HHS Public Access

Author manuscript

J Addict Med. Author manuscript; available in PMC 2015 March 16.

Published in final edited form as:

J Addict Med. 2009 March ; 3(1): 33–41. doi:10.1097/ADM.0b013e31819aa621.

A Behavioral and Circuit Model Based on Sugar Addiction in Rats

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Abstract

The distinction between natural addiction and drug addiction is interesting from many points of view, including scientific and medical perspectives. “Natural addictions” are those based on activation of a physiobehavioral system, such as the one that controls metabolism, foraging, and eating to achieve energy balance. “Drug addictions” activate many systems based on their pharmacology. This review discusses the following questions: (1) When does food produce a natural addiction? Sugar causes signs of addiction if the scheduling conditions are appropriate to cause binge eating. (2) Why does addictive-like behavior result? Bingeing on a 10% sucrose solution repeatedly releases dopamine in the nucleus accumbens, and it delays the release of acetylcholine, thereby postponing satiety. Opioid involvement is shown by withdrawal caused by naloxone or food deprivation. Bingeing, withdrawal, and abstinence-induced motivation are described as the basis for a vicious cycle leading to excessive eating. (3) Which foods can lead to natural addiction? A variety of sugars, saccharin, and sham feeding are compared with bingeing on high-fat diets, which seem to lack sugar's opioid-withdrawal characteristic. (4) How does natural food addiction relate to obesity? Low basal dopamine may be a common factor, leading to “eating for dopamine.” (5) In a neural model, the accumbens is depicted as having separate GABA output pathways for approach and avoidance, both controlled by dopamine and acetylcholine. These outputs, in turn, control lateral hypothalamic glutamate release, which starts a meal, and GABA release, which stops it.

Keywords

dopamine; acetylcholine; accumbens; binge; bulimia

NATURAL AND DRUG ADDICTIONS

The definition of addiction is open to debate. An early view described drug addiction as being due to a lack of will power, making addiction a moral condition.[1] Later, addiction was

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described in modern terms of neuropsychopharmacology as a "disease" caused by drug-induced chronic adaptations in brain function that change a voluntary behavior into an uncontrollable habit.[2] This view of drug addiction as a disease-state partially shifts the blame from the person to the drug; however, both views depict the end result in terms of compulsive behavior and loss of control. Recently, there has been a move in the direction of deemphasizing drugs and suggesting that addiction, including addiction to activities such as eating or sexual behavior, be framed as unusually strong, desires for pleasure.[3–7] The Diagnostic and Statistical Manual of Mental Disorders sidestepped the issue of addiction, per se, and focused on the criteria for "dependence," with continued, life-disruptive, substance abuse as the benchmark for diagnosis.[8] Disruptive behavior is continued despite knowledge of persistent physical or psychological problems, which are likely caused or exacerbated by the substance of abuse.[9] Debates are now appearing in anticipation of the next diagnostic manual.[10] Our view, based largely on evidence from laboratory animal research, is that addiction to sugar could be a problem and can involve the same neural adaptations and behavioral alterations as addiction to drugs.[11,12] These changes are observed in instances of aberrant feeding, which can be modeled in the laboratory. The closest human condition to our laboratory animal model would be binge eating disorder or bulimia nervosa. Evidence for addiction in patients with eating disorders has been presented.[13,14] Brain imaging studies have focused attention on addiction-like changes in the obese population, where the psychological risks of dependency are compounded by medical risks, including cardiovascular impairment and type-2 diabetes.[15,16]

To understand "addiction," one must identify the neural systems that cause it. Addictive drugs act, in part, via systems that evolved for ingestive and perhaps reproductive behaviors. This means that addiction to specific behavior patterns may have evolved through genetic benefits that selected animals with innately programmed addictive processes. If so, there are 2 major kinds of addiction, both of which can become compulsive and sometimes dangerous: (1) survival behavior, such as that which leads to risky behavior for eating and mating and (2) maladaptive behavior that bypasses the normal inhibitory sensory signals and artificially stimulates the reward systems, as in the case of drugs of abuse.

In summary, natural addiction can occur when environmental stimuli act via designated, normal receptor systems, such as sugar acting via glucoreceptors. In this case, the "system" involved is one that evolved with energy regulation as the survival benefit. Drug addiction can result from compounds that can bypass sensory inputs and act within a system that is characterized by its neurochemical function. Thus, drugs such as psychostimulants or opiates may activate multiple systems with diverse physiobehavioral functions. It would be illogical to claim that only drugs can be addictive, if it could be proven that natural stimulation, such as activation of the energy control system, can be sufficient for the addictive process to occur.

