Published in final edited form as:

Behav Pharmacol. 2019 June ; 30(4): 370–375. doi:10.1097/FBP.0000000000000439.

Dietary supplementation with fish oil reverses high fat diet-induced enhanced sensitivity to the behavioral effects of quinpirole

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Abstract

Consuming a high fat diet can lead to many negative health consequences, such as obesity, insulin resistance, and enhanced sensitivity to drugs acting on dopamine systems. It has recently been demonstrated that dietary supplementation with fish oil, which is rich in omega-3 fatty acids, can prevent this high fat diet-induced enhanced sensitivity to dopaminergic drugs from developing. However, it is not known if fish oil supplementation can reverse this effect once it has already developed. In order to test the hypothesis that dietary supplementation with fish oil will reverse high fat diet-induced enhanced sensitivity to quinpirole, a dopamine D₂/D₃ receptor agonist, male Sprague-Dawley rats were fed either standard chow (17% kcal from fat), high fat chow (60% kcal from fat), standard chow or high fat chow supplemented with 20% (w/w) fish oil. Body weight, food consumption, and sensitivity to quinpirole-induced (0.0032–0.32 mg/kg) penile erections were examined throughout the course of the experiment. Eating high fat chow enhanced sensitivity of rats to quinpirole-induced penile erections (i.e., resulted in a leftward shift of the ascending limb of the dose-response curve). Dietary supplementation with fish oil successfully treated this effect, since dose-response curves were not different for rats eating standard chow and rats eating high fat chow with fish oil. These results suggest that in addition to preventing the negative health consequences of eating a high fat diet, fish oil can also reverse some of these consequences once they have developed.

Keywords

addiction; obesity; dopamine; rat; omega-3 fatty acids; fish oil; quinpirole

Introduction

Eating a high fat diet can lead to obesity and type 2 diabetes (USDA, 2010). Preclinical reports have demonstrated that eating high fat laboratory chow increases sensitivity of rats to the behavioral effects of drugs that act on dopamine receptors (e.g., dopamine D₂/D₃

receptor agonists like quinpirole; see Baladi *et al.*, 2012 for a review). Quinpirole induces several unconditioned behavioral effects, including yawning and penile erections (PE), which often result in inverted U-shaped dose-response curves, such that smaller doses of quinpirole increase, while larger doses of quinpirole decrease, yawning and PE (Collins *et al.*, 2005; 2009). Further, it has been well established that the ascending limbs of the dose-response curves for both dopamine agonist-elicited yawning and PE are mediated by the dopamine D₃ receptor, while the descending limbs are mediated by the dopamine D₂ receptor (Collins *et al.*, 2005; 2009). Rats eating high fat chow are more sensitive to quinpirole-induced yawning than rats eating standard chow (Baladi & France, 2019; Hernandez-Casner *et al.*, 2017; see Baladi *et al.*, 2012 for a review), though it is not known if sensitivity to quinpirole-induced PE is also enhanced.

Dietary supplementation with fish oil, which is rich in omega-3 polyunsaturated fatty acids, is successful in preventing some of the negative health consequences associated with eating a high fat diet (e.g., insulin resistance and obesity; Hainault *et al.*, 1993). In previous reports, when fish oil was added directly to the high fat chow, rats never developed enhanced sensitivity to the behavioral effects of dopaminergic drugs (Hernandez-Casner *et al.*, 2017; Serafine *et al.*, 2016). In other words, dietary supplementation with fish oil prevented high fat chow-induced enhanced sensitivity to quinpirole (Hernandez-Casner *et al.*, 2017). However, it is not known if dietary supplementation can reverse the high fat chow-induced enhanced sensitivity to quinpirole after it has already developed (e.g., after the dose-response curve has shifted to the left). Clinically, drugs with similar mechanisms of action to quinpirole (e.g., apomorphine) are FDA approved for the treatment of erectile dysfunction. Therefore it is possible that if diet impacts sensitivity of individuals to PE produced by dopamine receptor agonists, it could have implications for individuals taking these drugs for erectile dysfunction. Drugs that work on dopamine systems are also used to treat a variety of other conditions (including schizophrenia, Parkinson's disease, and attention deficit hyperactivity disorder) and many recreational drugs also target this same neurotransmitter system (including cocaine and methamphetamine). As such, if the high fat diet-induced changes in sensitivity to dopaminergic drugs can be reversed with an over-the-counter dietary supplement, this could be a cost-effective approach to augment therapeutic drugs, especially among individuals that eat foods that are high in fat. The present report examined the ability of high fat chow to enhance sensitivity of rats to quinpirole-induced PE and the ability of dietary supplementation with fish oil to reverse the effects of eating high fat chow.

