) decreased sensitivity to quinpirole-induced yawning and raclopride-induced catalepsy without affecting sensitivity to quinpirole-induced hypothermia. Free access to a standard chow restored sensitivity to the behavioral effects of both drugs in rats that were previously food-restricted but not in rats that previously ate a high fat diet. These data confirm that food restriction can decrease sensitivity to behavioral effects of direct-acting dopamine receptor drugs, they provide evidence (i.e., no change in hypothermic effects) indicating that these changes are not due to pharmacokinetic mechanisms, and they provide initial evidence showing enhanced sensitivity to behavioral effects of dopamine receptor drugs in rats eating a high fat diet. These changes in sensitivity of dopamine systems could be relevant to understanding the impact of nutrition on therapeutic and recreational drug use.

1. Introduction

Eating disorders show high co-morbidity with substance abuse (Holderness et al., 1994; Krahn, 1991; Piran and Robinson, 2006) and because some foods and drugs can activate common dopamine systems (Di Chiara and Imperato, 1988; Wise and Rompre, 1989), nutrition might impact the effects of drugs acting on dopamine systems. Dopamine mechanisms mediate, in part, the positive reinforcing effects of some drugs (Gratton and Wise, 1994; Schultz et al., 1993) and some foods (Carr, 2006) and dopamine neurotransmission is impacted by nutrition in a manner that might be relevant to co-morbidity of eating disorders and substance abuse. Food restriction decreases extracellular dopamine in the nucleus accumbens (Pothos et al., 1995), increases dopamine D_2 receptor binding (Thanos et al., 2008), and increases coupling between dopamine receptors and G proteins (Carr, 2002). Food restriction also decreases (Patterson et al., 1998) mRNA levels and dopamine transporter activity in the ventral tegmental area.

Although any causal relationship between eating disorders and substance abuse is not understood, the notion that nutritional status impacts sensitivity to drugs has been examined in food-restricted animals. For instance, food restriction increases self-administration of some drugs, including indirect-acting dopamine receptor agonists (Carroll et al., 1981; Takahashi et al., 1978). Food restriction also increases sensitivity to the locomotor-stimulating effects (Carr et al., 2003) while decreasing sensitivity to the yawning and cataleptic effects (Collins et al., 2008; Sevak et al., 2008) of direct-acting dopamine receptor drugs. While food restriction can modify sensitivity to drugs, much less is known about whether other dietary conditions alter sensitivity to drugs (Davis et al., 2008). Obese rats are more sensitive than non-obese rats to the locomotor-stimulating effects of direct-acting dopamine receptor agonists, they have comparatively less dopamine D_2 receptor binding (Hajnal et al., 2008) and comparatively increased dopamine transporter mRNA (Figlewicz et al., 1998). Moreover, short-term access to a high fat diet increases (South and Huang, 2008) and long-term access decreases (Huang et al., 2006) dopamine D_2 receptor binding. Finally, imaging studies show decreased dopamine D_2 receptor binding in obese humans (Wang et al., 2004). Thus, obesity, like food restriction, might alter dopamine systems in a manner that impacts sensitivity to drugs.

* Corresponding author. Department of Pharmacology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229-3900, USA. Tel.: +1 210 567 6969; fax: +1 210 567 0104.
E-mail address: france@uthsca.edu (C.P. France).

0014-2999/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2009.03.048

In rats, direct-acting dopamine receptor agonists produce yawning and hypothermia (Collins et al., 2005, 2007; Sevak et al., 2006), direct-acting dopamine receptor antagonists produce catalepsy (Kanes et al., 1993; Sevak et al., 2004), and sensitivity to both of these classes of drugs is decreased by food restriction (Collins et al., 2008; Sevak et al., 2008). The current study used drug-induced yawning, body temperature, and catalepsy to examine changes in sensitivity to direct-acting dopamine receptor agonists and antagonists in rats with free access to normal chow, restricted access (10 g/day) to normal chow, or free access to a high fat chow. It was hypothesized that food restriction would decrease and free access to a high fat chow would increase sensitivity to the behavioral effects of drugs acting directly at dopamine receptors.

2. Materials and methods

2.1. Subjects

Twenty-four male Sprague–Dawley rats (Harlan, Indianapolis, IN), weighing 250–300 g upon arrival, were housed individually in an environmentally controlled room (24 ± 1 °C, 50 ± 10% relative humidity) under a 12/12 h light/dark cycle with free access to water. With the exception of food restriction for some rats (see below) and during observational periods for all subjects, rats had free access to food. 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).

2.2. Diet

Eight subjects continued to have free access to a standard laboratory chow (Harlan Teklad 7912), eight subjects had free access to a high fat chow (Harland Teklad 06414), and eight subjects were restricted to 10 g per day of the standard laboratory chow. The nutritional content of the standard laboratory chow (by weight) was 4.4% fat and 24.5% protein, with a calculated gross energy content of 3.93 kcal/g. The high fat chow contained 34.3% fat (by weight) and 23.5% protein, with a calculated energy content of 5.1 kcal/g. Animals had access to one of these feeding conditions (diets) for 5 weeks before and for 3 weeks after an 8-week period during which all rats had free access to the standard laboratory chow.

