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Journal of Endocrinology and Disorders
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Review Article

Interplay of Dopamine and Food Signals: Examining the Interaction of Dopamine and Homeostatic Signals in Food-motivated Behavior

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Received Date: 03 April 2024 | **Accepted Date:** 24 April 2024 | **Published DATE:** 08 July 2024

Citation: Cooper Farion, Ewell Dante, Fluitt Maurice, Odonkor Wolali, and Gambhir Kanwal K, (2024), Interplay of Dopamine and Food Signals: Examining the interaction of Dopamine and Homeostatic Signals in food-motivated behavior, *J. Endocrinology and Disorders*, 8(4): DOI:10.31579/2640-1045/182

Abstract

This paper investigates the intricate interplay between dopamine and insulin and other homeostatic inputs in regulating food-motivated behavior. Dopamine, traditionally associated with reward processing and motivation, interacts with insulin, leptin, and ghrelin, pivotal hormones in the modulation of behavior. In this paper, we examine how dysregulation in this interaction can lead to aberrant eating behaviors and contribute to metabolic disorders such as obesity and diabetes. Through a review of existing literature and experimental findings, we explore the mechanisms by which dopamine signaling influences these hormones and, how this interaction modifies food-motivated behavior. Furthermore, we discuss the implications of these interactions on food intake regulation. By elucidating the complex relationship between dopamine and these hormones, this research aims to provide insights into the neurobiological underpinnings of food-related behaviors, shedding light on potential avenues for intervention in disorders associated with disrupted appetite regulation.

Key words: obesity; dopamine; insulin; food behavior; reward; leptin; ghrelin; African American; Black; Afro-American

List of Abbreviations

CDC	Center for Disease Control and Prevention
APUD	Amine Precursor Uptake and Decarboxylation
DOPA	Dihydroxyphenylalanine
VMAT2	Vesicular Monoamine Transporter 2
DAT	Dopamine Transporter
COMT	Catechol-O-methyltransferase
MAO-B	Monoamine Oxidase-B
cAMP	Cyclic adenosine monophosphate
PKA	Protein Kinase A
ATP	Adenosine Triphosphate
T2DM	Type 2 Diabetes Mellitus
ADHD	Attention Deficit Hyperactivity Disorder
OCD	Obsessive Compulsive Disorder
O2	Oxygen
GLUT	Glucose Transporter

AD	Alzheimer's Disease
mRNA	Messenger Ribonucleic acid
BBB	Blood Brain Barrier
BEC	Brain Endothelial Cells
CNS	Central Nervous System
PI3K	Phosphatidylinositol 3-kinase
GABA	Gamma-Aminobutyric Acid
AMPK	Adenosine Monophosphate-Activated Protein Kinase
PVN	Paraventricular Nucleus
ARC	Arcuate Nucleus
NPY	Neuropeptide-Y
GnRH	Gonadotropin Hormone-Releasing Hormone
ICV	Intracerebroventricular
IR/IRS2	Insulin Receptor
NIRKO	Neuronal-specific Insulin Receptor Knockout
DA	Dopamine
VTA	Ventral Tegmental Area
PIP3	Phosphatidylinositol-Trisphosphate
SNC	Substantia Nigra
NAC	Nucleus Accumbens
mTOR	Mammalian target of rapamycin
STAT3	Signal Transducer and Activator of Transcription 3
LHA	Lateral Hypothalamic Area
JAK-2	Janus Kinase 2
OFC	Orbitofrontal Cortex
PIP3	Phosphatidylinositol-Trisphosphate

Introduction

It is widely known that obesity as a disease has become increasingly prevalent both in the United States, and throughout the world at large. According to the CDC, the prevalence ate of obesity in the US was 41.9% among adults between the years of 2017 and 2020 [1]. As a major burden on both the individual and national level, the estimated annual medical cost of obesity in the United States was nearly $173 billion in 2019 [1]. Additionally, medical costs for adults living with obesity were $1,861 higher than medical costs for people with healthy weight [1]. Moreover, this pandemic of obesity does not affect everyone's equally. There are ethnic disparities that exist among some populations. Most notably, Non-Hispanic Black adults had the highest prevalence of obesity of 49.9%, followed by Hispanic adults with a prevalence of 45.6%, non-Hispanic White adults with a prevalence of 41.4% and non-Hispanic Asian adults with a prevalence of 16.1% [1]. It has long been established that long-term obesity can lead to the development of other medical conditions such as heart disease, stroke, type 2 diabetes, and certain types of cancer [1]. Given both the severe economic and medical burden that obesity places on patients, it is important to understand how and why obesity continues to plague society [1]. To achieve this, it is essential that we elucidate the complex mechanisms of how food behavior affects the development of obesity through the interplay of various key hormones such as insulin and dopamine. In this literature review, through a systematic review of papers between the years of 2003 to 2024, we will explore the intricate interaction of key hormones, insulin, and dopamine, in food behavior and their role in the development of obesity.

