Towards a Translational Approach to Food Addiction: Implications for Bulimia Nervosa

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Abstract

Purpose of review: In recent years, the food addiction hypothesis of loss-of-control eating has gained traction in the field of eating disorders. In particular, the neural process of food addiction plays a dominant role in the recently formulated "addictive appetite" model of bulimia nervosa and binge eating disorder. Nonetheless, several components of the food addiction hypothesis, including the presence of withdrawal and tolerance effects, as well as the proposition that some foods possess "addicting" properties, remain highly controversial. In response, the current review synthesises existing evidence for withdrawal and tolerance effects in people with bulimia nervosa.

Recent findings: The recent development of a validated tool to measure withdrawal from highly processed foods will aid in measuring withdrawal symptoms and testing hypotheses related to withdrawal in the context of food addiction. We subsequently describe preclinical and human evidence for a central insulin- and dopamine-mediated pathway by which recurrent loss-of-control binge eating is maintained in bulimia nervosa.

Summary: Evidence in populations with bulimia nervosa and loss-of-control eating provides preliminary support for the role of food addiction in the maintenance of bulimia nervosa. Future longitudinal research is needed to develop a clearer profile of illness progression and to clarify the extent to which dysregulation in glucose metabolism contributes to food craving and symptom maintenance in bulimia nervosa.

Keywords: Food addiction; bulimia nervosa; eating disorders; sugar; dopamine

Background

The concept of “food addiction” has received increasing attention in the scientific literature of recent years. While cogent arguments have been made against the establishment of food addiction as a psychiatric diagnosis in its own right [1], there is substantial evidence to suggest that processes similar to those observed in substance abuse disorders play a significant role in the maintenance of eating disorders in which loss of control of eating is a feature (e.g., anorexia nervosa -binge purge type, bulimia nervosa and binge eating disorder) [2]. In this article, we will use bulimia nervosa (BN) as the exemplar. The “Addictive Appetite Model” proposes that three primary processes maintain psychopathology in BN: 1) The high salience of palatable foods [3], which is moderated by a genetic susceptibility to food approach tendencies, reduced efficiency in satiation processes [4], and/or episodes of food restriction; 2) Chronic stress and interpersonal difficulties resulting in a deficiency of alternative rewards and a primed stress system [5]; and 3) Large swings in blood glucose, caused by the consumption of foods with a high glycaemic index, self-induced vomiting or insulin resistance (and insulin omission in diabetes mellitus). These pathways may contribute to compulsive binge eating behaviour through aberrations in dopaminergic function in a similar way to substance addictions.

The current review presents a synthesis of the literature investigating some of the controversial aspects of applying the food addiction paradigm to eating disorders. For instance, there is uncertainty as to whether tolerance and withdrawal criteria for an addictive disorder as specified within the DSM-5 are met. We also present a synthesis of molecular, preclinical, clinical, and neuroimaging evidence illustrating how fluxes in glucose and insulin moderate central dopaminergic functioning.

Does Bulimia Nervosa Meet DSM-5 Criteria for an Addictive Disorder?

The DSM-5 criteria for an addictive disorder are presented in Table 1. The extent to which BN meets these criteria has been reviewed extensively elsewhere [6]. In his 2014 review, Brewerton acknowledges significant phenotypic overlap between disorders of substance dependence and BN but highlights a paucity of systematic clinical evidence for tolerance and withdrawal in the latter, a point frequently cited as a major weakness of the food addiction hypothesis [7]. Much research on tolerance and withdrawal symptoms in humans to date has been largely anecdotal [8]. However, herein we synthesise the evidence from new assessment methods.

Tolerance

The most compelling evidence for food tolerance is demonstrated in animal models, as previously reviewed by Murray, et al. [9]. Rats who voluntarily overeat highly palatable food exhibit evidence of a neural reward deficit due to downregulated dopamine D2 receptors, which worsens as weight is gained [10-12]. This decreased sensitivity to reward is directly linked to the onset of compulsive food seeking in rats [11]. Repetitive bingeing on sucrose interspersed with periods of dietary restriction causes rats to triple their overall daily sugar consumption [13], a finding which may be of particular importance to BN as it is characterised by intermittent fasting and binge episodes [14]. A similar downregulation of dopamine D2 receptors is found in humans addicted to drugs of abuse [15] and is thought to be a key driver of compensatory overconsumption in the Reward Hyposensitivity Theory [16, 17]. Behavioural observations in people with substance use disorders mirror these findings.

