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Feature Editor

Anorexia and Cachexia in Renal Failure—Is Leptin the Culprit?

Role of Leptin and Melanocortin Signaling in Uremia-Associated Cachexia. *J Clin Invest* 115: 1659–1665, 2005
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It has been known for decades that renal failure, and particularly end-stage renal disease, is a catabolic state often associated with anorexia and wasting (1). The problem of identifying the substance(s) responsible for anorexia, wasting, and cachexia of uremic patients with and without dialysis has plagued nephrologists from the very beginning of dialysis (2). Ten weeks after the first patient ever had been placed on maintenance hemodialysis, Belding H. Scribner stated in his preliminary report, "Basic problems include nutrition—It becomes increasingly important to identify the substances removed by dialysis. Then it would become possible to study. . . the rate of appearance of both toxic substances and the uremic syndrome." The idea that substances in the molecular weight range of "middle molecules" had a role in causing anorexia had been around for a long time (3), and by pursuing a line of research of the late J. Bergström it could be shown that intraperitoneal and intracerebroventricular injection of uremic plasma ultrafiltrate or urine selectively inhibited carbohydrate uptake but not sexual behavior in rats (4).

With the use of modern molecular methods this issue has now taken a quantum leap forward: The study of Cheung *et al.* (5) has led to the identification of the signal substance and the neuroendocrine pathways in the hypothalamus through which the anorectic effect of uremia is mediated.

For the non-expert it may be useful to first describe briefly the pathways involved to better understand the strategies used by the investigators. Against the background of the modern epidemic of obesity and stimulated by the incentive to modulate appetite by pharmacologic agents, enormous progress has been made recently in understanding the complex neuroendocrine system controlling food intake (6). The basic principle is that circulating hormones carry information about energy balance to the hypothalamic structures that control eating and energy output. Both long-term and short-term regulators are involved. The former comprise mainly leptin and insulin, which monitor the amount of body fat. When the stores are filled, the concentrations of these hormones increase. Leptin is taken up by the brain *via* a saturable transport system and binds to the long form of the leptin receptor in the hypothalamic nucleus arcuatus (7). Elevated leptin concentration leads to inhibition of food intake and stimulation of energy expenditure. Conversely, when body fat stores decrease, leptin and insulin concentrations decrease in parallel. This is sensed by the hypothalamus. As a result of the decreasing hormone concentrations, hypothalamic inhibition is less and as a result appetite and energy expenditure are stimulated. There are also short-term regulators triggering onset and termination of eating (*e.g.*, ghrelin) which is abnormal in uremia (8,9), but this is of less interest in the above context.

Which are the signaling pathways in the arcuate nucleus of the hypothalamus upon which the circulating hormones act? The signal is mediated through the melanocortin system (10). Proopiomelanocortin, a propeptide precursor, releases the α-melanocyte-stimulating hormone (α-MSH), an agonist which acts mainly on one specific receptor, the melanocortin receptor 4 (MCR4). The stimulation of MCR4 by α-MSH inhibits food intake. Another molecule acting on MCR4, the antagonistic agouti-related peptide (AgRP), has an opposite action: Chronic treatment with AgRP increases food intake, fat mass, and plasma leptin (11). The important role of AgRP is illustrated by the observation that even the cachexia of cancer could be reversed and prevented by administration of AgRP (12).

The role of further molecules (*e.g.*, neuropeptide Y), is of less interest in the context of the above study.

Which strategies did the investigators use to identify the circulating signal molecule and the

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subsequent neurocirculatory pathways involved in the genesis of anorexia and cachexia in renal failure?

The authors used C57BL/6J mice and genetically manipulated mice with the same genetic background. First they created nonacidotic uremia by renal ablation in the wild-type mice and noted, as expected, that these mice—compared to sham-operated mice—gained less weight and lost lean body mass as well as fat mass under pair-feeding conditions. They thus presented the full syndrome of decreased food intake, increased metabolic rate, loss of lean body mass, and diminished efficiency of food consumption (*i.e.*, gain of body mass per unit weight of food consumed). In these mice the leptin concentration was significantly increased.

The authors next investigated leptin-receptor knockout mice (db/db mice) and MCR4 knockout mice with renal ablation. If leptin was a causal agent in the genesis of the anorexia, hypercatabolism, and cachexia, the deleterious effects of renal ablation on these parameters should be absent in these genetically manipulated mice—and this was exactly what was found in the experiments.

The authors went one step further and asked whether, in addition to deletion of the MCR4 receptor and the resulting disruption of the anorexigenic leptin signal, blockade of the MCR4 receptor by the antagonist AgRP would produce the same effect as did deletion of the receptor—and this was indeed the case.

The study thus confirmed the working hypothesis that the cachexia and anorexia in renal failure is triggered and perpetuated by increased circulating concentrations of leptin (and potentially other cytokines), which causes anorexia and wasting *via* the melanocortin receptor 4. The importance of the ubiquitine-proteasome pathway in the genesis of muscle wasting has been documented in models of uremia with acidosis (13,14), but this confounder could be clearly excluded in this model of nonacidotic uremia.

Plasma leptin concentrations have repeatedly been shown to be elevated in uremia (15), and their role in anorexia and malnutrition had been often suspected (16–18). But the study of Cheung *et al.* (5) fullfills the postulate of Scribner (2) to identify substances causing malnutrition. Whether leptin is the only anorexigenic substance remains to be seen. Whether leptin levels can be modulated by intervention will become a high priority. In view of the study of Mamoun *et al.* (4), which suggests an anorexigenic circulating middle molecule of 1.0 to 5.0 kD in size, additional targets for removal may also become available. The pharmacology of central regulation of appetite is one of the fastest-moving areas in pharmacology, and the option of pharmacologically modulating appetite and antagonizing wasting may become available as well.

