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Review

Dopamine and binge eating behaviors

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ABSTRACT

Central dopaminergic mechanisms are involved in the motivational aspects of eating and food choices. This review focuses on human and animal data investigating the importance of dopamine on binge eating behaviors. Early work examining dopamine metabolites in the cerebrospinal fluid and plasma of bulimic individuals suggested decreased dopamine turnover during the active phase of the illness. While neuroimaging studies of dopamine mechanisms in bulimia nervosa (BN) and binge eating disorder (BED) are limited, genetic studies in humans have implicated an increased frequency of dopamine transporter and associated D2 receptor polymorphisms with binge pathology. Recent studies in rodent models of dietary-induced binge eating (DIBE) have investigated plausible dopamine mechanisms involved in sustaining binge eating behaviors. In DIBE models, highly palatable foods (fats, sugars and their combination), as well as restricted access conditions appear to promote ingestive responses and result in sustained dopamine stimulation within the nucleus accumbens. Taken together with studies on the comorbidity of illicit drug use and eating disorders, the data reviewed here support a role for dopamine in perpetuating the compulsive feeding patterns of BN and BED. As such, we propose that sustained stimulation of the dopamine systems by bingeing promoted by preexisting conditions (e.g., genetic traits, dietary restraint, stress, etc.) results in progressive impairments of dopamine signaling. To disrupt this vicious cycle, novel research-based treatment options aiming at the neural substrates of compulsive eating patterns are necessary.

Contents

1. Introduction

Eating disorders represent a set of psychiatric conditions characterized by disturbances in eating behaviors. These disturbances not only include alterations in eating patterns and diet choices, but involve distinct aberrant psychological perceptions towards food, eating, body

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weight, and body self-image (APA, 2000). Binge eating is a common behavioral feature of clinically diagnosed eating disorders including bulimia nervosa (BN), binge eating disorder (BED), and binge/purge subtype of anorexia nervosa (AN-BP). Although the definition of binge eating in AN-BP is not well-defined clinically and relies on subjective assessments relative to restrictive behaviors in AN-restrictive subtype (AN-R) (Wolfe et al., 2009), binge eating is clearly defined in BN and BED by the 4th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)(APA, 2000). The definition includes consuming an amount of food that is significantly larger than most individuals would eat under similar circumstances in a discrete period of time (Mitchell et al., 1998). Rather than simply overeating, binge eating also is accompanied by a sense of a "loss of control" over what or how much an individual has eaten. The calorie content of binges in some self-reports range from less than 550 to greater than 10,000 Kcal (Cooper et al., 1993; Mitchell et al., 1981; Wolfe et al., 2009). The size of the binge is largely dependent on food choice. Binge eating episodes are often over-represented by desert-items (e.g., cakes, cookies, and ice-cream) and snack items (e.g., candies and chocolates), which are food types frequently avoided during "non-binge" eating (APA, 2000; Elmore and de Castro, 1991; Hadigan et al., 1989). These binge foods tend to be high in calories with the major macronutrients being carbohydrates or fats or a combination of the two (Elmore and de Castro, 1991).

The loss of control over eating, food choice, and self-sustaining aspects of binge eating have generated considerable interest in examining the neural correlates involved in these behaviors. Dopamine is a neurotransmitter critically involved in the reward and motivational aspects of feeding (Baptista, 1999; Erlanson-Albertsson, 2005; Noble, 2003a; Szczypka et al., 2000). While other recent reviews have focused on central monoamine systems in eating disorders, such as serotonin (5-hydroxytryptamine) and norepinephrine (Hainer et al., 2006; Kaye, 2008), the purpose of the present review is limited to the role of dopaminergic mechanisms involved in sustaining bingeing behaviors.

Dopamine signaling is dependent on neurotransmitter release, the number of functional receptors and reuptake transporters, and responsivity of dopaminergic neurons. The primary focus of this review is to describe dopamine signaling in BN and BED in view of the fact that the phenomenology of the binge eating in these disorders is more firmly defined than for AN-BP. To further address how dopamine signaling is influenced by the dietary conditions that sustain binge eating; the present review includes data from relevant animal models of dietary-induced binge eating (DIBE). A differentiation of partial symptomatology of binge-like eating observed in rodent models from the occurrence of binge eating in BN and BED is necessary. There is a consensus that animal studies cannot reproduce the complex psychosomatic features of human eating disorders per se. Animal models, however, can provide us with the resources needed to separately examine the elements of the homeostatic and motivational impairments associated with compulsive eating behaviors.

2. Bulimia nervosa (BN)

The eating patterns of BN are characterized by a minimum of two bingeing episodes per week with inappropriate compensatory behaviors. The duration of this eating pattern needs to be endorsed for at least 3 months (APA, 2000). Based on the type of compensatory behaviors used to maintain normal weight, bulimics are classified as either being purging or non-purging. The purging subtype is characterized by the regular use of self-induced vomiting, abuse of laxatives, enema or other purgative means. In contrast, bulimics of the non-purging subtype use fasting or excessive exercise to compensate for the excess intake of calories consumed during binge eating episodes (APA, 2000).

