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The Addictive Dimensionality of Obesity

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Abstract

Our brains are hardwired to respond and seek immediate rewards. Thus, it is not surprising that many people overeat, which in some can result in obesity, whereas others take drugs, which in some can result in addiction. Though food intake and body weight are under homeostatic regulation, when highly palatable food is available, the ability to resist the urge to eat hinges on self-control. There is no homeostatic regulator to check the intake of drugs (including alcohol); thus, regulation of drug consumption is mostly driven by self-control or unwanted effects (i.e., sedation for alcohol). Disruption in both the neurobiological processes that underlie sensitivity to reward and those that underlie inhibitory control can lead to compulsive food intake in some individuals and compulsive drug intake in others. There is increasing evidence that disruption of energy homeostasis can affect the reward circuitry and that overconsumption of rewarding food can lead to changes in the reward circuitry that result in compulsive food intake akin to the phenotype seen with addiction. Addiction research has produced new evidence that hints at significant commonalities between the neural substrates underlying the disease of addiction and at least some forms of obesity. This recognition has spurred a healthy debate to try and ascertain the extent to which these complex and dimensional disorders overlap and whether or not a deeper understanding of the crosstalk between the homeostatic and reward systems will usher in unique opportunities for prevention and treatment of both obesity and drug addiction.

Keywords

Dopamine; drug addiction; obesity; prefrontal cortex; reward; self-control

Both addiction and obesity reflect imbalances in the responses of the brain to rewarding stimuli in the environment. For obesity, this imbalance can be triggered by endocrinological abnormalities that change the energetic threshold and modify the sensitivity to food rewards. However, obesity can also result from easy access to highly palatable food, excessive consumption of which can affect homeostatic signaling and disrupt the sensitivity to food reward. Repeated consumption of a drug, on the other hand, can directly disrupt the reward circuit, its main pharmacologic target. Thus, the dopamine (DA) system, through the mesoaccumbens/mesolimbic (reward and emotions), mesostriatal (habits, routines, and

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movement), and mesocortical (executive function) pathways, is a common substrate in the neurobiology of both disorders (Figure 1).

We propose that these two diseases share neurobiological processes that, when disrupted, can result in compulsive consumption, while also involving unique neurobiological processes. We present evidence of shared neurobiological substrates and do not claim that obesity is the result of food addiction but rather that food reward plays a critical role in overeating and obesity, referring to it as the dimensional component of obesity.

Genetic Overlaps

Social and cultural factors contribute to the obesity epidemic. However, individual factors also help determine who will become obese in these environments. Though genetic studies have revealed point mutations that are overrepresented among obese individuals, obesity is largely thought to be under polygenic control. Indeed, the most recent whole genome-wide association study conducted in 249,796 individuals of European descent identified 32 loci associated with body mass index (BMI). However, these 32 loci explained only 1.5% of the BMI variance (1,2), a situation that is unlikely to improve with larger samples because of the complex interactions between biological and environmental factors. This is particularly true whenever high-calorie content food is widely available, not just as a source of nutrition, but also as a strong reward that, by itself, promotes eating.

Perhaps, broadening the scope of what we understand by genetic risk for obesity beyond genes linked to energy homeostasis (3) to include genes that modulate our response to the environment would increase the percentage of the BMI variance explained by genes. For example, genes that influence personality could contribute to obesity if they erode the perseverance needed for sustained physical activity. Similarly, genes that modulate executive control, including self-control, may help counteract the risk for overeating in food-rich environments. This could explain the association of obesity with genes involved with DA neurotransmission, such as the *DRD2* Taq I A1 allele, which has been associated with addiction (4). Similarly, there are genes at the intersection between reward and homeostatic pathways, like the cannabinoid receptor 1 (*CNR1*) gene, variations in which have been associated with BMI and obesity risk by most studies (5), as well as with addiction (6). And, let us also remember in this context that endogenous opioids are involved in hedonic responses to food and to drugs and that the functional A118G polymorphism in the μ-opioid receptor gene (*OPRM1*) has been associated with vulnerability for binge-eating disorders (7) and alcoholism (8).

