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NUTRITION AND THE BRAIN (J NASSER, SECTION EDITOR)

# Impact of Brain Insulin Signaling on Dopamine Function, Food Intake, Reward, and Emotional Behavior

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## Abstract

**Purpose of Review** Dietary obesity is primarily attributed to an imbalance between food intake and energy expenditure. Adherence to lifestyle interventions reducing weight is typically low. As a result, obesity becomes a chronic state with increased co-morbidities such as insulin resistance and diabetes. We review the effects of brain insulin action and dopaminergic signal transmission on food intake, reward, and mood as well as potential modulations of these systems to counteract the obesity epidemic.

**Recent Findings** Central insulin and dopamine action are interlinked and impact on food intake, reward, and mood. Brain insulin resistance causes hyperphagia, anxiety, and depressive-like behavior and compromises the dopaminergic system. Such effects can induce reduced compliance to medical treatment. Insulin receptor sensitization and dopamine receptor agonists show attenuation of obesity and improvement of mental health in rodents and humans.

**Summary** Modulating brain insulin and dopamine signaling in obese patients can potentially improve therapeutic outcomes.

**Keywords** Diabetes · Obesity · Insulin · Insulin receptor · Dopamine · Mesolimbic pathway · Reward · Food intake · Mood · Depression · Anxiety · Depressive-like behavior

## Introduction

The world is facing a global obesity epidemic, with an estimated 1.9 billion people categorized as being overweight including 650 million obese people [1]. Obesity arises as the result of increased energy intake and decreased energy expenditure and greatly increases the risk of developing type 2 diabetes [2, 3]. Obesity and diabetes are characterized by insulin resistance, a condition where the body is unable to properly respond to insulin. Insulin resistance can be induced by multiple factors including glucotoxicity, lipotoxicity, low-grade inflammation or organelle stress. Importantly, insulin resistance impacts peripheral tissues as well as the brain. Food consumption is so far understood to be regulated by the homeostatic system, which apparently resides in the hypothalamus, and the reward system, which is thought to include the mesolimbic dopaminergic pathways from the ventral tegmental area to the nucleus accumbens and the prefrontal cortex [4]. The homeostatic system is regulated by peripheral hormones such as insulin and leptin, senses the current energy state of the body and controls food intake through hypothalamic neurons [5]. The reward system is regulated by physiological stimuli such as hunger [6], taste, cue-induced, and palatable food intake, thereby altering food liking and wanting [4, 7, 8]. Interestingly, homeostatic and reward systems interact and their dysregulation is linked to obesity [9, 10]. Conversely, the consumption of a diet enriched with long-chain saturated fatty acids impairs central insulin action and inhibits dopamine function in the brain [8, 11]. Dysregulation of both systems further promotes preference for high-calorie

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diets and results in hyperphagia, establishing a vicious cycle of over-eating (hyperphagia) that causes long-term obesity and the development of type 2 diabetes.

In addition, both systems play a crucial role in regulating emotional behavior. Thus, diabetes, insulin resistance, and reduced dopamine function are associated with behavioral abnormalities and mood disorders such as anxiety and depression. Depressive disorders, a severe category of mood disorders, are accompanied by lack of motivation and, in some cases, can lead to poor compliance to follow a therapy regime or even suicide [12, 13]. Obese and diabetic patients are prone to develop depressive disorders [14], whereas patients with depression have an increased prevalence for type 2 diabetes [15, 16]. This correlation is poorly understood but point to an interaction of insulin signaling and dopamine function. Here we will review the current understanding of this interaction. We will investigate for evidence that the dysregulation of both systems is responsible for the poor adherence for long-term weight loss after dietary interventions due to the inability to properly regulate the hedonic system and negatively impacts on mood and motivation.

## Brain Insulin Signaling Affects Food Intake and Reward

The brain is an insulin-responsive organ and brain insulin action has a crucial effect on food intake and reward. Mechanistically, insulin binds to the insulin and IGF-1 receptor (IR and IGF-1R) causing the autophosphorylation of the receptors, followed by the recruitment of insulin receptor substrate (IRS) proteins and their subsequent phosphorylation. Phosphorylated IRS proteins act as a critical node activating the PI3-kinase-AKT and the MAP-kinase-ERK pathway [17]. On the one hand, the PI3-kinase-AKT pathway regulates neuronal protein content, autophagy, synaptic function, plasticity, and proliferation of neuronal progenitors via activation of downstream proteins such as mTOR complex 1 (mTORC1), glycogen synthase kinase 3β (GSK3β), or Forkhead box O (FoxO). On the other hand, activation of the MAP-kinase-ERK pathway controls mitochondrial function, proliferation, and differentiation [18, 19]. This regulation can be influenced by the activation of stress-activated protein kinases (SAPK) such as c-Jun kinase (JNK), p38 kinase, or IκB kinase (IKK) in the brain. The activities of these kinases are induced by cytokines, long-chain saturated fatty acids, or oxidative stress. They are elevated in type 2 diabetes, cause inhibitory serine phosphorylation of IRS proteins and inhibit the interaction of insulin signaling proteins which results in the abrogation of the insulin signal [18].

