Jeff Friedman’s group’s seminal paper (Zhang et al. 1994) describing the presence of an ‘ob gene’, expressed in the white fat cell, was published as recently as December 1994.

The present symposium, the first in the British Isles on leptin, celebrates the flowering of research that discovery unlocked. During 1997 over 1000 papers were published on the ob gene and the polypeptide signalling hormone it codes: the ‘ob gene product’, or ‘leptin’ as it has come to be called (from the Greek, leptos, thinning).

This discovery did not come out of the blue; leptin was a hormone waiting to be discovered, or more precisely, to be demonstrated. Metabolic physiologists had deduced by inference from observation and experimental manipulation that body energy stores were regulated in the long term by a signal (for a review of this historic research, see Weigle, 1994). Kennedy (1953) refined this concept of a general regulation of macronutrient stores to the more specific theory of the presence of a lipostat controlling lipid stores, the principal storage molecule of the body. Kennedy’s (1953) theory envisaged a signal from the fat cell to the brain, related in strength to the state of fat storage. This signal when transcribed centrally in the hypothalamus would regulate dietary energy intake appropriately, fat stores thus remaining constant. It must be said that it was possible to hold the alternative view that there was no lipostat at all; rather that fat stores were built up or depleted as a consequence of other regulatory mechanisms, particularly those affecting food intake through gut status and/or the potent and fast-acting glucostatic mechanism controlling feeding.

However, a neglected piece of work by Hervey (1959) had shown unequivocally that a signal was present. In a parabiotic rat pair, when one animal was lesioned in the ventro-medial hypothalamus (thus destroying the ‘satiety centre’ so that the feeding drive was uninhibited by afferent signals), not only did the lesioned rat become grossly obese through hyperphagia, the unlesioned Siamese twin lost weight dramatically. Hervey (1959), quite correctly, supposed that the afferent signalling molecule indicating fatness could not be monitored in the lesioned animal because of the destruction of the ventro-medial hypothalamus, but could spill over through the blood link into the circulation of the unlesioned animal. This spill-over paradoxically signalled in the intact rat the fat repletion of the obese lesioned animal, causing the inappropriate suppression of food intake despite the actual loss of fat in that animal. Two decades later, Coleman (1973) did a similar study with parabiotic pairs of the db/db obese mouse with a normal animal, followed by a similar study on the ob/ob obese mouse, and was also able to demonstrate clearly a signalling hormone, correctly identifying signal insensitivity in the db/db model and lack of signal in the ob/ob mouse.

These findings of Hervey (1959) and Coleman (1973) were in the public domain for 40 years, noted by many, including myself, but we despaired of ways to investigate the phenomenon further. Great credit is due to Friedman, who, when presented with this information, had the imagination and determination to use the sophisticated molecular biological technique of positional cloning to search for the gene for this signal in the white adipose tissue of the ob/ob mouse. After much patient and hard work over a number of years, he was able to establish its presence. I would like to take this opportunity of publicly expressing my own indebtedness to Jeff Friedman; his work has unlocked a door in a stagnating subject, providing me with the opportunity for fresh and exciting work on this fascinating topic late in my research career.

Having a DNA sequence for the putative signal enabled the synthesis of probes for the mRNA of the ‘ob’ protein and, thus, early work demonstrating the changing expression of the gene appropriately to biological function. This was rapidly followed by the use of antibodies to the natural protein to enable its determination in the blood, genetic engineering to enable bacterial synthesis of leptin, and the means of investigating leptin receptors. Thus, by the end of 1995 the
elements of Kennedy's (1953) lipostat had been elucidated. Leptin indeed signalled body fat content, there being a very strong positive relationship between fat content and blood leptin levels. Much detail of this and later work on the leptin-mediated lipostat are given in the following papers in the present symposium (leptin production by the fat cell, see Trayhurn et al. 1998; central mechanisms of leptin signalling and efferent control of feeding, see Campfield & Smith, 1998).

This development led immediately to a disappointment; leptin was not to be the 'cure' for common obesity in man. It was soon established that leptin levels in obese subjects were normally related to the level of fat deposition, central leptin insensitivity appeared to be the problem (see Blum, 1998). However, in an extremely rare condition, hypoleptinaemia akin to that of the ob/ob mouse may be present (see Farooqi et al. 1998).

Questions remain to be answered: how are seasonal changes in adiposity in wild animals regulated? Appetite and fat storage are clearly uncoupled at certain stages of the annual cycle in many species during pre-winter or pre-migratory fattening. Is central sensitivity to leptin modulated by day length, perhaps through melatonin levels? Might this have some relevance to the presumed reduced receptivity to leptin in obese subjects? What is the significance of the acute changes in leptin concentration as reported to the present symposium by Coppack et al. (1998)?

However, the flowering of leptin research, especially the use of techniques to investigate isoforms of the leptin receptor and their distribution, has opened windows into surprising and unexpected areas of physiological function. Receptors, of several isoforms, are widely distributed in tissues of the body (De Matteis et al. 1998). Bodily functions are directly modulated by leptin. A main emphasis of the present symposium was on the emerging appreciation of leptin's pan-physiological role. The role of leptin in reproductive function (see Hoggard et al. 1998), its interaction with glucose regulation through leptin receptors on the pancreatic B-cells (see Cawthorne et al. 1998), and direct effects on peripheral metabolism through effects on inner mitochondrial proton leak, perhaps through interaction with uncoupling proteins (see Porter & Andrews, 1998), were discussed. Leptin is also necessary for haematopoiesis (Bennett et al. 1996), and recently there is evidence for its role in the stress response too (Bornstein et al. 1997).

The role of leptin in the modulation of reproductive function is an area of fascination and rapidly expanding interest (if discovered by a reproductive physiologist, perhaps we would have called the present symposium 'Reptin'!). Leptin is required for normal reproductive function; the ob/ob mouse which lacks functional circulating leptin is sterile. In an ongoing study, my group is injecting leptin into young ob/ob mice. Twice daily injections of leptin have normalized these animals with respect to their hyperphagia and body weight, and their general physical appearance, but especially their reproductive function. Last week a female ob/ob mouse maintained on leptin successfully delivered a litter, and as I write is now successfully lactating and feeding them; a male ob/ob mouse maintained on leptin has successfully sired a litter. These striking observations on the restoration by leptin of normal whole-body function, including reproductive capacity, vividly emphasize its pervasive role.

How can this pervasive function be rationalized? I'd like to propose a 'quartermaster' role for leptin. Leptin indicates to the bodily systems the state of the fat energy stores. Acting in the brain it appropriately controls feeding, although this loop must clearly be modulated by seasonal signals. Through direct tissue action it can signal whether or not it is appropriate to engage in such energy-demanding functions as reproduction, or conserve energy by down-regulation of whole-body metabolism.

Much has been discovered about leptin in a very short exciting period of intense research. The present symposium reports many of those findings, but equally demonstrates the unfolding complexity of the leptin system and the challenging questions still to be answered about the pan-physiological role of leptin.

References


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