HIGHLIGHT

Leptin-induced weight loss is not solely mediated by anorexia

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The discovery of the ob-gene product leptin in 1994 (1–2) and the subsequent identification of grossly obese children lacking leptin (3) or its receptor (4) considerably increased the expectation of finding an effective cure for grossly obese humans. Very soon after its discovery it became evident, however, that a deficiency of leptin did not account for obesity in the large majority of patients and the treatment of obese subjects with recombinant leptin was rather disappointing (5). One of the most important reasons for the lack of efficiency of leptin to regulate energy balance in the central nervous system (CNS) of humans is the saturable transport mechanism allowing for (or rather impeding) the penetrance of leptin into the CNS (6, 7). Alternative systems involved in the regulation of weight regulation have therefore been sought, such as leptin downstream peptides (8) or mechanisms confined to the regulation of peripheral weight and its metabolic implications (9).

In the last few years, one major focus of leptin research has shifted from central regulation of appetite and energy expenditure to the peripheral actions. Consistent with the cytokine structure of its receptors, the action of leptin has been linked to the proliferation of various tissues leading to effects such as wound healing (10).

However, there is increasing new evidence reviving the role of leptin in weight regulation. It has recently been demonstrated that patients with lipodystrophy have significantly reduced plasma leptin concentrations. Lipodystrophy consists of a heterogeneous group of rare disorders characterized by partial or generalized loss of adipose tissue. The application of leptin reduces hepatic fat mass and improves insulin sensitivity in humans suffering from this condition (11–13).

Direct evidence that leptin directly reduces hepatic lipid synthesis independent of its effect on appetite control now comes from Friedman's group (14). Using transcription profiling they identified the gene most specifically repressed in the liver of leptin-treated *ob/ob* (i.e. leptin-deficient) mice. It encodes for the stearoyl-CoA desaturase-1 (SCD-1). This iron-containing enzyme catalyses a rate-limiting step in the synthesis of hepatic fatty acids. The principal product of SCD-1 is oleic acid which is formed by desaturation of stearic acid. Therefore SCD-1 is a key enzyme leading to an increase in energy storage (15).

Cohen and co-workers (14) showed that in the leptin-deficient *ob/ob* mouse leptin treatment completely normalized the elevated SCD-1 gene expression and enzymatic activity. Levels of hepatic monosaturated fatty acids, the products of SCD-1 that were elevated in the leptin-deficient mice, normalized by 12 days of leptin treatment.

In order to distinguish between SCD-1 and non-SCD-1 leptin actions, *ob/ob* mice were compared with double mutant leptin-deficient *ob/ob* and SCD-1-deficient *ab¹/ab¹* mice. In both male and female double mutant mice, fat mass was reduced to approximately 60% and lean mass increased by 20–30% compared with the mice that were only lacking leptin.

Most importantly, it is evident that the effect of leptin on appetite regulation is independent from that on energy expenditure. Double mutant, leptin- and SCD-1-deficient mice had an extremely increased food intake, suggesting that the central lack of leptin induces hyperphagia as in the single mutant leptin-deficient *ob/ob* mice. On the other hand, SCD-1- and leptin-deficient mice had an energy expenditure, measured by total and resting oxygen consumption, that was approximately twice as high as in solely leptin-deficient mice. As a sign of increased fatty acid oxygenation, plasma ketone bodies increased significantly in the double mutant mice. As a consequence, hepatic lipid content and triglyceride concentration were significantly reduced in comparison with the SCD-1 active only leptin-deficient *ob/ob* mice.

These results imply that the weight reducing effect of leptin is predominantly exerted via an increase in energy expenditure through hepatic fatty acid oxygenation. However, Cohen and coworkers report unpublished results showing similar effects on the reduction of SCD-1 activity if leptin is administered into the CNS of wild-type mice. In addition, livers of mice with a liver-specific knock-out of the leptin receptor have normal livers, showing no accumulation of triglycerides (16).

It therefore remains obscure as to what extent the effect of leptin on energy expenditure in rodents is of peripheral nature. As a consequence, an experimental approach using mice with a CNS-specific knock-out of the leptin receptor in order to examine the direct effect of leptin on the hepatic SCD-1 appears to be warranted.

Figure 1 Effect of leptin on weight regulation by inducing anorexia and by reducing hepatic fatty acid synthesis.

Despite the exciting new data by Cohen *et al.* (14) which discriminate between the mechanisms of the anorectic and the energy expenditure effect of leptin in mice for the first time, the significance of leptin for the reduction of body weight in humans must not be overestimated. This is mainly due to the fact that leptin appears to work more on the central level to induce fatty acid oxidation. This limits the application of the new findings in the treatment of human obesity. Nonetheless, if the central effect of leptin could be bypassed and hepatic SCD-1 could be suppressed directly, a possible new target site for weight reduction seems to be possible.

In summary, the important new studies by Friedman's group (14) show that suppression of the fatty acid-synthesizing enzyme SCD-1 can correct the hypometabolic phenotype of leptin deficiency, showing that leptin not only works via central anorectic effects but also by increasing hepatic fatty acid oxidation (Fig. 1).

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