2.1. Dopamine metabolism in BN

Initially, the involvement of central monoamines in general, and dopamine in particular, was implicated in bulimic eating pathologies by measurements of monoamine metabolites in the lumbar cerebrospinal fluid (CSF) and plasma. Homovanillic acid (HVA), the major metabolite for dopamine in humans, has been found to be lower in the CSF of bulimics compared with healthy controls (Jimerson et al., 1992; Kaplan et al., 1989; Kaye et al., 1990). This effect, however, was related to binge frequency, with bulimics bingeing once a day (Kaye et al., 1990) or 14 times a week (Jimerson et al., 1992) demonstrating lower HVA concentrations than bulimics that binged less frequently. After treatment and normalization of eating behaviors, recovered bulimics showed similar HVA concentrations to controls, suggesting alterations in dopamine metabolism were state-dependent (i.e., occur during the active phase of bulimia) (Jimerson et al., 1992). Investigations into plasma HVA levels have reported mixed findings. In one study by Bowers and colleagues, bulimics ($n=11$), compared with controls ($n=29$), had higher plasma HVA following an overnight fast (Bowers et al., 1994). Although all subjects were BN inpatients receiving treatment, the length of treatment and severity or frequency of bulimic behaviors at the time of testing were not reported. In another study, in which 9 out of the 13 outpatient bulimics binged once a day, bulimic demonstrated ~30% lower baseline plasma HVA than control subjects (Kaplan et al., 1989). Aside from the study by Bowers and colleagues, evidence to date suggests that peripheral and central HVA levels are lower during in BN.

Reduced HVA levels are typically considered an index of reduced dopamine function and reduced dopamine turnover (dopamine to HVA ratio). Related to this, is the finding that certain polymorphisms of the catechol-o-methyltransferase (COMT) gene are associated with BN. Along with monoamine oxidase (MAO) and aldehyde dehydrogenase, COMT is an enzyme involved in metabolizing dopamine to HVA (Axelrod and Tomchick, 1958). In a study by Mikolajczyk and colleagues, blood samples were taken from women with an eating disorder ($n=103$) and healthy controls ($n=108$). They found that the presence of the GGCT and GGTT haplotypes in the rs4633/4680 loci of the *COMT* gene was associated with an increased likelihood of receiving a diagnosis of BN (Mikolajczyk et al., 2009). In previous genetic studies, it has been demonstrated that the C allele of rs4633 loci resulted in lower mRNA levels of the COMT in cortical tissue from postmortem specimens (Bray et al., 2003). Interestingly in the Mikolajczyk study, the rs4633 CC genotype reduced the risk of BN by 70% suggesting lower COMT and reduced dopamine metabolism to HVA could be a genetic contribution to protect against the development of BN.

2.2. Dopamine transporter regulation in BN

An alteration in dopamine turnover in BN is further supported by investigations into dopamine transporter (DAT) polymorphisms and gene regulation in eating disorder populations. DAT is located on dopamine neurons in the CNS and peripheral blood lymphocytes and terminates signaling by removing dopamine from the extracellular space. Increased frequencies of polymorphisms of the untranslated regions of the *DAT1 (SLC6A3)* gene have been associated with binge eating behavior in eating disorder subjects. In a study by Shinohara and colleagues, BN ($n=55$) and AN-BP ($n=35$) subjects had a higher frequency of *DAT1* polymorphisms with a short number (7 or 9) of tandem repeats compared with healthy controls (Shinohara et al., 2004). *In vitro* data demonstrates HEK cells transfected with *DAT1* constructs with10 tandem repeats have 50% greater binding density for DAT specific ligands than cells expressing the 9 tandem repeats (VanNess et al., 2005), similar findings were supported by in vivo imaging data (Heinz et al., 2000). In vivo imaging data obtained in a larger sample of healthy subjects ($n=96$), however, had different

results. Carriers of the short allele (9 tandem repeats) compared with homozygous individuals of the long allele (10 tandem repeat) had increased DAT availability as measured by SPECT of [^{123} I]β-CIT in the caudate and putamen (van Dyck et al., 2005). It is worth noting that there is a low frequency of homozygosity for the 9 tandem repeat of the *DAT 1* gene. Comparisons in most studies, therefore, are made between 10 tandem repeats homozygous and 9 tandem repeats heterozygous individuals (Davis et al., 2007a). As such, there is some contention over whether the 9 repeat allele results in an increase in DAT function (Krause et al., 2006). In fact, most often homozygosity for the 10 tandem repeats has been associated with greater DAT activity (Davis et al., 2007a; Heinz et al., 2000; Prata et al., 2009; VanNess et al., 2005). This suggests that a higher frequency of a lower number of tandem repeats (7 or 9) in *DAT 1* gene as reported by Shinohara and colleagues in eating disorder subjects could represent a decreased DAT function in eating disorder population with binge pathology. Contrary to this assertion, increased plasma DAT levels have been recently supported in a study by Frieling and colleagues (Frieling et al., 2009). At the time of admission for treatment, they found bulimics ($n=24$) had increased DAT mRNA blood levels compared with healthy control women ($n=30$). A hypermethylation of the DAT promoter, which is thought to decrease mRNA transcription level (Rosell et al., 2002), was also observed in the bulimic group compared with controls. Although the genotypes of these subjects were unknown, the hypermethylation of the DAT promoter could signify counter-regulatory epigenetic mechanisms aimed at reducing DAT levels. More studies, however, are needed to establish a direct association between DAT 1 genotype, central and peripheral DAT function, and the proclivity for bulimic pathology to establish a genetic-based dopamine-dependent causality for BN.

