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Weighing in the Role of BDNF in the Central Control of Eating Behavior

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Abstract The prevalence of obesity and its associated medical complications, including type 2 diabetes and cardiovascular disease, continues to rise globally. Lifestyle changes in the last decades have greatly contributed to the current obesity trends. However, inheritable biological factors that disrupt the tightly regulated equilibrium between caloric intake and energy expenditure also appear to play a critical part. Mounting evidence obtained from human and rodent studies suggests that perturbed brain-derived neurotrophic factor (BDNF) signaling in appetite-regulating centers in the brain might be a culprit. Here, we review findings that inform the critical roles of BDNF and its receptor TrkB in energy balance and reward centers of the brain impacting feeding behavior and body weight.

Keywords BDNF · Hypothalamus · Mesolimbic dopamine pathway · Obesity · Hedonic · Homeostatic · Feeding · Body weight

Introduction

BDNF is a highly conserved member of the family of neurotrophins comprising nerve growth factor, neurotrophin-3, and neurotrophin-4. It is expressed during development and in excitatory neurons in the mature brain. Initially identified as a growth factor supporting the survival of sensory neurons, BDNF is now recognized as a multifaceted trophic factor [1]. It signals through the tropomyosin-related kinase B(TrkB) receptor and activates phospholipase C-gamma (PLC-γ), mitogen-activated protein kinase (MAPK), and phosphatidylinositol-3 kinase (PI3-K) intracellular signaling cascades to promote differentiation, survival, and synaptic plasticity in neurons. For additional information on neurotrophins and their receptors, see Patapoutian and Reichardt [1] and Reichardt [2]. Mice carrying BDNF-null alleles exhibit excessive degeneration in several sensory ganglia and die perinatally due to cardiovascular abnormalities, attesting to the importance of this neurotrophin during developmental processes [3, 4]. In the adult central nervous system, BDNF promotes synaptogenesis, dendritic remodeling, long-term potentiation, and modulates synaptic vesicle pools in selected brain regions [5–7].

A role of BDNF in the control of feeding behavior was first suggested by early rodent studies showing that chronic intracerebroventricular (ICV) delivery of BDNF induced reductions in body weight gain [8–10]. The necessity of BDNF in appetite control was later demonstrated by the hyperphagic behavior and elevated body weights exhibited by $BDNF^{+/-}$ mutant mice [11, 12]. Similarly, TrkB hypomorphic mice, which express full-length TrkB at about 25% of normal levels, display excessive feeding [13]. A closer examination of meal microstructure in $BDNF^{+/-}$ mutants revealed increased meal number but normal meal size under standard chow conditions [14]. When fed a high-fat diet, BDNF mutant mice developed overeating at a younger age and exhibited increased meal size and duration but reduced meal frequency. The finding that selective depletion of BDNF in the mouse brain elicited hyperphagia and dramatic obesity indicated that this neurotrophin regulates appetitive behaviors through central mechanisms [15]. In addition to 80% (males) and 150% (females) increases in body weight,

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mutants with central BDNF depletion develop other aspects of the metabolic syndrome including leptin and insulin resistance, dyslipidemia, and hyperglycemia. However, these metabolic alterations are secondary to the obesity because pair feeding of BDNF mutant mice with wild-type animals is sufficient to normalize these metabolic parameters [16, 17].