Insulin receptors are expressed throughout the brain including the hypothalamus which controls energy homeostasis and the striatum as part of the dopamine system, revealing overlapping expression patterns of the insulin and dopamine systems [20]. In the late 1970s Woods et al. have already demonstrated that insulin infusion into the brain of baboons reduced food intake, which has been further confirmed and refined in various other models. Insulin reduces food intake by regulating the activation of POMC and Agrp neurons in the hypothalamus engaging anorexigenic signals in the hypothalamus [5]. Thus, diabetic and insulin-resistant mice as well as mice with a knockout of the insulin receptor in the brain exhibit hyperphagia and diet-induced obesity [21–23]. But central insulin action affects not only the homeostatic but also the reward system. The reward or hedonic system is mainly controlled by dopamine signaling. Although it is assumed that hypothalamic mechanisms controlling food intake and energy expenditure are important in modulating energy balance, the explosive prevalence of dietary obesity clearly implicates non-homeostatic mechanisms as significant contributors. In the midbrain, food and drug reward is mediated by dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens (ventral striatum), known as the mesoaccumbens pathway, from the substantia nigra pars compacta (SNpc) to the dorsal striatum, known as the nigrostriatal pathway, and from the VTA to the medial prefrontal cortex, known as the mesocorticolimbic pathway. In light of dopamine signaling and food intake, it is important to mention that dopamine signaling impacts the food consumption in a region-specific manner [24]. Dopamine action in the ventrolateral neostriatum and dorsal striatum affects food intake and food preference, whereas in the nucleus accumbens dopamine signaling controls food seeking [25–27]. Moreover, dopaminergic neurons in the VTA modulate reward-related and goal-directed behaviors and exhibit numerous interactions with different brain regions [28]. The dopaminergic system is regulated via insulin in at least three molecular ways: (i) insulin regulates the uptake of released dopamine by induction of dopamine reuptake transporter (DAT) expression, (ii) insulin alters dopamine half-life or action by regulating the protein expression of the dopamine-degrading enzymes monoamine oxidases (MAO) and DAT, and (iii) insulin affects the spike frequency of cholinergic interneurons and dopaminergic neurons [29••, 30, 31••, 32, 33•]. In addition, diet-induced insulin resistance decreases the rate-limiting enzyme for dopamine synthesis, tyrosine hydroxylase, suggesting that insulin might affect TH synthesis in the brain [34] (Fig. 1). A causal role of brain insulin and dopamine signaling on weight regulation was shown in mice deficient for the insulin receptor in dopaminergic, tyrosine hydroxylase (TH)-positive neurons. These animals exhibit increased body weight due to increased food intake, showing that reduced dopaminergic insulin sensitivity is crucial for the development and manifestation of obesity [32]. Intra-ventral tegmental area (VTA) injection of insulin reduces food anticipatory behavior in mice by suppressing excitatory synaptic transmission onto dopamine neurons, which is reduced in the presence of hyperinsulinemia [35•, 36, 37]. This indicates that insulin alters neuronal plasticity