WHEN DOES SUGAR PRODUCE A NATURAL ADDICTION? EATING IN BINGES CAN FACILITATE ADDICTION

After 10 years of research on sugar addiction,[11,17,18] we still use the same basic technique to obtain clear signs of food dependency by imposing a feeding schedule that repeatedly

induces sugar bingeing after a period of fasting. In our animal model of sugar bingeing, a "binge" is defined simply as an unusually large meal, compared with animals eating the same diet ad libitum. Periodic, 12-hour food restriction is used to create hunger and anticipation of eating. Then the animals are offered 25% glucose (or 10% sucrose to simulate the sugar concentration of a soft drink) along with their rodent chow. The opportunity to begin the first meal of the day is delayed 4 hours beyond the time they would have normally started eating at dark onset.[19] Over the course of 3 weeks, this daily food restriction and delayed feeding results in 32% of the rat's caloric intake coming from sugar. Rats on this daily 12-hour schedule of sugar and chow escalate their total daily sugar intake during the weeks of access. It is interesting to note that some rats with 12-hour access to sugar take not only a large meal at the onset of access but they also binge spontaneously throughout the feeding period.[11]

Rats with ad libitum access to the sugar solution are a valuable control group. They drink sugar even during the inactive, light phase. These animals consume the same large quantities of sugar solution as bingeing rats; however, it is spread out over the course of 24 hours. We do not see evidence of binge-eating behavior with ad libitum sugar access.[11] As a result, they do not show signs of dependency. Thus, it is the intermittent feeding schedule that seems to be critical for inducing bingeing and the subsequent signs of dependency. In Figure 1, bingeing is indicated as the first stage in route to addiction.

WHY DOES SUGAR BINGEING RESULT IN ADDICTIVE-LIKE BEHAVIORS?

Bingeing causes repeated, excessive dopamine (DA) release and opioid stimulation that is followed, during abstinence, by progressive changes that enhance the likelihood of relapse.

Opioid Adaptations and Signs of Withdrawal

The comparison of sugar addiction with drug addiction has been reviewed in detail.[20,11] In just a few weeks on the intermittent, 12-hour sugar-chow feeding schedule, rats will show signs of opiate-like "withdrawal" in response to naloxone (3 mg/kg s.c.), which proves opioid involvement and suggests opioid "dependency."[21] Withdrawal is also seen without naloxone, when both food and sugar are denied for 24 hours.[11,21,24] Our quantitative polymerase chain reaction (qPCR) and autoradiographic evidence in sugar-bingeing rats shows downregulated enkephalin mRNA[22] and upregulated mureceptor binding in the nucleus accumbens (NAc).[23] This is interpreted to mean that repeated sugar bingeing releases opioids, such as enkephalin or beta-endorphin, and the brain compensates by expressing less of these opioid peptides in certain regions. Perhaps the postsynaptic cells respond to less of these peptides by expressing or exposing more mu-opioid receptors. If the receptors are then blocked by naloxone, or the rats are food deprived, the animals display anxiety in an elevated plus-maze[24,21] and depression in a swim test (Kim et al, unpublished). These behavioral and neurochemical alterations are accepted indications of opiate-like "withdrawal" in animal models.[25]

Dopaminergic Adaptation and Signs of Sensitization

An opioid system in the ventral midbrain is partially responsible for stimulating DA cells during the consumption of highly palatable foods.[26,27] In various parts of the striatum, sugar bingeing results in an increase in DA binding to D1 receptors coupled with a decrease in D2-receptor binding.[23] This may occur because each binge releases DA sufficiently to raise extracellular levels to about 123% of baseline.[28,29] Unlike typical feeding patterns, DA release in response to binge eating does not diminish with repeated meals, as normally seen with food that is no longer novel.[30,27] As seen in Figure 2, the restriction-refeeding conditions imposed by our laboratory model of binge eating cause a surge of DA, even after 21 days of daily exposure. Repeated surges of DA may alter the gene production and intracellular signaling mechanisms of postsynaptic neurons, presumably leading to neural adaptations that compensate for excessive DA stimulation.[31]

Repeated psychostimulant activation of the mesolimbic DA system causes behavioral sensitization.[32–36] Evidence suggests that the mesolimbic DA system is also altered by sugar bingeing. An amphetamine challenge causes locomotor hyperactivity in rats with a history of bingeing on sugar.[37] The effect occurred 9 days after the rats stopped bingeing, suggesting that changes in DA function are long lasting. Conversely, when rats are sensitized by daily injections of amphetamine, they show hyperactivity 10 days later when they drink sugar.[38] We interpret this to mean that sugar bingeing and amphetamine injections sensitize the same DA system, resulting in behavioral cross-sensitization.

