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The dark side of food addiction

Sarah L Parylak[a,b,c], **George F Koob**[a,c], and **Eric P Zorrilla**[a,b,c,1]

Sarah L Parylak: sparylak@ucsd.edu; George F Koob: gkoob@scripps.edu; Eric P Zorrilla: ezorrilla@scripps.edu

[a]Committee on the Neurobiology of Addictive Disorders, The Scripps Research Institute, 10550 N Torrey Pines Rd, La Jolla, CA, 92037, USA

[b]Harold L Dorris Neurological Research Institute, The Scripps Research Institute, 10550 N Torrey Pines Rd, La Jolla, CA, 92037, USA

[c]Neurosciences Graduate Program, University of California, San Diego, 9500 Gilman Dr 0634, La Jolla, CA 92093, USA

Abstract

In drug addiction, the transition from casual drug use to dependence has been linked to a shift away from positive reinforcement and towards negative reinforcement. That is, drugs ultimately are relied on to prevent or relieve negative states that otherwise result from abstinence (e.g., withdrawal) or from adverse environmental circumstances (e.g., stress). Recent work has suggested that this "dark side" shift also is key in the development of food addiction. Initially, palatable food consumption has both positive reinforcing, pleasurable effects and negative reinforcing, "comforting" effects that can acutely normalize organism responses to stress. Repeated, intermittent intake of palatable food may instead amplify brain stress circuitry and downregulate brain reward pathways such that continued intake becomes obligatory to prevent negative emotional states via negative reinforcement. Stress, anxiety and depressed mood have shown high comorbidity with and the potential to trigger bouts of addiction-like eating behavior in humans. Animal models indicate that repeated, intermittent access to palatable foods can lead to emotional and somatic signs of withdrawal when the food is no longer available, tolerance and dampening of brain reward circuitry, compulsive seeking of palatable food despite potentially aversive consequences, and relapse to palatable food-seeking in response to anxiogenic-like stimuli. The neurocircuitry identified to date in the "dark" side of food addiction qualitatively resembles that associated with drug and alcohol dependence. The present review summarizes Bart Hoebel's groundbreaking conceptual and empirical contributions to understanding the role of the "dark side" in food addiction along with related work of those that have followed him.

[1]To whom correspondence should be addressed: Eric P. Zorrilla, Committee on the Neurobiology of Addictive Disorders, The Scripps Research Institute, 10550 North Torrey Pines Road, SP30-2400, La Jolla, CA 92037 USA, tel: 858-784-7416, fax: 858-784-7405, ezorrilla@scripps.edu.

Conflict of Interest

EPZ and GFK are inventors on a patent filed for CRF1 antagonists (USPTO Applicaton #: #2010/0249138).

Keywords

Palatable food addiction; withdrawal or abstinence or dependence; negative affect or anxiety or depression; stress; binge eating disorder or bulimia; sugar or sucrose or glucose or chocolate or high-fat

1. Introduction

Drug addiction is a chronic, relapsing disorder with three distinct phases: a binge intoxication phase driven and characterized by the rewarding properties of the drug, a withdrawal phase accompanied by a negative emotional state as the acute rewarding drug properties wear off, and a preoccupation and anticipation phase that precedes renewed drug intake. Dr. Bartley Hoebel is among the very earliest pioneers who hypothesized that intake of sugar, and perhaps of other palatable foods, also could become governed by these three phases of addiction. His leadership has been instrumental not only in bridging the fields of addiction and feeding behavior through his experimental work, but also in his efforts to increase awareness of and legitimize what once was an unpopular and even controversial hypothesis within the scientific community – that one could become "food addicted." Now, food addiction symposiums, such as the Food & Addiction Conference on Eating and Dependence hosted by the Rudd Center for Food Policy and Obesity at Yale, the "Food Addiction: Fact or Fiction" session at the 2008 Experimental Biology meeting in San Diego, and the Obesity and Food Addiction Summit of 2009, regularly bring together scientists, physicians, public policy makers, and health advocates from diverse backgrounds. Further, Dr. Hoebel's groundbreaking work has helped spur the creation of institutes devoted specifically to advancing food addiction research, including the Food Addiction Institute and the Refined Food Addiction Research Foundation.