To date, only one in vivo neuroimaging study is published in BN subjects (Tauscher et al., 2001). The findings support a reduction in DAT in BN, as bulimics ($n=10$) demonstrated a 15% reduction in DAT availability in striatal regions of bulimics ($n=10$) compared with controls ($n=10$). However, this finding from an apparently underpowered SPECT [^{123} I]β-CIT study requires further validation. One major limitation of the study is how the subjects were screened and classified. Ten bulimic subjects were studied, 6 of which had a lifetime Axis I diagnoses other than BN (i.e., 5 had comorbidity with major depression, 2 had comorbidity with AN, and 1 had comorbidity of both AN and depression). Two subjects in the BN group did not meet the DSM-IV-TR diagnosis of BN, with a binge frequency of greater than once a month, but less than once a week. In addition, the controls were not weight-matched and had a significantly greater BMI (Body Mass Index) than the bulimics. Bulimics also underwent a "short-term" cognitive behavioral therapy that led to partial symptom control before scanning. The role of DAT availability in BN, therefore, needs to be established in a study with a larger sample size and during the active phase of BN in subjects that meet the diagnostic criteria for the illness. Apart from whether DAT is upregulated or downregulated in BN, such findings collectively support the notion that dopamine metabolism is altered in BN. What is important is whether the dopaminergic alterations have a causal significance to bulimic pathology.

2.3. Dopamine receptor functions in BN

Only a few related studies to date have addressed the question of dopamine dysfunction in clinical populations. This is achieved, for example, by evaluating pituitary hormone secretions following injections of dopamine agonists (Duval et al., 2006; Lal, 1988; Schellekens et al., 2009a; Schellekens et al., 2009b). While these are peripherally mediated responses, they are thought to reflect central dopamine impairments (Lal, 1988; Schellekens et al., 2009a; Schellekens et al., 2009b). Apomorphine, which is often used in acute dopamine challenge tests, is a short-acting dopamine receptor agonist with slightly higher in vivo affinity for D2-subtype receptors over D1-subtype receptors (Andersen and Jansen, 1990). Following peripheral administration, apomorphine produces a distinct hormonal response to increase growth hormone and decrease prolactin secretions (Lal, 1988). While dopamine challenge studies have been used extensively in other psychiatric disorders (Duval et al., 2006; Lal, 1988; Schellekens et al., 2009a; Schellekens et al., 2009b), similar studies in eating disorders subjects are scarce. One study with a relatively small sample size comparing apomorphine-induced hormone responses found no differences between bulimics ($n=7$) and controls ($n=8$) (Brambilla et al., 2001). In contrast, subjects with anorexia nervosa demonstrated a blunted growth hormone response to apomorphine; an effect that was seen in both anorexia subtypes (AN-R, $n=8$; AN-BP, $n=8$). Also for the AN-R group, the growth hormone releasing hormone produced an exaggerated growth hormone response, suggesting that dopaminergic hypothalamic changes may be secondary to the perturbed growth hormone release caused by AN. In all bulimic and anorectic patients, but not in the control subjects, apomorphine (0.5 mg, IV bolus) elicited extreme nausea and vomiting. A heightened sensitivity to the nausea and emetic properties of apomorphine in AN and BN could indicate enhanced dopamine receptor sensitivity at hindbrain "chemoreceptor" sites, such as the area postrema and nucleus of the solitary tract. Further investigations are needed in eating disorder patients to assess whether dopamine-mediated hormonal responses are related to bulimic pathology and have predictive or diagnostic value for the course of treatment.

3. Binge eating disorder (BED)

Similar to BN, BED is characterized by a minimum of two bingeing episodes per week. In contrast to BN, in BED the bingeing episodes are not accompanied by compensatory behaviors and the two bingeing episodes per week frequency is maintained for at least 6 months (APA, 2000). Binge eating in the absence of compensatory behaviors, according to DSM-IV, are given a clinical diagnosis of eating disorder not otherwise specified (EDNOS), but a provisional research diagnosis of BED (APA, 2000). The consensus is that BED is a distinct clinical eating disorder from BN and EDNOS (Striegel-Moore and Franko, 2008), some have suggested that BED should be further delineated into distinct categories based on the frequency of binge eating episodes (Wilson and Sysko, 2009). Individuals with BED are typically overweight or obese with ~25% of those seeking treatment for obesity meeting all of the criteria for BED (Yanovski, 2003).

3.1. Dopamine transporter regulation in BED

The function of the *DAT 1* gene polymorphisms have been assessed in BED (Davis et al., 2007a). Comparisons in appetitive responses were accomplished by measuring the subjective ratings to seeing and tasting a "favorite snack food item" in genotyped BED ($n=32$) and non-BED control individuals ($n=46$). To determine whether inhibiting the dopamine uptake differentially influenced these responses oral methylphenidate (0.5 mg/kg up to 50 mg) was given to both groups. Methylphenidate is a non-selective norepinephrine transporter/DAT inhibitor used for the treatment of attention deficit hyperactive disorder with anorexia as an often reported side effect (Schertz et al., 1996). Reduced appetite ratings following methylphenidate were observed in the BED individuals that were carriers of 9 tandem repeat allele compared with non-BED and 10 tandem repeat homozygous individuals (Davis et al., 2007a). It should be noted that in this study the BED and non-BED controls were not weight-matched. In fact, BED had a significantly higher BMI in comparison with non-BED (31.9 ± 7 versus 21.2 ± 2.5). Accordingly, the reduced appetite rating in the 9 tandem repeats BED carriers could have also been a consequence of weight-status instead of genotype. Taken together with the observation that 10 tandem repeat allele produced increased

DAT function (VanNess et al., 2005), obese or overweight BED individuals that were carrier of the 9 tandem repeats could have increased responsivity to methylphenidate because of dopamine dysfunction rather than a larger number of available drug binding sites. Nevertheless, further in vivo neuroimaging studies are needed in BED subjects to clarify these findings.

