Leptin Deficiency

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Introduction

The leptin/melanocortin pathway plays a key role in the hypothalamic control of food intake. It is activated following the systemic release of the adipokine leptin (LEP) and its subsequent interaction with the leptin receptor (LEPR) located on the surface of neurons of the arcuate nucleus region in the hypothalamus (figure 1). The downstream signals that regulate satiety and energy homeostasis are then propagated via proopiomelanocortin (POMC), cocaine-and-amphetamine-related transcript (CART), and the melanocortin system (1). While POMC / CART neurons synthesize the anorectic peptide α-melanocyte stimulating hormone (α-MSH), a separate group of neurons express the orexigenic neuropeptide Y (NPY) and the agouti-related protein (AGRP), which acts as a potent inhibitor of melanocortin 3 (MC3R) and melanocortin 4 (MC4R) receptors. Mutations in human genes coding for proteins involved in this pathway lead to severe early-onset obesity (Table 1) with a rapid and dramatic increase in weight soon after birth. Especially, mutations in LEP gene are responsible for congenital leptin deficiency with severe obesity and associated endocrine abnormalities.

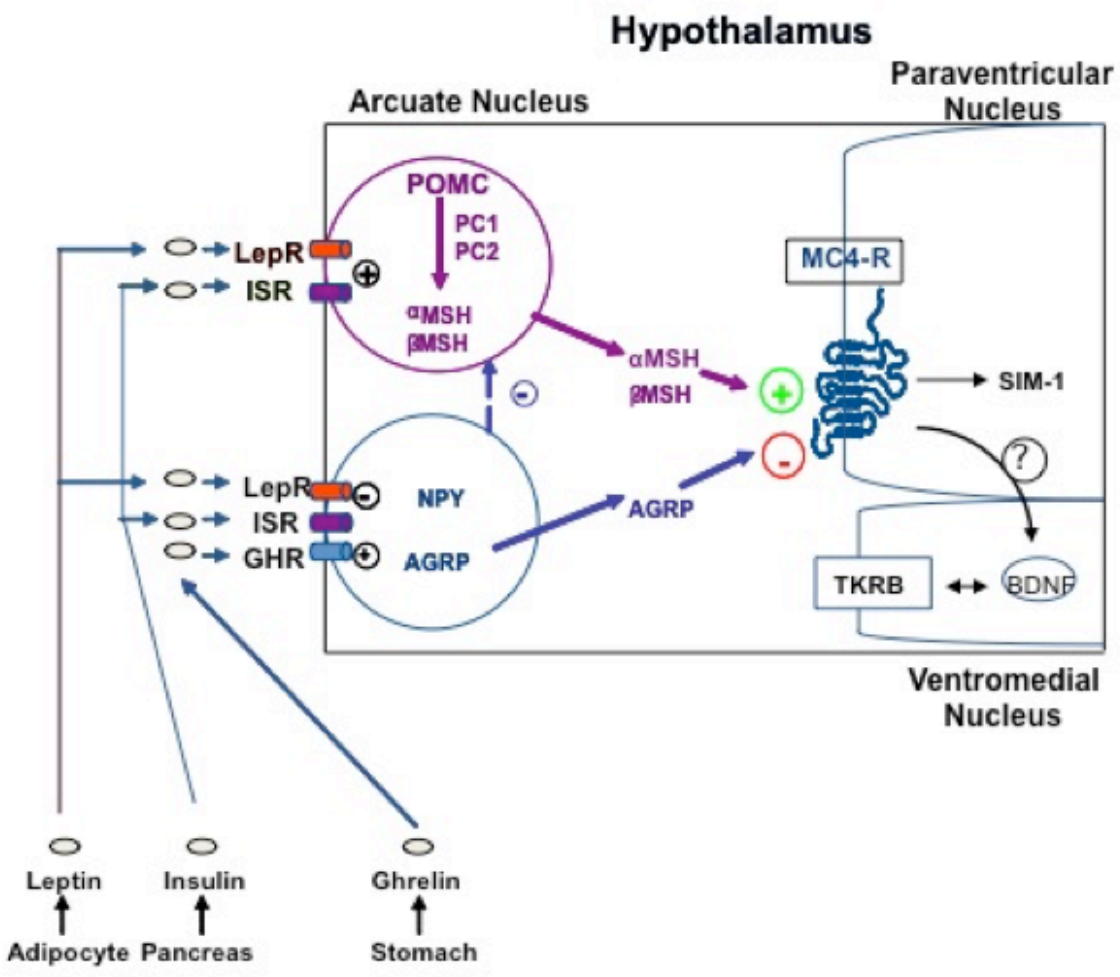

Figure 1: The leptin/melanocortin pathway

Neuronal populations propagate the signaling of various molecules (leptin, insulin, ghrelin) to control food intake and satiety. POMC-neurons in the arcuate nucleus are activated by leptin and insulin and produce the α-melanocyte stimulating hormone (α-MSH), which then activates the MC4R receptor in the paraventricular nucleus resulting in a satiety signal. The downstream roles of SIM1, BDNF and TKRB are currently being explored. A separate group of neurons expressing NPY and AGRP produce molecules that act as potent inhibitors of MC4R signaling. Several mutations of those genes involved in the leptin/melanocortin pathway are responsible for early-onset and severe obesity. POMC, proopiomelanocortin, LepR; leptin receptor; ISR, insulin receptor; GHR, ghrelin receptor; NPY, neuropeptide Y; AGRP, agouti-related protein; SIM1, single-minded 1; BDNF, brain-derived neurotropic factor; TRKB, tyrosine kinase receptor; PC1 and 2, proconvertase 1 and 2.

