Molecular studies of leptin: implications for renal disease

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Introduction

The recent discovery of the ob gene product leptin has markedly increased our understanding of the complex physiological system that regulates satiety and eating behaviours. Moreover, as leptin receptor isoforms have now been reported in several peripheral organs, it may be conjectured that leptin, besides having central effects also has a pleiotropic action. A number of recent studies have demonstrated that most uraemic patients have inappropriately high leptin levels and it has been speculated that leptin may be one factor that mediates anorexia and wasting in this patient group. However, besides regulating appetite, leptin may also play a role in sympathico-activation, insulin secretion and sensitivity, renal sodium handling and haematopoiesis (Figure 1). More research is therefore needed to determine whether uraemic hyperleptinaemia affects other organ systems in uraemic patients. The aim of this review is to summarize recent data on leptin regulation and function in animal models, as well as in humans, with a special focus on leptin in renal disease.

The discovery of leptin

The notion that the brain regulates food intake and body weight dates back to the beginning of this century when it was first observed that damage to the human hypothalamus sometimes resulted in extreme obesity. In the early 1950s, a genetic trait that results in marked obesity, hyperphagia, glucose intolerance, insulin resistance, low energy expenditure and sterility was identified in a particular type of mice, the ob/ob mice. Subsequent parabiosis experiments, in which obese mutant homozygote ob/ob mice and normal mice were cross-connected circulatorily resulted in decreased food intake and weight loss in the obese mice suggesting that the ob/ob mice were deficient in a blood-borne factor that regulates nutrient intake and metabolism [1]. The molecular basis for the ob/ob type of obesity had eluded investigators for many years, until Friedman and collaborators [2], using positional cloning, identified and sequenced the missing blood-borne factor in 1994; i.e. the ob gene product, which has been named leptin from the Greek word leptoς ‘thin’. Apart from ob/ob mice, which lack adipose tissue ob mRNA, all other genetic and experimental models of obesity have been shown to have increased levels of adipose tissue mRNA (Table 1). Another well-characterized recessive obesity mutation, diabetes (db), also results in profound and early-onset obesity. Moreover mice homozygous for the db mutation exhibit an obesity phenotype identical to the phenotype of the ob/ob mice [1]. However, if the circulatory system of a normal mouse is linked to that of a db/db mouse by parabiosis, the normal mouse will lose its appetite and finally starve to death [3]. This suggests that homozygote db mice have a defective receptor response to the leptin satiety signal which in turn leads to a compensatory increase in ob gene expression and plasma leptin levels (Table 1).

Factors regulating leptin gene expression

The ob gene and obesity

The human ob gene homologue is 84% identical to the mouse gene and is located in a synthetic region of chromosome seven [2]. Recent results from Comuzzie et al. [4] also suggest linkage of a region on chromosome two with serum leptin levels. Consequently, their results indicate that this region could contain an important human obesity gene. An impressive amount of research during the last few years has demonstrated that a number of physiological factors affects the expression of leptin mRNA and leptin levels in humans (Table 2). Plasma leptin levels are very high in obese patients and a markedly increased expression of leptin mRNA has been found in subcutaneous tissue in...
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leptin gene, has recently been demonstrated in two severely obese and hypo leptinaemic children [9]. This provides the first genetic evidence that leptin is an important regulator of energy balance in humans. The expression of the \(ob\) gene exhibits diurnal variation and varies with changes in food intake. Fasting has been shown to prevent the cyclic variation in leptin mRNA and reduce the expression of the \(ob\) gene which has been shown to increase within 4 h following food intake [10]. Another factor that might affect leptin gene expression is exercise which has been shown to reduce leptin mRNA by 85% in rats [11].

**Leptin levels are higher in women**

Independent of obesity, leptin levels are usually higher in women than in men and a marked influence of gender on the leptin–obesity axis has been found in several studies [12–14]. Lönnqvist et al. [15] have found that elevated circulating levels of leptin in obese women above all result from accelerated secretion rates of the peptide from adipose tissue because of increased \(ob\) gene expression. Ovarian steroid hormones exert major influences on eating behaviour and body-weight regulation and it has been found in rats that ovariectomy decreases leptin mRNA expression [16]. Moreover, premenopausal women have higher leptin levels than postmenopausal women [17] and it is probable that ovarian steroid hormones may be one important factor involved in the regulation of the \(ob\) gene in humans.

