

Neuro-endocrinology

BRIEFINGS

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SUMMARY

The discovery of leptin resulted in a gear change in obesity research. Exploiting its therapeutic potential has proved to be a long game, although encouraging progress is now being made with leptin monotherapy in conditions of relative deficiency, and with combination therapy against common obesity. Leptin's role in early brain development constitutes an exciting area for mechanistic study with potential therapeutic implications.

LEPTIN – BACK AND FORWARD

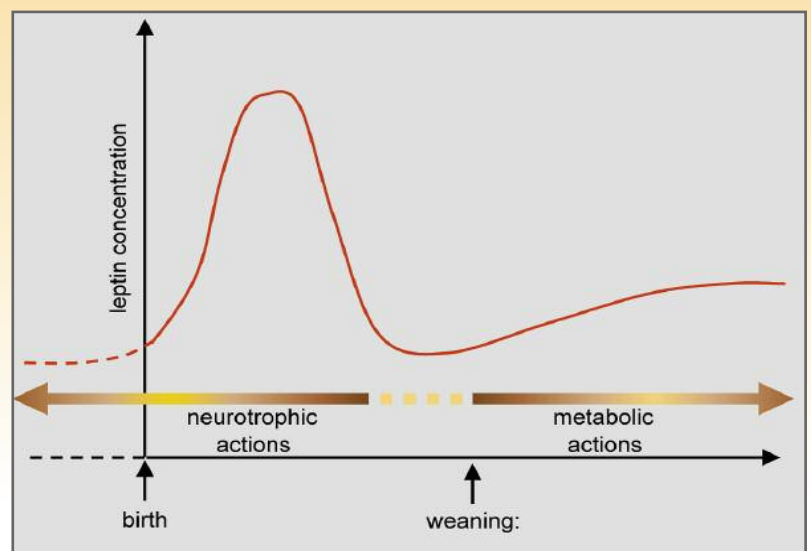
The elusive lipostat

The cloning in 1994 of the *ob* or leptin gene, as it was subsequently named, caused enormous excitement in the obesity field: the product of the leptin gene was likely to be a key component of the hypothesized, but hitherto elusive, lipostat regulating the size of body fat reserves through the sensing by the hypothalamus of a circulating product of fat metabolism. The potential of this molecule in obesity therapy was clear: the absence of leptin due to the mutation in the *ob* gene was the root cause of the massive obesity in the *ob/ob* mouse, and administration of recombinant leptin protein to *ob/ob* mice reversed the excessive food intake and weight gain in these animals. Subsequently, leptin receptors were mapped to key hypothalamic areas already known to be involved in the

regulation of energy balance (e.g. arcuate, ventromedial, dorsomedial, paraventricular nuclei).

Therapeutic potential

The initial hopes that leptin might have direct therapeutic potential in human obesity were undermined when it was realised that far from having low concentrations of leptin in the bloodstream, most human obesity was accompanied by high leptin levels, although these levels were variable with respect to body fat content or body mass index (BMI). Nevertheless, the discovery of loss of function mutations in the leptin gene in a small number of individuals with very debilitating early onset morbid obesity served to emphasise that the product of this gene is essential for normal body weight regulation in both humans and laboratory rodents.



Schematic of developmental and metabolic actions of leptin during early life

The full biological potency of the leptin hormone was further underlined by the truly remarkable outcomes of the pioneering therapeutic use of leptin in these deficient individuals, completely transforming otherwise blighted lives.

By contrast, clinical trials of recombinant leptin in obese adults who are not deficient in leptin have been disappointing, with minimal additional weight loss compared to placebo on a calorie restricted prescribed diet. However, despite this set-back, clinical trials of combination therapy involving leptin are the subject of active ongoing investigation, a strategy that appears to be bearing fruit with other drug/hormone combinations. In addition, there is growing evidence of the effectiveness of leptin monotherapy in chronic negative energy balance states of relative leptin deficiency such as lipodystrophy. Here, leptin replacement improves glycaemic control and dyslipidaemia.

“Several threads of evidence point to an active role for leptin in early brain development . . .”

Catalysing obesity research

Despite what might be seen to be the failure of leptin to fulfil its initial promise (or perhaps, more accurately, to match the hopes and expectations of the researchers), there is little doubt that the cloning of the leptin gene has been the catalyst for an upsurge in research in the obesity field in general. From research on the leptin system itself, it is now clear that this hormone is involved in a

wide range of physiological processes. Intervention studies in states of congenital or relative leptin deficiency have highlighted a number of neuroendocrine, metabolic and immune disturbances that can be reversed by leptin administration. One of the most fascinating areas of active research is the emerging role of leptin in early development.

A developing role . . .

The concept of developmental programming is based on observations that environmental conditions during critical developmental phases can permanently influence subsequent physiology, metabolism and behaviour. The brain may be particularly sensitive to nutritional programming events, especially during early life when neuronal projection pathways are developing. Several threads of evidence point to an active role for leptin in early brain development and in the establishment, or wiring, of the hypothalamic energy balance circuits.

Leptin receptors are widely expressed in the developing rodent brain from embryonic life, and there is a surge in circulating leptin concentrations, independent of body fat mass, during the early postnatal period in rats and mice. The ‘leptin surge’ does not appear to influence feeding behaviour and metabolic responses at this age - rodent pups feed independently from around the time of weaning, and are sensitive to the metabolic effects of leptin from this point onwards - but may have a direct neurotrophic action. Leptin-deficient, *ob/ob*, mice have small brains compared to wild types, and neuronal projections from the arcuate nucleus to the paraventricular nucleus fail to

develop. Delivering leptin by injection to *ob/ob* mice to coincide with the timing of the leptin surge in wild type animals increased the density of projections between the two nuclei, an effect that could not be replicated when leptin was only delivered in adult life. Similarly, leptin treatment specifically during early life in *ob/ob* animals is able to restore brain weight. Finally, a direct effect of leptin has been shown in the promotion of neurite outgrowth *in vitro*.

Perspective

All too often popular coverage of science stories concludes with a statement to the effect that it will be 10 years before the benefits of ‘x’ are seen in the clinic. Fifteen years on, the path from bench to bedside for the leptin molecule, and the insights it has provided, continues to hold promise. In the future, this may include neonatal interventions for healthier later life.

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