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REVIEW ARTICLE

Mesolimbic dopamine and its neuromodulators in obesity and binge eating

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Obesity has reached epidemic prevalence, and much research has focused on homeostatic and nonhomeostatic mechanisms underlying overconsumption of food. Mesocorticolimbic circuitry, including dopamine neurons of the ventral tegmental area (VTA), is a key substrate for nonhomeostatic feeding. The goal of the present review is to compare changes in mesolimbic dopamine function in human obesity with diet-induced obesity in rodents. Additionally, we will review the literature to determine if dopamine signaling is altered with binge eating disorder in humans or binge eating modeled in rodents. Finally, we assess modulation of dopamine neurons by neuropeptides and peripheral peptidergic signals that occur with obesity or binge eating. We find that while decreased dopamine concentration is observed with obesity, there is inconsistency outside the human literature on the relationship between striatal D_2 receptor expression and obesity. Finally, few studies have explored how orexigenic or anorexigenic peptides modulate dopamine neuronal activity or striatal dopamine in obese models. However, ghrelin modulation of dopamine neurons may be an important factor for driving binge feeding in rodents.

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Key words: Diet-induced obesity, hormones, mesolimbic dopamine, neuropeptides, striatum, ventral tegmental area.

Introduction

The current obesity epidemic has provided a strong impetus for research aimed at investigating the neurobiological basis of overeating. Mesocorticolimbic dopamine circuits are critically involved in motivated behavior. With cell bodies originating in the ventral tegmental area (VTA) and projecting to various regions including the nucleus accumbens (NAc), caudate putamen, amygdala, and prefrontal cortex,[1] dopamine neurons have long been studied in the context of motivation and drug addiction, as all drugs of abuse share the ability to stimulate dopamine neurotransmission.[2] Recently, dopamine circuits have emerged as an important mediator of food intake and overeating, and thus represent an ideal target for the development of drug therapies aimed at curbing overeating. The goal of the present review is to compare changes in mesolimbic dopamine function in human obesity with diet-induced obesity in rodents. Additionally, we will review the literature to determine if dopamine signaling is altered with binge eating disorder in humans or binge eating modeled in rodents. Finally, we assess modulation of dopamine neurons by neuropeptides and peripheral peptidergic signals occurring with obesity or binge eating. Obesity and binge eating represent 2 types of overeating, and both pathologies reveal significant alterations in dopamine function. Contrasting the similarities and differences in dopamine function between the two might provide important insights into these pathophysiological states. In the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5),[3] binge eating disorder (BED) is defined as "recurring episodes of eating significantly more food in a short period of time than most people would eat under similar circumstances, with episodes marked by feelings of lack of control." Similar to humans, rodent obesity is defined as increased weight and adipose tissue compared to controls and often co-occurring with acquired insulin resistance and hyperleptinemia.[4] In the first part of this review, we will contrast dopamine function in obesity and BED, with an emphasis on dopamine metabolism in striatal regions, the activity of the dopamine transporter, the main uptake mechanism of dopamine in the

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striatum, and the dopamine D_2 receptor. In the second section, we will discuss how the hormonal and neuropeptide profiles observed in obesity and binge eating might explain the differences and similarities in dopamine function observed in the first section of the review.

Contrasting Mesolimbic Dopamine Function in Obesity and Binge Eating Disorder

Dopamine metabolism

Both human and animal studies demonstrate that striatal responses are altered in diet-induced obesity. In human studies, the direction of these effects is inconsistent. For example, functional magnetic resonance imaging (fMRI) studies using human obese subjects have demonstrated blunted striatal responses to the receipt of palatable foods[5–7] and a cue predicting sucrose,[8] but increased striatal responses to visual palatable food stimuli.[9–11] Based on these divergent findings, Carnell *et al*[12] have proposed a "dynamic" model of striatal modulation in obesity with hypersensitivity to visual stimuli and hyposensitivity to the consumption of food reward. The rodent literature reveals more consistent results, with most studies showing blunted striatal dopamine in diet-induced obesity. Most studies use a 60% high fat diet or a cafeteria diet to induce obesity in rats or mice. However, there is considerable variability in the duration and onset of the exposure to the test diet. For the purposes of this review, only experiments using long-term dietary manipulations (minimum of 6 weeks) and demonstrating significant weight gain will be discussed. Diet-induced obesity is associated with decreased tyrosine hydroxylase (TH) expression, the rate-limiting factor in the synthesis of dopamine in dopamine-relevant brain regions.[13–15] Furthermore, blunted striatal dopamine concentrations in diet-induced obesity have been described using several techniques, including total dopamine concentrations and/or dopamine turnover in the striatum in brain punches,[16,17] decreased extracellular concentrations measured with microdialysis,[18,19] and decreased evoked release with electrochemistry.[18] Only one study revealed an increase in nucleus accumbens dopamine measured with microdialysis in obesity prone rats on an 8-week high fat diet.[20] Taken together, in rodent models of diet-induced obesity, there is a decrease in striatal dopamine concentration.

