REVIEW

Dopamine and Food Addiction: Lexicon Badly Needed

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Over the last few years, the concept of food addiction has become a common feature in the scientific literature, as well as the popular press. Nevertheless, the use of the term addiction to describe pathological aspects of food intake in humans remains controversial, and even among those who affirm the validity of the concept, there is considerable disagreement about its utility for explaining the increasing prevalence of obesity throughout much of the world. An examination of the literature on food addiction indicates that mesolimbic and nigrostriatal dopamine systems often are cited as mechanisms that contribute to the establishment of food addiction. However, in reviewing this literature, it is important to have a detailed consideration of the complex nature of dopaminergic involvement in motivational processes. For example, although it is often stated that mesolimbic dopamine mediates reward, there is no standard or consistent technical meaning of this term. Moreover, there is a persistent tendency to link dopamine transmission with pleasure or hedonia, as opposed to other aspects of motivation or learning. The present article provides a critical discussion of some aspects of the food addiction literature, viewed through the lens of recent findings and current theoretical views of dopaminergic involvement in food motivation. Furthermore, compulsive food intake and binge eating will be considered from an evolutionary perspective, in terms of the motivational subsystems that are involved in adaptive patterns of food consumption and seeking behaviors and a consideration of how these could be altered in pathological conditions.

One of the first suggestions that food could have addictive properties was provided by Randolph (1) in 1956. Although this idea was relatively dormant for some time, there has been an explosion of research in this area during the last few years. A MEDLINE search reveals that there were only 9 articles published with food addiction as a key phrase from 1956 to 2007; since 2008, there have been more than 65 articles published. There have been many reasons for this explosion. Hoebel et al. (e.g., [2]) have provided a body of animal work that offers a potential rodent model of this phenomenon, with all the associated opportunities for investigating physiological mechanisms. Clinicians have developed rating scales and structured interview techniques that have allowed for the characterization of addiction-like behaviors and yielded insights into pathological aspects of eating behavior in humans (3,4). Furthermore, though this is a scientific review, it is hard to ignore the impact of the concept of food addiction on the general public. In the midst of a dramatic increase in obesity in the developed world that some would say has reached epidemic proportions, the discussion of food addiction in venues ranging from the internet to television talk shows has also become an epidemic of sorts.

Of course, like most scientific endeavors, research on food addiction and related phenomena, such as binge-eating disorder, is much more complex than the popular media would suggest. Though many researchers argue strongly for the validity of the concept of food addiction (5,6), others urge caution (7). It has been noted in multiple articles that many of the behavioral characteristics of food addiction or binge eating resemble some of the diagnostic criteria established for drug dependence, including the compulsive nature of the food seeking and taking behavior, the escalation of consumption, and the resistance to the effects of consequences (5,8). Nevertheless, considerable controversy remains. Researchers and clinicians who focus on drug addiction often talk about dependence and withdrawal phenomena; applied to food as a general category, this concept is meaningless, because nutrients are a genuine physiological need. This recognition has led many to consider that, in some general sense, food addiction is an oversimplified term (9), because people and other animals that are said to have this condition are not addicted to food, per se, but rather to foods with particular macronutrient contents (2,9–12), under certain environmental conditions (9). Moreover, the relation between food addiction and binge-eating disorder, as well as the role that these conditions play in subtypes of obesity, remains uncertain. For example, it has been suggested that the number of food-addicted people is relatively small compared with the number who are obese (13) and that there are sizeable proportions of underweight, normal weight, and overweight individuals who could be classed as food addicted based upon the Yale Food Addiction Scale (4).

In view of the continuing controversies in this area, it seems reasonable to suggest that the scientists and clinicians should exercise caution in interpreting these emerging findings, not only in the scientific literature, but also in terms of how this information is disseminated to the general public (14,15). For example, Rogers and Smit (14) argued that the vast majority of self-reported cases of food addiction should not be viewed as addictive behavior and noted that overweight people attempting to resist consumption of sweets could be mislabeling cravings and desire for more as a sign of addiction. In addition, Esptein and Shaham (15) suggested that food addiction should not be viewed by patients as an excuse for overeating and that the unhealthy eating associated with food addiction should not be equated with obesity. Certainly, too much exposure to superficial discussion of food addiction in the media, coupled with casual use of the term by health care professionals, could promote these kinds of misconceptions in the general public. Furthermore, one

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can question whether the general trend of labeling more and more patterns of behavior as addictive is diluting the meaning this term. There are drug addictions for a wide array of substances. In addition, terms such as gambling addiction, sex addiction, email addiction, internet addiction, pornography addiction, and video game addiction are becoming every more widely used. There are, of course, alcoholics but also workaholics and chocoholics. Indeed, one could be forgiven for wondering if neuroscientists and clinicians have become addicted to the term addiction, since the use of this term is escalating so much. But on a very serious note, one must always wonder in psychiatry whether the apparent increase in prevalence of a disorder stems from increased awareness, or sensitivity of the diagnostic tools, or if, instead, it represents overuse and overdiagnosis. Furthermore, one must exercise caution in the use of labels for disorders (7).

