symptoms. Parathyroid hormone is usually within the normal range but is inappropriately elevated considering the calcium level. Several mutations in the CaSR gene have been identified in FBHH. Those mutated CaSRs when expressed in vitro display reduced activity, suggesting that the mutation is responsible for the disorder. The identification of DNA markers linked to FBHH loci on chromosomes 3q and 19q has permitted definition of the genetic relationship between FBHH and neonatal severe hyperparathyroidism (NSHPT). This rare disorder has occurred in several kindreds with FBHH, and now we know that a single defective allele causes FBHH while two defective alleles cause neonatal severe hyperparathyroidism (1).

As has been described in other G protein-coupled receptors, activating mutations of the CaSR gene have also been demonstrated. A missense mutation of CaSR gene, inappropriately activating the calcium receptor at low calcium concentration, causes familial hypocalcaemia (2).

In sporadic parathyroid tumours, deletions or mutations of the CaSR gene have been reported but they do not commonly contribute to the pathogenesis of parathyroid tumours.

The recent work by Ho et al. further specifies the role of CaSR in calcium homeostasis (3). They have developed mice with a knock-out of the CaSR in order to elucidate the mechanism by which inherited human CaSR gene defects cause diseases. Their knock-out heterozygous mice (CaSR+/-) have a 50% reduction of the wild-type receptor, while homozygous animals (CaSR-/-) lack the CaSR. Interestingly, the mouse model mimics human disorders. Heterozygous mice (CaSR+/-) reproduce most features of familial hypocalciuric hypercalcaemia, while homozygous animals (CaSR-/-) exhibit the neonatal severe hyperparathyroidism phenotype. Heterozygous mice (CaSR+/-) display a small increase in serum Ca2+, Mg2+ and PTH levels as well as hypocalciuria and an altered relationship between PTH and serum calcium; they conserved the capacity to modulate PTH secretion in response to calcium feeding, but this regulation was not to the same extent as normal. Homozygous mutant mice display markedly elevated serum Ca2+, Mg2+ and PTH levels, parathyroid gland hyperplasias associated with reduced growth and a marked decrease in radiodensity of all bones. These mice died prematurely (between days 3 and 30). The results provide definitive evidence for the role of a CaSR gene mutation in causing diseases in humans. They highlight that the number of receptors on the cell surface is crucial for setting serum calcium concentration.

Both mutant mice have elevated serum Mg2+ levels. These results thus also provide evidence for the role of CaSR in regulating extracellular Mg2+ concentration, because CaSR was detected in selected tissues outside the parathyroid glands, such as brain, nerve terminals, neurons of the myenteric plexus and AT-20 cells. This new knock-out model therefore could be a tool for better understanding the functional significance of CaSR in these tissues.

The new data emphasize the pivotal role of CaSR in maintaining systemic calcium homeostasis. Targeting this receptor is expected to be a new interesting approach to the treatment of bone and mineral disorders. Calcimimetic compounds could provide a new pharmaceutical approach to the treatment of hyperparathyroidism. The CaSR knock-out mouse model opens new possibilities for further understanding calcium homeostasis.

References

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Leptin secretion and action: an update

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The discovery and anti-obesity effects of the ob gene product leptin were the subject of a Highlight in December 1995. Since then, some novel data have accumulated bearing on the regulation of secretion as well as the potential mode of action of this adipocyte-derived factor involved in reducing food intake and increasing energy expenditure.