As drug users progress from casual use to addiction, the factors motivating drug use are hypothesized to shift in importance. While initial use is motivated by the hedonically rewarding properties of the drug, use in addicts is hypothesized to become motivated less by positive reinforcement (e.g., a euphoric high), but rather by negative reinforcement: to prevent or relieve a negative emotional state that arises from abstinence (e.g., drug withdrawal) or from adverse experience of the environment (e.g., stress) [1]. At the neurobiological level, this shift corresponds to a downregulation of brain reward systems that subserve appetitive responses to the drug and a concurrent amplification of brain stress or "antireward" systems. In this framework, the shift to the "dark side" of food addiction may similarly be conceptualized as a key transition in the addiction process. As individuals progress towards compulsive intake of palatable foods, the acute rewarding value of food items may hold less importance for motivating additional intake than does preventing or ameliorating negative states (e.g., anxiety, depression, irritability, and possibly even somatic withdrawal symptoms) that are experienced when such preferred foods are not available or when environments are adverse.

2. Evidence for the "dark side" from human studies

To determine whether an addiction-like "dark side" motivates intake of palatable food, a useful starting point is to identify the human population(s) whose eating habits most closely resemble addictive behaviors. Although obesity and addiction-like eating behaviors likely overlap, "food addiction" is unlikely to explain all cases of human obesity, and some normal weight individuals likely engage in addiction-like eating patterns. No consensus diagnostic criteria for "food addiction" currently exist [2, 3]. Recently, however, the Yale Food Addiction Scale (YFAS) has been introduced as an index of addictive-like eating behaviors

that mimic the diagnostic criteria for substance dependence in the DSM-IV-TR [4]. The YFAS measures the extent to which (a) individuals overeat specific foods despite repeated attempts to limit their consumption, (b) their eating behaviors interfere with social and professional activities, and (c) withdrawal symptoms emerge when abstaining from specific foods. Preliminary application of these criteria suggest that the compulsive, uncontrollable intake of greater-than-expected amounts of food seen in binge eating disorder maps most neatly onto the current diagnostic criteria for substance dependence. Accordingly, scores on the YFAS predicted binge eating behavior and emotional eating [4] but did not correlate with body mass index (BMI) in women participating in a weight maintenance trial who reported no eating disorder [5]. These results suggest that the "dark side" of food addiction, as operationalized by the YFAS, might be more fruitfully studied in individuals with binge eating than in randomly selected obese individuals.

2.1 Psychiatric comorbidity in binge eating

Consistent with a possible role for a "dark side" in food addiction, binge eaters have greater rates of psychiatric diagnoses involving negative emotional states compared to the general population. For example, adults and adolescents with bulimia nervosa or binge eating disorder show increased prevalence of major depression, bipolar disorder, anxiety disorders, and alcohol or drug abuse than do individuals without an eating disorder [6-8]. Rates of major depression are also elevated in the obese, but the association of binge eating with increased depression scores remains even in weight-matched comparisons of overweight and obese individuals [9]. Extremely high rates of suicidal ideation in binge eaters attest to the severity of mood disturbance in this population. Over half of teenage bulimics and one-third of those with binge eating disorder report suicidal ideation, and a third of teenage bulimics report attempting suicide [6]. The direction of causality between binge eating and major depression is not firmly established and may be reciprocal [10-12]. Such psychiatric comorbidity is associated with poor long-term treatment outcome [13] and a greater frequency of binge eating [14]. Conversely, many antidepressants, such as SSRIs or tricyclics, can reduce the frequency and severity of binge eating symptoms [15].

2.2 Negative emotional states increase palatable food intake in vulnerable populations

The prevalence and severity of depression and anxiety in binge eaters suggests the hypothesis that negative emotional states can trigger relapse to bingeing behavior. Indeed, self-reported negative emotional traits of depression, low self-esteem, and neuroticism are associated with binge eating in both men and women [16]. During negative emotional states and situations, normal and underweight individuals report consuming less food than during positive emotional states and situations. In contrast, this undereating in response to negative states is not observed in overweight individuals, who report eating significantly more during negative states than do other groups [17]. Consistent with a role for negative emotional states in driving binge behavior, mood scores in bulimics are lower immediately prior to a binge than on days when no binges occur [18].

