Editorial Commentary

Control of Renal Na⁺ Excretion by Heme Oxygenase

Thomas L. Pallone

In the current issue of Hypertension, Li et al provide evidence that supports acute and chronic roles for renal medullary heme oxygenase (HO) in the regulation of salt and water excretion by the kidney.¹ Their findings may be summarized as follows: HO activity and expression rises with production of O₂ yields reactive oxygen species (ROS) including superoxide anion (O₂⁻) and hydrogen peroxide (H₂O₂), which, in turn generate hypochlorous acid and hydroxyl radicals. O₂⁻ consumes NO, reducing its availability as a vasodilator, producing peroxyxynitrite, a species that has independent injurious effects through protein nitrosylation. ROS are generated by endogenous pathways, including mitochondrial oxidative phosphorylation, activities of various O₂-utilizing enzymes, auto-oxidation of cysteine, substrate limited activity of NO synthase, and, perhaps most importantly, through the regulated activity of NADPH oxidase. Antioxidant systems that remove ROS include superoxide dismutases (SOD), which converts O₂⁻ to H₂O₂, and catalase that convert H₂O₂ to water. Free radical scavengers such as vitamin C and E also limit ROS. In the latter context, HO, through its generation of the endogenous antioxidant bilirubin, has been recognized to play a prominent role. In addition to effects on salt and water excretion, renal HO-1 activity favors protection from ischemia-reperfusion injury, inflammatory diseases, and transplant rejection.⁴

HO-1 and HO-2 are regulated microsomal and constitutive mitochondrial enzymes, respectively, that degrade heme to form CO and biliverdin. CO, like NO, signals through cGMP to favor vasodilation and saliuresis. Biliverdin is converted by biliverdin reductase to bilirubin, an effective ROS scavenger. Bilirubin exerts further antioxidant effects by inhibiting the activities of NADPH oxidase and protein kinase C. In the renal medulla, HO-1 is under the transcriptional control of hypoxia inducible factor α1 (HIFα1), as well as urea concentration and toxicity.⁵⁻⁷ The demonstration by Li et al that medullary HO-1 is upregulated by a high salt diet adds to existing evidence that HO-1 participates in the regulation of Na⁺ balance.

Renal ROS are involved in cell signaling and have pathophysiological roles in hypertension, the exacerbation of renal injury, and inflammation. Generation of hypertension has been traced to ROS generation in the medulla. Medullary interstititial administration of the SOD inhibitor, diethyldithiocarbamate, reduces medullary blood flow and raises arterial blood pressure. Conversely, the SOD mimetic, tempol, increases medullary blood flow and Na⁺ excretion, particularly when H₂O₂ is concomitantly eliminated with catalase.⁵ Reduced expression of medullary SOD accompanies hypertension in the Dahl salt-sensitive rat. Infusion of the of the HO inhibitor zinc deuteroporphyrin 2,4-bis glycol into the renal interstitium preferentially reduces medullary blood flow and cGMP content.⁸ Pharmacological treatment with cobalt protoporphyrin upregulates HO-1, reduces levels of the vasoconstrictor 20-HETE, and reduces blood pressure in the spontaneously hypertensive rat. Finally, ROS are known to affect tubular reabsorption of Na⁺ through protein kinase C and inhibition of the saliuretic effects of NO.⁹ The demonstration by Li et al that acute and chronic medullary HO inhibition blunts pressure natriuresis and induces salt-dependent hypertension, respectively, adds to the growing evidence that key regulation of extracellular volume occurs within the medulla.¹

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Division of Nephrology, Departments of Medicine and Physiology, 22 S. Greene St, N3W143, University of Maryland at Baltimore.

Correspondence to Thomas L. Pallone, MD, Division of Nephrology, N3W143, 22 S. Greene St, UMMS, Baltimore, MD 21201. E-mail tpallone@medicine.umaryland.edu


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Pressure natriuresis refers to the diuresis and saliuresis that occurs when renal perfusion pressure becomes elevated. Considerable attention has been paid to mechanism(s), set-point, and gain of that feedback loop because it favors amelioration of hypertension through reduction of extracellular fluid volume. Despite intense investigation, the mechanisms that underlie pressure natriuresis remain controversial. Diverse processes such as removal of Na\(^+/\)H\(^+\) exchangers from the brush border of the proximal nephron, resetting of tubuloglomerular feedback, alterations of medullary blood flow, increases in interstitial Starling forces, and generation of NO have been invoked as participants. Increasingly, attention has been paid to a putative role for NO. NO is a diffusible mediator generated by endothelia and nephrons that inhibits renal Na\(^+/\)H\(^+\) reabsorption at several sites. CO, like NO, signals through cGMP and can augment NO levels. Similarly, bilirubin might enhance NO levels by reducing its rate of consumption by O\(_2\)). Li et al have shown that interstitial CrMP infusion blunts the rise in medullary CO and NO that otherwise accompanies pressure natriuresis, hinting at a vital link between HO, CO, NO, and Na\(^+\) excretion. Given that <1% of the filtered load of Na\(^+\) is excreted to maintain its balance, subtle resetting of transport in the medullary thick ascending limb and, particularly, collecting duct might explain their findings. Whether this system can also be driven by formation of the principal substrate, heme, is unknown. Similarly, the pivotal pathway that links the increase in RPP to activation and upregulation of medullary HO-1 remains to be elucidated.

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**References**
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