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Diet matters: Glucocorticoid-related neuroadaptations associated with calorie intake in female rhesus monkeys

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A B S T R A C T

Exposure to psychosocial stressors increases consumption of palatable, calorically dense diets (CDD) and the risk for obesity, especially in females. While consumption of an obesogenic diet and chronic stress have both been shown to decrease dopamine 2 receptor (D2R) binding and alter functional connectivity (FC) within the prefrontal cortex (PFC) and the nucleus accumbens (NAcc), it remains uncertain how social experience and dietary environment interact to affect reward pathways critical for the regulation of motivated behavior. Using positron emission tomography (PET) and resting state functional connectivity magnetic resonance neuroimaging (rs-fMRI), in female rhesus monkeys maintained in a low calorie chow (n = 18) or a dietary choice condition (chow and a CDD; n = 16) for 12 months, the current study tested the overarching hypothesis that the adverse social experience resulting from subordinate social status would interact with consumption of an obesogenic diet to increase caloric intake that would be predicted by greater cortisol, lower prefrontal D2R binding potential (D2R-BP) and lower PFC-NAcc FC. Results showed that the consequences of adverse social experience imposed by chronic social subordination vary significantly depending on the dietary environment and are associated with alterations in prefrontal D2R-BP and FC in NAcc-PFC sub-regions that predict differences in caloric intake, body weight gain, and fat accumulation. Higher levels of cortisol in the chow-only condition were associated with mild inappetence, as well as increased orbitofrontal (OFC) D2R-BP and greater FC between the NAcc and the dorsolateral PFC (dlPFC) and ventromedial PFC (vmPFC). However, increased cortisol release in females in the dietary choice condition was associated with reduced prefrontal D2R-BP, and opposite FC between the NAcc and the vmPFC and dlPFC observed in the chow-only females. Importantly, the degree of these glucocorticoid-related neuroadaptations predicted significantly more total calorie intake as well as more consumption of the CDD for females having a dietary choice, but had no relation to calorie intake in the chow-only condition. Overall, the current findings suggest that dietary environment modifies the consequences of adverse social experience on reward pathways and appetite regulation and, in an obesogenic dietary environment, may reflect impaired cognitive control of food intake.

1. Introduction

The World Health Organization reports that the global prevalence of obesity approached 600 million adults in 2014 (WHO, 2016) and additional data suggest that 32% of men and 36% of women in the United States are obese (Flegal et al., 2010). Because the health (Hill, 2006) and economic burden (Withrow and Alter, 2011) imposed by obesity are enormous, effective programs to prevent or alleviate obesity are a high priority. Although obesity can be explained in biological terms as the consequence of prolonged positive energy imbalance, complex gene by environment interactions likely affect both sides of energy balance (Feng et al., 2010; Haslam and James, 2005; Ogden et al., 2007). Clearly, a dietary environment that includes calorically dense foods, high in fats and sugars, often leads to increased caloric intake and obesity (la Fleur et al., 2011). However, the underlying neuroadaptations resulting from exposure to an obesogenic diet that lead to

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sustained food intake, increasing the risk for obesity, remain unclear.

Previous studies have shown that intake of calorically dense diets (CDD) induces dopamine (DA) release and activates reward pathways similar to what has been described in psychostimulant use (Volkow et al., 2008; Wise, 2006). Decreases in DA D2 receptor (D2R) binding potential (D2R-BP) within the ventral striatum, including the nucleus accumbens (NAcc) (Haber and Knutson, 2010), involved in reward and motivational processes (Cohen et al., 2010), are predictive of an addictive phenotype (Volkow et al., 2003; Volkow and Wise, 2005) and are observed in obese humans (Wang et al., 2001). This decrease in striatal D2R-BP with drugs of abuse is attributed to increased presynaptic DA release (Volkow and Li, 2004). Prefrontal cortex (PFC) regions, which are connected with the NAcc and are involved in regulating reward and goal-directed behaviors (Haber and Knutson, 2010), are also altered in obese individuals (Volkow et al., 2008). Reduced metabolic activity in the PFC of obese individuals is associated with reductions in striatal D2R (Volkow et al., 2008). Importantly, sustained intake of CDDs reduces striatal D2R expression in obese rats, whereas experimental knockdown of D2R expression increases intake of a CDD in rats (Johnson and Kenny, 2010). Together, these data suggest that impaired DA function within the NAcc and associated changes in PFC activity may be causally linked as well as a consequence of CDD consumption (Kenny, 2011), as is the case with psychostimulant abuse (Koob and Kreek, 2007; Koob and Le Moal, 2001; Tomasi and Volkow, 2013). Additionally, obesity in humans is associated with altered PFC-striatal functional connectivity (FC), as assessed by functional MRI (fMRI) methods (Contreras-Rodriguez et al., 2017; Coveleskie et al., 2015; Stoeckel et al., 2009). In the context of food intake, this decreased corticostriatal FC may reflect lack of cognitive restraint on caloric intake (Nummenmaa et al., 2012). These neuroadaptations are characteristic of a hypodopaminergic state and may contribute to the maintenance of increased caloric intake in an obesogenic dietary environment. However, it remains unclear how these reductions in D2R relate to alterations in PFC-striatal FC and associated increased calorie intake.

