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Mini Review

Dysregulation of Leptin in Clinical Depression

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Abstract

Appetite, energy expenditure and metabolism are critically regulated by the central nervous system. To achieve energy homeostasis, neural circuits receive and integrate signals relaying information about the status of energy fluxes and stores from the periphery. Such information is mediated by the adipokine, leptin, which is putatively known as the "satiety hormone", which is expressed by adipocytes and whose receptors are widespread, but are particularly concentrated in the arcuate nucleus of the hypothalamus. In most cases, depression leads to hyperphagia and weight gain, leading to increased leptin production, leptin resistance and decreased activity of neuronal survival signaling pathways and expression of brain-derived neurotrophic factor (BDNF). As a result of lowered BDNF levels, neurons in the hippocampus and hypothalamus atrophy and die. The diminishment of neuronal survival signaling pathways can be reversed by antidepressant-like interventions, such as physical exercise, which increases monoamine neurotransmission, leading to increased hippocampal BDNF levels.

Keywords: *Leptin; Depression; Exercise; BDNF; Norepinephrine; Serotonin*

Abbreviations

AgRP: Agouti-Related Peptide; BDNF: Brain-Derived Neurotrophic Factor; CREB: cAMP Response Element Binding Protein; GABA: Gamma-Amino Butyric Acid; MAPK: Mitogen-Activated Protein Kinase; NS: Nervous System; nt(s): Neurotransmitters; PI-3K: Phosphatidylinositol- 3' Kinase; PKA: Protein Kinase A; POMC: Pro-Opiomelanocortin

Introduction

There is mounting evidence that clinical depression is much more than a disorder of the central nervous system, but rather, is also systemic, manifesting itself in disorders in the cardiovascular system, inflammation and metabolism, to name only a few [1]. In fact, over the past two decades, it has become increasingly well known that the cellular and molecular hallmarks of depression, such as pruning of dendrites, neuronal atrophy and death [2] can be reversed by lifestyle interventions, such as regular physical exercise [3-5]. Indeed, there is evidence that antidepressant drugs ameliorate depressive symptoms by activating the same neurotransmitter and neurotrophic receptors and intracellular signaling cascades that exercise does in hippocampal neurons [6-8]. Conversely, chronic stress can reverse the neurogenesis that exercise promotes [4]. Because physical exercise profoundly influences appetite, metabolism and energy expenditure, it makes intuitive sense that some of the mediators of these variables are also influenced by depression.

One such mediator is leptin. Depression and obesity are positively correlated, if not reciprocally causal, where obesity increases the risk of clinically diagnosed depression and *vice versa* [9]. In this brief review, the regulation of leptin, its receptors and the development of leptin resistance and obesity will be examined, followed by the role of chronic stress-induced depression or physical exercise-induced intermittent stress and their influence on brain-derived neurotrophic factor (BDNF), the neurotrophin that plays a critical role ameliorating cellular and molecular energy imbalance and neuroprotection [10,11].

Sites of Leptin Production

In Greek, *leptos* means "thin". Leptin is a protein hormone, produced mainly by subcutaneous white adipose tissue, whose adipocytes express the obese (*ob*) gene [12]. It acts mainly in the hypothalamus and increases energy expenditure by decreasing feeding. Indeed, leptin deficiency in $Lep^{ob/ob}$ mice or that of the receptor (leptin resistance, see below) in $Lepr^{db/db}$ mice, results in hyperphagia and obesity, severe hyperglycemia and insulin resistance [12]. Leptin circulation is proportional to long-term energy stores: increased fat storage promotes increased leptin production, resulting in decreased food intake and energy expenditure [13]. Conversely, weight loss decreases leptin production, resulting in decreased feeding and decreased energy utilization [12].