Human studies also lend support to a critical role of the BDNF/TrkB pathway in energy balance regulation. For example, a *de novo* missense mutation in the *TrkB* gene that impedes TrkB autophosphorylation and MAP kinase activation was identified in a human patient exhibiting overeating and severe obesity [18]. Increased *ad libitum* food intake and body weight were also reported in an 8-year-old female with one functional copy of *Bdnf* due to a *de novo* chromosomal inversion [19]. Additional evidence comes from recent investigations of individuals afflicted with Wilms' tumor, aniridia, genitourinary anomalies, and mental retardation (WAGR) syndrome due to large truncations within chromosome 11, which contains the human *Bdnf* gene. Han et al. reported that 100% of WAGR patients rendered BDNF haploinsufficient by truncations encompassing the *Bdnf* gene were obese by 10 years of age [20]. In contrast, only 20% of WAGR patients with intact *Bdnf* alleles developed obesity. Positive correlations between serum levels of BDNF and body mass index (BMI) have also been reported, suggesting that changes in circulating BDNF concentration are secondary to dysregulated energy balance [21, 22]. However, one study showed that caloric restriction in overweight individuals was significantly associated with reduced BMI and increased serum levels of BDNF, indicating a negative correlation between BDNF and body weight. Finally, several studies have linked the functional *Bdnf*Val66Met polymorphism to obesity susceptibility in humans [23–26]. This highly prevalent mutation [27] impedes activity-dependent secretion and signaling of BDNF [28]. Together, the cumulative data outlined here and by others [29] strongly support a required role of BDNF in feeding regulation.

Food intake is a complex behavior coordinated in the brain not only by homeostatic mechanisms balancing nutritional requirements and caloric status but also by hedonic factors that regulate the sense of pleasure and reward derived from consuming palatable foods. Whereas homeostatic mechanisms act primarily within the hypothalamus and dorsal vagal complex, hedonic feeding is thought to involve the mesolimbic dopamine reward pathway. These neural substrates constitute distinct yet interrelated pathways, the underlying workings of which are not completely understood. Here, we discuss evidence indicating that BDNF and TrkB participate in the regulation of both homeostatic and hedonic feeding by acting in energy balance and reward centers of the brain.

BDNF and Feeding Circuits of the Hypothalamus

The role of the hypothalamus in the homeostatic control of food intake and energy balance is well demonstrated. It integrates hunger, satiety, and adiposity signals transmitted from the periphery via the bloodstream to inform the energy status of the animal. In response to those cues, hypothalamic cells modify the expression and secretion of selective intra- and extrahypothalamic peptides and neurotransmitters to impact caloric intake and energy utilization [30, 31]. In the fed state, high levels of nutrients and appetite-suppressing hormones including adipocyte-derived leptin, gut-derived peptide YY (PYY), and pancreatic insulin act directly on hypothalamic cells to increase the anorexigenic tone. When energy levels are depleted, reduced concentration of satiety factors and enhanced gastric secretion of the orexigenic ghrelin facilitate the activation of hypothalamic signaling cascades that promote eating. Several interconnected hypothalamic nuclei influence feeding behavior including the arcuate nucleus (Arc), paraventricular nucleus (PVN), ventromedial hypothalamus (VMH), dorsomedial hypothalamus (DMH), and lateral hypothalamus (LH). BDNF is synthesized in the VMH, DMH, LH, and PVN but not in the Arc [13]. TrkB, for its part, is broadly expressed in all hypothalamic areas [32].

The Arc contains two antagonistic populations of appetite-regulating neurons that contain neuropeptide Y (NPY) or proopiomelanocortin (POMC), a precursor for α-melanocyte stimulating hormone (α-MSH) [30, 31]. Whereas NPY^+ cells induce eating, $POMC^+$ neurons suppress appetite. These cell populations receive and are regulated in opposite ways by peripheral energy status signals, including leptin and ghrelin, and project to intra- and extrahypothalamic regions. Arc cells that contain the potent orexigenic NPY co-express agouti-related protein (AgRP), which also induces eating. POMC-containing neurons also produce the anorexigenic cocaine and amphetamine-regulated transcript (CART). Although BDNF is not synthesized in the Arc, TrkB receptors and BDNF-containing nerve fibers are present in this region, suggestive of neurotrophin signaling involvement in local processes influencing feeding behavior [32]. The role of BDNF there, however, remains to be defined. Studies by Wang et al. provide some clues by showing that BDNF delivery to the PVN prevents elevations in NPY expression in the Arc induced by fasting and, notably, reduces NPY-induced feeding [33]. Of note, the number of excitatory and inhibitory inputs onto NPY^+ and $POMC^+$ neurons in the Arc dynamically changes in opposite ways in response to nutritional cues, effectively impacting activity of these cells [34, 35]. For example, the strength of excitatory inputs from the VMH to appetite-inhibiting POMC neurons in the Arc is significantly reduced in the presence of low energy stores [35]. The rewiring of hypothalamic feeding circuits has been