Phenotype

The role of leptin was first discovered in studies of severely obese ob/ob mice, which harbor mutations in the LEP gene resulting in a complete lack of circulating leptin (2). Close to ob/ob mice, less than 20 individuals carrying a mutation in the LEP gene have been identified since 1997.
Firstly, two severely obese cousins from a highly consanguineous family of Pakistani origin were reported with undetectable serum leptin levels (<1 ng/ml). They carried a homozygous frameshift mutation in the LEP gene (Δ133G), which resulted in truncated and not secreted protein (3). Since then six affected individuals from four other unrelated families were identified homozygous for the same mutation (4,5). In addition, a large Turkish family (5 subjects) carrying a homozygous missense mutation (C105T) and an obese Egyptian patient with a N103K substitution were described (6-8).

Finally, one 14-y old Austrian child carrying a new homozygous mutation in LEP gene (L72S) was recently described leading also to undetectable serum leptin levels (9).

Almost all patients are characterized by severe early-onset obesity with severe hyperphagia and endocrine abnormalities such hypogonadotrophic hypogonadism. Indeed, LEP deficient patients develop their obesity rapidly during the first months of life (weight > 30 kgs before the age of 4y). Their BMI is higher than 40 kg/m² with an increased fat mass with more than 50% body fat and relatively normal resting energy expenditure. Feeding behavior is characterized by major hyperphagia and ravenous hunger (10) except in rare cases such as described recently in the Austrian girl with less severe obesity (BMI 31.5 kg/m², Zscore BMI 2.46 SD), extremely low energy intake in everyday life despite an increased consumption of calories in a test meal (9). Despite this specific case, severe early-onset obesity with major hyperphagia is recognized as the main clinical presentation of LEP deficiency and justifies measurement of circulating leptin (4,10).

Endocrine abnormalities such as hypogonadotrophic hypogonadism are present in all patients. Especially LEP mutation carrier adults failed to undergo pubertal development (8). In contrast to ob/ob mice, which are markedly hypercortisolaemic, subjects with LEP deficiency show plasma cortisol levels in the normal range. High rate of infection associated is also described with a deficiency in T cell number and function suggesting the implication of leptin in the immune system (11, 12). Concerning metabolic characteristics, hypersinsulinemia is present in all subjects as described in ob/ob mice. Ozata et al. reported abnormalities of sympathetic nerve function in LEP deficient humans consistent with defects in the efferent sympathetic limb of thermogenesis (8).

Treatment

LEP deficiency is a unique situation of extreme obesity where a therapeutic option is available. Indeed, LEP deficient children and adults benefit from subcutaneous daily injection of leptin, resulting in weight loss, mainly of fat mass, with a major effect on reducing food intake and on other dysfunctions including immunity as described previously [4]. After leptin therapy, the detailed microanalysis of eating behavior of 3 LEP-deficient adults before and after leptin treatment, revealed reduced overall food consumption, a slower rate of eating and diminished duration of eating of every meal in the three subjects. This study

supports a role of leptin in influencing the motivation to eat before each meal (13).

Leptin treatment was able to induce aspects of puberty even in adults, as illustrated by the effect of leptin treatment in one 27 year-old adult male with hypogonadism (10). In two women between 35-40 years, leptin treatment led to regular menstrual periods and hormonal peaks of progesterone evoking a pattern of ovulation. Although cortisol deficiency was not initially found in LEP-deficient patients, eight-months of leptin treatment modified the pulsatility of cortisol with a greater morning rise of cortisol. Leptin could have a previously unsuspected impact on human hypothalamic-pituitary-adrenal function in humans. Finally, metabolic parameters of leptin deficient patients improved in parallel with fat mass loss.

Conclusions

Diagnosis of LEP deficiency needs to be mentioned in case of an early-onset extreme form of obesity associated to endocrine abnormalities (hypogonadotrophic hypogonadism) close to the murine models. Undetectable circulating leptin (< 1 ng/ml) and identification of a LEP gene mutation by direct sequencing confirm the diagnosis leading to substitutive treatment. Indeed, LEP deficiency is a unique situation of extreme obesity where a therapeutic option is available.

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Her main research topic is the identification of genes implicated in early onset obesity and studied especially the role of the genes in the leptin/melanocortins pathway. She worked with Dr Christian Vaisse in San Francisco on MC4R and LEPR genes and is now part of Pr K Clement's team in the cardiometabolic institute ICAN, Paris

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