

# Neurobiology of food addiction

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## Purpose of review

To review recent work on disorders related to food use, including food addiction, and to highlight the similarities and differences between food and drugs of abuse.

## Recent findings

Recent work on food use disorders has demonstrated that the same neurobiological pathways that are implicated in drug abuse also modulate food consumption, and that the body's regulation of food intake involves a complex set of peripheral and central signaling networks. Moreover, new research indicates that rats can become addicted to certain foods, that men and women may respond differently to external food cues, and that the intrauterine environment may significantly impact a child's subsequent risk of developing obesity, diabetes, and hypercholesterolemia.

## Summary

First, work presented in this review strongly supports the notion that food addiction is a real phenomenon. Second, although food and drugs of abuse act on the same central networks, food consumption is also regulated by peripheral signaling systems, which adds to the complexity of understanding how the body regulates eating, and of treating pathological eating habits. Third, neurobiological research reviewed here indicates that traditional pharmacological and behavioral interventions for other substance-use disorders may prove useful in treating obesity.

## Keywords

drug abuse, food addiction, obesity, process addiction

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## Introduction

A growing body of empirical and experiential evidence indicates that certain individuals can develop maladaptive patterns of consuming behaviors and substances that are essential for survival, including food and sex [1•]. This paper will review current, and proposed, definitions of substance use disorders, recent advances in our understanding of the physiology of addiction and food consumption, newly published evidence of food addiction, freshly developed tools to better characterize pathological appetitive behaviors, and pharmacological treatments for obesity currently under development.

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## Defining substance use disorders

The fifth edition of the Diagnostic Statistical Manual (DSM-V), set to be released this year, includes a number of revisions to the types and definitions of substance-related disorders that were recognized in the DSM-IV. The DSM-V does away with the DSM-IV's catchall diagnosis of 'substance dependence', and replaces it with the diagnosis of 'substance-use' disorder. A substance-use

disorder, as the DSM-V will define it, is 'A maladaptive pattern of substance-use leading to clinically significant impairment or distress, as manifested by two (or more) of the listed criteria occurring within a 12-month period (see Table 1) (<http://www.dsm5.org/ProposedRevisions/Pages/Substance-RelatedDisorders.aspx>)'. Also included will be severity, course, and physiological specifiers.

These revisions will better align diagnostic definitions with widely accepted, evidence-based theories about the behavioral and physiological progression of substance-use disorders. Indeed, addiction, which is a chronic and relapsing illness, lies on one end of a continuum of maladaptive patterns of substance use. Although some individuals never progress beyond experimentation, others advance to regular drug use, drug abuse, drug dependence, or all [1•]. This pathologic progression of substance use is characterized by 'preoccupation; escalation; tolerance; denial; a series of medical, psychological, and social consequences related directly to the continued use; and what has been referred to as a 'fatal attraction' between the substance (or activity, e.g., gambling) and the patient (p. 42) [1•]'.

**Table 1 Fifth edition of the Diagnostic Statistical Manual's proposed criteria for substance-use disorder**


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Substance-use disorder  
A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by two (or more) of the following, occurring within a 12-month period

1. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)
2. Recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)
3. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication and physical fights)
4. Tolerance, as defined by either of the following:
  - (a) Need for markedly increased amounts of the substance to achieve intoxication or desired effect
  - (b) Markedly diminished effect with continued use of the same amount of the substance (Note: tolerance is not counted for those taking medications under medical supervision such as analgesics, antidepressants, anti-anxiety medications, or beta-blockers)
5. Withdrawal, as manifested by either of the following:
  - (a) The characteristic withdrawal syndrome for the substance (refer to Criteria A and B of the criteria sets for withdrawal from the specific substances)
  - (b) The same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms (Note: withdrawal is not counted for those taking medications under medical supervision such as analgesics, antidepressants, anti-anxiety medications, or beta-blockers)
6. The substance is often taken in larger amounts or over a longer period than was intended
7. There is a persistent desire or unsuccessful efforts to cut down or control substance use
8. A great deal of time is spent on activities necessary to obtain the substance, use the substance, or recover from its effects
9. Important social, occupational, or recreational activities are given up or reduced because of substance use
10. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance
11. Craving or a strong desire or urge to use a specific substance

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Addiction progresses through three distinct stages, each with a defining sign or symptom: bingeing is the signature attribute of stage 1, withdrawal is the cardinal feature of stage 2, and substance cravings characterize stage 3 [2]. Cross-sensitization, defined as the enhanced response to use of a new substance that results from prior use of a different drug, also suggests vulnerability to addiction [2]. Stress can also predispose to addiction and to relapse.

