

New Evidence Linking Obesity and Food Addiction

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Obesity rates have skyrocketed over the past few decades. In the United States, approximately 35% of adults are now considered obese, with more than 60% categorized as overweight (1). The health consequences of obesity are substantial. Obesity increases the risk of developing several debilitating conditions, such as diabetes, heart disease, stroke, and mental illness. Because the global obesity epidemic is generally believed to be caused by excessive caloric intake, there has been increasing interest in understanding the neurobiological mechanisms contributing to overeating, defined as continued eating in the absence of metabolic necessity leading to weight gain.

The decision to eat involves many body and brain systems. Homeostatic mechanisms in the hypothalamus coordinate food intake with energy expenditure to keep the individual supplied with the necessary nutrients while maintaining a healthy body weight. Hypothalamic nuclei sense and respond to macronutrient and hormonal signals from the gut and adipose tissue to assess satiety and hunger. Evidence is accumulating that brain reward circuits also regulate food consumption. Highly palatable foods, such as processed foods that are rich in sugar and fat, are associated with increased eating. Presumably because of their strong hedonic qualities, these foods can override internal homeostatic mechanisms and lead to overeating and fat deposition. Weight-loss efforts can lead to alterations in metabolism, which also uncouple hunger signals from metabolic need, and lead to further weight gain once a typical diet is resumed. The extreme difficulty that so many obese individuals face in losing weight, and then maintaining a healthy weight, has reinforced the common belief that obese individuals are addicted to food.

The notion that excessive food intake might be a form of addiction has a long history in both science and the world at large. The phrase “food addiction” was first used in a scientific publication in the 1950s (2). Since then, human studies have provided some evidence for shared neurobiological features between obesity and drug addiction. Neuroimaging studies have demonstrated that obese individuals have similar over-activation in brain reward circuits as those observed in people with drug addiction (3). Rodent studies have contributed behavioral evidence to suggest that food addiction occurs (4). For example, rats given intermittent access to sugary substances exhibit increased bingelike behaviors, symptoms of withdrawal, and signs of cravings, and have sensitization to drugs of abuse, such as alcohol. Sugar also results in neurochemical brain changes similar to those of drug addiction, such as alterations in dopaminergic and opioid signaling. Perhaps in parallel with the scientific evidence, the possibility

that weight problems arise from food addiction has become a common public belief and the vocabulary of drug addiction, including terms such as *junkie*, *cravings*, and *withdrawal*, have joined the common vernacular with respect to discussions about overeating and dieting, and are even used by the food industry to advertise highly palatable foods.

Despite the general acceptance of a link between food addiction and obesity, controversy exists in the scientific community about the validity of this assumption (5). At the root of this conflict is the fact that not all overweight individuals display addictive eating behavior, and while binge eating is common in people who are obese, many people with binge eating disorder are not obese, and a large number of obese individuals do not have a binge eating disorder. Because individual differences are a hallmark of human obesity, neurobiological explanations that involve a single process are unlikely to be true. Proponents of the food addiction–obesity link have correctly pointed out that individual differences in addictive behavior when eating are similar to individual differences in drug addiction, with some people displaying more vulnerability than others. In this issue of *Biological Psychiatry*, Brown *et al.* (6) have capitalized on the fact that rats also exhibit individual differences in eating and weight gain when provided unlimited access to palatable food (a high-fat diet) to investigate whether synaptic changes associated with drug addiction also occur specifically within obesity-prone rats. First, using a variable-ratio operant self-administration paradigm, the researchers established that obese rats were more likely to exhibit addictive-like behaviors, including excessive motivation to obtain palatable food, consumption of large amounts of palatable food during operant testing, and continued seeking of palatable food even when it was unavailable, compared with nonobese rats. Next, they searched for alterations in synaptic plasticity in the nucleus accumbens core (NAc), part of the brain reward circuitry, which were consistent with those observed in models of drug addiction (7). Using whole-cell recordings in the NAc, Brown *et al.* found marked alterations in synaptic plasticity of obesity-prone rats, including lasting deficits in the ability of glutamatergic synapses to undergo long-term depression (LTD) (Figure 1). This LTD deficit was observed in obese rats prior to their exposure to the operant training, and may confer susceptibility to develop more rigid compulsive behaviors, which may escalate food consumption, as occurred in the obesity-prone rats exposed to operant training.

Medium spiny neurons, the main neuronal subtype of the NAc, exhibit low spontaneous activity and depend on excitatory glutamatergic transmission, primarily through alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors,