Leptin Pharmacokinetics

The pharmacokinetics of leptin are affected by its ability to bind to a plasma carrier molecule which increases its half-life; its association with abundant peripheral tissue binding sites, which create an additional pool of leptin. Moreover, the rate of leptin synthesis may be secondary to its prolonged half-life and the additional pool of tissue binding sites (e.g., in the heart, liver, small intestines), which directly determine its plasma concentration [14]. Leptin occurs in both free and bound forms. The bound pool of leptin include binding to tissue receptors, to non-specific sites in the tissues, and to carrier molecule(s) in plasma, such as albumin, and are retained longer than the free form [14]. As noted above, plasma leptin levels increase with weight gain and decrease with weight loss, consistent with its role as a signal of adipose tissue stores. Indeed, circulating levels of serum leptin and total body fat mass are positively correlated, which can be explained by increased release of leptin from large compared to small fat cells [15,16]. More specifically, it is the free leptin levels that are correlated with subcutaneous fat; the bound/free ratio significantly decreased in obese subjects due to a major increase in free leptin, relative to the bound form, which may be influenced by insulin and glucocorticoids [16].

Serum leptin levels display a diurnal rhythm with the highest levels between 2300 and 0100 hr, after which, plasma leptin declines until early afternoon. This diurnal rhythm is likely due to mealtime, given that a 6-hr delay after meals is correlated with a shift in plasma leptin levels [17]. This periodic nature of leptin production might reflect the ability of adipose tissue to store significant amounts of leptin in intracellular membrane-bound fractions [18]. As for leptin degradation, both lysosomal enzymes and proteosomal disposal mechanisms contribute to the degradation of newly-synthesized, albeit misfolded or used-up, leptin [16]. Moreover, the kidney has been found to be an important site for leptin clearance as total nephrectomy in rats and chronic renal failure in humans results in increased plasma leptin concentrations [16].

Leptin production is also influenced by age, with older people producing less than their younger counterparts, and by gender, with women producing more than males, due to a higher percentage of subcutaneous fat in the former [19].

Hypothalamic Arcuate Nucleus

The hypothalamic arcuate nucleus located between the third ventricle and the median eminence and is fed with semi-permeable capillaries, which convey neuronal feedback from vagal afferents and sympathetic nerves [20,21], ascending up to the nucleus of the solitary tract in the brainstem and several hypothalamic nuclei. The arcuate nucleus is composed of two principle groups of neurons that play a central role in the regulation of energy homeostasis as dictated by leptin input: the Agouti-related peptidergic (AgRP) neurons and pro-opiomelanocortin (POMC) neurons; leptin enters the arcuate nucleus and has an inhibitory effect on the former, but a stimulatory effect on the latter. POMC neurons are further regulated by inhibitory GABAergic input from AgRP neurons. POMC neurons send long branching axons to synapse with secondary neurons, which express on their plasma membrane, melanocortin-3 and -4 receptors (MCR3, MCR4), which bind α / β -melanocyte stimulating hormone, released from POMC neuron pre-synaptic terminals. This POMC neural activity, stimulated by leptin, is turned on under anorexigenic conditions (when energy expenditure exceeds feeding). On the other hand, AgRP neurons also send long branching axons to synapse with the same secondary neurons as those innervated by the POMC neurons, except that in the AgRP neural input, AgRP and/or GABA is presynaptically released to also bind MCR3 or MCR4. This AgRP neural activity, inhibited by leptin, is activated under orexigenic conditions (when feeding exceeds energy expenditure) [22,23].

Leptin Receptors

Besides being found in several diverse organs, such as liver, lungs, kidneys, heart, small intestines, reproductive organs, spleen and adipose tissue, leptin receptors are also expressed in several hypothalamic nuclei, including the arcuate nucleus, ventromedial, dorsomedial, lateral hypothalamic nuclei, and the paraventricular nucleus. The arcuate nucleus, in particular, is a key area for mediating leptin actions on energy homeostasis [24] and is where leptin receptor mRNA is densely transcribed. Several isoforms of ObR exists (6 variants as of this writing, [25]), with the long signaling form being the main mediator of leptin's signaling effects. Mice lacking leptin receptors only in arcuate POMC neurons or AgRP neurons are only mildly obese, demonstrating that both nuclei of neurons are required for maintenance of body weight homeostasis by leptin [26]. Further, re-expression of leptin receptors in exclusively in POMC neurons of the receptor-deficient *Lepr*$^{db/db}$ mice modestly reduces body weight and caloric intake.

