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Social change and access to a palatable diet produces differences in reward neurochemistry and appetite in female monkeys

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HIGHLIGHTS

- Social subordination is a model to study the etiology of stress-induced hyperphagia.
- Exposure to a calorically dense diet (CDD) increases overall caloric intake.
- Exposure to CDD increases preference for a CDD over a standard low calorie diet (LCD).
- Less aggression emitted was associated with increased caloric intake with CDD exposure.
- Increased caloric intake was correlated with decreased D2R binding in OPFC.

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ABSTRACT

Understanding factors that contribute to the etiology of obesity is critical for minimizing the effects of obesity-related adverse physical health outcomes. Emotional eating or the inability to control intake of calorically dense diets (CDD) under conditions of psychosocial stress exposure is a potential risk factor for the development of obesity in people. Decreases in dopamine 2 receptors (D2R) availability have been documented in substance abuse and obesity in humans, as well as animal models of chronic stressor exposure. Social subordination in macaques is a well-established animal model of a chronic psychogenic stressor that results in stress axis dysregulation, attenuated striatal D2R levels, and stress-induced hyperphagia in complex dietary environment. However, it remains unclear how these phenotypes emerge as the stressor becomes chronic during the formation of new social groups. Thus, the goal of the current study was to assess how the imposition of social subordination over a four-month period would affect food intake, socioemotional behavior, and D2R binding potential (D2R-BP) in female rhesus monkeys maintained on a typical laboratory chow diet (LCD) compared with those having a choice between a LCD and a CDD. Results showed that access to a CDD leads to increased total caloric intake and preference for a CDD over a LCD. For the dietary choice condition, females directing less aggression towards group mates during the four-month period, a characteristic of lower social status, consumed progressively more calories over the four-month period than more aggressive females. This relation between agonistic behavior and appetite was not observed for females in LCD-only condition. Finally, decreased D2R-BP in the orbitofrontal cortex was predictive of increased overall caloric intake in all females regardless of dietary environment, suggesting that reduced availability of D2R within the prefrontal cortex is associated with unrestrained eating. Studies are continuing to determine how newly imposed dominance ranks continue to affect reward neurochemistry and appetite over time, and how this is influenced by the dietary environment.

1. Introduction

With the prevalence of obesity across the United States estimated to rise to 50% of the population by 2030 [1], understanding its etiology is critical to minimizing the effects of obesity-related adverse physical health outcomes [2,3]. The inability to control intake of highly palatable foods, high in sugars and fats, is one behavioral phenotype that has been linked to increased risk for the development of obesity [4]. Importantly, environmental factors, including access to calorically dense diets (CDD; high in fat and sugar) during exposure to psychosocial stressors, increase individual risk for unrestrained emotional eating and accumulation of body weight and fat mass in humans [5,6]. The importance of the

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dietary environment is highlighted by rodent data that show that exposure to diverse forms of physical and psychosocial stressors results in anorexia in the absence of CDD availability [7–9] and increased caloric intake in the presence of a CDD [10–12]. However, studies are most typically short term in nature, and do not completely address what initiates and sustains this phenotype in people [13–18].

Exposure to chronic psychosocial stressors may lead to stress-induced emotional eating phenotypes via stress-induced alterations in cortico-striatal-limbic reward pathways, similar to what has been described in individuals with substance abuse [19]. While multiple neurochemical systems are likely involved [20], the availability of dopamine D2 receptors (D2R) within the striatum, including the nucleus accumbens, is reduced in humans chronically abusing cocaine [21] or with an obese phenotype [22]. The importance diet for this change in D2R availability is supported by data in male rats fed an obesigenic diet [23]. While psychostimulants or CDDs may reduce D2R availability, results from animal models indicate that exposure to chronic stressors induces a hypodopaminergic state in part by decreases in D2R levels and increases individual risk for substance addiction [24–27]. However, it remains unclear how consumption of a CDD and exposure to a stressor alters D2R availability in cortico-striatal regions that are critical for modulating goal-directed behaviors such as feeding behavior [28].

One translational model of uncontrollable, unpredictable psychogenic stressor exposure typical of human populations that has been employed more recently to study a number of stress-related phenotypes, including hyperphagia in a complex dietary environment, is social subordination in macaque monkeys. When group-housed, macaques (rhesus and cynomolgus monkeys) are organized socially by matrilineal dominance hierarchies that function to maintain group stability [29] and are enforced via threat of aggression or harassment from higher-ranking monkeys towards lower-ranking animals within the social group [29,30]. Lower ranking, or more subordinate animals, are thereby exposed continuously to an adverse social environment, similar to that experienced by people [31]. Critically, the experience of social subordination in female macaques results in diminished glucocorticoid negative feedback inhibition of the limbic-hypothalamic-pituitary-adrenal (LHPA) axis [32,33], a physiological phenotype similar to what has been describe in humans suffering from psychopathology such as depression [34,35]. Furthermore, subordinate macaques show reduced D2R binding potential (D2R-BP) in striatal regions as assessed by positron emission tomography (PET) [27,36].