Another construct that implicates stress and negative emotions as triggers of overeating is dietary restraint. Attempts to control body weight (e.g. via dieting, exercise, appetite suppressants, or laxatives) are paradoxically associated with increased weight gain in female adolescents [19]; dietary restriction similarly is associated with long term weight gain in female adults [20]. A possible explanation for these apparent contradictions is the consistent finding that restrained eaters overeat in response to a variety of stressful situations [21]. For example, anticipation of a social stressor (a public speaking task) increased food intake in restrained eaters while not altering that of unrestrained eaters [22]. Similarly, restrained eaters who reported high subjective stress and negative affect following a series of cognitive tasks showed greater intake after the stressor than did those reporting low levels of

subjective stress [23]. Dietary restraint also may have temporally restricted importance in binge eaters because the intent to restrict intake is greater prior to a binge as compared to days on which no binges occur [18].

Though laboratory mood induction studies may be criticized as not modeling real world eating practices under natural mood conditions [24], they also broadly support the "dark side" hypothesis that overeating can be triggered by stressful or negative emotional responses in subsets of individuals. For example, obese binge eaters consumed significantly more chocolate after viewing a sad film in a laboratory setting than following a neutral film [24]. All participants in this study reported mood as one of their triggers to binge eat, with "depression" or "sadness" most often implicated. In non-obese females, those with greater salivary cortisol responses to a battery of social stressors ate more after the stressful experience than did those with lower cortisol responses [25]. Induction of a negative emotional state via autobiographical recall of a sad memory also increased the amount of snack food consumed in a study of non-dieters, and the effect was particularly pronounced in participants who reported greater "emotional eating" [26]. Unlike the reviewed findings and what occurred in restrained eaters, unrestrained eaters *reduced* their snack food intake after viewing a sad film [27, 28].

Such negative affect-driven food intake can disrupt body weight maintenance. Weight regain in the 6 months following successful weight loss is associated with eating in response to stressful life events, eating in response to negative mood, and the use of food to regulate mood [29]. Perhaps accordingly, adding cognitive therapy to help manage general mood and coping, and not only eating behavior and diet, can reduce relapse to obesity [30]

2.3 Influence of palatable food intake on mood and reward function

Eating in response to emotionally negative situations suggests that overeating may be an attempt to self-medicate with "comfort food." The typical foods consumed during a binge tend to be palatable and energy dense; further, they often are carbohydrate-laden items such as breads, pastas, and sweets [31]. Initially, such carbohydrate-rich foods may have the intended negative reinforcement effect, because they reduce subjective reports of anger [32] and tension [33] and increase calmness within 1-2 hr of consumption. Repeated overconsumption of such palatable foods, however, may produce long term neuroadaptations in brain reward and stress pathways that ultimately promote depressive or anxious responses when those foods are no longer available or consumed. Consistent with this "dark side" hypothesis, after eating a high fat diet (41%) for one month, men and women who were switched to a lower-fat (25%), high-carbohydrate diet reported increased anger and hostility during the subsequent month than did subjects who continued eating the high fat diet [34]. Increased anger may have resulted either from the reduction in dietary fat (or perceived palatability) or from neuroadaptations to increased dietary carbohydrates.

Repeated overconsumption of highly palatable foods may downregulate dopaminergic reward circuitry via mechanisms that mirror those commonly observed in drug addiction: reduced striatal dopamine D2 receptor availability and blunted dopamine release [35, 36]. Indeed, obese individuals show lower striatal availability of the dopamine D2 receptor than do non-obese controls, and this reduction in striatal D2 is correlated directly with BMI [37, 38]. Caudate activation in response to a chocolate milkshake is also reduced in obese relative to lean individuals [39]. This blunted activity level is especially pronounced in individuals with the TaqIA A1 polymorphism of the D2 receptor, which is associated with reduced D2 receptor expression [39]. Another polymorphism linked to reduced dopamine function, the 7R allele of the dopamine D4 receptor, has been associated with higher lifetime maximum BMI in bulimics [40] as well as with binge eating behavior in women with seasonal depression [41]. The collective genetic data suggest a predisposition towards