Amidst all this uncertainty and controversy related to food addiction, there is another set of concerns related to the hypothesized involvement of reward mechanisms that are said to involve dopamine (DA) systems. A significant fraction of the published studies in this area posit some type of DAergic mediation or regulation of food addiction. In many cases, these studies seem to rely on an uncritical acceptance of a series of tenets, which include the following concepts: 1) reward is a valid term to describe a psychological or neurobehavioral process and there is a substantial uniformity or consensus in the meaning of this term across articles and laboratories; 2) there is a reward system that mediates this neurobehavioral process; 3) DA is a central component, perhaps the linchpin, of the reward system; 4) the DAergic reward system is a critical mediator of drug addiction; and 5) DAergic involvement in reward therefore provides a plausible explanation for the phenomena that scientists are attempting to capture by the use of the term food addiction. Yet, despite the fact that many investigators uncritically accept the idea of DAergic mediation of reward (e.g., [16]), this hypothesis is no less controversial and contested than the idea of food addiction itself (e.g., [17–19]). Therefore, the present review will briefly deconstruct these traditional and often-mentioned tenets of the DA hypothesis of reward, highlight the complex findings in the literature that call them into question, and then re-examine the hypothesized involvement of DA in food addiction in light of this revised view of DA function. Finally, food addiction and binge eating will be considered from an evolutionary perspective, in terms of the motivational subsystems that are involved in adaptive patterns of food consumption and seeking behaviors and a consideration of how these could be altered in pathological conditions.

Conceptual Problems with Dopamine Hypothesis of Reward: What Is Reward, Anyway?

Of course, when the term reward is used as a noun, essentially as a synonym for reinforcer, its meaning is clear (e.g., "The child received a reward at school"). Also, when it is used as a verb to signify the presentation of a reinforcer, that also has a clear meaning (e.g., "The child was rewarded for good behavior"). However, when someone uses the term reward to signify a psychological process that is mediated by neural mechanisms, there are several problems. There is no standard scientific meaning of this term, when used in this way. As noted before (19–24), people tend to use the term reward in one of three ways: 1) as a synonym for pleasure or hedonia; 2) as a general term

for appetitive motivation; and 3) as a synonym for reinforcement. To obfuscate things even more, at times the term reward is used to refer to some hybrid process that includes combinations of 1, 2, and 3 above, and in some cases, it can be used to mean different things in different parts of the same article. One of the difficulties with this is that when articles only use the term reward, it is not clear which of these definitions is being employed. It is arguable that the psychological language would be clearer if, when one meant pleasure, one would use words like pleasure or hedonia, rather than reward. Similarly, since reinforcement has been the accepted psychological term in the lexicon of instrumental conditioning for almost a century, it is reasonable to suggest that when one is attempting to refer to reinforcement (in the sense of strengthening responses during acquisition and maintenance of instrumental behavior), then that term should be used. The same is true for appetitive motivation, which is arguably a more useful term as a general descriptor of the processes regulating approach or seeking behavior (i.e., increasing the proximity, probability, or availability of stimuli), as well as consumption or taking. The term appetitive motivation does not necessarily or explicitly connote subjective pleasurable emotions, per se, and provides a clear contrast with the term aversive motivation. Is pleasure isomorphic with appetitive motivation and reinforcement? Aren't these just three different ways of saying exactly the same thing? No. It is clear from the behavioral neuroscience literature that hedonia, appetitive motivation, and positive reinforcement learning are dissociable processes. Indeed, much of the work from Berridge, Robinson, and colleagues over the last 20 years serves as a testament to the dissociability of these processes (e.g. [25,26,27,28,29]). In view of this research, ambiguities about the definition of reward are not merely some esoteric semantic exercise; words are tools as much as any scientific technique, and the term reward, when used to refer to a neurobehavioral process, is a very blunt instrument. While one article may maintain that DA systems mediate reward but not hedonia, other articles use reward and hedonia synonymously. Exactly what is meant when an article states that palatable food "activates the reward system" (e.g., [30])? Clearly, one can question the utility of the concept that DA mediates reward and that this involvement has anything to do with food addiction, when one considers that reward can be made to mean so many different things.

