Cachexia in chronic kidney disease: a link to defective central nervous system control of appetite

William E. Mitch

Commentary

Anorexia is one of several abnormalities characterizing chronic kidney disease (CKD) that cause cachexia, the loss of muscle and adipose stores. It has been attributed to mechanisms ranging from accumulation of toxic "middle molecules" to psychological problems. In this issue of the *JCI*, Cheung and coworkers used elegant techniques to demonstrate that CKD-associated anorexia is caused by defective hypothalamic regulation of appetite. They attributed the defect to an alteration in the hypothalamus's response to leptin and inflammation. Since similar hypothalamic defects suppress appetite in inflammatory states and in cancer, it is possible that anorexia in several cachexia-inducing conditions results from a common set of hypothalamic abnormalities. The development of small molecules capable of preventing these regulatory abnormalities holds the promise of eliminating the contribution of anorexia to the development of cachexia.

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Anorexia is one of several abnormalities characterizing chronic kidney disease (CKD) that cause cachexia, the loss of muscle and adipose stores. It has been attributed to mechanisms ranging from accumulation of toxic "middle molecules" to psychological problems. In this issue of the *JCI*, Cheung and coworkers used elegant techniques to demonstrate that CKD-associated anorexia is caused by defective hypothalamic regulation of appetite (see the related article beginning on page 1659). They attributed the defect to an alteration in the hypothalamus's response to leptin and inflammation. Since similar hypothalamic defects suppress appetite in inflammatory states and in cancer, it is possible that anorexia in several cachexia-inducing conditions results from a common set of hypothalamic abnormalities. The development of small molecules capable of preventing these regulatory abnormalities holds the promise of eliminating the contribution of anorexia to the development of cachexia.

The explosion of information emerging from several fields, including molecular and cellular biology and neuroscience, has helped elucidate specific mechanisms that regulate appetite. A major impetus for investigating why we eat is the increasing prevalence of obesity. However, there is a flip side: we also need to understand how catabolic conditions cause anorexia, which can contribute to cachexia — the loss of fat and protein stores. In chronic kidney disease (CKD) there is evidence that the intake of calories, including protein, decreases as renal insufficiency advances (1). Although this is one reason for weight loss in CKD patients, metabolic abnormalities other than poor diet can also cause cachexia (2).

Early studies of the anorexia associated with CKD established a link between this condition and the circulation of "middle molecules" — compounds with molecular weights between 1.0 and 5.0 kDa. While the structures of these anorexigenic middle molecules are unknown, injection of a mixture of them into a normal rat's peritoneal cavity has been shown to decrease carbohydrate intake (3). Other potential causes of anorexia in CKD patients include a decreased ability to distinguish flavors (i.e., abnormal taste), stomach irritation caused by medicines such as iron compounds or phosphate binders, hemodynamic insta-bility as a result of exposure to antihypertensive medicines or hemodialysis, and a sensation of fullness during peritoneal dialysis, as well as psychological and economic factors.