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### The neurobiology of addiction

Drug addiction results from the usurping of neurobiological pathways that are involved in, and help to regulate, reward, motivation, decision-making, learning, and memory [3\*\*]. More simply, drugs of abuse ‘hijack’ these neural systems, hindering them from carrying out their normal physiological roles and forcing them to become responsive to the drug of abuse. Drug-seeking behavior is motivated and reinforced not only by a drug’s positive effects – the ‘high’ associated with drug use – but also the negative state or ‘antireward’ that accompanies abstinence from drug use [4]. Different neural networks mediate each of these forces. Indeed, dopaminergic, gabaergic, opioid, and serotonergic neural circuits in the striatum, amygdala, orbitofrontal cortex (OFC), and midbrain are the primary drivers of the feelings of pleasure and reward that flow from drug use [4]. The irritability, anhedonia, and dearth of motivation for natural rewards that characterize the state of antireward result not only from the loss of function of the brain’s reward systems but also from the activation of stress systems in the amygdala [4].

Although all drugs of abuse activate dopamine pathways, stimulants – including cocaine and amphetamines – activate this system to the most extreme degree, and dopamine appears to be the primary mediator of stimulant dependence. In contrast, ethanol, opioids, and nicotine appear to exert their acute reinforcing effects predominately through activation of opioid receptors [2].

Ultimately, however, dopamine appears to be the predominate mediator of addiction. Evidence of de-novo gambling, eating, and sexual addictions in patients with Parkinson’s disease is, perhaps, one of the most persuasive examples of dopamine’s potent ability to influence consumptive behaviors. Patients with Parkinson’s disease – a disease characterized by deficiencies in dopaminergic neurotransmission, and which is associated with very low rates of substance abuse, and with a personality type that ‘is the polar opposite of the addictive personality (p. 502)’ – can become addicted to the dopamine supplements that are used to treat this disease, or develop behavioral addictions [5\*\*].

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### Physiology of food consumption

Both central neuronal circuits and peripheral signaling systems help to regulate food consumption [3\*\*]. Four brain regions appear to be involved in the regulation of feeding: the amygdala/hippocampus, insula, OFC, and the striatum [6•]. Together, these neural circuits assist with ‘learning about (food) rewards, allocating attention and effort toward (food) rewards, setting the incentive value of stimuli in the environment, and integrating

homeostatic information about energy stores and gut contents with information about the outside world such as the availability of food (p. S30) [6<sup>•</sup>]. Dopaminergic 'reward' pathways in the midbrain are responsible not only for motivating food consumption but also for the pleasurable feelings that eating produces [3<sup>••</sup>,6<sup>•</sup>]. Dopaminergic systems project throughout the brain and interact with opioid-mediated gabaergic, cholinergic, and serotonergic circuits. These circuits are essential for survival, precisely because they drive and reinforce behaviors that promote energy intake. The hypothalamus and the arcuate nucleus have been implicated in weight regulation [3<sup>••</sup>]. Orexin and melanin play important signaling roles in hypothalamic circuits, whereas neuropeptide Y and alpha-melanocyte-stimulating hormone figure prominently in neural signaling in the arcuate nucleus [3<sup>••</sup>].

Four gut and fat-derived hormones – ghrelin, leptin, insulin, and peptide YY – facilitate the homeostatic regulation of feeding by providing critical feedback to the brain about hunger, satiety, and energy needs [3<sup>••</sup>]. Ghrelin (the 'hunger peptide') is released from the stomach and acts on the hypothalamus to raise food consumption [3<sup>••</sup>]. Serum ghrelin levels typically rise during a fast and fall after feeding. Leptin relays information to the brain about the body's fat reserves. This hormone acts on the hypothalamus to decrease food intake and increase metabolic rate, and thus plays a critical role in maintaining long-term energy homeostasis [3<sup>••</sup>]. Insulin and peptide YY, from the pancreas and small intestine, respectively, relay to the brain information about acute changes in energy levels.