Methods

Subjects

Adolescent male Sprague-Dawley rats ($n=31$), approximately 20 days of age and weighing 62.1 ± 1 g at the beginning of the experiment, were purchased from Envigo (Envigo, Indianapolis, IN, USA). Rats were housed individually in an environmentally controlled room (20–26°C, 30–70% relative humidity) and in a 12/12 light dark cycle with lights on at 08.00 h. All rats had free access to food and water in home cages, except during experimental testing (described below). Animals were maintained and experiments were conducted in accordance with the Institutional Animal Care and Use Committee at The

University of Texas at El Paso, and in accordance with the 2011 Guide for Care and Use of Laboratory Animals (Institute of Laboratory Animal Research, Division of Earth and Life Sciences, the National Research Council, and the National Academy of Sciences).

Feeding Conditions and Body Weight

All rats had free access to standard laboratory chow upon arrival and during initial quinpirole testing for the first week of the study. Subjects were then assigned to one of two pretreatment feeding conditions. Specifically, rats had free access to either standard laboratory chow (17% kcal from fat, $n=15$), or high fat chow (60% kcal from fat, $n=16$) for 8 weeks of the study following baseline testing. Following this 8-week pretreatment phase, subjects were assigned to one of four treatment feeding conditions. Separate groups of rats had free access to standard laboratory chow ($n=7$) with a gross energy content of 4.1 kcal/g, high fat chow ($n=8$) with a gross energy content of 5.1 kcal/g, standard chow supplemented with 20% (w/w) fish oil ($n=8$) with a gross energy content of 4.28 kcal/g, or high fat chow supplemented with 20% (w/w) fish oil ($n=8$) with a gross energy content of 5.9 kcal/g. The study was conducted in two different cohorts of rats ($n=7-8$ for pretreatment conditions and $n=4-5$ for treatment conditions, per cohort). Since there were no differences between cohorts, rats from both cohorts are represented in all figures. Rats were fed at the same time daily throughout the experiment (approximately 08.00–10.00 h). Body weights were measured on a daily basis throughout the experiment, immediately before feeding.

Penile Erections

On testing days, rats were moved to clear, plastic test cages (identical to home cages; $365 \times 207 \times 140$ mm) without food, water or bedding, and animals were restricted to half of the cage length (using Plexiglas® dividers) to maintain visibility for behavior. The animals were habituated to the chamber for 15 minutes. Rats were injected (i.p.) with saline followed by increasing cumulative doses of quinpirole (0.0032, 0.01, 0.032, 0.1, 0.32 mg/kg). Quinpirole was administered every 30 minutes and beginning 20 minutes after each injection, PE behavior was observed for 10 minutes. Quinpirole was administered every week on the same day and time for a total of 17 weeks, including under baseline conditions (e.g., when all rats were eating standard chow during the first week of the experiment). PE observations were recorded on several occasions throughout the study. PE was defined as an upright posture with repeated pelvic thrusts and an emerging engorged penis (Collins *et al.*, 2008). PE were observed in the last 10 minutes of each 30 minute interval.

Body Temperature

During quinpirole experiments, body temperature was measured immediately before each injection. Rectal body temperature was observed in a temperature controlled room (20–26°C and 30–70% humidity) by inserting a lubricated thermal probe attached to a thermometer approximately 3 cm into the rectum. All rats were adapted to this procedure by measuring body temperature prior to baseline testing.

Drug

Quinpirole dihydrochloride (Sigma-Aldrich) was dissolved in sterile 0.9% saline and administered i.p. in a volume of 1ml/kg body weight.