**Glucocorticoid hormones stimulate leptin gene expression**

The expression of the \(ob\) gene, encoding leptin, is under multi-hormonal control. Some of the most powerful regulators of leptin expression are glucocorticoid hormones. It has been demonstrated that adrenalectomy results in a significant reduction in leptin gene expression [18]. Accordingly, short-term administration of corticosteroids up-regulates the expression of the leptin gene in rats as well as in humans [18–21], whereas chronic treatment with corticosteroids over 3 weeks does not seem to increase leptin gene expression [18]. A recent report by De Vos et al. [22] demonstrated that glucocorticoids induce the expression of the leptin

**Table 1. Different mice models for studying appetite and obesity**

<table>
<thead>
<tr>
<th>Type of mice</th>
<th>Functional defect</th>
<th>Leptin gene expression</th>
<th>Leptin resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>(ob)/(ob) (type 1)</td>
<td>Twenty-fold increase in leptin mRNA production</td>
<td>Mutation that produces a truncated inactive protein</td>
<td>Not present</td>
</tr>
<tr>
<td>(ob)/(ob) (type 2)</td>
<td>No mature leptin mRNA is synthesized</td>
<td>Mutation that produces no protein</td>
<td>Not present</td>
</tr>
<tr>
<td>(db)/(db)</td>
<td>Lack functional leptin receptor (Jak,STAT)</td>
<td>Up-regulated leptin mRNA</td>
<td>Total resistance</td>
</tr>
<tr>
<td>Zucker fa/fa</td>
<td>Lack functional leptin receptor (dimerization)</td>
<td>Up-regulated leptin mRNA</td>
<td>Very resistant</td>
</tr>
</tbody>
</table>
gene through a non-classical mechanism of transcriptional activation.

**Insulin regulates leptin gene expression**

Another important regulator of leptin gene expression in man is insulin. MacDougald et al. [23] have reported that insulin deficiency, provoked by streptozotocin, markedly down-regulated leptin mRNA. Within 4 h of insulin administration the levels of leptin mRNA in adipose tissue increased by 60% [10,23]. These results have subsequently been confirmed by others [24,25]. Furthermore, Patel et al. [26] have demonstrated that both the decrease in leptin mRNA and plasma leptin during fasting and the increase in feeding depend on changes in the plasma insulin concentration. However, not all studies have found that insulin had a stimulatory effect on ob gene expression and leptin secretion [27], which might be explained by the duration of hyperinsulinaemia in the various studies. Whereas short-term euglycaemic hyperinsulinaemia does not seem to affect leptin levels, long-term (72 h) hyperglycaemic hyperinsulinaemia has been shown to increase ob gene expression [28]. Consequently, in the short term, insulin does not increase leptin secretion in humans, whereas an indirect trophic effect on adipocytes is found in chronic hyperinsulinaemia.

**Cytokines stimulate leptin gene expression**

Depressed appetite and weight loss accompany many chronic wasting disorders such as AIDS, cancer, chronic infections and chronic renal failure. Little is known about the specific mechanism(s) responsible for altered appetite and metabolism in these conditions, although a role for cytokines, such as TNF-\(\alpha\) and IL-1, has been proposed [29]. In this context it is of interest that Kirchgessner et al. [30] have demonstrated that TNF-\(\alpha\) can act directly on the adipocytes to regulate the release of a preformed pool of leptin in mice. Berkowitz et al. [31] have also found that endotoxaemia in a induction of leptin mRNA and that this could be mediated by alterations in TNF-\(\alpha\). Grunfeld et al. [32] likewise found that TNF-\(\alpha\) and IL-1 increased leptin mRNA in hamsters and noted a strong inverse correlation between leptin mRNA and subsequent food intake. Similar results were observed by Sarraf et al. [33], who reported that multiple cytokines and acute inflammation raise mouse leptin levels, and Moshyedi et al. [34] who found increased leptin expression in mice with bacterial peritonitis. Taken together, these findings suggest that elevated leptin levels may be one mechanism by which anorexia is induced during inflammatory conditions in animal models.

