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The leptin hypothesis of depression: a potential link between mood disorders and obesity?

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Summary

The adipose-derived hormone leptin is well known for its function in the control of energy homeostasis. Recent studies suggest a novel role for this adipokine in the regulation of mood and emotion. Low levels of leptin have been found to be associated with depressive behaviors in rodents and humans. Pharmacological studies indicate that leptin has antidepressant-like efficacy. Both leptin insufficiency and leptin resistance may contribute to alterations of affective status. Identifying the key brain regions that mediate leptin's antidepressant activity and dissecting its intracellular signal transduction pathways may provide new insights into the pathogenesis of depression and facilitate the development of novel therapeutic strategies for the treatment of this illness.

Keywords

antidepressant; stress; adipokine; leptin insufficiency; leptin resistance

Introduction

Depression is the most prevalent and life-threatening mental disorder with an overall lifetime prevalence rate of ~20% of the population worldwide. Current treatment of depression is dominated by antidepressants that exert their therapeutic effects via promoting monoaminergic neurotransmission [1,2]. However, the monoamine-based antidepressants do not fulfill our expectations in terms of efficacy, onset of action and tolerability. A substantial proportion of depressed patients show no response to current available antidepressants, and only less than half of drug-responsive patients achieve full remission. In addition, the slow onset of therapeutic action and side-effects press the need for new antidepressants with novel mechanisms of action. Recent research suggests that leptin, secreted by adipocytes, may be a novel antidepressant. In this review, recent findings on the potential role of leptin in depression and possible mechanisms by which leptin functions as an antidepressant will be discussed.

Leptin and its receptors

Leptin is a peptide hormone, encoded by the obese (*ob*) gene. Once secreted from adipocytes, leptin circulates in the blood as a 16-kDa protein and enters the brain by a saturable transport

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mechanism. Leptin was initially identified as an anti-obesity hormone, acting as a negative feedback adiposity signal to control energy homeostasis by binding to its receptors in the hypothalamus [3]. The leptin receptor is a single membrane-spanning protein that belongs to the class I cytokine receptor superfamily. Alternative splicing of the leptin receptor (*db*) gene generates six isoforms, termed LepRa-f, which differ in the length of their intracellular domains but share a common extracellular leptin binding domain [4]. The long form of LepR, LepRb, is crucial for leptin's actions because of its ability to activate intracellular signal transduction pathways. Accumulating evidence has expanded the function of leptin from the control of energy balance to the regulation of other physiological processes such as reproduction and cognition [5,6]. Supporting this notion, the leptin receptor is widely distributed in discrete brain regions. Particularly, LepRb is highly expressed in brain areas implicated in the control of mood and emotion such as the hippocampus, cortex and amygdala.

Leptin and depression

Animal studies

Chronic stress acts as a predisposing and participating factor in the onset of depression in humans. Rats or mice exposed to chronic unpredictable stress or chronic social defeat stress develop behavioral deficits and endocrine abnormalities, mimicking the symptoms of human depression. While acute stress had no effect on levels of leptin, rats exposed to chronic unpredictable stress or chronic social defeat stress showed decreased basal levels of leptin in plasma [7]. This decrease in chronically stressed animals was independent of body weight alterations but correlated with behavioral changes. Interestingly, prior experience of chronic stress appears to sensitize the response of leptin secretion to acute stress. Rats subjected to two weeks of chronic unpredictable stress displayed a rapid fall in plasma leptin levels in response to acute restraint stress. This response of leptin is opposing to the sensitized surge of corticosterone in the same animals, which has been considered as a pathophysiological feature of hyperactive HPA axis in human depression [8]. However, the stress-induced fall in leptin concentrations is unlikely to be mediated by corticosterone, as glucocorticoids have been shown to stimulate, rather than to inhibit, leptin production and release [9–11].

