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The drive to eat: comparisons and distinctions between mechanisms of food reward and drug addiction

Ralph J. DiLeone, **Jane R. Taylor**, and **Marina R. Picciotto***
Department of Psychiatry, Yale University School of Medicine, 34 Park Street, 3rd Floor Research, New Haven, CT 06508, USA

Abstract

The growing rates of obesity have prompted comparisons between the uncontrolled intake of food and drugs; however, an evaluation of the equivalence of food- and drug-related behaviors requires a thorough understanding of the underlying neural circuits driving each behavior. Although it has been attractive to borrow neurobiological concepts from addiction to explore compulsive food seeking, a more integrated model is needed to understand how food and drugs differ in their ability to drive behavior. In this review, we will examine the commonalities and differences in the systems-level and behavioral responses to food and drugs of abuse, with the goal of identifying areas of research that would address gaps in our current understanding and ultimately identify novel treatments for obesity or drug addiction.

INTRODUCTION

Over the last several decades, the developed world has experienced a surge in obesity, with more than 30% of the United States population currently considered obese, and a much greater proportion considered to be overweight (http://www.cdc.gov/obesity/data/facts.html). The health consequences of obesity are enormous, leading to more than 200,000 premature deaths each year in the United States alone. While the obesity epidemic is thought to have multiple causes, many of these converge to produce excess intake. The inability to control intake is reminiscent of drug addition, and comparisons between the uncontrolled intake of food and drugs have become a predominant[1], and somewhat controversial[2], component of obesity models. In this review, we will examine the systems-level and behavioral responses to food and drugs of abuse. We will highlight the differences, as well as the commonalities, between the mechanisms driving food intake and drug seeking in order to identify areas of research that could cover gaps in knowledge of both obesity and addiction.

In our view, obesity should be treated as a behavioral problem in that many people want to use self-control to diet and lose weight, but cannot. The distinction between the mechanisms involved in the physiological control of food intake and reward, and those involved in the physio-pathological conditions leading to eating disorders and obesity are not yet understood. The distinction between “normal” and “disease” is not clear in animal models and is also less clear for sub-threshold eating disorders that do not reach clinical diagnosis. This is the case with obesity (is it abnormal or normal to overeat?) and eating disorders, where no well-accepted animal model exists. While caloric need clearly drives food seeking under conditions of scarcity, over-eating when food is ubiquitous is driven by intake of highly palatable foods and continued eating even when metabolic demand has been met. It is

*To whom correspondence should be addressed, Marina R. Picciotto, Dept. of Psychiatry, Yale University School of Medicine, 34 Park Street – 3rd floor research, New Haven, CT 06508, Phone: 203-737-2041; Fax: 203-737-2043; marina.picciotto@yale.edu.

this aspect of eating that has been compared most directly to drug addiction; however, in order to understand whether food- and drug-seeking behaviors are equivalent, it is critical to measure food reward and compulsive eating in models that have face-validity for human eating and to define these behaviors more precisely. For example, tests of food intake behavior are often conducted in animals that have been food-restricted, and this may not reflect the neural mechanisms relevant in the overweight condition. In addition, an evaluation of the equivalence in food- and drug-related behaviors requires a thorough understanding of the underlying neural circuits driving each behavior in order to determine whether surface similarities in behavior are indeed related to common mechanisms. Many components of the neural systems contributing to food intake have been identified. These include identification of the molecules, such as the orexigenic and anorexigenic peptides, that contribute to food seeking under different conditions, as well as the neuroanatomical basis for some aspects of these behaviors (reviewed in[3–5]). Although it has been attractive to borrow neurobiological concepts from addiction to explore compulsive food seeking, important pieces of the story are still missing, and a more integrated vision of the underlying neurobiology is needed to understand how food and drugs differ in their ability to drive behavior.

Circuit-level comparisons between food- and drug-seeking

The decision to eat or not to eat and strategies to obtain food are core elements of survival, and are therefore highly susceptible to selection pressures during evolution. Drug addiction is commonly seen as “hijacking” these natural reward pathways, and this view has informed much of the basic research that compares neural substrates of food and drug reward. We speculate that drugs of abuse engage only a subset of the circuits evolved for behaviors related to seeking the natural rewards essential for survival. That is, food intake is an evolved behavior that engages many integrated body systems and brain circuits. Drug addiction is also complex, but starts with a pharmacological event that triggers downstream pathways that did not evolve to transmit that chemical signal.