In humans, there is also evidence that cytokines stimulate leptin synthesis. In a study of six patients with solid tumours, infusion of TNF-\(\alpha\) caused a 65% increase in serum leptin levels [35] and, in diabetic patients serum levels of TNF-\(\alpha\) have been found to be directly correlated with leptin levels [36]. Moreover, infusion of IL-1 for 5 days has been shown to be associated with increasing serum leptin levels in patients with cancer [37] and in uremic patients, we have observed elevated leptin mRNA levels in those patients who had an inflammatory response [38]. However, not all studies have found an association between inflammation and elevated leptin levels in humans and further studies are needed to clarify whether elevated leptin levels may be one mechanism by which anorexia is induced during inflammatory conditions in humans.

**Localization and role of leptin receptors**

**Leptin receptors in the central nervous system**

The leptin receptor (OB-R), which belongs to the class 1 cytokine receptor family, has been cloned, and to date at least six various alternatively spliced forms of leptin receptor mRNA have been reported [39-41]. The short-length Ob-Ra receptor is present in virtually all tissues examined but it is not known whether this receptor has any functional signalling activity. However, the Ob-Ra receptor is expressed in the choroid plexus and it has been suggested that Ob-Ra may transport leptin across the blood–brain barrier to the cerebrospinal fluid [40]. The full-length variant of the leptin receptor (OB-Rb), which has a 304-amino-acid-long intracellular domain capable of signal transduction, contains interaction sites for Jak kinase and STAT proteins (Jak/STAT pathway), both of which are second messengers for receptor signalling. OB-Rb is expressed at a high level in the hypothalamus and is abnormally spliced in db/db mice which are insensitive to leptin administration. It has been found that the cytoplasmatic region of the receptor which interacts with the Jak/STAT pathway is missing in db/db mice [40,42]. In another type of obese mice, Zucker fa/fa rats, a missense mutation in the rat leptin receptor results in leptin resistance [43]. The functions of the Ob-Re and Ob-Rd receptors are not yet fully understood although it has been speculated that they may transport leptin across the blood–brain barrier, whereas the soluble receptor Ob-Re has been reported to function as a transport protein contributing to binding and activation of circulating leptin [40].

**Leptin receptors in peripheral organs**

While most attention on the biological effects of leptin has been focused on the hypothalamus, the mRNA of
several leptin receptor isoforms has been found in some non-neuronal tissues such as the pancreas, kidney, liver and in reproductive and haematopoietic organs [41,45–47]. It is important to point out that the full-length receptor splice variant (Ob-Rb) has not been found in all these tissues. However, the kidney has been shown to express mRNA for the full-length Ob-Rb receptor, which suggests that leptin may exert functional effects on this organ. The findings of leptin receptors in several peripheral organs might indicate that leptin is involved in pathways other than energy metabolism and, as a true pleiotropic hormone, could mediate a variety of peripheral actions.

**Action of leptin on the central nervous system**

**Appetite-inhibiting effects of recombinant leptin in ob/ob mice**

Several studies have shown that recombinant leptin purified from *Escherichia coli* can correct the obesity-related phenotypes in ob/ob mice when administered exogenously [48–50]. Friedman and colleagues [48] demonstrated that as early as four days after daily injection with recombinant leptin, morbibly obese ob/ob mice consumed 60% less food than untreated ob/ob mice and their physical activity increased. No obvious side-effects of leptin administration were observed and the metabolic control improved considerably during this period. Leptin appears to produce its effects on body fat stores via a number of hypothalamic mediators. Using radiolabelling, it has recently become possible to localize the binding sites for leptin in the hypothalamus [51]. The most interesting candidate is Neuropeptide Y (NPY), which is the most potent appetite stimulant described to date. NPY has also been implicated in the control of energy balance and is overproduced in the hypothalamus of ob/ob mice. Erickson et al. [52] have demonstrated, that in the absence of NPY, ob/ob mice are less obese because of reduced food intake and increased energy expenditure, suggesting that NPY is a central effector of leptin deficiency. In accordance with this finding, Schwartz et al. [53] demonstrated that the injection of leptin intracerebroventricularly decreased the levels of mRNA for NPY in the arcuate nucleus. In addition, leptin increased the levels of mRNA for an inhibitor of food intake (corticotrophin releasing hormone) in the paraventricular nucleus [53]. It has also been reported that leptin stimulates the melanocortins [54], which also might affect eating behaviour. Brain serotonin systems have also been strongly implicated in the neural regulation of appetite and it is possible that leptin and serotonin receptors might interact in the regulation of feeding and body weight. Recently, Nonogaki et al. [55] found that mice with a targeted mutation of the serotonin 5-HT$_{2c}$-receptor consumed more food, despite normal responses to exogenous leptin administration suggesting that serotonin and leptin signalling pathways might interact to regulate feeding and energy expenditure. The importance of leptin in regulating appetite in man is not yet elucidated. However, it has been demonstrated that relatively low leptin levels precede weight gain in Pima Indians [56], and this suggests a pivotal role of leptin in the regulation of energy balance in humans also. Recent evidence suggests that leptin is more important in the regulation of energy balance as a long-term adiposity-related signal rather than a short-term meal-related factor [57]. Moreover, it has been proposed that cholecystokinin, which is a short-term meal-related satiety signal, may act synergistically with leptin to control long-term feeding [58]. Taken together, available data suggest that leptin acts as an important modulator of appetite via a number of hypothalamic mediators.

