

Leptin and psychiatry

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ABSTRACT

Leptin, a protein, is secreted mainly by adipocytes. It is important in the regulation of food intake and energy balance. It also has metabolic and neuroendocrine functions. Numerous studies have exploited the relationship between leptin levels and various psychiatric conditions and treatments. To date, no conclusive relationship has been established although there may be a greater role for leptin than is currently understood.

Keywords: Leptin, Depression, Psychiatry, Psychotropic, Anorexia

Introduction

Leptin, a protein transcribed from the obese (ob) gene and secreted mainly by adipocytes, was only discovered recently.¹ This ob gene product was called 'leptin' (derived from the Greek 'leptos' meaning 'lean') indicating the function it was thought to have. It has since become evident that leptin is important in the regulation of food intake and energy balance, and functions as a metabolic and neuro-endocrine hormone. Leptin has been shown to be involved in:

- glucose metabolism,
- interactions with hypothalamic-pituitary-adrenal, thyroid and growth hormone axes,
- the haemopoietic and immune systems,
- normal sexual maturation and reproduction.

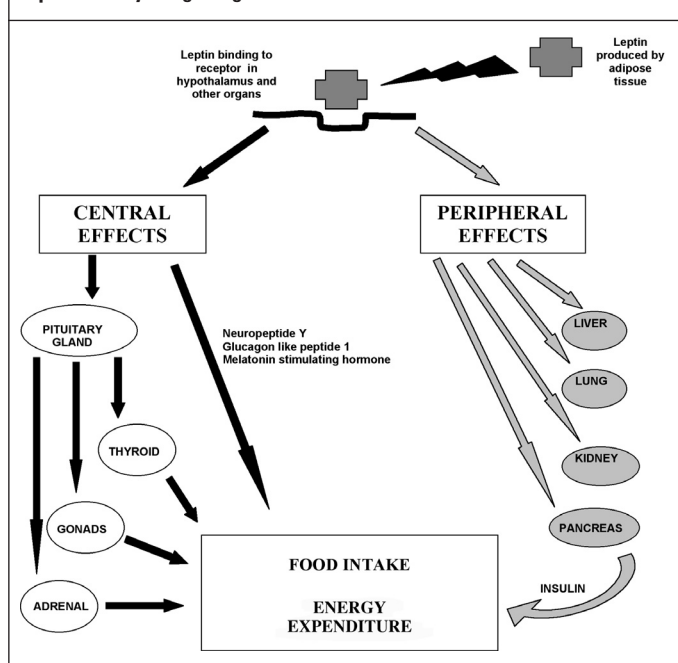
Leptin and body weight regulation

The first function described after the discovery of leptin was its role in body weight regulation, especially that of body fat stores. Leptin is synthesized mainly by fat cells, and its plasma levels in humans are strongly correlated with body mass index and fat mass.² A clear gender difference in leptin levels exists.¹ Leptin levels were found to be two to three times higher in women than in men for the same body mass index. These differences reflect the difference in body composition between men and women, with women in general having a higher percentage of body fat and a higher ratio of subcutaneous to visceral fat.

Leptin is secreted into the bloodstream and acts both centrally and peripherally, informing the brain about the amount of fat mass in the body (Fig.1).^{3,4}

The leptin receptor in the brain is mainly present in the hypothalamus and choroid plexus. Here food intake is directly

Fig. 1. A schematic representation of the central and peripheral actions of leptin on body weight regulation.

