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Dysregulation of Dopamine D2 Receptors and μ-Opioid Systems in Reward Memory in Binge Eating Disorders

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ABSTRACT: Where food becomes both the enemy and the only source of comfort, binge eating disorder (BED) overturns the narrative that eating disorders are a chase for thinness. In our society, dominated by social media and diet culture, BED exists as a search for control, but is it merely a byproduct of cultural pressures? This review examines the roles of the dopamine D2 receptor (DRD2) gene, the μ-opioid system, and the correlation between these pathways in contributing to altered reward processing and the development of BED. The hypothesis that genetic polymorphisms leading to a reduction in *DRD2* gene expression, coupled with dysregulation of the μ-opioid system, contribute to impulsive behaviors and cognitive deficits is reviewed. Furthermore, it is highlighted that the significant overlap between reward regulatory systems involved in BED and other addiction disorders, such as substance abuse, suggests potential shared vulnerabilities and therapeutic targets. To assess these findings, this review will focus on examining 3 key studies as they have the most significant data and address neurobiological pathways that maintain BED. Ultimately, by addressing these neurological mechanisms, this review aims to provide insights for developing novel treatments that target the neural circuits governing maladaptive reward learning in BEDs.

KEYWORDS: Biology, Neurobiology, Reward Memory Binge, Eating Disorder, Dopamine D2 Receptor, μ-Opioid Receptor.

Introduction

When food becomes the only source of comfort, individuals develop unhealthy eating habits, making what was once a source of comfort an enemy. Binge eating disorders (BED) are reported to be one of the most common eating disorders. Despite its high prevalence, the etiology and neurobiological mechanisms of binge eating disorder are not fully understood since it is suggested to have multiple regulating factors.[1] The abnormal eating behaviors underlying BED include loss of control, excessive food consumption beyond satiation, feelings of disgust and embarrassment towards oneself, and intense guilt after overeating.[2] Although there are cultural factors underlying binge eating disorders and bulimia nervosa (BN), an eating disorder that's characterized by bingeing followed by compensatory behaviors to prevent weight gain, studies have recognized that there are neurobiological and genetic bases associated with aberrant reward regulation and cognition in the development and preservation of BEDs.[3] Given the existing research, this article reviews how the role of dopamine D2 receptor (*DRD2*) genes, μ-opioid system dysregulation, and the correlation between these two systems contribute to reward memory alterations in BED subjects.

Although we have collected evidence from both human and rodent studies linking high-fat and sugar diets to cognitive deficits (like in obesity), our current understanding of cognition and reward memory is limited and lacks clarity regarding binge eating disorders. Despite the commonalities between rodent and human brains, experimental results are not able to fully replicate the complexity of neurological pathways in individuals with BED.[4] However, existing studies have led to the hypothesis that the reduction in *DRD2* genes via polymorphisms and increased opioid receptor binding likely causes food-seeking behaviors and increased food intake in BED and BN subjects. However, an aspect that's worth noting is that binge eating disorders exhibit similar characteristics to other addiction disorders; comorbidities associated with BED, such as substance addiction, are discovered to have overlaps in reward regulatory systems (dopaminergic and opioidergic), thus similar consequences in memory and cognitive features.[5] These findings pose questions regarding the relevance of eating addictions and drug addictions, if one disorder can contribute to the susceptibility of the other, and if existing treatments of one condition can guide the innovation of therapies for the other.

Ultimately, this review will focus on how the reduction of dopamine receptor density through polymorphisms of the dopamine D2 receptor gene, the decrease in μ-opioid receptor binding, and the interactions between the two systems likely contribute to distorted reward processing and the development of binge eating disorders. These changes play a role in not just food addiction, inhibitory control deficits, and decreased performance in cognitive abilities, but also vulnerability to comorbid diseases. It's worth remembering that food addiction and eating disorders are ongoing areas of research and that whether alterations in endogenous systems are consequences of binge eating disorder, or are a genetic basis that drives the development of BED, should be an important focus of future studies. By addressing these gaps, this review aims to provide insights into the underpinnings of BED, which may lead to novel therapeutic strategies that target the neural circuits governing maladaptive reward learning and cognitive impairments.