Does DA Mediate Hedonia Instigated by Food Consumption?

For many years, it was thought that DA, especially mesolimbic DA, mediated pleasure or hedonia. One still can hear this mentioned at scientific meetings or see it referred to in an article, including one that is focused on phenomena related to food addiction/binge eating (e.g., [31]). Nevertheless, evidence has been accumulating for some time indicating that this is a grossly oversimplified view of DAergic function. Although consumption or preference of sucrose solutions is sometimes used as a measure of food-related hedonia (32), there are several reasons why consumption measures per se are not a reliable index of the emotional state (28,33). If sucrose consumption is impaired by a particular manipulation, it could reflect changes in a number of different processes, including oral motor function, approach to the drinking tube, or sensorimotor processes (18,28,33). One of the tests that has become widely accepted as a measure of hedonic reactivity to sweet solutions is the taste reactivity

paradigm. A substantial body of work from Berridge and Robinson (25,26) and Berridge (28,34) has demonstrated that systemic administration of DA antagonists, as whole forebrain or nucleus accumbens DA depletions, did not blunt appetitive taste reactivity for food. Moreover, microinjections of amphetamine into nucleus accumbens, which elevates extracellular DA, failed to enhance appetitive taste reactivity for sucrose (29). Sederholm et al. (33) reported nucleus accumbens shell D2 receptors regulated aversive taste reactivity and that brainstem D2 receptor stimulation suppressed sucrose consumption, but neither population of receptors mediated hedonic taste reacitivity.

Because of the proposed similarity between food addiction and drug abuse, it is relevant to examine the literature on the effects of DA antagonism on drug-induced hedonic responses in humans. Several years ago, it was reported that DA antagonism could blunt the subjective pleasure induced by amphetamine (35). Since that time, the preponderance of evidence in this area has failed to support this observation. Gawin (36) found that the DA D2 antagonist haloperidol did not reduce the self-reported euphoria produced by cocaine, and several subsequent studies have shown that DA D2 antagonism did not blunt stimulant-induced high or euphoria (37,38). The D1 antagonist ecopipam did not reduce the subjective euphoria induced by cocaine (39). Inhibition of catecholamine synthesis induced by tyrosine/phenylalanine depletion did not blunt the subjective euphoria induced by cocaine (40). In a recent study, catecholamine synthesis inhibition failed to reduce the self-reported craving and hedonic reactions to cigarettes, though it did reduce progressive ratio operant responding for this reinforcer (41). Liggins et al. (42) found that L-DOPA, which enhances catecholamine synthesis, did not have any effect on self-reported positive mood. Interestingly, a recent imaging article showed that doses of L-DOPA that enhanced the striatal representation of appetitively motivated actions did not affect the neural representation of reinforcement value (43).

In the literature related to food addiction and binge eating, it is reported that repeated exposure to sucrose in a manner that instigates binge consumption is associated with increases in mesolimbic DA activity (10,44). Moreover, this response does not habituate in animals exposed to the conditions that induce binging on sucrose. To researchers who are not familiar with the specifics of DAergic involvement in aspects of motivation, this finding could be misinterpreted as signifying a simple state of hedonia or pleasure. But as pointed out by Avena et al. (10), this finding is much more complicated, because DA release is involved in many features of appetitive motivation, including "food seeking and reinforcement of learning, incentive motivation, stimulus salience and signaling a stimulus change" (10, p 22). Indeed, the literature describing the response of mesolimbic DA to appetitive stimuli that act as positive reinforcers is complicated and needs to be interpreted with caution (45). In a general sense, does food increase DA neuron activity or accumbens DA release? It depends upon the conditions. There are a number of methods that are used to study DA release or neural activity, which provide measures across various time scales (45–59). Electrophysiology methods record fast phasic activity of putative or identified DA neurons (46,55–59), electrochemical methods such as fast cyclic voltammetry measure DA transients, which are fast phasic changes in extracellular DA that are thought to represent the release from bursts of DA neuron activity (45,47,51). In contrast, microdialysis methods provide a measure of extracellular DA that is integrated over larger units of time (i.e., slow phasic activity) relative to electrophysiology or