2.3. Yawning

Yawning was defined as an opening of the mouth such that the lower incisors were completely visible (Collins et al., 2005; Kurashima et al., 1995; Sevak et al., 2008). 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. Initially, and while all rats had free access to standard laboratory chow, dose–response curves were generated for cumulative doses of quinpirole (0.01, 0.032, 0.1, 0.32, 1.0 mg/kg s.c.) administered every 30 min. Subsequently, rats were randomly assigned to a dietary condition (free access to a standard chow, free access to a high fat chow, or restricted access to a standard chow), and dose–response curves were generated weekly for cumulative doses of quinpirole. Lastly, when all animals again had free access to a standard chow, dose–response curves were generated weekly for cumulative doses of quinpirole. Beginning 20 min after each injection, the total number of yawns was recorded for 10 min.

2.4. Catalepsy

The same rats that were used for studying quinpirole-induced yawning were also used to assess catalepsy produced by raclopride with at least 48 h between consecutive tests. Catalepsy was examined using a bar test, whereby both forelimbs were placed on a horizontal, cylindrical metal bar (diameter, 1.0 cm; height, 10 cm), and the time until both forelimbs touched the table surface was recorded, up to a maximum of 120 s (Sevak et al., 2006). For each rat, there were five consecutive 25-min cycles with vehicle or raclopride injected every 30 min. For instance, at the beginning of the first cycle, 1 ml/kg saline was administered, forelimbs were placed on the bar, and the time until both forelimbs touched the table surface was recorded. At the beginning of the second and each of the remaining cycles, cumulative doses of raclopride (0.1, 0.32, 1.0, 3.2 mg/kg s.c.) were administered with catalepsy assessed 25 min after each injection.

2.5. Body temperature

Rectal body temperature was measured in a temperature controlled room (24 ± 1 °C and 50 ± 10% relative humidity) by inserting a lubricated thermal probe attached to a thermometer 3 cm into the rectum. Animals were adapted to the experimental situation by measuring body temperature on multiple occasions before studies with vehicle or drug. During yawning experiments, body temperature was measured after completion of each 10 min observation period and prior to the next injection. During catalepsy experiments, body temperature was measured after completion of the bar test and prior to the next injection. In this way, dose–response curves were generated for quinpirole- and raclopride-induced changes in body temperature. Body temperature was measured not more than twice per week with 48 h between consecutive tests. The effect of raclopride (1.78 mg/kg) on quinpirole-induced hypothermia (0.01, 0.032, 0.1, 3.2, 10.0 mg/kg) was determined during weeks 15 and 16 when separate groups of rats had free access to a standard chow, free access to a high fat chow, or restricted access to a standard chow.

2.6. Data analyses

Results are expressed as the mean ± S.E.M. for each group of eight rats. A two-way, repeated-measures ANOVA with post hoc Bonferroni's test was used to determine whether drug-induced yawning, body temperature, and catalepsy in rats with free access to a high fat chow and restricted access to a standard chow were significantly different from the same effects in rats with free access to a standard chow throughout the study (Graphpad Prism; GraphPad Software Inc., San Diego, CA). A two-way repeated-measures ANOVA also was used to determine whether yawning was different in the same group of rats before and during access to a high fat diet.

For each group, differences between quinpirole dose–response curves to produce yawning and to produce hypothermia in the absence and presence of raclopride were analyzed by simultaneously fitting straight lines to the linear portion of the dose–response curves by means of GraphPad Prism. 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 the slopes and intercepts of the curves were analyzed with the F-ratio test (GraphPad Prism), as detailed elsewhere (Koek et al., 2006). ED_{50} values and potency ratios, and their 95% confidence limits, were calculated by parallel line analysis (Tallarida, 2000). The common slope values calculated by GraphPad Prism were used to constrain the fit of the parallel line assay.

2.7. Drugs

Quinpirole dihydrochloride and raclopride tartrate were purchased from Sigma-Aldrich (St. Louis, MO). Quinpirole was dissolved in sterile water and administered s.c. in a volume of 1 ml/kg. Raclopride was dissolved in sterile 0.9% saline and administered s.c. in a volume of 1 ml/kg.

3. Results

After 5 weeks of free access to a standard chow or to a high fat chow, the body weight of rats increased an average of 48 g and 72 g, respectively; after 5 weeks of food restriction the body weight of rats decreased an average of 81 g (Fig. 1). During weeks 6–13 when all rats had free access to a standard chow, rats that previously ate a high fat chow gained an average of 24 g and rats that previously had restricted access to a standard chow gained an average of 157 g; rats with free access to a standard chow gained an average of 47 g over the same 8-week period. During the last 3 weeks of the study when rats again were assigned to the same feeding conditions employed during weeks 1–5, rats with free access to a standard chow gained an average of 8 g, rats with free access to a high fat chow gained an average of 44 g, and rats with restricted (10 g/day) access to a standard chow lost an average of 74 g.