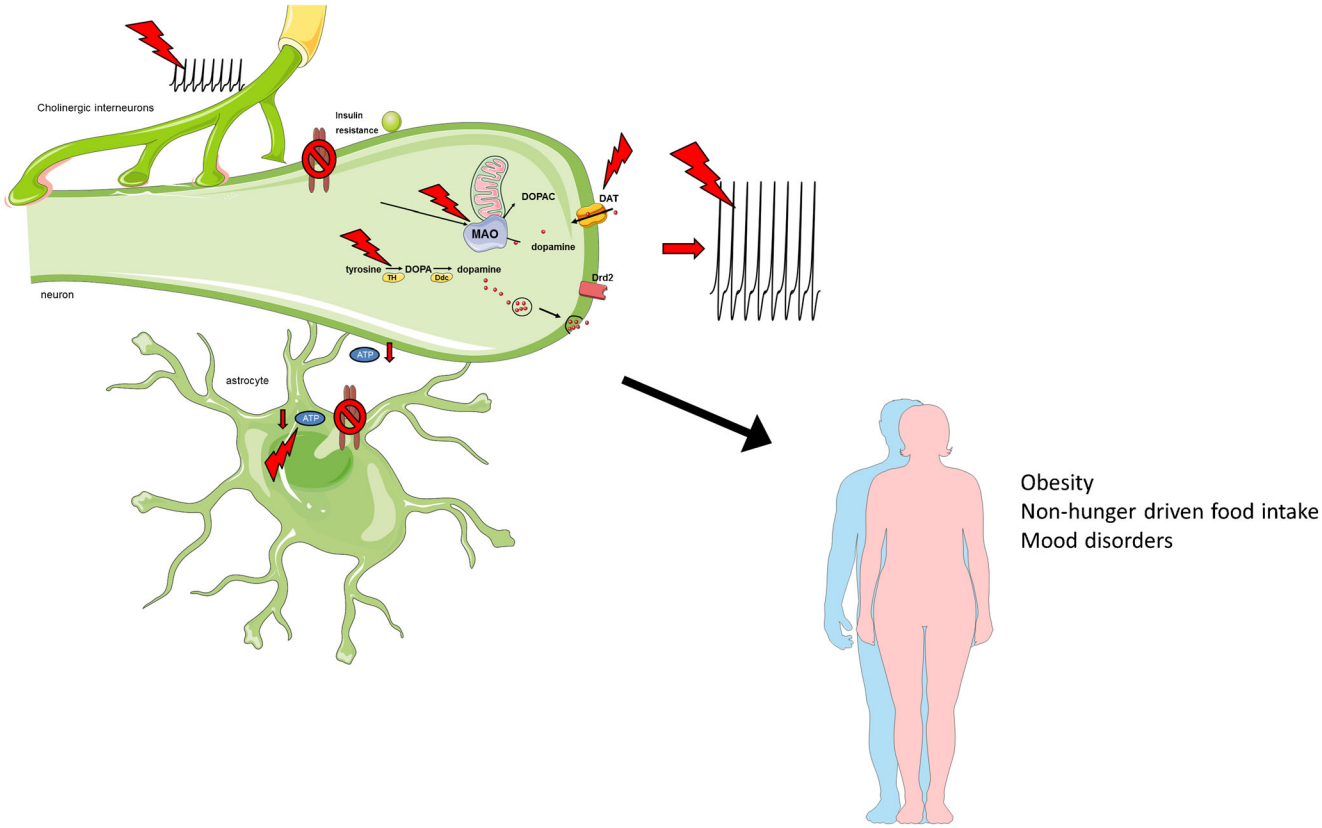


**Fig. 1** Brain insulin resistance impacts dopamine function on multiple molecular levels. Obesity-induced insulin resistance causes a reduction in TH expression [24], the rate-limiting enzyme in dopamine production. Further insulin receptor deficiency in brain causes unrestraint MAO expression and with it decreased dopamine half-life in the dopaminergic brain regions [21]. Insulin receptor deficiency on astrocytes reduces ATP exocytosis, leading to decreased purinergic signaling on dopaminergic neurons [19]. Besides these effects, insulin regulates DAT activity and thus dopamine action in the synaptic cleft [20], while also increasing spike frequency in cholinergic interneurons [23] and TH-dopaminergic neurons [22], highlighting the profound effect of insulin action on dopamine function. TH tyrosine hydroxylase, MAO monoamine oxidase. Lightning symbol highlights impact of insulin on dopamine function

