



Bulimia nervosa and evidence for striatal dopamine dysregulation: A conceptual review

Allegra I. Broft*, Laura A. Berner, Diana Martinez, B. Timothy Walsh

Columbia University College of Physicians and Surgeons, 630 W. 168th Street, New York, NY 10032, USA
New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY 10032, USA

ARTICLE INFO

Article history:

Received 9 March 2011
Received in revised form 15 April 2011
Accepted 20 April 2011

Keywords:

Bulimia nervosa
Eating disorders
Dopamine
Reward
Substance abuse
PET imaging

ABSTRACT

Objective: This article reviews concepts and evidence, based in particular on the work of Bartley G. Hoebel and colleagues, which suggest that a better understanding of the role of striatal dopamine (DA) in the initiation and/or maintenance of bulimia nervosa (BN) may result in a clearer characterization of mechanisms underlying BN.

Methods: Literature review, using PubMed search.

Results: Several lines of evidence, including the work of Bartley G. Hoebel, implicate the importance of striatal DA in feeding behavior, as well as in the disordered eating behaviors relevant to BN. Preclinical models of 'BN-like' eating behaviors have been associated with changes in striatal DA and DA receptor measures. Emerging clinical research also suggests that striatal DA abnormalities exist in individuals with BN.

Conclusion: Alterations in striatal DA may exist in patients with BN. While the precise relationship between these findings and the etiology and maintenance of bulimic symptomatology remains unclear, further investigation of brain DA systems is a fruitful avenue of future research in BN.

© 2011 Elsevier Inc. All rights reserved.

1. Introduction

Bulimia nervosa (BN) is a common disorder among women (lifetime prevalence in women of approximately 1.5% [1]), which continues to lack a comprehensive pathophysiological model. This brief review focuses on what is known about the potential role of striatal dopamine (DA) in the neurobiology of BN, with emphasis on what Bartley G. Hoebel and colleagues' preclinical studies of food reward may suggest for future studies in BN. Animal models of the neurobiology of substance use disorders have been translated into human studies, such as neuroimaging studies, with promising results. Likewise, studies elucidating the biological basis of food reward, including those conducted by Hoebel and colleagues, may form a basis for a similarly translational approach to the neurobiology of BN, a disorder in which aspects of the compulsive binge eating of food, and compensatory behaviors, resemble addictive behavior.

BN is characterized behaviorally by frequent episodes of binge eating, or eating an unusually large amount of food within a discrete period of time and experiencing a sense of loss of control, combined with inappropriate compensatory measures (e.g. vomiting, abuse of laxatives, diuretics, or excessive exercise) [2]. Between binges, in-

dividuals with BN often restrict their intake or fast [3]. A substantial portion of what is known to date about the neurochemistry of cycles of binge eating and restricting is due to the large body of Bartley G. Hoebel's preclinical work. As early as 1989, Dr. Hoebel posited that "bulimia [nervosa] with vomiting may be a similar addiction to reward [as seen with intraaccumbens amphetamine and cocaine] that bypasses satiety; food without absorption, dopamine without calories" [4]. Two decades later, considerable efforts by Dr. Hoebel and colleagues have begun to elucidate the neurochemical consequences of repetitive overconsumption of high sugar foods that models the binge eating seen in BN. The neurochemical changes, particularly those involving dopamine and opioids, that he and his colleagues have observed are similar to those seen in addictive disorders. These efforts are but one small part of Dr. Hoebel's lifetime commitment to understanding reward-related behaviors, neurobiological changes in response to rewards, and the neurobiology of addiction.

While multiple other neurotransmitter systems are also involved in feeding processes and satiety (including serotonin, acetylcholine, glutamate, and gamma-aminobutyric acid), we focus here on striatal DA's potential involvement in BN, as there is a large body of evidence suggesting DA's role in food reward, substantial evidence indicating the role of striatal DA in addictive disorders, and a phenomenological overlap between addictive disorders and eating disorders. Further, the work of Dr. Hoebel and colleagues has significantly contributed to our understanding of striatal DA function in dysregulated eating behavior; indeed, this body of research indicated DA's relevance to the etiology, maintenance, and treatment of BN and has laid crucial preclinical

* Corresponding author at: Eating Disorders Research Unit, Columbia University College of Physicians and Surgeons, 1051 Riverside Drive, Unit 98, New York, NY 10032, USA. Tel.: +1 212 543 6147 (office); fax: +1 212 543 5607.

E-mail addresses: aib8@columbia.edu (A.I. Broft), lab88@drexel.edu (L.A. Berner), dm437@columbia.edu (D. Martinez), btw1@columbia.edu (B.T. Walsh).

groundwork for human neuroimaging studies of eating disorders. Preclinical and clinical evidence for a role for striatal DA in the disordered eating behaviors relevant to BN will be reviewed.