Mesolimbic dopamine system

The initial site of action for addictive drugs is predominantly on mesolimbic dopamine circuits[6]. In contrast, the role of mesolimbic circuits in food intake is more nuanced. Mesolimbic circuits influence many behaviors, including reward prediction[7], hedonia,[8], reinforcement[9], motivation[10], and incentive salience[11]. In contrast to behaviors related to drug addiction, nucleus accumbens dopamine depletion alone does not alter feeding[12]. Pharmacological blockade of D1 and D2 dopamine receptors in the nucleus accumbens affects motor behavior and has small effects on feeding patterns, but does not reduce the amount of food consumed[13]. Animals lacking dopamine throughout the brain and body do not eat[14,15]; however, it is difficult to distinguish effects on movement from those on intake and reinforcement *per se*. In fact, if food is placed into the mouth of animals lacking dopamine they will show normal sucrose preference, suggesting that animals can have hedonic responses for food in the absence of dopamine[16].

Hypothalamus

Although activity in the mesolimbic dopamine system is important for the rewarding and reinforcing properties of drugs of abuse and drives some aspects of food seeking as well, a major difference between food seeking and intake of addictive drugs is that hypothalamic nuclei receive and integrate signals, such as leptin and ghrelin, from peripheral tissues, and coordinate peripheral metabolic need and food seeking[17]. Whereas activation of VTA to NAc dopamine signaling is necessary for drug self-administration, direct stimulation of NPY/AgRP neurons in the hypothalamus is sufficient to drive food intake, even in the

absence of dopamine system activation[18]. Moreover, vagal feedback from the stomach and intestine has an important influence on brainstem activity, and ultimately food intake and metabolism[19]. The identification and study of these key signals has contributed greatly to our understanding of food intake and has resulted in models of feeding that incorporate both neural and whole body physiology. In contrast, neural models of drug intake often do not consider how the brain and body interact (although there are some exceptions, such as effects of corticosterone on addiction[20]). This is an area that deserves more attention in studies of drug addiction, however. Indeed, human studies, particularly studies of smokers, suggest that interoceptive cues are essential for ongoing drug taking behavior[21,22]. Similarly, we know that peripheral metabolic signals can influence dopamine system function and behavioral responses to both food and drugs of abuse[23,24].

Interestingly, hypothalamic nuclei, and particularly the lateral hypothalamus, also affect the rewarding properties of abused drugs[25]. This leads to the idea that the mesolimbic circuit mediates drug reinforcement, which is modulated by some hypothalamic systems, whereas the hypothalamus mediates food seeking and consumption, which is modulated by the dopaminergic system.

Hypothalamic-peripheral communication

In general, a distinction between drugs and food is most apparent when sensory and gustatory feedback is considered. In particular, gut-derived signals are critical determinants of both behavioral and metabolic responses to food[26]. This includes direct hormonal signals such as cholecystokinin (CCK) and ghrelin, as well as other physical and hormonal effects conveyed by the vagal nerves to the brainstem. Post-ingestive effects of food intake are also important regulators of food-related behaviors and food is reinforcing when directly infused into the stomach[27], suggesting that the digestive system is a key component in modulating food intake.

Consistent with the central role of hypothalamic circuits in driving food intake, the termination of food seeking can also be induced by activation of a specific circuit: the POMC expressing neurons in the arcuate nucleus and the subsequent release of melanocortin peptides, are thought to mediate satiety[18]. With drugs of abuse, recent work has identified the habenula as a brain area involved in aversion to nicotine[28,29]. This aversive component of drug response may be responsible for the well-known phenomenon of animals maintaining stable blood levels of drug in self-administration paradigms[30]. It is interesting that tastants can also become aversive and lead to decreased reward sensitivity when given before drug self-administration[31]. Finally, drug satiety may also occur via aversive feedback from peripheral homeostatic systems regulating heart rate and blood pressure, or gut systems indicating gastro-intestinal distress[32]. This highlights the need for further study of brain-periphery interactions in regulation of drug intake. It should be noted that under conditions of extended drug access, animals will escalate their drug intake and this self-regulation is disrupted[33]. This will be discussed further below.