within the dopaminergic system and this function is disrupted in hyperinsulinemic conditions such as obesity and insulin resistance. Insulin also reduces the intake of high-fat food in sated mice in the VTA [38], preventing over-eating in this state, a feature also present in obese subjects [39•, 40]. Intranasal insulin treatment in lean women modulates intrinsic reward circuitry [41], supporting that insulin in humans affects the dopamine system. In line, insulin not only reduces the response to food pictures in brain regions affected by dopamine of healthy, sated subjects but also reduces ratings of food palatability via mesolimbic pathways in insulin sensitive patients [42, 43]. Consistently, the response to food images is enhanced in type 2 diabetic patients compared to healthy controls [44]. Insulin is also able to regulate striatal function in lean men, while overweight men do not respond to insulin, indicating brain insulin resistance in this dopaminergic brain area [45•]. Indeed, aberrant dopamine signaling is present in obese humans and animals. In several rodent models of obesity, central dopamine neurotransmission is altered before, during, and after obesity develop. We have previously reported that this dopamine deficit is already in place as early as postnatal day 1 in rats inbred to become obese (obesity-prone (OP)) when compared to rats inbred to become lean (obesity-resistant (OR)) [46]. Therefore, the dopamine deficit predates the interaction of the dam with the pups during weaning and any effects of the offspring's dietary history. This finding effectively implicates the prenatal environment and potentially maternal hormonal levels, including insulin, in central dopamine deficits observed in OP rats and confirms transgenerational aspects of obesity. The response of insulin receptors in the offspring may be a crucial determinant of dopamine aberrations observed in OP and diabetes-prone animals. Obese patients exhibit decreased striatal D2 receptor density, which negatively correlated with BMI [47]. Although decreased D2 receptor availability in the striatum can be affected by genetic predisposition, environmental factors might also influence this phenomenon [48–51]. While dopamine antagonism does not result in a major alteration of food consumption, it alters food-related motivation [52]. Haloperidol, a D2 receptor antagonist, reduces lever presses for preferred food but increases consumption of freely available less preferred food in healthy mice [53]. Dopamine

injection into the lateral hypothalamus reduces food intake via reduced meal size in obese Zucker rats [54]. Bromocriptine, a dopamine agonist, has been shown to reduce obesity and improves glycemia in obese rodents and humans [55–57], indicating the therapeutic potential in counteracting obesity by enhancing the dopamine system. In summary, altered insulin and dopamine signaling is present in a variety of obese mouse models and humans [46, 58–64], highlighting insulin and dopamine action as a therapeutic target to regulate food intake and motivation-related behavior.

## Insulin and Dopamine Signaling Controls Emotional Behavior

Depressive disorders, diabetes, and insulin resistance associate [65, 66], yet the molecular mechanisms for this linkage are not well understood. Some epidemiological studies suggest an interaction of depression with type 2 diabetes and postulate inflammatory responses as a common mediator [67, 68]. Indeed, inflammation is one of many inducers of insulin resistance [18, 69]. In addition, psychological stress is linked to depression syndromes, affects the dopaminergic system, and has been shown to cause insulin resistance [70–73]. Children with increased depressive syndromes exhibit higher insulin resistance and the occurrence of depressive syndromes can predict the deterioration of insulin resistance [74]. Further, children with highest insulin resistance showed an association between altered brain morphology and depressive syndromes [75]. Thus, it seems that insulin resistance and depressive behavior might be functionally interconnected. Consistently, a variety of mouse models of insulin resistance exhibit signs of depressive-like behavior, suggesting that insulin resistance can influence this behavior. Mice fed a high-fat diet and db/db mice (mouse model of type 2 diabetes) exhibit central insulin resistance, depressive-like behaviors, and increased anxiety [29••, 31, 76, 77]. Depressive disorders are associated with impairment in neural circuits related to emotion and cognition and altered synaptic plasticity. This occurs in regions with high IR expression and insulin sensitivity such as the prefrontal cortex or hippocampus. Insulin improves synaptic plasticity and neuronal transmission, and exerts neuroprotective functions [19, 20], features which are impaired in depressive disorders. Further, treating obese animals with the insulin sensitizer rosiglitazone or pioglitazone ameliorated depressive-like behavior indicating that insulin action improves mood [78, 79]. Adding to this, prenatal stress reduces signaling of the closely related IGF-1R in hippocampus and frontal cortex and causes depression, which can be rescued by intracerebroventricular injection of IGF-1, which is able to activate the insulin receptor cascade [80, 81].

The monoamine deficiency hypothesis postulates that a reduction in serotonin, dopamine, and/or norepinephrine can be causal for the development of depressive disorders. Altered dopamine action has been shown to modulate depressive-like behavior [82–84]. A key region regulating dopaminergic VTA function represents the insulin-sensitive habenula (Hb) [28, 85, 86]. Structural and functional alterations of the Hb in humans are linked to depressive disorders [65, 87]. Altering the firing pattern of dopaminergic midbrain neurons or selective inhibition of VTA dopamine neurons induces depressive-like behavior [83, 84]. We were able to show that a neuronal and glial knockout of IR caused depressive-like behavior and anxiety with altered dopamine signaling. In neurons, insulin was able to suppress MAO A and B expression, enzymes crucial for monoamine degradation, and enhances dopamine half-life after electrically evoked dopamine release [31••]. IR deficiency in GFAP-positive glia cells caused reduced ATP exocytosis, resulting in decreased purinergic signaling on dopaminergic neurons and subsequently anxiety- and depressive-like behavior [29••]. Recent data show that knockout of the insulin receptor in dopaminergic neurons using the DAT-Cre mouse model does not affect food consumption or emotional behavior early in life, suggesting that loss of IR in distinct dopaminergic cell populations differentially affect metabolism and behavior [32, 88–90]. The combined lack of IR and IGF-1R only in the hippocampus or in the amygdala can induce increased anxiety-related behavior, supporting the hypothesis that insulin action can influence dopamine-dependent behavior [91]. Clearly, more research is needed to decipher the precise effect of insulin action in different brain cell populations and regions and on dopamine function regulating food intake and anxiety- and depressive-like behavior.

