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High fat diet augments amphetamine sensitization in mice: Role of feeding pattern, obesity, and dopamine terminal changes

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ABSTRACT

High fat (HF) diet-induced obesity has been shown to augment behavioral responses to psychostimulants that target the dopamine system. The purpose of this study was to characterize dopamine terminal changes induced by a HF diet that correspond with enhanced locomotor sensitization to amphetamine. C57BL/6J mice had limited (2hr 3 d/week) or extended (24 h 7 d/week) access to a HF diet or standard chow for six weeks. Mice were then repeatedly exposed to amphetamine (AMPH), and their locomotor responses to an amphetamine challenge were measured. Fast scan cyclic voltammetry was used to identify changes in dopamine terminal function after AMPH exposure. Exposure to a HF diet reduced dopamine uptake and increased locomotor responses to acute, high-dose AMPH administration compared to chow fed mice. Microdialysis showed elevated extracellular dopamine in the nucleus accumbens (NAc) coincided with enhanced locomotion after acute AMPH in HF-fed mice. All mice exhibited locomotor sensitization to amphetamine, but both extended and limited access to a HF diet augmented this response. Neither HF-fed group showed the robust amphetamine sensitization-induced increases in dopamine release, reuptake, and amphetamine potency observed in chow fed animals. However, the potency of amphetamine as an uptake inhibitor was significantly elevated after sensitization in mice with extended (but not limited) access to HF. Conversely, after amphetamine sensitization, mice with limited (but not extended) access to HF displayed reduced autoreceptor sensitivity to the D_2/D_3 agonist quinpirole. Additionally, we observed reduced membrane dopamine transporter (DAT) levels after HF, and a shift in DAT localization to the cytosol was detected with limited access to HF. This study showed that different patterns of HF exposure produced distinct dopamine terminal adaptations to repeated AMPH, which differed from chow fed mice, and enhanced sensitization to AMPH. Locomotor sensitization in chow fed mice coincided with elevated DAT function and increased AMPH potency; however, the enhanced behavioral response to AMPH after HF exposure was unique in that it coincided with reduced DAT function and diet pattern-specific adaptations.

1. Introduction

The increasing prevalence of obesity over the past few decades has prompted efforts to better understand the control of food intake, and has sparked debate as to whether over-consumption of food should be considered an addictive disorder. Evolutionarily, natural rewards such as food motivated humans to seek caloric sources out of necessity; however, now that food availability is at an all-time high, the palatability of food has become a primary motivator of consumption. Sweetened high fat (HF) foods are of particular interest because their consumption has been shown to activate reward circuitry in the brain, leading to increased dopamine release in the ventral striatum (Valdivia et al., 2014) in a manner similar to drugs such as cocaine and amphetamine (Volkow et al., 2009). Intake of highly palatable food in rodents has produced behavioral phenotypes that resemble psychostimulant abuse, namely reward deficiency (Johnson and Kenny, 2010) and increased sensitivity to dopamine receptor agonists (Baladi et al., 2012a for review). Recent studies have identified attenuated dopamine D_2 receptor binding in humans after prolonged consumption of high fat foods which resemble changes observed after chronic drug use (Volkow and Wise, 2005). Additionally, individuals seeking treatment for weight management are commonly

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prescribed pharmacotherapies that target the dopamine transporter (DAT), highlighting the involvement of the dopamine system in feeding and food seeking behaviors.

Mesolimbic dopamine signaling contributes to the reinforcing efficacy of psychostimulants (Baik, 2013), and elevated dopamine in the nucleus accumbens (NAc) is a neurochemical hallmark of all abused substances, including food (Wang et al., 2009, 2011). Adaptations in the dopamine system following drug abuse are well documented by neuroimaging studies in humans showing reduced D_2 receptor binding (Volkow et al., 1990) and reduced responsiveness to abused drugs (Volkow et al., 1997). Similar changes have been reported in clinical neuroimaging studies with obese patients, suggesting that they exhibit a comparable dopaminergic phenotype to drug addicts (Wang et al., 2009; Volkow and Wise, 2005). Obese individuals display significantly less D_2 binding than normal weight healthy subjects (Wang et al., 2001) and show reduced striatal activation during the consumption of highly palatable food (Stice et al., 2008). Imaging data provide valuable insight into functional changes that occur in the dopamine system with obesity, but the mechanisms that initiate these changes are not well understood.

Several rodent models of diet-induced obesity have been used to characterize dopaminergic changes produced by excessive food intake. Rats fed a HF-high sugar diet for five weeks had reduced dopamine D_1 and D_2 receptor gene expression in the NAc, an effect that persisted up to 18 days after removal of the diet (Alsio et al., 2010). Similar reductions in D_1 and D_2 gene expression have also been reported in mice after twelve weeks of access to HF (Carlin et al., 2013). Interestingly, increased D_2 receptor binding and decreased DAT protein have been shown after short term (20 day) HF consumption (South and Huang, 2008); however, a marked decrease in ^{3}H-raclopride binding to D_2 receptors and reduced membrane DAT levels were observed in rats given a HF diet for eight weeks (Narayanaswami et al., 2013). Moreover, dopamine reuptake in the NAc was attenuated after six, but not two, weeks of consumption of a HF diet in rats (Cone et al., 2013). Overall these data suggest that the length of HF exposure contributes to the severity of dopamine system impairment, and that dopaminergic dysfunction persists beyond the removal of an obesogenic diet.