These central and peripheral signaling pathways are highly interconnected. Ghrelin stimulates dopaminergic reward pathways, whereas leptin and insulin inhibit these circuits. Moreover, signaling circuits in both the hypothalamus and the arcuate nucleus receive peripheral signals and project to other regions of the brain, including midbrain dopaminergic centers [3<sup>••</sup>]. Importantly, these midbrain dopaminergic circuits also modulate 'survival-related' activities, including feeding and sex [1<sup>•</sup>,3<sup>••</sup>].

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### **New insights into the physiology of food consumption and abuse**

Recent research on the drivers of alcohol and fat consumption suggest that both alcohol and fat intake lead to the production of hypothalamic orexigenic peptides, which not only stimulate increased consumption of these substances but also mediate elevations in circulating triglycerides. First, Barson *et al.* [7] and Karatayev *et al.* [8] have demonstrated that, in rats, alcohol use leads to increased consumption of fatty foods and vice versa. Second, alcohol and fat appear to have a direct and

synergistic effect on increasing serum triglyceride levels. Third, administering gemfibrozil to rats on a high-fat diet lowered serum triglycerides, levels of hypothalamic orexigenic peptides, and subsequent alcohol intake. Furthermore, mice overexpressing the orexigenic peptide galanin exhibit a greater preference for fatty foods and alcohol than do wild-type rats [8]. In another study using rats Karatayev *et al.* [9] found that after a high-fat meal, the circulating triglycerides were a predictor of increased caloric intake and orexigenic peptide expression.

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### **Evidence of food addiction from animal studies**

Avena *et al.* [10<sup>••</sup>] have developed a rat model of binge eating on sugar and sugar/fat solutions. They have shown that rats provided with 2 h of access to a sugar/fat solution will consume the majority of their daily energy intake during this window, despite having continuous access to normal laboratory chow [10<sup>••</sup>]. Moreover, sugar-bingeing rats consume more sugar solution over time (evidence of tolerance), demonstrate increased sugar consumption after a period of abstinence (deprivation effect), and exhibit signs of opiate-like withdrawal, including 'teeth chattering, forepaw tremor, and head shakes (p. 625)' when given a high dose of naloxone, an opioid antagonist [10<sup>••</sup>]. Sugar-bingeing rats become cross-sensitized to both amphetamines – which has no effect on naive rats – and cocaine.

Sugar bingeing, like drug abuse, consistently stimulates dopamine release in the nucleus accumbens (NAc) [10<sup>••</sup>]. After 4 weeks on a high-fat diet, mice demonstrated large increases in NAc levels of deltaFosB, a molecule that both enhances many drugs' rewarding properties and drives users to acquire them [11<sup>••</sup>].

Geiger *et al.* [12<sup>•</sup>] showed that rats that became obese on a cafeteria-style diet exhibit lower baseline levels of mesolimbic dopamine activity than normal-weight rats fed a standard chow diet. Furthermore, although a cafeteria meal stimulated dopaminergic activity in the obese cohort, a challenge with normal rat chow did not [12<sup>•</sup>]. The implication is that obese rats' abuse of palatable food depressed baseline levels of extracellular dopamine, which in turn led them to rely on palatable food consumption to increase dopamine release [12<sup>•</sup>]. These findings suggest that the rats developed a dopamine-mediated addiction to palatable food. Mathes *et al.* [13<sup>•</sup>] recently showed that mice bred to exercise excessively had significantly higher concentrations of dopamine in the dorsal striatum and NAc than did mice bred for obesity and controls. Additionally, they found large differences in dopamine gene expression between the high-exercise and obese mice on the one hand and control mice on the other hand. These results highlight

the critical role that dopaminergic pathways play in regulating both consumptive behaviors and activity levels, and suggest that common alterations in these pathways may underlie overeating and excessive exercise [13•]. Although dopamine's role in controlling appetitive behavior is fairly well established, current work has begun to advance our understanding of how other signaling channels – including muscarinic and serotonergic pathways – modulate food consumption. For example, Perry *et al.* [14•] demonstrated that intra-NAc cholinergic blockade significantly reduced food consumption in food-deprived rats, but had no effect on water intake. Moreover, Pratt *et al.* [15] showed that selective stimulation of different serotonergic receptors subtypes in the NAc of living rats resulted in distinct changes in the rats' feeding behaviors. For example, although intra-NAc infusion of a 5-hydroxytryptamine (5-HT) 1/7 receptor agonist led to a dose-dependent reduction in rats' consumption of both laboratory chow and a highly palatable food/sucrose solution, selective stimulation of NAc 5-HT<sub>6</sub> receptors resulted in a dose-dependent rise in food consumption [15].