proposed to facilitate food intake control and energy homeostasis. Because BDNF is a known facilitator of structural and synaptic plasticity in the cerebral cortex, hippocampus, and cerebellum [5–7], it is reasonable to speculate that it might also participate in synaptic remodeling in the Arc during the fed state to promote satiety. This possibility warrants further examination.

A major target of NPY^+ and $POMC^+$ neurons is the PVN, a hypothalamic area that serves as a substrate for the anorexigenic actions of BDNF. It contains known energy balance-regulating peptides including thyrotropin-releasing hormone (TRH), corticotrophin-releasing hormone (CRH), urocortin, and CART [36–38]. Focal delivery of BDNF to the PVN reduced food intake in normal rats and ameliorated diet-induced obesity [39, 40]. The anorexigenic effects of BDNF in this region appear to involve the CRH pathway [39]. Accordingly, TrkB receptors co-localize with CRH in the PVN and ICV infusion of BDNF results in elevated levels of CRH. Importantly, co-administration of the CRH receptor 1 and 2 antagonist, α-helical-$CRH_{9–41}$, with BDNF attenuates the satiety effect of this neurotrophin. BDNF also induces PVN expression of urocortin, a member of the CRH family [39], suggesting that its effects on food intake might also be mediated by this anorexigenic peptide. Consistent with this idea, BDNF-induced anorexia was significantly attenuated by blockade of CRH R2, which has high affinity for urocortin but low affinity for CRH [39].

Hypothalamic expression of BDNF is highest in the VMH [13, 17]. This region plays a paramount role in appetite suppression as illustrated by the hyperphagia and obesity triggered by lesions to this region in rodents [41, 42]. Furthermore, electrical stimulation of the VMH results in decreased food intake [43]. The VMH is connected to several hypothalamic areas including the Arc and DMH and contains glucose sensing systems and receptors for nutritional status signals including leptin [44]. Expression of BDNF mRNA in the VMH is positively regulated by leptin and steroidogenic factor 1 (SF-1) [45, 46]. Whereas leptin is an anorexigenic adipocyte-derived factor and prominent regulator of energy homeostasis, SF-1 is a member of the NR5A subfamily of nuclear receptors and a transcription factor essential for VMH development and organization. The rodent *Bdnf* gene consists of eight untranslated exons that splice to a single coding exon, and expression of its many transcript variants is controlled by multiple tissue-specific promoters [47]. SF-1 promotes BDNF expression through interactions with *Bdnf* promoters I and IV [46]. In addition to aberrant VMH cytoarchitecture, SF-1 mutant mice exhibit deficient expression of BDNF in the VMH [46, 48]. Because BDNF has ascribed roles in neuronal survival and differentiation and synaptic connectivity, it is possible that it facilitates the effects of SF-1 in the developing VMH. Accordingly, high levels of BDNF are evident in the fetal and neonatal rodent VMH, followed by reduced but persistent expression in adulthood [49].

It remained unclear whether BDNF acted as a required satiety factor in the adult brain or as a developmental facilitator of neural feeding circuits. Consistent with a role in mediating satiety in the mature animal, BDNF infusion into the VMH of adult wild-type rats resulted in decreased food intake and body weight [50]. Furthermore, central and systemic administration of BDNF mitigated body weight gain and improved glucose metabolism in various models of obesity including leptin and leptin receptor-deficient mice [51, 52]. To differentiate effects of BDNF in the developing and adult brain influencing energy balance, we interrogated its role in the adult VMH. As reported previously by others [13, 46], we saw a robust effect of energy status on expression of BDNF in the VMH of adult wild-type mice. Indeed, prolonged fasting significantly depleted transcript levels of this neurotrophin. Moreover, glucose, a caloric signal, acted centrally to induce rapid elevations in BDNF mRNA content in the VMH. Energy signals appear to preferentially influence BDNF expression in the VMH directed by promoter I and promoters II and IV to a lesser extent [17, 46]. We also discovered that mice with intact levels of BDNF throughout development but deletion of *Bdnf* in the VMH in adulthood exhibited 27% and 41% increases in standard chow intake and body weight, respectively [17]. These findings indicate that BDNF acts as a required satiety factor in the adult brain and that the VMH is an essential source of this neurotrophin for food intake control. However, they do not preclude the possibility that BDNF exerts important developmental effects on feeding circuits.