It is likely that the persistent strong aversion to foods that cause nausea or gastric pain evolved as protection against consumption of toxic agents. One pathway thought to be involved in disgust is the projection from the POMC neurons in the arcuate nucleus to the parabrachial nucleus[34]. A great deal of work has also implicated the amygdala and brain stem in conditioned taste aversion (the avoidance of a stimulus paired with a noxious tastant)[35]. Human imaging studies have suggested that disgust is also likely mediated by the brainstem as well as the insular cortex[36], providing converging evidence that brain stem nuclei encode information about avoidance of noxious foods. The consequence of the existence of dedicated pathways mediating disgust is that the connection between the periphery, in particular the digestive system, and the brain centers mediating food seeking

provide a hard-wired brake on food reward. This connection has been harnessed to provide protection against alcohol consumption, the one addictive drug that is caloric, and is consistent with the consensus among clinicians that the effects of disulfiram (Antabuse) are due to the nausea and other aversive symptoms it causes if alcohol is consumed[37]. Although the dysphoric effect of antabuse may be akin to the disruption of habitual responding to drug-paired cues following pairing with a noxious tastant, it may also be related to the peripheral connections from the digestive system that are particularly important for alcohol. In contrast, since most drugs of abuse are not ingested, this pathway has no effect on other drug seeking or taking.

Sensory perceptions of food are also key elements of intake, food memory, and the drive to eat[38]. The sight and smell of food drive anticipatory behavior and motivation to eat. Again, it seems that drugs have co-opted circuits that evolved to connect our behavior to our environment. These sensory components of anticipatory behavior and consumption are also critical in addiction and relapse to drug intake[39]. Cues associated with drug use become secondary, or conditioned, reinforcers[39]. As these cues have gained incentive value, similar neural circuits appear to be engaged that are normally triggered by sensory stimuli that predict food reward. An example of this is conditioned potentiation of feeding, in which a cue associated with eating can later increase food intake in a sated state[40]. This paradigm depends on amygdala-prefontal-striatal circuits that also influence drug-associated conditioned reinforcers[40] (cue-driven drug taking will be discussed in more detail below).

While we have emphasized the behavioral control of food intake here to draw analogies with drug addiction, it is clear that metabolic adaptations also have significant effects on body weight. It is notable that most manipulations that affect food intake in one direction also influence metabolism in a complementary fashion. For example, leptin decreases food intake while also increasing metabolic rate (decreased efficiency) leading to reduced weight[41]. There is no clear equivalent to this dual mode of action in drug addiction, where drug taking or seeking is the relevant measurement. This integration with other physiological systems can make the study of obesity more challenging since motivation to eat is only one component of overall weight control.

Cerebral cortex

Studies of drug addiction have incorporated frontal regions of the brain that have not been incorporated fully into animal models of intake. The prefrontal cortex (PFC) can influence drug reinstatement via interactions with mesolimbic and amygdala systems[42]. These models are generally consistent with the view that the PFC influences inhibitory control and alterations in limbic cortico-striatal circuitry may be both a vulnerability factor for, and consequence of, addiction[43,44]; however, rodent studies have shown little effect of PFC lesion on food intake[45]. It is notable that PFC lesions can also leave addictive behaviors such as self-administration intact[46], while impairing drug reinstatement[47]. The negative data showing little effect of cortical lesions on food intake are in contrast to a key study exploring the role of prefrontal u-opioid receptors in food intake and locomotor behavior[48]. Infusion of a u-opioid agonist into the PFC increases intake of sweet food. In addition, recent studies have identified molecular changes in the cortex in response to high-fat diets in the cortex, suggesting that neuronal plasticity in cortex may contribute to diet-induced behavioral changes[49]. Molecular and cellular changes in prefrontal cortex have also been identified in response to diets such as highly palatable food[50,51]. These studies suggest that the PFC likely has a complex role in modulation of feeding behavior, and it is reasonable to assume that some sets of neurons may drive intake, while others might inhibit the behavior. In addition, future work could focus on a role for the orbitofrontal cortex (OFC) in impulsive or perseverant behaviors related to food intake, since cocaine, sucrose and food can all maintain responding in tasks dependent on the OFC.