Molecular Overlaps: Focus on Dopamine

The decision to eat (or not) is not only influenced by the internal state of the caloric equation but also by nonhomeostatic factors, such as food palatability and environmental cues that trigger conditioned responses. The past decade has uncovered numerous molecular and functional interactions between the homeostatic and reward levels of food regulation. Specifically, several hormones and neuropeptides involved in energy homeostasis influence the DA reward pathway (9). Overall, homeostatic orexigenic signals increase the activity of ventral tegmental area (VTA) DA cells when exposed to food stimuli, whereas anorexigenic

ones inhibit DA firing and decrease DA release (10). Moreover, neurons in VTA and/or nucleus accumbens (NAc) express glucagon-like peptide-1 (11,12), ghrelin (13,14), leptin (15,16), insulin (17), orexin (18), and melanocortin receptors (19). Therefore, it is not surprising that these hormone/peptides can influence the rewarding responses to drugs of abuse. Such interactions could explain the findings of attenuated responses to the rewarding effects of drugs in animal models of obesity (20). Similarly, human studies found an inverse relationship between BMI and illicit drug use (21) and a lower risk for substance use disorders in obese individuals (22), including lower rates of nicotine (23) and marijuana (24) abuse. Moreover, interventions that decrease BMI and reduce plasma levels of insulin and leptin enhance the sensitivity to psychostimulant drugs (25), and bariatric surgery for obesity is associated with an increased risk for relapse to alcohol abuse and alcoholism (26). Taken together, these results strongly suggest the possibility that food and drugs may be competing for overlapping reward mechanisms.

The phenomenological and neurobiological overlaps between obesity and addiction can be predicted on the basis that drugs of abuse tap into the same neuronal mechanisms that modulate the motivation and drive to seek and consume food (27). Since drugs activate brain reward pathways more potently than food, this helps explain (together with homeostatic satiety mechanisms) the greater ability of drugs to induce loss of control and compulsive consummatory behavior. Brain DA pathways, which modulate the behavioral responses to environmental stimuli, play central roles in obesity (also in addiction). Dopamine neurons (both in VTA and substantia nigra) modulate not only reward but also the motivation and sustainability of effort necessary to accomplish behaviors needed for survival. Indeed, DA-deficient mice die of starvation, likely as a result of a decreased motivation to consume the food, and replenishing the dorsal striatum with DA restores feeding and rescues them (28). There is another DA pathway (tuberoinfundibular pathway) that projects from the hypothalamus to the pituitary gland, but we are not considering it here because it has not yet been implicated in the rewarding effects of drugs (29), even though it can be affected by drugs of abuse (30). To achieve its functions, DA neurons receive projections from brain regions involved with autonomic responses (hypothalamus, insula), memory (hippocampus), emotional reactivity (amygdala), arousal (thalamus), and cognitive control (prefrontal cortex) through a diverse set of neurotransmitters and peptides (31). Predictably then, many neurotransmitters implicated in drug-seeking behaviors are also implicated in food intake (9).

Of all the signals implicated in the effects of food and drugs, DA has been the most thoroughly investigated. Experiments in rodents have shown, for example, that DA signals through both D1 receptors and D2 receptors (D2R) in the dorsal striatum are necessary for feeding and other eating-related behaviors (28). For example, upon first exposure to a food reward, the firing of DA neurons in the VTA increases with a resulting increase in DA release in the NAc (32). With repeated exposure, the DA neurons stop firing when receiving the food and fire instead when exposed to the stimulus that predicts food delivery (33). Moreover, since the increases in DA induced by the conditioned stimulus predict the behavioral price the animal is willing to pay to receive it, this will ensure that the motivational drive (fueled by DA signaling) occurs before the animal is eating the food itself. Interestingly, when the cue does not lead to the expected food reward, DA neuron