Abstinence-induced Signs of Increased Motivation

Other long-lasting effects of sugar bingeing include a) enhanced lever pressing for sugar after 2 weeks of abstinence,[39] b) enhanced voluntary alcohol intake in rats with a history of sugar-bingeing,[40] and c) enhanced responding for sugar-associated cues.[41] These phenomena are referred to as the sugar “deprivation effect,” the alcohol “gateway effect,” and cue “incubation effect,” respectively. They all occur during abstinence, weeks after daily sugar bingeing stopped. Because they are seen during abstinence, it is tempting to categorize them as signs of “craving.” Conservatively, they can be viewed as signs of enhanced motivation, which is integral to relapse to substance abuse.[15,42,43]

In summary, sugar has the addictive-like properties of both a psychostimulant and an opiate. Cross-sensitization with amphetamine is clearly dopaminergic and important in some stages of addiction. The naloxone-induced withdrawal[21] and abstinence-induced incubation of responding for sugar-associated cues have opioid components.[44] This leads to the suggestion that sugar bingeing results in behavioral and neurochemical signs of excessive dopaminergic and opioid stimulation, which contribute to long-term changes in motivational behavior (Fig. 1).

Compulsion and life-disruptive consequences are evident in some people who suffer from binge eating disorder, bulimia nervosa, or obesity; thus, some people may be “dependent” by Diagnostic and Statistical Manual of Mental Disorders criteria. This raises the obvious question: do they have a food addiction? The animal model discussed above suggests it is possible that some binge eaters and bulimics could be addicted to sugar, but this does not

explain all eating disorders or obesity although much has been published on this highly speculative topic.[45–50]

WHICH FOODS ARE POTENTIALLY ADDICTIVE? THERE IS SOMETHING SPECIAL ABOUT SUGAR

Sugar

There is more to food addiction than food restriction and bingeing. The type of nutrient that the animal ingests is also important. Our studies of food addiction have largely focused on sugar (sucrose or glucose). The positive results may relate to sugar as a special nutrient. It has its own receptor system in the tongue,[51,52] the intestines,[53,54] the liver,[55] pancreas,[55] and brain.[56] Glucoreceptors provide life-saving information to the ingestive behavior system and its associated learning, emotion, and motivational systems. In all probability, sugar addiction in rats is engendered by excessive, repeated activation of this pervasive sugar sensory system.

Saccharin and Sweet-taste

It would be interesting to test artificial sweeteners to see whether the oral component of sweetness is sufficient to produce dependency. We used 12-hour intermittent access to chow and 0.1% saccharin solution to simulate the taste of a “diet soft drink.” After 8 days of this dietary regimen, animals were deprived of food and saccharin for 36 hours, with somatic signs related to anxiety scored every 12 hours. Depriving the rats of food and saccharin led to increased instances of teeth chattering, head shakes, and forepaw tremors over the 36hour period. This aversive state was readily counteracted by 5 mg/kg of morphine or access to a saccharin solution (Hoebel and McCarthy, unpublished). Thus, we suspect that scheduled saccharin binges may stimulate dopamine and opioid-induced dependency, much like the case with sucrose. This is not surprising, given extensive research in the Carroll laboratory suggesting that saccharin can be a substitute for cocaine, and saccharin preference is a marker for addiction liability.[57,58] Further support for the extreme reinforcing value of saccharin, and its relation to addiction, comes from Ahmed and coworkers,[59] who have shown that some rats prefer saccharin to cocaine self-administration.

