Archival Report

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Addiction-like Synaptic Impairments in Diet-Induced Obesity

Robyn Mary Brown, Yonatan Michael Kupchik, Sade Spencer, Constanza Garcia-Keller, David C. Spanswick, Andrew John Lawrence, Stephanie Elise Simonds, Danielle Joy Schwartz, Kelsey Ann Jordan, Thomas Clayton Jhou, and Peter William Kalivas

ABSTRACT

BACKGROUND: There is increasing evidence that the pathological overeating underlying some forms of obesity is compulsive in nature and therefore contains elements of an addictive disorder. However, direct physiological evidence linking obesity to synaptic plasticity akin to that occurring in addiction is lacking. We sought to establish whether the propensity to diet-induced obesity (DIO) is associated with addictive-like behavior, as well as synaptic impairments in the nucleus accumbens core considered hallmarks of addiction.

METHODS: Sprague Dawley rats were allowed free access to a palatable diet for 8 weeks then separated by weight gain into DIO-prone and DIO-resistant subgroups. Access to palatable food was then restricted to daily operant self-administration sessions using fixed ratio 1, 3, and 5 and progressive ratio schedules. Subsequently, nucleus accumbens brain slices were prepared, and we tested for changes in the ratio between α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and *N*-methyl-D-aspartate currents and the ability to exhibit long-term depression.

RESULTS: We found that propensity to develop DIO is linked to deficits in the ability to induce long-term depression in the nucleus accumbens, as well as increased potentiation at these synapses as measured by AMPA/*N*-methyl-D-aspartate currents. Consistent with these impairments, we observed addictive-like behavior in DIO-prone rats, including 1) heightened motivation for palatable food; 2) excessive intake; and 3) increased food seeking when food was unavailable.

CONCLUSIONS: Our results show overlap between the propensity for DIO and the synaptic changes associated with facets of addictive behavior, supporting partial coincident neurological underpinnings for compulsive overeating and drug addiction.

Keywords: Food addiction, Glutamate, Long-term depression, Nucleus accumbens, Obesity, Synaptic plasticity

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Obesity is rapidly approaching tobacco use as the leading cause of death in the industrialized world (1). While many factors may underlie obesity, the increasing availability of highly palatable, processed foods is a major contributor. Similar to drugs of abuse, highly palatable foods are powerful reinforcers and interact with brain reward circuitry to promote intake (2–7). As with drug addiction, this can lead to pathological overconsumption in susceptible individuals. Thus, it could be argued that in addition to homeostatic feeding mechanisms, excessive intake of palatable food may be explained by dysfunctions in reward circuitry. Indeed, there is emerging evidence in both humans and rodents that supports a hypothesis that the brain's reward circuitry is dysregulated in certain types of obesity, specifically that which results from compulsive overeating (5,7–17). This can manifest in symptoms that parallel those observed in drug addiction such as uncontrolled and excessive consumption, unsuccessful attempts to cut back or reduce intake, and the continuation of overeating despite adverse consequences (18–20).

The transition to drug addiction has been strongly linked to changes in prefrontal cortex regulation of basal ganglia circuitry (21,22). Using animal models of self-administration and relapse, enduring impairments in glutamatergic transmission and synaptic plasticity have been shown on medium spiny neurons in the nucleus accumbens (22). Neuroadaptations in these synapses can be shared between different chemical classes of addictive drugs (22–25). For example, repeated use of drugs such as cocaine and nicotine produces a long-lasting potentiation of these synapses together with a deficit in the ability to induce synaptic plasticity (23,26–28). Critically, an enduring impairment in the ability to induce long-term depression (LTD) in the nucleus accumbens core subcompartment (NAcore) of animals classified as addiction vulnerable to cocaine, but not as addiction resilient, has been implicated in the transition to addiction (27). These data point to potentiated glutamatergic synapses in the accumbens with an impaired ability to undergo LTD as a pathology in psychostimulant addiction. Thus, we sought to

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examine whether rats prone to obesity due to excessive intake of palatable food would exhibit these cardinal synaptic impairments and show similar characteristics toward food that rats classified as addiction vulnerable show toward drugs. We assessed in rats three addiction-like behaviors, used as hallmarks of both drug addiction and pathological overeating (19,25,29,30): 1) a high motivation to obtain the substance; modeled using a progressive ratio schedule, whereby the effort required to obtain food increases progressively within the session; 2) the rapid consumption of significantly larger than normal amounts of the substance; modeled by measuring intake when access to palatable food was limited; and 3) a lack of control to refrain from seeking the substance; modeled by measuring the persistence of lever-pressing during periods that signaled reward unavailability.