## Neuroinflammation Impacts Insulin and Dopamine Function

Increased food intake and especially the increased consumption of saturated, long-chain fatty acids cause a low-grade inflammation in peripheral tissues and the brain. There is a strong association between inflammation and depression in humans and rodents [92•]. Major contributors of the inflammatory response are activated macrophages. Macrophages have been proposed to play a pivotal role in the pathogenesis of depression [93]. Macrophages secrete cytokines, such as tumor necrosis factor (TNF) α, which does affect not only the inflammatory response but also the insulin signaling cascade [94]. Increased pro-inflammatory cytokines affect synaptic plasticity and neuronal transmission and are implicated in the development of depressive disorders [95]. In line, adipose tissue secretes vast amounts of TNFα in obesity, which induces insulin resistance and is upregulated in depressive states [96]. Treating mice with the x TNFα monoclonal antibody infliximab results in protection against depressive-like behavior [97]. In addition, the widely used antidepressant bupropion reduces TNFα and improves metabolism in stressed rodents [98]. A prominent effector of TNFα

represents the stress-activated kinase JNK [99]. Type 2 diabetic mice exhibit increased activation of JNK in brain, which induces insulin resistance due to serine phosphorylation of insulin receptor substrates [100, 101]. Conversely, JNK1 deficiency improves brain insulin sensitivity and reduces anxiety- and depressive-like behavior [102, 103]. In addition, inhibition of JNK protects dopaminergic neurons and improves behavior in a mouse model of neurodegeneration [104, 105].

Further, there seems to be an association between microbial-associated molecular patterns (MAMPs) generated by the gut microbiome, inflammation, insulin resistance, and dopamine function [106]. Obesity is associated with insulin resistance, altered dopamine function, and an altered microbiome [107]. Microbes produce MAMPS such as lipopolysaccharide (LPS), which can cause neuroinflammation, insulin resistance and depressive-like behavior [107–109]. Supporting this, healthy C57BL/6 mice which received an adoptive transfer of microbiota of high-fat diet (HFD) donor animals exhibited increased anxiety-like behavior compared to mice given the fecal transplants of normal chow diet-fed mice [110]. HFD feeding impairs membrane integrity, and with this there is an increase of endotoxin release, including LPS, into circulation [107, 111]. LPS per se induces insulin resistance and affects dopamine function representing a potential mechanism of how inflammation, altered insulin, and dopamine function are interlinked [108, 112]. Further, some microbes can generate short-chain fatty acids and precursors of neurotransmitters, such as dopamine [113], which affect insulin and dopamine function. Yet, whether actually these gut-derived metabolites penetrate the brain and affect dopamine-dependent behavior warrants further investigation.

The hypothalamus-pituitary-adrenal (HPA) axis regulates responses to stress and affect metabolism and emotional behavior. A dysregulated HPA axis is present in obesity and depression and inflammation can activate the HPA axis [114, 115]. Pro-inflammatory cytokines can induce a heightened response of the HPA axis and has been observed in depression syndromes [116]. Increased levels of glucocorticoid levels can induce insulin resistance but also affect dopamine function pointing to an additional mechanism of how inflammation might impact brain insulin signaling and dopamine function [117, 118]. Here, time and strength of the HPA axis activation differentially affects dopamine function, further complicating this crosstalk [118]. Overall these data highlight the close relationship between inflammation, insulin resistance, and depression.

## Conclusion

Dietary obesity other metabolic disorders, and diabetes all share significant central monoamine neurotransmitter aberrations with psychoactive disorders like depression. In this article, we attempted to highlight some of recent advances in understanding how such deficits may be linked to central insulin receptor signaling. Beyond the role of peripheral insulin resistance in obesity and diabetes, there is substantial promise in the study of the role of brain insulin in behavioral and mood disorders that may open new pathways in novel drug target discovery and in drug development for the treatment of such disorders.

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## Compliance with Ethical Standards

**Conflict of Interest** André Kleinridders and Emmanuel N. Pothos declare they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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