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Eating high fat chow increases the sensitivity of rats to 8-OH-DPAT-induced lower lip retraction

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Abstract

Eating high fat food can alter sensitivity to drugs acting on dopamine systems; this study examined whether eating high fat food alters sensitivity to a drug acting on serotonin (5-HT) systems. Sensitivity to (+)-8-hydroxy-2-(dipropylamino) tetralin hydrobromide (8-OH-DPAT; 5-HT_{1A} receptor agonist)-induced lower lip retraction was examined in separate groups (n=8-9) of rats with free access to standard (5.7% fat) or high fat (34.3% fat) chow; sensitivity to quinpirole (dopamine D₃/D₂ receptor agonist)-induced yawning was also examined. Rats eating high fat chow gained more body weight than rats eating standard chow and, after 6 weeks of eating high fat chow, they were more sensitive to 8-OH-DPAT (0.01-0.1 mg/kg)-induced lower lip retraction and quinpirole (0.0032-0.32 mg/kg)-induced yawning. These changes were not reversed when rats that previously ate high fat chow were switched to eating standard chow and sensitivity to 8-OH-DPAT and quinpirole increased when rats that previously ate standard chow ate high fat chow. These data extend previous results showing changes in sensitivity to drugs acting on dopamine systems in animals eating high fat chow to a drug acting at 5-HT_{1A} receptors and they provide support for the notion that eating certain foods impacts sensitivity to drugs acting on monoamine systems.

Keywords

Serotonin; 8-OH-DPAT; high fat chow; quinpirole; rat; dopamine; lower lip retraction; yawning

Introduction

Amount and type of food can impact brain neurochemistry and the behavioral effects of drugs. For example, in rats food restriction eliminates yawning produced by the direct-acting dopamine receptor agonist quinpirole (Sevak et al., 2008) whereas eating high fat chow increases sensitivity to both unconditioned (Baladi and France, 2009) and conditioned (Baladi and France, 2010) behavioral effects of quinpirole and accelerates the development of sensitization to the locomotor effects of the indirect-acting dopamine receptor agonist methamphetamine (McGuire et al., 2011). Eating high fat chow decreases dopamine turnover, electrically evoked dopamine release, and dopamine transporter binding, while increasing dopamine D₂ receptor density (Davis et al., 2008; Geiger et al., 2009; South and Huang, 2008; York et al., 2010).

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Eating high fat chow can also impact other neurochemical systems. Brain serotonin (5-HT) concentration, release, turnover, as well as binding at some 5-HT receptor subtypes are reduced in rats eating high fat chow (Kirac et al., 2009; Schaffhauser et al., 2002; York et al., 2010). The functional consequences of these neurochemical changes are not known although other changes in food intake (e.g., food restriction) can affect the actions of drugs acting on 5-HT systems (France et al., 2009; Li et al., 2008, 2009; Slaiman, 1989). Abnormalities in 5-HT systems are important in a number of psychiatric disorders and 5-HT systems are the target for many therapeutic drugs. Moreover, there is a high co-morbidity between eating disorders and various psychiatric disorders (Enns et al., 2001; Fox and Power, 2009; Holderness et al., 1994; Piran and Robinson, 2006) and obesity is associated with decreased effectiveness of antidepressant drugs (Uher et al., 2009). Thus, the impact of food intake (amount and type) on 5-HT systems might be important for understanding the etiology of psychiatric disorders and also for identifying factors that contribute to the sometimes highly variable effectiveness of drugs targeting 5-HT systems.

This study begins to examine whether eating high fat chow alters the sensitivity of rats to drugs acting on 5-HT systems. Among 5-HT receptor subtypes, 5-HT_{1A} receptors are thought to be especially important in the antidepressant actions of selective serotonin reuptake inhibitors (SSRIs). Activation of 5-HT_{1A} receptors in rats (e.g., (+)-8-hydroxy-2-(dipropylamino) tetralin hydrobromide [8-OH-DPAT]) results in characteristic behavioral effects that include lower lip retraction which, unlike some other 5-HT_{1A} receptor mediated effects, is not modified by dopamine receptor antagonists (Berendsen et al., 1989). Separate groups of rats eating standard or high fat chow were tested repeatedly for their sensitivity to 8-OH-DPAT-induced lower lip retraction. Because eating high fat chow increases the sensitivity of rats to quinpirole-induced yawning (Baladi and France, 2009), quinpirole was also studied in order to verify that the feeding conditions in the current study were adequate to change sensitivity to a drug acting on a neurochemical system other than 5-HT. After 6 weeks, rats eating high fat chow were more sensitive than rats eating standard chow to 8-OH-DPAT and to quinpirole; consequently, the reversibility of this enhanced sensitivity was examined by switching feeding conditions for both groups of rats and testing again with 8-OH-DPAT and quinpirole.

