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Dietary supplementation with fish oil prevents high fat diet-induced enhancement of sensitivity to the locomotor stimulating effects of cocaine in adolescent female rats

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ABSTRACT

Background: Eating a diet high in fat can lead to obesity, chronic metabolic disease, and increased inflammation in both the central and peripheral nervous systems. Dietary supplements that are high in omega-3 polyunsaturated fatty acids can reduce or prevent these negative health consequences in rats. Eating high fat chow also increases the sensitivity of rats to behavioral effects of drugs acting on dopamine systems (e.g., cocaine), and this effect is greatest in adolescent females.
Methods: The present experiment tested the hypothesis that dietary supplementation with fish oil prevents high fat chow induced increases in sensitivity to cocaine in adolescent female rats. Female Sprague-Dawley rats (post-natal day 25–27) ate standard laboratory chow (5.7% fat), high fat chow (34.4% fat), or high fat chow supplemented with fish oil (20% w/w). Cocaine dose dependently (1–17.8 mg/kg) increased locomotion and induced sensitization across 6 weeks of once-weekly testing in all rats; however, these effects were greatest in rats eating high fat chow.
Results: Dietary supplementation with fish oil prevented enhanced locomotion and sensitization in rats eating high fat chow. There were no differences in inflammatory markers in plasma or the hypothalamus among dietary conditions.
Conclusions: These results demonstrate that dietary supplementation with fish oil can prevent high fat diet-induced sensitization to cocaine, but they fail to support the view that these effects are due to changes in proinflammatory cytokines. These data add to a growing literature on the relationship between diet and drug abuse and extend the potential health benefits of fish oil to stimulant drug abuse prevention.

1. Introduction

Feeding conditions (i.e., type and amount of food consumed) can impact sensitivity of rats to the behavioral effects of drugs acting on dopamine systems (Baladi et al., 2012a; Collins et al., 2008). For example, eating high fat chow increases yawning induced by direct-acting dopamine receptor agonists (i.e., quinpirole; Baladi et al., 2011; Baladi and France, 2010). Similarly, eating high fat chow enhances the sensitivity of rats to cocaine-induced locomotion and sensitization (Baladi et al., 2012b, 2015). Females are more sensitive than males to cocaine (Anker and Carroll, 2011; Lynch and Carroll, 1999; Chin et al., 2001) and the impact of eating high fat chow on sensitivity to cocaine is greater in females than in males (Baladi et al., 2015, 2011; Serafine et al., 2014b) and is more dramatic in adolescent rats compared with adults (Baladi et al., 2012b, 2015).

The mechanism underlying this diet-induced enhancement in drug sensitivity is not known; however, eating high fat chow also causes several other negative health consequences, including obesity and insulin resistance (Baladi et al., 2011; Liu et al., 2013; Serafine et al., 2014a). Insulin signaling can impact dopamine systems (Daws et al., 2011); for example, dopamine transporter expression and function are decreased in obese rats and in rats that are insulin resistant (Narayanswami et al., 2013; Owens et al., 2012; South and Huang, 2008; Speed et al., 2011; Williams et al., 2007). However, enhanced sensitivity to drugs acting on dopamine systems occurs even in the absence of diet-induced obesity (see

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Baladi et al., 2012b, 2015) and insulin resistance (Serafine et al., 2014a). Thus, eating a high fat diet in the absence of obesity or insulin resistance is sufficient to alter sensitivity to drugs.

Eating high fat chow also increases inflammation, both in adipose tissue and in the hypothalamus (Thaler et al., 2012; Wang et al., 2012). For example, the proinflammatory cytokines tumor necrosis factor (TNF)-alpha and interleukin (IL)-6 are significantly increased in hypothalamic tissue from rats eating high fat chow (Maric et al., 2014; Wang et al., 2012). Diet-induced elevations in proinflammatory markers might underlie the diet-induced enhancement in drug sensitivity; however, this hypothesis has not been systematically examined.

Dietary supplements that are high in omega-3 polyunsaturated fatty acids (e.g., fish oil) can prevent high fat chow-induced obesity, insulin resistance, and hypothalamic inflammation (Cintra et al., 2012; Pimentel et al., 2013). To examine whether fish oil prevents high fat chow-induced enhanced sensitivity to the behavioral effects of cocaine, the present experiment investigated the locomotor stimulating effects of cocaine in female rats eating standard chow, high fat chow, or high fat chow supplemented with fish oil. To examine whether proinflammatory markers (e.g., TNF-alpha and IL-6) that are increased in male rats eating high fat chow are also elevated in female rats eating high fat chow, protein levels of 27 different chemokines and cytokines were analyzed using a Luminex-based assay from plasma and hypothalamic samples taken 24 h after the last cocaine test.