voltammetry (45,48,49,52–54). Electrophysiology studies have shown that presentation of novel food reinforcers is accompanied by increases in activity of putative ventral tegmental DA neurons but that this effect goes away with repeated exposure or training (46). In an article employing voltammetry methods to measure rapid and transient changes in DA release, Roitman et al. (47) showed that, in trained animals, exposure to a conditioned stimulus signaling that lever pressing would result in sucrose delivery was accompanied by an increase in DA transients; however, the actual presentation of the sucrose reinforcer was not accompanied by an increase in DA transients. Bassareo et al. (48) showed that consumption of a 20% sucrose solution increased prefrontal cortex DA release but did not increase nucleus accumbens DA release. However, exposure to novel palatable snack foods significantly increased extracellular DA in nucleus accumbens as measured by microdialysis (48). This increase in extracellular DA rapidly habituated in the accumbens shell but persisted in the core if food was presented again 24 hours after initial exposure (48). A recent microdialysis article demonstrated that presentation and consumption of high-carbohydrate food reinforcers in previously exposed rats (i.e., rats that had consumed the food for several weeks) did not produce any change in extracellular DA in accumbens core or shell (49). Nevertheless, the acquisition and maintenance of fixed ratio responding was associated with increases in extracellular DA. Similar results were observed when markers of DA-related signal transduction (c-Fos and DARPP-32) were measured (50). Thus, the animal literature does not support the widely held belief that food presentation per se, including that of palatable foods, increases accumbens DA release across a broad range of conditions. Rather, the response of accumbens DA to food consumption varies depending upon the type of food, the degree of pre-exposure, the environmental context, and the DA terminal region (51).

In this context, it also is worth noting that enhancement of mesolimbic DA activity is not unique to appetitive conditions; this system also is activated by aversive stimuli. Research with animals has shown that a wide array of aversive conditions (e.g., shock, restraint stress, aversive conditioned stimuli, aversive drugs, social defeat stress) can increase nucleus accumbens DA release as measured by microdialysis (52–54). In addition, electrophysiological activity of putative or identified DA neurons has been shown to increase in response to aversive stimuli (46,55–59). Furthermore, imaging methods in human research have demonstrated that the nucleus accumbens/ventral striatum also responds to stress, aversion, and hyperarousal/irritability (60–66). Putting all this together, the finding that conditions promoting sucrose binging also increase nucleus accumbens DA release clearly are significant, but they do not in themselves serve as an unambiguous marker that DA is specifically mediating some type of hedonic emotional experience. Rather, increased DA transmission could be participating in a number of behavioral functions associated with aspects of learning, motivation, emotion, or stress.

What is the Role of Mesolimbic DA in Food Motivation?

A thorough review of the involvement of forebrain DA systems in food motivation is beyond the scope of this article. Nevertheless, several important points are worth emphasizing for the present discussion. First of all, there are multiple DA systems, and different pathways have distinct functions. Pharmacological studies have demonstrated that hypothalamic DA is involved in

appetite modulation and indicate that blockade of hypothalamic DA receptors stimulates food intake (67), while stimulation of DA receptors, specifically in the perifornical hypothalamus, is associated with a suppression of food intake (68,69). Neostriatal DA, particularly in the lateral neostriatum (70–72) is particularly important for sensorimotor and motor aspects of food intake, including food handling and oral motor function. Interestingly, it is often assumed that DA depletions or antagonism in the so-called reward system (i.e., nucleus accumbens DA) would exert a powerful effect on food intake. However, this is not supported by the literature. Rather, it has been shown several times over the last few decades that, in contrast to neostriatal DA depletions, interference with nucleus accumbens DA transmission by DA depletions or antagonism has little or no effect on food intake (70–75). In fact, food intake is most greatly affected by DA depletions in ventrolateral neostriatum (70–72), but there is no evidence that these impairments are related specifically to motivational dysfunctions. Rather, the effects of ventrolateral neostriatal DA depletions on food intake are related to motoric dysfunctions affecting feeding rate and forepaw usage during feeding and occur in parallel with the induction of oral tremor that has the characteristics of parkinsonian resting tremor (18,71,76).