Methods

Subjects

Seventeen adult male Sprague-Dawley rats (Harlan, Indianapolis, Indiana, USA) were housed individually on a 12/12-h light/dark cycle (lights on at 0700 h; experiments were conducted during the light period) with free access to water in the home cage. Rats had free access to either a standard laboratory chow (Harlan Teklad 7912) or to a high fat chow (Harlan Teklad 06414), depending on the stage of the experiment (see below). The nutritional content of the standard laboratory chow (by weight) was 5.7% fat and 19.9% protein, with a calculated gross energy content of 4.1 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. All 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 the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources on Life Sciences, National Research Council, National Academy of Sciences, Washington DC, USA).

Experimental Procedure

Drugs with agonist actions at 5-HT_{1A} receptors (e.g., 8-OH-DPAT) can produce lower lip retraction (i.e., so that the lower incisors are visible) in rats (Berendsen et al., 1989; Li and

France, 2008). Drugs with agonist actions at dopamine D₃ and D₂ receptors (e.g., quinpirole) can produce yawning (i.e., phasic opening and closing of the mouth) in rats (Kurashima et al., 1995; Collins et al., 2005; Baladi and France, 2009). Studies on lower lip retraction were conducted in the home cages and studies on yawning were conducted in test cages (same dimensions as the home cages but with no food, water or bedding). A cumulative dosing procedure was used to determine the dose-response curves for 8-OH-DPAT-induced lower lip retraction and quinpirole-induced yawning as described previously (Li and France, 2008; Baladi and France, 2009). For lower lip retraction, each cycle was 10 min in duration; lower lip retraction during the last minute of each 10-min cycle was scored as present or absent. Rats received vehicle (saline; intraperitoneally [i.p.]) at the beginning of the first cycle and increasing doses of 8-OH-DPAT (0.01–0.1 mg/kg, i.p.) at the beginning of subsequent cycles with the cumulative dose increasing by 0.5 log units per injection. For yawning, each cycle was 30 min in duration; yawns were counted and recorded during the last 10 min of each 30-min cycle. Rats received vehicle (i.p.) at the beginning of the first cycle and increasing doses of quinpirole (0.0032–0.32 mg/kg, i.p.) at the beginning of subsequent cycles with the cumulative dose increasing by 0.5 log units per cycle.

At the beginning of the study all rats had free access to standard chow and a dose-response curve was determined for 8-OH-DPAT-induced lower lip retraction (week 0). Rats were then randomly assigned to two groups: for the next 8 weeks (weeks 1–8; phase 1), rats in group 1 (n=8) continued to have free access to standard chow while rats in group 2 (n=9) had free access to high fat chow. Feeding conditions were then reversed and for the next 7 weeks (weeks 9–15; phase 2) rats in group 1 had free access to high fat chow and rats in group 2 had free access to standard chow. Dose-response curves were determined for 8-OH-DPAT-induced lower lip retraction during weeks 1, 2, 6 (phase 1) as well as weeks 9, 10, and 14 (phase 2) while dose-response curve for quinpirole-induced yawning were determined in week 7 (phase 1) and week 15 (phase 2). Rats were weighed on all test days and at other times throughout the study.

Drugs

Quinpirole hydrochloride and 8-OH-DPAT hydrochloride were purchased from Sigma-Aldrich (St. Louis, Missouri, USA) and dissolved in sterile 0.9% saline. Quinpirole and 8-OH-DPAT were injected i.p. and injection volumes were 0.2–1.0 ml.

Data Analyses

Data were analyzed using NCSS statistical software version 2004 for windows (NCSS, Kaysville, UT, USA). Body weight data were analyzed with a repeated-measures ANOVA. A post-hoc Bonferroni test was used to examine significant differences between feeding conditions at each time point. For each 8-OH-DPAT dose-response curve, the smallest dose to produce lower lip retraction was determined for each rat (i.e., minimal effective dose). These doses were log transformed and analyzed (ANOVA) separately for the two phases of the study (i.e., weeks 0–6 for phase 1 and weeks 6–14 for phase 2) and for phase 2 compared to baseline (week 0). Post-hoc tests were used to examine significant differences between feeding conditions at each time point.

