Energy policy of the kidney: launch of AMPK as a novel therapeutic target

Masaomi Nangaku
Division of Nephrology and Endocrinology, The University of Tokyo School of Medicine, Tokyo, Japan
Submitted 3 July 2013; accepted in final form 4 July 2013

CHRONIC HYPOXIA in the tubulointerstitium is the final common pathway of chronic kidney disease (CKD) that leads to the development of end-stage renal disease (3, 4). The interrupted supply of oxygen results in anaerobic metabolism and loss of adequate production of ATP. A number of studies focused on hypoxia-inducible factor (HIF), the master transcription factor that regulates adaptive responses against hypoxia. HIF induces a variety of defensive mechanisms against hypoxia, including enhancement of erythropoiesis and angiogenesis to increase oxygen delivery via upregulation of erythropoietin, VEGF, and other HIF target genes (10). However, from a point of view of energy metabolism, AMP-activated protein kinase (AMPK) also plays a crucial role in the hypoxic organ. AMPK is a cellular energy sensor, and it promotes ATP production by increasing the activity or expression of proteins involved in catabolism (e.g., fatty acid oxidation and glycolysis) while conserving ATP by switching off biosynthetic pathways (e.g., fatty acid and cholesterol synthesis) once activated by falling energy status. In contrast to HIF, which has been a focus of intensive researches for a decade, a role of AMPK has been relatively ignored in the field of nephrology. A group at the University of California-San Diego has contributed a number of great works in the field of hypoxia and energy metabolism in the kidney. In this volume of American Journal of Physiology-Renal Physiology, they extended their previous findings and elucidated a role of AMPK in 5/6th nephrectomy model, the most commonly studied model of nondiabetic CKD (7). They measured renal blood flow using an ultrasonic transit time flow probe, glomerular filtration rate by inulin clearance, and measured oxygen contents by color spectrophotometer. The remnant kidney at 1 wk exhibited diminished metabolic efficiency as determined by oxygen consumption per Na
transport. This is consistent with previous pioneering works that showed an inappropriate increase in the oxygen demand of the diseased kidney induced by ROS-dependent activation of uncoupling protein-2 (1, 5).

Because of the high oxygen consumption and hypoxia in the remnant kidney, a requirement for increased AMPK activity as an adaptive response is logical. However, the early pathophysiological changes were accompanied by a paradoxical decrease in AMPK activity. There are two major pathways to activate AMPK. As ATP levels fall, there is an increase in AMP levels. The upstream regulator of AMPK, liver kinase B (LKB)-1, allows for AMP phosphorylation at a specific site on the α-subunit of AMPK. Ca2+/calmodulin-dependent protein kinase kinase kinase-β is also able to activate AMPK in response to changes in intracellular Ca2+ concentrations but not to changes in the AMP-to-ATP ratio. The reason for dysregulation of AMPK activation in the remnant kidney remains a question to be pursued in the future.

The authors investigated a possible therapeutic modality based on their findings. There are two representative AMPK activators used in vivo today: N1-(β-D-ribofuranosyl)-5-aminoimidazole-4-carboxamide (AICAR) and metformin. A recent study (2) in a model of acute kidney injury induced by ischemia-reperfusion showed protection of the kidney by activation of AMPK with AICAR. In contrast, a study (9) in a diabetic model of Zucker diabetic fatty rats showed that metformin protected the kidney by a decrease in oxygen consumption of tubular cells and a subsequent increase in cellular oxygen tension in an AMPK-independent manner. In the present study (7), induction of AMPK activity with either metformin or AICAR increased AMPK activity, which was associated with correction of kidney metabolic inefficiency and amelioration of kidney fibrosis. The beneficial effects of the two different agonists implied that renoprotection was conferred by the activation of AMPK in this study.

While AMPK regulates the activity and expression of key rate-limiting enzymes that control metabolic pathways to enhance energy-producing pathways and inhibit energy-consuming pathways, AMPK also regulates other important cellular processes, including inflammation via the IκB kinase/nuclear factor-κB pathway, cell growth and proliferation via the mammalian target of rapamycin, transcription and protein synthesis, and a number of membrane transport proteins in the kidney (6). Transport is an energy-consuming process, and the relative contribution to renoprotection of direct regulation of metabolic pathways and indirect regulation of energy consumption by changing transports remains unknown in tubular epithelial cells with activation of AMPK.

Previous studies have shown that HIF activation can be a good therapeutic modality in CKD. However, the disease kidney may have already upregulated HIF expression to some extent to adapt to hypoxia, conferring resistance of endogenous kidney cells to a further decrease in oxygen tension (8). While pharmacological activation of HIF can protect the kidney even further, it is important that this study showed a paradoxical decrease in AMPK in CKD. It is reasonable to propose activation of a dysregulated defensive mechanism to treat disease. Replenishment of a defective defensive mechanism may be more logical than reinforcement of an already activated defensive system. Activation of AMPK can be a promising therapeutic approach, opening a new avenue in the quest for novel drugs to treat CKD.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: M.N. conception and design of research; M.N. interpreted results of experiments; M.N. drafted manuscript; M.N. edited and revised manuscript; M.N. approved final version of manuscript.

Address for reprint requests and other correspondence: M. Nangaku, Div. of Nephrology and Endocrinology, Univ. of Tokyo School of Medicine, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan (e-mail: mnangaku-tky@umin.ac.jp).

http://www.ajprenal.org

1931-857X/13 Copyright © 2013 the American Physiological Society
REFERENCES