Biochemistry And Physiology of Dopamine

Dopamine is one of the major neurotransmitters in the central nervous system and hormone throughout the body that controls a variety of key functions such as locomotion, cognition, feeding behavior, energy homeostasis, motivation, reward, memory, mood, learning, and hormone secretion [1, 2, 3, 4]. As a result of the multiple functions of dopamine as a neurotransmitter, there are many different biological pathways in which dopamine executes its role. For example, in the central nervous system, there are four major dopaminergic pathways which include: the nigrostriatal, mesolimbic, mesocortical, and tuberoinfundibular pathways [5]. In the nigrostriatal pathway, dopaminergic neurons originate from the substantia nigra and project their axons to the dorsal striatum to coordinate voluntary movement [5]. In the tuberoinfundibular pathway, dopaminergic neurons that originate from the hypothalamus and project toward the pituitary gland regulate prolactin synthesis and secretion through the inverse effects of dopamine [5]. Neurons originating from the ventral tegmental area in the brainstem project to the nucleus accumbens and the prefrontal cortex to form the mesolimbic pathway and the mesocortical pathway, respectively [5]. The mesolimbic pathway, often referred to as the reward pathway, is highly implicated in. behaviors related to motivation and reward [6]. The mesocortical pathway is thought to mediate the cognitive aspects of the drug experience, craving, altered executive function, and loss of control over compulsive drug use [7]. Both the mesolimbic and mesocortical pathways are thought to have been implicated as key circuits that are disrupted in addictive behaviors [8]. Outside of the central nervous system, dopamine has a major role in the body as a catecholamine hormone. Derived from the synaptic terminals of the peripheral nervous system, dopamine regulates several processes such as hormone secretion (i.e. insulin), vascular tone, renal function, and gastrointestinal motility [9]. Dopamine mainly originates from three sources, namely sympathetic neuronal fibers, adrenal medulla, and neuroendocrine cells (found in the kidney, pancreas, retinal cells and leukocytes), also named amine precursor uptake and decarboxylation (APUD) cells [10]. Interestingly, because of this, dopamine can be viewed as both dependent and independent of neuronal elements.

Taking place completely within the presynaptic neuron, the synthesis of dopamine begins with the amino acid phenylalanine, and proceeds sequentially through tyrosine, dihydroxyphenylalanine (DOPA), then finally, to dopamine [11]. After the synthesis of dopamine, it is incorporated into synaptic vesicles by the action of vesicular monoamine transporter 2 (VMAT2). It is then discharged by exocytosis into the cell membrane and dumped into the synapse [4]. DA can be used as a precursor in the biosynthesis of other catecholamines such as norepinephrine and epinephrine. Norepinephrine is synthesized from dopamine by the catalytic action of dopamine β-hydroxylase [4]. Epinephrine can then be produced from norepinephrine through the action of various enzymes [4]. After the release of dopamine, a transmembrane protein, dopamine transporter (DaT) draws dopamine back from the synaptic cleft into the cell. Although reuptake is the primary way that cells terminate dopamine activity, two different enzymes metabolize dopamine: catechol-O-methyltransferase (COMT) and monoamine oxidase-B (MAO-B) [11].

With regards to dopamine receptors, there have been 5 subtypes that have been identified, which include: D1, D2, D3, D4, and D5. The five different dopamine receptors can be subdivided into two categories: D1 and D5 receptors as one group, and D2, D3, and D4 as another group [12]. D1 and D5 receptors couple to G stimulatory sites, activating adenylyl cyclase which leads to the production of the second messenger cAMP, and ultimately protein kinase A (PKA) for use in the cell nucleus [12]. D2 through D4 receptors couple to G inhibitory sites, inhibiting adenylyl cyclase, which activates K+ channels [12]. The D1 receptor is the most abundant out of the five in the central nervous system, while D4 is the least [12]. D1 and D5 receptors have high density in the striatum, nucleus accumbens, olfactory bulb, and substantia nigra and are essential in regulating the reward system, motor activity, memory, and learning. As activators of phospholipase C, D1 and D5 receptors can induces the induction of intracellular calcium and thus, protein kinase C which plays a role in neurotransmitter release. Additionally, D1 and D5 receptors are also involved in the kidney through the inhibition of the Na/K ATPase which can lead to an increase in electrolyte excretion and renal vasodilation [12]. On the other hand, D2, D3, and D4 receptors are expressed mainly in the striatum, as well as the external globus pallidus, core of the nucleus accumbens, hippocampus, amygdala, and cerebral cortex [12]. These receptors also affect the postsynaptic receptor-medicated extrapyramidal activity and help to regulate sleep, fear, cognition, impulse control, and attention [12]. Dopamine receptors 2-4, can even inhibit the secretion of the procoagulant von Willebrand factor from human endothelial cells and regulate vascular contractibility [10]. Regulation of dopamine via these receptors, or the lack thereof, has been associated with a variety of disease processes such as glucose intolerance and T2DM, hypertension, obesity, Parkinson's Disease, Huntington's Disease, Restless Leg Syndrome, various autoimmune diseases, ADHD, OCD, depression, anxiety, bipolar disorder, schizophrenia, and drug abuse and addiction. [4, 10, 13].

