Is a Picture Worth 1000 Calories: The Neuroimaging of Obesity

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Abstract

In healthy weight individuals, complex brain circuits interact with peripheral feeding signals to control feeding behavior, and it is thought that the dysregulation of these circuits can lead to excessive food intake and obesity. Human neuroimaging studies have shown BMI-dependent deficits in dopamine neurotransmission encoding reward, suggesting a "hypodopaminergic reward deficiency" whereby obese individuals overeat to compensate for a hypofunctioning reward circuitry. However, other imaging studies demonstrate hyperactivation of dopamine networks that positively correlate with BMI in obese individuals. Animal studies link these seemingly opposing theories, revealing that insulin promotes the intracellular trafficking and surface expression of the dopamine transporter (DAT) while inhibiting that of the norepinephrine transporter (NET). Together these transporters control dopamine levels in the striatum and cortex respectively, areas critically involved in reward, habits, and cognitive control. The purpose of this review is to integrate the molecular aspects of food overconsumption and obesity with human neuroimaging data, focusing on the role and dysregulation of dopamine in the neural circuits subserving food intake.

Keywords
Obesity
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Habits
Dopamine transporter
Response inhibition

An Introduction to the Obesity Epidemic

The fundamental neurocircuitry of the homeostatic feeding system and its interactions with peripheral feeding signals to modulate appetitive behavior and energy expenditure around a physiologic set point has maintained a relatively stable human body composition until only recently, when the prevalence of obesity has increased dramatically[1]. The rapid elevation in obesity over the past generation, with nearly seventy percent of the United States population meeting criteria for being overweight[2], suggests environmental factors play a key role. Current research indicates the presence and dysfunction of expanded neural circuits controlling reward, habits, and decision-making may mediate feeding behavior and subsequent overconsumption, contributing to the obesity epidemic[3-7].

Animal research has been critical for elucidating molecular aspects of obesity, with studies showing that food overconsumption is both driven and paralleled by broad changes in dopaminergic circuitry. Indeed, an overarching question in the field is how the physiologic response to food consumption augments brain dopaminergic circuits that enable the progression and maintenance of obesity. Neuroimaging is an important and novel tool for non-invasively examining the structural, molecular, and functional correlates of obesity[8]. The purpose of this review is to integrate the molecular aspects of food overconsumption and obesity with human neuroimaging data, focusing on the role and dysregulation of dopamine in the neural circuits subserving food intake.

Molecular Aspects of Dopamine in Obesity

Homeostatic Feeding, Dopamine, Reward

The hypothalamus regulates homeostatic feeding (i.e. food consumption for the purpose of maintaining energy balance; for review, see[1, 9, 10]), by responding to peripheral hormonal signals relaying information about the body's energy state[11, 12]. The anorexigenic gut peptides leptin and insulin, negative feedback adiposity signals circulating in proportion to body fat mass, indicate a positive energy balance while the orexigenic gut peptide ghrelin, whose levels inversely correlate with adiposity, signals a negative energy balance. In addition to their homeostatic action in the hypothalamus to regulate future feeding behavior, these peripheral hormonal signals also act on the mesolimbic dopamine system. Activity in mesolimbic reward circuitry (for review, see [13]), an area that is acutely activated with all drugs of abuse[14], implies that feeding signals operate outside of brain circuits subserving homeostatic feeding and that feeding itself may have rewarding properties.

Current evidence suggests that gut peptides signaling a positive energy balance function to negatively modulate midbrain dopamine (DA) neurotransmission and food reward while those signaling a negative energy balance are positive DA modulators. For example, as determined by both electrophysiology and receptor knockout studies, leptin acts directly on the DA neurons of the ventral tegmental area (VTA) to inhibit action potential firing[15, 16] and reduce food intake[15] and reward-seeking behaviors[17, 18]. In contrast, ghrelin activates VTA DA neurons, triggering feeding[19]. New research points to a critical role for insulin in the regulation of reward circuitry. Insulin promotes the intracellular trafficking and surface expression of the dopamine transporter (DAT) via the PI3K/Akt signaling pathway, regulating the high-affinity uptake of dopamine from the mesolimbic synapse[20-23] while reducing food-intake[17]. Further, dopamine receptor (D2R) expression[24] is impaired in insulin-depleted states, suggesting a hypofunctioning of the dopamine reward system with insulin resistance. These findings together demonstrate the role of peripheral feeding signals, particularly insulin, in fine-tuning extracellular synaptic dopamine in the reward circuitry and subsequently influencing feeding behavior.