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Discussion

2. Genetic Polymorphisms of Dopamine D2 Receptor Genes:

2.1. Dopamine's Role in Reward Memory:

Dopamine is an abundant neurotransmitter in the brain, and depending on the location where it is present, its functions–including regulating inhibitory control and working memory in the prefrontal cortex, motivation processing in mesolimbic systems of the ventral striatum, impulsivity control in the striatum, etc–vary. Furthermore, dopamine synthesis and release occur in dopamine neurons located in three main regions of the midbrain: the ventral tegmental area, the substantia nigra, and the retrorubral field.[4] In particular, DA projection in the mesolimbic pathway, the primary neural network involved in reward processing and pleasure,[6] reinforces behaviors that signal positive sensations, which helps the brain remember the rewarding stimuli. In the case of binge eating disorder, dysregulation of the dopaminergic pathway via polymorphisms in dopamine D2 receptor genes exaggerates this process, solidifying the strong memories that food is pleasure and reward.[3]

Recent studies have corroborated that several polymorphisms of the dopamine D-2 like genes (a subfamily of dopamine receptors that include D2, D3, and D4 subtypes), specifically the dopamine D2 receptor, are associated with irregular reward sensitivity and decision making, thus contributing to impulsive and continuous binge eating behaviors reports that food restriction leads to an upregulation in DA transporter,[1,3] and bingeing behaviors are speculated to cause changes in dopaminergic gene expression, with a reduction of DRD2 mRNA and an increase of DRD3 mRNA in the nucleus accumbens(NAc): a brain region crucial for motivation, reward processing, and reinforcement learning commonly related to addiction. In addition, animal models have shown that binge eating sucrose results in continual DA release in the NAc.[3] These observations are noteworthy as they suggest that different types of dopamine proteins have distinct modifications and changes from each other, and that the different variants in binding and density contribute to the susceptibility and continuation of binge eating disorders.[4]

2.2. Dopamine 2 Receptor Gene Polymorphism:

The *DRD2* gene is frequently associated with Reward Deficiency Syndrome, a condition where individuals have difficulty experiencing satisfaction and pleasure, causing them to resort to compulsive behaviors to compensate, which can manifest as overeating, drug/alcohol addiction, and gambling. It's hypothesized that the substances (like drugs and palatable food)that elevate brain dopamine are used as a method of'self-treatment' to enhance the unresponsive DA system and increase hedonic sensations.[7]

Several polymorphisms of the D2 receptor gene have been studied, including the Taq1A, C957T, and 141Ins/Del polymorphism. In the Taq1A C/T polymorphism, the T (A1) allele is correlated with diminished levels of DRD2 density and binding affinity in comparison to the C (A2) allele. However, recently it was shown that this single-nucleotide polymorphism does not reside in DRD2, but in a gene further downstream called Ankyrin Containing Kinase 1 (ANKK1).[1] In C957T, the T/T allele is associated with increased DRD2 availability and binding affinity relative to C/T and C/C. Lastly, the 141 Ins Del polymorphism is related to reduced D2 receptor expression.[4]

Of the studied variants of the *DRD2* gene, Taq1A+ (A1/A1 and A1/A2 genotypes), is reported to cause a reduction in dopamine function compared to Taq1A- (A2/A2), as there's a diminished level of DRD2 receptor density in the striatal region.[1] It's reported that lower DRD2 density in this brain region leads to aberrant reinforcement learning and impulsive decision-making related to rewards. Therefore, it is usually assumed that BED subjects who carry more than one A1 allele are more likely to possess a relatively low level of sensitivity to reward, a factor that is likely relevant to their bingeing behaviors.[7]

2.3. Case-control study on Taq1A Polymorphism and Subject Diagnostic:

This case-control study was chosen as other literature had limitations on ANOVA analysis data regarding both diagnostic groups and dopamine receptor polymorphism, and how they interact. A 2008 study carried out a case-control study on binge eating disorder regarding reward sensitivity and the D2 dopamine receptor gene in humans, trying to find if there was a correlation between genetic predispositions and patient backgrounds.[7]

2.3.1. Subjects & Methods:

The study involved comparing samples of adults (N=166) with BED to samples of normal-weight and obese controls on reward sensitivity. The researchers looked at six different markers (specific locations on the gene) of the *DRD2* gene. By examining the markers, they can conclude if certain genetic variations are more related to irregular reward processing and if that contributes to the development of BED. *Genotyping*: The blood of subjects was extracted, and a high-salt procedure was used to collect the DNA from samples to identify specific genetic variations and DNA sequences.[7]