3.2. Dopamine D2 receptor functions in BED

Dopamine D2 receptors (D2Rs) are G-protein coupled receptors with downstream effects to inhibit adenylate cylcase activity, enhance potassium conductance, and inhibit Ca^{2+} entry through voltage-gated channels. These receptors are located presynaptically and post-synaptically to regulate dopaminergic and dopaminoceptive neuronal activity (Baldo et al., 2002; Chen and Pan, 2000; Noble, 2003a). Alterations in D2Rs and their influence on feeding behaviors have received considerable attention, in part, because body weight gain is a reported side effect of long-term administration of typical and atypical antipsychotic drugs (Baptista, 1999). The weight gain associated with these classes of drugs was initially ascribed to their varying degrees of D2R antagonism (Baptista et al., 1999; Stigler et al., 2004). Recent work has implicated several non-dopaminergic targets (e.g., histamine, serotonin, α-adrenergic) and their role in weight gain associated with typical and atypical antipsychotics (Basile et al., 2001; Kroeze et al., 2003; Tardieu et al., 2003). Nonetheless, dopaminergic signaling has been shown to be critical for diet-induced weight gain by several studies using various experimental approaches (Baldo et al., 2002; Berridge and Robinson, 1998; Geiger et al., 2009; Singer and Wallace, 1984; Smith, 2004; Smith and Schneider, 1988; Szczypka et al., 2000; Wise and Schwartz, 1981). One often cited evidence for the central dopamine dysfunction in obesity is a PET imaging study that used [C^{11}] raclopride that demonstrated lower striatal D2R availability in morbidly obese individuals (Wang et al., 2001). While higher body weights were correlated with lower striatal D2R availability (Wang et al., 2001), BED status was not investigated in this study. A recent longitudinal PET study also using [C^{11}] raclopride in a small number of female subjects ($n=5$) found increased D2R availability in obese subjects following gastric bypass surgery (Steele et al., 2009). The increase in D2R availability in these subjects was proportional to the weight loss, suggesting central dopamine dysfunction to some degree is related to the obese phenotype. Thus, further understanding the role of D2R is likely to distinguish the pathology of BED from the consequences of obesity.

Polymorphisms in the TaqIA allele (A1 carriers) (Laruelle et al., 1998), are associated with reductions in D2R binding in postmortem striatal tissue, in vivo D2R availability, and reduced glucose metabolism in striatal regions compared with individuals homozygous for the A2 allele (Jonsson et al., 1999; Noble, 2003b; Noble et al., 1997; Pohjalainen et al., 1998; Thompson et al., 1997). In a recent study comparing the genotypes of obese individuals with BED ($n=66$) and without BED ($n=55$), BED was associated with an increased frequency of the A2 homozygosity (Davis et al., 2009). The genotype frequency for A2/A2, for example, was 67.7% for the BED compared with 48.5% for the obese group without BED. In this population, there was also an interaction for the A2/A2 genotype and a functional polymorphism of the mu-opioid receptor gene (*OPRM1*). The combination of D2 and mu-opioid genotypes was observed in 80% of the BED individuals, but also in 20% of the obese non-BED controls. Such data not only provides a basis for distinguishing BED obese from non-BED obese, but also lends support for the notion that increased D2R (and enhanced mu-opioid receptor activation) contribute to binge eating pathology.

4. Animal models of dietary-induced binge eating (DIBE)

An alternative approach to using clinical populations for elucidating the role of dopaminergic systems in bingeing behaviors has been to use animal models of *dietary-induced binge eating (DIBE)*. A discrimination in terminology is critical for comparison, since animal models rely on the increased stimulatory properties of dietary factors rather than psychosomatic factors that maintain binge eating. Utilizing an animal model to study a complex human disease, such as an eating disorder, allows the experimenter to control for and assess aspects of feeding physiology that are extremely difficult, not feasible, or unethical in human populations. The obvious limitations of using animal models are that they cannot incorporate every pathological feature, etiology, or clinical symptomatology, which define the human illness. In the case of binge eating, while the relative amount of calories during a binge episode can be modeled and studied (Bello et al., 2009; Corwin and Buda-Levin, 2004), the sense of "losing control," which accompanies human binge eating episodes, cannot be assessed. Dietary-induced binge eating is often operationally or conditionally defined by the experimenter, but have similar elements to the binge eating displayed by clinical populations (Avena, 2009; Corwin and Buda-Levin, 2004). In particular, the two experimental variables frequently introduced in animal models of DIBE are access to palatable food and calorie restriction.

To further define DIBE, however, a distinction between hyperphagia (i.e., overeating) and binge-like eating is warranted. An important principle in the design of DIBE models is that highly palatable foods are presented along with access to standard chow (Colantuoni et al., 2001; Dimitriou et al., 2000; Hagan and Moss, 1997), whereas in hyperphagia models the rats are maintained on high fat or high energy diets as their exclusive source of food (Ricci and Levin, 2003). The rationale for optional food sources in DIBE is based on the premise that binge foods are highly palatable (Kales, 1990) and that bingeing is a source of extra calories (Drewnowski et al., 1987; Kales, 1990). In hyperphagia models, the palatable diet is typically offered ad libitum (Woods et al., 2004). As opposed to DIBE models, where the palatable foods are presented for a limited time period (20 min or 1–2 h) daily or intermittently on certain days (Bello et al., 2003; Colantuoni et al., 2001; Cottone et al., 2008; Dimitriou et al., 2000; Hagan and Moss, 1997).