Individuals with BN endorse higher levels of tolerance-like symptoms measured using the Yale Food Addiction Scale (YFAS) [8], compared with healthy controls [18, 19]. There are clinical reports of subthreshold BN patients initiating larger and more frequent binge episodes over time [20]. Consistent with these accounts is cross-sectional evidence of the correlation between higher body weight and frequency and severity of binge eating episodes [21]. Individuals with binge-type eating disorders endorse significantly greater levels of eating for purposes of reward enhancement compared with weight-matched controls [22]. Such evidence, although compelling, remains indirect and is insufficient to prove the existence of tolerance in humans.

A preference for intensely sweet food and larger quantities of sweeteners in individuals with BN is a characteristic often presented as an indicator of tolerance [3, 23-25]. Furthermore this preference remains after ingesting a glucose load [26]. Magnetic resonance imaging (MRI) studies indicate hypofunctioning of gustatory and limbic circuitry in BN patients when tasting palatable food compared with controls [27, 28] and compared with individuals recovered from BN [29, 30]. This evidence is consistent with the idea that individuals with BN ingest more food over time because of a decreased sensitivity to sweet taste resulting from repeated binging on hyperpalatable foods [27].

The development of impaired satiety mechanisms may be an indirect indicator of tolerance [6, 31, 32]. For example, a recent functional MRI (fMRI) study found that women in remission from BN exhibited the same response to taste stimuli in brain regions implicated in translating sensory information about taste into motivated behaviour, regardless of whether the individuals were hungry or sated, whilst healthy controls showed an increased response to taste stimuli when hungry versus when fed [33]. The authors also found an increased amygdala response in their remitted BN sample when fed compared to healthy controls, which they propose might project to the hypothalamus and motivate eating in the absence of hunger [33, 34]. It is possible that brain circuitry in BN fails to de-value food reward when in a fed state, leading to eating beyond metabolic need.

Five years on from Brewerton's 2014 review, there remains a paucity of direct evidence of tolerance in humans in relation to food intake and prospective, longitudinal studies are needed.

Withdrawal Syndromes

Preliminary evidence for a withdrawal syndrome in relationship to palatable food comes from animal models. There are consistent observations of strong physical (e.g., forepaw tremor, teeth chattering) and psychological (e.g., aggression, anxiety) withdrawal responses in rats during periods of withdrawal from sucrose [35-37]. The same observations, however, are not found with removal of high-fat foods [38] and have not yet been studied with removal of highly processed foods [39]. Neuroimaging studies show patterns consistent with this behavioural data. Sugar-dependent rats show a significant increase in extracellular acetylcholine and a decrease in dopamine release in the nucleus accumbens shell, as compared to control groups, during a 36-hour period of food deprivation [35], effects which are similar to withdrawal from morphine, nicotine, and alcohol.

Traditionally withdrawal symptoms have not been clearly defined in the context of addictive-like eating, prompting criticism of the food addiction framework [40]. To date, the food addiction field has largely relied on observational and anecdotal clinical reports based on small cohorts or single case studies [41-46] and on self-reported endorsement of withdrawal symptoms on the YFAS [18] and other withdrawal scales [47]. Cross-sectional self-report accounts are consistent in describing physiological symptoms of withdrawal similar to those experienced during opiate withdrawal [8, 48]. Headaches, irritability and flu-like symptoms are reported by individuals abstaining from sugar [42], stomach pains, muscle spasms and shakiness by individuals abstaining or reducing intake of carbohydrates [43, 45], and nausea by individuals abstaining from salted food [49]. Furthermore, tiredness and irritability have been cited as motivating factors for eating [45], providing some suggestion of food being used as a “pick-me-up”, or to avoid an experience of negative feelings of withdrawal.