activity is inhibited, decreasing the incentive value for the cue (extinction). Animal models of both food and drug reward have shown that after extinction, the behavior for drug or food consumption can be triggered either by exposure to the cue, the reward, or a stressor (34). This vulnerability to relapse has been extensively studied in animal models of drug administration and reflects neuroplastic changes in alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid and *N*-methyl-D-aspartate receptor glutamatergic signaling (35). For drug reward, studies have also shown that an imbalance between D1 receptor signaling (enhanced) and D2 receptor signaling (decreased) facilitates compulsive drug intake (36); one could predict that a similar imbalance may favor compulsive food intake. This possibility is consistent with a recent report in which a D1-like antagonist blocked and a D2-like antagonist increased the reinstatement of food-seeking behavior (37).

Taken together, these results suggest that the homeostatic circuitry has evolved to take advantage of the dopaminergic circuitry to imbue feeding behaviors not only with the conditioning/rewarding properties subsumed initially by the ventral striatum but also with the subsequent utilization of dorsal striatum outputs to cortical structures directly involved in coupling motivation with the motor responses needed for goal-directed behaviors (38).

Neurocircuitry and Behavioral Overlaps

The overwhelming urge to seek and consume the drug in addiction involves disruption not only of the reward circuitry but also of other circuits, including interoception, inhibitory control, mood and stress regulation, and memory (39). It can be argued that this neurocircuitry model of addiction also applies to certain types of obesity.

Reward, Conditioning, and Motivation

Drugs of abuse work by activating the DA reward circuit, which, if chronic, in vulnerable individuals, can result in addiction. Certain foods, particularly those rich in sugars and fat, are also potently rewarding (40) and can trigger addictive like behaviors in laboratory animals (41) and humans (27). Indeed, high-calorie foods can promote overeating (i.e., eating that is uncoupled from energetic needs) and trigger learned associations between the stimulus and the reward (conditioning). This property of palatable foods used to be evolutionarily advantageous when food was scarce, but in environments where such foods are plentiful and ubiquitous, it is a dangerous liability. Thus, palatable foods, like drugs of abuse, represent a powerful environmental trigger, which, in vulnerable individuals, has the potential to facilitate or exacerbate the establishment of uncontrolled behaviors.

In humans, the ingestion of palatable food releases DA in the striatum in proportion to the ratings of meal pleasantness (42) and activates reward circuitry (43). Consistent with preclinical studies, imaging studies have also shown that anorexigenic peptides (e.g., insulin, leptin, peptide YY) decrease the sensitivity of the brain reward system to food reward, whereas orexigenic ones (e.g., ghrelin,) increase it [see review (44)]. Surprisingly, both addicted and obese subjects exhibit less activation of reward circuits when given the drug or the palatable food, respectively (45). This is counterintuitive since the increases in DA are believed to mediate the rewarding values of drug and food rewards; hence, blunted DA responses during consumption should predict behavioral extinction. Since this is not what is

seen in the clinic, it was suggested that blunted DA activation by consumption (of drug or food) could trigger overconsumption to compensate for the blunted response of the reward circuit (46). Preclinical studies showing that decreased DA activity in VTA results in a dramatic increase in the consumption of high-fat foods (47) partially support this hypothesis.

In contrast to the blunted reward responses during reward consumption, both addicted and obese subjects show sensitized responses to conditioned cues predictive of drug or food reward. The magnitude of these DA increases in addicted subjects predicts the intensity of cue-induced cravings (48), and in animals, they predict the effort that an animal is willing to exert to get the drug (49). Compared with normal-weight individuals, obese individuals observing pictures of high-calorie food (stimuli to which they are conditioned) showed increased activation in regions of the reward and motivation circuits (NAc, dorsal striatum, orbitofrontal cortex [OFC], anterior cingulate cortex [ACC], amygdala, hippocampus, and insula) (50). Similarly, in obese individuals with binge-eating disorder, higher DA release—when exposed to food cues—was associated with the severity of the disorder (51).