4.1. Potential contribution of palatability and calorie restriction on DIBE

Some DIBE models have used an intermittent schedule of access to highly palatable foods. These paradigms do not incorporate experimenter-induced calorie restriction and have more relevance to the eating patterns of BED because rats are presumably "eating while not hungry" (Berner et al., 2008; Corwin and Wojnicki, 2006; Dimitriou et al., 2000; Kinzig et al., 2008). In particular, these DIBE models use a protocol whereby fat emulsions, sucrose solutions or the combination of the two is given 1 h or 2 h three times a week for 6–8 weeks. Despite the slight variations in the experimental design, the pattern of calorie consumption between "binges" in this entrainment protocol is fairly consistent. In fact, rats typically overeat on binge days during the palatable food access period and under-eat on non-binge days (Berner et al., 2008; Corwin and Buda-Levin, 2004; Corwin and Wojnicki, 2006; Kinzig et al., 2008). Intermittent access to food without calorie restriction or "meal entrainment" has been demonstrated to increase food anticipatory behaviors, feeding-related neuropeptides, and meal preparatory hormones (Drazen et al., 2005; Mendoza et al., 2005; Woods et al., 1977). Using the DIBE models without calorie restriction, Corwin and colleagues have demonstrated that the D2R antagonist, raclopride, produces an effect on the binge-like intake that is dependent on both the intermittent access schedule and the type of palatable food offered. That is, raclopride (0.1 mg/kg, IP) increased the intake of vegetable shortening (fat) when the "binge" food was offered intermittently, but had no effect when it was offered daily. At a higher dose, raclopride (0.3 mg/kg, IP) effectively suppressed the intake of sucrose solutions (3.2%–32%) regardless of the access schedule (Corwin and Wojnicki, 2009). A similar divergence of the effect of raclopride on intake was noted when sucrose (3.2%, 10%, or 32%) was

added to vegetable shortening, with raclopride (0.3 mg/kg, IP) having the greatest suppression of intake with the 10% sucrose/vegetable shortening blend (Wong et al., 2009). The clinical relevance of DIBE without calorie restriction is that similar patterns of overeating with compensatory under-eating have been self-reported in human subjects with 7-day diet diaries (de Castro, 2000). This suggests that cognitive restraint may not be the only psychological process resulting in self-restriction following overeating episodes (Hagan et al., 1999).

Along the lines of the work of Corwin and colleagues, paradigms of DIBE have different patterns of binge intakes over time that is dependent on the type of "binge food" offered (Corwin, 2005; Corwin and Buda-Levin, 2004; Corwin and Wojnicki, 2006; Corwin et al., 1998; Dimitriou et al., 2000; Wojnicki et al., 2007). For instance, in DIBE protocols utilizing sugar solutions (i.e., glucose or sucrose) there is an incremental increase in "binge" intake over time (Avena et al., 2004; Avena et al., 2005; Avena et al., 2006a; Avena et al., 2006b; Bello et al., 2003; Colantuoni et al., 2002; Colantuoni et al., 2001). Rats on an intermittent DIBE schedule with a 10% sucrose solution demonstrated an ~50% escalation in sucrose intake during the first hour from day 1 to day 21. Similar increases over time were not observed in rats with ad libitum sucrose or rats exposed to sucrose twice (i.e., day 1 and day 21) (Rada et al., 2005). In studies using semisolid fat emulsions (i.e., partially or fully hydrogenated vegetable shortening), the pattern of intake seems less consistent across studies. When given optional limited access (1 or 2 h) to fat three times a week with intervening days off, the intake of fat has been demonstrated to increase (Corwin et al., 1998; Dimitriou et al., 2000) or remain relative stable over 4–8 weeks (Davis et al., 2007b; Kinzig et al., 2008). In these experiments, bingeing is often distinguished not as an escalation in intake over time, but is operationally defined as consuming more during the scheduled limited access than rats receiving the "binge food" everyday (Corwin and Wojnicki, 2006; Dimitriou et al., 2000). More robust increases in intake over time have been observed when the "binge foods" are more complex fatty and sugary foods or nutritionally complete diets (Bello et al., 2009; Berner et al., 2008; Cottone et al., 2009; Hagan and Moss, 1997). Such data suggests that the sugar component of "binge foods" is likely a stronger moderating factor on the increase in intake over time during repeated bouts of exposure. The notion of sugar being the predominant dietary reinforcer has been experimentally addressed by others in a different behavioral paradigm with similar findings (Naleid et al., 2008).

Further differences have been demonstrated in "sugar bingeing" versus "fat bingeing" with respect to somatic signs of precipitated withdrawal and reinstatement behavior following a period of abstinence (Avena et al., 2009; Bello et al., 2009; Rada et al., 2005; Wojnicki et al., 2008), suggesting the effects of "fat bingeing" are more transitory or state-dependent. A potential confounding factor in describing the differences between "fat bingeing" and "sucrose bingeing" could be in what form the "binge" food was made available to the animals. In the experiments that use "sugar" DIBE-sugars were presented as liquid solutions, whereas in "fat" DIBE-fats were presented as semisolid foods. Similarly, mixtures of fats and sugars are presented as semisolid or solid food sources (Bello et al., 2009; Berner et al., 2008; Cottone et al., 2009; Hagan and Moss, 1997). While the fats and fat/sugar mixture "binge foods" have more calories per gram, the liquid sugar solutions could be consumed at a faster rate and provide greater oral sensory stimulation to facilitate the feed-forward dopamine mechanisms of ingestion (Hajnal and Norgren, 2001; Hajnal and Norgren, 2005; Hajnal et al., 2004; Schneider, 1989). Direct comparison between fats, sugar solutions and fat/sugar combinations in DIBE paradigms are needed to clarify the apparent differences in reinstatement behavior and the "transitory" nature of diet type.