### Imaging evidence of food addiction

Functional MRI (fMRI) imaging studies in humans demonstrate that food and drug cues activate the same regions of the brain – the amygdala, insula, OFC, and striatum (of course, only addicts' brains are responsive to drug cues) [6•,16•]. Additionally, food cravings also lead to changes in fMRI signals in the hippocampus, insula, and caudate, brain areas that are involved in drug cravings, and in the integration of memory with sensory information [16•]. Drug cravings can activate cortical and limbic regions of the brain, which regulate self-control, motivation, and memory. Interestingly, these same areas of the brain become activated in obese individuals in response to gastric stimulation [3••].

Like drug addicts, obese individuals exhibit decreased striatal D<sub>2</sub> receptor availability and demonstrate elevated levels of metabolism in the somatosensory cortex, suggesting 'an enhanced sensitivity to the sensory properties of food (p. 8) [3••]'. Taken together, these findings indicate that the brains of obese individuals may change in ways which not only reinforce food consumption but which also impair their ability to derive pleasure from activities other than eating [3••].

### New clinical and behavioral evidence of food addiction in humans

Certain pathologic patterns of food consumption – particularly consistent overeating, binge eating, stress-induced eating, and emotional eating – bear a striking resemblance to substance-use disorders [17•,18]. Studies of women who report carbohydrate cravings have found that carbohydrates 'seem to have an almost medicinal

value in women who crave them (p. 2) [17•]'. Over time, women who crave carbohydrates develop an increased preference for this type of food ('liking', or sensitization) and tolerance to the food's ability to ameliorate dysphoria. These findings support the conclusion that carbohydrates have abuse potential [17•].

People can also learn to associate food consumption with external cues – including advertisements, sights, smells, and sounds. Once made, these associations, or external food sensitivities, can trigger food cravings, overeating, and an increased preference for highly palatable foods [17•]. Furthermore, the majority of people consume more food when stressed, and demonstrate a preference for high-fat or high-carbohydrate foods [5••]. Stress also predisposes drug addicts to relapse, and is a 'significant cause of failure in dieters (p. S31) [6•]'.

As evidence of food addiction has mounted, experts have proposed new explanations for how and why this illness has evolved. For example, Ifland *et al.* [18] hypothesized that humans can become addicted to refined foods (the 'refined food hypothesis'), which contain processed sugars, fat, salt, flour, caffeine, or all, but not to unrefined foods. Building on evidence that opiate addicts consume increased amounts of salted foods and gain weight while withdrawing, Cocores and Gold [19•] proposed that salt is a mild opiate agonist.

### Gender differences in appetitive behavior

Recent works by Wang *et al.* [20•] and Cornier *et al.* [21•] have yielded intriguing hypotheses about the neurobiological underpinnings of sex-based variations in food consumption patterns. Wang *et al.* [20•] demonstrated that the 'presentation of appetitive stimuli to fasting individuals increased self-reports of hunger and desire for food and increased whole brain metabolism to a similar (p 1251)' degree in both sexes. Furthermore, both men and women reported decreased hunger and desire for food during deliberate cognitive inhibition of their wish to eat. However, although men's brains demonstrated reduced activity in limbic and paralimbic areas during cognitive inhibition, women's brains showed no change in metabolic activity during this exercise [20•]. These findings suggest that the brains of men and women respond differently to efforts to control or regulate appetitive behaviors. Cornier *et al.* [21•] reported a number of sex-based differences in consumptive behavior. First, during ad-libitum feeding, men were more prone to overeating, whereas women tended to match caloric intake with energy expenditure. Second, women reported higher postprandial satiety than did men. Third, Cornier *et al.* [21•] noticed significant sex-based differences in neuronal activation in response to visual food stimuli. Women in Cornier *et al.* [21•]'s study were able to control their consumptive behaviors more effectively than men, and