A limited number of studies have measured dopamine concentration in subjects with binge eating disorder. An interesting study conducted by Wang *et al*[21] found that food stimuli and the administration of methylphenidate (a weak, long-acting catecholamine transporter inhibitor) induced a significant increase in striatal dopamine in obese binge eaters but not in obese subjects without binge eating disorder. This study suggests that dopamine tone is elevated in binge eating disorder. Elevated striatal dopamine tone has also been observed in animal models of binge eating, including rats given intermittent access to 10% sucrose and chow followed by 12 hours of food restriction[22] and in rats on a restricted feeding schedule with access to sucrose or water followed 2 hours later by chow.[23] It is important to note that in these animal studies, periods of food restriction are used to induce bingeing behavior. A large body of evidence indicates that food restriction and weight loss augment dopamine tone (reviewed in Carr[24]), limiting our ability to make conclusions about dopamine tone enhancement in these bingeing models. While c-fos activation in VTA TH positive neurons has been observed with an intermittent access to high fat diet model of binge eating that does not require food restriction,[25] dopamine metabolism in animal models of bingeing without food restriction has not been measured. Taken together, preliminary evidence suggests that diet-induced obesity and binge eating may have different effects on dopamine concentration in the NAc, such that dopamine concentration is decreased in obesity, but likely increased with binge eating. Further studies are required to determine if this difference is due to a degree of adiposity associated with obesity and not binge eating, or if there are other factors underlying this difference.

D2 receptors

Most studies examining the relationship between human obesity and dopamine D_2 (and D_4) receptor availability have revealed a decrease in D_2 receptor availability in obesity,[26–28] although increased availability has also been reported in fasted obese subjects.[29] One important caveat with some of the human literature is that raclopride, which is used in positron emission tomography (PET) studies, has lower affinity for the D_2 receptor than dopamine.[30] Thus, conditions with high dopamine concentration would appear as low D_2 receptor binding. However, other studies using fallypride have also demonstrated decreased D_2 receptor availability obese subjects.[31] An important question is what is the underlying cause of decreased D_2 receptor availability in obesity? For example, overconsumption leading to obesity may induce decreased D2, genetic differences in expression of D_2 receptor leading to increased susceptibility of weight gain, or both factors may occur together. Variants in the Taq1A allele of the *ANKK1* gene (neighboring the 3′ untranslated region of the DRD_2 gene)[32] are associated with decreased D_2 receptor expression.[33] Some studies have observed positive correlations between the TaqIA allele with body mass index,[34,35] while others have failed to observe this correlation.[36] Additionally, the DRD4-L allele has also been associated with higher body mass index (BMI) in

humans, including individuals with bulimia nervosa.[37] Taken together, high BMI is associated with decreased D_2 receptor availability in the striatum. However, it is important to consider the metabolic state of the individual (fasted or sated) when they are being assessed, and whether obesity induces decreased D_2 receptor function or if this is a trait that infers susceptibility to obesity.