2.3.2. Data:

Collected from the case-control study of binge eating disorder, Table 4 displayed a two-way ANOVA summary, with two variables: Group and Genotype as independent variables, and the dependent variable: sensitivity to reward. Data of the diagnostic group included a comparison between normal-weight controls (N=59), BED individuals (N=56), and obese controls (N=51); ($F=5.75$, df effect=2, df error=160). Additionally, data of variable Taq1A genotype included A1/A1 and A1/A2 compared to A2/A2; ($F=4.53$, df effect=1, df error=160). There was also a recorded interaction between Group and Taq1A genotype on reward sensitivity ($F=3.75$, df effect=2, df error=160).

2.3.4. Results:

By using the ANOVA data table from the 2008 case study, I found the effect size of the two main variables and their interaction by calculating eta-squared to represent the proportion

of variance in the dependent variable that is explained by the independent variable.

Partial η^2 & ω^2 (latter only for One-Way ANOVA)			
F	5.75	ηp^2	0.067055
df effect	2	ωp^2	0.055072
df error	160	*p*	0.003876

Figure 1: Effect of group on sensitivity to reward. The effect of Group on sensitivity to reward has a medium effect size of ηp^2=0.067, suggesting that the differences in reward sensitivity between the diagnostic groups (normal weight, BED, and obese) are meaningful and have a moderate impact.

Partial η^2 & ω^2 (latter only for One-Way ANOVA)			
F	4.53	ηp^2	0.027532
df effect	1	ωp^2	0.021325
df error	160	*p*	0.034836

Figure 2: Effect of Taq1A genotype on sensitivity to reward. Impact of Taq1A genotype on reward sensitivity is np^2=0.028, falling between a small and medium effect, leaning towards the smaller effect.

Partial η^2 & ω^2 (latter only for One-Way ANOVA)			
F	3.75	ηp^2	0.044776
df effect	2	ωp^2	0.032640
df error	160	*p*	0.025610

Figure 3: Effect of group x Taq1A interaction on sensitivity to reward. The interaction effect between diagnostic groups and Taq1A allele on reward sensitivity is between a small and medium effect (ηp^2= 0.045), demonstrating that the way Taq1A genotype influences reward sensitivity across diagnostic groups is moderately different.

The results from Figure 1 indicate that the diagnostic groups have meaningful differences in reward sensitivity, aligning with the hypothesis that binge eating is associated with an altered dopamine system, as DA is central to reward sensitivity.

On the other hand, the ηp^2 value of the effect of Taq1A genotype on reward sensitivity is 0.028, which falls between a small and medium effect, but it's closer to the small effect value displayed in Figure 2. This signifies that the genotype on its own has a limited, but still present, impact on reward sensitivity. While the presence or absence of the Taq1A allele has a statistically significant effect, the magnitude of its impact on reward sensitivity is relatively small on its own, suggesting that one's genotype isn't a sole determinant, but rather one of many contributing factors. The small effect of the Taq1A allele associated with lower DRD2 levels, hence lower dopamine binding and signaling, shows that this genetic variant contributes to a less responsive reward system. We can speculate that BED subjects act on impulse to compensate for this dopamine deficit, leading to a cycle of excessive consumption of foods high in fat and sugar to achieve adequate dopamine signaling.

Figure 3 illustrates the interaction effect between diagnostic groups and Taq1A allele on reward sensitivity, being between a small and medium effect (ηp^2= 0.045), demonstrating that the way Taq1A genotype influences reward sensitivity across diagnostic groups is moderately different. A significant interaction effect would mean that having the A1+ allele is strongly related to BED subjects relative to obese or normal weight controls. However, the resulting medium effect size suggests that BED is driven by complex factors, where genetic predisposition may only express itself in certain environmental conditions or specific populations (like the diagnostic groups).[6] This supports the hypothesis that binge eating behaviors aren't solely caused by a single gene, but are influenced by a complex combination of genetic predispositions and compulsive behaviors. Finally, the result highlights how more studies are needed to thoroughly understand and investigate the relationship of Taq1A polymorphism and environmental factors on BED susceptibility and sustainment.