**Abnormal leptin transport across the blood–brain barrier in obesity**

Despite a strong correlation between leptin and body fat content, a great interindividual variation in circulating levels both in normal-weight and obese subjects has been observed [59,60]. Leptin is too large (16 kDa) to readily penetrate the blood–brain barrier by passive diffusion. Entry of leptin into the cerebrospinal fluid appears to occur via a specific saturable and temperature-dependent transport mechanism [61]. It is of interest that a decreased efficiency of leptin transport across the blood–brain barrier has been reported in obese patients which indicates resistance to the actions of leptin [62,63]. Accordingly, the hypothalamus of obese subjects is not exposed to abnormally elevated leptin concentrations as a result of a blunted transport across the blood–brain barrier. Consequently the subject continues to eat. Most probably, the resistance to leptin is only partial and in a diet-induced obesity model, mice exhibit resistance to peripherally administered leptin, while retaining sensitivity to centrally administered leptin [64]. Obese subjects with moderate leptin deficiency could be excellent candidates for leptin therapy as a treatment for weight reduction and ongoing trials will demonstrate whether peripheral administration of leptin will cause weight reduction in man.

**Bound and free leptin in the circulation**

Another factor that might affect the availability of leptin in the hypothalamus is protein binding. In lean rodents and humans a high percentage (60–98%) of leptin circulates bound to several serum proteins, whereas free leptin is increased in the serum of obese subjects [65]. Thus, increased levels of free leptin, which presumably is the biologically active form, suggests that an even greater leptin resistance occurs in obesity than could be anticipated by simply measuring total circulating leptin levels. Moreover, the fact that almost all leptin circulates bound to proteins in lean subjects has been thought to reduce the bioavailability of leptin to hypothalamic leptin receptors and thus reduce leptin effects on food intake and energy meta-
bolism. At present, available data suggest that increased leptin levels in end-stage renal disease (ESRD) are not due to the accumulation of leptin degradation products [66,67], but more studies are needed to confirm these findings. Alterations in protein binding might alter leptin bioactivity, transport and/or clearance and could be an important mechanism to change the availability of leptin to hypothalamic leptin receptors.

**Does leptin contribute to anorexia in uraemia?**

Uraemia is a wasting syndrome characterized by inadequate food intake and malnutrition. If we could understand the mechanism(s) causing anorexia in uraemia it would be possible to develop methods to prevent and ameliorate these symptoms. The pathophysiologic significance of the elevated circulating leptin levels in uraemia is not clear, but it seems possible that hyperleptinaemia may affect several metabolic processes if leptin receptors are not down-regulated. However, for leptin to suppress appetite in uraemic patients, we have to assume that (i) leptin is present mostly in its unbound bioactive form, (ii) that there are no defects in leptin receptor or post-receptor signalling and (iii) that transport of leptin across the uraemic blood–brain barrier is normal. To the best of our knowledge these issues have not been studied in uraemic patients. Although no direct evidence is available that increased levels of leptin cause anorexia and no longitudinal studies have been conducted, some indirect evidence from cross-sectional studies suggests that leptin may mediate anorexia in uraemic patients. First, a significant negative relation between the serum leptin has angiogenic activity both in vitro and in vivo. Recent results presented by Sierra-Honigmann et al. [76] demonstrated that leptin has angiogenic activity both in vitro and in vivo. By providing a local angiogenic signal, leptin might improve the efficiency of lipid release from fat stores to maintain energy homeostasis [76]. Elevated energy expenditure has been found in haemodialysis patients [77] and more studies are needed to determine whether increased leptin levels can contribute to a negative energy balance in uraemia.