How does the central nervous system integrate hunger and satiety?
A study by Cheung and colleagues reported in this issue of the *JCI* (4) provides a quantum increase in our understanding of CKD-associated anorexia. Using animal models of CKD, the authors uncovered defects in the complex neuroendocrine pathways that regulate food intake. To appreciate the scope of their studies, a brief background is needed (see Figure 1). For over 50 years, it has been recognized that inhibitory signals proportional to body fat stores act to decrease food intake (5). The so-called long-term regulators of appetite — insulin and leptin — are produced in the pancreas and adipose cells, respectively. These regulators circulate at levels proportional to body fat and enter the brain in proportion to their plasma levels. In the hypothalamus, they influence neural pathways that integrate feeding and satiety as well as energy expenditure (6, 7). High levels of either leptin or insulin decrease food intake and increase energy expenditure, while low levels stimulate appetite and suppress energy expenditure. There are, however, important differences between the actions of insulin and leptin. A low leptin level increases fat accumulation, which ultimately raises cir-
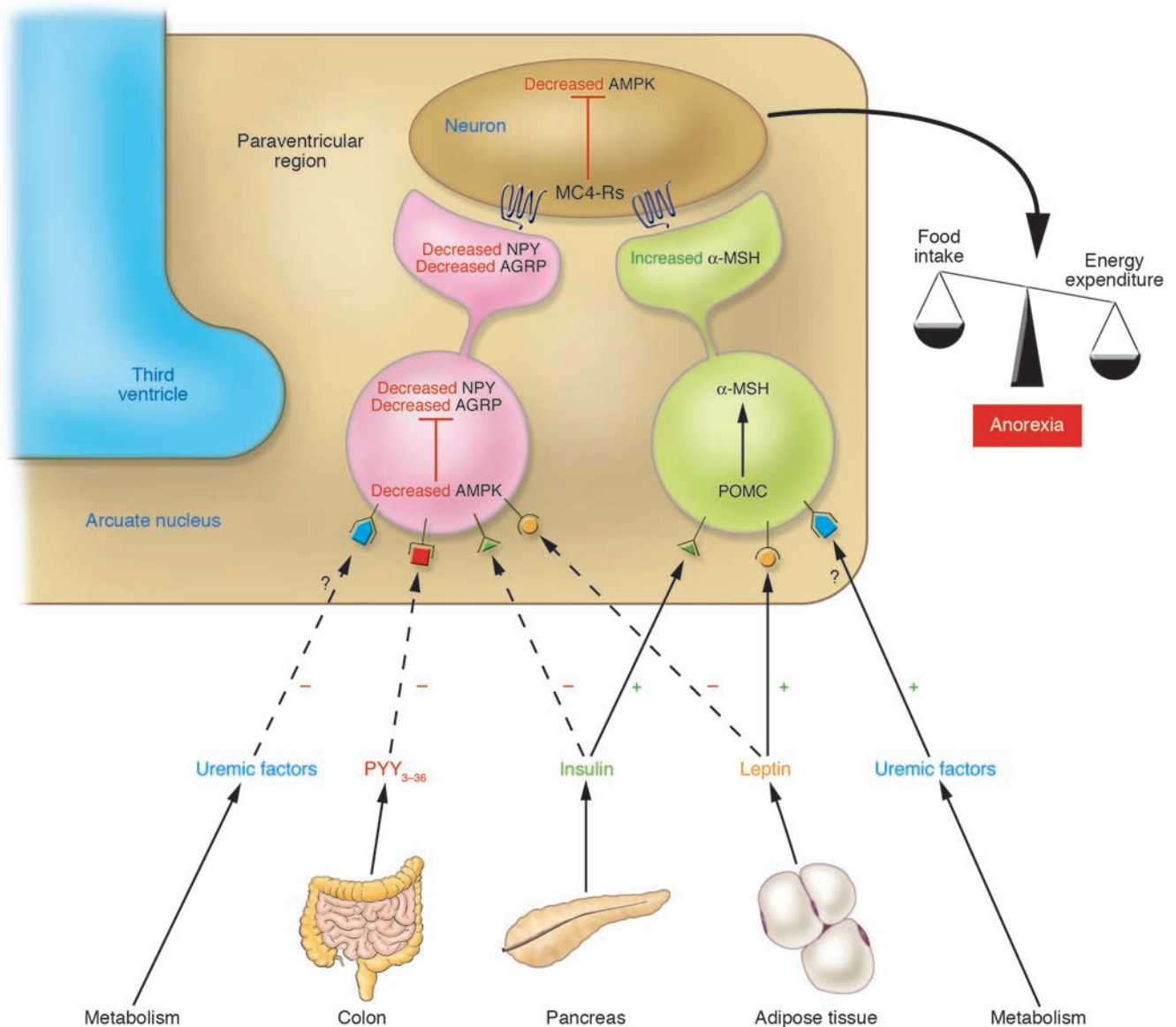
Figure 1
Neuroendocrine mechanisms that can cause anorexia. Hormones produced by the pancreas (insulin), adipose tissue (leptin), colon (PYY$_{3-36}$), and possibly metabolites (uremic factors) that accumulate in patients with CKD are long-term factors that result in anorexia. Responses to these factors result in increased activity of MC4-Rs, which suppresses AMPK activity and leads to decreased food intake, increased energy expenditure, and weight loss. MC4-R activity is increased by 2 pathways: suppression of short-term, antagonistic, orexigenic hormones NPY and AGRP; and activation of POMC-expressing neurons to produce α-MSH, which directly stimulates MC4-R. High levels of insulin, leptin, and possibly uremic metabolites can activate both pathways that stimulate MC4-R. The influence of ghrelin is less clear, as the stomach produces ghrelin when appetite rises, but this source of ghrelin appears to be less important in stimulating hunger than ghrelin that is produced in the hypothalamus. Figure modified with permission from *Nature* (6).

culating leptin levels. In addition, leptin is a member of the IL-6 cytokine family and can therefore contribute to cytokine-mediated changes in metabolism (8). Serum leptin levels are high in CKD patients, in part because leptin is degraded in the kidney, but serum leptin levels are more closely associated with inflammation than with dietary habits (9). In contrast, insulin is required for the accumulation of fat. As a result, a reduced level of insulin prevents accumulation of body fat and ultimately decreases leptin production.