Dopaminergic proteins and various polymorphisms are thought to be responsible for the development and maintenance of Binge Eating Disorder (BED). It's suggested that food restriction and subsequent binging alter dopaminergic gene expression, highlighting the distinct roles of different dopamine proteins in reward memory and reward sensitivity.7 While a Genotype × Group ANOVA showed a significant effect of the Taq1A polymorphism on reward sensitivity, this genetic factor only accounted for a small portion of the variance. This suggests that other factors, such as different genetic variations, environmental influences, or comorbidities, are also at play.

3. μ-Opioid Dysregulation in Binge Eating Behaviors:

The μ-opioid (mu-opioid) system is an important part of the body's endogenous opioid system involved in motivation, reward, and addictive behaviors. The μ-opioid receptor (MOR) is a crucial G protein-coupled receptor that can be activated by opioid drugs like morphine or the body's natural opioid peptides, including enkephalin. Among the different opioid receptor subtypes, μ-opioid receptors strongly contribute to the rewarding impact of palatable food intake, as the system regulates motivation for food and hedonic overeating, the consumption of food solely for pleasure and not to maintain energy homeostasis.[2] Research in both humans and animal models suggests that alterations of the μ-opioid system in the brain's limbic areas are a key factor in the modulation of hedonic responses to food, hence, the maintenance of binge eating disorder, especially when subjects are involved in a cycle of food deprivation followed by access to feeding.

3.1. Role of μ-Opioid in Hedonic Overeating & Incentive Motivation:

The μ-opioid system regulates hedonic responses by generating feelings of pleasure and satiation through μ-opioid binding in the nucleus accumbens, and it modulates motivation by interacting with the dopamine system to amplify the desire to experience reward.[3] Although it's been acknowledged that the mesolimbic dopamine system drives the motivational aspects of binge eating, it has been proposed that opioids can mediate incentive motivational processes that underlie the tendency to consume palatable foods.[2]

When individuals consume palatable foods, especially those rich in fat or sugar, the brain releases endogenous opioid peptides, which bind to μ-opioid receptors in regions of the brain that regulate reward and motivation, triggering a signal

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that produces positive feelings and satisfaction.[2] Binge eating behaviors are reinforced through this pleasurable feeling, making individuals more vulnerable to seek out that food again.[8] According to existing rodent studies, a reduction of opioid mRNA levels was found in sucrose-dependent rats.[9] However, other animal studies have proven that binge behavior and motivation are likely related to increased μ-opioid binding in brain regions associated with reward, specifically the nucleus accumbens, where opioids are abundant, which elevate appetite for food.[1,3] To elaborate, appetite-enhancing effects can be potentiated with repeated activation of MOR binding; over time, environmental triggers (seeing specific food packaging, sensing the smell of food) can be linked to heightened appetite, leading to cravings even in the absence of food itself.[10]

Given these results, the premise is that μ-opioid binding varies in distinct areas of the brain as the density of μ-opioid ligands and μ-opioid-receptors is not uniform throughout the brain. To support this statement, the varying density allows both endogenous opioids and pharmacological drugs, like morphine, to have targeted effects.[9] This proposes a hypothesis that BED subjects with comorbid drug addiction could be more susceptible to sustained binging as they're likely to have increased MOR binding in the nucleus accumbens, creating stronger feelings of motivation to hedonic sensations. Moreover, if this hypothesis is proven, researchers could use the more abundant and well-studied drug therapies to aid the development of effective treatments for binge eating disorder, since the two addiction disorders have similar reward pathways. Overall, a dysregulation of μ-opioid binding and repeated activation of MOR in the NAc, along with environmental cues and comorbid diseases, are able to enhance motivation and pleasure, leading to an exaggerated sense of reward from food and overpowering the body's natural signals for satiety and contributing to compulsive eating behaviors.

3.2. μ-Opioid Binding and Fasting Frequency:

This study was specifically chosen as it had significant data regarding a relationship between fasting and binge eating, while other literature lacked this interaction. A 2005 rodent study by Badreddine Bencherif (2005) found that food deprivation followed by excessive eating changes μ-opioid binding in the brain's limbic areas; alterations in μ-opioid binding in the insular cortex/insula, a brain region in that facilitates gustatory sensory information and cognitive functions,[1] may be an underlying factor that maintains the pathogenesis of cyclic binging behaviors of bulimic subjects.