**Peripheral actions of leptin**

**Leptin inhibits pancreatic insulin secretion**

Leptin receptor isoforms have now been reported in several peripheral organs and it may be conjectured that leptin, besides having central effects, may also have multiple peripheral effects as discussed below (Table 3). A variant of the Ob-R receptor has been reported in human hepatic cells by Cohen et al. [46] who demonstrated that if hepatic cells were exposed to leptin in vitro, at concentrations comparable with those present in obese patients, several insulin-induced activities, such as tyrosine phosphorylation of the insulin receptor substrate-1 and down-regulation of gluconeogenesis, were attenuated. This study was the first to suggest that leptin might modulate insulin activities. Shortly afterwards, Emberlin et al. [44] mice were given equal amounts of a low-calorie diet, the leptin-treated mice lost more weight, which strongly supports an additional role of leptin energy expenditure [49]. The mechanism of increased energy expenditure appears to involve increased thermogenesis in brown adipose tissue [71], as well as increased sympathetic nerve activity and norepinephrine turnover in brown adipose tissue [72]. The key element in brown adipose tissue is the unique expression of a mitochondrial transport protein called uncoupling protein-1 (UCP-1) which is under strict transcriptional control. UCP-1 is a proton carrier that, upon activation, causes the uncoupling of respiration from oxidative phosphorylation, which results in the generation of heat without driving ATP synthesis. The UCP-1 gene induction in brown adipose tissue is mediated largely by the sympathetic activation of β3-adrenergic receptors [73]. However, it was recently found that leptin infusion increased energy expenditure is through increased UCP-2 and UCP-3 expression in white adipose tissue [74]. Another member of the UCP family, UCP-3, has recently been identified and characterized in skeletal muscle and was shown to be up-regulated by leptin infusion in ob/ob mice [75]. Taken together, these recent data suggest that one mechanism by which leptin may increase energy expenditure is by a local stimulatory effect on angiogenesis. Recent results presented by Sierra-Honigmann et al. [76] demonstrated that leptin has angiogenic activity both in vitro and in vivo. By providing a local angiogenic signal, leptin might improve the efficiency of lipid release from fat stores to maintain energy homeostasis [76]. Elevated energy expenditure has been found in haemodialysis patients [77] and more studies are needed to determine whether increased leptin levels can contribute to a negative energy balance in uraemia.

**Leptin increases energy expenditure**

In addition to its effects on appetite, leptin increases energy expenditure and this may be an additional mechanism by which leptin regulates body weight [48,49,71]. When both leptin-treated and untreated ob mice were given equal amounts of a low-calorie diet, the leptin-treated mice lost more weight, which strongly supports an additional role of leptin energy expenditure [49]. The mechanism of increased energy expenditure appears to involve increased thermogenesis in brown adipose tissue [71], as well as increased sympathetic nerve activity and norepinephrine turnover in brown adipose tissue [72]. The key element in brown adipose tissue is the unique expression of a mitochondrial transport protein called uncoupling protein-1 (UCP-1) which is under strict transcriptional control. UCP-1 is a proton carrier that, upon activation, causes the uncoupling of respiration from oxidative phosphorylation, which results in the generation of heat without driving ATP synthesis. The UCP-1 gene induction in brown adipose tissue is mediated largely by the sympathetic activation of β3-adrenergic receptors [73]. However, it was recently found that leptin infusion increased energy expenditure is through increased UCP-2 and UCP-3 expression in white adipose tissue and skeletal muscle, as well as an increased sympathetic activation of UCP-1 gene expression in brown adipose tissue. Another intriguing mechanism by which leptin may increase energy expenditure is by a local stimulatory effect on angiogenesis. Recent results presented by Sierra-Honigmann et al. [76] demonstrated that leptin has angiogenic activity both in vitro and in vivo. By providing a local angiogenic signal, leptin might improve the efficiency of lipid release from fat stores to maintain energy homeostasis [76]. Elevated energy expenditure has been found in haemodialysis patients [77] and more studies are needed to determine whether increased leptin levels can contribute to a negative energy balance in uraemia.

