

HISTORICAL NEWS AND VIEWS: FEEDING BEHAVIOR

Dopamine and diet-induced obesity

In 2010, Johnson and Kenny provided conclusive evidence that extended access to a Western-style diet promotes addictive-like behavior in rats by downregulating D₂ receptors while promoting obesity. This focused attention on the parallels between drug addiction and overeating and fueled a decade of food addiction research.

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Researchers have been drawing parallels between the neural circuits regulating food and drug reinforcement for many years (for example, see refs ^{1,2}). Because addictive drugs act on neural circuits that evolved for natural rewards, such as food, conceptualizing drug addiction as a form of ingestive behavior provided a framework for studying it. However, with the rising rates of obesity, the tables turned and researchers began to consider how the neuroscience of drug addiction could inform understanding of overeating in an environment laden with “hyper-palatable energy-dense foods” that may even be drug-like³. Although papers emerged that supported this idea⁴, it was the 2010 paper by Johnson and Kenny⁵ that really galvanized this approach and sparked an intensive debate over the existence (and utility) of the concept of ‘food addiction’ that continues today (Fig. 1).

All drugs of abuse increase striatal dopamine levels and, following extended access, produce adaptations in the dopamine system that are associated with behavioral hallmarks of addiction, such as compulsive responding for the drug². While it had been established that food consumption can increase striatal dopamine and that intermittent access to sugar can produce neural adaptations and binge-like behavior⁴, the Johnson and Kenny paper was the first to show that extended access to a high-fat and high-sugar diet, which causes obesity, also leads to adaptations in the dopamine system and the emergence of addictive-like behaviors, including reward deficits and compulsive responding for food.

In their experiment, rats were fed regular chow or a ‘cafeteria diet’, including foods like bacon, cheesecake, and frosting for 40 days. One group of animals had restricted access and the other extended access to the diet. The animals with the extended access, but not the restricted access, rapidly gained weight and showed a parallel increase in their threshold for brain stimulation reward, a marker of

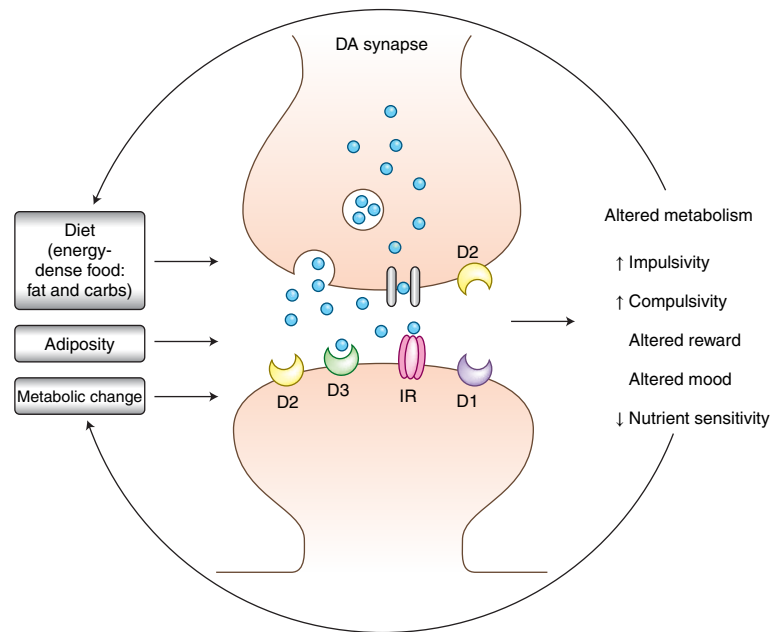


Fig. 1 | Possible pathways from diet to dopamine adaptation. There are multiple direct and indirect mechanisms by which a high-fat and -sugar diet may impact dopamine signaling and eventually lead to adaptation and behavioral change. Overconsumption can produce neural plastic changes that have long-term influences on dopamine signaling. Nutrients and their metabolites can directly influence neural afferent signals that regulate dopamine release, and they can cross the blood brain barrier (BBB) themselves or activate hormonal signals to impact dopamine signaling. In these instances, adaptations occur in the absence of increased adiposity or the onset of glucose intolerance. Diet can also affect dopamine signaling indirectly by producing excess weight or obesity and glucose intolerance, which in turn promote numerous pathophysiological processes that could promote alterations in dopamine signaling.

reward dysfunction often associated with drug addiction. A second cohort of rats was then subjected to the diets, the mice were killed for analysis upon substantial weight gain and their D₂ dopamine receptor (D₂R) expression was measured. Expression was noticeably reduced in animals with extended access and slightly reduced in the restricted-access animals who had gained weight. Next, and critically, viral knockdown of D₂Rs accelerated the onset of reward deficit and induced compulsive-like eating in animals on the extended-access,

but not chow, diet. This established a causal link between diet-induced obesity, downregulation of D₂Rs, and the emergence of addictive behavior.

