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EDITORIAL

THE UNFOLDING TALE OF LEPTIN

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The discovery of leptin, a product of the *ob* gene, in 1994 (1) has raised hopes of many an obese population throughout the world for a probable solution to their fatness. Its discovery has seemingly provided the missing link in the regulation of body weight and energy balance and has added an extra impetus to research in obesity. Within a short period of time, research on leptin has spread to numerous laboratories throughout the world and beyond obesity, so much so it is now becoming increasingly difficult trying to keep pace with the rate at which new knowledge on the physiology of leptin is being generated, let alone making sense of the data that is being published.

As has been the case with a lot of other discoveries, the discovery and identification of leptin, for some reason, took a long time in coming. It began way back in 1950 with the appearance of a recessive mutant colony of house mice kept in captivity. These mice, which have now been found to lack the *ob* gene (*ob*/*ob*), had hyperphagia, decreased energy expenditure and early onset obesity (2). In 1953, the lipostatic theory of weight control was proposed (3) where it was hypothesized that a circulating factor produced by the adipocytes interacted with the hypothalamus to regulate food intake, body weight and overall long-term energy balance. The ingenious experiments of Hervey (4) in 1958, in which he produced obesity in rats after lesioning the ventromedial hypothalamus, and parabiotic experiments of Hausberger (5) a year later confirmed the probable presence of this circulating factor. However it was some 40 years later that this factor, which we now refer to as leptin, was eventually detected and characterised. Through positional cloning, the mouse *ob* gene was discovered and has been shown to encode a 4.5 kilobase mRNA transcript with a highly conserved 167 amino acid chain (1). The mouse and human *ob* genes have been localized to chromosome 6 and 7q31.3 respectively (1, 6, 7).

It is now some six years since the discovery of leptin and the obese saddled with fat however are still awaiting delivery of that promised "fat-melting" hormone. The euphoria and the enthusiasm that was raised by the discovery of leptin has now settled and an aura of realism is beginning to prevail. Whilst the discovery of leptin has in a way provided a logical direction to research in obesity, there is still a long way to go before we can say for certain how significant the discovery of leptin has been in the understanding and control of obesity. From early on it became evident that leptin deficiency may not by itself totally explain obesity. Whilst parabiosis between *ob*/*ob* mice and normal mice leads to weight reduction in the former (5), similar experiments between normal mice and another obese strain of mice (*db*/*db*) leads to starvation and death in the normal mice (8). Harris *et al* (9) found the same with *fa*/*fa* obese rats and their normal counterparts. Evidently these obese mice and rats had, in their blood, a surfeit of an appetite-inhibiting circulating factor, presumably leptin, that it starved to death the normal mice and rats when their circulations were connected respectively. The fact that it was not affecting the obese mice or rats themselves indicated that there was present an element of resistance in these animals. These observations when interpreted on the basis of what we know about leptin today, suggest that obesity may not just be due to the absence or deficiency of leptin per se but due more to the presence of leptin

resistance. That this may indeed be the case is further indicated by observations that in the general population plasma leptin levels correlate positively with fat mass i.e. the higher the fat mass the higher the plasma leptin levels (10). Moreover, a change in leptin responsiveness in a model of diet-induced obesity in the mouse, where 5-10 times more leptin was required to achieve the equivalent weight loss of that produced in the *ob/ob* mouse (11), substantiates further this possibility.

To date two leptin receptor isoforms have been identified i.e. the long form receptor (*obRb*) which has a 340 amino acid intracellular domain and the short form receptor (*obRa*) with a 34 amino acid intracellular domain. The long form leptin receptor belongs to the class I cytokine family and its mRNAs have been identified in the arcuate nucleus, dorsomedial nucleus, ventromedial nucleus and ventral premamillary nuclei. The short form leptin receptor mRNAs have been identified in the choroid plexus, vascular endothelium, liver, lung, gonads and kidney. The short form receptors are involved in the transport of leptin across membranes, particularly the blood brain barrier and the kidney. Incidently, leptin is mainly cleared in the kidney and hence in chronic renal failure leptin levels rise and probably contribute to the loss of appetite and weight loss in these patients. The biological effects of leptin however are thought to result from its binding to the long form receptors followed by the activation of a JAK-STAT signaling pathway (Janus Kinase - signal transducer and activator of transcription) which then alter the expression in the target cell.