Small doses of quinpirole increased and larger doses decreased yawning, resulting in an inverted U-shaped dose–response curve (Fig. 2, top left panel). Free access to a high fat chow resulted in a significant leftward shift ($P<0.05$) of the dose–response curve for quinpirole-induced yawning, as compared with the effects of quinpirole in rats with free access to a standard chow (compare circles and squares, Fig. 2, middle left panel). The ascending limbs of quinpirole dose–response curves for yawning (0.01 and 0.032 mg/kg) before and during access to a high fat diet were not significantly different. However, the linear portion corresponding to the descending limb of the quinpirole dose–response curves in rats with free access to a high fat chow or to a standard chow could be fitted with a common slope but different x-intercepts, indicating that free access to a high fat chow shifted the curve significantly to the left. When rats that previously ate a high fat chow had free access to a standard chow, their sensitivity to quinpirole remained significantly different from the sensitivity of rats that had free access to a standard chow throughout; for example, the average number of yawns was significantly less for the former group of rats at doses of 0.032 and 0.1 mg/kg quinpirole ($P<0.05$; Fig. 2, bottom left panel). In addition, the linear portion corresponding to the descending limb of the quinpirole dose–response curves in the two groups could be fitted with a common slope but different x-intercepts, indicating that the descending limb of the dose–response curve remained shifted leftward in rats that previously had access to a high fat chow. Specifically, a dose of quinpirole (0.1 mg/kg) that produced yawning prior to dietary changes failed to induce yawning in rats that ate a high fat diet, even after 8 weeks of free access to a standard chow.

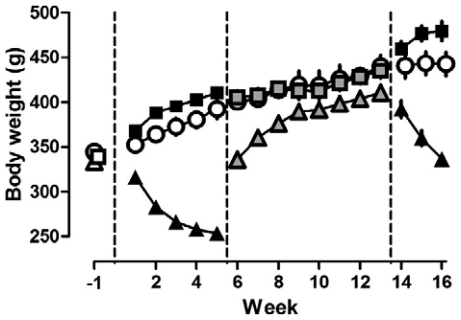

Fig. 1. Body weight of separate groups of rats with free access to a standard laboratory chow, free access to a high fat chow, or restricted access to a standard chow. The vertical dashed lines indicate 4 phases of the study as follows: week -1 (all rats had free access to a standard chow); weeks 1–5 (different groups of rats had free access to a standard chow [circles], free access to a high fat chow [squares], or restricted access [10 g/day] to a standard chow [triangles]); weeks 6–13 (all rats had free access to a standard chow); and weeks 14–16 (individual rats had access to the same feeding conditions as in weeks 1–5). Each symbol represents the mean ± S.E.M. of 8 rats. The symbol shape (e.g., square) refers to the same group of rats across the different phases of the study; symbol shading (e.g. filled) designates different feeding conditions within a group.

Food restriction significantly decreased ($P<0.001$) sensitivity of rats to quinpirole-induced yawning, compared to rats with free access to a standard chow (compare circles and triangles, Fig. 2, middle left panel). In fact, over the doses studied (0.01–1.0 mg/kg), quinpirole failed to produce any yawning in any food-restricted rat. When rats that previously had restricted access to a standard chow were given free access to a standard chow, sensitivity to quinpirole-induced yawning recovered rapidly and after 2 weeks was not different from the sensitivity of control rats (i.e., those with free access to a standard chow throughout) to quinpirole-induced yawning (compare circles and triangles, Fig. 2, bottom left panel).

Quinpirole dose-dependently decreased core body temperature in all rats and changes in dietary conditions across groups had very little impact on quinpirole-induced hypothermia (Fig. 2, right panels). With the exception of a greater effect of 1.0 mg/kg of quinpirole ($P<0.001$) in rats with restricted access to a standard chow, as compared to rats with free access to the same chow, there was no difference in sensitivity of rats to quinpirole-induced hypothermia across feeding conditions (Fig. 2, middle right panel).

Raclopride dose-dependently increased catalepsy (Fig. 3, top panel) without significantly affecting body temperature (data not shown). Free access to a high fat chow did not significantly affect the sensitivity of rats to raclopride-induced catalepsy (compare circles and squares, Fig. 3, middle panel). In contrast, restricted access to a standard chow significantly ($P<0.001$) decreased sensitivity to raclopride-induced catalepsy, compared with rats that had free access to a standard chow (compare circles and triangles, Fig. 3, middle panel). When rats that previously had restricted access to a standard chow were given free access to a standard chow, sensitivity to raclopride-induced catalepsy recovered rapidly and after 2 weeks was not different from the sensitivity of control rats (those with free access to a standard chow throughout) to raclopride-induced catalepsy (compare circles and triangles, Fig. 3, bottom panel).

Raclopride antagonized the hypothermic effects of quinpirole as indicated by shifts to the right in the quinpirole dose–response curves (data not shown). Table 1 shows ED_{50} values for quinpirole in the presence and absence of 1.78 mg/kg raclopride in the three groups of rats. Despite differences in the absolute potency of quinpirole among the three groups, the magnitude of shift to the right in the quinpirole dose–response curve was similar across all three groups. For example, raclopride shifted the quinpirole dose–response curve 8.8-fold to the right in rats with free access to a standard chow, 8.5-fold to the right in rats with free access to a high fat chow, and 8.4-fold to the right in rats with restricted access to a standard chow.

