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Leptin in obesity

Tells the brain how much fat there is, but in obese people the message may not get through

See p 965

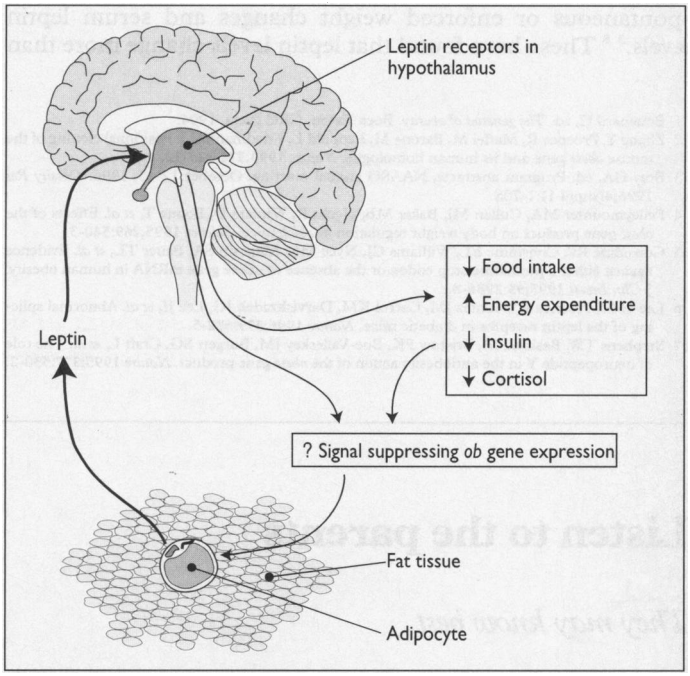
Obesity runs in families, mainly due to genetic factors.[1] Several different mendelian inherited, monogenic forms of obesity exist in rodents, but they are rare in humans.[1] Analysis of the distribution of fatness in families suggests that a few major genes may act on a polygenic and environmental background, but it remains unclear which genes are involved.[1]

The identification and sequencing of the mouse *obese (ob)* gene by Friedman's group in 1994[2] opened important new avenues in obesity research and have already led to overwhelming research activity.[3] In homozygous *ob/ob* mice, the mutation of the *ob* gene results in increased food intake, reduced energy expenditure, elevated insulin and cortisol levels, and subsequently, in massive obesity and non-insulin dependent diabetes mellitus.[2] The *ob* gene encodes a protein, leptin, which is produced only in fat cells and secreted into the blood. There are two different strains of *ob/ob* mice: one with a mutation that establishes a stop codon within the ob gene, resulting in the production of a truncated, inactive protein; the other with a mutation that produces no protein at all.[2] Administration of leptin corrects the multiple metabolic disturbances.[4]

The finding of a human homologue of the *ob* gene[2] immediately raised the question of whether similar mutations contribute to human obesity. However, several screening studies have found no such mutations,[5] although two rare ones have been found that have no apparent biological effects (S Echwald *et al*, unpublished findings). The mutation that produced a stop codon within the mouse *ob* gene consisted of a single nucleotide substitution.[2] A similar effect in the human *ob* gene would require substitutions of two nucleotides at that codon—a very unlikely mutation.[5]

Leptin is thought to be a bloodborne signal from the adipose tissue that informs the brain about the size of the fat mass.[2] A gene has been identified that encodes several different forms of leptin receptors by splicing different segments of the gene.[6] The alternatively spliced receptors are expressed at different levels in different tissues of mice, mainly in the brain, heart, testis, and adipose tissue. One of these receptors seems to be responsible for transporting leptin across the blood-brain barrier in the hypothalamus.[6] This receptor is defective in obese, diabetic *db/db* mice. The mutated gene produces an abridged receptor protein that lacks the intracellular segment necessary for the signal transduction, implying that the coupling of leptin to the extracellular part of the receptor does not elicit the expected intracellular process.[6]

One of leptin's main effects may be to inhibit synthesis and release of the hypothalamic neuropeptide Y, which increases food intake, decreases thermogenesis, and increases levels of insulin and corticosteroid in the plasma,[7] but leptin may have other targets and pathways both in and outside the brain.[3 6] A particularly important effect may be to suppress ingestion of fat without affecting carbohydrate ingestion.[3]



Leptin feedback loop

In several animal species, including humans, the level of serum leptin is highly correlated with size of the body fat mass; and the increased expression of the *ob* gene in the adipocytes of obese people suggests that this is due to increased synthesis of leptin.[3 8] In this week's *BMJ*, Zimmet *et al* (p 965) report a similar link between serum leptin and levels of obesity among Western Samoans in the South Pacific,[9] a population with a particularly high prevalence of severe obesity and non-insulin dependent diabetes. As in other studies, leptin levels were not related to the presence of non-insulin dependent diabetes.