In the regulation of energy balance, leptin first crosses the blood brain barrier aided by its binding to the short form receptor, and then binds to the long form receptors in the hypothalamic nuclei. In the hypothalamus, the long-form of leptin receptor is co-expressed with neurons producing Neuropeptide Y (NPY), Agouti-related peptide (AgRP), proopiomelanocortin (POMC) and Cocaine and amphetamine regulated transcript (CART). NPY and AgRP both stimulate feeding behaviour whereas POMC and CART suppress feeding. Leptin binding to the NPY and AgRP neurons suppresses NPY and AgRP release whereas its binding to POMC and CART containing neurons increases the release of POMC (precursor of a MSH) and CART. The net effect is a suppression of appetite and feeding, increased autonomic activity and thermogenesis. (For a more detailed review readers are referred to ref 12, 13)

In obesity, in addition to leptin deficiency, leptin resistance is hypothesized to occur at various levels in the leptin pathway. It may be a result of (a) the presence of leptin antibodies, or (b) increased leptin binding proteins, or (c) defective transporter system at the blood brain barrier, or (d) defective receptors, or (e) defective intracellular signaling, or even (f) resetting of leptinstat in the hypothalamus. Whilst naturally occurring antibodies or increased leptin binding proteins in obesity have not been demonstrated so far, there is however evidence for the absence of leptin in some obese mice (2) and in a rare form of human obesity (14), mutations in the leptin receptor (15), impaired leptin signal transduction (16, 17) and even a possibility of decreased leptin transport across the blood brain barrier (18). Apart from leptin deficiency, which is inherited as an autosomal recessive trait, it is uncertain whether the rest of the abnormalities observed are present at birth or occur later on in life. Clearly, there is still a need of much work to fully understand the nature of these abnormalities and how we could overcome them.

Although there has been disappointment that leptin deficiency was not the answer to the common obesity, since its discovery however, leptin has very quickly become a subject of study beyond obesity. Numerous possible neuroendocrine roles for leptin are being explored and the adipose tissue is seemingly functioning as part of the endocrine system.

Leptin is believed to permissively activate the hypothalamic-pituitary-gonadal axis during puberty (19, 20, 21, 22) as mutations of *ob* and *db* genes result in hypothalamic hypogonadism in humans (23). In normal children leptin levels increase before puberty and reach their peak at the onset of puberty (24) after which they begin to decline in boys but continue to increase in girls with the levels depending upon the fat mass. Administration of leptin to pre-pubertal mice and non-human primates accelerates puberty (25). Besides, leptin stimulates GnRH release from hypothalamic explants (26). Low leptin and absent diurnal leptin rhythm occur with exercise-induced amenorrhea (27). On the other hand, there is also evidence that LH and FSH responses to GnRH administration in young girls correlate negatively with body mass index and circulating leptin (28). These observations however do not exclude the permissive role for leptin in puberty as chronic hyperleptinaemia in transgenic skinny mice accelerates puberty and late onset hypothalamic hypogonadism (29) suggesting dual

effects of leptin. Leptin in the required concentrations stimulates puberty but in excessive amounts leads to infertility.

Leptin is now considered an important link between obesity and infertility. It affects reproduction and fertility not only through its action on the hypothalamic-pituitary-gonadal axis but also through direct ovarian action. Follicular fluid leptin concentration has been shown to be a promising marker of assisted reproduction treatment success in normal women. The role for leptin in the follicular fluid is unclear but it has been reported that a lower follicular leptin concentration favoured a successful outcome of assisted reproduction in women with polycystic ovarion syndrome (30). In addition, IGF-1 augmentation of FSH-stimulated estradiol production by the ovarion granulosa cells is inhibited by leptin (31) and this may be one of the possible mechanism of infertility in obese women. A functional deficiency in the long form leptin receptor in the endometrium has also been linked to subfertility in some women (32). Increased leptin levels in serum and peritoneal fluid of patients with pelvic endometriosis have also been reported (33).