Data Analysis

Quinpirole-induced PE are expressed in figures as $PE \pm SEM$ in each 10-minute observation and plotted as a function of cumulative doses of quinpirole. Cumulative doses of quinpirole increased, then decreased PE, resulting in an inverted U-shaped dose-response curve. Differences in weekly dose-response curves between rats eating different diets were analyzed using a two-way repeated measures Analysis of Variance (ANOVA) with diet and dose as factors. In the event of a significant interaction effect, for weeks when there were only two groups (rats eating standard chow and rats eating high fat chow) Sidak's multiple comparisons tests were used to analyze differences between groups. For weeks when there were four groups (rats eating standard chow, rats eating high fat chow, and rats eating standard chow or high fat chow with fish oil dietary supplementation) Tukey's multiple comparisons tests were used to examine differences between groups. Similar ANOVAs were used to compare differences among body weight, food consumption and body temperature.

Results

Body Weight

All rats gained weight throughout the study; however, a two-way ANOVA revealed significant main effects of day [$F(56, 1539) = 168.5, p < 0.0001$] and diet [$F(3, 1539) = 1137, p < 0.001$], but not a significant day by diet interaction (Figure 1A). Bonferroni's multiple comparisons revealed that rats eating high fat chow alone weighed more than rats in all other groups (all $p < 0.001$). Rats eating standard chow with fish oil supplementation weighed more than rats eating standard chow alone and rats eating standard chow alone weighed less than rats in all other groups (all $p < 0.001$).

Food Consumption

Food consumption was measured in grams consumed and is described as a function of day (Figure 1B). A two-way repeated measures ANOVA revealed significant main effects of day [$F(56, 1539) = 65.87, p < 0.001$] and diet [$F(3, 1539) = 2973, p < 0.001$] and a significant day by diet interaction effect [$F(168, 1539) = 5.26, p < 0.001$]. Bonferroni's multiple comparison test revealed that rats eating standard chow consumed more grams on average than rats in all other groups (Figure 1B, all $p < 0.001$). Rats eating standard chow supplemented with fish oil consumed more grams per day on average than rats eating high fat chow alone and rats eating high fat chow supplemented with fish oil (all $p < 0.001$). Rats eating high fat chow alone consumed more grams per day on average than rats eating high fat chow supplemented with fish oil ($p < 0.001$).

When total kcal consumed were analyzed, (Figure 1C) a two-way repeated measures ANOVA revealed significant main effects of day [$F(56, 1539) = 1341, p < 0.001$] and diet [$F(3, 1539) = 10753, p < 0.001$], and a significant day by diet interaction effect [$F(168, 1539) = 111.8, p < 0.001$]. Bonferroni's multiple comparisons test revealed that rats eating standard

chow supplemented with fish oil consumed more kcal per day on average than rats in all other groups (Figure 1C, all $p<0.001$), likely contributing to the significant effects on body weight mentioned above (e.g., rats eating standard chow with fish oil weigh significantly more than rats eating standard chow alone). Rats eating high fat chow consumed more kcal per day on average than rats eating high fat chow supplemented with fish oil and rats eating standard chow alone (all $p<0.001$). Finally, rats eating high fat chow supplemented with fish oil consumed more kcal per day on average than rats eating standard chow alone ($p<0.001$).

Penile Erections

After 4 weeks (e.g., 4 weeks eating high fat or standard chow alone), PE was examined in a subset of animals ($n=7-8$ /group) and a two-way repeated measures ANOVA revealed significant main effect of dose [$F(5, 65) = 21.62, p<0.001$], and a significant diet by dose interaction effect [$F(5, 65) = 6.1, p=0.001$]. Sidak's multiple comparisons test revealed that at the smallest dose of quinpirole (0.0032 mg/kg) induced significantly more PE among rats eating high fat chow, than rats eating standard chow (adjusted $p=0.0009$; Figure 2A). That is, eating high fat chow for 4 weeks significantly enhanced sensitivity of rats to quinpirole-induced PE (Figure 2A) as compared to standard chow fed controls.

