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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 medullary axis; inner medulla > outer medulla > cortex. Acute elevation of renal perfusion pressure (RPP) induces a rise in the medullary tissue carbon monoxide (CO) and NO concentrations accompanied by natriuresis. Chromium mesoporphyrin (CrMP) inhibits the HO activity of medullary homogenates and, when infused into the renal interstitium, reduces both basal- and RPP-stimulated CO, NO levels, and salt and water excretion. Li and colleagues carried their investigation an important step further by examining chronic interstitial infusion of CrMP in rats maintained on either a 1% or 8% NaCl diet. Those on a 1% NaCl diet experienced a transient, 1-week elevation of mean arterial pressure of 5 to 10 mm Hg. By comparison, on an 8% NaCl diet, CrMP induced a sustained and impressive rise of 25 to 30 mm Hg. Finally, expression and activity of inducible HO-1 but not HO-2 was increased by the high salt diet.

The effectiveness of basal HO blockade shows a tonic effect of the products of heme degradation on epithelial Na⁺ reabsorption. Moreover, HO inhibition by CrMP blunts the diuresis and natriuresis associated with an acute increase in RPP; it blocks “pressure natriuresis” (Figure). These fundamental findings point to the importance of HO in the regulation of Na⁺ balance and raise many questions. What pathway connects RPP to HO activity? How does HO enhance salt and water excretion and affect blood pressure? What insights do these findings provide into the mechanisms that underlie pressure natriuresis? Because HO products arise from heme degradation, do pathways exist that increase availability of that substrate?

The myriad effects of HO have been traced to the antioxidant and vasodilatory properties of its products.²⁻⁴ Reduction 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 peroxynitrite, 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, inflammation, and transplant rejection.⁵

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 (HIF1α), 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 interstitial 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 deuteroporphrin 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
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. CO, like NO, signals through cGMP and can augment NO levels. Similarly, bilirubin might enhance NO levels by reducing its rate of consumption by O2. 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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Disclosures
None.

References