2. Overview: relevance of addictive disorders to BN

The relationship between BN and substance use disorders has long been of interest to clinicians and clinical investigators, for several reasons. The clinical features of BN bear significant similarities to those of substance use disorders. The binges of individuals with BN are often described as a source of relief from depression or anxiety, just as drugs of abuse are sources of relief from these negative moods for their abuser [5,6]. Binge eating, like abusing drugs, purportedly serves as a way of moving from a state of anxiety, anger, sadness, or nervousness to one of calm and relaxation and as such can be qualified as a type of reward-mediated behavior [7]. Like maladaptive substance use behaviors, recurrent binge eating interferes with normal life, is often done in secret, can lead to significant morbidity via compensatory behaviors, and involves intense cravings for binge “highs” followed by stress and guilt [8]. Both binge-eating disorders and substance dependence are characterized by loss of control, high rates of relapse, compulsivity, and continuation of a behavior despite its known negative consequences [6]. Patients who binge eat report withdrawal-like feelings of panic and distress when required to delay their binge eating behaviors, and a sense of deprivation with abstinence [7]. Patients even claim that removing certain foods from their diet can result in symptoms of withdrawal such as headaches, sweats, irritability, and panic [8].

Though beyond the scope of this review, several other lines of clinical evidence suggest the overlap between eating disorders and substance use disorders, including epidemiological data [1], some family history studies [9], and semi-starvation studies indicating the role of food restriction in augmenting substance use in humans [10]. It should also be acknowledged that some lines of clinical evidence are not as consistent with the notion of etiological similarity between substance use disorders and eating disorders [11,12]. However, overall, the clinical similarities between the two disorders strengthen the case for the possibility that a neurobiological model of addictive behavior may also bear some relevance to BN.

3. Striatal dopamine in reward and addictive processes: possible relevance to BN

A large body of scientific work suggests that striatal DA is a key neurotransmitter in the neurobiological regulation of consumption of both food and drug rewards. While a detailed description of DA reward circuitry and function is beyond the scope of this paper, a brief review will provide a model for subsequent consideration of the ways in which DA may be involved in the pathophysiology of BN.

DA is released by neurons originating in the ventral tegmental area and substantia nigra, and these neurons project to dorsal striatum, ventromedial striatum (including nucleus accumbens), and prefrontal and other cortical regions. The distinction of DA function in striatal subregions is somewhat limited due to functional overlap [13]. However, DA projections to these various subregions are thought to play somewhat distinct roles. Dorsolateral striatal circuits appear to mediate aspects of habitual reward processing, while accumbens DA released at the time of receipt of a novel reward (food or otherwise) appears to be involved in learning associated with the reward, including the conferral of salience of that reward, the association of the pleasure of that reward with desire, and the learning of behaviors associated with acquiring that reward (reviewed in Ref. [14]). Repeated increases in levels of DA (from repeated exposure to rewards) may serve to mediate the shifting of attentional bias towards cues associated with reward. Additionally, striatal DA release appears to shift over time, to occur more predominantly in response to cues rather than the reward itself [15].

Within the substance abuse literature, “non-natural” rewards (i.e. drugs of abuse) release unusually high levels of DA in reward-related circuits, which may confer a ‘better than expected’ signal, stimulating over-learning of behaviors, cues, and desire related to these non-natural rewards [14]. Preclinical studies of repeated drug taking have shown sustained striatal DA in response to drugs of abuse [16]. At the same time, clinical neuroimaging studies have consistently shown that the chronically-addicted state is characterized by (1) low levels of ventral and/or dorsal striatal dopamine (as elicited by pharmacological “challenge” with psychostimulant medications), and (2) low striatal levels of the dopamine type 2 (D2) receptor (for review see Ref. [17]). Further, in these clinical neuroimaging studies, low striatal DA has been associated with the repetitive choice to use cocaine, indicating that low levels of striatal DA may be related to the inability of addicted patients to flexibly switch between and/or learn alternative rewarding behaviors [18].

In considering the relevance of DA theories of reward and substance abuse to the generation of a model for neurochemical contributors to BN, at least three BN-related behaviors might be considered. First, the binges of individuals with BN often consist of foods high in sugar and fat [19], such as cookies, cakes, and potato chips. One question regarding the ‘compulsive’ ingestion of some of these foods by patients who suffer from BN is whether these foods themselves may be associated with neurochemical responses similar to those seen in drug abuse, thus contributing to the pathophysiology of the disorder.