Imaging studies in human subjects have also implicated frontal cortical regions in responses to food and control over intake[2]. For example, the orbitofrontal cortex responds to the odors and flavor of a palatable drink when it is being consumed[52]. In agreement with these data, patients with frontotemporal dementia demonstrate increased drive to eat, suggesting that loss of cortical control can disinhibit circuits promoting food intake[53]. This is consistent with the rodent studies described above showing that association of a cue or context with eating during a highly motivated (food-restricted) state, will lead the animal to eat more in a sated state in response to the same cue or context[40].

Neuropeptides involved in food- and drug-seeking

The neuropeptide systems regulating food intake and satiety can also modulate behavioral responses to drugs of abuse. The mechanisms subserved by these neuropeptides in food- and drug-related behaviors are distinct, however. While there are some neuropeptides that modulate feeding and drug reward in the same direction, there is another group of neuropeptides that regulate food and drug intake in opposite directions. For example, the neuropeptides galanin[54] and neuropeptide Y (NPY)[55] both increase food intake, but NPY signaling increases cocaine reward[56] whereas galanin signaling decreases cocaine reward[57] (Table 1). While there is a consensus that neuropeptides that increase VTA dopamine neuron firing augment responses to drugs and food[1], there are clearly additional, more complex, interactions that can overrule this relationship. For example, MC4 activation augments cocaine reward[58], likely through increased dopamine signaling in the NAc, but decreases food intake through actions in the paraventricular nucleus of the hypothalamus[59]. Similar mechanisms are also involved in the ability of nicotine acting through nicotinic acetylcholine receptors (nAChRs) to potentiate conditioned reinforcement for sucrose through nAChRs in the VTA[60] and to decrease food intake through activation of nAChRs on POMC neurons in the hypothalamus[61].

It is important to note that the conditions under which drug reward or drug seeking and food intake are evaluated may contribute to some of these similarities and differences. There may be differences in the effects of neuropeptides on intake of highly palatable food and chow, or under satiated conditions and in obese animals[75]. Similarly, there may be differences in the effects of neuropeptides on drug seeking between animals that are drug naïve or drug dependent or are tested in different paradigms, such as conditioned place preference and self-administration[57,63]. This emphasizes the challenge and importance of studying food and drug intake using parallel, or equivalent, behavioral conditions.

Behavioral comparisons between food- and drug-seeking

In many ways, we have a greater understanding of the detailed neural and behavioral basis of drug intake and seeking than we do of food intake and seeking. Addiction studies often involve detailed analysis of self-administration and reinstatement (relapse) that can model the human condition closely; however, it is notable that most behavioral studies done with drugs of abuse, such as operant studies, have been performed in hungry animals. Nonetheless, there is much less consensus on behavioral models that best capture the factors underlying obesity. That is, behavioral models of food seeking, such as responding on a progressive ratio schedule, may not be face-valid models of human food seeking.

Interestingly, whereas drugs are *thought* to be very highly reinforcing, rodents are more likely to work for sweet rewards such as sucrose or saccharin, even when not food deprived, than they will for cocaine[76]. This may reflect a greater susceptibility to seeking of highly palatable foods as compared to drugs of abuse at baseline as a result of differential stimulation of reward circuits by sweet tastants. Although extended access to cocaine increases the reinforcing efficacy of the drug much more than for sweet tastants, rodents are

still more likely to work for sucrose or saccharin after chronic exposure to cocaine[76]. While the neurobiological reasons for these differences are not known, one possibility is that the evolutionary advantage of obtaining sweet and highly caloric foods has resulted in multiple neuronal mechanisms driving seeking of these food rewards, whereas only a subset of these mechanisms are recruited by cocaine. This is speculative, however, and must be investigated in more detail via human imaging studies as well as animal models.