Which factors regulate leptin expression? Three partly interrelated factors are known so far, including insulin, glucocorticoids, food intake and body lipid
content. The study of Auwerx et al. demonstrates a diurnal variation in ob mRNA levels in normal rats, with a nocturnal increase prompted by food intake (1). Interestingly, a single injection of 1 U of insulin resulted in an increase in ob mRNA to levels comparable to those present in fed animals, a finding which can be reproduced in primary adipocyte cultures (1, 2). Similarly, the treatment of rats with hydrocortisone at a dose capable of inducing a decrease in food intake and body weight over a period of 3 weeks (100 μg/g body wt per day) was correlated with an increase in adipose leptin mRNA (3). Finally, a report from the group of Flier et al. finds a several-fold elevation of serum leptin levels in normal mice chronically fed a high-fat diet, with a significant correlation of leptin levels with total-body lipid content (4). Intriguingly, while the feeding of a high-fat diet increased serum leptin levels, the level or activity of this satiety factor was insufficient to prevent diet-induced obesity in these mice. This observation suggests that a high-fat diet may be associated with an inadequately low increase in leptin concentration or, alternatively, it may induce a state of resistance to this polypeptide. This hypothesis is in keeping with the first study investigating serum leptin levels in normal-weight and obese humans (5). The group of Caro et al. measured serum immunoreactive leptin levels in 136 normal and 139 obese (BMI > 27) subjects. The mean serum leptin concentrations were four times higher in obese as compared to normal subjects (31 vs 7.5 ng/ml). As in the animal studies, leptin levels in the serum (immunoreactivity) and adipose tissue (mRNA) correlated logarithmically with the percentage of body fat. Assuming that the immunologically detected leptin levels reflect the biological activity, these results again suggest that obesity may be associated with a resistance to leptin action.

Given the above observations, the quest for a better characterization of the biological effects and target cells for leptin is of potentially significant interest for a better understanding of the pathophysiology of human obesity. Previous work suggested that intraventricular injection of leptin decreases appetite and increases energy expenditure, a profile of action compatible with an inhibition of the hypothalamic neuropeptide Y (NPY). NPY is known to stimulate food intake and decrease thermogenesis, which is due in part to an increase in serum insulin and glucocorticoid levels. In addition, intraventricular infusion of NPY causes obesity in normal rats (6, 7). A study in ob/ob mice, deficient in functional leptin, revealed high-affinity binding sites for leptin in the hypothalamus. In addition, leptin has been shown to inhibit NPY release from perfused hypothalami by 35%. Similarly, treatment of ob/ob mice with recombinant leptin over 30 days resulted in a more than 60% decrease in pre-pro-NPY mRNA in the hypothalamic arcuate nucleus, which is located outside of the blood–brain barrier (8). This was paralleled by a decrease in food intake and body weight. Hence, it is possible that some of the anti-obesity actions of leptin are mediated through a decrease in hypothalamic NPY.

Shortly after the above description of hypothalamic high-affinity leptin binding sites, the cloning of a leptin receptor (OB-R) has been reported (9). Using labeled leptin in a binding survey of cell lines and mouse tissues, leptin binding sites were found most prominently in the choroid plexus. Using a cDNA library from this tissue, a leptin binding protein was identified by expression cloning. The sequence reveals a single membrane-spanning protein, which is most related to the signal-transducing moiety of the receptors for interleukin-6 and granulocyte colony-stimulating factor. However, the mouse clone of the OB-R has a short cytoplasmic domain (34 amino acids), which could lack the functionality for intracellular signaling. In contrast, the human homolog of the mouse OB-R contains a longer cytoplasmic tail, which is possibly sufficient for signal transduction. Although the mRNA for the OB-R is most strongly expressed in the choroid plexus, it is also present in lung, kidney and, after amplification by reverse transcription polymerase chain reaction in the hypothalamus. Taken together, this study identified a leptin binding protein that may possibly represent a leptin receptor. However, further data are needed to clarify whether this protein serves any role in signal transduction and/or transport of leptin into the brain. Once its function as a bona fide leptin receptor can be ascertained, the mechanisms of the apparent resistance to leptin under circumstances of a high-fat diet described above will undoubtedly receive attention.

Note added in proof

Subsequent papers have now established that the OB-R gene can be alternatively spliced to yield a mRNA with a long intracellular domain (302 aa.). In the leptin-resistant db/db mouse a point mutation in this gene leads to aberrant splicing resulting in the lack of this region, which is likely to be involved in signal transduction. Taken together, these data strengthen the hypothesis that the OB-R is indeed a functional receptor for leptin (Cell 1996:84:491f; Nature 1996:379:632f; Science 1996:271:994f).

References

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