Another way to test the power of the sweetness of sugar without the concomitant calories is to purge the stomach by opening a gastric fistula while rats drink 10% sucrose. As one would expect, sham drinkers consume excessive amounts of sugar because of the relative lack of satiety signals.[60] After 3 weeks of sham-binge eating, the taste of a sham-meal of sucrose will still increase extracellular DA to 131% of baseline.[61]

Postingestive Carbohydrates

Real sucrose intake is probably more addictive than either saccharin or sham intake, because extensive evidence shows that intestinal glucose receptors and other postingestional factors are important for the sugar reward that is manifested in conditioned taste preference.[62] Flavors associated with intragastric feeding are preferred,[63] and they release accumbens DA.[64–67] We conclude on the basis of these conditioning studies that carbohydrate

postingestive cues could contribute to the DA or opioid release that is triggered by sugar during acquisition, maintenance, and reinstatement of a binge.

A Surprising Feature of Fat

We were surprised by our inability to obtain naloxone-induced anxiety using the plus-maze test as an indication of a withdrawal state in rats on a high-fat diet. Withdrawal failed to emerge in rats given vegetable fat (Crisco) along with standard chow pellets, or given a nutritionally complete diet of high-sucrose, high-fat pellets. Both the pure vegetable fat and the high-fat pellets were consumed avidly on a binge-inducing schedule.[68] Either the animals were not dependent on the fat or it was a type of addiction that does not cause opiate-like withdrawal. In terms of withdrawal, fat may be to sugar as cocaine is to heroin; that is to say, there are fewer observable behavioral manifestation of withdrawal with cocaine compared with heroin and similarly, fat compared with sugar. Because of this, we have been biased toward looking for signs of opiate-like withdrawal in rats bingeing on sugar. If the opioid system is not perturbed to a significant degree in rats bingeing on fat, then opiate-like withdrawal signs will not emerge. Although it is clear that sugar releases opioids that prolong a meal,[69,70] fat might not be effective in this way. Fat is less satiating than carbohydrate, calorie for calorie, but sugar may actually suppresses satiety, just as it can suppress pain and discomfort in general.[71,72] We have also speculated that fat-stimulated peptides such as galanin, which show increased mRNA expression in response to a high-fat meal and also inhibit some opioid systems,[73] might thus reduce sugar-stimulated opioid-based withdrawal.[68] Thus, although fat does not seem to produce opioid-based dependence, it may still be addictive, but in a way that we have not yet measured.

IS THERE A LINK BETWEEN BINGE EATING AND OBESITY? IT DEPENDS ON THE DIET

Sucrose or Glucose Bingeing, Alone, Does Not Cause Obesity

In terms of overall body weight, some studies have found that bingeing on fat or sugar does not result in weight dysregulation,[23,74–76] whereas others have shown an increase in body weight.[77–79] In our laboratory, rats that binge on glucose or sucrose show many of the same signs as animals taking drugs of abuse, as described above, and serve as animal models of sugar addiction, but they compensate for the sugar calories by eating less chow and thus control their body weight.[24,21] A control group with ad libitum access to sugar also compensates for their caloric intake such that they do not become obese.

Sweet-fat Bingeing Does Increase Body Weight

Although animals bingeing on a 10% sugar solution demonstrate an ability to regulate their body weight, those that are maintained on a similar bingeing diet, but with a sweet, high-fat food source, do show weight gain.[80] Animals that were given 2-hour access to this palatable diet showed bingeing patterns, even though they had ad libitum access to a nutritionally complete diet for the remainder of the day. Body weight increased because of the large binge meals, and then it decreased between binges as a result of self-restricted intake of standard chow. However, despite these daily fluctuations in body weight, the animals with

access to sweet-fat chow every day gained significantly more weight than the control group with ad libitum access to standard chow. This could lend insight to the connection between binge eating and obesity.[81]

Low Basal Dopamine

To test the theory that some obese people are food addicts, we need obese rats. Extensive work in the Pothos laboratory shows that inbred obesity-prone rats and obese cafeteria-diet rats have low basal DA and impaired DA release.[82] This is thought to have underlying causes related, in part, to weight-related changes in insulin and leptin sensitivity in the control of DA cell firing.[83,84] We know thatunderweight rats on a restricted diet also have low basal DA.[85] Thus, it seems that both high- and low-weight animals may be hyperphagic as a means of restoring their extracellular DA level. This is analogous to rats self-administering cocaine in a manner that keeps their DA elevated.[86] In fact, sugar-bingeing rats that are food restricted to the point of weight loss release more DA than usual when allowed to binge again, and thus they would raise their own DA level.[28]