PE was assessed again on week 16 (e.g., after 8 initial weeks of eating high fat or standard chow alone, and an additional 8 weeks of eating high fat chow, standard chow, or high fat and standard chow with fish oil supplementation; $n=7-8$ /group; Figure 2B). A two-way ANOVA revealed significant main effects of dose [$F(5, 135) = 18.49, p<0.001$] and diet [$F(3, 27) = 3.43, p<0.05$], and a significant dose by diet interaction [$F(15, 135) = 1.90, p<0.05$] effect. Tukey's multiple comparisons test revealed that the smallest dose of quinpirole (0.0032 mg/kg) induced significantly more PE among rats eating high fat chow than all other groups (all p values 0.0136). Additionally, the next larger cumulative dose of quinpirole (0.01 mg/kg) induced significantly more PE among rats eating high fat chow, than in rats eating high fat chow with fish oil supplementation ($p<0.0136$). Taken together, these results demonstrate that while eating high fat chow significantly enhanced sensitivity of rats to quinpirole-induced PE (open squares; Figure 2A and 2B), fish oil reversed this effect (closed squares; Figure 2B).

Body Temperature

A one-way ANOVA did not reveal any significant differences between groups regarding ED₅₀ values for quinpirole-induced hypothermia [$F(3,27) = 0.46, NS$] (data not shown). That is, quinpirole-induced hypothermia was comparable among all rats regardless of diet.

Discussion

The present report examined the impact of dietary supplementation with fish oil on the effects of eating a high fat diet. Consistent with previous work, eating high fat chow enhanced sensitivity of rats to drugs acting on dopamine systems (e.g. quinpirole; Baladi *et al.*, 2011). The present study assessed PE as the primary unconditioned behavioral effect produced by quinpirole, a dopamine D₂/D₃ receptor agonist, while previous studies were conducted using yawning (Baladi *et al.*, 2011; Baladi and France 2009; Serafine *et al.*,

2014b). Quinpirole-induced yawning and PE are mediated by the same dopamine receptor subtypes (Collins *et al.*, 2005; 2009). Specifically, dopamine D₃ receptor agonism induces yawning and PE, while dopamine D₂ receptor agonism inhibits both behaviors, resulting in inverted U-shaped dose-response curves (Collins *et al.*, 2005; 2009). In the present report, eating high fat chow resulted in a leftward shift to the quinpirole-induced PE dose-response curve (Figure 2A), as has been previously demonstrated with quinpirole-induced yawning (Baladi *et al.*, 2011). In contrast to this enhanced sensitivity to quinpirole-induced PE among rats eating high fat chow, the quinpirole-induced PE dose-response curves for rats eating high fat chow supplemented with fish oil and rats eating standard chow were not significantly different (Figure 2B). That is, dietary supplementation with fish oil reversed the high fat chow-induced enhanced sensitivity to quinpirole-induced PE. Further, the dose-response curve for PE among rats eating standard chow supplemented with fish oil was not different from that for rats eating standard chow alone (Figure 2B), suggesting that fish oil does not have any inhibitory effects on PE behavior when consumed in the absence of high fat chow.

While PE was only examined intermittently throughout the present report, it appears as though quinpirole induced more PE on week 4 than on week 16 (Figure 2A versus 2B). However, this is consistent with other effects induced by quinpirole. For example, from week to week, some fluctuations in maximal effect are observed with regard to quinpirole-induced yawning (see Ramos *et al.*, 2017). Further, in the present report, quinpirole-induced erections were examined at approximately postnatal day 55 (e.g., Week 4) and again at postnatal day 140 (e.g., week 16); therefore the slight decrease in amount of drug-induced PE observed between weeks might be a function of the age of the animals. A similar effect has been reported previously with quinpirole-induced yawning in adolescent versus adult male rats (see Ramos *et al.*, 2017 for a discussion).

Rats eating high fat chow weighed significantly more than rats in all other dietary groups, although all subjects gained weight throughout the study (see Figure 1A). Even though rats eating standard chow supplemented with fish oil gained less weight throughout the experiment than rats eating high fat chow, or high fat chow with fish oil, they consumed the most amount of kcal per day on average of any group (similar to what has been reported previously, Hernandez-Casner *et al.*, 2017). Greater kcal intake does not correlate with greater body weight; therefore, it is possible that fish oil supplementation is impacting metabolism. However, other quinpirole-induced effects (e.g. hypothermia) were comparable across all feeding conditions, suggesting that the pharmacokinetic effects of quinpirole are not different among rats eating different diets.