3.2.1. Subjects & Methods:

A study approved by Johns Hopkins examined 8 normal-weight women with bulimia nervosa and 8 normal-weight healthy controls. Both groups were similar in age and body mass index (BMI). Bulimic subjects underwent a psychiatric screening to confirm the absence of comorbid conditions. A psychiatric evaluation was conducted for all control participants to verify that they had a previous history of psychiatric illness and were off psychotropic medication; no control subjects reported fasting or having irregular eating behaviors in the last month.[8]

The methods for imaging include both MRI and PET scans to collect brain images of participants. To ensure data consistency, all subjects were informed not to eat 3 hours before their PET scan, and wore fitted thermoplastic facial masks to minimize head movement. The MRI was used to acquire high-resolution images for the detailed structure of the brain, while the PET scan allowed researchers to measure μ-opioid receptor binding by administering subjects with a dose of 11C-carfentanil, a radiotracer that binds to MOR. The results were used to reconstruct and produce detailed images of the opioid system's activity in the brain.[8]

3.2.2. Data:

The study's data reveal no statistical differences in age (P=0.35), BMI (P=0.21), or whole-brain μ-opioid receptor binding (P=0.41) between bulimia nervosa subjects and the control group. However, there was a 17% decrease in MOR binding in the left temporoinsular cortex of BN individuals.[8]

3.2.3. Results:

Reduced μ-opioid binding in the insular cortex, which is thought to be caused by a decrease in MOR due to a heightened release of natural opioids following food restriction, may be linked to the repetition and persistence of bingeing behaviors in bulimia nervosa. Results from the study presented a strong inverse relationship between μ-opioid binding and fasting frequency in the bulimia nervosa group, indicating that higher fasting frequencies correlate with lower levels of MOR binding, specifically in the temporoinsular cortex on both sides of the brain. Notably, researchers found that the frequency of fasting over the past month was the only eating behavior assessed that demonstrated a statistically significant relationship with MOR binding in the temporal cortex. Fasting in this experiment was defined as intentionally not eating food for more than eight hours at a time to influence one's physical figure or weight. Lastly, the MRI results revealed that diminished receptor binding wasn't a result of structural brain loss, reinforcing that fasting was the sole variable assessed that was related to MOR binding.[8]

Subsequent findings from this study have shown that insula activation only occurred when palatable food was enjoyable and desired.[8] However, once individuals reached satiation and no longer felt pleasurable sensations, insular activation stopped. This suggests that the insula is heavily involved in reward mechanisms, but doesn't have strong correlations with feelings of fullness.[1] It's worth mentioning that the brain's processing of food reward in the insula may vary significantly in people who are or have been obese, potentially making them more vulnerable to wanting palatable foods even when satiated. Not only does the insula play a role in reward-driven behaviors in binge eating and bulimia nervosa, but it's also been identified to implicate other conditions such as substance addiction, gambling, and anxiety disorders.[8]

The recurrence and preservation of bingeing behaviors in bulimia nervosa are likely correlated with reduced μ-opi-

oid binding in the insular cortex as a result of downregulated opioid receptors, a cellular response to increased endogenous opioid release after food restriction.[8] Ultimately, the reduction of MOR may be a trait-like indicator in bulimic susceptible individuals that increases the hedonic value of palatable foods in reward memory.[1,2] However, as much as we want to find effective treatments, clinical data suggest that certain people (like obese individuals) may possess a higher motivational value to food cues compared to others; thus, they're more susceptible to overeating.[2]

3.3. Opioid Agonists & Antagonists:

To better understand the neurobiological basis of binge eating in binge eating disorder and bulimia nervosa, animal models of these disorders have been developed to mimic the maladaptive responses in humans.[2] Recent work in this area indicates that the administration of μ-opioid receptor agonists generally increases food intake, while antagonists tend to decrease it.[11]