A SIMPLIFIED NEURAL CIRCUIT MODEL OF ACCUMBENS FUNCTION

Given that sugar dependency, like obesity, is related both to basal DA levels and to food-induced release of DA, we need a model depicting the role of DA circuitry in behavioral motivation. One would expect this circuit to interact with opioid systems. We have proposed a model in which the NAc has separate GABA outputs for motivation that are similar to the well-documented outputs in the dorsal striatum for locomotion.[87] Just as neurotransmitter imbalance in the motor system leads to Huntington Chorea and Parkinson disease,[88,89] neurotransmitter imbalance in the accumbens may be related to general motivational hyperactivity and depression. Specific instances may be manifest as hyperphagia and anorexia. Taking our clues from the extensive Parkinson disease literature,[90] we propose that there is an accumbens GABA output pathway that is specialized for positive, “go” motivation (“approach”), including learned approach and appetitive behavior, and another for negative, “no-go” motivation (“avoidance”), including learned aversion.[91,87] Focusing on the shell, the approach pathway would be the “direct path” with dynorphin and Substance P as cotransmitters. The avoidance path presumably uses enkephalin as a cotransmitter and takes an “indirect path” to the thalamus and ventral midbrain. Cortex-striatal-pallidum-thalamus-cortex loops may circle around several times in a spiral, leading from cognitive processes to motor activity.[92] Striatal-midbrain pathways have also been described as a spiral, with the shell influencing the core, which influences the medial striatum and then the dorsallateral striatum.[93] This brings the ventral midbrain with its ascending DA and GABA neurons into the schema for cognition to be transformed into action. Directly or indirectly the accumbens outputs also reach the hypothalamus.[94] In the lateral hypothalamus, glutamate inputs initiate eating and GABA stops it. This was shown by both microinjection and our microdialysis studies.[95,96]

As shown in Figure 3, DA input from the midbrain to the NAc may act to stimulate approach and inhibit avoidance, thus fostering behavior repetition. Excitation is envisioned via D1 receptors on the GABA-dynorphin “approach” neurons and inhibition via D2 types on the GABA-enkephalin “avoidance” neurons. Indeed, local D2 stimulation can induce

signs of aversion, such as gaping and chin rubbing.[97] DA acting via D2 receptors reduces GABA striatal-pallidum neuron responsiveness to glutamate and promotes long-term depression of glutamatergic transmission.[98] D1 receptors are reported to promote responses to strong-coordinated gluta-mate input and long-term potentiation, at least in the GABA neurons that project to the nigra.[99,100] D1 receptors in the caudate potentiated reward-related eye movements, and again, D2-receptor function was the opposite.[101] This provides support for the schema shown in Figure 3 to the extent that the accumbens shell is organized along lines similar to the dorsal striatum. There are different views expressed in the literature describing the paths from the accumbens to the pallidum, nigra, and the hypothalamus. Each may have different functions with regard to acquisition and expression of conditioned responses and instrumental performance.[102–104] Within the accumbens, the shell and core must be distinguished, in terms of both their functions and their action sequence.[105–109] Moreover, subsecond measurements by in vivo voltammetry show DA release within "microenvironments" of the accumbens may vary with functionally specific subpopulations of DA inputs.[110]

DA surges in response to drugs of abuse cause downstream changes, such as postsynaptic, intracellular accumulation of Delta FosB, which could alter gene production for receptors and other cellular components as a form of compensation; this could then foster restorative reinstatement of drug taking during abstinence.[31] We suggest that if this cascade of intracellular changes can occur in response to drugs of abuse, it might also occur when repeated surges of DA are caused by sugar bingeing.[11,61] This hypothesis is supported by recent evidence showing that natural reinforcers, such as sucrose and sexual behavior, alter Delta FosB expression in the NAc.[111]

Acetylcholine interneurons may act as an opponent process to halt behavior by doing the opposite of DA at some accumbens synapses as suggested in Figure 3. ACh theoretically inhibits appetitive approach and stimulates the aversion-avoidance path; this could be due to synaptic effects at muscarinic M2 and M1 receptors, respectively (Fig. 3). Numerous studies in the rat support the view that accumbens ACh interneurons inhibit behavior, including the inhibition of feeding behavior and cocaine intake.[61,91,112,113] A muscarinic agonist applied locally to the accumbens can cause behavioral depression in the swim test and a relatively specific M1 antagonist alleviates depression.[114] Dynorphin and other transmitters also enter into the control of this system with depression as one of the outcomes.[115] A conditioned taste aversion releases ACh[116] and neostigmine, used to raise local ACh levels, is sufficient to engender an aversion to a flavor that was previously paired with the cholinergic injection.[117] This suggests that excessive ACh can cause an aversive state that is manifest as a conditioned taste aversion. The possible actions of other muscarinic and nicotinic drugs in the accumbens do not fit our model[94,118,119] and are discussed elsewhere in light of the possibility that some muscarinic agonists release DA and some muscarinic antagonists may act via M2 receptors to release ACh.[87,120] ACh interneurons may be inhibited by DA via D2 receptors, as reviewed by Surmeier et al.[98] This suggestion fits with Figure 3, which indicates that less ACh release would reduce activity in the "avoidance pathway" and promote "approach."