**Table 2 New medications for treating obesity (in phase III clinical trials)**

| Drug name (manufacturer)  | Components (prior treatment use)   | Possible side-effects (seen in clinical trials)   |
|---|--|---|
| Lorcaserin (Arena)  | First in a new class of selective serotonin 2C receptor agonists; works by stimulating receptors in hypothalamus, area strongly associated with feeding behavior and satiety | Can cause or increase symptoms of depression, anxiety, and OCD via 5-HT <sub>2C</sub> activation inhibiting release of brain dopamine (infrequent events of depression, anxiety, and suicidal ideation) |
| Note: Lorcaserin does not appear to cause heart valve damage as previously withdrawn serotonergic weight loss drugs such as fenfluramine and chlorphentermine did |  |   |
| Qnexa (Vivus)   | Phentermine (appetite suppressant, was 1/2 of Fen Phen) and topiramate (seizures, migraines, and decrease cravings in alcohol dependence)                                    | Depression and depressed moods in both drug and placebo groups  |
| Contrave (Orexigen)   | Bupropion (antidepressant and nicotine dependence) and naltrexone (alcohol dependence)   | Two seizures that were possibly related to drug   |

5-HT, 5-hydroxytryptamine; OCD, obsessive-compulsive disorder.

demonstrated a greater prefrontal and parietal response to visual food stimuli than did men [21<sup>•</sup>]. The results of these two studies not only suggest that sex-based differences in appetitive behavior may help to explain disparate rates of obesity in men and women but also indicate that more work is needed to better characterize them.

### Genetic and environmental influence

The genetic and environmental influences on the risk of becoming overweight or obese are substantial and could not be adequately treated within the scope of this review. We know that the intrauterine environment may significantly impact a child's subsequent risk of developing obesity, diabetes, and hypercholesterolemia and new research indicates that exercise may decrease the effects of genetic influence in adolescents. For those interested in exploring this area further, we direct you to these references [22,23,24<sup>•</sup>,25,26<sup>••</sup>,27<sup>••</sup>].

### Assessing for pathological eating patterns: new developments

Gearhardt *et al.* [28<sup>•</sup>] created the Yale Food Addiction Scale (YFAS), a series of questions designed to identify and better characterize signs and symptoms consistent with food addiction. In early testing, the YFAS 'exhibited adequate internal reliability, . . . good convergent validity with other measures of eating problems, and good discriminant validity relative to related but dissimilar constructs such as alcohol consumption and impulsivity (p. 4) [28<sup>•</sup>]. As the authors recognize, the YFAS may not only help clinicians to better identify food-use disorders in their patients but may also help researchers to identify potential candidates to recruit for future studies in this area [28<sup>•</sup>].

### New pharmacological treatments for obesity

A number of pharmacological treatments derived from addiction models for obesity are either under development or in clinical trials (see Table 2). Three drugs are currently in phase III clinical trials: Contrave (Orexigen Therapeutics, Inc., La Jolla, California, USA), Qnexa (Vivus

Inc., Mountain View, California, USA), and Lorcaserin (Arena Pharmaceuticals, Inc., San Diego, California, USA) [29,30]. Many of these drugs have significant side-effects. For example, Lorcaserin can cause or increase symptoms of depression, anxiety, and obsessive-compulsive disorder (OCD) via inhibiting release of brain dopamine. In addition, bupropion (an element of Contrave) lowers seizure thresholds and topiramate (a component in Qnexa) has been associated with an increased risk of suicide, confusion, and memory deficits. Most of these treatments target pathways that have been discussed in this review, and which play critical roles in addiction. Importantly, experts anticipate that they will receive US Food and Drug Administration approval [29]. The organismic salience of these brain messengers has made psychopharmacological treatment developments for drug abuse and dependence slow and challenging. We may expect addiction-targeted antiobesity treatments to have a great risk of causing important mood and other side-effects, which will need to be carefully considered by the prescribing physician and closely monitored.

### Areas for further study

To date, research in animals has focused on the hedonic properties of sugar and fat. However, we know less about the rewarding or addictive properties of salt. More research is also needed to better understand the degree to which salt, sugar, and fat act synergistically to motivate hedonic eating. Investigations into the gut-brain interactions [31] and hormone-dopamine [32] addictive properties of other types of ingredients – particularly those found in processed or energy-dense foods – are warranted as well.