Secondly, food restriction is also a component of BN (as elaborated below), and may itself be “rewarding,” or otherwise interact with reward circuitry. The way in which food restriction may be “rewarding” to individuals with BN likely differs, at least to an extent, from how traditional primary reinforcers (e.g. food) are neurobiologically experienced and processed. However, in patients with eating disorders, regular decision-making which favors food restriction and weight loss may be experienced with a sense of pride, pleasure, or other positive psychological reinforcement [20]. Supported in part by functional magnetic resonance imaging (fMRI) evidence in anorexia nervosa showing high ventral striatal activation in response to viewing underweight images [21], Zink and Weinberger [22] have speculated that the DA-ventral striatal circuits may contribute to the inappropriate assignment of desire and pleasure to food restriction. While it is difficult to test this notion of “thinness as a psychological reinforcer” in preclinical models, the reward sensitivity changes associated with food restriction itself may contribute to the inappropriate attribution of salience to more ‘abstract’ rewards such as thinness. More empirically explored is the possibility that food restriction enhances the rewarding effects of a binge, a phenomenon which appears to be relevant to BN, and which has been explored in preclinical testing, notably by Hoebel and colleagues.

Thirdly, the self-induced purging behavior of BN may be “rewarding,” though this notion is highly speculative. Though based primarily on clinician reports and not yet supported by more rigorous, controlled human study (e.g., using ecological momentary assessment), purging may also, in some patients, be positively reinforcing via subjective effects including a “high,” and negatively reinforcing via relief from negative affect [20,23]. Characterization of such phenomena in the clinical literature is sparse. A question relevant to the role of purging in BN, however, is whether the act of purging itself alters subsequent sensitivity to food reward, and if so, whether this is mediated by a neurochemical change (in striatal DA, or other neurochemical substrates).

This last possibility (self-induced purging) is particularly difficult to model and study neurochemically, especially in animal studies. However, preclinical models of the first two of these behaviors (binge eating and food restriction) have been modeled by Hoebel and colleagues, and have indicated striatal DA changes related to these behaviors, as reviewed below.

4. Preclinical studies of dopamine abnormalities relevant to BN

4.1. Preclinical studies of 'BN-like' behaviors

While limited in modeling the psychological complexity of BN, animal models, like those used by Hoebel and his colleagues, have been developed to study some of the key behavioral features of BN, such as food restriction alternating with overconsumption of food, or limited access to food rewards (such as high sugar solutions) paired with ad libitum access to standard rodent chow. In utilizing limited-access schedules to food reward, these eating disorder models have found marked changes in sweet-reward ingestion behaviors, as well as changes in brain DA systems, similar to those found in animal models of addictive disorders (see Refs. [24,25] for comprehensive reviews). For example, a group of related studies of such a model, in rodents, has found (a) increased DA transporter density selective to the regions of the nucleus accumbens and the ventral tegmental area (the site of DA presynaptic cell bodies) [26], and (b) increased DOPAC/DA (a marker of DA turnover) in the nucleus accumbens [27].

Hoebel and his collaborators further expanded upon our understanding of the involvement of DA in binge eating. Rada et al. examined the possibility of a 'sensitized' DA response to this eating paradigm more directly: this study reported that the 130% rise in extracellular DA associated with novel exposure to sucrose ingestion extinguished over time in control groups but not in "binge eating" rodents maintained for 21 days on a paradigm that alternated 12-hour food deprivation and 12-hour 10% sucrose access [28]. Further, animals maintained on a schedule of alternating deprivation/access to sucrose have shown cross-sensitization with amphetamine [29].

Taken together, the findings support the possibility of neurochemical "sensitization" to food reward — i.e. persisting elevated DA response to reward, a finding classically associated with animal models of repeated drug taking. Though preliminary, these findings could, by extension, provide an indication of a neurobiological similarity between substance use disorders and the overeating of high-sugar foods, such as that seen in BN.

4.2. Preclinical studies of the effects of food restriction on DA

Though arguably more relevant to anorexia nervosa, food restriction is also hypothesized to be a key component the development and maintenance of BN. Many patients with BN have a history of premorbid AN, and/or oscillate between diagnoses of BN and anorexia nervosa, binge-purge subtype [30]. Cognitive behavioral treatment for BN (the treatment with greatest empirical evidence of success for the disorder), features food restriction prominently in the model of onset of illness, and a key component of the work is in helping patients to relax dietary restriction outside of binge episodes [31]. Additionally, many individuals with BN restrict their intake to the extent that significant weight loss results: the relative discrepancy between past highest and current weight, which Lowe named "weight suppression", has been repeatedly found to be high (between 9.6 kg and 12.0 kg in women with BN) [32,33]. Taken together, these findings suggest that food restriction features prominently in BN, and that the consequences of food restriction (alone) on the DA system may be of relevance to its neurobiology.