weight gain in individuals with low striatal dopaminergic signaling, and it has been hypothesized that such individuals overeat in an attempt to compensate for a perceived reward deficit. Recent data suggest, however, that weight gain (or a correlate of weight gain, perhaps overeating palatable food) downregulates striatal dopamine activity. Women whose BMI increased during a 6 month period showed reduced caudate activation to consumption of a chocolate milkshake than did women whose BMI remained stable, and the reduction in caudate activation was associated with greater BMI increases [42]. Conversely, gastric bypass increased striatal D2 receptor availability within 6 weeks of bariatric surgery in a small study of severely obese women [43].

Striatal D2 receptor availability in obese subjects also correlates directly with glucose metabolism in frontal cortical regions that subserve inhibitory control, including dorsolateral prefrontal, orbitofrontal, and anterior cingulate cortices [38]. This relationship suggests the hypothesis that reduced dopaminergic modulation from the striatum may lead to impaired inhibitory control over food intake and thereby increase risk of overeating. Perhaps analogously, a direct correlation between striatal D2 availability and glucose metabolism in dorsolateral and anterior cingulate cortices also has been observed in alcoholics, but not in non-alcoholics or non-obese controls [38, 44].

Consistent with reviewed behavioral differences in the ingestive response to stress, eating style also differentiates subpopulations with distinct mesolimbic dopamine system profiles. Non-obese individuals who reported greater “emotional eating” showed reduced baseline D2 receptor availability in the dorsal striatum as compared to non-emotional eaters; those high in dietary restraint had increased D2 binding in the dorsal striatum in response to food stimulation as compared to those low in dietary restraint [45]. Finally, obese binge eaters showed increased D2 receptor binding in the caudate in response to a combination of food stimulation and methylphenidate challenge as compared to obese non-binge eaters [44, 46].

3. Evidence for the “dark side” from animal models of food addiction

The development of animal models was key for validating the concept of food addiction and beginning to characterize its “dark side.” Bart Hoebel’s group has led the way in modeling aspects of food addiction in rodents [47]. While animal models cannot encompass all of the complex social factors that influence eating behavior in humans, they have the advantage of more easily distinguishing between antecedents and consequences of addictive-like eating behavior, establishing tighter dietary control, and allowing for a more detailed examination of the associated molecular mechanisms.

3.1 Induction of withdrawal-like states after cessation of palatable food access

Consistent with the “food addiction” hypothesis pioneered by Hoebel and colleagues, numerous studies in animal models have now observed behavioral and somatic profiles that resemble withdrawal-like states in animals withdrawn from intermittent access to palatable food. For example, Hoebel and colleagues provided evidence that daily bingeing on high sugar solutions (e.g., 25% glucose or 10% sucrose) may lead to endogenous opioid dependence. Rats provided with daily 12-hr access to glucose and chow alternated with 12-hr food deprivation displayed somatic signs associated with opiate withdrawal, including teeth chattering, forepaw tremors, and head shakes, when challenged with the opioid antagonist naloxone [48]. Precipitated withdrawal via naloxone pretreatment also increased anxiety-like behavior in 12-hr daily glucose-cycled animals, as shown by reduced open arm time on the elevated plus-maze, but not in animals receiving *ad lib* access to chow or glucose [48]. In the absence of naloxone pretreatment, somatic signs of withdrawal also occurred “spontaneously” 24-36 hr after the last glucose access session. In the absence of naloxone challenge, increased anxiety-like behavior on the plus-maze also was seen in

sucrose-cycled animals after a 36-hr fast, as compared to *ad lib* chow fed controls, providing evidence for a heightened anxiety-like state in cycled animals withdrawn from intermittent access to a sugar solution [49].