α-MSH-containing fibers originating in the Arc terminate in the VMH, where they positively regulate BDNF expression [13]. This effect is expected to be limited because these neuronal terminals are sparse in the VMH, whereas expression of BDNF spans the dorsomedial, central, and ventrolateral divisions of this nucleus. BDNF mediates the anorexigenic effects of α-MSH signaling via the melanocortin receptor-4 (MC4-R) in the VMH [13]. Supportive evidence includes reduced BDNF expression in the VMH of MC4-R null mice and of agouti yellow (A^y) mutant mice, in which melanocortin signaling is suppressed by ectopic expression of agouti protein, a MC4-R antagonist. Conversely, MC4-R stimulation with the synthetic agonist Melotan II (MTII) induced expression of BDNF mRNA in the VMH. Importantly, exogenous BDNF delivery abrogated the hyperphagia and body weight gain exhibited by mice with deficient MC4R signaling when administered a high-fat diet. The facilitative effects of BDNF on α-MSH-induced satiety are not limited to events in the VMH as this neurotrophin is also a downstream effector of melanocortins in the hindbrain

(discussed below). The possibility that it might exert a similar role in the PVN, a target of POMC/α-MSH-containing fibers, has not been investigated.

Far less is known regarding the role of BDNF and TrkB in the DMH and LH. The lateral hypothalamus has often been referred to as a feeding center as lesions to this region result in hypophagia and weight loss [41]. It contains cells synthesizing melanin concentrating hormone (MCH) and hypocretin, two known orexigenic factors [53, 54]. We found that these cell populations appear intact in mice with central depletion of BDNF, suggesting that BDNF is not required for their survival or maturation [15]. The DMH is rich in fibers originating in the Arc and projects to the PVN, LHA, and VMH and contains both orexigenic and anorexigenic systems. In contrast to its effects on the VMH, we found that energy status did not influence expression of BDNF mRNA in the DMH [17].

In addition to controlling food intake, hypothalamic neural circuits greatly influence energy expenditure. For example, projections from the VMH and PVN to sympathetic and parasympathetic areas of the medulla and spinal cord mediate regulation of autonomic nervous system function, influencing energy expenditure [55, 56]. The role of BDNF in these processes remains somewhat unclear. Pair feeding is sufficient to normalize body weights of $BDNF^{+/-}$ mutants and mice with depletion of BDNF in the VMH [16, 17], indicating that alterations in energy expenditure do not contribute to the obesity of BDNF mutants. In support of a role in energy expenditure, Wang et al. [57, 58] found that selective BDNF administration into the VMH or PVN resulted in elevated basal metabolic rate. Moreover, ICV BDNF administration in obese leptin receptor-deficient mice enhanced norepinephrine turnover and uncoupling protein1 expression with a concomitant increase in thermogenesis [59, 60]. It is important to note that the reported elevated level of locomotor activity in $BDNF^{+/-}$ mutants and mice with central depletion of BDNF [11, 15] is a confounding factor. Deficits in the basal metabolic rate of these mutants might be masked by increases in locomotor activity that also contribute to energy expenditure. However, this does not appear to be the case for mice with selective BDNF depletion in the VMH as they show normal levels of activity and normalized body weights when pair fed with control mice [17]. After considering the existing data, it is reasonable to conclude that in the hypothalamus, BDNF plays a critical part in the control of homeostatic food intake and an important but non-essential role in the regulation of energy expenditure.