If nucleus accumbens DA does not mediate food-related hedonic reactions, appetite, or food consumption, then what is the nature of its involvement in food motivation? This is a complex question, the study of which has been an area of very intense interest in behavioral neuroscience research over the last few decades. This area is too vast and detailed to cover in the present section, and there have been many reviews published over the last few years that provide a more detailed theoretical discussion (18,19,28,77–80). Briefly, there is considerable agreement that manipulations affecting nucleus accumbens DA transmission act to dissociate components of food motivation from each other; these manipulations leave core aspects of food-induced hedonia, appetite, or primary food motivation intact but nevertheless affect critical components of the instrumental (i.e., food seeking) behavior. Within that overall framework, there remains some uncertainty about the best way to characterize the involvement of mesolimbic DA in specific aspects of instrumental behaviors, including food reinforced ones. Investigators have suggested that nucleus accumbens DA is particularly important for behavioral activation (22,24,81,82), Pavlovian to instrumental transfer (22,83), flexible approach behavior (79), energy expenditure and regulation (80,84), and responding during delayed reinforcement (85,86). Considerable evidence indicates that accumbens DA is involved in the exertion of effort and the behavioral economics of overcoming work-related response costs in animals (19,77,78,87–90), which could be relevant for understanding effort-related motivational symptoms of depression in humans (19,23,91). Pharmacology and imaging studies in humans have shown that striatal areas are involved in making cost/benefit decisions involving effort (92–95). Several investigators have found it useful to make dichotomous distinctions between aspects of motivation that are impaired by DAergic manipulations and those that are intact (e.g., activational vs. directional aspects of motivation, instrumental vs. consummatory behavior, wanting vs. liking; Figure 1).

There is extensive evidence that DA systems, including mesolimbic DA, participate in motivational decision making related to effort and delay (19,85,86,88,96). For example, low doses of DA antagonists, as well as accumbens DA antagonism or depletions, bias animals being tested in effort-related choice

Figure 1. For several years, researchers have been making distinctions between aspects of motivated behavior that are differentially affected by dopaminergic manipulations. Salamone (82) emphasized the distinction between directional aspects of motivation (i.e., that behavior is directed toward or away from stimuli) and activational aspects of motivation (i.e., that motivated by behavior is characterized by a high degree of activity, vigor, and persistence) and suggested that dopamine (DA) antagonists impair activational aspects of food motivation but leave directional aspects intact. Blackburn *et al.* (135) suggested that DA antagonists impaired preparatory behaviors instigated by a conditioned stimulus at doses that did not impair consummatory behavior. Salamone (96) emphasized the distinction between consummatory behaviors and instrumental responses and also tried to link this distinction to others by stating that highly active instrumental behaviors elicited and supported by conditioned stimuli are very sensitive to disruption of accumbens DA transmission. Berridge (34) distinguished between the role of DA in liking versus wanting and suggested that interference with striatal and accumbens DA transmission affected incentive motivation (wanting) for sucrose but had little effect on hedonic reactions instigated by sucrose (liking). Foltin (136) distinguished between food seeking (i.e., instrumental responses reinforced by food) versus taking (consumption) and reported that amphetamine increased food-seeking behavior while decreasing food-taking behavior. More recently, Ikemoto and Panksepp (137) and Burgdorf and Panksepp (138) stated that it is useful to distinguish between consummatory reward, which is relatively unaffected by interference with accumbens DA transmission, and preparatory or anticipatory aspects of reward, which are more greatly impaired. Czachowski *et al.* (139) studied the effects of DA antagonism on ethanol seeking and intake and reported that the D2 antagonist remoxipride had substantial effects on measures of ethanol-seeking behavior (lever pressing) in a dose range that had little effect on ethanol intake.

procedures toward the selection of activities with relatively low work-related response costs (19,78,97,98). These effects do not occur because of changes in appetite or food preference (97,99,100) and are not dependent upon drug effects on delay discounting (86). Knockdown of the DA transporter or administration and amphetamine increase the tendency toward selection of high effort activities (95,101,102).

In view of the studies reviewed in this section and the vagaries involved in the use of the term reward, it appears that any general or unqualified statement that DA mediates reward is so oversimplified as to be practically meaningless. Moreover, in view of the frequent connotation of reward as referring to subjective pleasure or euphoria, such a statement appears to be largely a misrepresentation of the literature. For these reasons, researchers who are studying food addiction and binge eating in humans need to be careful before assigning any specific meaning to the role that DA may play in this phenomenon.

Dopaminergic Involvement in Motivational Aspects of Food Addiction/Binge Eating: Which Aspects?

The complex nature of DAergic involvement in specific aspects of food motivation should present a note of caution for those attempting to determine the role of DA in normal food consumption in humans, as well as food addiction, binge eating,

or related phenomena. Clearly, one cannot simply assume that DA directly mediates the pleasure induced by food consumption and that striatal DA directly controls the emotional basis of the intake of highly palatable foods, which, in turn, leads to binge eating and eventually obesity. Research on the role of striatal and accumbens DA in human food intake appears to be every bit as complex as the animal research described above (103). A review of this emerging area of research is beyond the scope of this article, but a brief summary can highlight some of the complexities seen in the literature.