4. Discussion

Results from this study indicate that a high fat diet increases sensitivity to quinpirole-induced yawning without changing sensitivity to quinpirole-induced hypothermia or raclopride-induced catalepsy. Furthermore, and consistent with prior studies, food restriction decreases sensitivity to quinpirole-induced yawning and raclopride-induced catalepsy without markedly affecting sensitivity to quinpirole-induced hypothermia. These data support the view that changes in diet significantly impact some behavioral effects of drugs acting on dopamine receptors, a finding that could be important for understanding individual differences in response to therapeutic and recreational drugs.

Quinpirole is an agonist at dopamine D_2 (i.e., D_2, D_3, and D_4) receptors with similar affinity for D_2 and D_3 receptors (Kebabian et al., 1997). In agreement with others (Collins et al., 2005, 2007; Sevak et al., 2006), quinpirole produced yawning and yielded an inverted U-shaped dose–response curve. It has been suggested (Collins et al., 2005) that the biphasic nature of this dose–response curve is due to the induction of yawning by activation of D_3 receptors at smaller doses and the inhibition of yawning by activation of D_2 receptors at larger

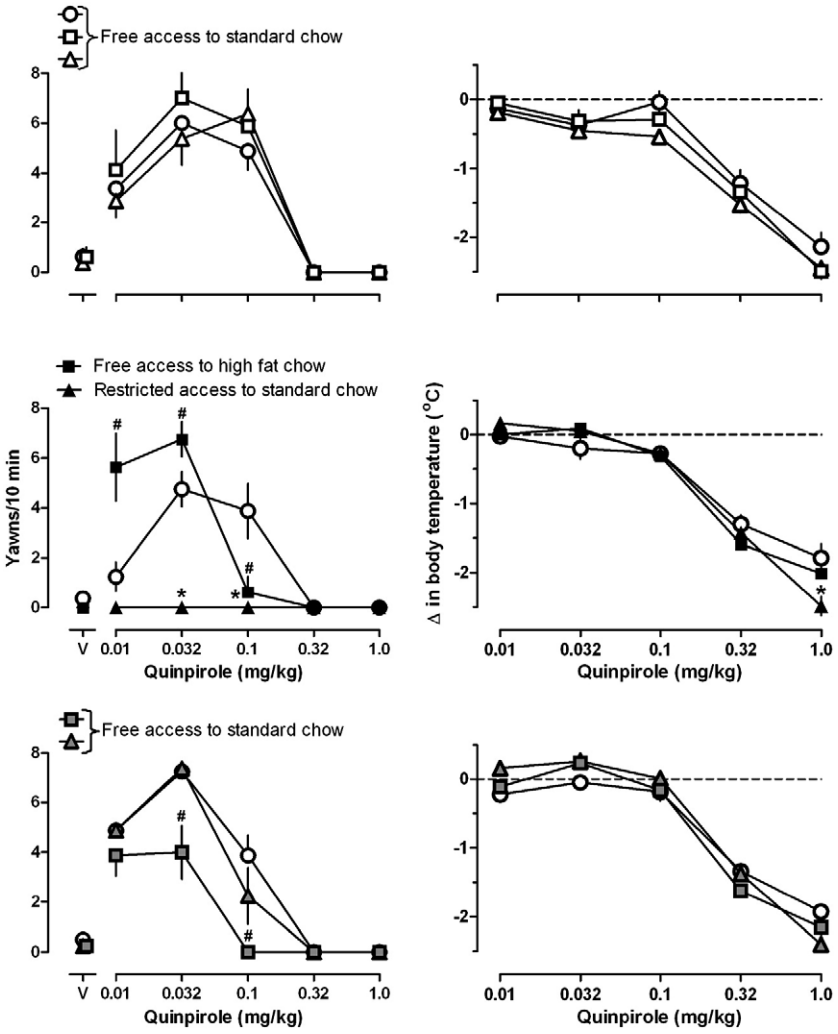

Fig. 2. The effects of a high fat and food-restricted diet on quinpirole-induced yawning (left panel) and quinpirole-induced hypothermia (right panel). Each symbol represents the mean ± S.E.M. of 8 rats. The top panels represent week -1, the middle panels represent week 5, and the bottom panels represent week 7 of the study (see Fig. 1). The points above V indicate the effects obtained with vehicle. #, $P<0.05$ and *, $P<0.001$, compared with rats that had free access to a standard chow throughout the study at the corresponding dose of quinpirole.