The extensive glutamatergic afferents to DA neurons from regions involved in the processing of reward (NAc), conditioning (amygdala, hippocampus, prefrontal cortex), and salience attribution (orbitofrontal cortex) modulate their activity in response to conditioned cues (31). More specifically, projections from the amygdala, hippocampus, and OFC to DA neurons and to NAc are involved in conditioned responses to food (52) and drugs (53). Indeed, imaging studies showed that when nonobese male subjects were asked to inhibit their craving for food when exposed to food cues, they decreased activity in amygdala, OFC, hippocampus, insula, and striatum; and OFC decreases were associated with reductions in food craving (54). A similar inhibition of OFC activity (and NAc) was observed in cocaine abusers when they were asked to inhibit their drug craving during exposure to cocaine cues (55). However, compared with food cues, drug cues are more powerful triggers of reinforcer-seeking behavior following a period of abstinence. Thus, once extinguished, drug-reinforced behaviors are far more susceptible to stress-induced reinstatement than food-reinforced behaviors (56). Still, stress is associated with increased consumption of palatable foods and weight gain and a potentiated OFC activation to food rewards (57).

It appears as if DA activation of the striatum by cues (including drug-related contexts) is involved with the desire (wanting), as the trigger of behaviors geared toward consuming the desired reward. Indeed, DA also modulates motivation and persistence (58). Because drug taking becomes the main motivational drive in addiction, addicted subjects are aroused and motivated by the process of obtaining the drug but withdrawn and apathetic when exposed to non–drug-related activities. This shift has been studied by comparing brain activation in the presence or absence of drug cues. In contrast to the decreases in prefrontal activity reported in detoxified cocaine abusers when not stimulated with drug or drug cues [see review (59)], ventral and medial prefrontal regions (including OFC and ventral ACC) become activated with exposure to craving-inducing stimuli (either drugs or cues) (60,61). Also, when cocaine-addicted subjects purposefully inhibited craving when exposed to drug cues, those who were successful decreased metabolism in medial OFC (processes motivational value of a reinforcer) and NAc (predicts reward) (55), consistent with the involvement of OFC, ACC, and striatum in the enhanced motivation to procure the drug seen in addiction. The OFC is

similarly involved in attributing salience value to food (62), helping to assess its expected pleasantness and palatability as a function of its context. Normal-weight subjects exposed to food cues showed increased activity in OFC, which was associated with food craving (63). There is evidence that the OFC also supports conditioned cue-elicited feeding (64) and that it contributes to overeating, irrespective of hunger signals (65). Indeed, several lines of research support a functional link between OFC impairment and disordered eating, including the reported association between disinhibited eating in obese adolescents and reduced OFC volume (66). In contrast, greater volumes of the medial OFC were seen in both bulimia nervosa and binge-eating disorder patients (67), and damage to the OFC in rhesus monkeys has been reported to result in hyperphagia (68).

The emergence of cue-conditioned cravings and incentive motivation for the reward, which for food also occur in healthy individuals who do not overeat (69), would not be as devastating were they not coupled with growing deficits in the brain's ability to inhibit maladaptive behaviors.

Self-Control and the Ability to Resist Temptation

The capacity to inhibit prepotent responses and exert self-control contributes to an individual's ability to suppress inappropriate behaviors, such as taking drugs or eating past the point of satiety, thus modulating the vulnerability to addiction or obesity, respectively (70,71). Preclinical and clinical studies have suggested that impairments in striatal DA signaling may undermine self-control as described below.