Symptoms of psychological withdrawal are also widely reported. Cross-sectional self-report accounts from patients with BN reveal that most feel tension, loneliness, and physical symptoms of anxiety before a binge, and the majority feel that their negative psychological states are alleviated whilst engaged in a binge [39]. Longitudinal studies using Ecological Momentary Assessment technology also report that binge eating and subsequent purging are usually preceded by dysphoric mood states [50-52]. However, there is high prevalence of depression and emotion dysregulation in BN populations [53], so it is not clear whether such presentations of low mood represent psychological withdrawal from food. Future research should aim to elucidate whether dysphoric mood states before bingeing are distinct from more permanent mood-related comorbidities, perhaps by comparing depressed versus non-depressed individuals with BN.

The first and only tool to evaluate withdrawal in the context of addictive-like eating has been developed recently: The Highly Processed Food Withdrawal Scale – ProWS [39]. This in part is derived from the premise that specific nutritional ingredients are capable of triggering addictive-like responses [54]. In a pilot study, the ProWS was found to be positively associated with elevated YFAS symptoms, BMI and weight cycling, in a community sample, and responses on the ProWS explained an additional 11.2% of the variance in self-reported dieting success [39]. This tool may help differentiate between the withdrawal effects from different types of palatable food [55, 56] .

The Impact of Glucose Metabolism on Hedonic Eating Behaviour

Preclinical Evidence

Sweet, palatable foods act as an unconditioned rewarding stimulus in humans and rodent models, with evidence suggesting that merely tasting sucrose without digestion produces activation of dopaminergic circuits within the striatum [57]. However, there is evidence to suggest that palatable foods with a high glycaemic index further contribute to the development of compulsive binge eating behaviour through changes in dopaminergic functioning triggered by wide swings in blood glucose. One candidate mechanism for this effect relates to the interaction between insulin and dopaminergic functioning.

The role of mesolimbic dopaminergic functioning in food approach behaviours has been reviewed extensively elsewhere [58]. Dopamine-deficient mouse models exhibit severe aphagia leading to weight loss and death [59]. Conversely the stimulation of dopaminergic activity within the striatum triggers food consumption in rats without enhancing "liking" responses (e.g., lip-licking and paw licking). Thus, dopaminergic functioning is thought to hold a role in food approach behaviours (wanting) that is discrete from the hedonic response to food receipt [60]. In contrast, central insulin suppresses feeding [61]. It is thought that the effects of central insulin and dopamine on food intake, are not independent, but rather interact to regulate hedonic eating behaviour.

Dopaminergic neurons within the ventral tegmental area (VTA) express insulin receptors [62, 63], presenting a possible mechanism by which insulin might influence the dopaminergic induction of feeding behaviour. Furthermore, central insulin enhances the expression of dopamine transporter protein within the VTA via a protein kinase B (Akt) signalling system [64, 65]. The enhanced expression of dopamine transporters on the cell surface induced by insulin exposure is associated with greater dopamine uptake [66], thus reducing levels of synaptic dopamine.

With regards to the effects of insulin on postsynaptic dopaminergic signalling, in vitro studies have found that insulin exposure invokes long-term depression of excitatory signalling within VTA dopamine neurons extracted from male C57BL/6J mice [67]. This effect appears to be long-lasting as, once induced, the long-term depression of VTA dopamine cells is not reversed by application of the insulin receptor antagonist S961 or through a tyrosine kinase inhibitor, which suppresses insulin receptor functioning [67].

The effects of central insulin on dopaminergic functioning within the VTA likely have downstream effects in suppressing feeding, and particularly hedonic feeding. For example, Bruijnzeel, et al. [68] found that injecting insulin directly into the VTA of female rats decreased 24-hour food intake. Mebel, et al. [69] have similarly found that injecting insulin directly into the VTA suppresses subsequent feeding in male C57BL/6J mice; however, this effect was dependent on the hunger status of the animals. That is, insulin in the VTA suppressed the quantity of sweetened high fat food consumed by sated mice but did not affect normal chow intake in hungry mice. This pattern of effects therefore suggests that insulin activity in the VTA acts selectively to suppress subsequent hedonic feeding, with weaker evidence for effects on homeostatic feeding behaviour.