Studies show that rats that binge on sweet or fatty foods show a decrease in enkephalin (endogenous opioid) expression but an increase in μ-opioid receptor binding in brain regions associated with reward, like the nucleus accumbens.[11] The NAc is a central part of the mesolimbic system responsible for reward and motivation, and its projections to other brain regions like the ventral pallidum are crucial in regulating these processes.[2] An important finding is that the ability of MOR agonists to increase food intake is specifically localized to a hotspot within the NAc shell (the rostrodorsal quadrant of the NAc medial shell). It's been discovered that this hotspot stimulates δ-opioid receptor subtype, which is implicated in its role in emotional processes, including the amplification of hedonic reactions to sweetness.[11]

Pharmacological studies have further explored this relationship. The injection of μ-opioid agonists into the nucleus accumbens is potently orexigenic (appetite-stimulating), particularly for high-calorie foods.[3] On the other hand, the effects of opioid antagonists are more complex and varied. The broad-spectrum antagonist naltrexone typically reduces sweet or fatty food intake only at high doses;[2] it's also been shown to inhibit stress-induced eating in rats with food restriction followed by refeeding. Additionally, the μ-opioid and κ-opioid antagonist nalmefene has been shown to reduce binge attenuation and binge-like consumption of a sucrose-rich diet in rats in a dose-dependent manner.[3] Similarly, the selective μ-opioid receptor antagonist GSK1521498 also reduced binge eating in rats and hedonic preference (specifically for higher concentrations of sugar and fat), supporting the idea that the endogenous opioid system promotes hedonic intake.[2,3]

Currently, the μ-opioid receptor antagonist GSK1521498 is undergoing clinical development for the treatment of compulsive eating disorders and obesity; it was tested and compared to naltrexone, a MOR antagonist clinically approved for alcoholism.[2] This reviews the hypothesis that established treatments for comorbid addiction diseases can be used to develop therapies for binge eating disorders. It also suggests that the same drug might be able to reduce addiction in people who are diagnosed with both substance addiction and BED.

In humans, there is evidence that the A118G allele of the μ-opioid receptor gene is overrepresented in people with binge eating disorders, suggesting a genetic predisposition. Some studies have shown that μ-opioid receptor antagonists can reduce the motivation to view high-calorie food images and may decrease the subjective pleasantness of palatable food in patients who binge eat.[11] However, despite these promising findings, treatment with μ-opioid receptor antagonists has revealed mixed results in consistently reducing binge eating in individuals with BED.

The discrepancy between animal and human studies suggests the relationship is more nuanced. One hypothesis is that binge eating behavior, which escalates over time in rodent models, is due to a form of plasticity in the NAc opioid system. This would mean that binge consumption becomes dependent on the activation of these receptors by endogenous opioids. This hypothesis predicts that opioid antagonists would be more effective in blocking binge-like consumption than in reducing non-binge eating, a prediction that has been tested in several studies.

4. Interactions Between the Opioid System and the Dopamine System in Addiction Behaviors:

The dopamine system and opioid system have been proven to be two key players in the mesolimbic pathway responsible for reward and motivation in binge eating disorders, with the DA system being primarily associated with the motivational aspect of reward and the opioid system being linked to liking palatable food.[1] Interestingly, however, the opioidergic pathway doesn't just impact hedonic responses, but can modulate dopamine release in the forebrain (like the nucleus accumbens), leading to the sustainment of rewarding emotions, hence, bingeing behaviors.[9] This interaction is crucial to fuel intense cravings and loss of control, which is characterized in this disorder. The question of whether the interaction between opioid pathways and dopamine neurotransmission is a direct or indirect pathway in BED, and if the dysregulation of one significantly impacts the other regarding impulsivity and pleasurable responses, is something to consider.

4.1. Opioidergic Regulation of the Dopamine System in Reward Processing:

The nucleus accumbens (NAc) is a terminal region of the interaction between the opioid and dopamine pathway; the mesolimbic dopaminergic system serves as the location where endogenous opioids act to both affect hedonic processes and modulate dopamine release.[3] Given existing research, it's suggested that this interaction is the effect of palatable foods on the midbrain's reward circuitry. The process begins with the release of opioids, which then act on μ-opioid receptors located on GABAergic neurons, a nerve cell that produces inhibitory GABA neurotransmitters, in the ventral midbrain.[1] By inhibiting the GABAergic neurons, the opioids disinhibit dopamine neuron firing, resulting in increased dopamine release in the forebrain, including the NAc. This amplifies DA release, cre-