Leptin receptors function through the JAK/STAT phosphatidylinositol-3' kinase (P1-3K) and mitogen-activated protein kinase (MAPK) signaling pathways. Leptin binding to the long form of the receptor triggers the autophosphorylation of JAK2 and its tyr1138, which promotes the recruitment and phosphorylation of STAT3 [13,22,27], which, in turn, binds to specific DNA elements to initiate or regulate gene transcription. STAT3 binding to AgRP and POMC promoters inhibits AgRP and increases POMC expression, respectively, thereby decreasing feeding. STAT3 regulates expression of the suppressor of cytosine signaling SOCS-3, which acts as a feedback inhibitor for the pathway by binding to Tyr985 on the long form of the leptin receptor and inhibiting JAK2 kinase activity. Phosphorylated Tyr985 of the long form also binds SHP-2, a protein that activates ERK (MAPK) signaling and is important for *c-fos* transcriptional activation [28,29]. Consistent with this role, mice with mutated long form (specifically the Tyr1138 residue) are unable to bind to STAT3 end up rapidly developing hyperphagia and obesity similar to that in *ob/ob* or *db/db* mice [29].

Leptin can also activate PI-3K through JAK2-mediated tyrosine phosphorylation of IRS proteins, which was first proposed to be a point of convergence for the integration of insulin and leptin signaling [23,27] in POMC neurons, but not in AgRP neurons, where insulin activates PI-3K and leptin inhibits it, presumably via presynaptic action. Moreover, the modulation of the electrical activity of these neuron populations also differs between the two hormones. Thus, while insulin hyperpolarizes and silences both POMC and AgRP neurons, leptin depolarizes POMC neurons and hyperpolarizes AgRP neurons [23].

Non-Arcuate Nucleus Neural Systems

Although much effort has focused on leptin's action in the hypothalamic arcuate nucleus "satiety center", leptidergic neurons in other feeding centers are also being recognized as crucial for leptin action. The effects of leptin on food intake appears to be mediated by leptin receptors, in part via reward-neurons located in the mid-brain (dopamine neurons in the ventral tegmental area [30], and by neurons in the nucleus of the solitary tract of the caudal brainstem, a major projection zone for sensory nerve input from the gastrointestinal system [20,31,32].

Obesity and Leptin Resistance

By binding to and activating the long form of its receptor in the hypothalamus, leptin decreases food intake while increasing energy expenditure (above). There is much evidence indicating that a major physiologic role of leptin is to respond to and defend against body fat reductions (and thus leptin) that might threaten survival. Except that body fat mass is markedly increased, both humans and rodents lacking leptin or its receptor mirror the physiological response to starvation (e.g. hunger, decreased metabolic rate, insulin resistance). Thus, leptin is required for the central nervous system to sense the relative sizes of energy stores and is thus essential for normal energy homeostasis.

Leptin replacement effectively reverses genetic leptin deficiency (i.e. Lept *ob/ob* mice and rarely humans with loss of function in the leptin gene due to mutations [25], inherited lipodystrophic syndromes (in which the lack of adipose tissue results in a corresponding decrease of circulating leptin [33], congenital leptin deficiency [34] and in normal humans who have lost weight and whose circulating

leptin, therefore, is decreased from less fat mass. Moreover, exogenous leptin acutely decreases feeding and body weight in normal animals and is a powerful determinant of energy expenditure in fasted animals (see above). Taken together, these observations establish leptin as a key regulator of metabolic and neuroendocrine responses to states of negative energy balance and weight loss [32].