BDNF and Energy Balance-Regulating Circuits in the Hindbrain

The dorsal vagal complex (DVC) is located in the caudal brain stem and comprises the area postrema, the nucleus of the solitary tract (NTS), and the dorsal motor nucleus of the vagus. Like the hypothalamus, it integrates energy status signals arising from the periphery and communicated via vagal nerve afferents, including the anorexigenic gastrointestinal peptide cholecystokinin (CCK). It also has a high density of MC4R and is an important site of melanocortin signaling [61]. Whereas BDNF-containing cell bodies and fibers are present in the NTS, numerous $TrkB^{+}$ cells are located in the NTS and area postrema [32, 62]. BDNF protein levels in the DVC are reduced by fasting and induced by refeeding [63]. Moreover, MC4-R stimulation and systemic administration of leptin and CCK elevate BDNF protein levels in the DVC [63, 64]. The functional significance of BDNF in this region was demonstrated by the reduced food intake and body weight elicited by infusion of this neurotrophin into the DVC of rats [63]. Data suggest that BDNF facilitates the appetite-suppressing effects melanocortins in the DVC. For example, the hyperphagia induced by MC4-R blockade via delivery of antagonists to the fourth ventricle can be prevented by co-administration of BDNF. Furthermore, pharmacological blockade of TrkB abrogated the anorexigenic effect of MC4R agonists [64]. Together, the data indicate that the DVC is an important target for BDNF and TrkB action that facilitates their inhibiting effects on food intake.

BDNF and the Mesolimbic Reward Circuitry

Individuals often eat beyond their homeostatic requirements because it is rewarding. This form of hedonic feeding typically involves consumption of energy-dense, highly palatable foods and has been linked to the mesolimbic dopamine pathway, a regulator of motivated and reward-seeking behaviors. The mesolimbic pathway is composed of dopamine (DA) neurons in the ventral tegmental area (VTA) and their projections to the nucleus accumbens (NAc) and medial prefrontal cortex (mPFC). This neural circuitry has long been recognized as one of the critical anatomical substrates orchestrating the behavioral effects of drugs of abuse and natural rewards such as food, all of which elicit synaptic release of DA in mesolimbic targets [65–67].

In support of a role in motivated eating, BDNF and TrkB are expressed in the mesolimbic dopamine reward pathway. BDNF is expressed in dopamine neurons in the VTA and in pyramidal neurons in the mPFC from which it is anterogradely transported to the NAc, a region with little or no BDNF expression [68–70]. TrkB is expressed in VTA dopaminergic neurons, mPFC and GABAergic medium spiny-projection neurons in the NAc [32, 68, 69, 71], suggesting several potential cellular targets for BDNF action in the reward pathway. Recently, we demonstrated an intimate involvement of BDNF in the regulation of

hedonic feeding by positive modulation of the mesolimbic dopamine pathway. Amperometric recordings in acute slices of NAc revealed deficient evoked DA release in the NAc shell but not in the NAc core of mice with central depletion of BDNF. Interestingly, *in vivo* microdialysis studies in wild-type rats showed that VTA-derived dopamine was preferentially released in the NAc shell, as opposed to the core following palatable food consumption [65]. The dopamine secretion deficit in BDNF mutant mice persisted in the presence of nomifensine, a dopamine transporter inhibitor, indicating that this alteration was due to reduced secretion rather than increased reuptake of dopamine.