Leptin is now known to be produced in the placenta (34) where it may serve an autocrine/ paracine role in human implantation and placentation (35). Matrix metalloproteinases are necessary during cytotrophoblast invasion and leptin has been shown to activate these proteases (36). Impaired placentation has been repeatedly observed in preeclampsia. Interestingly however, both serum free leptin levels (37) and placenta leptin levels (38) are raised in women with preeclampsia. Placental leptin release is augmented during advanced labour but it is absent during cesarian section (39). Leptin levels in the placental tissue also correlate positively to placental weight (40). Levels of leptin in the cord blood are positively correlated with body weight and fat mass of the newborn (41). In twin pregnancy, placental and cord blood leptin levels have been found to be lower (42) or higher (43) in the growth retarded infant when compared to its normal-sized twin. The amount of leptin mRNA in placentae from insulin treated diabetic women are higher when compared to normal placentae (44). Umbilical cord plasma concentration of leptin has also been reported to be higher in infants of diabetic women (45). Although considerable information exists implicating leptin in a number of gestational situations, the information however is still insufficient and at times conflicting for a cohesive interpretation of the physiological role for leptin in reproduction. Nevertheless, some involvements are emerging and there is a clear need for more work.

A significant relationship has been reported between leptinaemia and plasma renin activity in women with essential hypertension (46). The overall effect of leptin on arterial pressure however remains unclear. Chronic systemic administration of leptin increases arterial pressure and heart rate in conscious animals (47). Intravenous bolus administration of pharmacologic doses of synthetic murine leptin to denervated SHR however causes natriuresis (48). In another study leptin has been shown to have vasodilating properties, probably mediated through endothelium dependant hyperpolarizing factor (49). In addition to these, vitrous leptin has been reported to be elevated in proliferative diabetic retinopathy and retinal detachment (50). Higher plasma leptin levels have also been observed in cases of advanced proliferative or nonproliferative diabetic retinopathy (51). Leptin has also been postulated to have thrombotic tendency (52) and has been found to stimulate the proliferation of haematopoietic stem cells (53). Leptin evidently also enhances wound re-epithelialization (54), induces an angiogenic response or has angiogenic activity (55). Apart from that, leptin is evidently also involved in linking nutritional state to T cell function, as leptin replacement reverses the immunosuppressive affects of acute starvation in mice (56). In a recent report it was observed that patients who survived an acute septic episode had three times higher levels of leptin compared to non-survivors (57). Surgical stress is associated with increased serum leptin levels (58).

Clearly the discovery of leptin has not only further stimulated research in the study of obesity but also the role of leptin in a number of other areas of physiology and medicine. Little is known about the regulation of its synthesis or release although it appears that leptin is produced constitutively and released from the adipocyte continuously. Its interaction with insulin also needs further scrutiny. The influence of age and diet on leptin sensitivity or resistance are other areas that need to be researched. For the moment however, the mounting evidence which may still be somewhat hazy, patchy and at times contradictory, suggests that leptin may have a greater endocrine role than previously envisaged. Leptin functioning as a link between the adipose tissue and energy balance, reproduction, fertility and a number of other physiological functions, suggests that it may be time to re-look at our view of adipose tissue as purely an energy store and insulating tissue. Adipose tissue an endocrine

organ? No doubt it may be a wee bit too early to press for this but the possibility nevertheless exists. How many of it's hypothesized roles will eventually be confirmed or whether it shall become another "full of promise but failed to deliver" case is left to be seen Its discovery has nevertheless brought with it a very fertile area of investigation that should keep many scientists busy over the coming decade or so.

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