Because rats lack the capacity to vomit, most DIBE studies with relevance to bulimic pathology have incorporated some degree of calorie restriction or restricted feeding as a compensatory behavior. Not all self-reports of bingeing episodes in BN are preceded by periods of acute calorie restriction (Hetherington et al., 2000). Bouts of calorie restriction in DIBE models produces a robust re-feeding response during the "binge period" and chronic calorie restriction is likely to support the maintenance of repetitive bouts of overeating (Bello et al., 2009; Hagan and Moss, 1997). Calorie restriction, on the other hand, could serve to enhance the reinforcing properties of the binge food. Indeed, chronic calorie restriction resulting in weight loss has been demonstrated to augment the reinforcing potency of drugs of abuse (Carroll and Meisch, 1980; Takahashi and Singer, 1980). Initial studies examining the schedule induced effects of self-administration of amphetamine revealed that rats that were calorie restricted to ~20% lower body weight had 3 to 4 fold more drug infusions than normal weight rats or rats maintained at ~10% lower body weight (Takahashi et al., 1978). Another way to investigate this phenomenon has been to determine whether chronic calorie restriction affects the threshold of highly motivating lateral hypothalamic self-stimulation (LHSS) which stimulates fibers of the medial forebrain bundle. Similar to drug self-administration, chronic food restricted rats maintained at ~20% lower body weight decreased the threshold (i.e., leftward shift in the rate-frequency) for LHSS (Cabeza de Vaca and Carr, 1998). Hence, calorie restriction is interpreted as "augmenting" the reinforcing potency of the LHSS since rats also exhibit lower LHSS thresholds for drugs of abuse, such as amphetamine, phencyclidine, and dizocilpine (MK-801) (Cabeza de Vaca and Carr, 1998; Carr et al., 2000; Carr and Kutchukhidze, 2000). The mechanisms for a shift in reinforcing potency during calorie restriction is likely mediated by changes in dopamine receptor function — irrespective of whether such an effect was primary or secondary to altered dopamine signaling. Intracerebroventricular injections of the D2R agonist, quinpirole, increased locomotor activity and produced a more pronounced striatal neuronal activation in calorie restricted animals compared with ad lib fed controls (Carr et al., 2003). Similar enhanced responses were observed in calorie restricted animals compared with controls using the D1R agonist, SKF-82958, while striatal D2Rs also showed a greater effector coupling in striatal tissue from calorie restricted compared with control animals. This suggests that calorie restriction results in increased D2R receptor sensitization, which could partially explain the calorie restricted augmentation of reward stimuli.

4.2. Effects of calorie restriction and palatable food on accumbens dopamine

Either repeated scheduled access to palatable food stimuli or calorie restriction produces neurochemical alterations to promote robust feeding responses and anticipatory behaviors (Mogenson et al., 1988). Striatal dopamine signaling is thought to be critical for these behaviors, in particular dopamine signaling in the nucleus accumbens. The accumbens is a ventral striatal structure that receives dopaminergic projections from the mesencephalic ventral tegmental area (VTA; A10) (Kelley and Berridge, 2002; Schultz, 2002). The accumbens dopamine pathway is a component of a larger neural circuit, the "extended amygdala" (de Olmos and Heimer, 1999) a critical substrate for the central motivational system. It is believed that the extended amygdala integrates aspects of affective behavior to elicit the appropriate autonomic, endocrine, and motor responses to external stimuli (Koob, 1999). Accumbens dopamine levels have been demonstrated to increase in response to ingestive stimuli (i.e., food and water) following longer periods of deprivation (>24 h) (Yoshida et al., 1992), during scheduled access to a stimulus (Weissenborn et al., 1996), and in response to the consumption of palatable sucrose solutions (Hajnal and Norgren, 2001; Hajnal and Norgren, 2005; Hajnal et al., 2004) and liquid fat (Liang et al., 2006).

The nucleus accumbens was initially subdivided based on the distribution of acetylcholinesterase (Zaborszky and Cullinan, 1992) and calbindin immunohistochemistry (Jongen-Relo et al., 1994). The medial "shell" region contains low to moderate staining of these markers, whereas the dorsolateral "core" region surrounding the anterior commissure is more densely stained. Most studies have

focused on dopamine signaling in the medial shell or transitional area between the core and shell subregions in the nucleus accumbens. Dopamine signaling within the core and shell subregions is differentially regulated during feeding to subserve different aspects of reward-related behaviors. Dopamine levels have been shown to increase in the shell only if a food stimulus is novel and palatable, whereas dopamine levels increase in the core whenever the food stimulus is ingested regardless of palatability or novelty (Bassareo et al., 2002). Interestingly, taste reactivity scoring of the food stimulus, which is used as an objective metric of ingestion or rejection based on orofacial responses in rats (Grill and Norgren, 1978), is not related to the dopamine habituation in the shell or the persistence of dopamine signaling in the core (Bassareo et al., 2002). Incidentally, this further strengthens the assertion that dopamine in nucleus accumbens does not signal the hedonic (i.e., pleasurable) properties of a food stimulus, but is involved in the appetitive ('wanting') aspects of food reward (Berridge and Robinson, 1998). The habituation of dopamine signaling during repeated exposure to a food stimulus in the medial shell can be attenuated if animals are food restricted (66–75% of available daily intake) beforehand (Bassareo and Di Chiara, 1999). Hence, receiving a palatable food during periods of calorie restriction serves to not only to enhance accumbens dopamine release, but to prevent habituation of dopamine signaling in the medial shell with repeated stimulus exposure.