### Conclusion

Understanding the forces that sustain hedonic eating is essential to developing and implementing treatment and management strategies that address the root causes of the obesity epidemic. Neurobiological advances in modeling tobacco smoking, alcohol, and other drug addictions have

enabled clinical scientists to study the brain systems of interest in humans. PET and fMRI studies have been conducted for decades, detailing the changes that routinely occur in human addicts and providing neurobiological insights that have changed physician acceptance of the importance of brain change in the addiction process. Public health and treatment professionals, once tobacco addiction was accepted, could develop legal and taxation strategies aimed at delaying use, decreasing harm, and protection from second and third-hand exposure. Treatment professionals used these new insights to provide replacement, detoxify, and develop an entirely new class of anticraving and relapsing medications. Basic neuroscience studies, building on addiction neuroscience models, have demonstrated avid self-administration of glucose, fructose, and junk food [33\*] in laboratory animals with corresponding changes in addiction-relevant neurotransmitters and systems. Human neuroimaging studies, also using methods developed over decades of studying human alcoholics and addicts, have suggested that hedonic food can act like a traditional drug of abuse, causing brain changes almost indistinguishable from those produced by drugs. Studies have shown somatosensory cortex and other neurobiological changes that make losing weight much more difficult. In the absence of consistently effective lifestyle or pharmacological interventions that address these root causes, families are increasingly turning to invasive and expensive bariatric surgical treatments, including gastric bypass and gastric banding, to help themselves and their children lose weight. These procedures can yield dramatic weight loss, but also have significant, well known, and potential side-effects. Furthermore, 'psychosocial outcomes after weight loss surgery (WLS) have not been adequately studied, particularly in adolescents (p. 906) [34]'.

Obesity and its attendant complications place a tremendous and ever increasing burden on healthcare systems. Recent research on the neurobiological systems that motivate appetitive behavior strongly suggests that an acquired drive for highly energy-dense, reinforcing foods is contributing to the obesity epidemic. The limitations of current treatments compel healthcare professionals to develop more effective ways based on neurobiological addiction models to curb the obesity epidemic.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 492–493).

- 1 Gold MS, Graham NA, Cocores JA, Nixon SJ. Food addiction? *J Addict Med* 2009; 3:42–45.

An editorial in an issue that the *Journal of Addiction Medicine* devoted to the subject of food addiction. This editorial reviews important evidence of food addiction, and highlights some of the major findings and insights presented in the articles that are published alongside it.