O'Doherty et al. (104) reported that DAergic areas of the brain (e.g., midbrain, striatum, orbitofrontal cortex) showed functional magnetic resonance imaging activation in response to visual cues associated with a sweet taste (glucose) but not to the actual receipt of the reinforcer, a finding similar to much of the animal work described above. Volkow et al. (105) found that an imaging marker of extracellular DA (i.e., displacement of radioactive raclopride binding) was increased in the neostriatum, but not the ventral striatum/nucleus accumbens, of humans who were exposed to a display of food but did not consume it; this response was correlated with self-reports of hunger and desire for food. More recent imaging studies (106) have implicated a wider network of structures in anticipation of the delivery of palatable food, including ventral striatum, amygdala, and mediodorsal thalamus, though the most reproducible results were with the amygdala and thalamus. A recent meta-analysis identified the ventral striatum/nucleus accumbens, as well as the amygdala, insula, and orbitofrontal cortex, as being consistently responsive to food-associated cues in functional magnetic resonance imaging studies (107). The imaging literature related to the neural representation of primary gustatory reinforcement is equivocal about the responsiveness of striatal areas to consumption of palatable foods or sweet tastes. Frontal cortical areas, including orbitofrontal and insula/operculum regions, appear to respond relatively consistently to palatable gustatory stimuli (106,108). In contrast, studies of the responsiveness of ventral or dorsal striatum to palatable foods or sweet tastes have yielded mixed results (104,106,108–110). Wang et al. (110) recently used imaging methods to characterize putative markers of DA release in obese subjects. They reported that striatal DA release was not increased in response to food-related stimulation (i.e., seeing, smelling, and tasting a palatable food) in obese subjects not diagnosed with binge-eating disorder, even if they were treated with methylphenidate, which enhances extracellular levels of DA. Like the O'Doherty et al. (104) study, this is consistent with animal research showing a lack of DAergic responsiveness to palatable foods in organisms with previous experience of that food and appears to underscore the conclusion that it is difficult to make blanket statements about neostriatal or accumbens DA being released due to food presentation per se.

Interestingly, Wang et al. (110) did observe an increase in striatal DA release in response to food-related stimulation in obese binge eaters who were treated with methylphenidate. Although results can vary depending upon the methods, and this result needs to be replicated to demonstrate its reliability, the fact that these authors directly compared binge eaters and nonbinge eaters under the same conditions suggests that there may be something different about the striatal DAergic responsiveness of binge eaters. Moreover, these findings are consistent with the microdialysis results showing that increases in accumbens DA release in response to sucrose in binge-eating rats does not habituate in the same way as it does in normal rats (6,12). However, interpretation of these results is somewhat complicated

by findings from some pharmacology studies. For example, methylphenidate has been shown to decrease appetite in patients diagnosed with binge-eating disorder (111). Drugs that facilitate DA transmission have long been known to suppress appetite, and evidence indicates that this effect could be related to actions upon DA in the perifornical hypothalamus (68,69,112). Thus, the specific functional significance of increases in striatal DA release in binge eaters remains uncertain.

It is possible that increased ventral or dorsal striatal DA release in binge-eating people does not mediate appetite or food consumption in a general sense but instead acts to promote food-related learning, modulate quantitative or organizational features of the consummatory response (e.g., speed, compulsiveness, or perseveration), or enhance the tendency to engage in active food-seeking behavior. Such a suggestion is consistent with much of the animal work described above (19,24) and is compatible with the observation of Hoebel et al. (2) that mesolimbic DA acts as a kind of "go" mechanism that facilitates appetitive behavior. Moreover, it is consistent with recent research on the involvement of DA in regulating some of the motivational effects of leptin and ghrelin. Leptin is a protein that suppresses food intake and has actions on a number of brain areas, including mesolimbic DA neurons (113). A recent article showed that leptin acts on the lateral hypothalamus to regulate body weight, caloric intake, and body fat in rats, but interacts with mesolimbic DA to modulate effort-related responding for food (114). Also, antagonism of DA D1 receptors blocked the ability of ghrelin to stimulate the tendency of rats to work for sucrose on a progressive ratio schedule but did not affect licking parameters (115). Obesity in itself may be an important factor modulating the tendency to work for food. Berthoud et al. (116) reported that rats made obese by feeding on a high-fat diet showed a reduced tendency to work for food and that effort-related responding was restored after gastric bypass surgery. Moreover, human studies involving patients with binge-eating disorder indicate that the tendency to work for food is a potentially important measure of food motivation in these individuals, over and above any role of obesity. Nasser et al. (117) used progressive ratio performance reinforced by food access to study the motivation to eat across multiple groups of people (binge-eating disorder, obese and lean people who were not binge eaters). They observed that prefeeding people who were not binge eaters with a liquid meal before the operant test session reduced their work output on the progressive ratio schedule. In contrast, prefeeding the people who met criteria for binge-eating disorder actually led to increased progressive ratio responding for food access. In addition, in the prefed condition, people with binge-eating disorder worked on the schedule significantly more than obese people without binge-eating disorder. Future research should determine if mesolimbic or neostriatal DA is involved in this strong tendency of binge eaters to show enhanced work output in food-seeking behavior.