In rodents, studies examining the effects of diet-induced obesity on D_2 receptor expression have yielded mixed results. High-fat feeding and cafeteria feeding have been shown to reduce[38–40] and increase[41–43] striatal D_2 receptor expression. Putative reasons for differences include the availability of choice,[44] the macronutrient composition of the diet,[45] and the method employed to measure D_2 receptor expression. In an attempt to identify important factors, we mapped out differences in D_2 receptor expression across different studies (mostly focusing on animal studies and receptor expression, not mRNA) and identified the region of the striatum examined (ventral vs. dorsal), the species (rat vs. mouse), the type of diet, and the length of diet exposure. However, as observed in Figure 1, obesity does not predict alterations in D_2 receptor expression. One important caveat with many of these studies is that antibodies for D_2 receptors are generally not selective, and many of these studies did not show controls for D_2 antibody selectivity. Thus, more studies using more selective methods to measure D_2 receptor expression or function are needed to clarify how the development of diet-induced obesity impacts striatal D_2 receptors.

The association between the expression and function of striatal D_2 receptors and binge eating behavior has received very little attention in the literature. In a study comparing the genotypes of obese individuals with and without binge eating disorder, Davis *et al*[46] report that binge eating is associated with increased frequency of a gain of function allele (A2 homozygosity) in the dopamine D_2 receptor gene. Furthermore, in rodents, bingeing on sugar is associated with a significant decrease in D_2 receptor binding.[40,47] Thus, future studies are required to assess if binge eating is associated with alterations in D2 receptor expression or function.

The dopamine transporter (DAT)

Animal studies have reported alterations in DAT expression and function in diet-induced obesity, although human studies have yet to reveal consistent effects. Thomsen *et al*[48] observed no correlation between body mass index and striatal DAT availability in the striatum, caudate nucleus, and putamen and no significant group difference between obese and severely obese and normal weight controls. Similarly, in a study of 123 participants, the authors report no association between BMI and striatal DAT availability.[49] However, low striatal DAT levels were associated with elevated BMI in 50 human participants using single-photon emission computed tomography (SPECT).[50] Mixed results were obtained in animal models of obesity. Cone *et al*[51] report a deficit in the rate of dopamine uptake by the DAT in rats exposed to a high-fat diet for 6 weeks but no change in mRNA. It is important to note that the rats did not develop obesity in this study. Likewise, South *et al*[42] and Narayanaswami *et al*[20] report a reduction in DAT expression in obese rodents. Importantly, many of these studies use a variety of types and duration of diets to induce obesity, and a few measure hyperleptinemia or insulin resistance. Given that both leptin and insulin can also modulate DAT expression and function,[52,53] it is important to consider the metabolic state of the animal in these experiments.

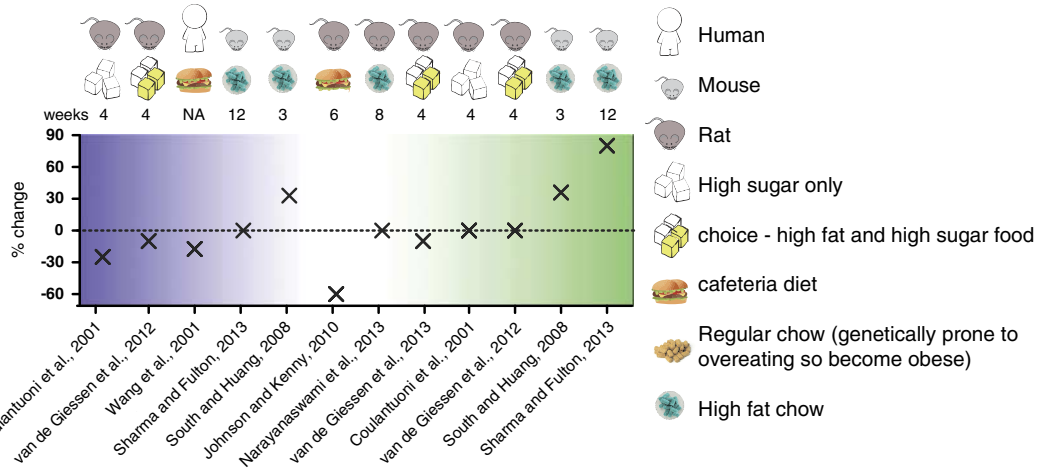

FIGURE 1. Dopamine D_2 expression in diet-induced obesity. Variations in the effects of diet composition and duration on D_2 receptors expression (% of experimental control group in each study) in subregions of the striatum (purple: dorsal striatum, green: ventral striatum, white: unspecified). Some studies report more than one subregion and are thus, represented for each subregion.