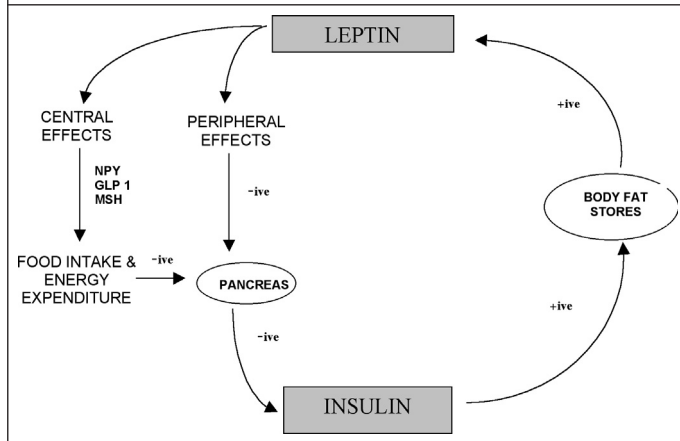


regulated through modulation of several neurotransmitter pathways such as neuropeptide Y (NPY), glucagon like peptide I (GLP I) and melanocyte stimulating hormone (MSH).⁵ Leptin modulates pituitary secretion of thyroid stimulating hormone (TSH), adreno- corticotrophic hormone (ACTH) and gonadotrophin releasing hormone (GnRH). These hormones influence the secretion of thyroid hormone, cortisol and sex hormones, all of which all have effects on the energy balance. The receptor is also widely distributed throughout peripheral tissues such as lung, liver, kidneys, pancreas and gonadal tissue. Leptin binds to these receptors, interacting with the production and secretion of insulin and sex steroids, which in turn influence leptin secretion by fat cells. Thus is the creation of a feedback system whereby high leptin levels signal that energy reserves

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Fig. 2. A schematic representation of the relationship between leptin and insulin.



are sufficient and low levels inform the brain about limited energy supplies.⁵

Leptin and the endocrine system

Insulin stimulates the mRNA expression and secretion of leptin.⁶ Leptin in turn probably acts at different intracellular levels to inhibit the synthesis as well as the secretion and action of insulin (Fig 2).

In humans insulin and leptin levels are associated, but whether insulin acutely regulates leptin levels remains controversial. A change in leptin levels is observed in response to insulin, but only with a certain delay.

Glucocorticoids have a potent central stimulatory effect on leptin expression by stimulating anabolic effector pathways like neuropeptide Y (NPY) and inhibiting catabolic pathways like cortisol releasing hormone (CRH) and melanocyte stimulating hormone (MSH) (Fig 3). Leptin on the other hand has a direct inhibitory effect on cortisol secretion by the adrenal gland.⁷ With weight loss, the low level of leptin^{8,9} is perceived by the body as harmful leading to adaptive changes mainly mediated through inhibition of the HPA axis.¹⁰

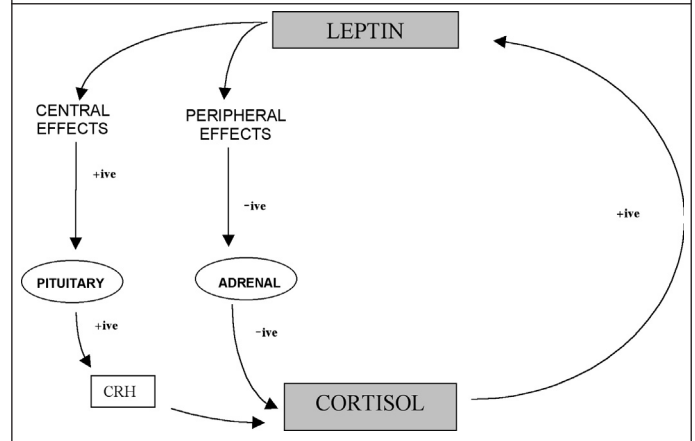
In summary, leptin can no longer be called a mere adipocyte-secreted hormone with a weight regulatory function, but is increasingly emerging as a hormone with an important neuroendocrine and metabolic role.

Leptin and Depression

Depressive episodes are frequently characterized by loss of appetite, reduced food intake and weight loss. Weight gain during antidepressant treatment can be either a sign of improvement in patients who have weight loss, a symptom of depression or a residual symptom in patients who overeat when depressed. Significant weight gain during the acute phase of treatment or weight gain that continues despite achieving full remission of depressive symptoms is likely to be a side effect of antidepressant treatment. As a result of these clinical observations in depressed patients, an alteration in leptin levels would be expected. There is, however, no published evidence confirming a role for leptin in appetite and body weight changes seen in depressed patients.¹¹

With the onset of a depressive illness there is decreased food intake and weight loss resulting in an initial reduction in

Fig. 3. A schematic representation of the relationship between leptin and cortisol.



leptin levels.¹² However, hypercortisolism, which is a feature of depression, has a stimulatory effect on leptin⁷, thus theoretically counteracting this reduction. The normalization of leptin levels in turn assists to restore a normal hypothalamo-pituitary adrenal axis via inhibiting cortisol secretion by the adrenal gland. With treatment however, the patient restores weight and leptin level further increases, which might promote CRH release and contribute to HPA system hyperactivity and hypercortisolism. It is in this context that leptin may play an indirect role in depression.