Although leptin administration reduces feeding in normal animals [13], food intake ultimately returns to normal during prolonged leptin administration, once body fat stores have been substantially depleted [32]. Moreover, treatment with leptin alone (even at very high doses) is ineffective as a means to decrease food intake and body weight in obese animals and humans. Indeed, the subset of overweight and obese human subjects who demonstrate the strongest catabolic response to leptin are those on the lower end of the obese body-mass-index range and those with relatively low leptin levels. These seemingly contradictory observations that leptin reduces food intake and body weight, but are found in obese subjects (proportional to subcutaneous fat mass), have inspired the idea of "leptin resistance" in common forms of obesity, analogous to the insulin resistance that contributes to type 2 diabetes, which often coexists with leptin resistance in obese individuals [13,22]. Myers., *et al.* [32] warn that terming this form of obesity "leptin resistance" obscures efforts to distinguish the mechanisms that predispose to weight gain from those that result from it. Although cellular and anorectic response to leptin under the obese condition in models can be expected to (and do) reveal cellular leptin resistance and decreased leptin action on energy balance, such studies do not address whether this impairment is secondary to obesity, or whether it occurs independently of obesity and might thereby contribute to obesity pathogenesis. Testing for a primary defect in cellular leptin receptor action, such as decreased STAT3 [35], that operates independently of obesity may shed light on which comes first, the leptin resistance or the obesity. The observation of partial reduction of food intake in response to leptin in the presence of normal leptin receptor signaling also requires cautious interpretation, as this might reflect disruption of either leptin-regulated downstream neural pathways, such as lateral hypothalamus and ventral tegmental area or other neural systems that modulate feeding [32].

Myers., *et al.* [32] instead propose that increased food intake and associated adiposity promotes cellular leptin resistance in diet induced obesity (DIO) and that this cellular leptin resistance prevents leptin receptor signaling from reaching the level that it would otherwise attain in response to the increased circulating leptin, thereby further facilitating the weight gain associated with the consumption of a high-calorie diet. Consistently, hippocampal [36] and hypothalamic [37] BDNF were lower in DIO mice than in control diet mice [36]. As Myers., *et al*. [32] observe, the DIO model has the advantage of incorporating the potential relevance of cellular leptin resistance in the pathogenesis of common forms of obesity while acknowledging that it cannot explain the entire pathogenesis of DIO. It also recognizes the potential for mechanisms of cellular leptin resistance as therapeutic targets, because mitigating these processes should enhance leptin receptor signaling, thereby reducing the degree of obesity.

DIO may not be induced by a failure of the central homeostatic circuits, but, rather, by raising the threshold for defended adiposity. Thus, in at least some rodent models, the restoration of normal chow to DIO animals reduces food intake and adiposity, but not necessarily to the levels observed in animals that were never exposed to the obesogenic diet [36]. Once obesity is established, therefore, an upward re-regulation of the defended level of body fat stores might occur [12]. Indeed, there are several otherwise confusing observations that can be reconciled by proposing that long-term reprogramming occurs in chronic obesity/hyperleptinemia. One example is the finding that chronic leptin overexpression in rodents, which initially promotes leanness, results in increased adiposity in the long term [38]. How the homeostatic system might become reset to a new and elevated level of adiposity and/or circulating leptin remains unknown. Although many components of cellular leptin resistance would be expected to diminish with decreasing adiposity, such as in the activation of Tyr985/SOCS3- dependent feedback inhibition, defective leptin transport across the blood-brain barrier at the median eminence, and hyperphagia-induced inflammation of the hypothalamus [27], other contributory processes might be relatively fixed and, hence, more difficult to reverse. Ryan., *et al.* [39] discuss some of these questions and rightly conclude that mechanisms by which nutritional environments interact with central homeostatic circuits to influence the threshold for defended adiposity represent critical targets for therapeutic intervention [32].