Hoebel and colleagues have hypothesized that reduced reward function and increased anxiety-like behavior during withdrawal may originate in part from alterations in the balance of dopaminergic and acetylcholinergic (ACh) signaling within the striatum. They found that naloxone challenge stimulated significantly greater ACh release in the nucleus accumbens (NAc) of rats with a cyclic history of daily 12-hr glucose and chow access followed by a 12 hr food deprivation than in animals maintained on *ad lib* chow [48]. This amplification of the ACh response is accompanied by a reduction in extracellular accumbens dopamine following naloxone challenge, similar to what occurs during morphine withdrawal [50, 51]. After a 36-hr fast, glucose/chow-cycled animals have lower dopamine and higher ACh levels extracellularly in the NAc even in the absence of naloxone, again resembling a spontaneous opiate withdrawal-like state during abstinence from the glucose diet [49]. Hoebel and colleagues propose that this shift towards enhanced ACh release concurrent with diminished dopamine release may reflect a broader behavioral shift away from dopamine-mediated approach behaviors and towards harm avoidance [52].

Using a sugar-rich solid diet, rather than a liquid diet, Cottone *et al.* similarly found spontaneously increased anxiety-like behavior in rats withdrawn from intermittent access to a high-sucrose, chocolate-flavored diet. Rats provided with alternating 5-day/2-day access to standard laboratory chow and the palatable diet spent less time on the open arms of the elevated plus-maze and more time within the withdrawal chamber in a defensive withdrawal task when tested during the chow phase of their diet cycle [53, 54]. The increase in anxiety-like behavior was accompanied by increased expression of the stress-related neuropeptide corticotropin-releasing factor (CRF) in the central nucleus of the amygdala (CeA), a system that also is activated during withdrawal from alcohol [55-59], opiates [60-63], cocaine [64], cannabinoids [65],and nicotine [66, 67]. Pretreatment with the selective CRF_1 antagonist R121919 blocked the food withdrawal-associated anxiety at doses that did not alter behavior of chow-fed controls [68-70]. Analogously, CRF_1 antagonists ameliorated aversive- or anxiety-like states during withdrawal from alcohol [59, 71, 72], opiates [73, 74], benzodiazepines [75], cocaine [76, 77], and nicotine [66]. CRF_1 antagonist pretreatment also blunted the degree to which diet-cycled animals overate the sucrose-rich diet upon renewed access at doses that did not alter intake of chow-fed controls or of animals fed the sucrose-rich diet, but without a history of diet cycling. Analogously, CRF_1 antagonists reduce excessive intake of alcohol [57, 78-82], cocaine [83], opiates [84], and nicotine [66] in models of addiction, while having lesser effects on drug and alcohol self-administration of non-dependent animals.

When diet-cycled animals were studied while receiving access to the preferred, sucrose-rich diet, both plus-maze behavior and CeA CRF levels normalized, supporting the hypothesis that increased activation of the amygdala CRF system and anxiety-like behavior reflected an acute withdrawal state [53, 54]. Finally, diet-cycled rats also showed increased sensitivity of CeA GABAergic neurons to modulation by CRF_1 antagonism. R121919 reduced evoked inhibitory postsynaptic potentials in the CeA to a greater degree in diet-cycled rats than in chow-fed controls, mirroring the enhanced modulatory influence of CRF_1 antagonists on CeA GABAergic synaptic transmission that is seen during withdrawal from alcohol [58]. Thus, the pattern of palatable food withdrawal-associated increases in CeA CRF expression and anxiety-like behavior, escalation of intake upon renewed access, and reversal of behavior via CRF_1 antagonist pretreatment resembles findings in both drug and alcohol addiction [68-70].

In a separate study, Cottone *et al.* also found that female rats with a history of receiving highly limited (10 min/day) access to the same chocolate-flavored, sucrose-rich diet exhibited not only dramatic escalation of their intake of the palatable diet (consuming over 40% of their daily intake within 10 min), but also an anxiogenic-like reduction in plus-maze open arm time when studied 24 hr after their last access session [85]. Diet-cycled rats that spent the least time on the open arms were also those that binged the most on the palatable diet, a correlation not evident in chow-fed controls. These results support the Hoebel hypothesis that intermittent access to a palatable sucrose-rich diet leads not only to binge-like intake of the diet, but also to a withdrawal-like state of increased anxiety in direct relation to the binge-like eating.