Based upon the finding of low circulating leptin levels in animal models of depression, it was hypothesized that leptin insufficiency may underlie depression-like behavioral deficits. One of the depression-like behaviors in chronically stressed animals is reduction of sucrose preference, which is regarded as an analog of anhedonia, a key symptom of depression in human [12,13]. Systemic administration of leptin can reverse the chronic stress-induced decrease in sucrose preference [7]. Sucrose preference in non-stressed rats, however, was not affected by leptin treatment, suggesting that leptin does not have hedonic-like effects in the absence of a hedonic deficit. Another symptom of clinical depression that is often modeled in rodents is behavioral despair, which can be assessed with tests such as the forced swim test (FST) and tail suspension test (TST). These two tests have high predictive validity for antidepressant activity and have been widely used for screening antidepressant drugs [14,15]. In both tests, the animals are subjected to an inescapable stressful situation and develop a characteristic immobile posture, which is believed to reflect behavioral despair. Immobility can be reduced by acute or chronic administration of various existing antidepressant drugs [14,15]. Systemic leptin administration was found to produce a dose-dependent reduction of the duration of immobility in both tests [7,16]. Locomotor activity was not affected by leptin treatment as compared with controls, suggesting that the immobility-antagonizing effects of leptin in the FST and TST are not due to nonspecific stimulation of locomotion [7]. Interestingly, a recent study showed that streptozotocin-induced diabetic mice had low circulating leptin levels and exhibited depression-like behavior in the TST, and treatment with leptin reversed the depression-like behavior [17]. These data together support the view that leptin has antidepressant-like efficacy. The sites of actions for leptin on depressive behaviors are thought

to be located in the limbic structures, where LepRb is highly expressed. Consistent with this hypothesis, analyses of leptin-induced c-fos mRNA expression revealed a link between behavioral actions of leptin with neuronal activity of specific limbic brain areas [7]. In particular, a robust increase in c-fos expression in the hippocampus was observed in rats that received systemic injection with leptin and exhibited antidepressive behavior in the FST. This result suggests that the hippocampus might be a target site for circulating leptin to exert its mood-promoting actions. Indeed, direct activation of the leptin receptor in the hippocampus by microinjection of leptin into this region elicited antidepressant-like behavioral effects [7].

Taken together, while available data have provided evidence supporting the view that leptin may act as an antidepressant, evidence for a causal relationship between depression and leptin insufficiency remains weak. Genetic deletion of the leptin receptor or pharmacological inhibition of leptin signaling in specific brain regions may help to determine whether a reduction in leptin signaling can directly lead to depressive behaviors.

Human studies

Available information about the role of leptin signaling in human depression is limited and controversial. One study reported that leptin levels did not differ between depressed patients and healthy controls [18]. Two studies found that plasma leptin levels were higher in depressed patients with a bias in female patients [19,20]. In contrast, other reports found that low leptin levels were associated with depression. With larger sample sizes, two research groups demonstrated that plasma leptin levels were decreased in patients with major depression independent of body mass status [21,22]. Also, lower levels of leptin in cerebrospinal fluid were found in suicide attempters with depression than those without depression [23,24]. Moreover, decreased levels of leptin in plasma were observed in patients with bipolar disorder [25] and obsessive-compulsive disorder with comorbid major depression [26]. Taken together, these clinical observations suggest a link between reduced leptin levels and major depression. One possible explanation for the seemingly contradictory data may be that leptin levels are influenced by certain factors such as age, sex, sample sizes, body mass status and comorbidity with other disorders. Another interpretation is that leptin insufficiency may only occur in a subpopulation of depressed patients. While leptin's antidepressant efficacy in humans awaits clinical investigations, it is speculated that depressed patients with low leptin levels might have a better chance to respond to leptin treatment.