Imaging studies revealed that reduced availability of striatal D2R receptors is a consistent abnormality across a wide variety of drug addictions and one that can persist months after detoxification [reviewed in (59)]. Similarly, preclinical studies have shown that repeated drug exposures are associated with long-lasting reductions in striatal D2R levels and signaling (72,73). In the striatum, D2 receptors mediate signaling through the indirect pathway that modulates frontocortical regions, and its down-regulation enhances drug sensitization in animal models (74), whereas its upregulation interferes with drug consumption (75). Moreover, inhibition of striatal D2R or activation of D1 receptor-expressing striatal neurons (mediate signaling in the striatal direct pathway) enhances the sensitivity to drug rewards (74). Dysregulation of striatal D2R signaling has also been implicated in obesity (76,77) and in compulsive food intake in obese rodents (78). However, the extent to which there are similar opposite regulatory processes for the direct (decreased) and indirect (increased) pathways in obesity remains unclear.

The reduction in striatal D2R in addiction and in obesity is associated with decreased activity in prefrontal regions involved in salience attribution (OFC), error detection and inhibition (ACC), and decision making (dorsolateral prefrontal cortex) (73,79,80). Thus, improper regulation by D2R-mediated DA signaling of these frontal regions in addicted and obese subjects could underlie the enhanced incentive motivational value of drugs or food and the difficulty in resisting them (70,71). In addition, because impairments in OFC and ACC are associated with compulsive behaviors and impulsivity, impaired modulation of dopamine in these regions is likely to contribute to the compulsive and impulsive patterns of drug (addiction) or food (obesity) intake.

Similarly, a pre-existing dysfunction of prefrontal regions could also underlie the vulnerability for excessive drug or food consumption, which would be further exacerbated by decreases in striatal D2R (either drug- or stress-induced; it is unclear whether obesogenic diets decrease striatal D2R). Indeed, we showed that subjects who, despite having a high genetic risk for alcoholism (positive family history of alcoholism) were not alcoholics, had higher than normal striatal D2R, which was associated with normal prefrontal metabolism (81) that might have protected them from alcoholism. Interestingly, a recent study of siblings discordant for their addiction to stimulant drugs found that the OFC of the addicted siblings was significantly smaller than that of nonaddicted siblings or control subjects (82).

Brain imaging data also support the notion that structural and functional changes in brain regions implicated in executive (including inhibitory) function are associated with high BMI in otherwise healthy individuals. For example, a magnetic resonance imaging study of elderly women found a negative correlation between BMI and gray matter volumes (including frontal regions), which, in the OFC, correlated with impaired executive function (83). Other studies found significant decreases in blood flow in the prefrontal cortex associated with higher weight in healthy control subjects (84,85), and a functional magnetic resonance imaging study reported impaired executive function in obese women (86). Similarly, in healthy control subjects, BMI was negatively correlated with metabolic activity in prefrontal regions for which the activity predicted the scores on tests of executive function (87). Interestingly, successful dieters activate prefrontal regions involved in inhibitory control (dorsolateral prefrontal cortex and OFC) while eating (88). These and other studies evince a correlation between executive function and addiction and obesity risk/phenotypes, and further research will help clarify details as well as differences between these phenotypes.

Clearly, individual differences in executive function can constitute a prodromal risk for later obesity in some individuals (89). Interestingly, a cross-sectional investigation of children's ability to self-regulate, solve problems, and engage in goal-directed health behaviors revealed executive function proficiency to be negatively correlated not only with substance use but also with the consumption of high-calorie snack foods and with sedentary behaviors (90).

Awareness of Interoceptive Signals

The middle insula plays a critical role in cravings for food, cocaine, and cigarettes (91–93). Its importance in addiction was highlighted when a study found that smokers who suffered a stroke that damaged the insula were able to quit easily and without experiencing either cravings or relapse (94). The insula, particularly its more anterior regions, is reciprocally connected to several limbic regions and supports interoceptive functions, integrating the autonomic and visceral information with emotion and motivation and providing conscious awareness of these urges (95). Consistent with this hypothesis, many imaging studies show differential activation of the insula during craving (95). Accordingly, the reactivity of the insula has been suggested as a biomarker to help predict relapse (96).

