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PAPER

Biology of leptin — its implications and consequences for the treatment of obesity

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The fundamental biology of leptin and the leptin system is summarised. The hormone is produced in several organs, but primarily white adipose tissue, and is subject to acute regulation, particularly by the sympathetic nervous system. Leptin receptors are widely distributed, both centrally and peripherally, and there are several neuroendocrine targets. Although leptin is a key hormone in the regulation of energy balance, the biological effects of the hormone are extensive. Increasing leptin levels is unlikely to be an effective strategy for the treatment of obesity — except in those limited number of cases where there is a genuine deficiency of the hormone (eg in individuals with mutations of the leptin gene).
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The discovery of the cytokine-like hormone, leptin (also known as OB protein) by Friedman and colleagues in 1994 has heralded a revolution both in understanding the regulation of energy balance and in attitudes to the scientific study of obesity.[1] Leptin provides a molecular basis to the lipostatic theory of the regulation of energy balance which was first enunciated in the 1950s.[2] Its discovery has provided a fresh focus on the importance of obesity as a public health issue and presented a substantial opportunity for biomedical research.

The rapid escalation in the incidence of obesity that has taken place in recent years in many Western countries is, of course, primarily a consequence of environmental factors — it cannot relate to genetics *per se*. In essence, our inherited physiological control mechanisms have been overwhelmed in the face of substantive environmental and cultural changes. Nevertheless, what the discovery of leptin has catalysed is renewed interest in the underlying physiological mechanisms involved in the control of energy balance and body weight. Five years after its discovery, however, it is now recognised that the biology of leptin extends far beyond the initial lipostatic paradigm. This is true in terms of where the hormone is produced, the nature and localisation of its receptors, and most importantly the physiological and metabolic functions with which it is involved.

Leptin is now recognised to be produced in a number of sites additional to white adipose tissue — particularly brown adipose tissue, the placenta, stomach and mammary gland, as well as foetal organs such as the heart and bone/cartilage.[3] There are even suggestions that leptin may be synthesised in the brain and that its expression can be induced in skeletal muscle. In many cases the leptin produced in sites other than adipose tissue is likely to have a local or paracrine effect. Despite the variety of tissues in which leptin is produced, the amount of body fat is the principal determinant of the circulating level of the hormone; in humans it is evident that there is a high correlation between indices of body fat and plasma leptin concentration.[4,5] Acute regulation of the synthesis of leptin occurs, however, and this is superimposed on the endogenous production associated with the amount of body fat. A number of factors which influence leptin production have been identified and these include fasting, insulin, glucocorticoids, testosterone and thiazolidinediones.[3,6] Some of the most potent effects on *ob* gene expression and leptin production are obtained with catecholamines and sympathomimetics operating through β3-adrenoceptors. This has led to the proposition that the sympathetic nervous system provides a negative feedback loop to adipose tissue regulating transcription of the *ob* gene; indeed there may be a tonic inhibition of leptin production by the sympathetic system.[6]

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The leptin receptor gene is expressed in a wide range of tissues, with the receptor occurring in several splice variants. The long form of the receptor, Ob-Rb, has an intracellular signalling domain which interacts with the JAK-STAT signalling system. The Ob-Rb receptor variant is strongly expressed in regions of the hypothalamus and leptin interacts with several neuroendocrine systems, including neuropeptide Y, CRH (corticotropin releasing hormone), CART (cocaine and amphetamine regulated transcript) and POMC/melanocortins.[3]

Regulation of the production of leptin in humans is generally similar to that described in rodents.[7] With the discovery of leptin, obesity was initially thought likely to result from hormone deficiency. However, with the advent of immunoassays for the hormone it immediately became evident that circulating leptin levels are generally increased in the obese rather than decreased. This has led to the view that leptin 'resistance' is a critical factor in the aetiology of obesity, although in practice there is little evidence for such a proposition. It is, of course, possible that the high circulating concentration of the hormone in obesity simply reflects the large amounts of the tissue from which it is derived.

The leptin system has been widely considered as a key potential target for the treatment of obesity through the administration of the hormone itself, modified leptins, leptin analogues or small molecular weight mimetics. Is the leptin system in practice a realistic target for the pharmacological treatment of obesity? There are several strands of argument which suggest that it is not. First, if the physiological range of leptin concentrations is considerably higher than the critical level required for the effects of the hormone on energy balance to be realised, as studies on lipodystrophic mice would suggest,[8] then increasing the effective level of leptin would be expected to elicit little response. Secondly, given the wide range of functions in which leptin appears to be involved there is a distinct probability that many processes will be altered by leptin therapy, ie that there will be unwanted side effects. Thirdly — and directly — the results reported to date have indicated that the effects on the obese of treatment with leptin are at best very limited.[9] There is, however, one clear exception to this last point and that is the case of a child with a mutation in the leptin gene where substantial weight loss has been achieved over many months with administration of the recombinant hormone.[10] This, and other reported mutations in leptin (or the leptin receptor) in patients with associated obesity, are particularly significant in that they demonstrate that a critical level of the hormone is important for the normal control of body weight in humans as in rodents.[11–13]

The clear conclusion seems to be that leptin therapy is unlikely to be a successful strategy for the general treatment of obesity. It may, nevertheless, prove valuable in those limited number of cases where leptin is not produced or where insufficient amounts of the hormone are synthesised, whether for genetic or other reasons. More appropriate targets for anti-obesity therapy appear to lie downstream of the leptin receptor in the neuroendocrine systems with which the hormone interacts, and this is increasingly the approach being pursued.

In essence, we have much exciting biology to unravel with leptin. However, it seems likely that above a certain critical amount — which is well below the normal physiological level of the hormone — there may be little effect on satiety and other processes which directly impact on energy balance. If this view is correct, then it is evident that increasing the circulating concentration of leptin will have minimal impact on energy balance and body weight. In conclusion, it is important to note that leptin is one of a number of protein factors secreted from white adipose tissue, the tissue now being recognised as a major secretory and endocrine organ playing a key role in metabolic and physiological regulation.

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