Repeated administration of sugar in a binge-like paradigm does increase the locomotor response to an acute administration of amphetamine, however, one behavioral difference between intermittent sugar administration and intermittent administration of drugs of abuse is that there does not appear to be significant locomotor sensitization in response to sugar administration[77]. Similarly, some studies have shown escalation of drug intake, but not sucrose intake in an extended access paradigm[33], although others have shown escalation of a vanilla flavored solution and in other cases, saccharin or sucrose intake[78]. This suggests that drugs of abuse may be more likely to provoke neuronal plasticity that leads to increased responding over time.

Recent work has applied reinstatement models from drug addiction to studies of food intake[79]. This is a welcome development that is likely to help extend eating behavior research beyond models of “free-feeding” of chow, and into more specific behaviors with better face validity for human patterns of eating. At the same time, it is not clear if this relapse model captures the neural circuits that are engaged when people attempt to control their food intake. Part of the challenge that is inherent in studies of feeding, unlike drug studies, is the inability to remove all food from the animals. The inability to provide a state of abstinence is a technical challenge, and also reflects the complexities of dieting in human populations. Much recent research has focused on high-fat or sugar foods as the “substance”, but clearly people can gain weight on a variety of diets given the current high rates of obesity.

Despite these caveats and the differences in initial escalation of food and drug intake, increased responding for both drug and a sweet tastant has been observed after increasing withdrawal time (incubation of craving)[80]. The incubation effect appears to be weaker for sucrose than for cocaine, however, and the increase in responding for sucrose peaks earlier in withdrawal than for cocaine[80]. In addition, after rodents have learned to self-administer cocaine or sucrose and the response has been extinguished, some studies suggest that stress (unpredictable footshock) can induce reinstatement of responding for cocaine, but not sucrose[81], although other studies have shown that stress can lead to food seeking[82]. This is relevant to the observation in human subjects that acute stress can precipitate binge eating[83]. Indeed, in rodent models, stress generally results in anorexia and decreased food seeking[84–86].

Some of these behavioral disparities may reflect differences in responses to substances that are ingested orally rather than administered through other routes. For example, rodents will approach and bite a lever that is presented with food and will slurp levers non-contingently presented with water, but these responses are not observed for cocaine, perhaps because no physical response is necessary to “ingest” intravenously-delivered drug[78].

Another area of difference between food intake and habitual responding for cues related to food, is that although animals and humans can become habitual in their food seeking (they will work for cues that predict food availability even if the food has been paired with an agent that causes gastric distress such as lithium chloride) consumption of that food will decrease although the animals have worked for its delivery[87]. In addition, the transition from goal-directed to habitual responding occurs more quickly for cues paired with drugs,

including alcohol, than for food[88]. Indeed, goal-directed drug-seeking behavior has been argued to become habitual after prolonged self-administration[42,89]. Rodents show habitual drug-seeking responding that appears insensitive to devaluation, as shown using 'chained' seeking-taking schedules of intravenous cocaine reinforcement. Although this study did not use lithium chloride to devalue cocaine, devaluation of the chained drug seeking-taking link by extinction did not disrupt habitual responding for cues after prolonged access to cocaine[90]. Recent work with food intake has shown that intake of high fat diets can lead to "compulsive" intake despite negative consequences[91], which is another way to test for habitual behavior.

Overall, cues associated with availability of abused drugs result in more reinforcer seeking behavior than food-paired cues after abstinence. Similarly, drug-associated behaviors appear to be more susceptible to stress-induced reinstatement than food-associated behaviors[78]. Of course, conditioned stimuli associated with drugs are both limited and discrete, and become tightly associated with the interoceptive effects of the drugs that are powerful unconditioned stimuli. In contrast, cues associated with food are multimodal and less salient in terms of their interoceptive effects. Thus, food appears to be a more potent driver of behavior at baseline, whereas drugs of abuse seem to be more able to potentiate the control of behavior by conditioned environmental stimuli. Taken together, it has been suggested that cues that predict cocaine availability promote drug seeking more persistently than cues that predict availability of palatable tastants such as sucrose; thus, palatable foods may begin as relatively strong reinforcers compared to drugs of abuse, but the important factor in development of addictive behavior may be that cocaine and other drugs can create associations that last longer than associations between stimuli paired with natural reinforcers such as food[78].

