Cheesecake-eating rats and the question of food addiction

David H Epstein & Yavin Shaham

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Johnson and Kenny^2 examined rats given access to a cafeteria-style diet of energy-dense (high fat and/or high carbohydrate) food, including bacon, sausage, cheesecake, pound cake, frosting and chocolate. The diet had two behavioral effects that were similar to those of exposure to addictive drugs.

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the lateral hypothalamus. They were then divided into three groups, with one receiving a diet of standard laboratory rat chow, one receiving the standard diet along with restricted access (1 h per d) to the cafeteria food and the third receiving the standard diet and extended access (18–23 h per d) to the cafeteria food. All of the rats weighed 300–350 g when the exposure started. Over the next 40 d, the first two groups gained 80–100 g, which is developmentally typical, whereas the extended-access group gained almost twice as much. The BSR threshold, the minimal level of electrical current required to keep the rats turning the wheel, remained stable in the chow-fed and restricted-access rats but increased in the extended-access rats, reflecting a disruption in brain reward function. Similar disruptions occur after self-administration of addictive drugs (Fig. 1a)1,2. Notably, the reward disruption associated with the cafeteria diet persisted at least 14 d after access ended, which is substantially longer than disruptions observed after withdrawal from nicotine, cocaine or alcohol (Fig. 1b)3–7.

The second behavioral effect involved a hallmark of addiction in humans: insensitivity to adverse consequences of drug self-administration. This has been successfully modeled in animal models of drug addiction. Another three groups of rats were given different types of food access for more than 40 d as described above, then some of the rats from each group were exposed to a fear-conditioning procedure in which an electric shock was paired with a light cue. On a subsequent test day, the rats were given access to the cafeteria food in the presence of the now fear-inducing light. The light suppressed cafeteria-food intake in the rats that had only received chow and the rats that had been given limited access to cafeteria food, but not in the rats that had extended access to the cafeteria food. Thus, as with addictive drugs, extended access to cafeteria food led to reward-seeking that was seemingly compulsive in that it was insensitive to a cue that warned of impending punishment.

In addition to these behavioral parallels between cafeteria-food intake and drug self-administration, Johnson and Kenny2 found a neurophysiological parallel between the two. Drawing on prior findings that human drug addiction and obesity are each associated with decreased expression of D2 dopamine receptors in the striatum8, the authors examined D2 receptor expression in the dorsal striatum of their rats after more than 40 d of exposure to cafeteria food and found that it was inversely related to weight gain. To determine whether reduced D2 receptor expression was actually causing addiction-like behaviors, the authors used a viral vector to knock down receptor expression in the dorsal striatum of rats that were exposed to cafeteria food for just 14 d, a period that is normally not long enough to induce changes in BSR threshold or fear-cue-induced suppression of feeding. When D2 receptor expression was knocked down, these addiction-like behavioral changes were seen within 14 d. This is an interesting, although anatomically imperfect, parallel with prior findings; escalation of voluntary cocaine intake in rats is associated with low D2 receptor expression in ventral, not dorsal, striatum9.

Johnson and Kenny’s work2 extends previous results from rat studies that had suggested addiction-like properties of prolonged access to palatable food. For example, earlier work has shown that intermittent sugar intake leads to physiological and behavioral symptoms on discontinuation that are similar to those seen during opiate withdrawal1 and a binge-like intake of sugar that to some degree resembled the behavior of rats given unlimited access to psychostimulants1. Rats that are given a choice between a sweet saccharin solution and cocaine strongly prefer saccharin10. Moreover, increased anxiety and other withdrawal-like symptoms after loss of access to high-fat food are mediated by the neuropeptide corticotropin-releasing factor, which also mediates symptoms of drug withdrawal11,12. Finally, studies using the reinstatement procedure (an animal model of drug relapse) have found overlaps between the neuronal mechanisms through which stressors or cues can cause rats to resume seeking of drugs or palatable food after loss of access12.

Given all of this, how far shall we go in drawing parallels between drug addiction and food addiction? Unlike drugs, food is essential for survival, but frequent consumption of bacon, sausage and cheesecake (the rats’ cafeteria diet) is not. The availability of such foods in most developed societies has increased so quickly that, similar to addictive drugs, they may stimulate brain reward systems more powerfully than we have evolved to handle, signaling a false fitness benefit and thereby reinforcing unhealthy patterns of consumption. In that respect, a parallel is defensible. But if we accept that parallel, there are at least two major caveats.

