A balancing act: protein-energy wasting in chronic kidney disease

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Protein energy wasting and its extreme form, cachexia, is common among patients with chronic kidney disease (CKD). This maladaptive metabolic state is fueled by inflammation and is characterized by anorexia, increased energy expenditure, inefficient utilization of nutrients, and augmented protein catabolism leading to loss of lean body mass. At the core of the regulation of energy balance is the complex and tightly regulated system of proopiomelanocortin (POMC) neurons, a panel of endogenous neuropeptides, and their receptors as described in Fig. 1. Peripheral signals regarding energy stores are received and processed by two distinct subtypes of neurons with opposing actions that are located in the arcuate nucleus (ARC) of the hypothalamus. One group of arcuate neurons express POMC, which is cleaved into biologically active peptides including melanocortins, which act through a family of melanocortin receptors (MC1R through MC5R) in mediating anorectic and catabolic responses. The second group of neurons expresses the orexigenic peptide neuropeptide Y (NPY) and agouti-related peptide (AgRP), an endogenous antagonist of MC3R and MC4R. Thus the gain and loss of body weight are determined by the balance between these two opposing regulatory systems.

It appears that the adaptive metabolic, immune, and behavioral response to maintain protein-energy homeostasis during acute disease processes goes awry in chronic disease states such as CKD. Chronic unregulated systemic inflammation seems to be central to this dysregulated response. Besides promoting muscle protein breakdown, cytokines also act on neural circuits in the hypothalamus and the brainstem and modulate energy homeostasis, hormone secretion, and autonomic function. Preliminary evidence indicates that hypothalamic sensitivity to the actions of melanocortins is accentuated in the presence of inflammation (6). Recently, activation of nuclear factor-κB (NF-κB) in hypothalamic POMC neurons was shown to be an important molecular mechanism for infection-associated cachexia (7). Given the elevated circulating level of endotoxin in patients with kidney disease (8), it is tempting to speculate that this could be a potential mechanism for the persistent anorexigenic/cachexic activity of the central melanocortin system observed in uremic cachexia.

The gain and loss of body weight, however, are only partly explained by the anorectic/orexigenic effects resulting from the interactions of α-melanocortin-stimulating hormone and AgRP/NPY. Muscle wasting in CKD could also be due to increased muscle proteolysis and decreased myogenesis. Breakdown of muscle occurs when the ubiquitin proteasome system is activated through E3 ligases, which can be controlled by forkhead transcription factors (FoxOs). Blocking FoxO1...
can prevent loss of muscle mass, as shown through knockout mouse models and microRNA-486 inhibition (10). Blocking muscle regeneration pathways can also cause muscle wasting, as shown in knockout CXCL-16 mice (11). This is an essential chemokine that promotes muscle regeneration by recruitment of macrophages. The balance of expression of other molecules, mainly myostatin and insulin-like growth factors (IGF-I), also affects muscle mass (9). Myostatin regulates the skeletal muscle mass, with higher expression associated with decrease in muscle mass through activation of proteolysis. Besides the direct effect of proinflammatory cytokines in mediating proteolysis and apoptosis (1), inflammatory cytokines, such as IL-6, activate the NF-κB pathway, which disrupts the balance between myostatin and IGF-I and leads to muscle wasting.

Treatment of uremic cachexia with nutrient supplementation and anti-inflammatory therapy has largely been disappointing. In an interesting series of elegant experiments, Mak and colleagues (2, 3) illustrated that genetic and pharmacologic blockage of leptin’s effects on MC4R in CKD mice attenuated the effects of CKD cachexia by decreasing energy expenditure and causing accumulation of lean body mass and fat mass. A study published in an issue of the American Journal of Physiology-Renal Physiology greatly increases our knowledge regarding how blocking the melanocortin pathway increases muscle mass and its effects on inflammatory and muscle signaling pathways that lead to wasting (4). The authors show that AgRP antagonism of MC4R alters the expression and protein levels of important molecules in inflammation and muscle signaling pathways, illustrating that the actions of AgRP extend far beyond their central nervous system functions. This is not surprising, considering the almost ubiquitous distribution of melanocortin peptides and their receptors across the body. AgRP administration to CKD mice normalized protein levels of IL-6, TNF-α, and monocyte chemotactic protein-1 when compared with untreated CKD mice. Abnormal gene expression levels also improved in signaling pathways involved in muscle mass turnover, such as IGF-I and myostatin, as well as for the proinflammatory cytokines IL-6 and TNF-α in CKD mice treated with AgRP, when compared with nontreated CKD mice (Fig. 1) (4). However, not all protein or mRNA levels for genes in muscle maintenance pathways and inflammation returned to completely normal levels, suggesting that AgRP does not completely ameliorate muscle wasting in CKD. This indicates that other mechanisms that induce cachexia in CKD need to be identified and targeted.

Although these results do increase our knowledge regarding how energy homeostasis pathways contribute to muscle wasting, there are several caveats to translating these results to humans. Mice were treated with AgRP intracerebroventricularly, which is not an ideal treatment for humans with CKD. Cheung et al. (3) also tested the use of intraperitoneal administration of NBI-12i, a MC4R antagonist, in uremic mice. This treatment resulted in an increased food intake and weight gain, as well as caused uremic mice to have a lower basal metabolic rate and to gain lean body mass and fat mass. Reversal of cachexia with NBI-12i, however, was not associated with change in plasma IL-6 levels, suggesting that the effect is not mediated by inflammation but through MC4R (3). In another study, Dallmann et al. (5) illustrated that the orally active MC4R antagonist BL-6020/979 increased food intake and decreased energy expenditure in normal mice as well as improved cachexia-like symptoms in the murine C26 adenocarcinoma model.

While considerable advances have been made in our understanding of the pathogenesis of uremic cachexia, it is obvious that it is far from complete. Nevertheless, as the underlying molecular mechanism, hormonal regulation, and neural signaling pathways are being unveiled, newer and novel therapeutic options may be available that could be translated into clinical practice. We can only cautiously hope that treatments based on selective targeting of melanocortin receptors could be one such treatment option, which could improve the debilitating consequences of uremic cachexia.

DISCLOSURES
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