2. Materials and methods

2.1. Subjects

Female Sprague–Dawley rats (n = 38; Harlan, Indianapolis, IN, USA; post-natal day [PND] 20 upon arrival) weighing 70–80 g at the beginning of the experiment (PND 25–27), were housed individually in cages measuring 21.5 × 24 × 20.5 cm high in an environmentally controlled room (24 ± 1 °C, 50 ± 10% relative humidity) that was maintained under a 12:12-h light/dark cycle (light period 0700–1900 h). Rats had free access to food and water in the home cage throughout the experiment (dietary conditions outlined in section 1.2.2.). Rats were weighed daily at 0800 h. Rats were maintained and experiments were conducted in accordance with the Institutional Animal Care and Use Committee, the University of Texas Health Science Center at San Antonio, and with the 2011 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. Feeding conditions

Rats were habituated to the laboratory as well as to the experimental procedures (PND 21–24). All subjects had free access to standard chow upon arrival and during initial tests with cocaine and saline (baseline; PND 25–27) before being randomly assigned to different dietary conditions. Thereafter, and for the duration of the experiment, separate groups of rats had free access to standard laboratory chow (n = 12), free access to a high fat chow (n = 13), or free access to a high fat chow supplemented with 20% (w/w) fish oil (n = 13). Half of the subjects in each diet group were treated with cocaine (n = 20), and the other half were treated with saline (n = 18). All other handling and activity recording were the same among the three groups with tests occurring once per week. The standard chow (Harlan Teklad 7912) had a calculated gross energy content of 3.1 kcal/g, with 17% kcal from fat. The high fat chow (Harlan Teklad 06414) had a calculated energy content of 5.1 kcal/g, with 60% kcal from fat. The supplemented chow contained the same high fat chow, but with 20% (w/w) fish oil (Nordic Naturals Omega-3 Pet), resulting in a calculated energy content of 5.9 kcal/g with 68% kcal from fat. The fish oil was manufactured with d-alpha tocopherol (a preservative) to limit oxidation. The product manufacturer guarantees a minimum of 31% total omega-3 fatty acid content per serving size (1 teaspoon), containing 15% eicosapentaenoic acid and 9% docosahexaenoic acid (www.nordicnaturals.com). Fish oil, and high fat food prepared with fish oil, were refrigerated; daily any uneaten fish oil or high fat chow was discarded and replaced with fresh food.

2.3. Insulin sensitivity

A sample of blood was collected from the tip of the tail following a small incision (using a sterile scalpel blade) and was expressed on a blood-glucose test strip. Glucose values were measured with a commercially available glucose meter (Accu-Chek Aviva; CVS). Based on previous work in this laboratory using female rats (Serafine et al., 2014a), glucose was measured prior to as well as 15, 30, 45, and 75 min after an i.p. injection of 2.0 U/kg insulin. Insulin sensitivity was measured once during the experiment, 4 weeks after assignment to dietary conditions, on a day when no cocaine or saline tests occurred.

2.4. Locomotor activity

Experiments were conducted in Plexiglas® chambers, measuring 26 × 61 × 23 cm high (Instrumentation Services, The University of Texas Health Science Center, San Antonio, TX), equipped with metal floors and located within ventilated sound-attenuating cubicles (MED Associates Inc., St. Albans, VT, USA). Horizontal activity was measured using four pairs of infrared photo beams (Multi-Varimex, Columbus Instruments, Columbus, OH, USA) positioned 4 cm above the floor of the chamber. Photo beams were separated by 15 cm with two photo beams located 8 cm from the ends of the chamber. An interface and computer monitored the experiments and recorded data.

For three consecutive days beginning on PND 21, rats were placed in locomotor chambers for 30 min, after which an i.p. injection of saline (0.2 mL) was administered every 15 min for a total of 5 injections (105 min). Beginning the following week (on PND 25–27), rats were again placed in locomotor chambers for 30 min, after which injections of saline (0.2 mL; n = 18) or cumulative doses of cocaine (1.0, 3.2, 10, 17.8 mg/kg; i.p.; n = 20) preceded by an injection of saline (0.2 mL) were administered every 15 min for a total of 5 injections (105 min). These doses include the ascending limb of the cocaine dose-response curve for locomotor stimulation (Baladi et al., 2012b). Only the ascending limb was included because it was expected that the curve would shift leftward after repeated injections of cocaine. Cocaine tests occurred once per week on the same day and time for a total of 5 weeks (i.e., until PND 60–62). For all locomotor activity experiments, the data are presented for 5-min periods beginning 10 min after injections.

2.5. Brain and plasma inflammation

Plasma and brain tissue were collected from all subjects 24 h following the last saline or cocaine test. Plasma was collected via extracting the trunk blood of the animal, funneling it into an EDTA-coated tube, and centrifuging the tube at room temperature at 10000 rmp for 10 min. The plasma supernatant was removed and stored in centrifuge tubes at −80 °C until analysis. Brain tissue was homogenized in a buffer containing 0.32 M sucrose, 1 mM EDTA, and a protease inhibitor cocktail (cOmplete™ Mini 11836153001, Roche, Indianapolis, IN), and the supernatants were stored at −80 °C until analysis. Concentrations of epidermal growth factor

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