The advent of an automated feeding system that allows for the continuous quantification of food intake in socially housed, free-feeding monkeys has been leveraged to assess how exposure to chronic psychogenic stress influences food intake in a complex dietary environment wherein animals can choose freely between a CDD and a low calorie standard laboratory monkey diet (LCD) [37]. Several studies using long established social groups of adult female rhesus monkeys show that subordinate group members consume significantly more calories compared to more dominant group mates [38,39] during a brief (two-three week) exposure to this choice dietary condition, a phenotype that is reversed during administration of the corticotropin releasing factor (CRF) type 1 receptor antagonist, Antalarmin [40]. While both dominant and subordinate females prefer the CDD to the LCD in the choice dietary condition, only subordinate females become hyperphagic [39]. This stress-induced hyperphagia in complex dietary environment was observed specifically in subordinate females and occurred in tandem with body weight gain [38]. While these findings parallel reports of stress-induced comfort food ingestion in people [41,42], it is unclear how appetite and changes in D2R-BP in a rich dietary environment are affected as a social stressor is imposed and becomes chronic, a situation that can be modeled in rhesus monkeys as social subordination is imposed during the formation of new social groups. Thus, we sought to determine how the formation of new social groups and the imposition of social subordination over a four-month period would affect food intake in adult female rhesus monkeys maintained on a typical laboratory chow diet compared with those having a choice between the chow diet and CDD. Based on our previous findings, we hypothesized that more subordinate female monkeys who receive more aggression from other group-mates would show significantly greater caloric intake, particularly of a CDD. We also sought to determine how D2R-BP in striatal and prefrontal regions was associated with total and CDD-specific caloric intake after four-months living in new social groups in the two dietary conditions. We hypothesized that increased caloric intake in the presence of the choice dietary environment would exacerbate the reduction of D2R BP in striatal and prefrontal D2R-BP associated with subordinate status.

2. Methods

2.1. Subjects and group formation

Adult female rhesus monkeys (n = 31) living in one of the six breeding groups located at the Yerkes National Primate Research Center (YNPRC) Field Station in Lawrenceville, Georgia were selected as subjects of the current study based on age and familiarity with other females. Upon study inclusion, females were removed from their natal groups to form new social groups of four to six females each as previously described [43]. Briefly, a staggered group formation process was employed to sequentially introduce females in indoor-outdoor pens measuring approximately 144 ft^2 (12 × 12 ft.). The first step of the group formation process was to place two females together in two adjacent pens. After 24 h, the two females were reduced to a single indoor-outdoor pen. A third female was then placed in the adjacent pen separated by a Plexiglas door that allowed for only visual and olfactory access to other females for 24 h, after which she was introduced to the pair of females by reducing the available space down to one pen. This protocol was repeated until all five females were living together in one pen where they remained housed for the duration of the current study. Importantly, the order of introduction was randomized and behavioral data were collected throughout the introduction process to monitor agonistic behavior and to intervene, if necessary [43]. More specifically, the outcome of dyadic interactions between females obtained from weekly 30-minute observations using an established ethogram [43] were used to capture the frequency of aggression received and submission emitted – the behavioral phenotypes used previously to determine dominance ranks of individuals within each group [44]. Based on the outcome of these dyadic agonistic interactions, ordinal ranks within each social group were assigned. Because groups differed in the number of members (4 to 6), relative ranks were calculated by dividing a female's ordinal rank by the number of animals in the group (i.e., rank 1 out of 6 monkeys would equal 0.17). This same ethogram was used during behavioral observations to quantify rates of anxiety-like behavior (i.e. yawning, body shakes, self groom/explore, and body scratching) and social behavior, including proximity initiated towards others and grooming duration [43]. 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

After all females were introduced to form new social groups as described above, the dietary intervention was imposed so that three social groups (n = 15) only had access to the standard monkey chow (LCD; 3.45 kcal/g, Purina 5038) and the other three groups (n = 16) had access to a choice dietary environment wherein both the LCD and a CDD (3.73 kcal/g Purina Typical American Diet #5038) were available. The caloric composition of the LCD was 12% fat, 18% protein, and 4.14% sugar carbohydrate and 65.9% fiber carbohydrate. The calories of the CDD were distributed as 36% fat, 18% protein, 16.4% sugar carbohydrate