Conclusions and goals for future work

Comparisons of drug addiction and compulsive food intake leading to obesity must take into account that there is a fundamental difference in modeling a "disease state" (ie: addiction) as compared to a complex physiological response that may lead to later somatic disease. The goal of experiments on feeding is to identify circuits that evolved to respond to food scarcity and to determine what happens with those circuits under conditions of food abundance. In contrast, the goal of experiments on addiction is to model a human disorder that uses particular circuits evolved for a different purpose, and, hopefully, to treat that disorder. Thus, abstinence is not a goal for control of food intake, but abstinence is an important goal of research on drug addiction.

The evolutionary pressures that lead to behaviors essential for survival have shaped feeding circuits to favor ongoing food intake over decreased food intake due to satiety-driven satiation. Similarly, the circuits evolved to protect against ingestion of toxic substances and promote disgust can dominate over the hedonic pathways that drive drug seeking. That said, it is important when considering distinctions between food and drug reward to distinguish between apparent differences based on existing research from unexplored commonalities. Of course, it should also be noted that the acute toxic effects of drugs of abuse are distinct from the long-term consequences of over-consumption of palatable foods that lead to obesity.

There are both advantages and limitations of existing animal models of food intake, food reward and obesity. In many respects, animal models of food intake are representative of key biological and physiological processes regulating hunger and satiety. Further, the molecular and neural pathways underlying food intake appear to be conserved across species[92]; however, there are unique evolutionary contexts across species with different

environmental pressures that result in differences between rodent models and the human condition.

One level of control that warrants further research, and may be different for behaviors related to food and drug intake, is the involvement of cortical activity. For example, the ability of discrete regions of the PFC to regulate self-control over subcortical motivational and hypothalamic circuits is not well-integrated into current animal models of food intake or binge eating. This is a major limitation considering data suggesting that top-down cortical control is critical for human food intake and regulation. In addition, there are excellent models for the integration of how whole-body systems and brain circuits contribute to food intake, but much less is known about how effects of drugs of abuse on peripheral systems contribute to addiction. Finally, there have been several behavioral studies that have used the same conditions to study the effects of food reinforcers and addictive drugs, but many comparisons have been made across studies that use different parameters and conditions to make conclusions about similarities or differences in food- or drug-related responses. Side-by-side comparisons will be necessary to conclude that food reinforcement involves equivalent circuits and molecular substrates to result in behaviors that resemble drug addiction. Many drug self-administration studies have already used food or sucrose intake as a control condition. Reanalysis of these existing “control” experiments may provide more information about the similarities and differences between food- and drug-related reinforcement and reinstatement, although additional naïve or sham conditions may be needed to determine adaptations specific to food.

In conclusion, food “addiction” does not have to be the same as drug addiction to be a major health problem. Moreover, many obese individuals may not show signs of addiction[93] as there are likely many behavioral paths to gaining weight. Identifying the parallels as well as the points of divergence between physiological and behavioral regulation of uncontrolled food and drug intake will provide greater possibilities for interventions to combat both obesity and drug addiction.