ED₅₀ values were determined for quinpirole-induced yawning as described elsewhere (Baladi and France, 2010a). Briefly, ED₅₀ values were calculated for individual rats using linear regression; a maximum effect was determined for each rat and that maximum value was used to calculate all ED₅₀s for that individual. The 95% confidence limits (CLs) were calculated from ED₅₀ values averaged among rats. When the 95% CLs did not overlap between two groups or conditions, the ED₅₀ values were considered to be significantly different.

Results

Body weight was not significantly different between the two groups of rats prior to their assignment to different chow types (i.e., week 0): 363 ± 6 and 372 ± 6 g for groups 1 and 2, respectively. Both groups of rats gained body weight; after 8 weeks of free access to standard chow rats in group 1 gained an average of 85 ± 4 g and after 8 weeks of free access to high fat chow rats in group 2 gained an average of 125 ± 6 g (Fig. 1). Subsequently, the chow type was switched for all rats. After 6 weeks of eating high fat chow, rats in group 1 gained an average of 72 ± 7 g and after 6 weeks of eating standard chow rats in group 2 lost an average of 14 ± 6 g (Fig. 1). Two-way ANOVA revealed a significant main effect of week [$F(9, 135) = 357.7, p < 0.001$] and a significant week by chow type interaction [$F(9, 135) = 38.3, (p < 0.001)$]. However, there was no significant main effect of chow type [$F(1, 135) = 0.7, \text{NS}$]. Multiple comparison analysis revealed that on weeks 1, 2, 6, 7 and 8, the body weight of rats in group 2 was significantly higher than the body weight of rats in group 1, while in weeks 14 and 15 the body weight of rats in group 1 was significantly higher than the body weight of rats in group 2 ($p < 0.05$).

At the beginning of the study when all rats had free access to standard chow, 8-OH-DPAT dose-dependently increased the percentage of rats showing lower lip retraction with all rats showing lower lip retraction at a cumulative dose of 0.1 mg/kg of 8-OH-DPAT (open and closed circles [week 0], upper and middle left panels, Fig. 2). With continued access to standard chow (group 1), sensitivity to 8-OH-DPAT-induced lower lip retraction did not change markedly (upper left panel, Fig. 2). However, in rats eating high fat chow (group 2), sensitivity to 8-OH-DPAT-induced lower lip retraction increased progressively (middle left panel, Fig. 2). The minimal effective dose of 8-OH-DPAT to produce lower lip retraction did not change significantly while group 1 was eating standard chow (open circles, lower panel, Fig. 2) whereas the minimal effective dose of 8-OH-DPAT decreased significantly while group 2 was eating high fat chow (closed triangles, lower panel, Fig. 2). ANOVA revealed a significant main effect of week [$F(3, 45) = 7.2, p < 0.001$]; however, the main effect of chow type [$F(1, 45) = 3.8, \text{NS}$] and the chow type $\times$ weeks interaction [$F(3, 45) = 1.4, \text{NS}$] were not significant. Multiple comparison tests revealed that for group 2 the minimal effective dose was significantly lower in week 6 (mean = 0.052 mg/kg [95% confidence limits = 0.028, 0.076]) as compared with week 0 (0.092 mg/kg [0.078, 0.107]); for group 1 there was no significant difference in the minimal effective dose of 8-OH-DPAT over tests conducted in weeks 0, 1, 2, and 6 (lower panel, Fig. 2).

To examine whether increased sensitivity to 8-OH-DPAT-induced lower lip retraction that was observed in rats eating high fat chow was reversible, feeding conditions were switched with rats in group 2 having free access to standard chow and rats in group 1 (that previously ate standard chow) having free access to high fat chow. With a change to high fat chow the sensitivity to 8-OH-DPAT-induced lower lip retraction of rats in group 1 increased significantly (upper right panel, Fig. 2). The increased sensitivity to 8-OH-DPAT induced lower lip retraction that was observed when rats in group 2 ate high fat chow (middle left panel, and closed triangles lower panel, Fig. 2) did not change when those rats ate standard chow; that is, the shift to the left in the 8-OH-DPAT dose-response curve that occurred when these rats ate high fat chow was also evident when these rats ate standard chow (middle panels and lower panel, Fig. 2). Two-way ANOVA revealed a significant main effect of week [$F(3, 45) = 4.2, p < 0.05$] and a significant week by group interaction [$F(3, 45) = 5.49, p < 0.005$], but there was no significant main effect of group [$F(1, 45) = 0.14, \text{NS}$]. Multiple comparison tests revealed that for group 1 the minimal effective dose in weeks 10 (0.057 mg/kg [0.026, 0.089]) and 14 (0.044 mg/kg [0.018, 0.069]) was significantly lower than in week 6 (0.083 mg/kg [0.061, 0.105]); for group 2 there was no significant difference in the minimal effective dose in weeks 9, 10 or 14 as compared with week 6 (lower panel,