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ating a powerful feedback loop where the pleasure regulated by opioids reinforces the desire created by dopamine to continue eating. Overall, the intense, rewarding sensation that reinforces binge behavior leads to the potentiation of the disorder.[9]

Interestingly, several neurochemical adaptations seen in intermittent sugar consumption, a model for binge behaviors, reflect those found in drug stimulants or opiate sensitization. These include increased μ-opioid receptor binding in the NAc shell, decreased D2 receptor sensitivity with opiates, and a decrease in baseline dopamine transmission, so that subsequent surges of glucose injection create an intense DA activation.[9]

4.2. Opioid and Dopamine Reward Processing in Comorbid Diseases:

As binge eating falls under addiction disorders, many studies have found that comorbidities such as substance addiction and gambling have similar reward pathways involving opioidergic and dopaminergic systems like BED. To understand comorbid conditions better, a study was conducted to find specific changes in the dopamine and opioid mRNA levels that lead to dysregulated reward processing in addiction disorders, and the connections between BED and drug addiction.[9] This study was chosen to be analyzed in depth as it demonstrates how the specific group of D2 dopamine receptor gene expression changes depending on where it is located. Other studies have limitations on which of the specific genes are involved, and lack information on how the genes' interactions vary in the nucleus accumbens compared to the caudate putamen.

4.2.1. Methods & Data:

Researchers obtained 16 male Sprague-Dawley rats and divided them into two groups. The experimental group (N=8) was put on a 21-day cycle of food deprivation followed by access to both standard food and a 10% sucrose solution, which led to signs of opiate withdrawal when the rats were given naloxone, an opioid receptor antagonist. The control group (N=8) followed the same cycle but without access to the sucrose solution.

To analyze the effects, all rats were sacrificed, and their brains were dissected and analyzed to measure mRNA expression for six genes previously studied in morphine-dependent rats by using PCR technology. Using a multivariate analysis method, researchers found significant differences between the nucleus accumbens and the caudate-putamen (CPu) in rats with sucrose dependency. The analysis, which looked at how genes interact in pairs and trios, was much more effective at distinguishing between treatment groups in the NAc than in the CPu.[9]

4.2.2. Results:

Researchers found that sucrose dependency had a more significant effect on gene expression in the nucleus accumbens than in the caudate-putamen. Specifically, the genes for the D2 dopamine receptor, preproenkephalin (pE), and protachykinin (pT) showed the most notable changes. Statistical analysis confirmed that these changes in D2, pE, and pT expression in the nucleus accumbens were significant (0.05 level).

In the nucleus accumbens, the D3 dopamine receptor gene was found to be the most critical interacting gene when analyzed with other genes, suggesting that D3 may play a key role in mediating the brain's response to sucrose dependency by interacting with other dopamine-related and neuropeptide genes. Additionally, all genes had only a moderate correlation with one another, showing no distinct pattern. This is the same region where the multivariate analysis was most effective at identifying sucrose-dependent rats. In contrast, the caudate-putamen showed a very different pattern where five genes (D1, D2, pE, pD, and pT) were highly correlated with each other. However, the D3 gene was only weakly and negatively correlated with these five genes. This region, with its high correlations, is where the multivariate analysis failed to find significant cooperative interactions.

Overall, moderate gene correlations in the nucleus accumbens seem to allow for the observation of cooperative gene interactions, while high correlations in the caudate-putamen appear to lack these interactions.[9]

4.2.3. Study Discussion:

The study's main finding is that the changes in gene expression in sucrose-dependent rats are very similar to those seen in morphine dependent rats. Both substances cause a decrease in dopamine D2 receptor and opioid mRNAs, and an increase in dopamine D3 mRNA in the striatal forebrain, which suggests that sucrose and morphine may activate similar neural pathways.