Comparisons between food addiction and drug addiction often are made in the literature, and although a thorough exploration of these similarities and differences is the focus of other articles, it is worthwhile to highlight some of the recent trends in drug addiction research. It often is stated that many of the brain mechanisms involved in aspects of food motivation also are involved in drug addiction. For example, imaging studies have demonstrated that similar brain areas are activated by food-related and drug-related cues (107). Another finding has been that obese people and drug addicts tend to show reduced

expression of DA D2 receptors in striatal areas (118,119). Yet, despite these findings, it is still not clear what these DA receptor data represent from a functional perspective. Reward deficiency has been suggested, but other explanations also are plausible, including psychomotor retardation (120), impaired behavioral flexibility or impulsivity, or reduced tendency to expend energy by exercising (80). Striatal D2 receptors were reported to be decreased in obese rats, and the development of compulsive eating was further enhanced by knockdown of D2 receptors (31). In summarizing their conclusion, the authors suggested that this meant that hedonic mechanisms were being altered and supported this by pointing out that intracranial self-stimulation thresholds were increased in obese animals. However, it should not be assumed that this measure is an unambiguous marker of anhedonia. For example, attaching a ratio work requirement also increases self-stimulation thresholds (121). Moreover, a recent article has emphasized that multiple factors contribute to self-stimulation thresholds and has demonstrated that DAergic modulation of self-stimulation thresholds is not due to drug-induced changes in reward value but instead involves shifts in the tendency to overcome response costs, such as effort or opportunity costs (122).

Emerging Concepts of DA Function and their Relation to Food Addiction

Based upon the literature reviewed above, one can see that there is a behavioral pattern that can be observed in humans and other animals that involves binge eating and or escalating consumption of food, compulsive patterns of food-related behavior, and resistance to the consequences of this activity. Some have labeled this as food addiction, whereas others are more cautious in the use of this term; some stress the role that this pattern may play in obesity, while others emphasize the myriad of other factors that contribute to obesity. At the very least, this pattern of behavior is present in a subset of people, some of whom are obese, while others are not. Thus, despite some of the ambiguities and concerns about this research or the specific labels used, a pattern of eating behavior with some of the features of addiction is indeed discernable in some humans, and some of these features can be modeled in animals. The discussion above has focused less on the details of the food addiction literature and more on the potential role of DA systems. In particular, the review emphasized that the involvement of DA in food motivation is highly selective for particular aspects and that the effects of DAergic manipulations are dissociative in nature, profoundly affecting some aspects of food motivation, while leaving others basically intact (18,19,23). Acknowledging these complexities in DAergic function (123), which is more nuanced than simply painting DA with the broad brush of being a mediator of reward or hedonia, can shed light on the potential involvement of DA systems in normal food-related behaviors, as well as obesity, food addiction, binge eating, and related phenomena.

In the last few years, much of the addiction literature has moved beyond the original DA hypothesis of reward. There has been a growing emphasis on the idea that addiction should be viewed as a compulsive incentive habit (22,124). According to this view, chronic drug exposure promotes the shift from drug-related action-outcome reinforcement to a compulsive response habit, and this process involves a shift from ventral to dorsal striatal regulation, as well as a transition from prefrontal executive control to striatal habit-related (i.e., stimulus-response) control (125). Viewed in this way, compulsive eating and drug addiction

could be seen as belonging to a larger group of impulsive-compulsive syndromes, which also includes attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, and compulsive gambling (126). This type of disorder is thought to be characterized by a failure of neural mechanisms involved in inhibitory control, which ultimately manifests itself as an escalating pattern of consumption and repeated relapse. Future studies with humans and in animal models (127) will be necessary to extend some of these emerging concepts from the drug addiction literature into the realm of compulsive eating and food addiction. Additional research in the drug abuse field has identified individual differences in behavioral patterns shown by rats during Pavlovian approach conditioning, which are related to the propensity to self-administer drugs. Rats that show greater response to conditioned cues (sign trackers) display different patterns of DAergic adaptation to training as compared with animals that are more responsive to the primary reinforcer (goal trackers) (128). It has been suggested that these distinct behavioral patterns may be related to the differential vulnerability of some individuals towards drug addiction (129). Moreover, sign trackers are more sensitive to cue-induced reinstatement of food-seeking behavior, which may be related to the effect that food-related cues have on people with compulsive eating disorders (130).