The insula is also a primary gustatory area, which participates in many aspects of eating behaviors, such as taste. In addition, the rostral insula (connected to primary taste cortex)

provides information to the OFC that influences its multimodal representation of the pleasantness or reward value of incoming food (97). Because of the insula's involvement in the interoceptive sense of the body, in emotional awareness (98), and in motivation and emotion (97), a contribution of insular impairment in obesity should not be surprising. Indeed, gastric distention results in activation of the posterior insula, a likely reflection of its role in the awareness of body states (in this case of fullness) (99). Moreover, in lean but not in obese subjects, gastric distention resulted in activation of the amygdala and deactivation of the anterior insula (100). The lack of amygdalar response in obese subjects could reflect a blunted interoceptive awareness of bodily states linked with satiety (full stomach). Even though the modulation of insular activity by DA has been poorly investigated, it is recognized that DA is involved in responses to the tasting of palatable foods that are mediated through the insula (101). Indeed, in humans, tasting palatable foods activated the insula and midbrain areas (102,103). In addition, DA signaling appears to also be necessary for sensing the calorie content of food. For example, when normal weight women tasted a sweetener with calories (sucrose), both the insula and DA midbrain areas became activated, whereas tasting a calorie-free sweetener (sucralose) only activated the insula (103). Obese subjects exhibit greater insular activation than normal control subjects when tasting a liquid meal with sugar and fat (102). In contrast, subjects who have recovered from anorexia nervosa show less insular activation when tasting sucrose and no association of feelings of pleasantness with insular activation as observed in control subjects (104).

Dark Side of the Addictive Dimension

The dark side of addiction was initially proposed by Koob and Le Moal (105) to describe the transition that drug-addicted individuals experience between the initial, pleasurable use of drugs to the one that, with repeated use, results in drug consumption to relieve negative emotional states. More recently, Parylak *et al.* (106) have proposed that a similar transition may occur in food addiction with exposure to obesogenic foods. They pointed out that both in drug addiction and in certain instances of obesity or eating disorders, stress and negative moods (depression, anxiety) can trigger compulsive drug (in addiction) or food intake in humans (obesity and eating disorders). Their model highlights the importance of brain circuits that modulate stress reactivity and antireward, which are enhanced after repeated drug exposures but also after intermittent access to palatable foods. Central to their model is an enhanced sensitivity of the extended amygdala and increased signaling through corticotropin-releasing factor and corticotropin-releasing factor related peptides, which mediate responses to stress.

In parallel, the recognition that the habenula mediates inhibition of VTA DA neuron firing when an expected reward does not materialize (107) also implicates this region in contributing to such antireward circuitry. Thus, an enhanced sensitivity of the habenula, as a result of chronic drug exposure, could underlie a greater reactivity to drug cues and also contribute to dysphoric states during withdrawal. Indeed, activation of the lateral habenula, in animal models of cocaine or heroin addiction, has been associated with relapse (108,109). The habenula is also implicated in food reward: neurons in the rostromedial tegmental nucleus, which receive a major input from the lateral habenula, project to VTA DA neurons and are activated after food deprivation (110). These findings are consistent with a role for

the lateral habenula in mediating responses to aversive stimuli or states such as those that occur during dieting or drug withdrawal.

Summary and Implications

The human brain is a complex biological system that is organized in the layered architecture of interactive networks, sometimes called bowtie (111), whereby a narrowing funnel of many potential inputs converges onto a relatively small number of processes before fanning out again into a diversity of outputs. Eating behaviors present a great example of this architecture where the hypothalamus is a central knot of the metabolic bowtie (Figure 2A) and midbrain DA nuclei (VTA and substantia nigra) and their projection regions (NAc; amygdala; hippocampus; dorsal striatum; and prefrontal, motor, and temporal cortices) represent a central knot for a system that reacts to salient external stimuli (including drugs and food), as well as relevant internal signals (i.e., hunger, thirst) (Figure 2B). These two systems can be viewed as examples of nested layered architectures (111), in which the DA bowtie subserves the internal signals mediated by hypothalamic signaling (Figure 2C). This model helps explain the proliferating examples of contact points between obesity and addiction, some of which were highlighted in this review.