This finding in rodents was also consistent with reports in humans suggesting that obesity was associated with altered D₂R signaling in the striatum. First, Wang and colleagues reported reduced binding potential for D₂Rs in morbidly obese individuals⁶. Second, Stice and colleagues found an association between blunted dorsal striatal response to a palatable milkshake

and subsequent weight gain among individuals possessing a copy of the A1 allele of the Taq1A A1 polymorphism, which is associated with reduced D₂Rs⁷. Consistent with the Johnson and Kenny manuscript, work from that group additionally suggested that the blunted response was a consequence rather than a cause of obesity, as it was associated with >4% increase in body weight in a 6-month period⁸, but not with risk for obesity by virtue of parental obesity⁹. Finally, Babbs and colleagues reported that in obese, but not healthy-weight, individuals blunted dorsal striatal response to milkshake was associated with increased impulsivity¹⁰. Collectively, this group of neuroimaging studies in humans suggested that the effects observed in rodents translated to humans and raised the possibility that food addiction has a role in driving the obesity epidemic (Fig. 1).

Perhaps the most innovative and promising new direction of this research concerns diet-induced gut regulation of central dopamine circuits and food reinforcement. Tellez and colleagues fed mice a high- or low-fat diet for 16 weeks and then used microdialysis to measure extracellular dopamine in the striatum upon intralipid infusion into the gut¹¹. A substantial rise was observed in the low-fat- but not the high-fat-fed animals, which also showed reduced sensitivity to orally presented lipids. This work demonstrates that gut lipid messengers, which are depleted by a high-fat diet, cause blunted dopamine and perceptual responses to fat. Intriguingly, the effects in this study could not be explained by adiposity, as animals in the two groups did not differ in body weight. This suggests that diet can contribute to D₂R downregulation independently of weight gain.

Several other studies support this claim and further suggest that saturated fat is the critical dietary feature driving D₂R adaptation. Adams and colleagues fed animals a high-fat, high-sugar, or chow diet for 12 weeks. Body weights did not differ between animals but, compared to the high-sugar- and the chow-fed groups, the high-fat-fed animals displayed impulsive responding for food that negatively correlated with a marker of D₂R density¹². Importantly, the animals fed the high-sugar

diet did not display similar effects, which is consistent with a report from van de Geissen showing that downregulation is promoted when diets have a higher ratio of fat to sugar content¹³.

The possibility that specific foods or nutrients impact D₂Rs also draws the parallel between food and drug addiction closer. Many foods that are abundant in the modern food environment are very high in saturated fat and may therefore possess addictive potential. Indeed, we have recently shown that processed foods containing fat and carbohydrate are more reinforcing, calorie for calorie, than foods with primarily fat or primarily carbohydrates¹⁴. If so, then foods such as donuts, pizza, burgers, and fries have potentiated rewarding properties that could promote brain adaptations and the emergence of compulsive eating.

The work on diet also sheds light on potential mechanisms. Saturated-fat intake depletes gut lipid messengers, which reduces intestinal sensitivity to fat intake and blunts vagal afferent signals and consequent dopamine release¹¹. However, this still leaves unknown the precise mechanism by which receptors are downregulated. We have argued that chronic exposure to excessive nutritional lipids triggers inflammatory-like responses in the brain that are partially mediated by lipid-activated receptors and activation of Toll-like receptors and NF- κ B, which in turn acts on transcriptional regulation of D₂Rs¹⁵. Uncovering the mechanisms by which diet and adiposity impact D₂R adaptations is an important direction for future work, foremost because it could identify therapeutic targets not only for obesity but also for other addictive disorders in which central dopaminergic circuits are affected.

Irrespective of what side of the food addiction debate you fall on, there can be no doubt that we have learned much about brain and obesity by adopting methodology and models borrowed from the field of addiction. However, there are some important differences between foods and drugs that require further investigation. For example, Johnson and Kenny noted that, when the extended-access animals

were tested in 'extinction' from the cafeteria diet (they only had access to lab chow), the increased threshold for brain stimulation reward, which indexed their reward deficit, persisted until the animals were killed two weeks later. This contrasts with the relatively transient deficits in animals undergoing abstinence from self-administered cocaine. Other critical outstanding questions also remain. What are the mechanisms of downregulation? Do diet, adiposity, and metabolic factors interact or produce separate effects on dopamine signaling? Can dopamine adaptations contribute to metabolic dysfunction and weight gain? Are these adaptations important in the link between diabetes and dementia? Are they dependent on genotype? Can the adaptations be reversed? What other behaviors and functions are affected? These and other questions will continue to drive the field for many years. □

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