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reported that leptin receptors are also present in the pancreas and that leptin, in a dose-dependent manner, inhibits pancreatic insulin secretion in hyperinsulinaemic ob/ob mice. Mouse leptin has also been shown to inhibit insulin mRNA expression in cultured cells and rat islets [78] and Chen et al. [79] have found that leptin impairs acetylcholine-induced insulin secretion from pancreatic islets of ob/ob mice. These findings suggest that leptin has a powerful acute inhibitory effect on pancreatic insulin secretion. Accordingly, when the level of circulating serum leptin is elevated markedly in relation to the per cent fat mass, fasting plasma insulin levels do not continue to rise as suggested by studies in uraemic patients [80]. This finding implies that markedly elevated serum leptin levels impair the pancreatic insulin secretion and that marked hyperleptinaemia could be a factor contributing to impaired glucose tolerance in ESRD.

Effects of leptin on diuresis and natriuresis

The kidney has been shown to express the full-length leptin receptor [45]. An acute infusion of leptin in high doses in rats increases diuresis and natriuresis, without significantly affecting renal blood flow and the glomerular filtration rate [81]. The maximum increase in sodium excretion was approximately threefold and it was confined to the infused kidney suggesting a direct tubular effect of leptin [81]. Reams et al. [82] have confirmed these results, and found an increase in sodium excretion of ~400% and a 50% increase in urine volume following intravenous administration of leptin. This group also noted a blunted natriuretic effect of leptin in spontaneously hypertensive rats. This observation suggests the existence of peripheral tubular leptin resistance in this particular type of mice [82]. More studies are needed to confirm these findings. It can be speculated that some of the peripheral actions of leptin, such as diuresis and natriuresis, act as compensatory mechanisms against the potentially deleterious effects of an increased body fat mass.

Leptin stimulates the sympathetic nervous system

It has been demonstrated that an intracerebroventricular injection of leptin increases the activity of the sympathetic nervous system and reduces the arterial blood flow to skeletal muscle [83]. Moreover, chronic elevation of leptin levels in the central nervous system increases heart rate and blood pressure in rats. This finding could indicate that leptin plays a role in hypertension of obesity [84]. Indeed, in obese, spontaneously hypertensive rats ob gene expression has been shown to be markedly augmented [85] and high leptin levels have been found in patients with essential hypertension [86]. If obese and uraemic patients with hyperleptinaemia are resistant to insulin sensitivity and sodium excretion by leptin, but not resistant to stimulation of sympathetic activity by leptin, one could possibly explain why sodium-sensitive hypertension and insulin resistance occur so often in obesity and uraemia. In any case, leptin has multiple actions that are potentially relevant to cardiovascular regulation.

Leptin stimulates angiogenesis and haematopoiesis

Recent evidence suggests that in normal rats leptin is an angiogenic factor, i.e. it promotes blood-vessel growth [76]. This novel observation could mean that leptin acts as an important functional link between adipocytes and the vasculature to drive the blood vessel to match the fat mass [76]. The leptin–angiogenesis relation also raises the question whether cancers use leptin to recruit blood vessels [87]. However, whether increased leptin levels might contribute to the documented higher incidence of cancer in obese patients remains to be proven.

Many cytokines exert their biological effect through members of the haemopoietin receptor family and recent research suggests that leptin may also be able to regulate various aspects of haematopoiesis and macrophage function. Cioffi et al. [41] were first to report that the leptin receptor (OB-R/B219) is expressed in CD34-positive haematopoietic stem cells. Shortly afterwards Gainsford et al. [47] reported that the long and short forms of the leptin receptor were co-expressed in haematopoietic populations, but only the long form could signal proliferation or differentiation, when expressed in haematopoietic cell lines. Moreover, recent in vitro studies have suggested that leptin can induce proliferation and differentiation of haematopoietic stem cells [47,88,89] and there might be synergism between leptin and erythropoietin (rHuEPO) [47]. Leptin has also been found to activate the function of mature macrophages [47]. Adipocytes participate in the bone-marrow microenvironment, but their exact role has not yet been determined. It is of interest that in a primary culture model Laharrague et al. [90] found high expression of leptin by human bone-marrow adipocytes. This finding suggests that bone-marrow adipocytes contribute to haematopoiesis via the secretion of leptin in the vicinity of haematopo-
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Whether these findings have clinical implications is not yet clear. Nevertheless, it has been suggested that leptin plays a role in leukaemic cell proliferation in the bone marrow [91]. Moreover, a negative relation between serum leptin levels and the weekly dose of rhHuEPO has been described in pre-dialysis patients [92]. Consequently, it is possible that in uraemia haematopoietic factors other than rhHuEPO, such as leptin, are important in stimulating erythropoiesis.

