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Pre-existing differences in motivation for food and sensitivity to cocaine-induced locomotion in obesity-prone rats

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HIGHLIGHTS

- OP rats are more motivated for food prior to altered metabolism or diet manipulation.
- OP rats are hyper-responsive to cocaine prior to the onset of obesity.
- OP rats over-eat "junk-foods", even in the face of over-abundance.

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ABSTRACT

Obesity is a significant problem in the United States, with roughly one third of adults having a body mass index (BMI) over thirty. Recent evidence from human studies suggests that pre-existing differences in the function of mesolimbic circuits that mediate motivational processes may promote obesity and hamper weight loss. However, few preclinical studies have examined pre-existing neurobehavioral differences related to the function of mesolimbic systems in models of individual susceptibility to obesity. Here, we used selectively bred obesity-prone and obesity-resistant rats to examine 1) the effect of a novel "junk-food" diet on the development of obesity and metabolic dysfunction, 2) over-consumption of "junk-food" in a free access procedure, 3) motivation for food using instrumental procedures, and 4) cocaine-induced locomotor activity as an index of general mesolimbic function. As expected, eating a sugary, fatty, "junk-food" diet exacerbated weight gain and increased fasted insulin levels only in obesity-prone rats. In addition, obesity-prone rats continued to over-consume junk-food during discrete access testing, even when this same food was freely available in the home cage. Furthermore, when asked to press a lever to obtain food in an instrumental task, rates of responding were enhanced in obesity-prone versus obesity-resistant rats. Finally, obesity-prone rats showed a stronger locomotor response to 15 mg/kg cocaine compared to obesity-resistant rats prior to any diet manipulation. This enhanced sensitivity to this dose of cocaine is indicative of basal differences in the function of mesolimbic circuits in obesity-prone rats. We speculate that pre-existing differences in motivational systems may contribute to over-consumption and enhanced motivation in susceptible individuals.

1. Introduction

Obesity is the leading cause of type 2 diabetes, and increases the risk of developing cardiovascular disease and some cancers [20,37,42]. While metabolic dysfunction and deregulation of hypothalamic circuits that regulate hunger and satiety play critical roles [30,36,70], numerous studies have highlighted the importance of neural circuits that mediate reward and motivation in over-consumption of calorie-dense, palatable foods [13,29,49,55,64,66]. These motivational circuits include convergent dopamine inputs from the ventral tegmental area (VTA) and glutamatergic inputs from the prefrontal cortex and amygdala to GABAergic medium spiny neurons in striatal regions including the nucleus accumbens (NAc) and dorsal striatum (DS).

In humans, activation of striatal regions in response to stimuli associated with food (food cues) is enhanced in obese individuals [49,58], even before the onset of obesity [17,40,57]. Thus, it has been proposed that enhanced striatal reactivity to food-cues may hamper weight loss and promote weight gain in susceptible people [7,8,28,31,55]. Furthermore, PET studies have found lower striatal D_2-dopamine receptor binding in obese individuals [68], and genetic variation in D_2-dopamine receptor and dopamine transporter alleles has been linked to obesity in humans [9,54,56], though see also [53]. These data suggest that basal differences in mesolimbic circuits, and striatal function in particular, may contribute to over-eating in people [1,55,67]. However,

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very few studies have examined basal differences in motivation and mesolimbic function in models that capture individual susceptibility to obesity.

Here, we used selectively bred obesity-prone and obesity-resistant rats to examine basal differences in motivation for food using instrumental procedures, and sensitivity to cocaine-induced locomotion as a read out of mesolimbic function. It is well established that the locomotor activating effects of stimulant drugs like amphetamine and cocaine rely in large part on striatal activation, particularly of dopaminergic projections from the VTA to the NAc [48,62], as well as glutamatergic and peptidergic transmission within the striatum [19,25,45,71]. Thus, differences in sensitivity to the locomotor activating effects of cocaine are indicative of alterations in striatal and mesolimbic function [38,63]. Although previous studies have examined the effects of high fat/high sugar diets on mesolimbic systems, no previous studies have examined basal differences in cocaine-induced locomotor activity in obesity-susceptible populations.

The selectively bred rats used here were originally developed by Barry Levin and colleagues (originally referred to as DIO and DR, respectively; [34]). Previous work has shown that basal insulin and leptin levels are disrupted in these obesity-prone rats prior to metabolic dysfunction and overt obesity [32]. These peripheral metabolic signals can directly and indirectly affect the firing of VTA neurons, and modulate dopamine- and glutamate-mediated transmission [5,43]. In addition, previous work has shown that basal and evoked DA release from brain slices is lower in the NAc shell of female obesity-prone rats prior to diet manipulation [21]. However, no studies have examined basal differences in the motivation to obtain food or sensitivity to the locomotor activating effects of cocaine prior to diet manipulation. Examination of basal differences is important because studies in people suggest that differences in the function of striatal circuits may drive the development of obesity [7,12,17,26,27,57–60].