Fig. 2). However, in comparison with week 0, the minimal effective dose of 8-OH-DPAT was significantly smaller in weeks 10 and 14 for group 1 and in weeks 9, 10 and 14 for group 2.

In tests conducted during week 7, small doses of quinpirole increased and larger doses decreased yawning in all rats, yielding an inverted-U-shaped dose-response curve (left panel, Fig. 3). The maximum number of yawns (mean $\pm$ S.E.M.) was 6.8 ± 1.0 in group 1 (standard chow) at a dose 0.1 mg/kg quinpirole and 9.1 ± 1.1 in group 2 (high fat chow) at a dose of 0.032 mg/kg quinpirole. The quinpirole dose-response curve was shifted significantly to the left in rats eating high fat chow compared with the quinpirole dose-response curve determined in rats eating standard chow; the ascending and descending limbs of the quinpirole dose-response curve in rats eating high fat chow (group 2) were shifted 4.5 fold and 2.1 fold to the left, respectively, of the dose-response curve determined in rats eating standard chow (group 1 [Fig. 3 and Table 1]).

With a change to high fat chow the sensitivity of rats in group 1 to quinpirole-induced yawning increased significantly (compare open and closed circles, Fig. 3). The ascending and descending limbs of the quinpirole dose-response curve were shifted 3.7- and 2.5-fold leftward, respectively (Table 1), when rats in group 1 ate high fat chow as compared with the quinpirole dose-response curve determined when the same rats ate standard chow (Fig. 3, Table 1). Moreover, the maximum number of yawns was greater (9.9 ± 0.9 for high fat chow and 6.8 ± 1.0 for standard chow) and occurred with a smaller dose (0.032 mg/kg for high fat chow and 0.1 mg/kg for standard chow) when rats in group 1 ate high fat chow. In contrast, after 7 weeks of access to standard chow, the quinpirole dose-response curve in group 2 remained shifted to the left compared with the dose-response curve determined when the same rats were eating high fat chow (Fig. 3, Table 1), although the maximum number of yawns was less when rats in group 2 ate standard chow (6.1 ± 1.0) as compared with high fat chow (9.1 ± 1.1). The initial difference in sensitivity to quinpirole (4.5- and 2.1-fold for the ascending and descending limbs of the dose-response curve, respectively [Table 1]) observed between groups (i.e., when group 1 had access to standard chow and group 2 to high fat chow) was no longer evident when feeding conditions were reversed (1.2- and 1.2-fold for the ascending and descending limbs of the dose-response curve, respectively [Table 1]).

Discussion

Results of the current study demonstrate that rats eating high fat chow are more sensitive than rats eating standard chow to the behavioral effects of a drug (8-OH-DPAT) acting directly at 5-HT_{1A} receptors. Moreover, sensitivity to 8-OH-DPAT-induced lower lip retraction did not return to normal when the high fat chow was replaced with the standard chow, suggesting that eating high fat food might produce long-lasting changes in 5-HT systems.

The amount and type of food rats eat can markedly affect brain neurochemistry and the behavioral effects of drugs; however, much of what is known about the impact of food intake on the unconditioned behavioral effects of drugs is from studies on drugs acting directly on dopamine receptors. The current study extends the impact of food intake on sensitivity to the behavioral effects to a direct-acting 5-HT receptor agonist. Lower lip retraction is an effect that occurs reliably with drugs that have agonist activity at 5-HT_{1A} receptors (e.g., Koek et al., 2000) and modest food restriction (10 g/day for 1 week) decreases the sensitivity of rats to 8-OH-DPAT-induced lower lip retraction; restoring free access to standard chow restores normal sensitivity to 8-OH-DPAT (Li and France, 2008). Food restriction also increases 5-HT clearance from brain and decreases the effectiveness of