Causes of hyperleptinaemia in uraemia

Impact of reduced renal function

Soon after leptin became measurable in humans, several studies found that uraemic patients, with or without dialysis treatment, had elevated serum leptin levels which were clearly out of proportion to their body fat mass [14,66–69,93]. As the kidneys are important for clearing various other polypeptide hormones such as insulin, parathyroid hormone and glucagon, it is reasonable to predict that leptin also accumulates in renal failure. Indeed, the kidney has been shown to be the principal site of elimination of circulating leptin in healthy subjects [93]. Urinary leptin levels are usually below the detection of the assay. In rats, bilateral nephrectomy reduces plasma leptin clearance by 80% [94]. Recent in vivo studies in rats show that uptake and degradation of leptin by renal tissue, rather than glomerular filtration, is the main mechanism of elimination [95,96]. The important role of the kidney in leptin metabolism is further underscored by the fact that renal transplantation normalizes leptin levels in humans [97]. However, not all patients with ESRD have elevated leptin levels [66,80,98] and one must bear in mind that some patients (especially males with low BMI and low plasma insulin levels) have normal or even low leptin levels. One can therefore assume that in at least some patients with ESRD other tissues become more active in leptin removal from plasma. Indeed, data presented by Garibotti et al. [99] show that non-renal tissues, i.e. splanchnic organs, contribute substantially to the removal of leptin. It is therefore possible that increased leptin removal by non-renal tissues occurs in uraemia, but to the best of our knowledge this has not yet been documented. It is also possible that, by an efflerent feedback mechanism, elevated leptin levels in ESRD may decrease adipocyte leptin synthesis. Nordfors et al. [38] recently found lower ob gene expression in uraemic patients than in controls. The authors speculated that elevated leptin levels, resulting from decreased renal clearance, downregulate the expression of the ob gene. In uraemia, plasma leptin concentrations are apparently affected by: (i) decreased removal in the kidney and (ii) feedback inhibition of leptin production by adipose tissue. The latter mechanism might explain why normal leptin levels are observed in some ESRD patients.

Other factors that might affect leptin in uraemia

Other factors that stimulate leptin mRNA expression in non-uraemic subjects, e.g. increased body fat mass and hyperinsulinaemia, may also stimulate leptin mRNA in uraemic patients. Indeed, leptin, insulin concentrations and body weight are interrelated, and a direct correlation between insulin and leptin levels has been reported in uraemic patients [80,100]. We have found that uraemic patients with high serum leptin levels could be separated from those with normal leptin levels on the basis of their fasting plasma insulin, suggesting that insulin is a powerful modulator of leptin levels in ESRD [80]. In this context it is of interest that administration of hormones, such as growth hormone and IGF-1, can modify serum leptin levels in uraemic patients, suggesting that the metabolic regulation of leptin is conserved in this patient group [98]. Another possible reason for elevated leptin levels in uraemia is chronic inflammation, since elevated cytokine production is a common feature in these patients [101]. Indeed, Nordfors et al. [38] found that uraemic patients with elevated CRP levels have a higher expression of leptin mRNA than patients with little or no elevation in CRP.

Conclusion

The discovery of the ob gene, its product leptin and cerebral leptin receptors has undoubtedly widened our understanding of obesity and the underlying molecular and physiological mechanisms that regulate food intake and body weight. Moreover, the recent discovery of leptin receptor isoforms in several peripheral organs suggest that leptin, besides having a central function, also has several important peripheral biological functions. In general inappropriate elevation of circulatory leptin is found in uraemic patients. Further research is necessary to determine the potential biological effects of elevated leptin levels in ESRD.

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