An interesting question that remains to be addressed is the association between obesity and depression. In contrast to the above hypothesis that leptin insufficiency contributes to depression, epidemiologic and clinical studies suggest a link between obesity, which is commonly characterized by high, not low, levels of leptin, and depression [27–30]. It has been reported that obese people are approximately 20% more likely to have depressive disorders than non-obese subjects [29]. The high leptin levels associated with obesity are thought to be caused by leptin resistance, much as type 2 diabetic patients are resistant to insulin. Indeed, leptin treatment is ineffective on inhibiting food intake and increasing energy expenditure in obese people, whereas administration of leptin in people with normal weight leads to reduction in adipose tissue and weight loss [31]. It is well documented that leptin resistance is caused by defects in the leptin signaling pathway possibly at several levels, including impaired transport of leptin across the blood-brain-barrier, reduced function of the leptin receptor and defects in leptin signal transduction [32]. In light of leptin's ability to inhibit depressive behaviors in animal models, it is possible that leptin resistance may contribute to the higher rate for depression in obese people. This could also help to interpret some of the conflicting results obtained in relation to circulating leptin levels in depressed patients. A key question is whether leptin resistance serves as a common biological factor for the comorbidity of obesity and depression. For obese people with depression, it is anticipated that therapeutic interventions

that target leptin downstream pathways and bypass leptin resistance, rather than leptin itself, may be more beneficial.

Interaction of leptin with monoamines

Reduced monoaminergic transmission has been implicated in the pathogenesis of depressive disorders, and current antidepressants exert therapeutic actions by promoting monoaminergic neurotransmission via interaction with receptors, transporters and/or metabolism. One important question that needs to be addressed is whether leptin modulates monoamine neurotransmission. A high percentage of 5-HT neurons in the raphe nuclei and dopamine neurons in the ventral tegmental area (VTA) express the leptin receptor [33–35], which supports the possibility of interactions. However, evidence supporting a functional interaction between leptin and monoamines remains ambiguous. Chronic intracerebroventricular infusion of leptin was found to decrease the number of binding sites for paroxetine, a selective 5-HT transporter inhibitor, in the frontal cortex but not in the raphe nucleus of rats [36]. In contrast, reduced mRNA expression of 5-HT transporter was observed in the raphe nucleus of leptin-deficient *ob/ob* mice [37]. In addition, 5-HT content and metabolism was increased in the forebrain by leptin [38,39]. These results draw attention to the possible role of leptin in the regulation of components of the 5-HT system; however, it is unknown whether leptin could modulate synaptic availability of 5-HT in the brain areas involved in depressive behaviors. On the other hand, leptin activates the Signal Transducer and Activator of Transcription 3 (STAT3), a key downstream mediator of leptin receptor signaling, in dopamine neurons in the VTA [40,41], suggesting possible interaction between leptin signaling and the mesolimbic dopaminergic pathway. One study demonstrated that ob/ob mice lacking leptin had diminished dopamine release and reduced concentrations of tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis, in the nucleus accumbens [40]. Importantly, these effects can be reversed by leptin treatment [40]. These findings are suggestive that leptin enhances the mesolimbic dopamine activity. However, another study reported that leptin treatment inhibited the firing of dopamine neurons in the VTA [41]. Thus, additional studies are necessary to clarify the exact role of leptin on dopamine neurotransmission.

Impact of leptin on HPA

Hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis is a common feature of some patients with major depression. The HPA axis abnormality is characterized by the overproduction of corticotrophin-releasing hormone (CRH), elevated cortisol levels, exaggerated cortisol response to adrenocorticotropic hormone (ACTH), dexamethasone-mediated negative feedback resistance, and enlargement of the pituitary and adrenal glands [8]. The malfunction of the HPA axis can be corrected by antidepressant drugs when clinical improvement occurs [8]. Accumulating evidence suggests that leptin modulates HPA function. Studies on mouse models with mutations in the leptin gene (*ob/ob*) or the leptin receptor gene (*db/db*) have provided valuable information on the relationship between leptin and the HPA axis. Hypercorticosteronemia was observed in both *ob/ob* and *db/db* mice [42–44]. Chronic leptin administration can reverse the hypercorticosteronemia in *ob/ob* mice prior to significant weight loss [44], suggesting a role of leptin in HPA function independent of its effects on energy homeostasis. An interaction between leptin and the HPA axis is further supported by the inverse relation of circadian rhythmicity between plasma leptin and glucocorticoids [45]. Consistent with these data, leptin treatment diminishes the secretion of ACTH and corticosterone in response to stressful events. For example, leptin treatment blocks elevation of ACTH and corticosterone levels following restraint [46] and ether stress [47]. Furthermore, leptin decreases mRNA expression of CRH in the PVN [47–49] and CRH release from the hypothalamus [50]. These findings suggest that the inhibitory effect of leptin on ACTH and corticosterone is probably mediated by hypothalamic CRH. Moreover, studies have suggested