Pothos et al. reported that basal extracellular levels of DA in the nucleus accumbens were reduced by as much as 50% in adult male food-restricted rats. This change was not seen in the dorsal striatum. Following amphetamine administration, accumbens DA release was higher in the underweight animals relative to DA release in normal-weight rats. Conversely, DA release was reduced in underweight vs. control rats in response to less-potent releasers of DA (e.g. a meal, morphine) [34,35]. Consistent with these findings, other studies have found that cocaine or amphetamine given to adult male food-restricted rats produced locomotor sensitization [36], as well as sensitization of DA

response in the nucleus accumbens core region. In contrast to these findings, food restriction in adolescent female rats resulted in a reduced DA response to methamphetamine, as measured by micro-PET imaging [37]. The reason for such a discrepancy is unclear, and may be related either to a difference in the tool used for the measurement (dialysis vs. PET), or may be a gender-related discrepancy.

Finally, in a paradigm combining food restriction with binge-like eating behavior, Dr. Hoebel's former graduate student and continued collaborator, Nicole Avena, found that rats that had daily intermittent access to palatable food following the previously described Colantuoni access model [38], when reduced to 85% body weight via food restriction, released more extracellular DA in the nucleus accumbens shell in response to drinking a 10% sucrose solution compared to both their own normal-weight baseline values and to normal-weight controls [39]. These findings again support the notion of a sensitized DA response in a "BN-like" and/or underweight condition. Taken together, while food restriction may not be equivalent to the chronic dieting state of BN (especially given that patients with BN are not markedly underweight in absolute terms, by current convention of the definition of the disorder), there is evidence to suggest that chronic food restriction may, in itself, alter DA response to reward exposure. Though speculative, it could follow that such neurochemical changes induced by food restriction could predispose to increased vulnerability to maladaptive reward seeking (e.g. binge eating).

4.3. Preclinical studies of brain DA receptors and binge eating

Alterations in reward-related DA receptor systems related to abnormal eating processes have been reported. Hoebel and his colleagues were among the first to report findings of altered DA receptor binding with binge eating. For example, animal models have found that binge eating of sugar results in increased dopamine type 1 (D1) receptor binding, increased D3 mRNA in the nucleus accumbens, and decreased D2 receptor binding in the striatum [38,40,41] — changes similar to those seen in animal models of repeated drug taking. Consistent with the finding of increased accumbens D3 mRNA in binge eating rodents, blockade of D3 receptors decreased food intake in obese (and lean) rats [42]. A recent microPET study of food-restricted rodents associated increased D2 receptors with the food restricted state [43], while another intriguing recent study reported low striatal D2 receptors in obese rodents, and that a striatal D2 receptor knockdown rodent model hastened the development of compulsive eating of palatable food [44]. Additionally, a recent study of D2 blockade, in an intermittent-access feeding model, demonstrated that D2 blockade (by raclopride) stimulated fat intake [45]. Taken together, these findings further suggest the presence of alterations in accumbens DA transmission in maladaptive eating states; as with other findings described previously, these receptor changes and effects bear resemblance to findings seen in animal models of repeated drug taking.

4.4. Preclinical studies of brain DA related to purging

Preclinical models of self-induced purging have inherent limitations, namely that rodents are incapable of the self-induced vomiting seen in BN. However, at least one study from Bartley G. Hoebel and colleagues has examined striatal DA and acetylcholine responses in sham-fed rodents maintained on a binge-eating schedule [46]. In these rodents, a fistula allows for 'purging' via draining of gastrointestinal contents. In this study, sustained DA responses to sucrose taste was overall similar between sham-fed and real-fed rodents, suggesting that the sensitized DA effect was attributable to preingestive effects (i.e. taste), as opposed to postingestive effects (such as volume ingested). Additionally, the accumbens acetylcholine satiety response was blunted in the sham-fed rodents, suggesting acetylcholine as an alternate neurotransmitter, specific to purging, which may promote further binge eating [46]. This study complements other sham-feeding studies, such as the study of

Hajnal et al. [47], which demonstrated that accumbens DA increases with escalating sugar concentrations, but overall does not support the notion of striatal DA alterations specifically related to presence of purging behavior, given the lack of difference in DA response between the sham-fed and real-fed groups.