2. Methods

2.1. Subjects

Twelve obesity-prone (OP) and obesity-resistant (OR) non-sibling breeding pairs were purchased from Taconic Laboratories (Hudson, NY). These rat lines were originally established through selective breeding of Sprague Dawley rats [34] and are being maintained by the University of Michigan Breeding Core using an outbred rotational system within closed populations. For all studies, male rats were 70 days old at the start of experiments and were pair-housed on a reverse 12-hour light/dark cycle. All rats had free access to food and water throughout and all measures were made in age-matched rats. Procedures were approved by The University of Michigan Committee on the Use and Care of Animals.

2.2. "Junk-food"

The "junk-food" diet is composed of a mash of: Ruffles original potato chips (40 g), Chips Ahoy original chocolate chip cookies (130 g), Jiff creamy peanut butter (130 g), Nesquik powdered chocolate flavoring (130 g), powdered Lab Diet 5001 (200 g) and water (180 ml), giving a diet composed of 19.6% fat, 14% protein, and 58% carbohydrates (4.5 kcal/g). Ingredients were combined in a food processor. These foods contain a rich mix of sugars, salt, and fats, and were chosen as representatives of "junk foods" implicated in human obesity. Diet composition was based on previous studies establishing individual differences in susceptibility to weight gain due to over consumption [34,35] and was closely matched to kcal/g of standard lab chow (Lab Diet 5001: 4 kcal/g; 4.5% fat, 23% protein, 48.7% carbohydrates; % of caloric content).

2.3. Confirmation of phenotypic differences between obesity-prone and obesity-resistant rats

2.3.1. Weight gain, home cage food intake, and body composition

Selectively bred obesity-prone and obesity-resistant rats were given free access to either standard lab chow or the junk-food mash described above (OP-Junk-food N = 6, OR-Junk-food N = 8; OP-Chow N = 6, OR-Chow N = 6) and were weighed once per week for 4 weeks. After this initial 4-week period, daily home cage consumption was measured in the chow-fed groups (4 consecutive days). Next, these same chow-fed rats were given free access to both junk-food and chow in their home cages and consumption of each diet was measured for an additional 4 days. Body composition measures were made in the chow-fed rats prior to junk-food diet exposure (late adulthood, ~120 days old) and in a separate cohort of chow-fed rats during early adulthood (~70 days old; OP N = 10, OR N = 12). Body composition (fat, lean, and free fluid mass) was measured using an NMR-based analyzer (Minispec LF90II, Bruker Optics) by the University of Michigan Animal Phenotyping Core. Conscious rats were placed in an oblong measuring tube during the 2-minute scan.

2.3.2. Home cage locomotor activity and body temperature

Home cage locomotor activity and body temperature changes were observed over 48 h. Locomotor activity was measured via radio transmitter telemetry devices (model ER-4000 E-Mitter, Mini Mitter Co., Bend, OR) placed within the abdominal cavity (OP N = 6 OR N = 6, ~90 days old). Animals were housed in a standard 12:12 light:dark cycle. Rats were anesthetized with ketamine (90 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.), the abdomen was cleaned with betadine and alcohol, and then a 1–2 cm rostral-caudal incision was made in the skin and underlying musculature to expose the peritoneal cavity. The telemeter was placed inside the peritoneal cavity and the incision closed with absorbable Ethicon Vicryl 5–0 coated suture (muscle) and non-absorbable Ethicon Nylon 5–0 suture (skin). Rats were allowed to recover for 6–8 days before making measurements. The telemeter transmitted activity and temperature data to a receiver (model ER-4000 Receiver, Mini Mitter Co.) placed directly under the home cage of each rat. Locomotor and body temperature data were collected every 5 min over 48 h and were processed in 1 hour bins using Vital View software (Mini Mitter Co.).

2.3.3. Fasted plasma insulin levels

Fasted (16 h) plasma insulin levels were determined after free access to either chow or junk-food in the home cage for 4 weeks (OP-Junk-food N = 6, OR-Junk-food N = 6; OP-Chow N = 4, OR-Chow N = 4). Blood samples were collected via tail nick into tubes containing EDTA (1.6 mg/ml, Sarstedt), and plasma was then isolated by centrifugation (1000 ×*g*, 4 °C, 10 min) and stored (−20 °C) for subsequent analysis. Plasma insulin levels were determined by double-antibody radioimmunoassay using a 125I-Human insulin tracer (Linco Research, St. Charles, MO), a rat insulin standard (Novo Nordisk, Plainsboro, NJ), a guinea pig anti-rat insulin first antibody (Linco Research), and a sheep anti-guinea pig gamma globulin-PEG second antibody (Michigan Diabetes Research Core). The limit of sensitivity for this assay was 1 μU/ml. Inter-assay and intra-assay variability were 11.2% and 3.2%, respectively, at 30.5 μU/ml.

2.4. Over-consumption and instrumental responding for food

2.4.1. Discrete junk-food consumption outside the home cage

Above we measured daily home cage food consumption. Here, using another cohort of rats, discrete junk-food consumption outside the home cage was measured prior to, and during home-cage junk-food diet exposure using a within subjects design (OP N = 9, OR N = 8). Two days prior to the first consumption test rats were given 5 g of junk-food in their home cages to familiarize them with this new food. Rats were then habituated to the test chamber (20 min/day, 3 days) prior to testing.