Although it has been well established that eating a high fat diet can cause dysfunction to dopamine systems (Baladi *et al.*, 2012; Serafine *et al.*, 2014b), the mechanisms underlying this effect are not well understood. Dysregulation of adipokines have been linked to metabolic disease such as obesity and type 2 diabetes (Kalupahana *et al.*, 2010). It is possible that this dysregulation is also impacting dopamine pathways through increases in inflammatory cytokines and the development of insulin resistance (Flock *et al.*, 2013). In fact, changes to insulin signaling have been shown to directly impact dopamine systems by decreasing dopamine transporter function (Speed *et al.*, 2011). Further, insulin-activated

protein kinases are decreased in rats eating high fat chow (Speed *et al.*, 2011; Ramos *et al.*, 2017). However, the effects on sensitivity to dopaminergic drugs are apparent prior to the development of insulin resistance and in the absence of any significant increases in proinflammatory cytokines (Serafine *et al.*, 2016). That is, these effects all occur as a result of eating high fat chow, but perhaps the effects on immune and insulin systems are occurring concurrently to (rather than underlying) the high fat chow-induced enhanced sensitivity to dopaminergic drugs described here and elsewhere (Hernandez-Casner *et al.*, 2017).

The mechanisms by which fish oil reverses the effects of eating high fat chow in the present report also remain unclear. Fish oil, which contains eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), long-chain omega-3 polyunsaturated fatty acids, prevents obesity, insulin resistance and inflammation caused by eating high fat chow (Hainault *et al.*, 1993; Pimentel *et al.*, 2013). Furthermore, supplementation with EPA alone has been successful in reducing high fat chow-induced insulin resistance (Kalupahana *et al.*, 2010). One important caveat is that in the present report, only one concentration of fish oil was used, based on previous work (Hernandez-Casner *et al.*, 2017; Serafine *et al.*, 2016). An estimate of 1 gram per day is recommended for humans (NIH Office of Dietary Supplements, 2016), suggesting that the concentration used in the present report might be relatively large compared to what the general population typically ingests. Future experiments will investigate both smaller concentrations of fish oil, as well as the relative contribution of the individual omega-3 fatty acid constituents found in fish oil in mediating this effect. Finally, given that changes in drug sensitivity occur prior to changes in insulin sensitivity and inflammation, these data suggest that changes in sensitivity to dopaminergic drugs could be a possible early indicator of future development of metabolic disease. Such an early indicator would allow for the evaluation of early therapeutic interventions for metabolic disease.

Acknowledgments

This work was supported by a grant from the Library, Equipment, Repair and Rehabilitation program through The University of Texas Systems (KMS). Research reported in this manuscript was supported by the National Institute of General Medical Sciences of the National Institutes of Health under linked Award Numbers RL5GM118969, TL4GM118971, and UL1GM118970 as well as the National Institute on Drug Abuse of the National Institutes of Health under Award Number 2R25DA033413-06. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Figure 1.

Mean ($\pm$ SEM) body weight of rats eating standard chow, high fat chow, standard chow with fish oil or high fat chow with fish oil (left panel); $n=7-8$ /group. Mean ($\pm$ SEM) daily food intake in grams (middle panel) and in kcal (right panel) for rats eating standard chow, high fat chow, standard chow with fish oil, or high fat chow with fish oil; $n=7-8$ /group.

Figure 2.

Mean ($\pm$ SEM) number of PE observed, during week 4 (Figure 2A) and week 16 (Figure 2B), in each 10-min observation period for rats eating standard chow (black circles), high fat chow (white squares), standard chow with fish oil (gray circles), or high fat chow with fish oil (gray squares); $n=7-8$ /group. *denotes that 0.0032 mg/kg quinpirole induced significantly more PE among rats eating high fat chow than among rats in all other groups; ^denotes that 0.01 mg/kg quinpirole induced significantly more PE among rats eating high fat chow, than among rats eating high fat chow with fish oil supplementation.