Furthermore, a recent study by Hryhorczuk *et al*[54] demonstrates that the type of dietary fat is an important determinant of DAT function, as exposure to saturated fat, but not monounsaturated fat, induced significant reductions in DAT expression. Taken together, in rodents, obesity, leptin, insulin, and saturated fat can modulate DAT number or function. In human studies, there is no consistent effect of DAT availability in obese subjects.

The relationship between binge eating disorder and DAT has exclusively been examined in studies aimed at identifying genetic polymorphisms in dopamine transporter genes. To date, one polymorphism for DAT has been identified. In the 3′ untranslated region of the dopamine transporter gene (*DAT1*), the frequency of a short allele was significantly higher in a cohort of Japanese women with BED, and this polymorphism has been associated with lower DAT function.[55] However, a Canadian study failed to replicate these findings.[56] In an animal model of bingeing, restricted feeding with scheduled sucrose access resulted in an upregulation of the rat DAT.[57] Taken together, binge eating may be associated with increased dopamine reuptake.

Conclusions

Deficits in dopamine function observed in humans and animals have led to the "reward deficiency" hypothesis of obesity,[58] which proposes that reduced dopamine tone leads to overeating as an attempt to restore striatal dopamine concentrations. However, it is important to also consider dopamine's role in energy expenditure, such that decreased dopamine function may simply reduce movement and thus energy expenditure, leading to obesity.[59] Furthermore, striatal dopamine is thought to encode a reward prediction error (the difference between actual and expected reward), therefore reduced blood-oxygen-level dependent (BOLD) signal or dopamine concentration upon food receipt may result from increased reward anticipation and hence a reduced reward prediction error signal.

Influence of Obesity and Binge Eating on Orexigenic or Anorexigenic Peptide Modulation of Dopamine Neurons

A variety of neuropeptides and circulating hormones acts on VTA dopamine neurons to influence their activity and output. For example, peptides that typically promote food intake increase the activity of dopamine neurons and dopaminergic output. In contrast, anorexigenic peptides administered in the VTA decrease food consumption, but their modulation of dopamine does not necessarily predict feeding. Most studies examining the role of neuropeptides and peripheral hormones on dopamine neurons have been explored in naïve animals, and this work has been reviewed in detail elsewhere.[60] However, less is known about how dopamine neurons are modulated by peptides during obesity or during binge eating. In this section, we outline the evidence for orexigenic and anorexigenic modulators of dopamine neurons in obesity and binge eating.

Ghrelin

Ghrelin, a peptide hormone produced from the enteroendocrine cells of the stomach,[61] is implicated in hunger and meal initiation. Circulating levels increase prior to expected mealtimes and decrease with feeding.[62] Ghrelin injections robustly stimulate food intake rapidly and transiently primarily by increasing appetitive feeding behaviors.[63] In naïve adult animals, ghrelin in the VTA increases locomotor activity, palatable food consumption, and a robust motivated feeding response via its only known receptor, growth hormone secretague receptor (GHSR).[63–67] Furthermore, ghrelin increases excitatory plasticity onto dopamine neurons[68] and increases dopamine release in the NAc.[51,63,65,69,70] Therefore, ghrelin's actions at promoting appetitive behaviors may be mediated by the VTA.

In opposition to increased ghrelin levels in response to energy deficiency, ghrelin levels are depressed with weight gain resulting from high caloric diets[71–73] or overfeeding by intragastric gavage.[74] Because ghrelin action on dopamine neurons increases food motivation, one might expect alterations in ghrelin modulation of the mesolimbic system in obesity. Indeed, it has been proposed that ghrelin's ability to enhance the reward value of food by its actions in the VTA might drive overeating, leading to obesity.[75,76] However, it is not clear how ghrelin signals in the VTA once obesity has set in. Using search terms such as "ghrelin/VTA/obese" or "ghrelin/dopamine/obese" in PubMed, it appears that there are no published reports of alterations of ghrelin signaling in the VTA or ghrelin-mediated dopamine output using models of obese animals. In a rodent model of binge eating disorder, where *ad libitum* fed rodents were exposed to a high fat diet 2 hours per day for 4 days (intermittent access to a high-fat diet), significant c-fos activation in VTA dopamine neurons was observed with escalating food intake.[25] This effect was not observed in GHSR knockout mice or in high-fat diet fed controls,[25] which suggests that ghrelin signaling is required for escalation of food intake associated with binge eating.