Chronic Depression can be reversed by Physical Exercise through Brain-derived Neurotrophic Factor and the Effects on Leptin

BDNF is a neurotrophin, whose expression is highest in the hippocampus [40,41], but is also expressed in the hypothalamus [42] and has been the subject of numerous reviews over the years for its pivotal role in plasticity, neuronal survival, the promotion of neural networks and neurogenesis [40,41,43-47]. Hippocampal BDNF mRNA and protein are significantly up-regulated in response to antidepressant medications [6-8,48] and/or running exercise in rodents [6-8,45,49]. Chronic stress activates the sympathetic nervous system and the concomitant increased release of catecholamines and cortisol. The former is stimulating, by binding to its G-protein-coupled receptors, leading to the eventual activation of cAMP-dependent protein kinase A, which then phosphorylates the transcription factor, CREB, which, in turn, participates in the expression of BDNF. Chronic stress-induced release of cortisol, however, is damaging to hippocampal neurons [2,50,51] and promotes catabolism of proteins and fats in order to meet the carbohydrate demands of a stressed animal. This breakdown of adipose tissue would normally decrease leptin production, were it not for increased feeding (and weight gain), in association with the hedonic response, and which can (and does) more than offset the initial breakdown of adipose stores. Increased fat mass means increased leptin production, which then can ultimately lead to increased leptin [44] and insulin resistance. The increased leptin will then decrease PI-3K activity [52], leading to decreased CREB phosphorylation and BDNF expression [44]. Deprived of this critical neurotrophin, hippocampal [53] and hypothalamic [21] neurons atrophy as their dendritic spines and axons are pruned, and neurons atrophy, giving rise to hyperphagia [42]. Such changes have been putatively recognized as cellular hallmarks of depression [51,54-56], which is often accompanied by satisfying the hedonic aspects of eating and subsequent weight gain [56] and increased leptin production [9]. Specifically, excitatory inputs into POMC neurons and inhibitory inputs into AgRP neurons were observed in BDNF [42] and TrkB [57] knock-out mice, leading to drastically decreased arcuate projections into the paraventricular, dorsolateral and lateral hypothalamus, manifesting as increased hyperphagia [42]. Ultimately, this could mean that adipose tissue becomes catecholamine-resistant, due to leptin resistance [58].

Physical exercise, however, although also a form of stress, is intermittent, occurring episodically, rather than chronically, and is often done voluntarily, underscoring some aspect of pleasure associated with it. This stress also releases monoamine neurotransmitters, which can then activate the PKA-CREB-BDNF cascade. Shortly after its release, BDNF can then bind its TrkB receptor [46], and activate intracellular survival signaling cascades, namely, that of PI-3K [59, 60] and MAPK [61]. Through the activation of such cascades, BDNF will save hippocampal neurons from death [62,63] and can even give rise to new neurons in the dentate gyrus [64]. Moreover, like BDNF, leptin also acts through PI-3K [52]/glycogen synthase kinase-3 β , a putative key regulator in controlling hippocampal neuronal proliferation and synaptogenesis [65], mood, and response to mood-stabilizing medications and physical exercise [44]. Consistently, leptin receptor blockade results in overeating, weight gain and reduced running activity levels, whereas leptin overexpression increased wheel-running exercise [66], which may be one way that leptin promotes cell survival [67] by cross-talking with growth factor receptors [27].

At the same time, exercise increases metabolism of fat stores, including subcutaneous white adipose tissue, thereby decreasing leptin production and, therefore, decreasing leptin resistance. Although the mechanisms which regulate leptin expression and circulation levels during exercise are not yet fully elucidated, studies have demonstrated that prolonged endurance exercise, such as marathon running, will definitely decrease serum leptin levels because of less fat mass. Shorter bouts of exercise of less than, say, 40 minutes, will not produce as notable a change unless the exercise is truly exhaustive as with marathon running [68].

Although obesity is correlated with increased feeding and leptin and chronic stress-induced depression, not all people cope in the same way; some individuals lose their appetite and then lose weight, in which case, leptin levels will also decrease [69,70]. Although there is little evidence indicating what happens to BDNF under these circumstances, regular physical exercise and/or antidepressant medications – anything that increases the levels of circulating monoamines (e.g., norepinephrine, serotonin [3, 48,71,72] – will increase BDNF [73] and *vice versa* [41], which will result in weight loss [74] and increase in leptin sensitivity [69]. This is because serotonin levels have been shown to be inversely correlated with feeding [69]. Less feeding means smaller fat stores, which mean less leptin expressed, less leptin resistance, increased PI-3K cascade activation [13] and increased resultant BDNF (Figure 1).