METHODS AND MATERIALS

Experimental Subjects

Experimentally naive, outbred male Sprague Dawley rats (Charles River Laboratories, Raleigh, North Carolina) weighing 250 g to 300 g at the start of the experiment were housed individually with nesting/enrichment material made available. A 12-hour light/dark cycle was maintained at all times, with lights turned off at 6:00 AM. Experimental procedures were approved by the Medical University of South Carolina Institutional Animal Care and Use Committee. Rats were given ad libitum access to water and either standard chow (Tekland Global 2018, 18% kcal fat; total density = 3.1 kcal g^{-1}; Harlan Laboratories Inc., Indianapolis, Indiana) or palatable diet (D12451, 45% kcal fat; total density = 4.73 kcal g^{-1}; Research Diets Inc., New Brunswick, New Jersey). Rats were given 7 days to acclimate before experimentation began. A second cohort of Sprague Dawley rats (Monash University, Melbourne, Australia) was housed in similar conditions. Their standard chow diet was obtained from Barastoc (8720610, 9% kcal rat; total density = 3.1 kcal g^{-1}; Barastoc, Melbourne, Australia).

Model of Diet-Induced Obesity

Obesity and drug addiction share the characteristic that when a population is exposed to palatable food or drug, only a subpopulation will develop obesity or addiction. We wanted to model the subpopulation of obese individuals that develop obesity due to excessive overeating of palatable food, as opposed to obesity caused by other factors. We employed a naturalistic diet-induced obesity model that separates outbred rats into obesity-prone (OP) and obesity-resistant (OR) groups based on weight gain in response to a palatable diet (31,32). Diet-induced obese rats in this model exhibit hyperphagia, increased adiposity, and the typical metabolic disturbances found in human obesity (33–36). Rats were placed on a highly palatable diet (D12451, 45% kcal fat; total density = 4.73 kcal g^{-1}; Research Diets Inc.) for a period of 8 weeks. Food intake and body weight were determined twice per week. Rats were then separated into diet-induced OP (top third) and diet-induced OR (bottom third) groups based on weight gain (Figure 1) (31). Weight gain was determined from weeks 3 to 8 of the 8-week period to avoid weight gain due to normal development during the first 2 weeks. A second group of rats was split into two groups and given access to either standard chow or palatable diet (SF04-001, identical formulation to D12451, 45% kcal fat; total density = 4.73 kcal g^{-1}; Specialty Feeds, Glen Forrest, Australia) for a period of at least 8 weeks before being separated by weight gain (also determined from weeks 3 to 8 of the 8-week period) and utilized for electrophysiology experiments.

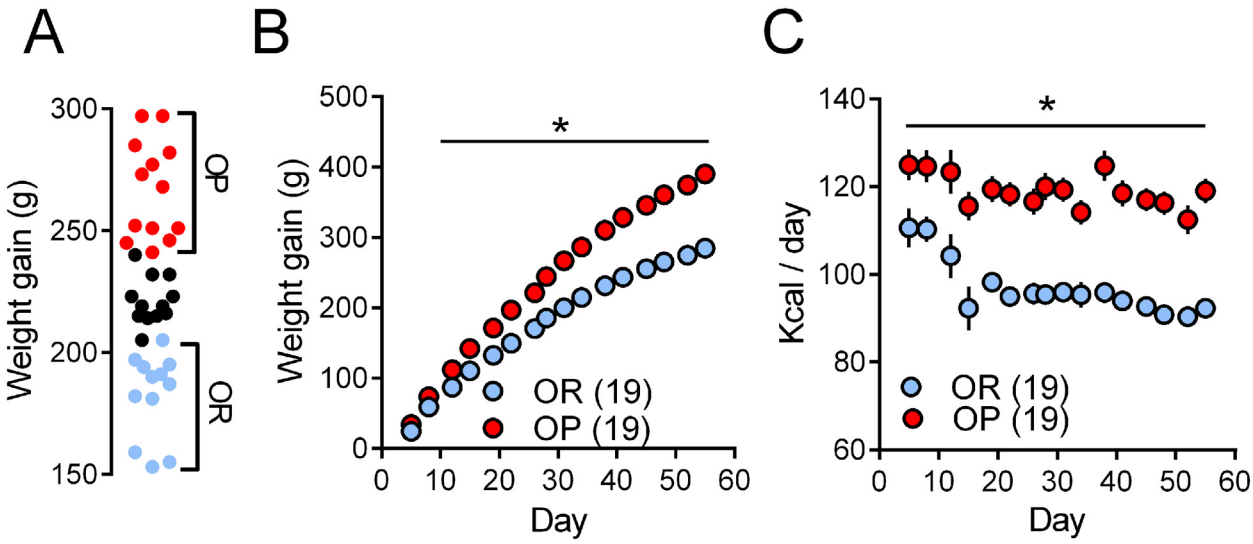

Figure 1. Free access to palatable food diet causes obesity in some rats but not in others. **(A)** Weight gain spread of a representative group of rats following 8 weeks of ad libitum palatable food diet in their home cages. Top third: diet-induced obesity-prone (OP) rats. Bottom third: diet-induced obesity-resistant (OR) rats. **(B)** OP rats gained more weight than OR rats (two-way analysis of variance, $F_{1,36} = 96.64$, $p < .0001$ for weight gain main effect) during the 8-week diet period. **(C)** OP rats consumed more calories than OR rats (two-way analysis of variance, $F_{1,36} = 69.69$ for kcal consumed main effect) during the 8-week diet period. *$p < .05$. Data represent mean ± SEM.