Thus, strategies that borrow from successful prevention and treatment strategies in addiction might be beneficial in obesity. Future research in this area should include social and policy strategies to decrease the availability of obesogenic food (restricting its sales, increasing their costs), increase access to alternative reinforcers (healthy food that can compete in price for high-calorie food and access to physical activity), and develop education (taking advantage of schools, families, and communities). Similarly, treatment research could focus on clinical and social strategies to decrease the reinforcing properties of food and re-establish/enhance the rewarding properties of alternative reinforcers (incorporate social rewards, physical activity, contingencies), inhibit conditioned learned associations (extinguishing conditioned responses, learning new associations), decrease stress reactivity and improve mood (physical activity, cognitive therapy), and strengthen general purpose self-control (cognitive and behavioral treatments). The translational aspects that emerge from recognizing the overlapping nature of these diseases represent just one of several possible future research directions identified in this review (Table 1).

It is telling that the two largest preventable threats to public health (smoking and obesity) involve the reward circuit that drives the motivation of individuals to consume rewards despite the fact that they are harmful to their health. Solutions to both of these epidemics will require, in addition to individual tailored approaches, broad public health initiatives that promote smart changes in the environment.

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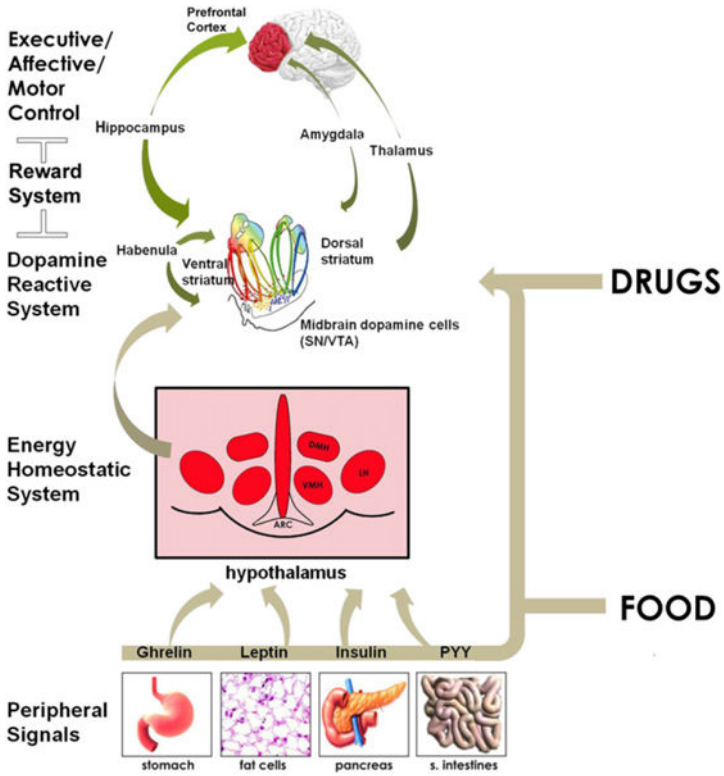

Figure 1.

In striking contrast to drugs whose actions are triggered by their direct pharmacologic effects in the brain reward dopamine pathway (ventral tegmental area [VTA], nucleus accumbens, and ventral pallidum), the regulation of eating behaviors and hence the responses to food are modulated by multiple peripheral and central mechanisms that directly or indirectly convey into the brain's reward pathways, including those involved with pleasure, aversion, habituation, and cognitive control [Diagram of the organization of striatocortical connectivity loops reprinted with permission from Haber *et al.* (112), copyright 2000 Society for Neuroscience]. PYY, peptide YY; s. intestines, small intestines; SN, substantia nigra.