doses of quinpirole. A shift rightward or downward in the quinpirole dose–response curve in rats with restricted access to food, as shown in the current study and by others, might be due to decreased sensitivity at D_3 receptors, increased sensitivity at D_2 receptors, or to both decreased sensitivity at D_3 and increased sensitivity at D_2 receptors. In contrast to a decrease in the effectiveness of a dopamine receptor agonist under conditions of food restriction, unlimited access to a high fat diet resulted in a leftward shift in both arms of the inverted U-shaped dose–response curve for quinpirole-induced yawning. That both arms of the dose–response curve shifted left might indicate an increased sensitivity at D_3 receptors (ascending limb), a decreased sensitivity at D_2 receptors (descending limb), or to increased sensitivity at both D_3 and D_2 receptors. Moreover, when rats eating the high fat diet were given free access to a standard chow, sensitivity to quinpirole-induced yawning did not return to normal, suggesting that changes in dopamine systems resulting from the a high fat diet might be very long lasting. Consistent with that possibility, a maternal high fat diet during the perinatal period in rats induced long-term effects in dopamine functioning and in behavior in adult offspring (Naef et al., 2007). In addition, upon completion of 20 days of eating a high fat diet, 7 days of access to a low fat diet did not restore normal binding densities of dopamine D_2 receptors or dopamine transporters (South and Huang, 2008). Collectively these data extend prior studies on food restriction and suggest that a high fat diet might induce changes in dopamine systems and are similar (i.e., increased sensitivity at D_2 receptors) or possibly opposite (increased sensitivity at D_3 receptors) to those induced by food restriction.

A large body of literature suggests that activation of dopamine D_2 receptors can significantly decrease body temperature. Among a variety of D_3 and D_2 selective agonists and antagonists there was a strong positive relationship between actions at D_2 receptors and effects on body temperature (Chaperon et al., 2003; Collins et al., 2007; Nunes et al., 1991). Moreover, dopamine receptor agonists failed to produce hypothermia in D_2 receptor knock-out mice (Boulay et al., 1999). In the current study, quinpirole significantly decreased body temperature in all rats. Although free access to a high fat chow resulted in a leftward shift of the dose–effect curve for quinpirole-induced yawning, it had no effect on sensitivity to quinpirole-induced hypothermia. These seemingly contradictory effects might be due to a selective increase in sensitivity at dopamine D_3 receptors (i.e., induction of yawning) and not at dopamine D_2 receptors (i.e., inhibition of yawning and hypothermia) in rats eating a high fat diet. Food restriction resulted in a slightly greater decrease in body temperature at the largest dose of quinpirole, as compared to rats with free access to a standard chow or a high fat chow. Although this effect of food restriction on quinpirole-induced hypothermia is very modest, it is consistent with the notion that food restriction increases sensitivity at dopamine D_2 receptors. Dopamine receptor

agonist induced hypothermia might be mediated by D_1 as well as D_2 receptors (Chaperon et al., 2003); thus, variations in how diet affects sensitivity to different effects of quinpirole might reflect the relative contribution of different dopamine receptor subtypes in mediation of those effects.

Drugs, including raclopride, that have antagonist actions at dopamine receptors reliably produce catalepsy (Kanes et al., 1993; Sevak et al., 2004). Antagonist activity at dopamine D_2 receptors is thought to be responsible for catalepsy since dopamine D_3 receptor selective antagonists do not produce catalepsy (Reavill et al., 2000). In the current study, free access to a high fat chow did not change sensitivity to raclopride-induced catalepsy. That eating a high fat diet did not change an effect (i.e., catalepsy) that is thought to be mediated by dopamine D_2 receptors, suggests that the increase in sensitivity to quinpirole-induced yawning that was observed in rats eating a high fat diet is due to an increased sensitivity at D_3 receptors. On the other hand, food restriction decreased sensitivity to raclopride-induced catalepsy, confirming results of previous studies in rats (e.g., Sevak et al., 2008).

Raclopride antagonized the hypothermic effects of quinpirole in all rats and the magnitude of that antagonism was not different across the three dietary conditions. Because this indicator of the dopamine receptor antagonist effects of raclopride was not impacted by diet, it is possible that diet-induced changes in sensitivity to the behavioral (cataleptic) effects of raclopride administered alone could reflect a change in non-dopamine systems or a change in dopamine D_2 receptor density since catalepsy requires high receptor occupancy (Wadenberg et al., 2000) and food restriction can significantly increase dopamine receptor density (Thanos et al., 2008). It has been suggested that cholinergic mechanisms are necessary for producing catalepsy with dopamine receptor antagonists (Klemm, 1985). Moreover, cholinergic muscarinic receptor antagonists reduce the cataleptic effects of dopamine receptor antagonists (Alcock et al., 2001; Ushijima et al., 1997). Interestingly, food restriction can significantly modify cholinergic systems (Persinger et al., 2002), suggesting that food restriction might alter the direct effects of dopamine receptor antagonists by actions on other (e.g., cholinergic) systems without directly altering dopamine receptor antagonist activity (e.g., antagonism of quinpirole-induced hypothermia).