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Lowering Albuminuria—Does It Lower the Cardiovascular Risk?

Reduction in Albuminuria Translates to Reduction in Cardiovascular Events in Hypertensive Patients: Losartan Intervention for Endpoint Reduction in Hypertension Study. *Hypertension* 45: 198–202, 2005

Ibsen H, Olsen MH, Wachtell K, Borch-Johnsen K, Lindholm LH, Mogensen CE, Dahlöf B, Devereux RB, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Lederballe-Pedersen O, Nieminen MS, Omvik P, Oparil S, Wan Y

Recently, a great number of studies have provided solid support for the concept that microalbuminuria, originally described in diabetics (1–3) as a predictor of renal and cardiovascular risk, is a strong predictor of cardiovascular and renal risk in nondiabetic patients as well (4–8). The Prevention of Renal and Vascular Endstage Disease (PREVEND) study showed that in the general population diabetes mellitus or hypertension as potential causal factors do not account for microalbuminuria in the majority of individuals (9). It has also been shown that microalbuminuria is a potent predictor of cardiovascular events and cardiovascular death in prospective studies (4–6,10). It has even been argued whether microalbuminuria, as defined by past studies in diabetic patients (11), is optimal for risk prediction. Both in diabetic (12) and nondiabetic patients (13,14), urine albumin concentrations in the high normal range are significant predictors of cardiovascular risk.

Following the hypothesis that proteinuria is a progression promoter (15,16), originally proposed by Remuzzi, convincing evidence has meanwhile been provided (17,18) that lowering of proteinuria is associated with less progression of renal disease. Consequently, proteinuria is today considered a valid target for renoprotective treatment in patients with manifest nephrop-

athy. Beyond this, somewhat unexpectedly, reduction of proteinuria was also associated with a reduction of cardiovascular events in proteinuric patients with advanced diabetic nephropathy (19).

So far it had not been known, however, whether this relation between regression of proteinuria and reduction of cardiovascular risk extends into the range of albumin excretion seen in microalbuminuric patients.

The study by Asselbergs *et al.* (20) had shown that in microalbuminuric patients intervention with an angiotensin-converting enzyme inhibitor lowered the frequency of cardiovascular events.

The recent Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study had shown a five-fold increase of cardiovascular events from the lowest to the highest decile of albumin excretion (14). The above study of Ibsen *et al.* now provides a further *post hoc* analysis of the LIFE study, which was designed to compare the effects of the angiotensin receptor blocker losartan and the β-blocker atenolol in patients with left ventricular hypertrophy (21). The analysis of Ibsen *et al.* yielded the remarkable result that the response of the albumin excretion rate to antihypertensive treatment predicts the frequency of future cardiovascular events. The urinary albumin/creatinine ratio was measured at baseline and annually thereafter. The change of albuminuria with time was closely related to the risk of the primary composite endpoint, *i.e.*, the first occurrence of nonfatal stroke, nonfatal myocardial infarction, or cardiovascular death. The population was divided according to median baseline urinary albumin/creatinine ratio (1.21 mg/mmol) and 1-yr urinary albumin/creatinine ratio (0.67 mg/mmol). The risk of the occurrence of a primary endpoint was lowest in those individuals in whom the value was low, *i.e.*, below the median, at baseline and remained low at 1 yr (frequency, 5.5%). The risk was higher in those with a low ratio at baseline but a high ratio at 1 yr (8.6%), and higher still in those with a low baseline but high 1-yr ratio (9.4%). The highest risk was found in those individuals who had a high ratio both at baseline and at yr 1 (13.5%). Interestingly, baseline and in-treatment systolic pressure as well as the choice of the antihypertensive agent, *i.e.*, losartan or atenolol, explained only a small proportion of the risk modification.

The consistency of the finding in this large population ($n = 8206$) is underlined by the fact that this relationship also was seen for the individual components of the primary endpoint, *i.e.*, cardiovascular death, stroke, and myocardial infarction.

Obviously one cannot draw conclusions with respect to causality from such associations, particularly in a *post hoc* analysis. Nevertheless, one can firmly state that a very tight relationship exists between change in albuminuria and cardiovascular risk, albuminuria thus providing useful clinical information. Both in diabetic (22) and in nondiabetic patients (23), microalbuminuria has been shown to be associated with generalized vascular leakiness for albumin and evidence of endothelial cell dysfunction and microinlammation (24), so microalbuminuria and presumably also high normal albuminuria can be considered as an index of microcirculatory disturbances. The nature of the link between the two abnormalities, *i.e.*, albumin leak in the glomerulus and endothelial cell dysfunction, remains moot. Is it a podocyte problem? A hint in this direction could be the observation of Pereira *et al.* (25) that the risk of microalbuminuria is higher for individuals with a polymorphism of the podocin gene. How does this tie in with the evidence of an endothelial cell dysfunction? This is difficult to explain, but a pointer may be the observation that intense cross-talk exists between podocytes (as specialized pericytes) and (at least glomerular) endothelial cells (26,27).

One can certainly conclude that it makes a lot of sense to monitor albumin excretion in high-risk patients at baseline and under antihypertensive treatment as proposed by the authors (28). Treatment should be adjusted or modified, including management of modifiable risk factors such as smoking, obesity, and dyslipidemia, if albumin excretion rates are not lowered appropriately by antihypertensive intervention. This study is one further piece of evidence which identifies albuminuria as a therapeutic goal. This conclusion is in line with recent efforts of our societies to heighten awareness of this novel risk factor in the medical community (29).

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