Having suggested that surges of DA caused by sugar bingeing might act via known mechanisms to promote addiction, it is cogent to note that sham feeding, which can reduce ACh satiety signals,[61] would make the overall accumbens response even more like the DA response one sees with some drugs of abuse such as opiates[121] and alcohol.[122] It is tempting to speculate that this translates to human binge-purge disorder as seen in bulimia. Sugar bingeing and purging, according to the rat experiments, would produce DA release that is uninhibited by ACh in the accumbens.

The accumbens GABA outputs, under the opposing influences of DA and ACh, participate in the control of lateral hypothalamic glutamate and GABA release. Rada's group has new data showing that the accumbens GABA output cells have muscarinic receptors, and that a muscarinic agonist injected in the NAc causes significant changes in glutamate and GABA release in the lateral hypothalamus (Rada et al, unpublished). This is consistent with microdialysis and local injection evidence that lateral hypothalamic glutamate is involved in starting a meal and GABA in stopping it.[95,123,124] Thus, the model is supported by evidence that accumbens outputs participate in the control of hypothalamic feeding and satiety systems. In the accumbens, DA and ACh may start and stop the motivation to eat by controlling these functions through glutamate and GABA release in the hypothalamus. Clearly, this is an oversimplification, but it is a theory that our data currently support and may, therefore, be part of the larger picture that will eventually emerge.

CONCLUSIONS

This article summarizes data suggesting that, repeated, excessive sugar intake can lead to changes in brain and behavior that are remarkably similar to the effects of drugs of abuse. Thus, sugar may be addictive under special circumstances. On the other hand, bingeing on fat, or even sweet-fat, has given negative results as far as withdrawal is concerned, suggesting that different neural systems are involved. A high-fat diet, if rats binge on it every day, can lead to extra weight gain. Rats prone to obesity on a high-fat diet show low-basal DA levels in the NAc, as do underweight rats, suggesting that both may overeat opportunistically in a manner that restores DA levels. Surges of binge-induced DA may be partially responsible for the neural adaptations manifest as locomotor sensitization and abstinence-induced enhancement of motivation for the food. Opioids are another important part of the picture, but the exact system is not known, because opioids can induce feeding in many brain regions. It seems that opioids may be responsible for the withdrawal signs and for abstinence-induced incubation of cue-induced relapse. ACh in the NAc is one of the countervailing forces in this process. Sugar bingeing seems to postpone ACh release, and sham feeding greatly attenuates it. This is all consistent with a model in which DA stimulates approach and inhibits avoidance outputs in the NAc. ACh does the opposite, unless it is circumvented by drugs of abuse, sugar bingeing, or purging.

Acknowledgments

Supported by USPHS Grants DA10608, MH65024, and AA12882 (to BGH) and fellowship DK-079793 (to NMA).

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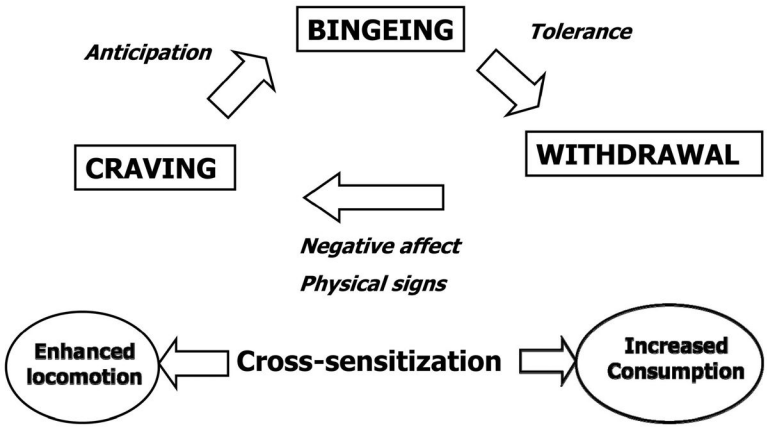

FIGURE 1.