Central insulin functioning may play a role in blocking the memory of palatable food reward or attenuating the incentive salience of cues associated with palatable food. Evidence for this hypothesis comes from studies demonstrating that injecting insulin either into the cerebral ventricles [70] or VTA [67] of rats at the time of memory retrieval reduces conditioned place preference for palatable food. Furthermore, Bruijnzeel, et al. [68] found that injecting insulin at a dose of .005mU/side into the VTA elevated the reward threshold for intracranial self-stimulation, thus indicating a reduction of reward functioning.

Evidence in Humans

Insulin resistance impacts on central dopaminergic systems in humans. For example, Dunn, et al. [71] conducted a positron emission tomography (PET) study using the dopamine D2/D3 receptor radioligand [18F]fallypride, and found that insulin sensitivity is negatively correlated with dopamine type 2 receptor availability in the ventral striatum in a heterogeneous sample of lean and obese women. In men, Anthony, et al. [72] found that exogenously administered insulin increases metabolism in the ventral striatum and prefrontal cortex, while decreasing metabolism in the right amygdala, hippocampus, and cerebellar vermis. Furthermore, the effect of insulin in increasing metabolism in the ventral striatum and PFC was lower in insulin-resistant, versus insulin-sensitive participants [72]. This pattern of findings is thus indicative of trait-level differences in the effects of central insulin on dopaminergic mesolimbic regions, known to be critical for food craving and food approach behaviour [59, 73].

Interactions between insulin resistance and central dopaminergic functioning may have functional significance for food craving in humans. Chechlacz, et al. [74], in an fMRI study, found that people with Type II diabetes mellitus (characterised by insulin resistance) exhibit greater blood oxygenated level dependent (BOLD) response to food versus non-food images in the insula, orbitofrontal cortex (OFC), and basal ganglia, when compared to people without diabetes mellitus. Moreover, this increased activation within the insula and OFC is positively correlated with self-reported external eating. These findings, taken together, thus provide evidence that insulin resistance, commonly observed following repeated excess consumption of fructose in combination with an overall excessive energy intake [75], is positively correlated with a pattern of neural response to food stimuli which is associated with greater external cue-driven eating. However, it should be noted that the correlational nature of these findings limits the ability to draw firm causal inferences. Although there is relatively less evidence regarding food craving in Type I diabetes, an fMRI study has found that insulin detemir, which more readily enters the brain compared to standard forms of insulin, is associated with reduced BOLD response to food images in the bilateral insula, a brain region associated with the regulation of appetite [76]. The authors have speculated that insulin detemir may therefore induce a more effective satiety reaction, thus explaining the reduced levels of weight gain observed in people with Type I diabetes mellitus taking insulin detemir [77].

In a related study, Jastreboff, et al. [78] recruited 25 men and women in the obese weight range and 25 lean controls. Fasting insulin and glucose were taken to measure insulin resistance. During a subsequent fMRI task, audio scripts designed to provoke relaxing imagery or favourite food imagery were played. Food craving was assessed before and after each imagery trial. The degree of food craving following food imagery trials was positively associated with insulin resistance in the obese, but not lean, participant group. Furthermore, the relationship between insulin resistance and food craving within the obese participant group was mediated by BOLD responses in dopaminergic regions including the ventral tegmental area (VTA) and substantia nigra. These studies suggest that insulin resistance moderates craving and associated neural circuits in response to food related imagery.

Thus, the above studies illustrate that interactions between central insulin and dopaminergic systems, known to impact on feeding behaviour in animals, also regulate food craving in humans. While this evidence therefore supports a potential mechanism linking the short- and long-term physiological effects of sugar consumption to food craving in humans, it is also of interest to disentangle the effects of sweet taste on dopaminergic incentive sensitisation from the physiological effects of sugar in food approach behaviour in humans. In support of the physiological effects of glucose consumption on central dopaminergic functioning, regardless of sweet taste. Haltia, et al. [79] found that the intravenous administration of glucose, versus placebo, was associated with increased D2 receptor binding potential in the right caudate nucleus and bilateral putamen in both lean and overweight women. However, intravenous glucose administration was rather associated with reductions in D2 receptor binding potential in the bilateral caudate nucleus, left putamen, and right thalamus. It should be noted that the intravenous method of administration employed in this study bypassed the gastrointestinal system, thus failing to stimulate the production of gastrointestinal hormones, such as glucagon-like peptide 1, which also impact on appetitive functioning [80, 81]. This study is therefore limited in the extent to which it directly bears upon the oral consumption of glucose versus calorie-free sweet taste. Nonetheless, these findings provide evidence for the impact of glucose on mesolimbic dopaminergic functioning in the absence of sweet taste. The functional significance of the sexual dimorphism in brain response is not yet clear and would be an interesting avenue for future research.