3.2 Sugar vs. fat addiction: Is there a difference?

Hoebel and colleagues also have recently proposed that there may be something different about the ability of simple sugars (vs. fats) to promote “food addiction” [86]. Whereas somatic and anxiety-like signs of withdrawal have been observed following cessation of intermittent access to sugar solutions or solid diets, the case for withdrawal signs following diets consisting predominantly of fat or sweet-fat mixtures is less clear. As with sugar diets, rats develop binge-like eating patterns when receiving intermittent access to pure fats such as vegetable shortening [87] and sweet-fat chow mixtures [88]. Unlike the robust findings of opiate-like withdrawal in glucose-cycled rats, however, naloxone challenge and fasting have failed to produce opiate-like somatic withdrawal signs in rats with intermittent access to vegetable fat or sweet-fat chow [86].

Still, a lack of somatic opiate withdrawal-like signs does not preclude the possible development of a negative emotional state in animals withdrawn from high-fat food (i.e. “affective withdrawal”). Indeed, some have observed altered behavioral responses to mild stressors after removal of a preferred high fat diet. Mice maintained continuously on a high-fat diet showed increased activity in the open field test 24 hr after being switched to standard chow, an effect not seen in rats withdrawn from a high-sucrose diet [89]. Moreover, 24-hr withdrawal from high fat diet also resulted in increased CRF mRNA levels in the CeA [89], similar to the findings of Cottone *et al.* with a sucrose-rich diet [53]. On the other hand, group differences were not observed in other indices of anxiety-like behavior, including marble burying or elevated plus-maze behavior. Additional considerations for interpreting results from this experiment vis-à-vis previously reviewed studies of sugar “withdrawal” include that the palatable diets were provided continuously rather than intermittently; that the high-fat diet here was more preferred than the high-sucrose diet; and that the high-sucrose diet was an admixture of macronutrients, rather than a predominantly or pure sugar diet.

Withdrawal-like signs of anxiety upon removal of a palatable diet also may be moderated by genetic factors. Cottone *et al.* observed stable individual differences in the degree to which rats binged on a high-sucrose diet that correlated with their degree of anxiety-like behavior 24-hr post-access [85]. Pickering *et al.* found that obesity-prone, but not obesity-resistant, rats showed reduced activity in the center of an open field 2 weeks after being switched to a standard chow diet subsequent to 7 weeks of access to a palatable high-fat, high-sugar diet [90]. The obesity-prone animals continued to undereat the chow relative to both chow-only controls and obesity-resistant animals across three weeks of withdrawal.

Rodents withdrawn from preferred diets will also endure negative consequences to obtain renewed access [89, 91]. For example, mice withdrawn from a high-fat diet spent more time in a brightly-lit aversive environment where they can eat a high-fat pellet than did mice not withdrawn from the high fat diet or chow-fed controls [89]. Rats with a history of extended access to a palatable cafeteria diet also did not reduce responding for the palatable diet

despite the presence of a footshock-conditioned cue [91]. The latter behavior resembles the persistence of cocaine-seeking behavior in rodents despite the presence of a cue that predicts footshock. The results suggest the development of compulsive eating patterns, perhaps analogous to compulsive drug intake, that are resistant to potentially aversive outcomes [92].

3.3 Stress-induced food-seeking and intake

Because palatable food can have negative reinforcing, or "comforting," effects, heightened anxiety and stress are not merely consequences of being withdrawn from a palatable diet, but also motivating factors that promote relapse to increased intake after a period of abstinence. By extension, increases in the motivation to obtain, consume and select palatable "comfort" foods under environmental stress can be hypothesized to reflect negative reinforcement processes analogous to those operating during withdrawal from palatable food [49, 54, 93, 94]. The well-established ability of consumption of palatable foods under certain conditions to attenuate exogenous activation of stress systems, as evidenced in behavioral, autonomic, neuroendocrine, and neurochemical measures [94-111], strongly supports this hypothesis.