Several DIBE models using restricted feeding conditions have demonstrated a persistence of accumbens dopamine signaling. In particular, work by Hoebel and colleagues have utilized a daily schedule where rats are given 12 h calorie restriction followed by access to standard chow with sugar solutions (25% glucose or 10% sucrose) concurrently available for 12 h (Avena, 2009; Avena and Hoebel, 2003; Avena et al., 2006a; Avena et al., 2006b; Colantuoni et al., 2001). Chow and sugar access is given 4 h after the onset of dark, a time in which rats normally have high calorie intakes (Clifton, 2000). Rats on this 12 h intermittent access schedule initially lose body weight, but regain weight at a level similar to control animals after 7–10 days. As mentioned previously (Rada et al., 2005), rats demonstrate ~50% escalation in sugar intake during the first hour over the course of the ≥21-day experiments (Colantuoni et al., 2002; Colantuoni et al., 2001). Rats exposed to this intermittent access schedule demonstrate increased accumbens dopamine (~130% of baseline) to 10% sucrose on day 1, day 2, and day 21. In contrast, rats exposed to sucrose twice on day 1 and day 21, had ad libitum sucrose or intermittent chow access did not elevate dopamine above baseline on day 21 (Rada et al., 2005). Similar intermittent patterns of sugar access for 30 days were also demonstrated to decrease D2R binding in dorsal striatum and increases in D1R binding in the dorsal striatum, nucleus accumbens core and shell regions (Colantuoni et al., 2001). Using a 7-day paradigm that promotes DIBE of 0.3 M sucrose solutions (10.26%), Hajnal and colleagues have demonstrated an increase in accumbens dopamine turnover to sucrose (Hajnal and Norgren, 2002). This was shown to be accompanied by an upregulation of DAT in nucleus accumbens core and shell, and VTA with decreased D2R binding in the nucleus accumbens core and shell (Bello et al., 2002; Bello et al., 2003; Hajnal and Norgren, 2002). This suggests that short-term (i.e., 7 days) dopamine-dependent alterations to sugar solutions under restricted-fed conditions could be essential for sustaining bingeing behaviors seen with more protracted DIBE schedules (i.e. ≥21 days).

With relevance to DIBE, calorie restricted rats below ~25% of normal body weight have decreased baseline accumbens dopamine ~50%, an effect not observed in other terminal regions of dopaminergic neurons, such as the dorsal striatum or medial prefrontal cortex. However, higher accumbens dopamine levels were observed in underweight rats compared with controls either in response to locally infused amphetamine or from tissue homogenates (Pothos et al., 1995). Taken together with the work by Carr and colleagues (Cabeza de Vaca and Carr, 1998; Carr and Kutchukhidze, 2000; Carr et al., 2003), ingestion of sugars, fats or other dopamine stimulating substances (e.g., drugs of abuse) by underweight animals would presumably produce a relatively greater phasic dopamine release.

The persistence of accumbens dopamine signaling and neuroadaptive alterations under restricted feeding conditions observed in DIBE models occurs without significant reductions in body weight (Bello et al., 2003; Colantuoni et al., 2002; Colantuoni et al., 2001). However, rats maintained at 85% body weight on a DIBE restricted feeding schedule have larger accumbens dopamine responses to sucrose. In one particular experiment, rats were placed on a daily schedule in which they received 8 h access to chow with 10% sucrose only available during the first 2 h. Accumbens dopamine was measured in response to sucrose on day 21 and then animals were maintain at a 15% reduced body weight for 1 week. When given the same volume of 0.3 M sucrose as on day 21, there was >45% increase in accumbens dopamine on day 28 from day 21. A similar relative increase was not observed in non-bingeing rats only given 10% sucrose on days 1 and 21, maintained at 15% reduced body weight for 1 week and given the same volume of sucrose (from day 21) again on day 28 (Avena et al., 2008b).

In summary, manipulations of dietary conditions in rodents can promote the expression of binge-like eating behaviors. One common feature of all described DIBE models is the intermittent optional access to highly palatable foods. These foods typically resemble the macronutrient composition of "binge" foods being comprised of sugar, fat, or some combination of sugars and fats. Another common feature of some, but not all DIBE models, is the use of periods of calorie restriction. Prolonged periods or repeated bouts of calorie restriction can serve to maintain the overeating during periods of food access. Calorie restriction, on the other hand, may serve a secondary role by maintaining salience of the "binge" food — an effect likely mediated by a persistent responsivity of the accumbens dopamine system.

5. Discussion

Effective long-term treatment of eating disorders is a significant challenge not only for the affected individual, but also for the health care provider. Even with prolonged clinical treatment aimed at normalizing feeding patterns and attitudes towards food, the remission rates for eating disorders are still less than 50% (Keel et al., 2002; Keel et al., 1999). This necessitates developing better research-based treatment options designed at normalizing eating patterns and mitigating factors involved in sustaining binge eating behaviors. A combination of human and animal studies has implicated dopamine mechanisms in binge eating. In both BED and BN, the frequency of polymorphisms of the *DAT1* and associated polymorphisms of D2 receptor suggest that dopamine alterations are *trait-related* to binge pathology. The data from DIBE animal models suggest that palatable food access under restricted conditions may prevent food-related dopamine release from habituation and in turn, a sustained activity of the accumbens dopamine system may be involved in the *state-dependent* mechanisms of binge eating.