Orexin

Intracranial administration of the lateral hypothalamic peptide orexin, also known as hypocretin, promotes

food intake.[77] Interestingly, ghrelin-induced conditioned place preference for high-fat food[78] or ghrelin-induced food intake[79] was blocked with orexin receptor antagonists in the VTA, suggesting that ghrelin modulation of reward value of food requires orexin signaling. Importantly, orexin modulates VTA dopamine neurons to promote motivated food intake.[80] Orexin increases neuronal firing,[81] synaptic efficacy,[82] and output[83,84] of dopamine neurons in naïve animals. In rats that have been self-administering high-fat pellets, orexin-mediated potentiation of excitatory synaptic transmission onto dopamine neurons is enhanced.[85]

Using obesity models, reports have indicated that there is increased expression of orexin 1 (OX1R) and orexin 2 (OX2R) receptors in the rostral lateral hypothalamus of obesity prone, but not obesity resistant, Sprague Dawley rats on a chow diet.[86] Notably, the obesity resistant rats had increased food consumption and spontaneous locomotor activity induced by intracerebroventricular orexin administration,[86] suggesting that orexin signaling may provide resistance to the development of obesity. Consistent with this, mice overexpressing orexin peptides on a high-fat diet were resistant to weight gain compared to wild type mice, due to increased energy expenditure. These effects were mediated via the OX2R.[87] Mice already obese from an 8-week high-fat diet showed decreased number of immunopositive orexin neurons in the lateral hypothalamus,[88] which might decrease orexin's impact energy expenditure once animals are obese. In an obese state, where there is hyperleptinemia and leptin receptor deficiency, one might predict an increase in orexin-induced feeding, as leptin is known to suppress this activity in naïve animals.[89,90] However, leptin and orexin appear to act cooperatively to coordinate energy sensing and behavior. In naïve animals, orexin neurons receive primarily excitatory input expressing cannabinoid 1 receptors (CB1Rs). However, in the obese state, the ratio of CB_1-expressing inputs to orexin neurons is predominantly inhibitory. In obese animals, leptin treatment restores excitatory CB1R-terminal bias onto orexin neurons similar to that of lean mice.[91] Taken together, obesity changes signaling at inputs onto orexin neurons that may influence orexin release in target regions.

In the VTA, a 6-week high-fat diet increases OX1R expression compared to chow-fed controls.[92] However, so far, it remains to be determined how orexin signaling in the VTA is altered in the obese state. Acute high fat diet consumption (2 h) increases c-fos activation of both orexin neurons and that of dopamine neurons in the VTA. Increased high-fat diet-induced c-fos activation in the VTA is blocked by a systemic OX1R antagonist.[93] Using a binge-feeding model of intermittent access to a high-fat diet, these authors found increased c-fos expression in the VTA and escalation of food consumption. However, this was not blocked with an OXR1 antagonist.[25] Taken together, these studies suggest that while orexin signaling may be protective against obesity, orexin signaling may be altered once animals are in an obese state. A high-fat diet may increase activation of dopamine neurons in an orexin-dependent manner, but orexin signaling does not appear to underlie escalation of food intake associated with binge eating.