Another long-acting anorectic factor is peptide YY$_{3-36}$ (PYY$_{3-36}$), a member of the neuropeptide Y (NPY) family (10). After eating, this hormone is secreted into the blood by endocrine cells in the distal small intestine and colon and subsequently activates neural pathways that suppress appetite. PYY$_{3-36}$ levels in the blood remain high between meals. When PYY$_{3-36}$ is infused into humans, it has been shown to reduce food intake by 33% over a period of 24 hours (10). Two other peptides produced in peripheral organs, cholecystokinin in the intestine and ghrelin in the stomach, do not act directly

on the hypothalamus. Instead, cholecystokinin (and possibly ghrelin) act via the vagus nerve to suppress appetite (5). Ghrelin is also produced in the hypothalamus and directly stimulates neurons that produce NPY and agouti-related protein (AGRP), both of which stimulate appetite (6, 11).

Integration of these multiple signals takes place in the hypothalamus. The key player is melanocortin receptor 4 (MC4-R), found in neurons of the paraventricular region (12) (Figure 1). When stimulated, MC4-Rs suppress AMP-activated protein kinase (AMPK) activity and thereby suppress food intake (13). At least 2 other types of neurons cause MC4-R–related anorexia. One type produces pro-opiomelanocortin (POMC), the cleavage of which produces α–melanocyte-stimulating hormone (α-MSH) and in turn stimulates MC4-R activity. Other neurons decrease their production of NPY and AGRP, both antagonists of MC4-R, apparently through a mechanism involving suppression of AMPK activity by leptin, insulin, etc. (13). In this case, the reduced NPY and AGRP cannot sufficiently block MC4-Rs, which leads to anorexia (6, 13). Finally, appetite and energy expenditure are regulated inversely in the hypothalamus; when appetite falls, energy expenditure rises (6).

CKD and impaired hypothalamic regulation of hunger

How does CKD impair this elegant regulatory system? Using mouse models, Cheung and colleagues employed modern approaches to assess whether the complex neuroendocrine pathways depicted in Figure 1 function abnormally in CKD in mice and whether CKD-induced abnormalities contribute to impaired appetite and growth (4). When they injected AGRP into the lateral ventricle of mice with CKD, food intake increased, resting metabolic rate declined, and growth improved, which suggests that CKD causes a defect in the ability of AGRP to block MC4-Rs in the hypothalamus. A link between growth and MC4-R activity was also found in studies of mice

lacking this receptor, as MC4-R knockout mice grew despite the existence of CKD. Finally, the authors linked CKD-associated growth impairment to leptin activity because uremic, leptin receptor–deficient (*db/db*) mice grew in a manner similar to sham-operated, pair-fed *db/db* mice.

As with most investigations of the pathophysiology underlying complex disorders, these results raise several questions. First, is the dysfunctional pattern of hypothalamic regulation of appetite unique to CKD? Apparently not, because Marks and colleagues studied mice using similar strategies and found that the weight loss caused by injection of lipopolysaccharide or by the presence of a cancer is linked to increased MC4-R activity and suppressed AGRP activity (14). Second, what are the therapeutic implications for CKD? The strategies used by Cheung et al. (4) required injections into the third ventricle, a clinical impracticality in humans. However, MC4-R agonists and antagonists are being developed, and some of these molecules have been shown to influence appetite even when administered parenterally (10, 15, 16). It also is tempting to speculate that the anorexigenic circulating middle molecules of 1.0–5.0 kDa in size (3) might in fact be related to PYY$_{3-36}$ (which has a molecular weight of approximately 3.9 kDa). In this case, a therapeutic strategy could be developed to remove this molecule. Finally, would correction of the abnormalities identified by Cheung et al. correct CKD-mediated loss of lean body mass? This seems unlikely, since other complications of CKD such as the development of acidosis, insulin resistance, and increased cytokine expression stimulate muscle protein loss by mechanisms that do not depend on anorexia (2). Moreover, if dietary protein intake is excessive, the growth of rats with experimental CKD is impaired, despite an adequate intake of total calories (17). However, identifying these abnormalities in the control of appetite by the central nervous system will stimulate research and could lead to new therapeutic strategies that combat cachexia in CKD and other catabolic states.

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