In another PET study conducted in nineteen participants with BMIs ranging from the lean to obese weight range dopamine functioning was measured following the consumption of a 75g oral glucose drink versus a calorie-free sucralose drink of equal volume and sweetness. Within the lean participant group, consuming the glucose drink, versus the calorie-free sucralose drink, was associated with increased dopaminergic binding potential within the ventral striatum, while the opposite was observed in the obese participant group (Wang, et al. [82]. Thus, there is evidence that glucose impacts upon dopaminergic functioning separately from the effects of sweet taste alone, with BMI modulating the direction of that effect. The reduced activation stimulated by sugar consumption in obese participants is in line with previous evidence of down-regulated striatal response to the receipt of sugar solutions, including chocolate milk and milkshakes [83, 84].

There is a relative paucity of research investigating the effects of glucose metabolism on dopamine-mediated feeding in BN and binge eating disorder without obesity. A recent meta-analysis of studies analysing insulin sensitivity in BN and binge eating disorders has found significantly reduced insulin sensitivity in both disorders [85]. Such insulin resistance therefore leads to greater flux in blood glucose following the consumption of foods with a high glycaemic index, thus potentially contributing to food craving in a similar manner to that described above for populations with obesity [78]. The effect of insulin resistance on glucose flux is further exacerbated by the wide swings in blood glucose induced by intermittent fasting followed by objectively large binge eating episodes in people with BN [86]. Frank, et al. [87] found evidence of some trait differences in brain response to glucose, with participants recovered from BN exhibiting suppressed BOLD response to a glucose, versus artificial saliva solution, in the anterior cingulate cortex and left cuneus in comparison to the control group. However, this study is confounded by the difference in sweet taste as well as nutritional content (glucose versus calorie-free liquid). It will therefore be critical to carry out similar research to that described above for obesity in populations with bulimia-spectrum disorders in order to clarify the functional role of a glucose metabolism pathway in loss-of-control binge eating versus the chronic overeating which commonly characterises overweight and obesity.

Conclusion

The current literature review has thus far served to illustrate the existing state of the evidence with regards to food tolerance and withdrawal effects in BN. Additionally, preclinical and preliminary evidence in human studies has elucidated an insulin-dependent mechanism whereby foods with a high glycaemic index interact with mesolimbic dopamine systems and heighten food craving in cases of insulin dysregulation. Nonetheless, there are several lines of evidence that should be explored further before definite conclusions can be drawn with regards to withdrawal and tolerance in BN and the physiological mechanisms which maintain addictive responses to palatable food.

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Table 1. DSM-5 criteria for an addictive disorder (American Psychiatric Association, 2013)

Criteria 1.	The substance is often taken in larger amounts or over a longer period than was intended
Criteria 2.	There is a persistent desire or unsuccessful efforts to cut down or control use of the substance
Criteria 3.	A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects
Criteria 4.	Craving, or a strong desire or urge to use the substance
Criteria 5.	Recurrent use of the substance despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of its use
Criteria 6.	Continued use of the substance despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of its use
Criteria 7.	Important social, occupational, or recreational activities are given up or reduced because of use of the substance
Criteria 8.	Recurrent use of the substance in situations in which it is physically hazardous
Criteria 9.	**Tolerance, as defined by either of the following:** **(a) A need for markedly increased amounts of the substance to achieve intoxication or desired effect** **(b) A markedly diminished effect with continued use of the same amount of the substance**
Criteria 10.	**Withdrawal, as manifested by either of the following:** **(a) The characteristic withdrawal syndrome for other substance** **(b) The substance (or a closely related substance) is taken to relieve or avoid withdrawal symptoms**