Biochemistry and Physiology of Insulin

Insulin is a peptide hormone comprised of 51 amino acids that are distributed among two peptide chains (A chain = 21 amino acid residues and B chain = 30 amino acid residues) that are connected by disulfide bonds of cysteine residues [14]. Preproinsulin is the main precursor protein of insulin that is a single-chain polypeptide consisting of proinsulin and signal peptide sequences [14]. Preproinsulin can be cleaved at its signal peptide to release proinsulin and ultimately cleaved again to release insulin along with a C-peptide [14]. Until it is metabolically needed, insulin is usually stored within glucose-regulated secretory vesicles [14].

Food intake can trigger glucose metabolism that ultimately leads to the simultaneous production of insulin by β cells in the pancreas and decreased glucagon secretion by α cells in the pancreas [15]. Insulin is then circulated systematically until it reaches hepatocytes, where they are programmed to store glucose as glycogen [15]. Just like many other protein hormones, insulin triggers glucose uptake, skeletal muscle protein synthesis, glycogenesis, and lipogenesis via the tyrosine kinase receptor pathway [15]. Located in the plasma membrane, insulin receptors act enzymatically to transfer phosphates from ATP to tyrosine residues on intracellular target proteins [15]. Following the binding of insulin to the α subunits of the receptors, the β subunits phosphorylate and, consequently, activate the receptor's catalytic function [15]. Additionally, the now activated receptor can now phosphorylate several intracellular proteins that also regulate the metabolic activities of insulin, cell growth, and cell differentiation-related gene expression [15].

For years, this hormone was thought to be solely produced by the beta cells of the islets of Langerhans in the exocrine tissue of the pancreas [14, 15]. However, most recently, it has been shown that there are low concentrations of the insulin found in certain neurons of the central nervous system [15]. Insulin has been well documented to play a significant role in controlling energy conservation efforts within the body as well as energy utilization during the fasting and fed states [14]. Extensive amounts of literature show that insulin is critical for transporting intracellular glucose to insulin-dependent cells/tissues, such as liver, muscle, and adipose tissue [15]. In the liver, insulin is responsible for the nutrient homeostasis, mainly in the form of synthesizing glycogen from glucose and the conversion of excess glucose into fatty acids and precursor triglyceride [15]. Incidentally, it has been shown that insulin upregulates glucose-utilizing activity via accelerated hepatic glucose utilization, glycolysis, and glycogenesis, and downregulates glucose production by suppressing net glucose production, gluconeogenesis, and glycogenolysis [15]. During postprandial hyperglycemia, in skeletal muscle, it has been observed that an increase in plasma insulin concentration triggers the uptake and use of glucose by skeletal muscle [15]. Most notably, adipose tissue is responsible for almost one-tenth of the insulin for whole-body glucose uptake, with several aspects of adipose cell development and differentiation being regulated by insulin [15]. Additionally, it has been demonstrated that blood triglyceride concentration is one of the main factors affecting the production of insulin [15]. Within the vasculature, insulin is thought to be important for several functions relating to the endothelium, most importantly, as an anti-inflammatory agent via the stimulation of the expression of endothelial nitric oxide synthase and the suppression of the generation of O2 radicals and reactive oxygen species [14, 15]. Regarding the central nervous system, there is growing evidence that suggests that insulin can increase the glucose uptake in the spinal cord tissues and some brain regions, such as the choroid plexus, the pineal gland, and the pituitary gland [15]. In addition to glucose metabolism and the energy homeostasis, insulin is reported to control neuronal plasticity, memory processing, and cognition [15]. There is an increasing body of literature that supports a substantial role of insulin in the regulation of glucose metabolism in the kidneys, signaling of osteoblast development and born resorption in bone maintenance, and the mitigation of cell damage in the skin and hair follicles [15].

Dopamine, Insulin, and the Central Nervous System

Effect of Insulin on the Functionality of the Brain

For many years, the brain has long been thought to be an insulin-insensitive organ, mainly because insulin was not thought to affect the uptake of glucose in the brain [16, 17, 18]. However, over the past few decades, there is growing evidence that elucidates the presence and many functions that insulin has in the brain [16, 19]. In the central nervous system, glucose is transported into most neurons via GLUT3 while the glia and brain endothelial cells depend on GLUT1 activity for glucose uptake from brain interstitial fluid (ISF) and plasma [17, 20]. Although GLUT1 and GLUT 3 are both insulin-independent transporters that negate the necessity of insulin for glucose transport, the role of insulin as a neuroregulatory peptide in the brain is slowly being unraveled [17].

After insulin is made in and secreted from the β-cells of the pancreas, it can pass into the brain via two mechanisms. These are either by circumventing the blood-brain barrier (BBB) crossing the median eminence or by crossing the vascular endothelium via transport proteins [16, 21]. The transport of insulin into the brain is a highly regulated process that, although not completely understood, can potentially be

altered by disease states such as obesity, T2DM, and Alzheimer's disease (AD) [16]. Once transported into the brain, insulin binds to α subunits of the insulin receptors (IRs) which triggers the activation of the β subunit tyrosine-kinase activity, thus, stimulating the phosphorylation of its own receptor in both neuronal and glial cells [18]. After a series of downstream insulin signal transduction pathways, IRs are then rapidly aggregated and internalized for use in recycling and/or degradation [18]. Additionally, it has been proposed that some regional-specific actions of insulin in the brain may be based on areas of increased insulin receptor expression within the olfactory bulb, hypothalamus, hippocampus, cerebral cortex, and cerebellum [16]. Earlier studies have even found evidence of the presence of insulin mRNA and C-peptide in the central nervous system (CNS), suggesting that some amount of insulin may be synthesized in the brain [16, 18, 19].