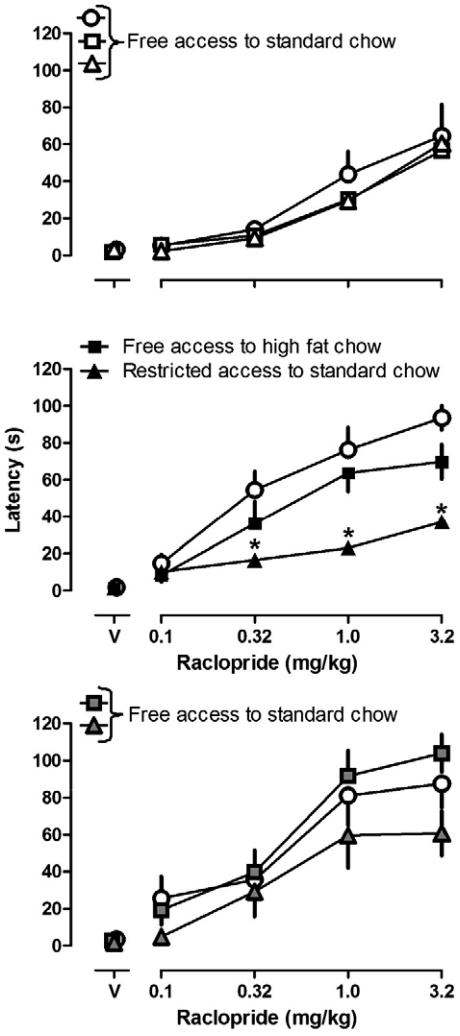

Fig. 3. The effects of a high fat and food-restricted diet on raclopride-induced catalepsy. Each symbol represents the mean ± S.E.M. of 8 rats. The top panel represents week -1, the middle panel represents week 5, and the bottom panel represents week 7 of the study (time line shown in Fig. 1). The points above V indicate the effects obtained with vehicle. *, $P<0.001$ compared with rats that had free access to a standard chow throughout the study at the corresponding dose of raclopride.

Table 1
Antagonism of the hypothermic effects of quinpirole by raclopride in rats under different dietary conditions.

Diet	ED_{50} value		Potency ratio
	1.78 mg/kg raclopride	Vehicle	Raclopride vs. vehicle
Standard	1.21 (.93–1.60)[a]	.14 (.11–.18)	8.80 (6.20–12.40)
High fat	1.10 (1.00–1.27)	.13 (.11–.15)	8.50 (6.80–10.70)
Food restricted	.93 (.77–1.12)	.11 (.10–.13)	8.40 (6.70–10.60)

[a] Each entry is the average ED_{50} for quinpirole in decreasing body temperature in 8 rats. Values in parentheses indicate the 95% confidence limits.

In summary, this study demonstrates that free access to a high fat diet increases, while food restriction decreases sensitivity to the behavioral effects of some direct-acting dopamine receptor drugs. The mechanisms that mediate these changes in dopamine systems are not known; however, hormones, such as insulin, leptin, and ghrelin can directly affect dopamine systems (for review, Palmiter, 2007) and might contribute to these changes. These hormones activate receptors on dopamine neurons and either inhibit (insulin and leptin) or stimulate (ghrelin) dopamine signaling. Moreover, hyperinsulinemia increases and hypoinsulinemia decreases dopamine transporter activity (Figlewicz et al., 1994; Owens et al., 2005, respectively) and amphetamine self-administration is reduced in hypoinsulinemic rats (Galici et al., 2003). Since hormone levels are markedly affected by diet, these hormones might influence changes in sensitivity to the behavioral effects of dopamine drugs. Understanding the functional relationship between nutritional status and the behavioral effects of drugs acting on dopamine systems could facilitate studies on the co-morbidity of eating disorders and substance abuse and might help account for individual differences in sensitivity to therapeutic and recreational drugs.

Acknowledgment

CPF is supported by a senior scientist award (KO5 DA17918).

References

Alcock, S.J., Hemsley, K.M., Crocker, A.D., 2001. Atropine acts in the ventral striatum to reduce raclopride-induced catalepsy. Eur. J. Pharmacol. 424, 179–187.
Boulay, D., Depoortere, R., Perrault, G., Borreill, E., Sanger, D.J., 1999. Dopamine D2 receptor knock-out mice are insensitive to the hypolocomotor and hypothermic effects of dopamine D2/D3 receptor agonists. Neuropharmacology 38, 1389–1396.
Carroll, M.E., France, C.P., Meisch, R.A., 1981. Intravenous self-administration of etonitazene, cocaine, and phencyclidine in rats during food deprivation and satiation. J. Pharmacol. Exp. Ther. 217, 241–247.
Carr, K.D., 2002. Augmentation of drug reward by chronic food restriction: behavioral evidence and underlying mechanisms. Physiol. Behav. 76, 353–364.
Carr, K.D., 2006. Chronic food restriction: enhancing effects on drug reward and striatal cell signaling. Physiol. Behav. 91, 459–472.