Leptin and Psychosis

There is little information related to the amount of circulating leptin in psychotic disorders such as schizophrenia although appetite, food intake and weight are frequently altered in these disorders. The estimated percentage of persons with schizophrenia who are overweight is higher than that of the general population and the increased mortality rate is largely due to obesity-related diseases.

The few studies investigating weight and body mass index (BMI) have yielded variable results. Kraus et al showed that schizophrenia is associated with decreased systemic leptin concentrations that cannot be explained by medication or an altered BMI.¹³ They conclude that leptin might play an important pathophysiological role in these psychiatric disorders and that it deserves further scientific attention.

Leptin and Anorexia Nervosa

Anorexia nervosa is an eating disorder characterized by decreased caloric intake, increased physical activity, low weight, and resistance to an increase in body weight. The pathogenesis of this potentially fatal illness remains poorly understood. Multiple abnormalities of the neuroendocrine system, in large part thought to reflect starvation-induced changes, include activation of the hypothalamic-pituitary-adrenal axis and suppression of the thyroid and gonadal axes.¹⁴ Leptin levels appear to be positively correlated with percent body fat in the obese and normal body weight controls, and negatively correlated with weight loss due to food restriction.

Reports of studies of leptin in patients with anorexia nervosa are limited. In starved female anorexics at very low body weights, leptin levels are reduced significantly.^{15,16} Leptin in-

creases with weight gain, suggesting a normal physiological response of leptin to weight gain in anorexics. However, leptin levels tended to be higher in weight recovering anorexics than in controls of comparable body weight, although in the normal range.

Leptin levels in patients affected by severe eating disorders namely anorexia nervosa, bulimia nervosa and non-specific eating disorders, are not related to the specific pathology but are correlated with the individual body mass index. The analysis of leptin values may be a useful index of assessing the adipose tissue stores in the clinical setting, but appear to be of little help for the diagnosis or prognosis of severe eating disorders.¹⁷

Leptin and Impulsive, Aggressive Behaviour

The association between low or lowered cholesterol and impulsivity, aggressive behaviours and suicide remains controversial. There are a growing number of studies examining the relationship between suicide and lipid metabolism suggesting that cholesterol-lowering procedures may increase the risk of death due to suicide or impulsive-aggressive behaviour. Atmaca et al showed a positive correlation between cholesterol and leptin levels in suicide attempters suggesting an association with decreased serum cholesterol and leptin levels.¹⁸ In borderline personality disorder, characterised by impulsivity, aggressive behaviours and suicide attempts, low leptin and cholesterol levels are associated with all dimensions of this disorder.¹⁹ Leptin is strongly associated with lipid metabolism and could influence these behaviours.

Leptin and Psychotropic Medication

Antidepressants

Weight gain is a relatively common problem during both acute and long-term treatment with antidepressants and is an important contributing factor to non-compliance.

Tricyclic antidepressants may be more likely to cause weight gain than the selective serotonin reuptake inhibitors or the newer antidepressants without alterations in leptin levels.²⁰ In a study of 36 patients, Hinze Selch et al concluded that weight gain induced by antidepressant agents might occur without increased circulating levels of leptin.²¹ Further to this, Kraus et al showed that the significant weight gain of 2.4 kg in 4 weeks associated with mirtazepine treatment was accompanied by a very small increase in leptin levels.²²

The effect of fluoxetine on food intake, body weight, and mood of obese individuals is variable.²³ Fluoxetine can reduce food intake in non-depressed obese individuals without specifically affecting carbohydrate intake. Weight is lost during the first few weeks of daily fluoxetine administration, and subsequently regained even though food intake remains reduced. Fluoxetine selectively inhibits serotonin reuptake, leading to enhanced serotonergic function and a decrease in food intake beginning with the first dose.²⁴ After multiple doses there is either a decrease or a gain in body weight.

Dryden et al suggested that serotonin might influence food intake and energy balance by inhibiting the arcuate-paraventricular projection.²⁵ Two neurotransmitters (serotonin and neuropeptide Y, which respectively inhibit and stimulate food intake) may act together to regulate feeding and energy homeostasis.

In summary, studies to date have shown that antidepressants

lead to either a decrease in food intake and body weight or in weight gain, however there is no conclusive evidence to suggest that it correlates with altered leptin secretion.