Perhaps accordingly, the alpha-2 adrenergic antagonist yohimbine, a pharmacological stressor that produces high anxiety states in humans and rodents, and that triggers reinstatement of cocaine-, alcohol-, and methamphetamine-seeking behavior in rats [112-114], also triggers reinstatement of responding for palatable food pellets and sucrose solutions [115-117]. Yohimbine induces reinstatement of seeking for a variety of energy-containing food pellets, including non-sucrose carbohydrate, sucrose and high-fat pellets, but not of energy-devoid and, perhaps also less palatable, cellulose fiber pellets [118]. Multiple neurotransmitter systems have been implicated as downstream modulators of this effect, including the CRF, orexin, and dopaminergic systems. Systemic pretreatment with the CRF_1 receptor antagonist antalarmin strongly attenuates yohimbine-induced reinstatement of palatable food seeking [115], as does pretreatment with the orexin-1 antagonist SB334867[117]. The site(s) of action for these compounds in blocking yohimbine-induced reinstatement remains unknown. Based on the neuroanatomy of stress- or yohimbine-induced reinstatement of drug seeking [119], however, regions involved in the extended amygdala or in inhibitory control are plausible candidates. Indeed, microinjection of CRF into the nucleus accumbens can potentiate cue-induced responding for sucrose [120] and administration of the dopamine D1 antagonist SCH23390 into the dorsomedial prefrontal cortex can attenuate yohimbine-induced reinstatement of food seeking [121].

Stressful environmental conditions also can promote ongoing intake of palatable foods by rodents. Under chronic variable stress, mice select more of their daily caloric intake from a high fat diet, than from high protein or high carbohydrate diet options [111]. CRF_2 deficient mice, which show an exaggerated HPA-axis response to stress, increase their intake of high fat diet following chronic variable stress to a greater degree than do wild type controls, if the high fat diet is provided for 1hr daily rather than *ad libitum*. These mice also show a reduction in CORT release to restraint stress after 2-3 weeks of concurrent exposure to high fat, carbohydrate, and protein diets during chronic variable stress [111].

Boggiano and colleagues have identified a synergistic relationship between food restriction and stress in promoting binge-like food intake in rats that may model the previously reviewed interaction of dietary restraint and stress in triggering binge eating in humans. In the model, neither a history of caloric restriction nor footshock stress alone are sufficient to promote binge-like eating relative to unstressed+unrestricted chow-fed rats. Rather, the combination of repeated cycles of dietary restriction+footshock leads to increased intake of palatable food (cookies) following the stressor [122, 123]. The increased intake is not driven by current metabolic need because the diet schedule allows restricted groups to re-feed on

chow to normal body weight prior to the footshock challenge [124]. If only standard chow is available, no binge-like behavior occurs, but if a small sample of palatable food is provided alongside the standard chow diet, then the rats proceed to binge on chow. These data echo findings from human bulimics, who are much more likely to initiate a binge (on any food) if they first consume a craved food [125]. Other groups have observed similar binge-like behavior following a history of cyclic food restriction if the footshock stressor is replaced with a 15-min period of visual and olfactory exposure to palatable food, during which consumption is not permitted [126]. Although the precise neurobiological changes induced by repeated cycles of restriction, stress, and refeeding remain to be elucidated, endogenous opioids may contribute to the stress-triggered binge-like behavior. Naloxone challenge decreases and the mu/kappa agonist butorphanol increases palatable food intake in the restricted+stressed group specifically [127],

3.4 Loss of hedonic value of previously rewarding stimuli

One of the hallmarks of the “dark side” of drug addiction is the development of tolerance, in which larger and larger quantities of drug are required to produce the same hedonic effect. Lesser quantities are no longer perceived as rewarding. A similar loss of hedonic response to food rewards may occur in animals with a history of palatable food access. Indeed, Hoebel and colleagues observed dramatic increases in glucose intake over successive days of 12-hr limited access and increasingly rapid glucose consumption during the first hour of access, consistent with the development of tolerance and a shift towards binge-like eating [128] Enhanced motivation to obtain the glucose diet was also observed following a two week period of abstinence [47]. Other investigators have since replicated such binge-like escalation that may indicate tolerance using a variety of diets and degrees of limited access [85, 87, 129, 130].