5. Alterations in DA in patients with BN and related eating disorders

A few studies of striatal DA in patients with eating and weight disorders have been conducted. Neuroimaging methods, particularly PET (positron emission tomography) or SPECT (single photon emission computed tomography) neurochemical imaging, provide one of the most direct methods for measuring brain neurochemistry in clinical populations. No studies investigating the DA circuitry of subjects with BN using PET technology have been published to date, though one study, using SPECT, found a 15% reduction in DA transporter availability in the striatum of individuals with BN [48]. This preliminary finding, however, is limited by its inclusion of individuals with subthreshold DSM-IV-TR diagnosis of BN, delivery of some treatment and symptom remission prior to scanning, and non-matched healthy controls. Other imaging studies exist that implicate striatal DA's involvement in BN more indirectly, including a functional MRI study indicating altered striatal activity in BN during reward-related tasks [49], and another suggesting incomplete activation of cortico-striatal-thalamo-cortical loops, including loops involving the caudate, in BN during a self-regulatory control task [50]. Taken together, these studies complement previous findings of low CSF DA metabolites in BN which were associated with binge eating frequency, suggesting alterations in brain DA during illness which may specifically be related to the core eating pathology of BN [51].

No imaging studies investigating the role of DA in binge eating disorder (BED) have yet been conducted, which may also bear relevance to the neurochemistry subserving the overeating component of BN. However, a significant proportion of individuals with BED are overweight or obese [52], and among obese individuals, striatal D2 receptor binding potential (BP, a measure of receptor density) is decreased, as measured by PET [53]. D2 receptor BP was inversely associated with body mass index in these subjects, suggesting that low striatal D2 receptor BP might be associated with increased food consumption [53]. Differences by striatal subregion were not reported, nor was status of eating disorder symptomatology (e.g. presence of objective binge eating), which indicates that further study will be required to disentangle the dopaminergic effects of weight status from those of binge eating behavior. Additionally, as previously noted, purging itself may also interact with reward-related transmitters, though no studies to date have directly investigated DA system abnormalities in individuals who engage in purging behaviors without objectively large binge eating episodes.

Though few studies have been conducted overall of striatal DA measures in BN, these preliminary clinical findings suggest disturbances of striatal dopaminergic systems in eating and weight pathology relevant to BN.

6. Conclusions

There is growing evidence to suggest a role for abnormalities in brain DA in BN. The studies of Bartley G. Hoebel and colleagues, utilizing preclinical models of “BN-like” eating behavior, including binge eating and restrictive eating, have revealed changes in striatal DA release and receptor binding which appear similar to those seen in response to drugs of abuse. The biobehavioral link established between binge consumption of palatable food and DA-related changes has not only led to further preclinical study but also inspired neuroimaging studies of human subjects with BN that have begun to demonstrate indirect evidence of striatal DA alterations.

BN, like other psychiatric disorders, is likely to emerge from a complex interaction of predisposing, precipitating, and perpetuating factors. In the substance use disorders, dopaminergic factors such as sensitized DA response to drugs, low striatal D2 receptors, and low striatal DA transmission, have been observed in preclinical and/or clinical studies, and are thought to serve as predisposing and/or perpetuating factors. Predisposing factors to BN are likely to be multifactorial, and may include gender, genetics, preexisting personality traits (e.g. perfectionism, anxiety), and cultural/environmental pressure to be thin, amongst other factors [54]. Precipitating factors for BN are likely to relate to some of the known risk factors for BN, including “thin ideal internalization, higher BMI, neuroticism, weight teasing, social pressures, and negative life events” (summarized in Ref. [54]). Speculatively, other factors, such as a high-sugar/high-fat food supply (perhaps only intermittently consumed), may come into play, leading to repeated ‘better than expected’ striatal DA signaling and subsequent maladaptive overuse of food reward (i.e. binge eating). The studies of Hoebel and colleagues indicate neurochemical changes (i.e. sensitization) in response to repeated, intermittent high-sugar ingestion, which are consistent with this hypothesis. Further, an overvalued desire for a thin ideal may also be present prior to the onset of BN, with success in dieting (i.e., chronic mild food restriction) leading to weight suppression, as described by Lowe and others, which subsequently leads to additional modulation of DA reward circuits, as seen in the reviewed preclinical work. In later stages of BN, low levels of striatal DA (as seen in clinical neuroimaging studies of substance use disorders, and as supported by the few published neurochemical studies of DA measures in BN to date) may contribute to impairment in shifting between alternative rewards. This may in turn render the development of more adaptive eating patterns, and thus recovery from BN, difficult. Low numbers of striatal DA type 2 receptors, suggested by the clinical neuroimaging literature and some preclinical studies to be a possible contributing factor to the development of substance use disorders and obesity, may further predispose individuals to binge eating as well.

Clinical neuroimaging studies provide one of the most direct routes for evaluation of neurochemical measures in clinical populations. Beyond Tauscher and colleagues' SPECT study, there are still no published imaging studies in BN similar to those that have been conducted in obesity and substance use disorders, such as PET neurochemical imaging studies. Given the potential parallels between substance use disorders and BN previously discussed and similar findings from preclinical models of binge eating, one might expect to find DA alterations in reward-related brain regions in BN similar to those previously found in multiple PET imaging studies of substance use disorders in humans (i.e. low striatal D2 receptors; low striatal DA transmission [17]), and for such alterations to be associated with extent of eating disorder symptomatology.

