Dehydration: a new modulator of klotho expression

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According to the Greek myths, life and death of all individuals are in the hands of three sister goddesses: Klotho, Lakhesis, and Atropos. The first spins the thread of life, the second determines the length of the thread, while the last cuts the thread. Following this credence, once a putative age-suppressing gene has been identified, it was named klotho (11). Mice lacking klotho have a syndrome resembling premature aging, while mice overexpressing klotho show a longer life span (12). The klotho gene encodes a single-pass transmembrane protein composed of three domains; through ectodomain shedding, a secreted form is released into the extracellular space and is detectable in various fluids including blood and urine. Accordingly, the klotho protein is found in two forms: membrane and secreted klotho (10).

Membrane klotho is mainly expressed in the kidney and brain, but it is also found in parathyroids and heart (14). The function of membrane klotho was clarified when it was shown that both klotho- and fibroblast growth factor (FGF23)-deficient mice have the same phenotype. FGF23 is synthesized by bone and released in the plasma. It enhances urinary phosphate excretion and inhibits renal calcitriol synthesis, thus inducing a negative phosphate balance. It is now fully demonstrated that membrane klotho serves as a coreceptor for FGF23, amplifying and finalizing its action (19).

Secreted klotho operates like a humoral factor with pleiotropic activities, including inhibition of oxidative stress, regulation of growth factor signaling, and modulation of several membrane transport proteins. With respect to renal calcium transport, circulating klotho activates the transient receptor potential v-5 (TRPV5) by entrapping the calcium channel in the luminal plasma membrane and thus enhancing calcium reabsorption along the distal nephron (1, 2). In addition, klotho increases the activity of the Na-K-ATPase α1-subunit, which activates basolateral calcium exit via the sodium calcium exchanger (NCX1)-(1) (9).

Further evidence suggests that secreted klotho promotes phosphate excretion also in a FGF23-independent way through a direct inhibition of the sodium phosphate cotransporter NaPi-2a along the proximal tubule (6).

Besides calcium-phosphate homeostasis, klotho is also implicated in the pathogenesis of acute kidney injury (AKI). In rats, ischemia-reperfusion injury reduced klotho in the blood, kidneys, and urine. Interestingly, kidney and plasma klotho concentrations decline earlier than neutrophil gelatinase-associated lipocalin (NGAL), a recognized biomarker of renal injury. Fascinatingly, patients with AKI have a severe reduction in urinary klotho. Conversely, mice overexpressing klotho have milder functional and histological alterations when subjected to AKI compared with wild-type mice. All these data suggest that circulating klotho is an early biomarker for AKI and may be used as a renoprotective factor (8).

Both plasma and urinary levels of klotho decrease in experimental chronic kidney disease (CKD) as well as in patients with renal failure. Interestingly, transgenic CKD mice overexpressing klotho are characterized by larger phosphate excretion, better renal function, and much less soft tissue calcification compared with CKD wild-type mice. On the contrary, klotho-haplo-insufficient mice with CKD have poorer renal function and severe calcification. The beneficial effect of klotho on vascular calcification may be related to preservation of glomerular filtration, an increase in phosphaturia, and direct inhibition of phosphate uptake by vascular smooth muscle cells (5, 7).

It has been proposed that the downregulation of klotho expression both during AKI and CKD may be related to the NF-κB pathway (15), a signal cascade associated with interstitial inflammation and tubular injury (16).

The paper by Tang et al. (18) in an issue of the American Journal of Physiology-Renal Physiology tests the hypothesis that dehydration causes downregulation of klotho, which in turn has adverse effects on the physiology of aging. Indeed, enhanced plasma osmolarity favors disability, frailty, and early mortality in the elderly (17). On the other hand, dehydration is common in the elderly as a consequence of a reduced renal concentrating capability, scarcity of thirst sensitivity, and vasopressin efficacy (13). These defects are more common in elderly diabetic patients and may contribute to boost their morbidity and mortality (4). The authors found that water-deprived mice showed a decreased renal klotho mRNA and protein abundance; this effect was paralleled by increased plasma antiuretic hormone (ADH) and aldosterone levels as expected, as well increased 1,25(OH)2D3 levels. The role of ADH and aldosterone in the regulation of klotho was confirmed in vitro; in HEK293 cells, both ADH and aldosterone showed a negative control of klotho transcription and protein synthesis. Whether ADH and aldosterone directly downregulate klotho expression in vivo is still unknown. The effect of klotho on these hormones has been addressed in a previous paper by Fischer et al. (3). This study showed that klotho-deficient mice do manifest volume depletion, at least in part due to hypercal-

Fig. 1. Potential mechanism explaining the increased mortality associated with water depletion. ADH, antidiuretic hormone.
cemia with compensatory increased plasma ADH and aldosterone concentrations. Interestingly, a salt-rich diet extended the longevity of klotho-deficient mice, demonstrating that volume depletion has a strong impact on survival of these mice. With respect to vitamin D levels, klotho decreases the 1,25(OH)2D3 production by inhibiting 1α-hydroxylase and 1,25(OH)2D3 in turn stimulates Klotho expression (20). Thus the increase in 1,25(OH)2D3 in dehydrated animals can be considered as an effect of klotho downregulation.

Since the discovery of the klotho gene, several reports have highlighted the role of klotho in various pathophysiologic states. This study (18) suggests a potential pathway elucidating, at the gene level, the effect of dehydration on the morbidity of aging subjects (Fig. 1).

REFERENCES