The first caveat is that food addiction is not identical to public health’s cause célèbre, obesity. If diagnostic criteria for food addiction were written to parallel the current diagnostic criteria for drug addiction, focusing on patterns of consumption that are maladaptive or problematic in any way, one could even argue that food addiction is neither necessary nor sufficient for obesity. The current draft of the Diagnostic and Statistical Manual includes criteria for a food addiction–like syndrome known as binge-eating disorder (BED), which is characterized by distress-inducing,
subjectively hard-to-control episodes in which one eats “an amount of food that is definitely larger than most people would eat in a similar period of time under similar circumstances.” The cumulative lifetime risk of BED in the US is only 3.9%; even when combined with subthreshold BED and “any binge eating,” this only rises to 11%, about one-third of the current prevalence of adult obesity (body mass index ≥ 30), 34%. Among adults with BED, the point prevalence of obesity is 42%, which is only about 8% higher than that seen in the general population. BED is also distinct from obesity in terms of prognosis (BED is associated with a lower quality of life than obesity) and treatment response (BED responds to antidepressants, but obesity generally does not).

Of course, food addiction could be defined more broadly as frequent heavy consumption of energy-dense foods without frank binging. In that case, its overlap with obesity is large and predictable. Despite Johnson and Kenny’s findings of changes in BSR sensitivity, human addicts are not always hyporesponsive to alternative rewards, even in studies that have been interpreted as evidence that they are. This caveat is important because it underlies behaviorally based treatments for addiction. And if the kinds of alternative-reinforcer treatments that are effective in drug addiction can reduce regular overindulgence in energy-dense food (with or without frank binging), health benefits are likely to accrue regardless of whether appreciable weight loss occurs.

To restate the two caveats, whatever entity we call food addiction should not be seen as an excuse for unhealthy eating and the unhealthy eating associated with food addiction should not be equated with obesity. Johnson and Kenny’s rat data suggest something interesting but not something that reduces to an enticing headline or sound bite. We would be mistrustful of any summary simpler than this: given enough access to cheesecake and bacon, rats display patterns of eating that resemble those that account to some unknown degree for human obesity and these patterns seem behaviorally similar to, and share some neurophysiological substrates with, patterns of drug self-administration and withdrawal symptoms that resemble those seen in drug addiction.

Competing financial interests
The authors declare no competing financial interests.


Regulating brain size

In this issue on page 551, Silver and colleagues report a surprising regulator of neural stem cell mitosis and brain size in mice and investigate how its disruption might lead to microcephaly.

In a previous mutagenesis screen, the authors had isolated a mutant mouse with a small body size, hypopigmentation and a reduced brain size. Here they identify Magoh as a candidate gene responsible for the microcephalic phenotype. The Magoh gene, which is completely conserved between mice and humans, encodes a component of the RNA-biding exon junction complex (EJC). Mice homozygous for the Magoh loss-of-function mutation died prenatally, whereas the brains of adult mice heterozygous for the mutation showed disordered cortical layering and fewer neurons as compared with wild-type mice. The figure shows wild-type embryonic day 16.5 (E16.5) cortex, with Trf2 (red) labeling intermediate progenitors, BrdU (green) indicating proliferating cells and DAPI (blue) staining all nuclei. Dividing intermediate progenitors appear yellow. In the Magoh mutant cortex, the number of dividing intermediate progenitors was reduced from E12.5 onwards, whereas the numbers of cells expressing immature neuron markers were increased. The prematurely born neurons, however, did not survive by E18.5.

How does an EJC component maintain the intermediate progenitor pool and prevent precocious neurogenesis? Dividing cells in the Magoh mutants had altered mitotic spindle orientations and aberrant chromosome numbers, a phenotype similar to that of Lis1 mutant mice. Lis1 encodes a microtubule-associated protein that is critical for mitotic spindle integrity; in humans, altered LIS1 dosages have been associated with microcephaly syndromes. Lis1 protein levels were decreased in the Magoh mutant cortex. Critically, Silver et al. rescued the Magoh microcephaly phenotype with Lis1 expression. By finding that Magoh controls neural stem cell division by regulating levels of Lis1 protein, Silver and colleagues have identified a new role for the EJC in determining brain size. Kathleen A Dave