the SSRI escitalopram in a forced swimming test (France et al., 2009), a procedure that is used widely to evaluate drugs with antidepressant activity in humans. Not all effects of SSRIs in rats are decreased by food restriction; for example, fluoxetine-induced hypothermia is not significantly altered by food restriction (Li et al., 2009). Little is known about the impact of other feeding conditions on the effects of drugs acting on 5-HT systems. The current study shows that free access to the high fat chow increases sensitivity to 8-OH-DPAT-induced lower lip retraction. In rats eating high fat chow the 8-OH-DPAT dose-response curve shifted to the left in a time-dependent manner, as compared with rats eating standard chow. This leftward shift in the 8-OH-DPAT dose-response curve in rats eating high fat chow was not due to repeated testing because the 8-OH-DPAT dose-response curve did not change significantly after repeated testing in rats eating standard chow. Moreover, when the chow type was switched, rats that previously ate standard chow became more sensitive to 8-OH-DPAT-induced lower retraction when they ate high fat chow. Increased sensitivity to 8-OH-DPAT induced lower lip retraction in rats eating high fat chow was not reversed when those rats instead ate standard chow, suggesting that diet-related changes in drug sensitivity are long lasting. These results are consistent with a recent report (Baladi et al., 2011) showing significant increases in sensitivity to drugs acting on dopamine systems in rats eating high fat chow, even under conditions where access to chow was restricted so as to match the body weight of rats eating standard chow. Thus, eating fat, and not gaining excessive body weight, can alter sensitivity to the behavioral effects of drugs acting on monoamine systems.

Recently it was reported that free access to high fat chow decreases the effectiveness of fluoxetine in an unpredictable chronic mild stress procedure in mice (Isingrini et al., 2010). Differences in species (rats versus mice), drugs (escitalopram versus fluoxetine), and procedures (forced swimming versus unpredictable chronic mild stress) preclude a simple comparison between studies; however, it appears as though both eating high fat chow (Isingrini et al., 2010) and food restriction (France et al., 2009) decrease sensitivity to SSRIs. In contrast, eating high fat chow increases whereas food restriction decreases sensitivity to a direct-acting 5-HT receptor agonist. Thus, the amount and type of food eaten might differentially regulate sensitivity to drugs acting at 5-HT receptors or transporters.

Quinpirole has agonist activity at dopamine D₂ and D₃ receptors and produces yawning in rats (Baladi and France, 2009, 2010b; Collins et al., 2005, 2007). Similar to what is observed with 8-OH-DPAT-induced lower lip retraction, food restriction decreases (e.g., Sevak et al., 2008) whereas free access to high fat chow increases (Baladi and France, 2009) the sensitivity of rats to quinpirole-induced yawning. And just as sensitivity to 8-OH-DPAT-induced lower lip retraction did not return to normal (current study) when rats that previously ate high fat chow were given access to standard chow, increased sensitivity of rats to quinpirole-induced yawning also did not return to normal when rats were returned to eating standard chow. A prior study (Baladi and France, 2009) showed that sensitivity to quinpirole-induced yawning in rats eating high fat chow did not return to normal after 2 weeks of eating standard chow; the current study extends those findings and shows that sensitivity does not return to normal after 7 weeks of eating standard chow. Thus, eating high fat chow markedly alters sensitivity to the behavioral effects of drugs acting directly on 5-HT or dopamine systems and those changes appear to persist even when rats no longer have access to high fat chow. These results are consistent with studies showing that in rats maternal consumption of high fat chow during the perinatal period induces long lasting effects in dopamine function and in the behavior of adult offspring (Naef et al., 2007).

This study examined whether eating high fat chow, which has been shown to increase sensitivity of rats to the behavioral effects of drugs acting directly at dopamine receptors, increases the sensitivity of rats to the behavioral effects of a drug acting directly at 5-HT_{1A}

receptors. Free access to high fat chow increases sensitivity to 8-OH-DPAT-induced lower lip retraction and, in the same rats, to quinpirole-induced yawning. For both drugs, increased sensitivity continued when rats were returned to eating standard chow. The mechanism(s) mediating these changes is unknown; however, hormones such as insulin and leptin might be involved. For example, hypoinsulinemia decreases sensitivity to the behavioral effects of the SSRI fluoxetine (Miyata et al., 2004a) and to behavioral effects of agonists acting at 5-HT_{1A} or 5-HT₂ receptors (Li and France 2008; Li et al., 2009; Miyata et al., 2004b). Hyperinsulinemia increases and hypoinsulinemia decreases dopamine transporter activity (Figlewicz et al., 1994; Owens et al., 2005, respectively) and amphetamine self-administration behavior is reduced in diabetic rats (Galici et al., 2003). Since hormone levels are markedly affected by diet, these hormones might contribute to the changes of sensitivity to 5-HT and dopamine receptor agonists. Understanding the functional relationship between nutritional status and the behavioral effects of drugs acting at 5-HT and dopamine systems could promote understanding of co-morbidity of eating disorders, depression, and substance abuse.