One critical question which frequently emerges in the consideration of overlap between eating disorders and addictions is: how does this characterization lead to the successful treatment of eating disorders? With successful treatment, drugs can be removed from an addict's environment, while food and eating are necessary for life. This remains an irrefutable reality, which may make recovery from an eating disorder particularly difficult. Indeed, Bartley G. Hoebel's recognition, though a lifetime of work, of the interaction of sucrose with reward systems, gives biological credence the struggle of cessation of binge eating, particularly in the context of our current high-sugar/high-fat food environment. It may be of note that psychotherapy treatments which stress engagement in alternative activities that are positively reinforcing (as is emphasized in Cognitive Behavioral Therapy) are some of the best validated treatments to date, both for substance use and for BN. Although abstinence is not a possibility for eating as it is for drugs of abuse, the development of a regular pattern of eating aimed at eliminating both binge consumption and periods of restriction, both of which have been demonstrated

to affect the striatal DA system, is also a key element of Cognitive Behavioral Therapy. Further investigation of the ways in which our growing knowledge of DA's involvement in the phenomenology of BN can inform treatment development may be of interest.

In conclusion, preclinical evidence from Bartley G. Hoebel and colleagues, as well as limited evidence from clinical populations with eating pathology, supports the broad hypothesis of striatal DA circuitry involvement in BN. Additional translational studies that build upon this research would be of great interest in furthering our neurobiological understanding of BN, a disorder in which few maintaining factors have been identified.

Financial disclosures

Dr. Broft, Dr. Martinez, and Ms. Berner report no biomedical financial interests or potential conflicts of interest. Dr. Walsh has received research support from AstraZeneca.

Acknowledgments

The authors respectfully acknowledge Bartley G. Hoebel, Ph.D., for his longstanding commitment to the science of eating, and for preclinical research that lays groundwork for reward-related translational research approaches in eating disorders. The authors would also like to thank Evelyn Attia, MD, Nicole Barbarich-Marsteller, PhD, Michael Devlin, MD, Diane Klein, MD, Laurel Mayer, MD, and Joanna Steinglass, MD for their contributions to this manuscript. This publication was made possible by NIMH grants T32MH15144, R21MH65024, and K23MH082097, a 2006 NARSAD Junior Investigator Award, and grant number KL2 RR024157 from the National Center for Research Resources (NCR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCR or NIH. Information on NCR is available at <http://www.ncr.nih.gov/>. Information on Re-engineering the Clinical Research Enterprise can be obtained from <http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp>.