There is an increasing body of literature that supports the extensive physiological role that localized insulin plays in the brain and central nervous system, at large. For example, at the cellular level, constituting the blood-brain barrier (BBB), brain endothelial cells (BECs) possess insulin binding sites that act both as insulin transporters across the BBB and as classic receptors [18]. These binding sites allow them to carry out multiple functions such as inducing neurochemical modifications in brain micro-vessels via multiple biochemical pathways and activating intracellular machinery that can lead to the increase in transport of compounds such as tyrosine, tryptophan, and leptin [18]. Additionally, there is a growing body of evidence that highly implicates insulin's role in the differentiation, proliferation and growth of neurons and other types of brain cells via complex signaling in the CNS. [16, 18, 22]. Insulin is also seen as a potent neuroprotective agent that acts mainly against apoptosis, beta amyloid toxicity, oxidative stress, and ischemia [16, 18]. Insulin is involved in these processes through the utilization of PI3K pathway (anti-apoptosis), glucose uptake and pyruvate formation (oxidative stress), and direct and indirect mechanisms of glucose metabolism (ischemia) [18]. Any reduction in these protective mechanisms can lead to an increased risk of development of neuropsychiatric, neurodegenerative, and even, metabolic disorders via mitochondrial, apoptotic, and dopaminergic pathway dysfunction [16, 23, 24]. In addition to its neuroprotective effects, insulin also plays a role as a neuromodulator by acting on the electrophysiological levels, concentration, and function of various neurotransmitters such as GABA, norepinephrine, and serotonin [18].

Much well-known, it has been established that insulin does not induce a significant glucose uptake in the brain as compared with peripheral tissues. However, it may play other important roles in glucose homeostasis. Namely, insulin functions as a key afferent signal to the CNS mainly through catabolic effects that inhibit food intake [25]. Additionally, through a series of several mechanisms, central insulin can act to lower blood glucose levels by suppressing hepatic glucose production and even induce lipogenesis [16, 19, 25]. Moreover, any alteration to insulin concentrations in the brain can affect the functional capacity of hypothalamic glucose-sensitive neurons to modify the glucose response [18]. It has been shown that insulin can act both acutely and chronically to regulate CNS glucose sensing, and thus, the counterregulatory response to hypoglycemia [16, 26].

Not only involved directly in the process of energy homeostasis, but insulin also plays a role in the indirect regulation of energy within the body. Specialized neuronal networks in the brain coordinate adaptive changes in food intake and energy expenditure in response to altered metabolic conditions [27]. Within the satiety and hunger networks of the brain, there lie orexigenic and anorexigenic receptors that closely interact with metabolic sensors such as GLUT-2, glucokinase, AMP-activated protein kinase (AMPK), PAS kinase (PASK) and many others [18]. Cells of several hypothalamic nuclei (i.e. paraventricular nucleus (PVN) and arcuate nucleus (ARC) detect circulating satiety signals from these interactions and transmit this information to other areas of the brain which may affect feeding behavior [18, 27]. It is believed that through the PI3K pathway, insulin along with other neuroactive chemicals like leptin and serotonin, may play a key role in the central control of food intake. Additionally, Sirtuin 1, an anti-aging gene, has been identified as a key player in the insulin release and its regulation of appetite [28, 29] Research has shown that a defective Sirtuin 1 gene is associated with glucose dysregulation via inhibition of insulin signaling which, in turn, can further disrupt regular feeding habits [28, 29]. It has also been observed that the SIRT1/p53 pathway is essential for the orexigenic response to ghrelin and is even linked to leptin with relevance to metabolic health and obesity [30, 31] These interactions that heavily influence appetite and even food palatability have been found to affect food intake and body weight [16, 30, 31, 32, 33]. Although brain insulin has been shown to reduce weight, insulin's anabolic effect on peripheral tissues is most dominant and leads to overall weight gain [16]. Furthermore, insulin also plays a role in the regulation of energy expenditure through mechanisms such as increasing outflow of the sympathetic nervous system and thermogenesis via the hypothalamus [25, 27]. Additionally, as insulin and cortisol exert reciprocal actions on energy acquisition throughout the day, it has been proposed that this balance of the stimulation of food intake (cortisol) and inhibition of food intake (insulin) is mediated through regulation of hypothalamic neuropeptide-Y (NPY) synthesis and secretion in the arcuate nucleus of the hypothalamus [25].