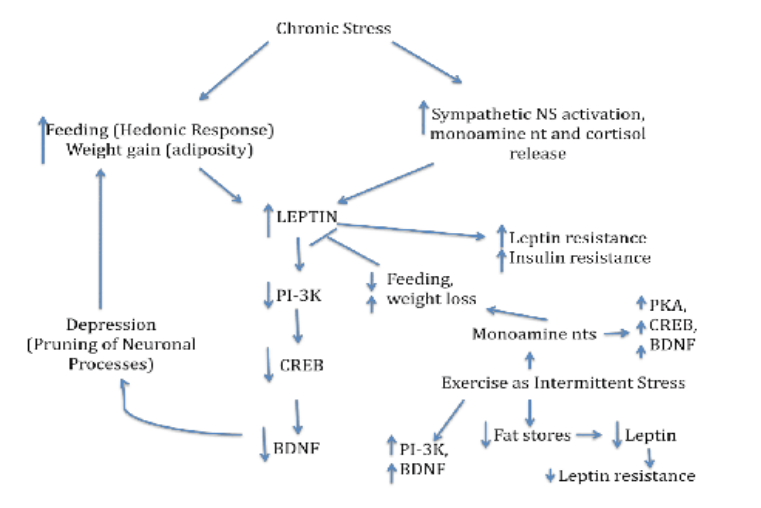

Figure 1: *Leptin plays a central role in regulating response to stress and weight gain and energy expenditure. Leptin must remain below critical levels: too much results in leptin resistance; but at lower concentrations, leptin is pro-survival and would complement the neuro-protecteive effects of BDNF. Pathways and effects are described in the text. Abbreviations are: nt(s),NS, nervous system; neurotransmitters; PI-3K, phosphatidylinositol- 3' kinase; PKA, protein kinase A; CREB, cAMP response element binding protein; BDNF, brain-derived neurotrophic factor; →, arrow indicates cause-and-effect, or at least correlation; ⊥, inhibition; ↑, increase; ↓, decrease.*

Because the hypothalamus sends afferents into the hippocampus, leptin influences hippocampal-dependent functions [13], such as cognition, memory and pathologies, such as depression and even dementia [65]. Because the hippocampus expresses leptin receptors, low leptin levels promote cognition and memory, while too much leptin results in its resistance and is consistent with impaired hippocampal synaptic plasticity and cognitive function and depression in those with obesity [13,75].

Conclusions

Since its discovery in 1994, and despite extensive investigations, there is still much to learn about the leptin axis and its interactions both centrally and peripherally [76]. Although the proposed roles of leptin in satiety and energy expenditure were originally thought to be centrally focused in the arcuate nucleus of the hypothalamus, it is now clear that there is great overlap among hypothalamic systems and other neural systems, particularly the limbic hippocampus, that respond to nutrient levels to modulate peripheral metabolism. Leptin has, therefore, effects on a myriad of other tissues via interactions with BDNF, which has profound influences on neural plasticity and major depressive disorder. Although plasma leptin concentrations are correlated with level of obesity and white adipose tissue stores, many other factors also interact. Clearly, determination of the primary mechanisms of DIO and the role of "leptin cellular resistance" should be a major focus of future research, particularly in light of new studies on the mechanism of defense of adiposity and leptin's role in re-setting that threshold. Success at tackling the complex co-morbidity of obesity, depression, type II diabetes and cardiovascular disease that affect so many people throughout the world will depend on a thorough understanding of the complex interplay among leptin, insulin, BDNF and many other hormones that play a role in these diseases.

Conflicts of Interest

The author declares no conflict of interest.

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Volume 5 Issue 6 April 2017