that leptin can enhance the negative feedback effect of glucocorticoids on CRH. In adult *ob/ob* mice, leptin treatment prevents the adrenalectomy-induced upregulation, and potentiates the corticosterone-induced downregulation of CRH expression in the paraventricular nucleus of hypothalamus (PVN) and amygdala [48]. In addition, administration of leptin in developing rats increases the expression of the glucocorticoid receptor in the PVN and hippocampus [51], presumably leading to increased sensitivity of the glucocorticoid receptor. On the other hand, the leptin receptor is present in the adrenal gland, and leptin treatment can directly inhibit basal and ACTH-stimulated cortisol release from adrenal gland in both humans and rodents [52,53]. Collectively, these data support the notion that leptin is capable of regulating the HPA axis at multiple levels.

Neurotrophic actions of leptin

Loss of neurotrophic support has been hypothesized to underlie depressive disorders. Patients with depression show atrophy of certain limbic structures, including the hippocampus and prefrontal cortex [54]. Conversely, antidepressant treatment can reverse neuronal atrophy and cell loss and stimulate neurogenesis [54]. Several lines of evidence suggest that leptin has neurotrophic effects. First, leptin deficiency in *ob/ob* mice leads to reduced brain weight and cortical volume and decreased expression of total neuronal and glial proteins [55,56]. These changes are likely to be caused by defects in leptin receptor signaling as leptin receptor-deficiency in *db/db* mice had similar effects on brain weight and protein contents [57]. The neurodegenerative changes in *ob/ob* mice can be rescued by leptin replacement [55,56]. Secondly, leptin treatment increases expression of growth-associated proteins and synaptic proteins in the hippocampus in neonate rats [51]. In a clinical study, leptin replacement in leptin-deficient patients was shown to increase the gray matter concentration in the anterior cingulate gyrus [58]. Finally, leptin has been shown to be an essential factor for the formation of specific neuronal projection pathways within the hypothalamus [59]. A recent *in vitro* study demonstrated that leptin increases the motility and density of dendritic filopodia and the number of hippocampal synapses [60]. Key issues that remain to be addressed, however, are whether leptin is required for the formation of the limbic circuit and whether leptin's neurotrophic effects mediate its antidepressant effects.

Conclusions and perspectives

Since its discovery more than a decade ago, leptin has been well-recognized as an adiposity negative feedback signal and a critical mediator of energy homeostasis. This review discusses an emerging, novel function of leptin: its role in depression. The data favor the hypothesis that leptin insufficiency and/or leptin resistance may contribute to the vulnerability to depression and that leptin and leptin receptor signaling may serve as potential targets for antidepressant drugs. The leptin hypothesis is complementary to, and may overlap with, other existing hypotheses of depression, e.g. the monoamine hypothesis, the HPA hypothesis and the neurotrophin hypothesis of depression. Depression is a complex and heterogenous disorder and these diverse theories may explain the pathogenesis of different subtypes of depression. The key to the leptin hypothesis of depression will lie in leptin's function not merely its circulating levels. Thus, it will be important in future studies to clarify the role of leptin insufficiency versus leptin resistance in depression as well as leptin's antidepressant efficacy in depressed patients. Equally important will be to characterize the neural circuits that respond to leptin and to elucidate the intracellular signal transduction pathways that mediate leptin's antidepressant activity and the crosstalk between leptin and other signaling processes involved in metabolic and mood disorders.

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