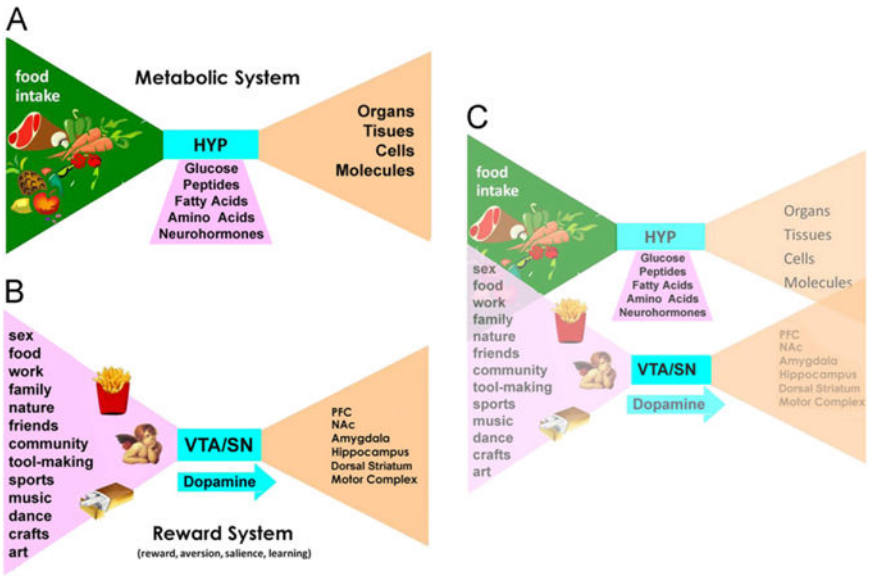

Figure 2.

Schematic representation of bowtie architectures in the brain as exemplified by the (**A**) energy homeostatic (metabolic) and (**B**) dopamine reactive (reward) systems. The human brain, like most complex biological systems, is characterized by the layered architectures of interactive networks [reprinted with permission from (111), copyright 2004 Elsevier]. These systems display an evolutionarily optimized organization, whereby a narrowing funnel of many potential inputs converges onto a relatively small number of processes before fanning out again into a great diversity of outputs. (**C**) The homeostatic and reward bowties are good examples of nested layered architectures [reprinted with permission from (111), copyright 2004 Elsevier], since the dopamine bowtie can be viewed as an integral part of the broader energetic network that includes hypothalamic (HYP) signaling and peripheral hormones. NAc, nucleus accumbens; PFC, prefrontal cortex; SN, substantia nigra; VTA, ventral tegmental area (modified with permission from an unpublished presentation, courtesy of Dr. John Doyle, Ph.D.).

Table 1

Some Open Questions for Future Research on the Addictive Aspects of Obesity

- Do imbalances between D1 receptor signaling (enhanced) and D2 receptor signaling (decreased), which facilitate compulsive drug intake, also favor compulsive food intake?
- To what extent is striatal D2 receptor dysfunction a clinical consequence of drug use or obesogenic diets as opposed to being a marker of differential vulnerability in addiction/obesity?
- What are the lessons, if any, that obesity research can derive from successful addiction prevention and treatment approaches? For example, are the cortical areas involved in inhibitory control (dorsolateral prefrontal cortex and anterior cingulate cortex) potential substrates for behavioral retraining in the treatment of addiction/obesity?
- Genetic research to explore the potential contribution of genes that influence personality (e.g., perseverance, sustained physical activity, and executive control traits) to obesogenic behaviors.
- What are the underlying biological mechanisms linking bariatric surgery to increased risk of alcoholism?
- What are the specific roles of the stress reactivity and antireward system in connecting dysphoric, negative affect, or stressful states with compulsive eating?
- Longitudinal studies are needed to investigate whether and how early food and lifestyle choices are associated with later body mass index and executive functioning.