Also potentially resembling tolerance, other previously acceptable rewards become less effective at supporting operant responding and engaging mesolimbic reward circuitry. Rats receiving intermittent access to a chocolate-flavored, sucrose-rich diet develop progressively lower break points when asked to respond for a less preferred, but otherwise palatable, corn-syrup sweetened chow on a progressive ratio schedule [53]. Motivational deficits to obtain the less preferred food are reversed by pretreatment with a CRF_1 antagonist, perhaps analogous to the ability of a CRF_1 antagonist to reverse blunted reward function during nicotine withdrawal [131].

Other evidence of reduced responses to less palatable, alternative rewards comes from microdialysis experiments in which extracellular dopamine levels were measured in rats with a history of cafeteria diet access. Cafeteria-diet feeding results in lower basal levels of dopamine in the nucleus accumbens after 14 weeks of access, and lower stimulation-evoked dopamine release in both the accumbens and dorsal striatum [132]. In chow-fed rats, increases in dopamine efflux were observed in response to a meal of standard laboratory chow, whereas this increase was no longer observed in the cafeteria-diet fed rats. Dopamine efflux in response to an alternative rewarding stimulus, amphetamine, was also markedly diminished in the cafeteria-diet fed rats. The cafeteria diet, however, continued to stimulate dopamine efflux in the accumbens, suggesting that continued consumption of the cafeteria diet is required for these animals to avoid a chronic dopamine release deficit [132]. Intermittency of access to a palatable diet may also impact its ability to sustain striatal dopamine release. In rats with 12-hr intermittent access to sucrose, sucrose continues to stimulate dopamine efflux in the accumbens after three weeks, but this effect is lost in animals with *ad libitum* sucrose access [133].

Intracranial lateral hypothalamic self-stimulation thresholds also increase in rats provided with extended, but not limited, access to a palatable cafeteria diet. [91]. Elevated self-

stimulation thresholds, an index of impaired brain reward function, arise concurrently with the development of diet-induced obesity and persist even after forced abstinence from the cafeteria diet for a period of two weeks. Analogous to previously reviewed findings in humans, striatal dopamine D2 receptor levels are also markedly reduced after extended access to the cafeteria diet; lentivirus-mediated knockdown of D2 receptor expression accelerated the increase in reward thresholds, implicating a causal role for this diet-induced neuroadaptation in subsequent brain reward system dysfunction [91]. Reductions in striatal D2 binding [134] and D2 receptor mRNA [135] have also been observed in response to daily, binge-like limited access to sucrose, while D3 receptor mRNA and dopamine transporter expression are increased [136]. Dampened mesolimbic dopaminergic transmission may have functional implications for risk of weight gain, because obesity-prone rats have lower basal extracellular dopamine levels in the accumbens than do obesity-resistant rats even prior to weight divergence, and injection of a lipid emulsion fails to increase accumbens dopamine levels in the obesity-prone group [137]. In contrast, food restriction is associated with increases in D2 levels in obese Zucker rats [138]. As a whole, the results suggest that palatable food consumption can lead to lasting impairments in brain reward systems.

4. Conclusions

Just as the transition from drug use to dependence is accompanied by a downregulation of brain reward circuitry and a concurrent enhancement of “antireward” circuitry, so does the transition to food addiction appear to involve a “dark side.” Studies of human binge eaters, whose behavior most closely aligns with the current conception of food addiction, have implicated stress and anxious and depressive mood states in the development and maintenance of this transition to consuming palatable food for its negative reinforcing effects.

Animal studies, initiated in large part by Bart Hoebel’s group and now gaining in momentum, have begun to clarify the specific roles of diet schedule, composition, and palatability in altering behavioral, neural, and endocrine stress systems as well as in dampening hedonic responses to food and alternative rewards. However, significant challenges remain. Further work is needed to reach consensus on diagnostic criteria for food addiction in humans. Refinement of such criteria will further the development of suitable animal models to better study the most critical aspects of this disorder.

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Research highlights

- Drug addiction has a substantial “dark side” involving relief from negative states.
- A similar dark side may be critical in the development of food addiction.
- Stress and negative affect can trigger excess consumption of palatable foods.
- Repeated palatable food consumption alters brain reward and stress circuitry.