An understanding of mesolimbic dopamine's function and behavioral correlates is critical for discerning the role of dopamine dysregulation in obesity. In the mesolimbic circuitry, dopamine encodes the expectation of, motivation for, and approach behaviors seeking reward[13, 25, 26], all processes which are "hijacked" in the early stages of addiction[14, 27]. Consistent with dopamine's role in reward, dopamine levels are elevated during food seeking[28, 29], exposure to and consumption of novel food stimuli[30, 31], and daily intermittent consumption of both sugar[32-34] and fat[35, 36]. Further, it is the phasic firing of these dopamine neurons that encodes this food reward[26, 37-39]. In contrast, evoked dopamine release, basal dopamine levels[35, 40, 41], and D2R availability[24, 42] are blunted in chronic obesity. One study links these two states, demonstrating increased basal DA and DA efflux in obesity-prone young, insulin-sensitive rats in the mesolimbic reward system but decreased basal DA and DA efflux in obesity-prone, adult, insulin-resistant rats[43]. These results, combined with evidence that short-term elevations in insulin or glucose increase basal DA[44] while decreasing D2R[42, 45], provides evidence for the progressive nature of dopamine dysregulation in obesity.

According to the dopamine reward hypothesis, dopamine signaling in the mesolimbic system encodes reward and promotes reward-seeking behavior; consequently, impaired dopamine signaling will focus and drive behaviors aimed at restoring dopamine tone[6, 46]. It is hypothesized that the blunted dopamine signaling in obesity may attenuate the rewarding aspects of food, a hypodopaminergic reward deficiency syndrome (HRDS), leading obese individuals to consume increasing quantities of palatable food to achieve the same level of reward[41, 47]. A problem with this "reward deficiency" hypothesis, however, is that decreased perceived reward might be expected to suppress rather than promote excessive feeding. An alternative view is that reduced dopamine receptor availability may be a consequence, rather than a cause, of obesity due to elevated dopamine levels from excessive food intake and/or abnormal food seeking[4, 5, 28-31, 37]. Several studies have, in fact, demonstrated a hyperresponsiveness to reward in the mesolimbic circuitry in obesity[5, 48, 49] corroborating this hypothesis. Indeed, dysregulation of dopamine circuitry is a clear component of obesity, but the exact nature of the dysregulation remains undefined.

Food-Seeking, Habits, and Addiction

Despite mesolimbic dopamine having a clear role in reward and feeding behavior, studies in dopamine deficient mice (a severely hypoactive phenotype which will die of starvation without supplemented dopamine) show that viral restoration of dopamine to the nucleus accumbens does not restore feeding behavior[6, 50]. However, restoration of dopamine to the dorsal striatum, specifically the dorsolateral striatum, rescues the dopamine-deficient phenotype and induces feeding[51-53]. These results suggest a role for dopamine action outside the mesolimbic reward system in feeding behavior. In fact, it is the dorsal striatum that mediates goal-directed behaviors and habit formation such as the repeated seeking of reward-conditioned, highly salient, food stimuli[54-56].

Habits are "sequential, repetitive, motor, or cognitive behaviors elicited by external or internal triggers that, once released, can go to completion without conscious oversight"[55]. Habits begin as goal-directed behaviors, where a salient[57] stimulus is achieved through a specific action sequence, but progress to cue-mediated behaviors with repeated reward training that persist even with reward devaluation[58, 59]. This progression involves an underlying ventral-to-dorsal striatal shift[14, 55, 60] as dopamine-directed reward behaviors of the ventral striatum are replaced by dorsal striatal cue-initiated action sequences [61, 62] mediated by multiple neurotransmitters that do not appear to be under the regulatory influence of insulin. Indeed, this shift is well defined with food reward, indicating that salient foods and their cues are sufficient to initiate reward-seeking and the subsequent habitual behaviors characteristic of addiction[14, 63].

Decision-Making and Disinhibition

The progression from reward learning to habit formation relies on active oversight by the prefrontal cortex (PFC)[64], a region responsible for 'top-down' regulation of subcortical function to promote situation-appropriate and task-relevant behaviors[65]. While the complexities of PFC function are beyond the scope of this article (for review, see [66-68]), there is strong evidence for the specific role of dopamine in regulating PFC activity[69, 70] through volume transmission maintaining extrasynaptic dopamine tone[70]. Dopamine appears to improve prefrontal cortical cognitive function[71-73] by enhancing glutamatergic signaling through D1 receptor binding[74, 75], however this effect is non-linear where either too much[76] or too little[77, 78] dopamine actually impairs proper PFC function. This non-linear impairment is readily seen in measures of response inhibition, where both deficits[79-82] and elevations[83] in central dopamine produce a faster cue-driven response and/or a decreased ability to rapidly inhibit unwanted responses.