Brain insulin has also been observed to exerts its effects on other physiological functions in the body via multiple interactions in the CNS. For example, intracerebral insulin has been observed as a stimulant and key regulator of pulsatile GnRH secretion and thus, reproductive function [18]. With evidence of insulin mRNA being found in the paraventricular nucleus, it has also been postulated that insulin also plays a role in the regulation of pituitary growth hormone production [16, 34]. It has also been reported that the peripheral or central administration of insulin by intracerebroventricular (ICV) or intrahippocampal routes to experimental animals has positive effects on memory and learning processes, mainly via an increase in both the IR expression and its signal transduction pathways [18]. Insulin administration has even been shown to provide cognitive benefits in healthy humans as well as in patients with T2DM and AD. This benefit is especially important to note in minority populations such as African Americans, who are particularly disproportionately affected by T2DM and vulnerable to cognitive decline and dementia [35]. Insulin has also been demonstrated to play a role in the development of depression and anxiety, where in neuronal-specific insulin receptor knockout (NIRKO) mice, the knockdown of insulin receptors, resulted in increased anxiety and depressive-like behavior in mice [16]. It was proposed that this was possibly due to decreased dopamine release via attenuated dopamine signaling [16].

Effects of Central Insulin, Leptin and Ghrelin on Dopamine Release and Regulation

In more recent years, research has shown that mesolimbic dopamine (DA) signaling has been implicated in the incentive, reinforcing, and motivational aspects of food intake [36]. Originating in the ventral tegmental area (VTA) and projecting to the prefrontal cortex, amygdala, and ventral striatum, dopamine neurons are critical for the regulation of behavior, more specifically, feeding behavior [36, 37]. More specifically,

dopamine release in the nucleus accumbens (NAc), is particularly important in the process of learning and the motor activity related to rewarding stimuli [37]. Due to the co-expression of tyrosine hydroxylase (a marker for dopamine neurons) within both the insulin receptor and the leptin receptor in these areas of the brain, it has been strongly suggested that midbrain dopamine neurons are direct targets of insulin [37, 38]. In addition to insulin receptors, midbrain dopamine neurons express receptors for numerous circulating signals associated with homeostatic mechanisms, including leptin, ghrelin and orexin [39]. As result of this, insulin and other homestatic inputs are postulated to modulate dopamine signaling and regulate reward processes, particularly those pertaining feeding behaviors and energy expenditure [40, 41].

Not only involved in the regulation of energy homeostasis via hypothalamic signaling, it has been suggested that central insulin also plays a role in mediating non-homeostatic feeding for pleasure by signaling within mesolimbic reward circuits [42]. The presence of insulin receptors, in addition to the intracellular substrates of insulin receptor activation (IRS2) and phosphatidylinositol-trisphosphate (PIP3) on dopamine neurons of the VTA and substantia nigra (SNc) indicate a potential role in the reward system via the regulation of dopamine [43, 44]. Stouffer et al have observed that insulin can initially cause an amplification of dopamine (DA) release in the nucleus accumbens (NAc) and caudate putamen, specifically right after food restriction, through an indirect mechanism involving striatal cholinergic interneurons that express insulin receptors [45]. This shows that in the fasted state, insulin can serve as a reward signal that is used to obtain palatable food. However, once under sated conditions, direct administration of insulin into the VTA has been shown to reduce hedonic feeding and depress somatodendritic DA in the VTA [42]. This insulin-induced depression of somatodendritic DA has been attributed to the increased expression of dopamine transporter (DAT) mRNA and upregulation of the number or function of DATs in the VTA via phosphoinositide 3-kinase (PI3K), PIP3, and mammalian target of rapamycin (mTOR) signaling [36, 39, 43, 44, 46]. Additionally, the injection of insulin into the brain decreased glutamatergic synaptic transmission onto VTA DA neurons [42]. This subsequently reduced DA burst activity, and ultimately, DA release in mesocorticolimbic regions [42]. After the action of increased number and function of DATs occurs, an increase in insulin-mediated DA clearance from the synaptic cleft may contribute to enhanced DA neuron excitability via reduced activation of inhibitory D2 autoreceptors on DA VTA/SN cells [47, 48]. This mechanism results in a post-depression effect of an increase in the firing rate of dopaminergic neurons in order to reset the homeostatic signals to a neutral state [44]. Currently, established evidence has pointed towards insulin's role in decreasing hedonic value signals and potentially reduce the reward value of food via modulation of dopamine in the VTA and NAc, once in the sated state [46, 47, 49].

Leptin, another homeostatic input, has also been shown to regulate dopamine signaling and hence, the reward mechanism behind food behavior. There is an increasing body of evidence that shows that the administration of leptin into the brain, mainly the VTA, results in phosphorylation of STAT3 primarily in dopamine neurons which ultimately decreases the firing rate of VTA dopamine neurons via a decrease in action potentials, subsequently reducing DA levels in the NAc [40, 44, 50]. Like insulin, presynaptic leptin can suppress excitatory synaptic transmission in DA neurons in the VTA and decrease DA concentrations, most likely by increasing the activity of DATs [51, 52]. Interestingly, the specific effects of leptin on the mesolimbic dopamine system seem to involve multiple mechanisms. Usually, leptin, along with insulin activate the intracellular PI3 kinase cascade, which results in the generation of the signaling molecule PIP3 [46]. However, receptors in the VTA and lateral hypothalamic area (LHA) have distinct leptin-activated pathways [44]. Most significantly, leptin activation of an alternative JAK-2 pathway in the VTA, rather than the usual mTOR or PI3K pathways in the hypothalamus, was associated with reduced food intake, most likely due to the action of leptin on dopaminergic neurons [44, 53]. Additionally, it was found that leptin modulated dopamine in the NAc and VTA by increasing the activity of tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis [44]. Taken together, this data suggest that leptin embraces a major role not only in its well-known hypothalamic signaling capacity, but also as modulator of the mesoaccumbens DA circuitry [37].