Anorexigenic peptides

Leptin

Hyperleptinemia and leptin receptor (LepRb) resistance is typically observed in the arcuate nucleus during obesity.[94,95] In addition to targeting hypothalamic circuits, leptin signals on VTA dopamine neurons via activation of LepRb and phosphorylation of signal transducer and activator of transcription 3 (pSTAT3)[39,40] or extracellular signal-regulated kinase-1 and -2 (pERK1/2).[96] Leptin decreases the firing rate of VTA dopamine neurons[96,97] and suppresses excitatory synaptic transmission onto dopamine neurons.[98] Leptin's effects on dopamine release are dependent on the satiety and motivational state of the animal.[60] For example, in food-restricted animals, leptin decreases dopamine release in the NAc[99] and food-cue–induced dopamine release.[100] In leptin deficient ob/ob mice, evoked dopamine release in the NAc is diminished, but can be restored with leptin administration into the VTA or NAc.[101,102] In mice fed a high fat diet for 6 months or in mice overexpressing leptin, cellular resistance to leptin signaling was observed in the VTA and the arcuate nucleus, but not in other hypothalamic regions.[103] Furthermore, central administration of leptin diminished preference for palatable food in the control group, but not in the obese animals.[103] In contrast, intra-VTA leptin decreased food intake in Sprague Dawley rats on a 16-week high fat diet similar to rats on a control diet.[104] However, there was no difference in weight gain on these diets, nor was peripheral leptin resistance measured, and therefore, it was unclear if hyperleptinemia occurred. When the high-fat diet–fed rats were separated into top and bottom quartiles of weight gain, those in the bottom quartile (diet-resistant) had a greater intra-VTA leptin-induced inhibition of food intake compared to rats in the top quartile (diet-induced obesity), indicating the possibility of leptin resistance in the VTA of rats that gain the most weight.[104] In contrast to this, male Wistar rats were given free choice to a high-fat, high-sugar diet for 7 days that induced peripheral hyperleptinemia, but no change in central leptin's effect on food intake.[105] Central leptin decreased TH expression in the VTA of control rats, but not those fed the high fat/high sugar diet for 7 days. Taken together, the duration and type of diet may play a key role in determining if leptin

resistance can occur in the VTA, and if this may influence leptin's effect on food intake.

Insulin

Plasma insulin levels rise prior to meal consumption in a cephalic response to cues predicting food, including sight, smell, and mealtime.[106] Higher concentrations of insulin are released postprandially and can act in the ventral medial hypothalamus and VTA to inhibit food intake.[107] Insulin receptors as well as intracellular substrates of insulin receptor activation, including insulin receptor substrate 2 (IRS2) and phosphatidylinostitol (3,4,5)-triphosphate, a product of phosphatidyl-inositol 3 kinase (PI3K), are expressed on dopamine neurons.[108–110] Insulin in the VTA induces a long-term depression (LTD) that is mediated by endocannabinoid suppression of excitatory synapses.[111] This LTD is selective for excitatory but not inhibitory synapses onto dopamine neurons of the VTA.[111] Insulin in the VTA also decreases somatodendritic dopamine via a PI3K dependent mechanisms and increased reuptake through dopamine transporters.[53] In normal weight animals, insulin in the VTA decreases hedonic feeding in sated animals[53] or that evoked by administration of mu-opioids to the VTA.[49] Consistent with this effect, insulin in the VTA can increase the threshold for brain stimulation reward.[108] Finally, intra-VTA insulin decreases preference for a context previously associated with palatable food in a dose dependent manner and reduces food anticipatory behaviors, but has no effect on the effort required to obtain palatable reinforcers.[112] Few studies have explored how intra-VTA insulin signaling or insulin's effects on food intake are altered by obesity. However, in mice with chronic loss of insulin receptors on TH-positive neurons exhibit increased body weight, fat mass, and hyperphagia.[113] Furthermore, in a mouse strain exhibiting higher plasma insulin levels, insulin-induced LTD onto dopamine neurons was suppressed, even though other forms of synaptic transmission onto dopamine neurons were intact.[110] In a model of early life obesity, whereby litter 'size was restricted, postnatal overfeeding led to an increase in insulin's ability to induce phosphorylation of downstream signaling cascades in the VTA, indicating increased insulin receptor sensitivity on dopamine neurons without any changes in peripheral insulin signaling.[114] These results suggest the possibility that insulin signaling in the VTA may be a region that does not succumb to insulin resistance, as has been observed with some areas in the hypothalamus.[115] The relevance of regional differences in obesity-induced insulin receptor insensitivity has not been determined. However, one can speculate that some intracellular cascades coupling to insulin receptors may be more vulnerable to desensitization than others. Taken together, insulin in the VTA decreases excitatory transmission to dopamine neurons as well as different aspects of hedonic food intake. Further study is required to determine if insulin resistance in the VTA can occur with obesity.

