

Neuro-endocrinology

3 BRIEFINGS

LEPTIN: YOUR BRAIN, APPETITE AND OBESITY

SUMMARY

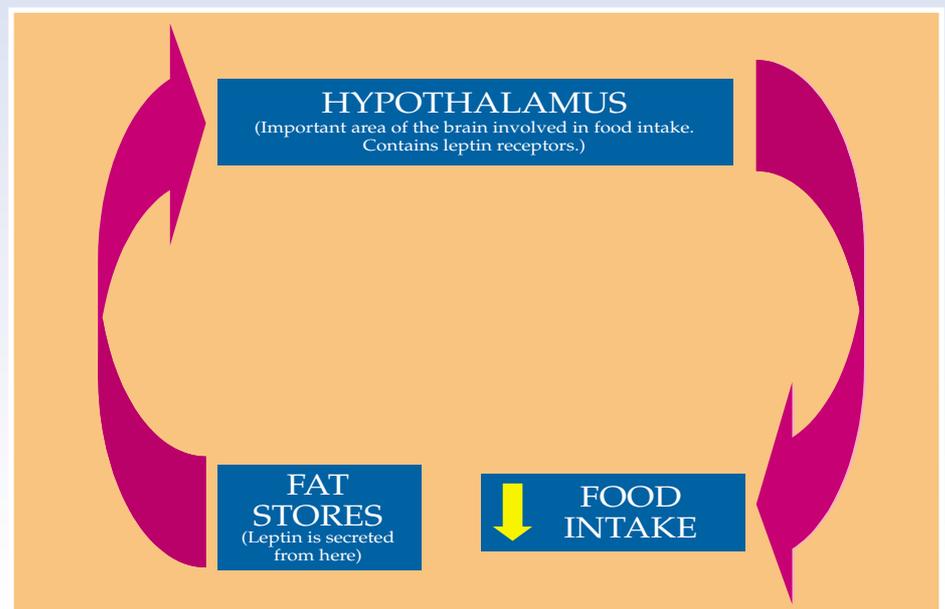
A cure for obesity was once a pipe dream. However, recent research into appetite regulation has revealed what could be a very important player in the control of appetite and body weight regulation. Amelioration of obesity, whilst having a profound social impact would also save lives. It would lead to reductions in diabetes, coronary heart disease and many forms of cancer, all of which are increased in obesity.

Flab Attack

The prevalence of obesity is on the rise. A consequence of this has been increased research into this problem. Behavioural therapies and diets can work in some cases, but in the majority of obese people, have little impact. At present the role of neuropeptides in appetite regulation is a hot area of research. Various peptides have been identified which control food intake. Some, such as neuropeptide Y, galanin, and the orexins, increase food intake. Others, for example glucagon-like peptide-1 (7-36)-amide, cocaine and amphetamine regulated transcript, and leptin, decrease food intake. This review will focus on leptin, a hormone that could make the word 'fatty' almost redundant.

Leptin, the product of the *obese* gene, is a member of the cytokine family of peptide hormones and is produced in and released from fat cells. Injection into the brain or bloodstream of rodents results in reductions of food intake and body weight, with increasing amounts having greater effects. Various forms of the receptor to which leptin binds and exerts its actions have been identified to date. These receptors are found in many tissues in the body, including the brain.

In situ-hybridization studies have revealed the presence of leptin receptors in the rodent brain. The long form of the leptin receptor is found in high abundance in the hypothalamus, an area of the brain important in the control of food intake. This long form (Ob-Rb) has



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the full intracellular ‘tail’ and performs signal transduction. A shorter form (Ob-Ra) is also found in the brain where it is thought to facilitate transfer of leptin from the periphery into the brain. There is some evidence that this form is also capable of signal transduction. It is co-expressed with Ob-Rb in the hypothalamus and may work with Ob-Rb in mediating the effects of leptin on food intake.

The amount of leptin produced by both humans and rodents has been found to be proportional to body fat. The amount produced per fat cell also increases with greater obesity. This rise in leptin should act over time to stem the amount of food eaten by an obese person. In reality, obese people have a blunted response to leptin and appear to be resistant to its effects.

Animal studies have revealed an important role for leptin in the control of food intake and body weight regulation. Mice with mutations in the *diabetes* gene, *db/db* mice, have a truncated form of the leptin receptor. Although these mice have high levels of circulating leptin, they are unresponsive to it. Their obese body pattern resembles that of the *ob/ob* obese mouse, which has a functional leptin receptor but lacks production of leptin itself. The *fa/fa* fatty rat has a mutation in the *fatty* gene. This rat has a leptin receptor with greatly attenuated signaling function. It has been found to respond to leptin, but at a much higher dose of leptin than that given

to lean controls. These three genetic models of obesity secondary to impaired leptin function are massively obese, several times heavier than normal.

At present it is not known how important leptin is in control of human body weight. Recently published studies on rodents have also shown it to be critical for pubertal maturation and reproductive function. People with defects in leptin production or receptor function, as well as being morbidly obese, do not undergo pubertal maturation. It is possible that leptin may be more concerned with pubertal maturation and reproductive function in humans. This remains to be elucidated.

“This is the first report of a defect in the leptin receptor in humans.”

Two young cousins, who have yet to enter puberty, have recently been found to be lacking in leptin and show severe early-onset obesity. A Turkish family has been identified with a mutation in the leptin gene. This mutation results in low plasma leptin and gross obesity in the affected members of the family. Two are adults, a 22-year-old man who has not gone through puberty and a 34-year-old female who has never menstruated. Even more recently, a paper published in ‘Nature’ describes a mutation in the human leptin receptor gene. The mutation results in receptors with no signaling function with all forms of the leptin receptor affected. The three affected sisters, members of a large family, are morbidly obese and have no pubertal development. This is the first report of a defect in the leptin

receptor in humans.

Research into obesity and appetite regulation is at a critical juncture. The challenge is to take the recent crucial findings and transfer them to the management of the evolving human epidemic of obesity. With the regular discovery of hormones involved in regulating body weight it is a diverse and rapidly expanding field. The end results of this research could possibly improve the quality of life of millions. Only time will tell.

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Neuro-endocrinology Briefings are produced by the British Neuroendocrine Group

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