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EDITORIAL

Uremic hyperleptinemia: Adaptive or maladaptive?

Interest in the regulation of body weight and pathophysiology of obesity has been rekindled by the cloning of the obese (*OB* or *LEP*) gene and identification of its protein product leptin (Greek *leptos,* thin) [1]. The *LEP* gene is expressed exclusively in fat cells, which remain the only known source of the hormone leptin. Administration of recombinant leptin elicits impressive biological effects in mice. These include inhibition of food intake, stimulation of energy expenditure, reversal of obesity, amelioration of insulin resistance, and acceleration of sexual maturation. Human fat cells synthesize and secrete leptin into the circulation, and emerging data indicate that leptin is a regulated hormone that may be involved in as yet uncharacterized aspects of human metabolism. Physiological factors associated with increased leptin secretion in humans include female gender, weight gain, puberty, and overfeeding; those associated with hypoleptinemia include fasting, strenuous exercise, menopause, and senescence. The hormonal and metabolic factors that regulate leptin are incompletely understood: Plasma leptin levels increase by ~40% following prolonged insulin infusion [2], and by ~100% within 48 hours of oral dexamethasone treatment [3].

Soon after leptin became measurable in humans, it was discovered that many patients with end-stage renal disease (ESRD) were hyperleptinemic, compared with healthy control subjects [4, 5]. Possible mechanisms for hyperleptinemia in ESRD patients include impaired clearance [5] and/or increased synthesis. Using arteriovenous differences, net renal extraction has been estimated at ~12% of circulating leptin in persons with normal kidneys, and ~0% in patients with renal failure [5]. Nonetheless, 25% of ESRD patients [especially those with a body mass index (BMI) less than 24 kg/m^2] maintain normal plasma leptin levels [6]. It is unclear how leptin is eliminated in these patients, but the ubiquity of leptin receptors suggests that receptor-mediated disposal could occur in nonrenal tissues. Thus, impaired renal elimination accounts for some but not all of the elevation in plasma leptin that is observed in ESRD; increased leptin synthesis (probably stimulated by certain hormones that accumulate in renal failure) is a possibility that awaits exploration. The relatively greater magnitude of hyperleptinemia that has been reported in patients treated by continuous ambulatory peritoneal dialysis (CAPD) [6] suggests that peritoneal dialysis may be less efficient in clearing leptin, or associated with a greater stimulation of leptin synthesis, than is hemodialysis.

The pathophysiologic significance of circulating leptin levels in ESRD patients is unclear. Conceivably, chronic elevation of serum leptin could affect metabolic processes, including appetite and nutritional status, if leptin receptors are not down-regulated. In this issue of *Kidney International,* Dr. Fouque and colleagues determined the acute effects of s.c. administration of recombinant human insulin-like growth factor-I (IGF-I) with or without recombinant human growth hormone (GH) on serum immunoreactive leptin concentration in 8 lean patients with ESRD maintained on chronic hemodialysis [7]. During IGF-I treatment, significant decreases were observed in serum insulin and leptin (but surprisingly not GH) concentrations. Combined treatment with IGF-I and GH increased serum concentrations of insulin, GH, and leptin fivefold, sixfold, and twofold, respectively. These results, if confirmed in a larger study, would add appreciably to our understanding of hormonal regulation of human leptin, albeit, among renal-impaired persons. Regression analyses showed a relationship between serum leptin and insulin (but not GH or IGF-I) concentrations, which led the authors to suggest a central role for insulin in explaining their main findings [7]. However, direct effects of IGF-I or GH on adipocyte leptin synthesis have not been excluded, since leptin mRNA levels were not reported.

The mean serum leptin concentration of the 8 ESRD patients studied by Fouque et al [7] was similar to that of healthy controls, most probably because of the small sample size and low BMI of these patients. However, the overall mean serum leptin in the authors' ESRD population was much higher than that of healthy subjects [7], consistent with numerous other reports [4–6]. The significance of uremic hyperleptinemia is unknown. The relationship between serum leptin and nutritional status in patients with ESRD has not been tested directly in longitudinal studies, but cross-sectional reports have showed no association with recent weight change, serum albumin, or protein catabolic rate [4, 6]. Obviously, further studies are needed to delineate the pathophysiologic significance and wider ramifications of circulating leptin levels in renal failure, especially in light of the high mortality associated with ESRD [8]. If future studies characterize leptin metabolism in ESRD as maladaptive, then interventions to prevent or reduce leptin accumulation would be desirable. Based on emerging information, interventions that can potentially

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normalize leptin levels in ESRD patients include control of body weight [6], use of high flux dialyzers [9], and renal transplantation [10]. The present report by Fouque et al identifies recombinant human IGF-I as another agent for correction of uremic hyperleptinemia [7], should studies establish a compelling rationale for so doing.

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