Pharmacological studies showed that defective dopamine transmission underlies the over-eating of palatable high-fat food triggered by central BDNF depletion. Indeed, the hyperphagic behavior of BDNF mutant mice could be overcome by stimulating dopamine 1 (D1) receptors with a selective agonist. Importantly, site-specific deletion of *Bdnf* in the VTA of adult mice did not affect consumption of standard chow but significantly increased intake of palatable high-fat food, leading to obesity [72]. The diet-specific effects of deleting *Bdnf* in the VTA suggest that BDNF signaling in the mesolimbic system is essential for the regulation of hedonic but not of homeostatic feeding. Interestingly, deletion of *Bdnf* in the mPFC did not impact body weight or intake of standard or high-fat chow (our unpublished observations), indicating that the VTA but not the PFC is a required source of BDNF. The disease mechanisms leading to reduced mesolimbic dopamine secretion in BDNF mutants remain unclear. BDNF is not essential for the survival of VTA dopamine neurons [73] or for dopamine synthesis in these cells [72]. We found that expression of TrkB and BDNF mRNA in the VTA of sated wild-type mice was influenced by intake of palatable HFF. The site of these expression changes suggests that BDNF might act presynaptically to modulate dopamine-producing cells in the VTA. One possibility is that BDNF regulates the excitability of this neuronal cell population during food reward-related processes. In agreement with this idea, Pu et al. showed that BDNF is required for the potentiation of excitatory synapses onto VTA dopamine neurons following cocaine withdrawal in rat brain slices [74].

How might deficient dopamine transmission in individuals with perturbed BDNF function lead to overeating? Hypoactivity of the mesolimbic dopamine pathway has been suggested to produce a reward deficiency syndrome that, behaviorally, manifests as compensatory overeating. In support of this idea, leptin-deficient *ob*/*ob* mice, which are hyperphagic and obese, exhibit reductions in food intake and body weight when treated with D1 receptor agonists [75], indicating that increased dopamine signaling reduces appetite. Similar to BDNF mutants, *ob*/*ob* mice also show decreased extracellular levels of dopamine in the NAc [76]. Additional evidence comes from studies of mice with overexpression of Δ-FosB, which display decreased dopamine signaling in the NAc and increased instrumental responding to food reward [77]. Six weeks of high-fat food administration completely ameliorated the observed deficits in dopamine signaling of Δ-FosB overexpressors. Finally, a human study further strengthens the reward deficiency model by showing that obese subjects exhibited decreased striatal activity compared to lean subjects in response to consumption of palatable food as measured by functional MRI [78].

The mesolimbic dopamine pathway has been implicated in the etiology of eating disorders involving binge eating as individuals typically binge on palatable, calorie-rich foods. Furthermore, alteration in this pathway have been reported in rodent models of binge eating [79]. This is intriguing because BDNF, a critical regulator of the mesolimbic reward pathway, has also been linked to the emergence of these afflictions. For example, the *Bdnf*Val66Met allele was associated with increased frequency and severity of bingeing in a population of Caucasian females diagnosed with bulimia nervosa or binge eating disorder [80]. Moreover, a significant increase in *Bdnf*Val66Met allele frequency was observed in a cohort of Japanese females with bulimia nervosa [81]. Reduced serum levels of BDNF were reported both in bulimic and anorexic individuals [82]. This is a seemingly contradictory finding; however, it is important to note that binge eating is part of the complex clinical picture presented by some anorexic individuals. In summary, the collective data indicate that the mesolimbic dopamine pathway is an important target of BDNF action for the regulation of hedonic feeding. Disruptions in this regulatory activity might underlie excessive intake of energy-dense palatable food and obesity and eating disorders involving binge eating.

Summary

BDNF is a pleiotropic growth factor that plays prominent and essential roles in the regulation of homeostatic and hedonic feeding through mechanisms acting in the hypothalamus, DVC, and mesolimbic dopamine reward pathway. Much remains to be elucidated in regards to the underlying cellular and molecular mechanisms. Virtually nothing is known in regards to the hypothalamic cell types expressing BDNF and TrkB and the precise role of BDNF in these cell populations. Additionally, the possibility that BDNF might act elsewhere in the brain to influence eating behavior warrants consideration. Given the high prevalence of obesity and mutations that interfere with BDNF signaling within the human population [27], defining the

mechanistic consequences of BDNF/TrkB signaling is one essential step toward developing novel treatment strategies for obesity and its many associated medical complications.

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