Dopamine tone is maintained in the prefrontal cortex by the norepinephrine transporter (NET)[84, 85] whose intracellular trafficking and surface expression, in contrast to the striatal dopamine transporter, is inhibited by insulin[86]. Insulin further inhibits dopamine release in the PFC[87], thus providing multiple mechanisms that would both serve to diminish cortical dopamine levels. As dopamine acts through an inverted-U response[88], even minor deviations from optimal tone can alter PFC function[70]. In the setting of impaired insulin signaling, such dysregulation may set the stage for the emergence of the habitual, cue-driven behaviors. Indeed, given that the increased availability of highly palatable food provided by the modern environment requires the continuous inhibition of cue-mediated feeding behaviors, it is easy to see how dopamine-mediated prefrontal disinhibition could unmask the established subcortical salience attributions and response patterns leading to obesity[89].

The Progression to Obesity

Here we propose a plausible molecular mechanism by which the physiologic response to food consumption promotes progressive neuroadaptations in brain dopaminergic circuits subserving reward, habits, and decision-making that further bias towards the maintenance of obesity. Insulin maintains dopamine homeostasis in reward circuitry, supporting a synaptic environment ideal for the perception of food reward. The onset of mild insulin resistance with repeated consumption of highly palatable food drives a striatal synaptic hyperdopaminergia from increased dopamine release, decreased dopamine clearance, and allostatic downregulation of dopamine receptor function, effectively blunting the impact of dopamine reward signaling and facilitating the emergence of cue-driven food seeking behavior. Further, concomitant insulin-mediated cortical neuroadaptations promote a prefrontal hypodopamineric tone serving to unmask response patterns directed at palatable food acquisition and consumption (see Figure 1). In the next section, we review how available neuroimaging evidence supports this model and identify important next steps for neuroimaging in unraveling obesity pathogenesis and implications for treatment.

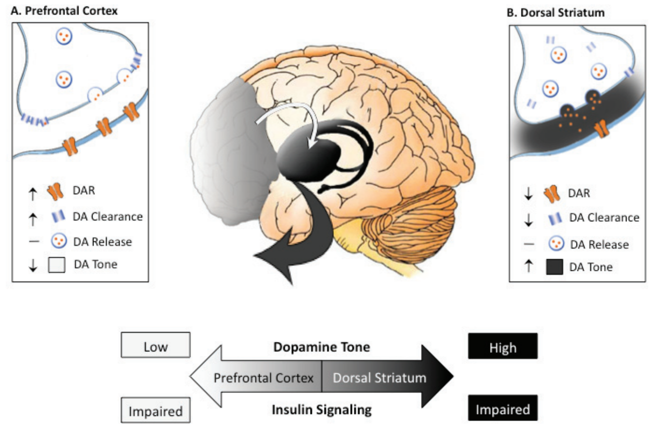

Figure 1. Model for Dopamine Neurotransmission in the context of impaired insulin signaling in A) prefrontal cortex and B) dorsal striatum

Translating Molecules to Systems

Neuroimaging in Obesity

Exploring feeding behavior with molecular (PET) and functional (MR) neuroimaging facilitates the systems-level study of feeding behavior and translation of molecular obesity research to humans. Such methods have in fact convincingly uncovered strong evidence for widespread neural dysregulation in obesity. The multisensory elements of food are reflected as its unified flavor[90] which, combined with individual and environmental factors, contributes to the pleasure derived from food consumption and its hedonic value[91]. In healthy individuals, flavor perception robustly activates the gustatory network, including the thalamus, insula, frontal operculum, inferior frontal gyrus, and orbitofrontal cortex[92-96]. Hunger elicits heightened activity in these areas and further activation in the striatum, midbrain, and prefrontal cortex[95, 96]. This activation correlates with perceived stimulus pleasantness[92, 97] and reward value[95], providing evidence for the representation of hedonic "liking" in these regions.