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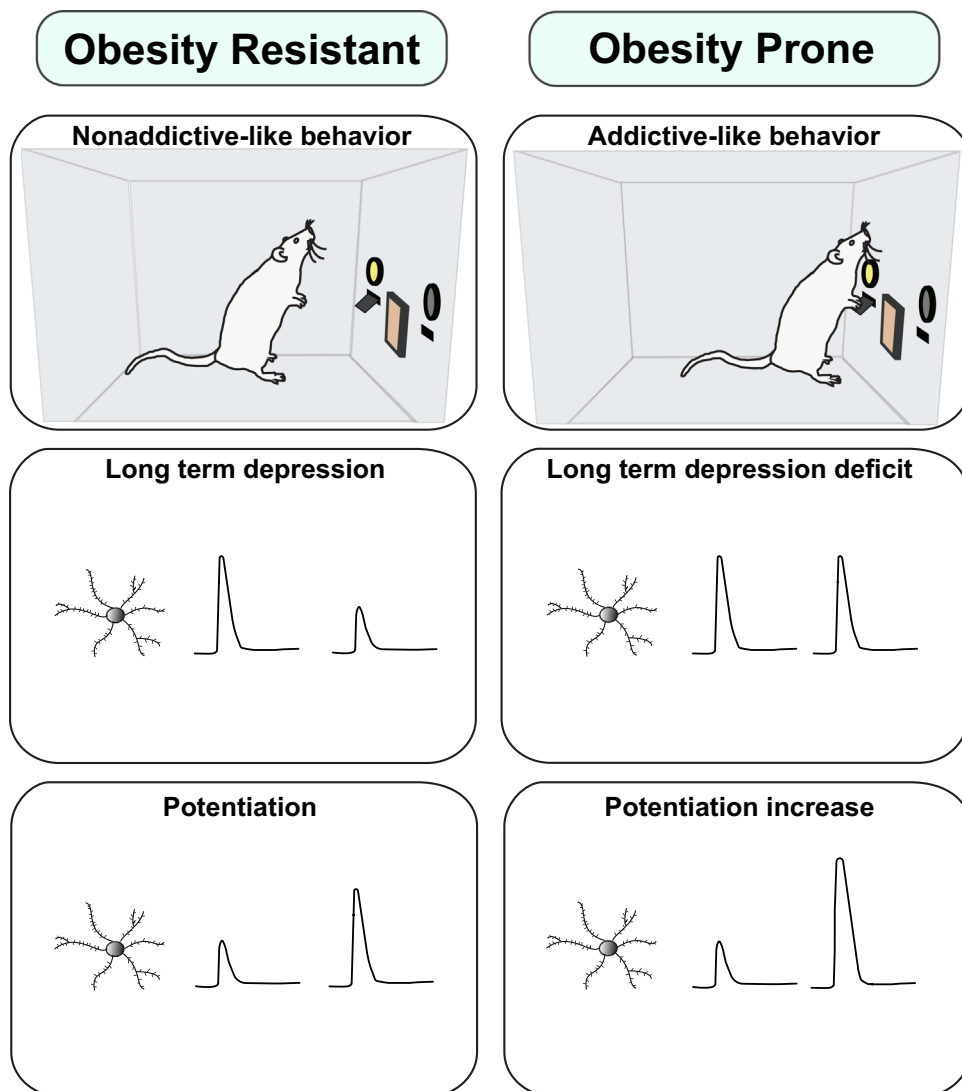


Figure 1. Obesity induces addictive-like behaviors and impaired synaptic plasticity in the nucleus accumbens core. Using an operant variable-ratio task with highly palatable food rewards, Brown *et al.* (6) found that compared with obesity-resistant rats, obesity-prone rats exhibit behaviors consistent with drug addiction. Following operant training, they found that glutamatergic synapses on medium spiny neurons in the nucleus accumbens core of obesity-prone rats fail to develop long-term depression and exhibit increased synaptic potentiation.

for their activation. Drugs of abuse, such as cocaine, are known to potentiate excitatory transmission within the NAc (7). Similarly, sugar and noncaloric sweeteners such as saccharin alter synaptic strength by AMPA receptor trafficking (8). In further experiments, Brown *et al.* (6) showed that obesity-prone rats have increased synaptic potentiation on medium spiny neurons, as measured by increased ratio of AMPA receptors to *N*-methyl-D-aspartate (NMDA) receptors (Figure 1). This increased ratio of AMPA receptors to NMDA receptors was only seen in rats that had undergone operant testing, suggesting that alternating bouts of restricted access and eating highly palatable foods may tip an already vulnerable system, with impaired LTD, toward increased synaptic potentiation. A previous study showing that medium spiny neurons in the NAc of obesity-prone rats have increased intrinsic excitability (9) suggests that lower thresholds for activation may set the stage for greater potentiation following operant training. Brown *et al.* further report that addiction scores were highly correlated with both impaired LTD and enhanced potentiation, suggesting that synaptic dysfunction predicts pathological

feeding behaviors. Taken together, these findings bear strong resemblance to those of drug addiction paradigms, supporting the link between addictive feeding behavior and obesity.

Although the data presented in Brown *et al.* (6) suggest that these obesity-related changes in medium spiny neurons are postsynaptic, it seems plausible that the effects are influenced by their afferents. The NAc receives excitatory inputs from multiple brain regions, including the medial prefrontal cortex (mPFC), a brain region involved in cognitive control. Obese, but otherwise naive (i.e., not trained on operant feeding tasks), rats are known to exhibit impairments on tasks of cognitive flexibility that are dependent on the mPFC (10). Obesity-induced cognitive decline is also associated with dendritic spine and synaptic protein loss in the mPFC (10). Similar to what has been observed with substance abuse, compromised function of the mPFC in obesity likely leads to lack of flexibility in changing eating habits, as well as diminished self-control, further contributing to an individual's inability to refrain from excessive eating.

The findings of Brown *et al.* (6) provide compelling evidence that diet-induced obesity leads to so-called food addiction by rendering the NAc vulnerable to an addictive behavioral experience that produces synaptic changes reminiscent of those seen with drug addiction. These results, however, are correlational, and there are still many unanswered questions. It seems critical to establish whether the changes in synaptic plasticity predict the development of obesity by excessive eating or whether these changes come about only after rats become obese. Some of the evidence reported in this article from control rats suggests that there is a high degree of variability in LTD, raising the possibility that individual differences in obesity-prone rats versus obesity-resistant rats were present prior to eating the high-fat diet and prior to weight gain. In addition, experiments designed to determine whether the reported changes in NAc synaptic plasticity are responsible for continued overeating in an addictive way could provide powerful evidence for a causal link between food addiction and obesity. If and when researchers establish this link and find that at least a subset of obese humans have a bona fide food addiction, the challenge will be devising therapeutic strategies to help these individuals. Even if they share similar neural mechanisms, food addiction differs from drug addiction in that the addictive substance is required to sustain life and cannot be completely eliminated in a total abstinence approach.

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