Ghrelin is a 28–amino acid peptide that, although known for its role in the regulation of growth hormone secretion, food intake, and energy homeostasis, has also been implicated in the regulation and modulation of dopamine. As previously known, ghrelin, the only known orexigenic gut hormone, is secreted from the stomach and primarily activates neurons in the hypothalamus that secrete neuropeptide Y and Agouti-related protein, leading to an increase in food intake [44]. However, ghrelin receptors have also been found to be expressed on GABA-ergic and dopaminergic neurons in the VTA and the substantia nigra [44, 54]. Ghrelin was also shown to have a profound effect on the regulation of dopamine through the activation of dopaminergic projections from the VTA to the NAc and activation of dopamine D1-like and D2 receptors in the NAc. This along with an increase in DA turnover in the nucleus accumbens and acetylcholine levels in the VTA led to an increase in the firing rate of VTA dopamine neurons, and overall increase in dopamine levels in the NAc [44, 54, 55]. In some animal studies, this administration of ghrelin into the VTA was shown to increase dopamine concentrations in the NAc which subsequently led to an increase in palatable food intake and locomotor activity [44]. Taking this data into consideration, ghrelin may act in conjunction with the brain reward system to enhance the rewarding value of palatable food intake.

To fully evaluate the relationship between dopamine and homeostatic hormones in the brain, we must also further elucidate how dopamine in the brain can affect the regulation of central insulin, leptin, and even ghrelin [44]. However, it is important to note that currently, there is a major dearth of information on this subject. This is an area of research that, if extensively explored, would be prove to be very reliable in further unlocking the intricacies of the interactions between the mesolimbic system and homeostasis [44].

Effects of Insulin, Ghrelin and Leptin on Dopamine-related food behavior

The behavior that explains the drive to intake food often be attributed to energy demands, otherwise known as "homeostatic" feeding. To date, this specific phenomenon has been well studied and outlined. However, food intake can also be driven by the palatability or pleasure associated with eating a preferred food, "non-homeostatic" feeding [39]. The mesolimbic dopamine system has been a primary focus for research into the relationship between food intake and brain reward systems and has been shown to be activated in humans and laboratory animals in response to palatable food, with insulin, leptin, ghrelin, and other regulators of appetite being of great influence on the activity in this system [44, 56]. This suggests that midbrain dopamine systems play an important role in palatable food consumption [44, 56]. More specifically, the VTA, may represent an central detector of peripheral metabolic signals, which responds by appropriately increasing or decreasing food intake via modulation of mesolimbic and mesocortical circuits [44, 50]. The NAc represents a functionally specialized subregion of the striatum which is a

critical anatomical component of CNS reward circuitry, with the extensive projection of DA neurons from the midbrain ventral tegmental area (VTA) and associated DA cell groups [39]. As the main neurotransmitter in the mesoaccumbens pathway, dopamine has been heavily implicated in the regulation of "hedonic feeding". Some examples of this is the pharmacological blockage of dopamine receptors leading to the attenuation of feeding and responses to food reward [43, 57, 58] According to Liu et al, dopamine in the NAc provides a cost-benefit signal that translates incentive motivation into physical effort for food reward [43]. Not only modulated by the homeostatic hormones of insulin, leptin, and ghrelin, the neural regulation of feeding behavior is also thought to be modulated by the prefontal cortex, which in turn seems to be sensitive to central insulin action [42].

According to Roitman et al, food is an incentive stimulus that strongly evokes the production of dopamine [59]. Approaching this phenomenon from an evolutionary perspective, palatable foods, especially those with high sugar and fat content, are perceived as so to ensure that food was eaten when available, enabling energy to be stored in the body for future need in environments where food sources were scarce [59]. In animal studies, palatable food is known to activate the dorsal and ventral striatum, VTA, lateral hypothalamus (LH), and central and basolateral nuclei of the amygdala and reward-related cortical structures in rats [56, 60]. Normally, ghrelin, insulin, and leptin work in concert with one another to modulate food behavior. As previously discussed, it was shown that ghrelin may act in conjunction with the brain reward system to enhance the rewarding value of palatable food intake, mainly by increasing dopamine levels in the NAc and VTA by multiple mechanisms [44, 56]. It was proposed that ghrelin, like caloric restriction, increases the sensitivity of the VTA to the effect of reward-seeking or reward-inducing stimuli, mainly by the activation of important brain regions such as the OFC, amygdala, insula, striatum, VTA, and SN [54, 56, 61]. Additionally, as previously discussed, in the fasted state, insulin can serve as a reward signal that is used to obtain palatable food [45]. After the intake of pleasurable foods occurs, insulin and leptin, two common satiety signals, are both peripherally and centrally. More specifically, brain insulin can act as a relevant satiety signal during the postprandial period by reducing food palatability preference ratings and suppressing food-value signals in the NAc through the negative modulation of projections from the VTA, via insulin-mediated depression of DA activity [32, 42, 44, 62]. Similar to insulin, as previously mentioned, leptin reduces food intake by decreasing DA concentrations through multiple mechanisms. As a result of these forces, the reward system is conventionally inhibited by leptin in the sated state [44]. Davis et al has further described this interaction, detailing that insulin action in mesolimbic neurons might affect the pleasure associated with palatable food consumption while leptin signaling in this region negatively regulates the motivation necessary to obtain a food reward [63]. Once these satiety signals act, the body is essentially reset and returns to a homeostatic state.