Ob/ob mice that have the mutation leading to production of the inactive protein, and mice with obesity caused by the mutated *db* gene or a chemical hypothalamic lesion, have increased expression of *ob* RNA in their adipocytes.[10] This suggests that the lack of a leptin induced signal from the hypothalamus leads to *ob* gene expression in the adipocytes as part of a negative feedback loop.[10] The raised leptin levels in

obese people have been interpreted as a consequence of relative insensitivity to endogenous leptin, possibly caused by deficient functioning of leptin receptors in the brain.[8] The ratio between leptin in the cerebrospinal fluid and the blood decreases with increasing obesity,[11] suggesting that in obese people the capacity for transporting leptin across the blood-brain barrier is diminished. Although giving exogenous leptin may result in weight loss in animals without obesity or with dietary induced obesity,[3 4] the possibility of leptin resistance makes exogenous leptin less suitable as a treatment for obesity in humans.

The crucial signal that induces *ob* gene expression and leptin production in fat cells is still unknown. Insulin and corticosteroids are obvious candidates.[3 12] Studies have shown that these hormones do have such an effect, but the evidence is not consistent.[3 12] Zimmet *et al*[9] and others[3] have found a correlation between insulin and leptin levels even after correcting for size of body fat mass. Fasting reduces insulin levels and leptin production, and insulin supplementation may reactivate leptin production.[3] Except in the fasting state, insulin does not have acute effects on leptin in humans, but prolonged supplementation increases leptin production, which suggests a more indirect mechanism.[12]

Several recent studies have investigated the relation between spontaneous or enforced weight changes and serum leptin levels.[3 8] These have found that leptin levels change more than would be expected from the changes in size of the body fat mass. On the other hand, obese subjects who have reduced their weight down to the normal range and maintained this weight for some time exhibit higher leptin levels than non-obese subjects with the same body fat mass.[3 8] One possible mechanism that deserves further investigation is that leptin production parallels the process of fat accumulation in the adipocytes rather than the current amount of stored fat. This relationship may also explain the residual variation in serum leptin as well as the correlation with insulin levels at any given size of the body fat stores.

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Listen to the parents

They may know best

See pp 983, 987, 991

There are two contrasting perspectives on the way patients and their parents use health services. When searching the literature on out of hours and emergency treatment, helpful keywords are "inappropriate" and "misuse."[1] Meanwhile, there is evidence that parents are more effective than professionals in the early diagnosis of a wide range of child health problems.[2 3]

Three qualitative studies reported in this week's *BMJ*[4-6] address these contrasting views, which are at the heart of general practice. Children with trivial complaints, parental anxiety, and out of hours calls make major demands on general practitioners' time. But the antecedents of these calls make demands on the wellbeing of parents, usually mothers, whose hours of work and on call duties can make the commitment of even the most overworked general practitioner seem modest.

The two papers by Kai (pp 987, 983) explore parental concerns about childhood illness and communication difficulties between professionals and parents.[4 5] Based on group discussions and one-to-one interviews with parents in a disadvantaged inner city area, his work indicates parents' anxiety, sense of lack of control, and bewilderment at what they see as inconsistent prescribing patterns, unhelpful explanations, and opaque decision making. Kai advocates more information and education for parents. His title, "parents' difficulties," suggests where the problem might lie. But it takes two to tango, and "empowering" patients means recognising their and their children's special expertise on their own bodies, lives, and environments, as well as getting professionals to relinquish "their monopoly on expert knowledge."[4]

Hopton and her colleagues (p 991) show that patients usually have a rationale for actions that may seem to the medical practitioner haphazard, perverse, or plain cussed.[6] In their qualitative analysis of service users' accounts of telephoning their general practitioner out of hours they draw, like Kai, on the context as well as the content of the consultation. For those interviewed, a key factor was their prior experience with health services. Hopton *et al* conclude that educating and informing patients is not enough.

So what should be done? Decision making, differential diagnosis, risk assessment, and living with doubt are part of the good general practitioner's stock in trade.[7] But this also goes for patients and parents of young patients. Douglas Black has suggested that there is a false antithesis between "the medical model" and "the social model" of health.[8] Whether or not the antithesis is false, these papers show that in some circumstances there remains at best a divergence of view—at worst a yawning gap—between users and providers of general medical services.