It is important to note that not all individuals maintained in an obesogenic dietary environment consume excess calories. Exposure to psychosocial stressors is a risk factor for increased intake of CDDs, a phenomenon that occurs more often in women than men (Laitinen et al., 2002). Furthermore, data from animal studies show calorie consumption increases, particularly those from a CDD, when animals experience chronic social (e.g. social defeat or subordination) (Arce et al., 2010; Foster et al., 2006; Meisel et al., 1990; Michopoulos et al., 2012c; Solomon et al., 2007; Tamashiro et al., 2006; Wilson et al., 2008) or physical (e.g. restraint) stressors (Dallman et al., 2003; Hagan et al., 2003; la Fleur et al., 2005; Warne, 2009). Signals from the limbic-hypothalamic-pituitary-adrenal (LHPA) axis, such cortisol and corticotropin-releasing hormone (CRH), target DA neurons in mesolimbic regions (Harfstrand et al., 1986; Sauvage and Steckler, 2001; Swanson et al., 1983) producing a dysregulation of DA neurotransmission (Izzo et al., 2005) that increases the expression of anhedonia and the risk for developing an addictive phenotype (Anisman and Matheson, 2005; Koob and Kreek, 2007; Koob and Le Moal, 2001). Data showing that stress hormones, particularly glucocorticoids (e.g. cortisol in primates), are key signals changing food salience and increased caloric intake (Warne, 2009) are consistent with the notion that emotional feeding is sustained by activation of the LHPA axis (Michopoulos et al., 2012c; Warne, 2009). The functional consequence of chronic stress is a "reward deficiency syndrome", characterized by reduced DA activity (Blum et al., 1996). Therefore, it is hypothesized that one biobehavioral strategy to overcome this reward deficiency may be to activate DA pathways compromised by stress exposure by consuming diets with fat and sugar to increase levels of DA in the NAcc, a finding not seen when consuming a low caloric diet or palatable food devoid of calories (Bassareo and Di Chiara, 1999; Blackburn et al., 1986; Marinelli et al., 2006; Small et al., 2003).

Our previous studies show that socially subordinate adult female rhesus monkeys, maintained in long-established stable social groups, are mildly inappetent compared with more dominant group mates when fed laboratory chow, but consume nearly twice as many calories as do dominant females when given a choice between chow and a CDD (Arce et al., 2010; Michopoulos et al., 2012c). More recent analyses show that the dietary environment affects DA neurochemistry and appetite in adult females immediately following new social group formation and the acquisition of new social ranks, with lower D2R-BP in the orbital PFC (OFC) was associated with increased caloric intake (Michopoulos et al., 2016). The present study extends these initial observations of these same female rhesus monkeys to determine how social experience and dietary environment interact to affect prefrontal D2R-BP and corticostriatal FC, using positron emission tomography (PET) neuroimaging and resting state (rs)-fMRI, respectively, after one year in a chow or a dietary choice condition. The current study tested the overarching hypothesis that the adverse social experience resulting from subordinate status would interact with consuming an obesogenic diet to increase caloric intake, body weight and body fat. We also hypothesized that greater calorie intake in an obesogenic dietary environment would be predicted by lower prefrontal D2R-BP and weakened PFC-NAcc FC. Specifically, the dorsolateral PFC (dlPFC), ventromedial PFC (vmPFC), OFC, and anterior cingulate cortex (ACC) were assessed due to their connections with the NAcc and their role in incentive-based behavioral responses, goal-directed behavior, reward coding, impulse control and salience/value of food, and anticipation of the benefit/risk ratio of rewards (Haber and Knutson, 2010; Knutson et al., 2005; Yacubian et al., 2006).

2. Methods

2.1. Subjects and group formation

Adult female rhesus monkeys (n = 34) living in one of six breeding groups located at the Yerkes National Primate Research Center (YNPRC) Field Station in Lawrenceville, Georgia were selected as subjects based on age and familiarity with other females. As described previously (Michopoulos et al., 2016), females were removed from their natal groups to form new social groups of four to six females each. Briefly, a sequential group formation process was employed to introduce females in indoor-outdoor pens measuring approximately 144 ft^2 (12 × 12 ft) with a randomized order of introduction, a process that results in immediate formation of a dominance hierarchy (Jarrell et al., 2008; Snyder-Mackler et al., 2016). The Emory University Institutional Animal Care and Use Committee approved all procedures in accordance with the Animal Welfare Act and the U.S. Department of Health and Human Services "Guide for Care and Use of Laboratory Animals."

2.2. Experimental design

Females were randomly assigned to be a member of a new social group (4–6 monkeys per group) and these groups were then randomly assigned to have either access to the standard, low calorie monkey chow (4 groups, n = 18 monkeys) or access to a choice dietary environment wherein both the chow and a CDD were available (3 groups, n = 16 monkeys). The caloric composition of the chow diet (3.45 kcal/g; Lab Diets, St. Louis MO, #5038) was 12% fat, 18% protein, and 4.14% sugar carbohydrate and 65.9% fiber carbohydrate (including 42.4% starch). The calories of the CDD (4.47 kcal/g; Research Diets, New Brunswick NJ, #D07091204S) were distributed as 36% fat, 18% protein, 16.4% sugar carbohydrate and 29.6% fiber-starch carbohydrate. While the chow diet contains a higher concentration of starch compared with the CDD, data show that starch intake is associated with reduced appetite and less body weight gain compared with intake of sugars in CDD (Aller et al., 2011). The rationale for providing access to