Carr, K.D., Tsimberg, Y., Berman, Y., Yamamoto, N., 2003. Evidence of increased dopamine receptor signaling in food-restricted rats. Neuroscience 119, 1157–1167.
Chaperon, F., Tricklebank, M., Unger, L., Neijt, H., 2003. Evidence for regulation of body temperature in rats by dopamine D2 receptor and possible influence of D1 but not D3 and D4 receptors. Neuropharmacology 44, 1047–1053.
Collins, G.T., Calinski, D.M., Newman, A.H., Grundt, P., Woods, J.H., 2008. Food restriction alters pramipexole-induced yawning, hypothermia, and locomotor activity in rats: evidence for sensitization of dopamine D2 receptor-mediated effects. J. Pharmacol. Exp. Ther. 325, 691–697.
Collins, G.T., Newman, A.H., Grundt, P., Rice, K.C., Husbands, S.M., Chauvignac, C., Chen, J., Wang, S., Woods, J.H., 2007. Yawning and hypothermia in rats: effects of dopamine D3 and D2 agonists and antagonists. Psychopharmacology 193, 159–170.
Collins, G.T., Witkin, J.M., Newman, A.H., Svensson, K.A., Grundt, P., Cao, J., Woods, J.H., 2005. Dopamine agonist-induced yawning in rats: a dopamine D3 receptor-mediated behavior. J. Pharmacol. Exp. Ther. 314, 310–319.
Davis, J.F., Tracy, A.L., Schurdak, J.D., Tschöp, M.H., Lipton, J.W., Clegg, D.J., Benoit, S.C., 2008. Exposure to elevated levels of dietary fat attenuates psychostimulant reward and mesolimbic dopamine turnover in the rat. Behav. Neurosci. 122, 1257–1263.
Di Chiara, G., Imperato, A., 1988. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc. Natl. Acad. Sci. U. S. A. 85, 5274–5280.
Figlewicz, D.P., Patterson, T.A., Johnson, L.B., Zavosh, A., Israel, P.A., Szot, P., 1998. Dopamine transporter mRNA is increased in the CNS of Zucker fatty (*fa/fa*) rats. Brain Res. Bull. 46, 199–202.
Figlewicz, D.P., Szot, P., Chavez, M., Woods, S.C., Veith, R.C., 1994. Intraventricular insulin increases dopamine transporter mRNA in rat VTA/substantia nigra. Brain Res. 644, 331–334.
Galici, R., Galli, A., Jones, D.J., Sanchez, T.A., Saunders, C., Frazer, A., Gould, G.G., Lin, R.Z., France, C.P., 2003. Selective decreases in amphetamine self-administration and regulation of dopamine transporter function in diabetic rats. Neuroendocrinology 77, 132–140.
Gratton, A., Wise, R.A., 1994. Drug- and behavior-associated changes in dopamine-related electrochemical signals during intravenous cocaine self-administration in rats. J. Neurosci. 14, 4130–4146.
Hajnal, A., Margas, W.M., Covasa, M., 2008. Altered dopamine D2 receptor function and binding in obese OLETF rat. Brain Res. Bull. 75, 70–76.
Holderness, C.C., Brooks-Gunn, J., Warren, M.P., 1994. Co-morbidity of eating disorders and substance abuse review of the literature. Int. J. Eat. Disord. 16, 1–34.
Huang, X.F., Zavitsanou, K., Huang, X., Yu, Y., Wang, H., Chen, F., Lawrence, A.J., Deng, C., 2006. Dopamine transporter and D2 receptor binding densities in mice prone or resistant to chronic high fat diet-induced obesity. Behav. Brain Res. 175, 415–419.
Kanes, S.J., Hitzemann, B.A., Hitzemann, R.J., 1993. On the relationship between D2 receptor density and neuroleptic-induced catalepsy among eight inbred strains of mice. J. Pharmacol. Exp. Ther. 267, 538–547.
Kebabian, J.W., Tarazi, F.I., Kula, N.S., Baldessarini, R.J., 1997. Compounds selective for dopamine receptor subtypes. Drugs Discov. Today 2, 333–340.
Klemm, W.R., 1985. Evidence for a cholinergic role in haloperidol-induced catalepsy. Psychopharmacology 87, 12–15.
Koek, W., Carter, L.P., Wu, H., Coop, A., France, C.P., 2006. Discriminative stimulus effects of flumazenil: perceptual masking by baclofen, and lack of substitution with gamma-hydroxybutyrate and its precursors 1,4-butanediol and gamma-butyrolactone. Behav. Pharmacol. 17, 239–247.
Krahn, D.D., 1991. The relationship of eating disorders and substance abuse. J. Subst. Abuse 3, 239–253.
Kurashima, M., Yamada, K., Nagashima, M., Shirakawa, K., Furukawa, T., 1995. Effects of putative dopamine D3 receptor agonists, 7-OH-DPAT, and quinpirole, on yawning, stereotypy, and body temperature in rats. Pharmacol. Biochem. Behav. 52, 503–508.
Naef, L., Srivastava, L., Gratton, A., Hendrickson, H., Owens, S.M., Walker, C.D., 2007. Maternal high fat diet during the perinatal period alters mesocorticolimbic dopamine in the adult rat offspring: reduction in the behavioral responses to repeated amphetamine administration. Psychopharmacology 197, 83–94.