Schematic representation of some criteria used to classify substances of abuse as described by Koob and Le Moal.[42] We have applied these criteria to the study of food addiction. Limited daily access to a sugar solution leads to bingeing and ensuing opiate-like withdrawal when animals are administered naloxone or food deprived. After a period of sugar abstinence, these animals show signs of craving, as measured by increased responding for sugar or sugar-associated cues. Cross-sensitization between sugar and drugs of abuse is shown by hyperactivity in response to a low dose of a psychostimulant and by avidity for alcohol.

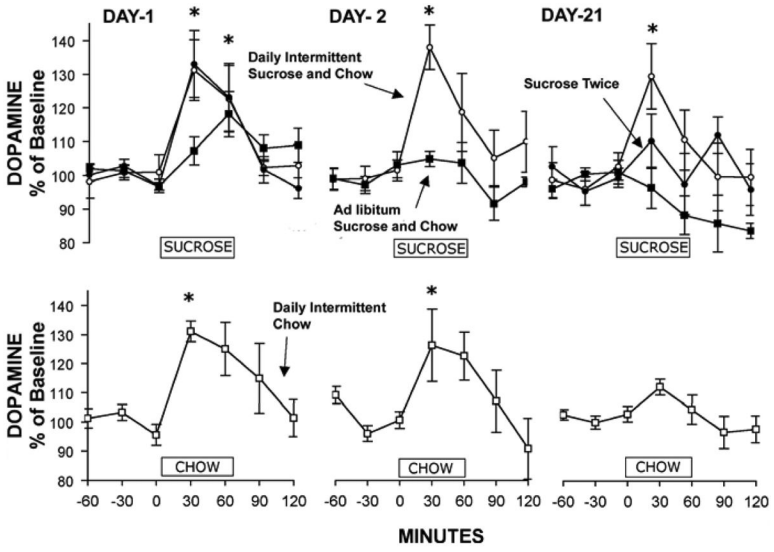

FIGURE 2.

Rats with intermittent access to sugar release DA in response to drinking sucrose for 60 minutes on day 21. DA, as measured by in vivo microdialysis, increases for the daily intermittent sucrose and chow rats (open circles) on days 1, 2, and 21; in contrast, DA release was attenuated on day 21 in 3 control groups as follows: a group that only had 1-hour access to sucrose on days 1 and 21 with ad libitum chow in the interim (sucrose twice, filled circles), ad libitum sucrose and chow group (filled squares), and the daily intermittent chow group (bottom panel). The bar on the ordinate indicates the hour (0–60 min) that sucrose or chow was available for the tests. *$P < 0.05$.[29]

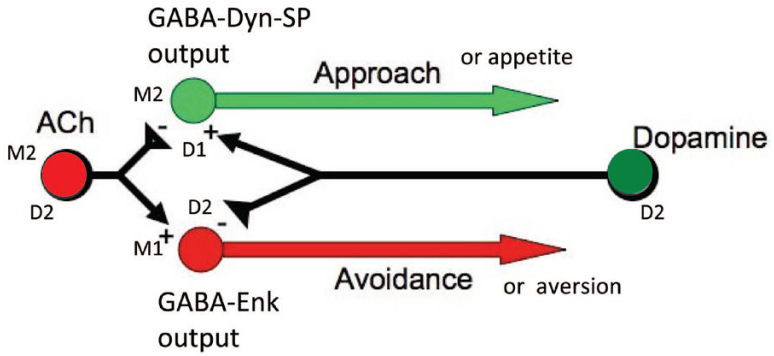

FIGURE 3.

Simplified diagram showing opposing DA and ACh influences on dual GABA outputs that are theoretically associated with approach behavior and avoidance behavior. The left side of the diagram represents the nucleus accumbens. Note that the DA input on the right is depicted as acting at D1 receptors to stimulate (plus sign) medium spiny output neurons (containing GABA, dynorphin, and SP) for approach and appetitive behavior. DA also acts at D2 receptors, which inhibit (minus sign) the output path (GABA-enkphalin neurons) labeled for avoidance and aversion. Acetylcholine from interneurons shown at the far left, may act at muscarinic M2 receptors to inhibit the approach system, and also act via M1 receptors to stimulate avoidance and aversion.