How does leptin contribute to uraemic cachexia?

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Malnutrition (wasting or cachexia) is frequently observed in uraemic patients, both in the predialysis phase and during renal replacement therapy [1,2]. According to the DOPPS, every 4th to 5th dialysis patient suffers from moderate or severe malnutrition [3]. It was also found that dietary energy and protein intakes are inadequate in the majority of haemodialysis patients [4]. For many years, it has been known that wasting or cachexia is an important predictor of morbidity and mortality due to cardiovascular and infectious diseases among uraemic patients [5]. However, the pathophysiology of wasting in these patients is very complex and not entirely known [6]. Several factors contribute to protein–energy malnutrition in patients with end-stage renal disease (ESRD) including: metabolic acidosis, chronic inflammation, low protein diet, resistance to anabolic hormones and anorexia [7]. The discovery of leptin immediately stimulated several additional areas of investigation [8]. These later studies stressed that adipose tissue is an active and important source of several hormones and proinflammatory cytokines [9]. They also increased interest in appetite regulation and the role of anorexia in the common phenomenon of wasting in uraemia [7].

Leptin is a protein hormone, predominantly produced by adipocytes and presumed to be involved in the maintenance of stable body mass [10]. High levels of leptin inhibit food intake and increase energy expenditure through several complicated pathways [10,11]. Low leptin levels stimulate appetite and suppress energy expenditure, thereby increasing fat accumulation, which in consequence raises plasma leptin concentrations again.

In recent years, some of the pathways involved in the regulation of appetite have been identified in detail. For non-specialists, it is important to stress that leptin, and to a certain extent insulin, exert their biological actions through increased activity of MC4-Rs (melanocortin receptors 4) located in the hypothalamus (paraventricular region), which suppresses AMPK (AMP-activated protein kinase). MC4-Rs activity is increased directly by suppression of such hormones which improve appetite and decrease energy expenditure like NPY (neuropeptide Y) and AGRP (Agouti Related Peptide) or indirectly through activation of POMC (pro-opiomelanocortin), which induces neurons to release α-MSH (α-melanocyte-stimulating hormone), i.e. a stimulator of MC4-Rs. High levels of leptin and insulin and most probably also certain uraemic metabolites can activate both of the above pathways [11]. For example, chronic treatment with AGRP increases food intake, body fat mass and plasma leptin concentration [12]. The same observations were made in cachexia induced by cancer, which was both reversed and prevented by the administration of AGRP [13].

The above data has been extended by a recent elegant and comprehensive study by Cheung et al. [14], who tested the hypothesis that cachexia associated with uraemia is caused by leptin signalling through the hypothalamic MC4-Rs. They found that uraemia-associated cachexia is attenuated in leptin receptor-deficient (db/db) mice and in MC4-Rs knockout mice. Pharmacological blockade of the MC4-Rs with AGRP obtained the same results. In their study, they also found that gene expression of ubiquitin C and proteasome subunits C2, C3 and C9 was not changed in uraemic mice. The ATP-dependent ubiquitin–proteasome pathway is involved in protein muscle degradation [15]. In acidotic rats with cancer-induced cachexia, an increase in skeletal muscle proteolysis was associated with the increase in gene expression for ubiquitin and proteasome subunits [16]. The authors interpret these results as showing that hypothalamic MC4-Rs, a central signalling system for cytokines such as leptin, play an important role in the pathogenesis of uraemic cachexia. As uraemia is characterized by significant elevations of plasma leptin concentration, the results of Cheung et al. [14] seem to clarify very elegantly the pathogenesis of anorexia and wasting in uraemic cachexia.
patients. This increases the hope for new drugs that affect MC4-Rs at the hypothalamic level and which thereby might exert a beneficial effect on uraemia-related cachexia.