References

- Hudson JL, Hiripi E, Pope Jr HG, Kessler RC. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. *Biol Psychiatry* Feb 1 2007;61(3):348–58.
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fourth edition – text revision. Washington DC: American Psychiatric Association; 2000.
- Davis R, FR, Garner D. A naturalistic investigation of eating behavior in bulimia nervosa. *J Consult Clin Psychol* 1988;56(2):273–9.
- Hoebel BG, Hernandez L, Schwartz DH, Mark GP, Hunter GA. Microdialysis studies of brain norepinephrine, serotonin, and dopamine release during ingestive behavior. Theoretical and clinical implications. *Ann NY Acad Sci* 1989;575:171–91 discussion 192–173.
- Heatherton TF, Baumeister RF. Binge eating as escape from self-awareness. *Psychol Bull* Jul 1991;110(1):86–108.
- Gold MS, F-PK. Overeating, binge eating, and eating disorders as addiction. *Psychiatr Ann* 2003;33(2):117–22.
- Huebner H. Endorphins: eating disorders and other addictive behaviors. New York: W. W. Norton and Company; 1993.
- McAleavey KMAFM. Eating disorders: are they addictions? A dialogue. *J Soc Work Pract Addict* 2001;1(2):107–13.
- Holderness CC, Brooks-Gunn J, Warren MP. Co-morbidity of eating disorders and substance abuse review of the literature. *Int J Eat Disord* Jul 1994;16(1):1–34.
- Keys A, Brozek J, Henschel A, Mickelsen O, Taylor HL. The biology of human starvation, Vol 2. Minneapolis, MN: The University of Minnesota Press; 1950.
- Kaye WH, Lilienfeld LR, Plotnicov K, Merikangas KR, Nagy L, Strober M, et al. Bulimia nervosa and substance dependence: association and family transmission. *Alcohol Clin Exp Res* Aug 1996;20(5):878–81.
- Kendler KS, Walters EE, Neale MC, Kessler RC, Heath AC, Eaves LJ. The structure of the genetic and environmental risk factors for six major psychiatric disorders in women. Phobia, generalized anxiety disorder, panic disorder, bulimia, major depression, and alcoholism. *Arch Gen Psychiatry* May 1995;52(5):374–83.
- Voorn P, Vanderschuren LJ, Groenewegen HJ, Robbins TW, Pennartz CM. Putting a spin on the dorsal–ventral divide of the striatum. *Trends Neurosci* Aug 2004;27(8):468–74.
- Hyman SE. The neurobiology of addiction: implications for voluntary control of behavior. *Am J Bioeth* Jan 2007;7(1):8–11.
- Schultz W. Reward signaling by dopamine neurons. *Neuroscientist* Aug 2001;7(4):293–302.
- Vanderschuren LJ, Pierce RC. Sensitization processes in drug addiction. *Curr Top Behav Neurosci* 2010;3:179–95.
- Volkow ND, Fowler JS, Wang GJ, Baler R, Telang F. Imaging dopamine's role in drug abuse and addiction. *Neuropharmacology* 2009;56(Suppl 1):3–8.
- Martinez D, Narendran R, Foltin RW, Slifstein M, Hwang DR, Broft A, et al. Amphetamine-induced dopamine release: markedly blunted in cocaine dependence and predictive of the choice to self-administer cocaine. *Am J Psychiatry* Apr 2007;164(4):622–9.
- Gendall KA, Sullivan PE, Joyce PR, Carter FA, Bulik CM. The nutrient intake of women with bulimia nervosa. *Int J Eat Disord* Mar 1997;21(2):115–27.
- Halmi KA. Perplexities and provocations of eating disorders. *J Child Psychol Psychiatry* Jan 2009;50(1–2):163–9.
- Fladung AK, Gron G, Grammer K, Herrnberger B, Schilly E, Grasteit S, et al. A neural signature of anorexia nervosa in the ventral striatal reward system. *Am J Psychiatry* Feb 2010;167(2):206–12.
- Zink CF, Weinberger DR. Cracking the moody brain: the rewards of self starvation. *Nat Med* Dec 2010;16(12):1382–3.
- Abraham H, Joseph AB. Bulimia vomiting alters pain tolerance and mood. *Int J Psychiatry Med* 1986–1987;16(4):311–6.
- Avena NM, Rada P, Hoebel BG. Evidence for sugar addiction: behavioral and neurochemical effects of intermittent, excessive sugar intake. *Neurosci Biobehav Rev* 2008;32(1):20–39.
- Bello NT, Hajnal A. Dopamine and binge eating behaviors. *Pharmacol Biochem Behav* Nov 2010;97(1):25–33.
- Bello NT, Sweigart KL, Lakoski JM, Norgren R, Hajnal A. Restricted feeding with scheduled sucrose access results in an upregulation of the rat dopamine transporter. *Am J Physiol Regul Integr Comp Physiol* May 2003;284(5):R1260–8.
- Hajnal A, Norgren R. Repeated access to sucrose augments dopamine turnover in the nucleus accumbens. *Neuroreport* Dec 3 2002;13(17):2213–6.
- Rada P, Avena NM, Hoebel BG. Daily bingeing on sugar repeatedly releases dopamine in the accumbens shell. *Neuroscience* 2005;134(3):737–44.
- Avena NM, Hoebel BG. A diet promoting sugar dependency causes behavioral cross-sensitization to a low dose of amphetamine. *Neuroscience* 2003;122(1):17–20.
- Fairburn CG, Harrison PJ. Eating disorders. *Lancet* Feb 1 2003;361(9355):407–16.
- Murphy R, Straebl S, Cooper Z, Fairburn CG. Cognitive behavioral therapy for eating disorders. *Psychiatr Clin North Am* Sep 2010;33(3):611–27.
- Butryn ML, Lowe MR, Safer DL, Agras WS. Weight suppression is a robust predictor of outcome in the cognitive–behavioral treatment of bulimia nervosa. *J Abnorm Psychol* Feb 2006;115(1):62–7.
- Lowe MR, Davis W, Lucks D, Annunziato R, Butryn M. Weight suppression predicts weight gain during inpatient treatment of bulimia nervosa. *Physiol Behav* Mar 30 2006;87(3):487–92.
- Pothos EN, Creese I, Hoebel BG. Restricted eating with weight loss selectively decreases extracellular dopamine in the nucleus accumbens and alters dopamine response to amphetamine, morphine, and food intake. *J Neurosci* Oct 1995;15(10):6640–50.
- Pothos EN, Hernandez L, Hoebel BG. Chronic food deprivation decreases extracellular dopamine in the nucleus accumbens: implications for a possible neurochemical link between weight loss and drug abuse. *Obes Res* Nov 1995;3(Suppl 4):525S–9S.
- Cadoni C, Solinas M, Valentini V, Di Chiara G. Selective psychostimulant sensitization by food restriction: differential changes in accumbens shell and core dopamine. *Eur J Neurosci* Oct 2003;18(8):2326–34.
- Barbarich-Marsteller N MD, Alexoff DL, Fowler JS, Dewey SL. Decreased dopaminergic response to a methamphetamine challenge measured with 11C-raclopride and microPET in an animal model of anorexia nervosa. Submitted for publication.
- Colantuoni C, Schwenker J, McCarthy J, Rada P, Ladenheim B, Cadet JL, et al. Excessive sugar intake alters binding to dopamine and mu-opioid receptors in the brain. *Neuroreport* Nov 16 2001;12(16):3549–52.
- Avena NM. Examining the addictive-like properties of binge eating using an animal model of sugar dependence. *Exp Clin Psychopharmacol* Oct 2007;15(5):481–91.
- Bello NT, Lucas LR, Hajnal A. Repeated sucrose access influences dopamine D2 receptor density in the striatum. *Neuroreport* Aug 27 2002;13(12):1575–8.
- Spangler R, Wittkowski KM, Goddard NL, Avena NM, Hoebel BG, Leibowitz SF. Opiate-like effects of sugar on gene expression in reward areas of the rat brain. *Brain Res Mol Brain Res* May 19 2004;124(2):134–42.
- Thanos PK, Michaelides M, Ho CW, Wang GJ, Newman AH, Heidbreder CA, et al. The effects of two highly selective dopamine D3 receptor antagonists (SB-277011A and NGB-2904) on food self-administration in a rodent model of obesity. *Pharmacol Biochem Behav* Jun 2008;89(4):499–507.
- Thanos PK, Michaelides M, Piyis YK, Wang GJ, Volkow ND. Food restriction markedly increases dopamine D2 receptor (D2R) in a rat model of obesity as assessed with in-vivo muPET imaging ([11C] raclopride) and in-vitro ([3H] spiperone) autoradiography. *Synapse* Jan 2008;62(1):50–61.
- Johnson PM, Kenny PJ. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. *Nat Neurosci* May 2010;13(5):635–41.