Yet feeding behavior extends beyond the mere liking of food, and whether food is sought for consumption depends on how much it is "wanted"[4]. This incentive value is influenced by the sight and smell of food; these sensory experiences reflect food availability and the anticipation of food, which can then be contrasted with the effort to achieve them[91]. Indeed, the presentation of a salient food cue elicits reward associated with food anticipation and subsequent food seeking[91, 98, 99]. Visual food stimuli increase activity in areas including the midbrain, amygdala, dorsal striatum, cingulate, insula, and orbitofrontal cortex[94, 96, 98, 100, 101], where activity is amplified by hunger[98, 100, 102, 103]. The fasting state also elicits activation of hedonic brain areas including the ventral striatum[102, 104, 105] which implies that fasting enhances the rewarding properties of food[106], consistent with behavioral studies.

Overweight and obese individuals in the fasting state also demonstrate activation in circuits subserving food reward[107-110]. In contrast to healthy individuals, obese individuals exhibit BMI-dependent potentiation of activation by salient food cues in gustatory areas such as the orbitofrontal cortex and insula, and in brain regions receiving dopaminergic inputs, including dorsal and ventral striatum[107, 108, 110, 111]. Hyperactivity in these areas could represent enhanced expected food reward promoting dopamine release, driving the motivation and behaviors aimed at food consumption[112]. Evidence for greater reward sensitivity in obesity[5, 113] is consistent with this hypothesis. Alternatively, if the obese state is characterized by prefrontal dysregulation of inhihibitory circuits under dopaminergic modulation, the observed hyperactivity results from the unmasking of habitual circuits normally under cortical regulation. One fMRI study examining response inhibition in adolescent girls demonstrated a BMI-dependent loss of activity in the prefrontal areas subserving inhibitory control[114], however the relationship of this attenuation to subcortical activity was not assessed. An important next step will be to determine how prefrontal functional brain activity changes with subcortical activity in light of differential dopamine clearance in these regions.

While fMRI studies indicate neural dysfunction in obesity, they do not assess the mechanism by which it occurs. Molecular imaging evidence directly demonstrating dopamine dysregulation comes from a small number of PET studies finding BMI-dependent decreases in striatal dopamine D2 receptor availability[47, 115]. This reduction depends on the magnitude and duration of overfeeding[42], supporting the hypothesis of an allostatic downregulation of D2 receptors with chronic overeating. However, these PET studies assessed D2 receptor availability using the radioligand [^{11}C]-raclopride which competes with synaptic dopamine for receptor binding, and therefore the decreased binding explained as a reduction in D2 receptor availability could also reflect increases in synaptic dopamine. This interpretation would suggest an elevated basal dopamine tone in obesity. Among adults viewing food cues who received an acute methamphetamine dose (stimulating presynaptic dopamine release), normal-weight individuals demonstrated increases in dopamine[116] while the dopamine levels of obese individuals remained constant[117], providing evidence for blunted dopamine signaling in obesity.

Implications for Treatment

While the precise etiologic nature of dopamine dysregulation in obesity remains unclear, several imaging studies support plasticity in the brain circuits underlying obesity and thus opportunities for treatment. Initial clinical observations of mild weight loss in patients receiving treatment with dopamine agonists[118] have been replicated in animal studies[119], however the cognitive/psychiatric side effects render these drugs problematic. Further, dopamine administration will be ineffective if post-synaptic dopamine signaling is impaired in obesity. Promising observations come from studies demonstrating that bariatric surgery[120] and weight loss[42] increase D2 receptor levels and decrease functional activity in dopamine reward circuitry[121] while increasing activity in the prefrontal cortex[122]. One explanation for these effects on dopamine circuits is the drastic changes in insulin levels following bariatric surgery; however, there have been no longitudinal controlled clinical trials to examine the direct effect of insulin on normalizing dopamine neurotransmission in obesity. Such research will be critical in understanding the pathogenesis of obesity, potential therapeutic targets in insulin signaling pathways, and future opportunities for treatment.

Conclusion

Recent scientific evidence demonstrating that central nervous system dopamine is under the regulatory influence of insulin offers a plausible mechanism for understanding obesity as a dysregulation of neural systems controlling reward, habits, and decision-making. Here we have reviewed the molecular processes underlying insulin's effect on dopamine circuitry and feeding behavior, and how these findings link the opposing theories of a hypodopaminergic reward deficiency versus a hyperresponsiveness to reward in the obese state. We further extend the interpretations of this research by proposing a novel model for obesity as a progressive disruption of subcortical and prefrontal brain circuitry initiated and perpetuated by insulin resistance and subsequent dysregulation of extracellular dopamine. While future research is necessary, the hypothesis of insulin's ability to reset central dopamine tone and subsequently reshape feeding behavior offers exciting new opportunities for the clinical management of obesity.

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