The length of exposure to a HF diet magnifies its impact on the dopaminergic system, but several studies suggest that the temporal pattern of HF diet availability contributes to HF reward salience. For example, rats with restricted access to a HF diet (2 h/day) show a binge-like escalation in food intake, which did not engender obesity, compared with rats that have continuous access to the same diet (Corwin et al., 1998). Additionally, intermittent access to HF (1hr, 3 d/week) increased progressive ratio responding for HF rewards compared with rats that received HF food daily (Wojnicki et al., 2010), indicating that the reinforcing efficacy of HF is partially driven by the pattern of HF diet availability. Intermittent access to HF resembles behavioral outcomes observed with intermittent access drug and alcohol paradigms that show escalated alcohol intake (Rosenwasser et al., 2013) and increased reinforcing efficacy of cocaine (Zimmer et al., 2012). Intermittent paradigms have also been shown to engender sensitization to the effects of cocaine or AMPH at dopamine terminals, and produce cross-sensitization to other drugs (Calipari et al., 2014).

The impact of a HF diet on reward-related behaviors has been examined both independently and in conjunction with abused drugs. Extended access to a highly palatable “cafeteria” diet (e.g. chips, cookies, and other calorie dense convenience foods) increased brain stimulation reward thresholds, suggesting a decrease in reward sensitivity, or anhedonia (Johnson and Kenny, 2010). The study by Johnson and Kenny found that elevated reward thresholds persisted for two weeks after the rats returned to normal chow, and that chow fed rats demonstrated an immediate increase in reward thresholds after D_2 receptor knock down, implicating reductions in D_2 receptor sensitivity in this response. Rats consuming a HF diet also showed greater behavioral sensitivity to repeated methamphetamine administration (McGuire et al., 2011) and increased locomotor activity after cocaine injections compared to controls (Baladi et al., 2012b, 2015; Serafine et al., 2015). Given the resemblance between the consequences of HF diet and drug abuse on the dopamine system, it is possible that consumption of a HF diet may influence the actions of psychostimulants by altering dopamine terminal function. Moreover, the consumption of a HF diet disrupts the anorexigenic hormones insulin and leptin, which have been shown to modulate dopamine neuron function (Kleinridders et al., 2015; Thompson and Borgland, 2013). Therefore, we also sought to identify if changes in anorexigenic hormones corresponded with dopamine system changes. The overall purpose of this study was to characterize dopamine terminal changes after unrestricted or limited access to a HF diet, and to evaluate dopamine terminal plasticity in the NAc of HF-fed mice after exposure to AMPH. We hypothesized that 1) access to a HF diet would enhance behavioral sensitization to AMPH by reducing dopamine reuptake and reducing D_2 autoreceptor function, and 2) the amount of exposure to HF would influence the magnitude of dopamine terminal changes.

2. Methods

2.1. Animals and diet

C57BL/6 mice originally purchased from Jackson Laboratories (Bar Harbor, ME) were bred in house to produce six-week-old male mice for all experiments. Two groups of mice ($n = 16$ each) were pair housed with free access to water and either standard lab chow (3.46 kcal/g) (5P00 – Prolab RMH 3000; LabDiet, St. Louis, MO) or a high fat (HF) diet (5.24 kcal/g) (DIO – D12492; Research Diets, New Brunswick, NJ) containing 14% and 60% total kcals from fat, respectively. A third group ($n = 13$) had free access to chow, but had limited access (LimA) to the HF diet for 2 h/day on M, W, and F. After six weeks of the dietary protocol half of the mice from each group went to slice voltammetry experiments (Chow, HF, and LimA), while the other half underwent locomotor testing for AMPH sensitization before proceeding to voltametric analysis (Chow (AMPH), HF (AMPH), and LimA (AMPH)). All experiments were in compliance with the Wake Forest Animal Care and Use Committee and the National Institutes of Health guide for the care and use of Laboratory animals.

2.2. AMPH sensitization

Locomotor experiments were initiated during the first hour of the light cycle, and were conducted using Med Associates mouse locomotor chambers (20 cm × 20 cm × 20 cm; Med Associates, St. Albans, VT) with SOF-811 Activity Monitor (v6.05) analysis software. Overall activity was recorded, and the total distance traveled (cm) was used to assess the behavioral response to AMPH. Mice were allowed to habituate to the chambers for 40 min, at which point they were given saline (ip), and baseline activity was recorded. At the 80 min mark, mice were given an ip injection of D-amphetamine sulfate (Sigma, St. Louis, MO) (0.5 mg/kg or 3.0 mg/kg). The total distance traveled was recorded for another 80 min and AMPH-induced increases in activity were expressed as percent baseline. Mice first received a low AMPH dose (0.5 mg/kg) followed by five high AMPH dose (3.0 mg/kg) trials administered every other day for ten days. Ten days after the last high-dose trial, mice were challenged with a second low AMPH dose to identify whether