Antipsychotics

The atypical antipsychotics have been shown to have superior efficacy compared with typical antipsychotics such as haloperidol, particularly in the treatment of negative symptoms of schizophrenia. Furthermore, they induce fewer extrapyramidal effects. However, following clinical use, marked weight gain has been frequently observed with some of the atypical antipsychotic drugs. In a comparative review, the frequency as well as the amount of weight gain was high in patients treated with olanzapine (average bodyweight gain 2.3 kg/month), clozapine (1.7 kg/month), quetiapine (1.8 kg/month), and possibly also zotepine (2.3 kg/month). Moderate changes in weight were observed in the treatment with risperidone (average weight gain 1.0 kg/month). Ziprasidone seems to induce only slight weight changes (0.8 kg/month).²⁶

The underlying pathomechanism still remains largely unclear. Some drugs induce weight gain associated with an increase in leptin levels whilst others do not. Short-term antipsychotic treatment with clozapine and olanzapine results in an increase in leptin levels.^{27,28} The most probable reasons were overeating and weight gain inducing increased leptin secretion. Pronounced early increase in circulating leptin may predict long-term weight gain in the course of clozapine administration.²⁹

In summary it appears that the influence of olanzapine and clozapine on leptin levels might be associated with their weight-gain-inducing ability, while other mechanisms may be involved in the weight gain caused by other antipsychotics.

Mood Stabilizers

Weight gain is an important adverse effect of valproate therapy. As in other types of obesity, elevation of serum leptin concentrations is related to the increase in body mass index.³⁰ Both obese and lean patients taking valproate for epilepsy have hyperinsulinemia, suggesting development of insulin resistance. This may be one of the factors leading to weight gain during valproate treatment. However, there is no evidence to suggest an independent role for leptin in the pathogenesis of valproate-related obesity.³¹

Topiramate reduced food intake acutely and increased metabolic rate in rats.^{32,33} There are also significant reductions in leptin, insulin, and cortisol but the mechanism through which the change in energy balance is achieved is unclear.

Weight gain is a frequent adverse effect associated with lithium use. There is a significant positive correlation between the changes in leptin levels and lithium-induced weight gain.³⁴

Conclusion

Although many questions concerning the pathogenesis of bodyweight gain remain unresolved, this adverse effect has to be taken into consideration when prescribing psychotropic medication, particularly in view its affect on compliance during long term treatment and the long term effects of obesity on mortality and morbidity. Our current and preliminary understanding of the role of leptin in metabolism and neuroendocrine regulation, is mainly derived from animal studies. Very few studies of the association between leptin levels and vari-

ous disease states in humans exist. The alterations documented in serum leptin concentrations cannot only be explained by medication or an altered body mass index. Leptin might play an important pathophysiological role in psychiatric disorders that deserves further scientific attention. As only future protocols can explore, leptin may have far greater roles than has been realized.

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Leptin and the neuroendocrinology of the brain

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The discovery by Friedman and colleagues in 1994 of leptin¹ led to a major shift in the current opinion on the metabolic role of adipose tissue. Leptin's functions as an indicator of body fat mass, appetite suppressant and stimulator of metabolic rate demonstrated that adipose tissue was an endocrine organ with both peripheral and central effects. Further research has confirmed the multifunctional nature of the adipocyte; it is the source of pro- and anti-inflammatory cytokines, growth factors, insulin sensitisers, hypertensive agents, coagulation factors and anti-fibrinolytic peptides.² The review by Moosa and Jeenah suggests that the adipocyte-derived hormone may possibly contribute to the pathology of psychiatric disorders.

Many studies have shown that leptin suppresses food intake by reducing hypothalamic levels of orexigenic agents which include neuropeptide Y (NPY), agouti-related protein (AGRP), orexins and melanin-concentrating hormone (MCH). Leptin also increases hypothalamic levels of anorexigenic peptides such as alpha-melanocyte stimulating hormone (MSH), cocaine and amphetamine-related transcript (CART) and corticotropin-releasing hormone (CRH).³ The up-regulation of CRH by leptin is intriguing as this factor may play a role in the hypothalamic-pituitary-adrenocortical (HPA) axis hyperactivity that is characteristic of depression.⁴ There is a complex interaction between the HPA axis and leptin; leptin increases CRH expression³, inhibits adrenal cortisol secretion⁵ and leptin secretion is in turn stimulated by glucocorticoids.⁶ As discussed by Moosa and Jeenah, the elevated cortisol levels associated with depression could therefore lead to increased leptin levels. However, the measurement of serum leptin levels in depressed subjects has provided inconsistent results with studies showing reduced⁷, elevated⁸ or similar levels⁹ to healthy, BMI-matched control subjects. Furthermore, reduced leptin levels have been observed in suicide attempters¹⁰ and the ob/ob mouse, which is severely hypoleptinaemic due to a mutation in the leptin gene, displays behavioural depression.¹¹ In addition, intracerebroventricular infusion of leptin has been shown to decrease serotonin transporter binding sites in the frontal cortex of rodents.¹² This direct effect of leptin may be a possible mechanism for induction of depression: the serotonin system is a prime target for drug therapy for depression, especially via the use of serotonin reuptake inhibitors.¹³ However, further studies on the