Nunes, J.L., Sharif, N.A., Michel, A.D., Whiting, R.L., 1991. Dopamine D2-receptors mediate hypothermia in mice: ICV and IP effects of agonists and antagonists. Neurochem. Res. 16, 1167–1174.
Owens, W.A., Sevak, R.J., Galici, R., Chang, X., Javors, M.A., Galli, A., France, C.P., Daws, L.C., 2005. Deficits in dopamine clearance and locomotion in hypoinsulinemic rats unmask novel modulation of dopamine transporters by amphetamine. J. Neurochem. 94, 1402–1410.
Palmiter, R.D., 2007. Is dopamine a physiologically relevant mediator of feeding behavior? Trends Neurosci. 30, 375–381.
Patterson, T.A., Brot, M.D., Zavosh, A., Schenk, J.O., Szot, P., Figlewicz, D.P., 1998. Food deprivation decreases mRNA and activity of the rat dopamine transporter. Neuroendocrinology 68, 11–20.
Persinger, M.A., Stewart, L.S., Richards, P.M., Harrigan, T., O'Connor, R.P., Bureau, Y.R., 2002. Seizure onset times for rats receiving systemic lithium and pilocarpine: sources of variability. Pharmacol. Biochem. Behav. 71, 7–17.
Piran, N., Robinson, S.R., 2006. Associations between disordered eating behaviors and licit and illicit substance use and abuse in a university sample. Addict. Behav. 31, 1761–1775.
Pothos, E.N., Creese, I., Hoebel, B.G., 1995. Restricted eating with weight loss selectively decreases extracellular dopamine in the nucleus accumbens and alters dopamine response to amphetamine, morphine, and food intake. J. Neurosci. 10, 6640–6650.
Reavill, C., Taylor, S.G., Wood, M.D., Ashmeade, T., Austin, N.E., Avenell, K.Y., Boyfield, I., Branch, C.L., Cilia, J., Coldwell, M.C., Hadley, M.S., Hunter, A.J., Jeffrey, P., Jewitt, F., Johnson, C.N., Jones, D.N., Medhurst, A.D., Middlemiss, D.N., Nash, D.J., Riley, G.J., Routledge, C., Stemp, G., Thewlis, K.M., Trail, B., Vong, A.K., Hagan, J.J., 2000. Pharmacological actions of a novel, high-affinity, and selective human dopamine D (3) receptor antagonist, SB-277011-A. J. Pharmacol. Exp. Ther. 294, 1154–1165.
Schultz, W., Apicella, P., Ljungberg, T., 1993. Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. J. Neurosci. 13, 900–913.
Sevak, R.J., Daws, L.C., Koek, W., Owens, W.A., Galli, A., France, C.P., 2008. Feeding conditions differentially affect the neurochemical and behavioral effects of dopaminergic drugs in male rats. Eur. J. Pharmacol. 592, 109–115.
Sevak, R.J., France, C.P., Koek, W., 2004. Neuroleptic-like effects of γ-hydroxybutyrate: interactions with haloperidol and dizocilpine. Eur. J. Pharmacol. 483, 289–293.
Sevak, R.J., Koek, W., Galli, A., France, C.P., 2006. Insulin replacement restores the behavioral effects of quinpirole and raclopride in streptozotocin-treated rats. J. Pharmacol. Exp. Ther. 32, 1216–1223.
South, T., Huang, X., 2008. High-fat diet exposure increase dopamine D2 receptor and decreases dopamine transporter receptor binding density in the nucleus accumbens and caudate putamen of mice. Neurochem. Res. 35, 598–605.
Takahashi, R.N., Singer, G., Oei, T., 1978. Schedule-induced self-injection of D-amphetamine by naïve animals. Pharmacol. Biochem. Behav. 9, 857–861.
Tallarida, R.J., 2000. Drug synergism and dose–effect data analysis. Boca Raton: Chapman & Hall/CRC.
Thanos, P.K., Michaelides, M., Piyis, Y.K., Wang, G., Volkow, N.D., 2008. Food restriction markedly increases dopamine D2 receptor (D2R) in rat model of obesity as assessed with in-vivo μPET imaging ([^{11}C] raclopride) and in-vitro [[^{3}H] spiperone) autoradiograph. Synapse 62, 50–61.
Ushijima, I., Kawano, M., Kaneyuki, H., Suetsugi, M., Usami, K., Hirano, H., Mizuki, Y., Yamada, M., 1997. Dopaminergic and cholinergic interaction in cataleptic response in mice. Pharmacol. Biochem. Behav. 58, 103–108.
Wadenberg, M.L., Kapur, S., Soliman, S., Jones, C., Vaccarino, F., 2000. Dopamine D2 receptor occupancy predicts catalepsy and the suppression of conditioned avoidance response behavior in rats. Psychopharmacology 150, 422–429.
Wang, G.J., Volkow, N.D., Thanos, P.K., Fowler, J.S., 2004. Similarity between obesity and drug addiction as assessed by neurofunctional imaging: a concept review. J. Addict. Dis. 23, 39–53.
Wise, R.A., Rompre, P.P., 1989. Brain dopamine and reward. Annu. Rev. Psychol. 40, 191–225.