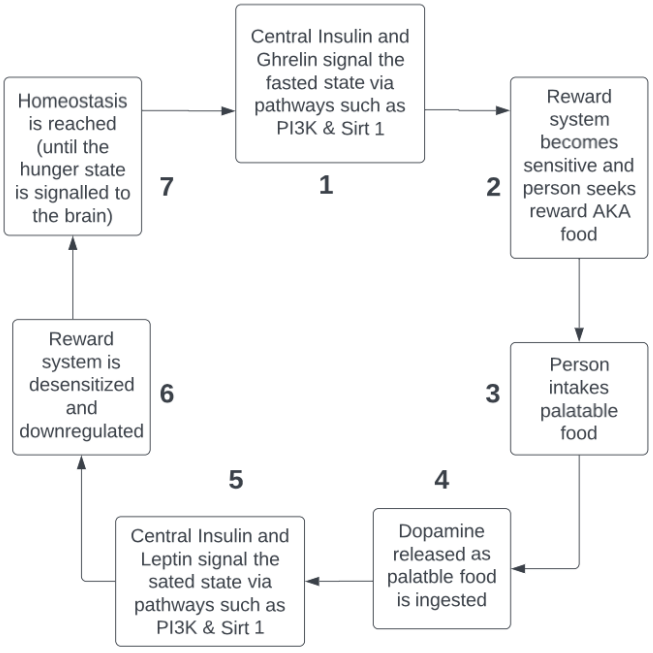

Figure 1: Diagram displaying the pathway of how insulin, leptin, and ghrelin affect the Dopamine Reward System to modulate food behavior under normal circumstances. Content adapted from Murray et al 2014 [44]

However, palatable foods often contain a high content of fats and sugars. It has been shown that ingestion of foods that contain this proportion of contents can lead to a greater-than-normal increase in dopamine after ingestion [64]. The consumption of high quantities of palatable food like these can upset the balanced interaction among the brain reward circuits, resulting in an enhanced reinforcing value of food and a weakening of the control circuits [65]. In some animal studies, obesity-prone animals chronically fed a high-fat, high-sugar diet exhibited signs of craving, increased anxiety and symptoms of withdrawal when the diet was removed [44]. Volkow et al proposes that this perturbation is a consequence of conditioned learning and the resetting of reward thresholds following the consumption of large quantities of high-calorie

foods [65]. Consequently, the overconsumption of palatable food triggers addiction-like neuroadaptive responses in brain reward circuitries and drives the development of compulsive eating [66]. Namely, the overconsumption of these foods can result in the downregulation of striatal dopamine D2 receptors (D2R) possibly via the depression of excitatory synaptic transmission in the VTA [42, 48, 64, 65, 66, 67, 68]. This blunting of the dopamine system can occur via mechanisms such as the reduced expression of several dopamine-related metabolites, including vesicular monoamine transporter-2, tyrosine hydroxylase, DAT and dopamine D2 receptors [44, 64, 69](Murray et al 2014, Rada et al 2010, Geiger et al 2008) Weight gain associated with this behavior of overeating has also been linked with further reduction in striatal activation in response to palatable food intake [42, 65, 66, 67]. This theory, known as the reward deficiency theory of obesity, posits that individuals with lower sensitivity in DA-based reward regions tend to overeat to compensate for decreased activation of these circuits [42]. This low striatal responsivity to food and overall state of reward hyposensitivity may increase risk for overeating and future weight gain, resulting an endless cycle that may contribute to the development of obesity [67]. On the other hand, the less popular theory of a hyper-responsive reward system due to evidence of increased activation of certain brain regions, has also been put forth as a potential explanation of this phenomenon [44, 70].

As a result of this food behavior, obesity can develop. Through various mechanisms such as adipose tissue fibrosis, inflammatory factors like macrophage cells and PAI-1and the production of exosomes, obesity can even induce insulin resistance [71]. Excessive consumption of high sugar and high fat foods can lead to neuronal insulin resistance, dysregulation of dopamine homeostasis, and HRDS (hypodopaminergic reward deficiency syndrome) in the brain [72]. The chronic state of hyperinsulinemia has been found to reduce the efficacy of insulin's effect on the depression of VTA DA neurons [42]. Additionally, brain insulin resistance appears to reduce the activity of the mesolimbic reward system by increasing the dopamine-degrading enzymes MAO A and MAO B and COMT, which results in reduced DA concentrations [72]. This can potentially translate to insufficient satiety signaling and increased hunger signaling, which might provide yet another mechanism that could underlie the reward deficiency theory of obesity [44, 65, 72]. Interestingly, in addition to insulin resistance, desensitization of reward regions to leptin, otherwise known as leptin resistance, could also lead to overconsumption of highly palatable food [44].