- [45] Corwin RL, Wojnicki FH. Baclofen, raclopride, and naltrexone differentially affect intake of fat and sucrose under limited access conditions. *Behav Pharmacol Sep* 2009;20(5–6):537–48.
- [46] Avena NM, Rada P, Moise N, Hoebel BG. Sucrose sham feeding on a binge schedule releases accumbens dopamine repeatedly and eliminates the acetylcholine satiety response. *Neuroscience* 2006;139(3):813–20.
- [47] Hajnal A, Smith GP, Norgren R. Oral sucrose stimulation increases accumbens dopamine in the rat. *Am J Physiol Regul Integr Comp Physiol* Jan 2004;286(1):R31–7.
- [48] Tauscher J, Pirker W, Willeit M, de Zwaan M, Bailer U, Neumeister A, et al. [1231] beta-CIT and single photon emission computed tomography reveal reduced brain serotonin transporter availability in bulimia nervosa. *Biol Psychiatry* Feb 15 2001;49(4):326–32.
- [49] Wagner A, Aizenstein H, Venkatraman VK, Bischoff-Grethe A, Fudge J, May JC, et al. Altered striatal response to reward in bulimia nervosa after recovery. *Int J Eat Disord* May 2010;43(4):289–94.
- [50] Marsh R, Steinglass JE, Gerber AJ, Graziano O'Leary K, Wang Z, Murphy D, et al. Deficient activity in the neural systems that mediate self-regulatory control in bulimia nervosa. *Arch Gen Psychiatry* Jan 2009;66(1):51–63.
- [51] Jimerson DC, Lesem MD, Kaye WH, Brewerton TD. Low serotonin and dopamine metabolite concentrations in cerebrospinal fluid from bulimic patients with frequent binge episodes. *Arch Gen Psychiatry* Feb 1992;49(2):132–8.
- [52] Yanovski SZ. Binge eating disorder and obesity in 2003: could treating an eating disorder have a positive effect on the obesity epidemic? *Int J Eat Disord* 2003;34 (Suppl):S117–20.
- [53] Wang GJ, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, et al. Brain dopamine and obesity. *Lancet* Feb 3 2001;357(9253):354–7.
- [54] Crow S, BB. Diagnosis, assessment, and treatment planning for bulimia nervosa. In: Grilo C, MJ, editors. *The treatment of eating disorders: a clinical handbook*. New York: Guilford Press; 2010. p. 28–43.