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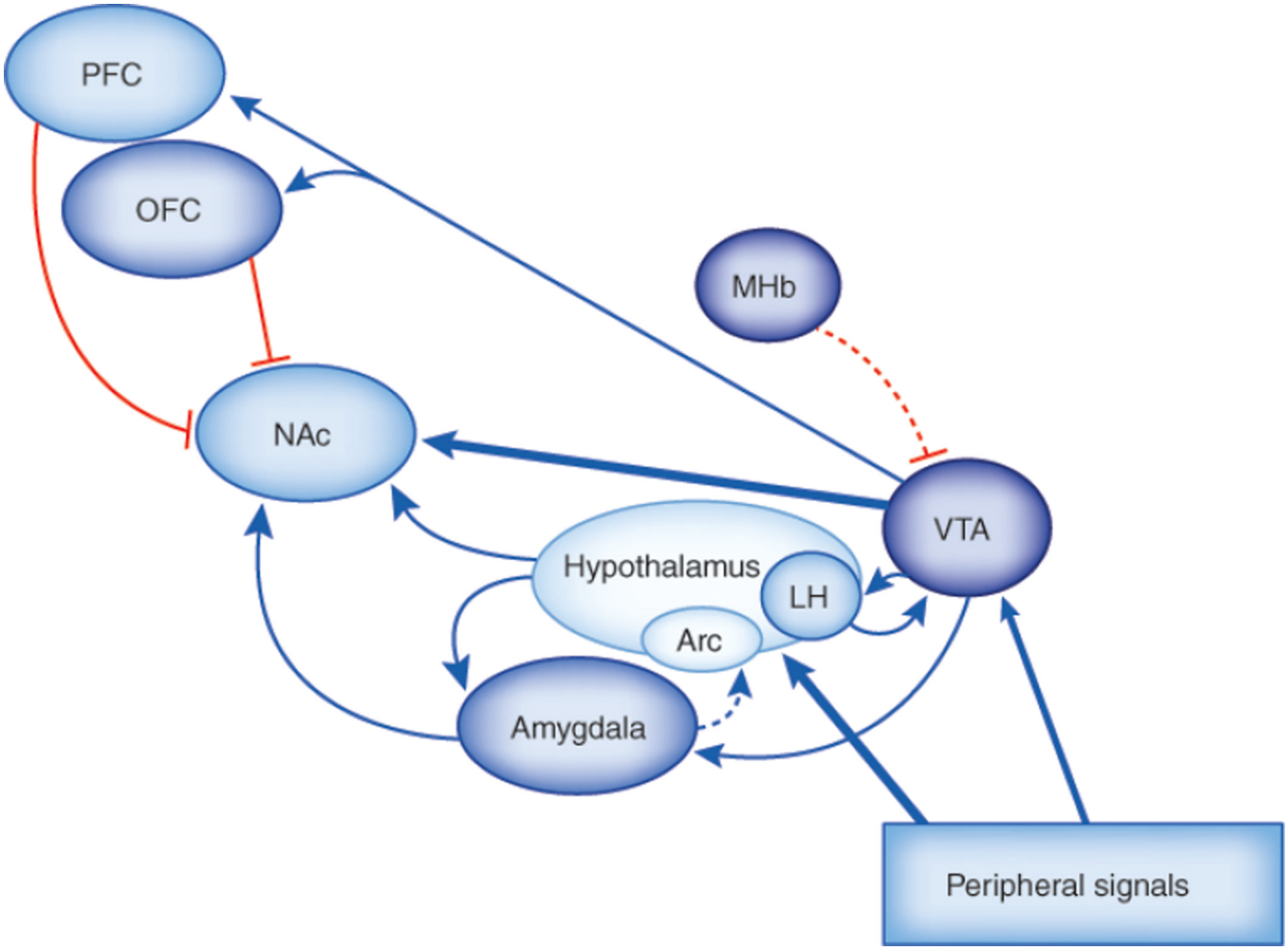

Figure 1.

Areas of the brain mediating food intake and drug seeking. Areas that are most critical for food intake are depicted in lighter shades and those areas most critical for drug reward and seeking are depicted in darker shades. Most areas have some influence on both food and drug intake, and the spectrum represents this overlap. The hypothalamus is critical for food intake and is modulated by the darker shaded areas. The VTA and NAc are critical for drug seeking and are modulated by many other brain areas. Inputs from cortex and amygdala provide control over both food- and drug-related behaviors. Arc, arcuate nucleus; LH, lateral hypothalamus; MHb, medial habenula. Red lines, inhibitory connections; dashed lines, indirect projections. Thicker lines indicate stronger connections.

TABLE 1

Effects of neuropeptides on food intake and cocaine reward

	Opioids	MCH	MC4	NPY	Galanin	Orexin	Leptin	NT	CART	Ghrelin
Food	+	+	−	+	+	+	−	−	−	+
Cocaine	+	+	+	+	−	+	−?	−	+	+

Results taken from[1,48,54–59,62–74].

MCH: melanin-concentrating hormone; MC4: melanocortin 4 receptor agonists; NPY: neuropeptide Y; NT: neurotensin; CART: cocaine- and amphetamine-regulated transcript.