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Fig. 1.

Body weight of rats with free access to standard laboratory chow (open symbols) or free access to high fat chow (closed symbols). The vertical dashed lines indicate a change in chow type for both groups of rats as follows: initially (week 0) all rats had free access to standard chow; during weeks 1-8 (phase 1) rats in group 1 had free access to standard chow (open circles) and rats in group 2 had free access to high fat chow (closed triangles); during weeks 9-15 (phase 2) rats in group 1 had free access to high fat chow (closed circles) and rats in group 2 had free access to standard chow (closed triangles). Each symbol represents the mean $\pm$ S.E.M. of 8 (group 1) or 9 (group 2) rats. * = significant ($p < 0.05$) difference between group 1 and group 2.

Fig. 2.

The percentage of rats showing lower lip retraction after receiving (+)-8-hydroxy-2-(dipropylamino) tetralin hydrobromide (8-OH-DPAT; upper and middle panels) and the minimal effective dose of 8-OH-DPAT for producing lower lip retraction (lower panel) under different feeding conditions. The vertical dashed lines indicate a change in chow type for both groups of rats as follows: initially (week 0) all rats had free access to standard chow; during weeks 1-8 (phase 1) rats in group 1 had free access to standard chow (open circles) and rats in group 2 had free access to high fat chow (closed triangles); during weeks 9-15 (phase 2) rats in group 1 had free access to high fat chow (closed circles) and rats in group 2 had free access to standard chow (closed triangles). In all panels, open symbols indicate results obtained in rats eating standard chow and closed symbols indicate results obtained in rats eating high fat chow. Upper and middle panels: horizontal axes, dose in mg/kg body weight; vertical axes, percentage of animals showing lower lip retraction. Lower panel: horizontal axis: week in the study; vertical axis minimal effective dose (mean $\pm$ S.E.M.) in mg/kg body weight. Each symbol represents the mean $\pm$ S.E.M. of 8 (group 1) or 9 (group 2) rats. * = significant difference between group 1 and group 2. \$ = significant difference between week 0 and week 6 for group 2 (open and closed triangles). # = significant difference between week 6 and weeks 10 and 14 for group 1 (open and closed circles).

Fig. 3.

Yawning in rats with free access to standard chow (open symbols) or to high fat chow (closed symbols). Left panel shows quinpirole-induced yawning in week 7 when rats in group 1 ate standard chow (open circles) and rats in group 2 ate high fat chow (closed triangles). Right panel shows quinpirole-induced yawning in week 15 when rats in group 1 ate high fat chow (closed circles) and rats in group 2 ate standard chow (open triangles). Horizontal axes: dose of quinpirole in mg/kg body weight; V = vehicle. Vertical axis: average number of yawns ($\pm$ S.E.M.) in a 10-min observation period for 8 (group 1) or 9 (group 2) rats.

Table 1

ED₅₀ values and dose ratios for quinpirole-induced yawning.

Group 1					
Standard Chow		High Fat Chow		Ratio (Standard/High Fat)	
Ascending	Descending	Ascending	Descending	Ascending	Descending
0.025 ^a	0.148	0.007	0.060	3.7	2.5
0.022, 0.029 ^b	0.136, 0.161	0.006, 0.008	0.057, 0.063		
Group 2					
High Fat Chow		Standard Chow		Ratio (High Fat/Standard)	
Ascending	Descending	Ascending	Descending	Ascending	Descending
0.006	0.070	0.006	0.052	1.0	1.3
0.005, 0.007	0.065, 0.074	0.005, 0.006	0.045, 0.061		
Ratio (Group 1/Group 2)					
Ascending	Descending	Ascending	Descending	Ascending	Descending
4.5	2.1	2.1	1.2	1.2	1.2

^aMean ED₅₀ in mg/kg (n = 8 [group 1] or 9 [group 2])

^b95% Confidence limits