Restrictive eating patterns are not commonly reported in individuals with BED (Greeno et al., 1999). Thus, the dopaminergic alterations reported under calorie restricted conditions seem to be less relevant to BED pathology. However, BED patients may express restricted eating within days rather than across days. Comparing obese BED with non-BED obese, it has been reported that the BED patients under-eat during the mornings and overeat during the evening hours (Raymond et al., 2003). In addition, while categories of food choices were not reported in the study, BED subjects on "binge days" had a shift in their macronutrient profile to favor high calorie foods. A pattern of eating whereby foods that are more palatable are underconsumed could result in a perceived reward deprivation and a compensatory overeating during binge days. A similar concept of "hedonic deprivation" has been suggested by Lowe and Levine (Lowe and Levine, 2005). Recent work by the Hajnal laboratory suggests that

if a food has more complexity and is *highly* palatable the accumbens dopamine signaling does not habituate with repeated exposure even when fed ad libitum (Hajnal et al., 2008). This observation suggests that periods of "hedonic deprivation" associated with more or less access to highly palatable food may be sufficient to cause dopamine alterations to promote bingeing.

Although the concept of reward sensitization and dependence in DIBE models has been reviewed in greater detail elsewhere (Avena, 2007; Avena et al., 2006a; Avena et al., 2008a), we have to emphasize the ability of highly palatable foods to increase accumbens dopamine signaling each time it is presented. Such an effect is similar to the self-administration of psychostimulants (i.e., cocaine and amphetamine) in rodents, which do not show blunting in accumbens dopamine signaling upon repeated exposure (Torregrossa and Kalivas, 2008). Thus, the binge eating behavior in BED could be driven by food palatability and altered daily eating patterns. All of these effects then could be exacerbated in a select population with polymorphisms in dopamine-related genes further increasing the susceptibility to developing BED.

The convergence of neural adaptive changes in general, and dopamine in particular, on the compulsive behaviors of binge eating and drug use would suggest an association between drug use and the clinical diagnosis of an eating disorder. This concept was examined in a recent meta-analysis of human data (Calero-Elvira et al., 2009). This study comprised a total of 42,236 subjects from 16 research articles comparing drug use in individuals meeting criteria for AN-R, BED, and BN between those without an eating disorder. There were three relevant findings from this study. First, for drug use in a clustering of all eating disorders there was a small, but significant, standardized positive effect size. Second, in parsing the classes of illicit drugs there was a positive effect for opiates-cannabis, and not psychostimulants. Third, a higher prevalence for drug use was found in BN, lower in BED and least in AN-R. Considering the data presented in this review, the relationship between drug use and BN/BED in the meta-analysis is not surprising. The finding that individuals with eating disorders use more opiate-cannabis drugs over psychostimulants does require further investigation.

The recent finding from the Hoebel laboratory that accumbens dopamine under restricted-fed conditions is enhanced in underweight rats seems to be more appropriate to AN-BP than to BN symptomatology. Even though bulimics tend to fall into the normal range of BMI, they still may be underweight from their individual premorbid body weight. Weight suppression is defined as the highest lifetime past weight minus current weight and has been suggested to be a predictor of treatment outcome in BN (Carter et al., 2008). Indeed, bulimic inpatients with the highest degree of weight suppression had the worst treatment outcome, an effect that was not associated with dietary restraint scores or other psychological assessments (Butryn et al., 2006). In addition, weight suppression and desire to lose weight has been directly related to binge frequency (Lowe et al., 2007). This suggests the degree of weight suppression could be another influential behavior in BN that might affect dopamine, an assertion that needs to be verified by prospective neuroimaging studies in bulimic subjects with varying degrees of weight suppression.

One of the defining features of binge eating is the sense of the loss of control of eating. The subjective feeling and the intensity of the loss of control have been regarded by some to be the defining criteria of binge eating, rather than the objective size of the binge (i.e., objective vs., subjective binge, reviewed in Wolfe et al., 2009). Nonetheless, loss of control is more associated with the helplessness and despair of the eating disorder as reported by patients (Wolfe et al., 2009). While the neural basis of loss of control was not directly addressed in this review and considering that loss of control is an aspect of drug use, dopamine mechanisms are likely to be involved (at least indirectly) in the loss of control associated with bingeing pathology. Not surprisingly, one effective strategy used in the cognitive behavior therapy of eating disorder is to normalize eating patterns (APA, 2000). Based on the reviewed studies, we believe that such cognitive control is likely to promote a normalization of dopaminergic functions including responsiveness to food-related cues and stimuli.

6. Conclusion

This review focused on genetic, dietary, and weight related factors that are likely involved in promoting neuroadaptive dopamine alterations. Mostly from the work with DIBE animal models, it has been demonstrated that non-normative eating patterns affect dopamine signaling. What is also evident from the available data is that dopamine alterations and binge eating behaviors are further perpetuated by dietary factors. Nonetheless, dopamine-dependent pathways are likely implicated in the wide variety of factors, not discussed in this review. Some of these factors are involved in initiating or triggering binge eating in BN and BED, such as psychological stress, body image dissatisfaction, and emotional well-being. In addition, investigating the interactions of other neuromodulators and neurotransmitters with dopamine signaling pathways are likely to uncover how different states and cues initiate and sustain shifts in the motivation for eating in absence of physiological needs. From a clinical perspective, novel treatment options based on research aimed at investigating the psychological basis of compulsive eating are required. The authors believe that cognitive therapy for normalizing eating patterns in BN and BED patients is one successful therapeutic manipulation likely to interfere with conditions responsible for the sustained stimulation of the dopamine systems. Lastly, more comprehensive translational research approaches are necessary to distinguish the interaction of dietary influences and dopamine dysfunction on the psychological and cognitive manifestations of eating disorders.

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