One possible mechanism for this commonality is through changes in dopamine transmission. While the exact process isn't fully understood regarding palatable foods, it's known that both morphine and sucrose are able to elevate dopamine release in the forebrain. Morphine does this by acting on opioid receptors in the midbrain, which then disinhibits dopamine neurons, causing more firing and releasing more dopamine. This process is similar to how the body's endogenous opioids facilitate natural behaviors like eating.[9]

In the context of binge eating disorder, opioidergic and dopaminergic interaction fuels a perpetual cycle of impulsiveness, aberrant motivation towards food, and lack of control. Decreased ventral-striatal and ventral-midbrain Dopamine D2-like receptors, coupled with increased dopamine release in the nucleus accumbens, have been linked to greater impulsivity and motivation abnormalities.[1] Simultaneously, increased opioidergic neurotransmission in the NAc is tied to the hedonic aspects of reward. The ability of opioids to increase dopamine release sustains these rewarding emotions, further reinforcing bingeing behaviors.

Animal studies of intermittent sugar bingeing show that bingeing behavior produces opiate-like effects on gene expression in the brain, especially in the NAc. In the study, the observed changes, a decrease in D2 dopamine receptor mRNA and an increase in D3 dopamine receptor mRNA, suggest a compensatory mechanism. Researchers believe that when rats consume sugar, a sudden rush of DA triggers changes in the expression of genes like D2 and D3. These gene changes aren't just random; they appear to be part of the brain's built-in

defense system, actively working to calm down or normalize the brain's response to the overwhelming dopamine release caused by sugar.[9] This finding raises an important question about cause and effect in human diseases. To elaborate, what the researchers observed as an altered biological marker in human diseases might not be the root cause they should target for treatment, but rather the body's attempt and response to cope with the disease.

This complex interaction demonstrates that the dysregulation of one system can significantly impact the other, creating a neurobiological vulnerability that contributes to the intense cravings and loss of control characteristic of binge eating.

■ Conclusion

Literature and research into binge eating disorder (BED) highlight a complex interplay of genetic, neurobiological, and psychological factors. A key finding is the similarity between the brain's response to bingeing on palatable foods and its response to drugs of abuse. This suggests that BED is not just a matter of self-control but is rooted in changes to the brain's reward circuitry.

Research points to two major systems involved: the dopaminergic and opioidergic systems. Specifically, a reduction in dopamine D2 receptors (DRD2), often linked to genetic polymorphisms, is associated with a less responsive reward system. This may drive individuals to seek out rewarding substances like high-fat and high-sugar foods to compensate for a lack of pleasure. Simultaneously, the μ-opioid system, which is responsible for the pleasure derived from eating, also becomes dysregulated. Studies show that bingeing and frequent cycles can alter μ-opioid receptor binding, particularly in the insular cortex, reinforcing the desire for palatable food.

Binge eating disorders are developed and sustained through various polymorphisms in dopaminergic proteins, and are thought to have specific conditions and populations that are more prone to certain genetic predispositions that alter hedonic aspects of reward memory which is supported by several literatures that states food restriction and subsequent binging episodes lead to an increase in DA transporter and alterations in dopaminergic gene expression, indicating different dopamine neurotransmitters and proteins have different roles in establishing reward memory and reward sensitivity. This pushes future studies to enhance research on various dopamines and their pathways to develop new therapies and treatments specifically targeted towards certain parts of the dopaminergic system; if we're familiar with the function of each type of dopamine in reward memory and BED, we're likely to create a more effective therapy. It is also thought that comorbidities like obesity could have alternative genetic variations that interact with the A1 allele in Taq1A that influence DA activity. Another hypothesis is that environmental factors, habitual features, or comorbidities of an individual make them more susceptible to bingeing behaviors, creating negative consequences over time that can disrupt reward memory and dopamine release.

Additionally, evidence suggests that the relationship between the dopaminergic and opioidergic system is crucial; the opioid system acts to disinhibit dopamine neurons, creating a powerful feedback loop that amplifies the rewarding sensation of binge eating, explaining why treatments targeting these systems–such as dopamine and opioid antagonists–have shown promise in reducing binge-like behaviors in animal models.

Ultimately, the research indicates that the neural changes seen in BED may be a compensatory response to a pre-existing vulnerability, rather than a cause in and of themselves. This poses questions like why teenagers/adolescents are more susceptible to binge eating disorders than any other age group? What combination of neurobiological markers and environmental factors increases the susceptibility to BED? And as our society is changing rapidly, how is binge eating disorder evolving, and what biological mechanisms are behind the changes? These questions are vital to future studies for developing effective therapies that go beyond traditional psychological approaches to target the underlying biological mechanisms.

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