There are, however, some pieces of evidence that complicate the above interpretation of Cheung's data. If the concept of Cheung et al. [14] is entirely true, then high plasma leptin concentrations should result not only in cachexia, but also in a decrease of fat mass. There are, however, several studies in the literature showing the opposite, namely that the plasma leptin concentration correlates positively with total fat mass in uraemic patients [17,18]. It has also been shown that haemodialysis patients with low body mass index are characterized by lower serum leptin concentration [19]. In addition, high caloric supplementation increases body fat mass and median serum leptin concentration [20].

Several studies have documented the fact that hyperleptinaemia in dialysis patients reflects a better nutritional status rather than cachexia. This statement is based on strong positive relationships between serum leptin concentration, body composition and gender (higher in females). Up to now, only a few studies have been performed concerning the leptin receptors’ number or function in uraemia. However, it has been demonstrated that despite markedly elevated serum leptin levels in these patients, soluble leptin receptors did not differ from healthy subjects [21].

These results suggest that although leptin gene expression is suppressed in uraemia [22] and that hyperleptinaemia is mainly due to decreased leptin clearance by the failure kidneys [23–25], the amount of fat mass actively participates in the final plasma leptin concentration. Elevated serum leptin concentrations in patients with chronic renal failure are a result of both decreased biodegradation and elimination by the kidneys and production by the adipose tissue (still proportional to the fat mass!). Elevated serum leptin via the negative feedback decreases leptin gene expression in adipocytes. This fact, however, does not exclude the possibility that with greater fat mass more leptin is produced and that such stimuli like TNF-α or IL-1, which indicate the inflammatory response, can increase the leptin gene expression in patients with chronic renal failure. Finally, there is data suggesting that increased plasma leptin concentrations in uraemia are related to the degree of inflammatory processes frequently observed in these patients [26]. These results may suggest that a high plasma leptin concentration does not fulfil all criteria of a new uraemic toxin, as already proposed by the EUTox group [27], but is rather a marker of better nutrition. This resembles the situation in obese individuals (especially females) who are characterized by high plasma leptin concentrations. However, even a markedly elevated plasma leptin concentration does not suppress the appetite in these individuals. It is well known that uraemia is characterized by a relative resistance to many hormones and cytokines. Therefore, for their biological action, significantly elevated plasma concentrations are mandatory. This is true for example for such hormones as parathyroid [28], growth hormone [29], insulin [30] and many others. This is probably true also for leptin. Following the concept of Cheung et al. [14], elevated plasma leptin concentration should predict changes in BMI (or better total fat mass) in the future. However, according to our own results, patients with chronic uraemia gain or lose body weight (and fat mass or lean mass assessed by the DEXA method) during the 12 months of initial haemodialysis therapy independently of their plasma leptin concentration [18]. Again, however, a significant relationship was found between changes of total fat mass and changes in plasma leptin concentration. Interestingly, plasma CRP concentrations decreased in the group of patients who gained total lean mass 12 months after the start of haemodialysis therapy [18]. These results, which are in agreement with other studies, stress the impact of chronic inflammatory processes on the nutritional status of these patients [31].

It was also found that treatment with recombinant human erythropoietin is followed by a significant decrease of plasma leptin concentration [17]. However, during 12 months of clinical follow-up, there was no change of BMI (unfortunately, fat mass and lean mass were not assessed in this study). This is an additional argument suggesting that plasma leptin concentration does not reflect the ability of these patients to gain or lose their body weight. Therefore, the answer to the question as to whether leptin is the culprit in anorexia and cachexia in renal failure [32], remains unanswered and a new pharmacological intervention in this devastating complication of uraemia seems a distant hope! According to the concept of the Stenvinkel group [31], it is probably only complex management, including life-style modification and treatment with targeted anticytokine drugs (thalidomide, pentoxifylline, etanercept, infliximab etc.) that will be useful in patients with ESRD. However, some initial anti-TNF trials were prematurely stopped because of increased mortality. Therefore, the influence of this kind of therapy on complications of ESRD such as wasting, needs further evaluation.


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References

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