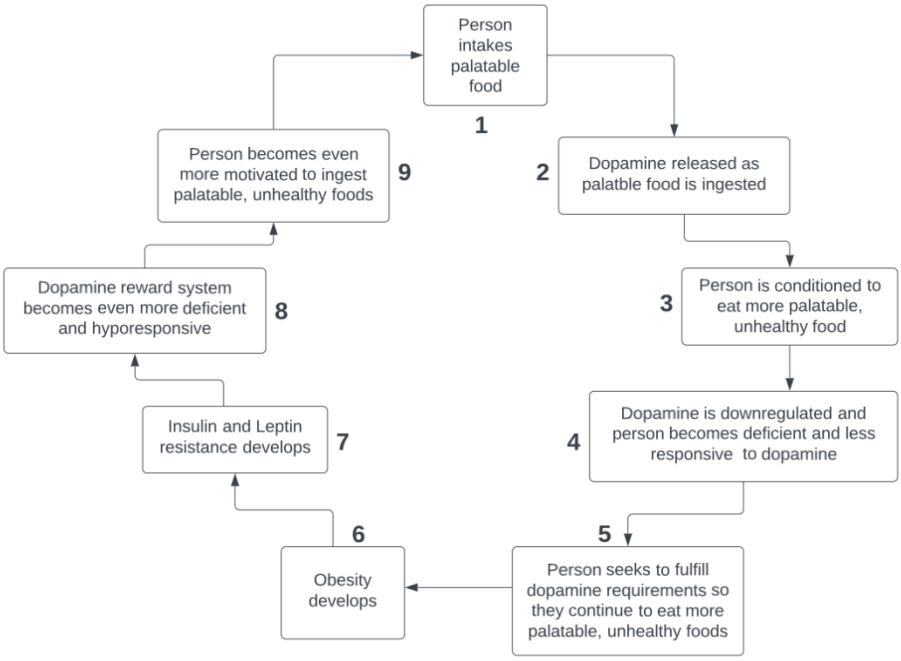

Figure 2. Diagram displaying how the hypodopaminergic reward deficiency syndrome theory effects food behavior and eventually the development of obesity. Content adapted from Tiedemann et al 2017 and Bukowska 2022 [42, 72].

As we continue to further uncover the complexity of the development of obesity and other comorbidities mainly through the mechanism of over consumption, it would be advantageous to search for potential solutions to this pandemic. Farr et al attempts to remedy this problem by suggesting that individuals take a multi-faceted approach [73]. They suggest that a holistic approach that includes the self-regulation of conscious decision making, controlling one's emotions and stress, and potentially disrupting the reward circuitry may prove effective in treating obesity [73].

Dopamine, Insulin, and the Obesity Epidemic in the African American Community

Over the last few decades, obesity, as a chronic disease, has widely become the most common, serious, and costly disease [1]. Most notably, the African American community has been one of the demographics most affected by this condition [1, 74]. The development of obesity can be attributed to many causes. Some of which may include socioeconomic

factors, physical activity, medications, other medical conditions, and even culture [74]. It is important to acknowledge that, in this group of individuals, systematic racism has further amplified the deleterious effects and roles that these factors play in the obesity pandemic [75]. Aside from these aforementioned factors, diet and genetics also play a major rale in the development of obesity [74]. In this review, we attempted to highlight any prior research that had been undertaken pertaining to any genetic factor, specifically at the intersection of the dopamine reward pathway and central homeostatic regulators such as insulin, that may predispose African Americans to the development of obesity. Unfortunately, we were not successful in this attempt, and we recognize that there is a significant dearth of information in this area of research. To fully understand the development and trajectory of the obesity epidemic, elucidating this potential avenue would truly prove to be advantageous.

Conclusion

In conclusion, there is evidence that shows that insulin, along with other homeostatic inputs such as leptin and ghrelin, work in concert to modulate the release and regulation of the dopamine reward system to ultimately control food behavior. Under normal conditions these hormones work together to achieve a homeostatic state with ebbs and flows of reward-seeking states and sated states. However, due to a multitude of reasons, this homeostasis can be disrupted, most likely due to the increased availability and palatability of unhealthy but pleasurable foods. Through several mechanism, weight gain and even obesity may develop from the dysregulation of this multi-tiered system. This provides yet another means of explaining the explosion of the obesity epidemic today. Further investigation is needed to unveil if this portion of the pathophysiology plays a role in the racial disparities seen with the prevalence of obesity today in the U.S.

Acknowledgements

Dr. Kanwal Gambhir conceived the idea and performed final edits on this paper. Farion Cooper and Dante Ewell produced the first draft of this paper. Drs. Fluitt and Odonkor made significant edits to the paper. We thank Dr. Gambhir for his consistent scholarly advice and guidance while conducting this scholarly project.

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DOI:10.31579/2640-1045/182