- 2 Koob GF, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology* 2010; 35:217–238.
- 3 Wang GJ, Volkow ND, Thanos PK, Fowler JS. Imaging of brain dopamine pathways: implications for understanding obesity. *J Addict Med* 2009; 3:8–18. The authors provide a careful review of the neurobiology underlying food consumption, the interactions between peripheral and central signaling systems that are involved in eating, and dopamine's role in mediating both normal and pathological patterns of food consumption. The article highlights important imaging evidence that dopamine is a central regulator of appetitive behavior, and that dopamine signaling may be dysregulated in obesity.
- 4 Koob GF. Dynamics of neuronal circuits in addiction: reward, anti-reward, and emotional memory. *Pharmacopsychiatry* 2009; 42 (Suppl 1):S32–S41.
- 5 Dagher A, Robbins TW. Personality, addiction, dopamine: insights from Parkinson's disease. *Neuron* 2009; 61:502–510. This article argues persuasively that dopamine is a central mediator of addiction. In making their case, they cite very low levels of addiction in patients with Parkinson's disease – an illness characterized by deficiencies in dopaminergic neurotransmission – and evidence that Parkinson's disease patients can become addicted to the dopamine agonists that are one of the cornerstones of Parkinson's disease treatment.
- 6 Dagher A. The neurobiology of appetite: hunger as addiction. *Int J Obes* 2009; 33 (Suppl 2):S30–S33. An excellent overview of the signaling networks that regulate food consumption, and of the similarities between drug use and eating.
- 7 Barson JR, Karatayev O, Chang GQ, et al. Positive relationship between dietary fat, ethanol intake, triglycerides, and hypothalamic peptides: counteraction by lipid-lowering drugs. *Alcohol* 2009; 43:433–441.
- 8 Karatayev O, Baylan J, Leibowitz SF. Increased intake of ethanol and dietary fat in galanin overexpressing mice. *Alcohol* 2009; 43:571–580.
- 9 Karatayev O, Gaysinskaya V, Chang GQ, Leibowitz SF. Circulating triglycerides after a high-fat meal: predictor of increased caloric intake, orexigenic peptide expression, and dietary obesity. *Brain Res* 2009; 1298:111–122.
- 10 Avena NM, Rada P, Hoebel BG. Sugar and fat bingeing have notable differences in addictive-like behavior. *J Nutr* 2009; 139:623–628. This study presents evidence that although bingeing on either sugar or fat have similar neurochemical effects in rats, sugar bingeing can induce opiate-like withdrawal symptoms, whereas fat bingeing does not. This article also provides a thorough and well sourced review of evidence of food dependence, and of a link between binge eating and obesity.
- 11 Lutter M, Nestler EJ. Homeostatic and hedonic signals interact in the regulation of food intake. *J Nutr* 2009; 139:629–632. This study provides a comprehensive and well structured comparison of appetitive behavior and drug use. The authors address, in turn, the motivations to eat and use drugs of abuse, the effects of repeated drug use and repeated consumption of highly palatable foods on neurochemistry, and links between these neurochemical changes and known clinical disorders that involve pathological eating habits.
- 12 Geiger BM, Haburcak M, Avena NM, et al. Deficits of mesolimbic dopamine neurotransmission in rat dietary obesity. *Neuroscience* 2009; 159:1193–1199. This study demonstrates an association between rat dietary obesity and decreased dopaminergic neurotransmission in the nucleus accumbens and dorsal striatum.
- 13 Mathes WF, Nehrenberg DL, Gordon R, et al. Dopaminergic dysregulation in mice selectively bred for excessive exercise or obesity. *Behav. Brain Res* 2010; 210:155–163. This study demonstrates that common genetically mediated alterations in central dopamine pathways of mice can lead both to obesity and excessive exercise, two very different phenotypes.
- 14 Perry ML, Baldo BA, Andrzejewski ME, Kelley AE. Muscarinic receptor antagonism causes a functional alteration in nucleus accumbens mu-opiate-mediated feeding behavior. *Behav Brain Res* 2009; 197:225–229. Food-deprived rats that received an intraaccumbens infusion of scopolamine, a muscarinic antagonist, demonstrated decreased food intake compared with food-deprived controls. The study's results suggest that muscarinic receptors in the nucleus accumbens are involved in the regulation of feeding behaviors in rats.
- 15 Pratt WE, Blackstone K, Connolly ME, Skelly MJ. Selective serotonin receptor stimulation of the medial nucleus accumbens causes differential effects on food intake and locomotion. *Behav Neurosci* 2009; 123:1046–1057.
- 16 Pelchat ML. Food addiction in humans. *J Nutr* 2009; 139:620–622. This study reviews similarities between food cravings and drug cravings that addictive appetitive behaviors may result from the way in which food is consumed and one's amount of access to food, as opposed to its palatability.
- 17 Corsica JA, Pelchat ML. Food addiction: true or false? *Curr Opin Gastroenterol* 2010; 26:165–169. A concise review of the literature, to date, on food addiction. The authors conclude that significant evidence exists to support the existence of food addiction, but make clear that the links between food addiction and obesity are not well understood.

- 18** Ifland JR, Preuss HG, Marcus MT, *et al.* Refined food addiction: a classic substance use disorder. *Med Hypotheses* 2009; 72:518–526.
- 19** Cocores JA, Gold MS. The Salted Food Addiction Hypothesis may explain overeating and the obesity epidemic. *Med Hypotheses* 2009; 73:892–899.  
The authors propose that salt may act as a mild opiate, thereby promoting food consumption and driving increasing rates of overweight and obesity. They present evidence that, normal weight–overweight opiate addicts consume increased amounts of salt and gain 6.6% of additional weight while withdrawing from opiates.
- 20** Wang GJ, Volkow ND, Telang F, *et al.* Evidence of gender differences in the ability to inhibit brain activation elicited by food stimulation. *PNAS* 2009; 106:1249–1254.  
This study presents neuroimaging evidence that men are better able than women to suppress feelings of hunger in response to a visual food stimulus. The authors suggest that this finding could help to explain gender differences in obesity rates.
- 21** Cornier MA, Salzberg AK, Endly DC, *et al.* Sex-based differences in the behavioral and neuronal responses to food. *Physiol Behav* 2010; 99:538–543.  
The authors found that women reported greater postprandial satiety, and demonstrated greater dietary restraint than did men. However, fMRI imaging of men and women who were presented with images of hedonic foods showed significantly greater prefrontal and parietal activation in women as compared with men.
- 22** Chen H, Simar D, Morris MJ. Hypothalamic neuroendocrine circuitry is programmed by maternal obesity: interaction with postnatal nutritional environment. *PLoS One* 2009; 4:e6259.
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