true leptin status in different depressive disorders must be performed before the role of leptin in the aetiology of depression can be fully understood.

Hypercortisolaemia is often observed in depression and is also associated with the metabolic syndrome.¹⁴ This syndrome is a clustering of different metabolic disorders e.g. type 2 diabetes, hypertension, cardiovascular disease, and insulin resistance in individuals who are viscerally obese. It has been shown that subjects with the metabolic syndrome are at increased risk of developing depression and vice versa.¹⁵ It has been hypothesised that stress-induced hypercortisolaemia may lead to visceral obesity and hence to increased insulin resistance and to the other.^{16,17} Manifestations of the metabolic syndrome, as well as depression. Leptin levels are also elevated in patients with this syndrome¹⁶ and raised leptin levels, independent of BMI have been shown to be predictive of future development of type 2 diabetes and cardiovascular disease.¹⁸ However, the role of leptin in the aetiology of depression in viscerally obese subjects is not known.

The leptin status of patients suffering from eating disorders such as anorexia nervosa, is also discussed by Moosa and Jeenah. This is again a poorly researched area with the few studies that have been conducted demonstrating lower leptin levels in anorexics than BMI-matched controls.^{19,20} Studies have also shown that anorexics display elevated physical activity when compared to non-anorexic subjects suffering from starvation-induced weight loss. The anorexic state in humans shares similarities with the starvation state in rodents and other species where starvation leads to increased physical activity.^{21,22} This phenomenon, termed activity-based anorexia, is reversed if animals are given exogenous leptin and activity levels in anorexic humans also fall after weight gain-induced increases in leptin levels.²¹ These data suggest that the lowered leptin levels observed in anorexic humans may be pathological and that some of the behavioural aspects of this disorder can be reversed after weight gain. Whether exogenous administration of leptin would also reverse these symptoms has not been investigated.

Leptin increases expression of the propeptide proopiomelanocortin (POMC) within neurons of the hypothalamic arcuate nucleus. POMC is cleaved by a number of proteolytic enzymes (endopeptidases) to yield nine different peptide hormones including beta-endorphin, alpha-MSH and ACTH. Alpha-MSH and beta-endorphin are both anorexigenic³ but the latter may also play a role in a number of different psychiatric disorders including depression and schizophrenia. Thus, a study examining the number of arcuate neurones expressing beta-endorphin in post mortem brain sections revealed that in

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schizophrenics and depressives these neurones were fewer in number than those in controls.²³ In another study serum levels of beta-endorphin were lower in depressed than healthy subjects and levels were elevated after treatment with fluvoxamine.²⁴ It is therefore possible that beta-endorphin may be involved in the aetiology of depression and schizophrenia but the interrelationship between leptin and the opiate in these disorders is not known.

The paper by Moosa and Jeenah discusses altered serum leptin levels observed in a number of different psychiatric disorders. These diseases also include bipolar disorder²⁵ and narcolepsy.²⁶ In both these syndromes leptin levels were lower than in healthy controls. Whether leptin plays any role in the pathophysiology of these disorders requires further investigation.

The review by Moosa and Jeenah highlights how little is known about the role of leptin in psychiatric diseases. More and larger studies are required to clarify the role of leptin, if any in these disorders. The presence of leptin receptors in various regions of the brain, including the hypothalamus, cerebral cortex and hippocampus²⁷ suggests that this hormone may have a number of central functions that have not yet been elucidated. The involvement of leptin in brain function is a fascinating area of neuroendocrinology and in future may hopefully yield major insights into the aetiology and pathology of a number of psychiatric disorders.

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