Glucagon-like peptide (GLP-1)

GLP-1 is released from the distal gut and neurons of the nucleus tractus solitarius (NTS) and stimulates insulin release from pancreatic beta-cells.[116–118] GLP-1 neurons of the NTS make monosynaptic connections with neurons of the VTA and NAc,[119] and GLP-1 receptors are expressed in both of these regions.[117,120] Intra-VTA application of the stable GLP-1 agonist, exendin-4, increases TH expression and decreases food intake, possibly via modestly increasing presynaptic glutamate release.[121] Consistent with this report, chemogenetic-mediated endogenous release of GLP-1 from NTS terminals in the VTA decreased high-fat food intake, an effect that was blocked by a systemic GLP-1 antagonist, exendin-9.[122] However, in contrast to previous studies, stimulation of GLP-1 receptors on NAc-projecting dopamine neurons suppressed excitatory, but not inhibitory, synaptic transmission.[122] This discrepancy is likely due to differences in GLP-1 receptor expressing subpopulations of dopamine neurons. Because GLP-1 plays a role in stimulating insulin release, it has been proposed to be an anti-obesity agent.[123] Indeed, chronic exendin-4 in weaned rats[124] and short-term extendin-4 in pre-weaned rats[125] reverse effects of diet-induced obesity and insulin resistance in offspring from obese dams. Interestingly, a systemic GLP-1R agonist can reduce binge eating in female mice on an intermittent high-fat diet.[126] At the time of writing, there are no reports on whether GLP-1R agonists administered in the VTA can reduce feeding in obese or binge-eating animals. However, a GLP-1R agonist has shown to be effective in reducing weight gain, cardiovascular measures, and binge eating episodes in obese nondiabetic humans,[127] suggesting that GLP-1 receptors may be a promising pharmacotherapeutic target for treatment of binge eating.

Conclusion and Future Considerations

In obesity, human studies reveal decreased activation of regions involved in food reward upon the presentation of food-predicting cues and upon consumption of palatable foods. Consistent with this, most rodent models of diet-induced obesity show reduced striatal dopamine concentration due to decreased TH expression or increased dopamine reuptake. Decreased D_2 receptor expression is associated with increased BMI in humans. However, it is important to consider that different radioligands used for PET imaging may give different results as well as the metabolic state of the individual (ie if the individual

is fasted) may influence D_2 receptor occupancy. In rodent studies, there appears to be no consensus on whether D_2 receptor expression is altered with obesity. However, there are several issues that may influence the differing results among these studies. First, the type (high-fat, high-sucrose, or cafeteria diet) and duration (anywhere from 5 days to 16 weeks) of the diet may influence D_2 receptor expression. Second, the strategy used to measure D_2 receptor expression may also influence the findings.

Neuromodulation of VTA dopamine neurons by orexigenic or anorexigenic peptides in obese animals has only begun to be explored. While orexin signaling may be protective against obesity due its effect on increased energy expenditure,[86] it is unclear if any of these effects is mediated by the VTA. Obesity increases inhibitory input to lateral hypothalamic orexin neurons[91]; thus reduced orexin release in target regions would likely be expected with obesity. Consistent with this, increased OX1Rs were observed in the VTA with obesity.[92] Anorexigenic agents such as insulin or leptin also target the VTA. In diet-induced obesity, studies conflict as to whether leptin or insulin signaling becomes desensitized. This factor may be due to the types and durations of diets used, and thus, direct measures of peripheral leptin or insulin resistance should be recorded along with measures of leptin or insulin signaling in the VTA. Indeed regionally selective insulin resistance has been observed in the hypothalamus, with the arcuate nucleus most susceptible to insulin resistance.[115]

Binge eating does not necessarily require animals or humans to be obese, and therefore different alteration in dopamine signaling may be expected. Indeed, dopamine metabolism may be increased in binge eating humans. In rodents, food restriction is often employed to promote escalating food intake modeling binge eating. However, because food restriction and weight loss can augment dopamine tone,[24] it is difficult to draw conclusions on how dopamine is modulated during binge eating. However, increased activation of VTA dopamine neurons was observed using intermittent access to a high-fat diet, which promotes escalation of food intake without food restriction.[25] This effect was dependent on ghrelin, but not orexin, signaling.[25] Future studies are required to elucidate the mechanism associated with increased c-fos expression in binge eating animals. Finally, targeting insulin, leptin, or GLP-1 receptor, which are known to depress synaptic transmission onto dopamine neurons, may provide a good pharmacotherapeutic strategy for treatment of binge eating disorders.

Disclosures

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