As described above, DA systems are involved in several aspects of motivational decision making. In dealing with a complex environment, organisms must assign relative value to, or establish preferences between, different stimuli or activities. This process can be very specific, because aspects of the neural mechanisms involved in selection of food versus water versus sexual activity are distinct from each other (indeed, there are multiple types of hunger and multiple types of thirst). On the other hand, there are neural mechanisms involved in aspects of reinforcement seeking that are more general and span multiple types of reinforcers; for example, mesolimbic DA is involved in reinforcer-seeking behavior for food, water, and sex (18,77,78). Ultimately, organisms must reconcile their preference structure with their behavioral output and allocate time and effort resources across multiple options. People who are addicts, whether drug addicts or ones addicted to foods, end up showing a radically altered preference structure for motivational stimuli, with selection of the particular drug or food taking a distorted position atop the hierarchy of possible motivational stimuli. Drug addicts, for example, can show markedly reduced behavioral activation in response to natural reinforcers and can display psychomotor retardation during drug withdrawal (120), but they also allocate a disproportionate amount of behavioral and financial resources into drug seeking. This exaggerated effort invested in stimulus seeking in addicts may involve DA, though it also is possible that it is relatively DA independent, relying instead upon the recruitment of other components of the brain circuitry involved in motivation. Nevertheless, these patterns of behavior indicate that the addiction process appears to be characterized by a substantial restructuring of both directional and activational aspects of motivation (131).

Conclusions: An Evolutionary Perspective

This issue of food addiction has vast public policy implications (132), and having considered food addiction, binge eating, and related phenomena from medical, neurobiological, and behavioral neuroscience perspectives, it is useful to finish by speculating about the evolutionary significance of this pattern of

behavior. First of all, why was this behavioral pattern not selected against by natural selection processes? In contemplating this question, it is useful to remember that only a few thousand years ago, humans were hunter-gatherers. It seems unlikely that the capacity for binge eating in adolescence, for example, would have conveyed enough evolutionary disadvantages such that it would have prevented most people from reaching reproductive age. Perhaps the only disadvantages would have been social or the ill effects of eating too much after a period of extended starvation. On the other hand, one can argue that the capacity to engage in some type of binge consumption would have had adaptive advantages for hunter-gatherers, who often combed wide areas foraging for food, hunting animals, and collecting fruits, nuts, and plants for consumption. Under these conditions, periods of relative scarcity of food would have alternated with periods of food excess. Although drying of fruits and smoking of meats or fish was available to humans for several thousand years before the agricultural revolution, it is still true that for many thousands of years before that, there was no way to store food for long periods. Therefore, food had to be consumed when available. In this context, the capacity to engage in overconsumption appears to provide some evolutionary advantages. A group of hunter-gatherers who had been through a period of deprivation could suddenly come upon a herd of game or a dense patch of berry bushes, and the ability to consume beyond fullness, even to the point of discomfort, would have enabled them to make better use of available resources by storing excess calories as fat. Thus, having central and peripheral mechanisms that enable this type of activity to occur would probably have conveyed some advantages. Of course, modern humans do not live this kind of existence; most of us do not burn thousands of calories each day foraging for food, and in the developed world, food is hardly scarce for most people. Thus, a pattern of behavior that may have conveyed some advantages in this evolutionary context has distinct disadvantages in a modern world in which calorically dense foods are available continuously and people are constantly bombarded by food-related stimuli (see the discussion of what is sometimes called evolutionary mismatch [133,134]). Dieting (in the sense of excessive caloric restriction) may act to stimulate the natural physiological response to food scarcity and ultimately lead to rebound periods of overeating. Perhaps the tendency to overeat every once in a while is present in virtually all of us; we can struggle to resist gorging ourselves at holiday parties or harvest festivals and try to rely on inhibitory control mechanisms to limit the impact of this tendency. However, for various reasons, individuals vary in the extent to which these control mechanisms work, and the result is that some people eventually experience an escalating tendency to have consumption of some foods spiral out of control. Ultimately, an understanding of food addiction and related conditions may depend upon our understanding of evolutionary, cultural, and anthropological factors, as well as neurobiological and psychological ones.

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