20-HETE or EETs: which arachidonic acid metabolite regulates proximal tubule transporters and contributes to pressure natriuresis?

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A MAJOR FUNCTION OF THE KIDNEY IS TO maintain body fluid and electrolyte homeostasis. Pressure natriuresis is a renal phenomenon that contributes to the long-term regulation of fluid and electrolyte balance and ultimately arterial blood pressure control. The basic phenomenon is that the kidney increases sodium excretion in response to an increase in renal perfusion pressure. A number of studies have demonstrated that pressure natriuresis involves elevations in renal medullary blood flow and renal interstitial hydrostatic pressure that result in inhibition of tubule sodium transport (8, 21, 27). It is also recognized that proximal tubule Na+/K+-ATPase activity decreases and the sodium/hydrogen exchanger (NHE3) internalizes from the apical membrane of the proximal tubule in response to an elevation in renal perfusion pressure (16, 28). The connection between the renal hemodynamic changes and the decreased proximal tubule sodium transport is poorly understood. The report by dos Santos et al. (6) in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology provides initial evidence that CYP450 metabolites of arachidonic acid contribute to the decrease in proximal tubule Na+/K+-ATPase activity and internalization of NHE3. Thus a CYP450 metabolite could be a possible messenger that couples the changes in renal hemodynamics to decreased proximal tubular sodium absorption.

CYP450 metabolites of arachidonic acid, 20-hydroxyeicosatetraenoic acid (20-HETE) and epoxyeicosatrienoic acids (EETs), have vascular and tubular actions and have been implicated in the control of sodium and water excretion (3, 12, 13, 20, 25). Because of their renal actions, CYP450 metabolites have been implicated in the pressure-natriuretic response. A piece of data implicating a CYP450 metabolite as positively contributing to pressure natriuresis is the chronic treatment of Dahl salt-sensitive (S) rats with inducers of CYP450 enzymes (1, 22). Decreased 20-HETE levels have been purported to be responsible for the blunted pressure natriuresis and salt-sensitive hypertension in the Dahl S rat (1, 20). Genetic and pharmacological manipulation to induce the kidney CYP4A hydroxylase enzyme increases 20-HETE levels and normalizes the pressure-natriuretic relationship as well as lowers blood pressure in the Dahl S rats (20). The importance of salt regulation to stimulate CYP2C enzymes and EETs and maintain body fluid and electrolyte homeostasis has also been demonstrated (13, 18, 29). CYP2C protein expression and urinary EET levels increase in response to a high-salt diet (18, 29). Along these lines, chronic administration of clotrimazole to inhibit epoxyxygenase enzymes induces hypertension in animals fed a high-salt diet (18). Conversely, acute inhibition of the CYP450 pathway increases papillary blood flow and sodium and water excretion without altering renal blood flow or glomerular filtration rate (30). Although contradictory to a positive role for CYP450 metabolites in the pressure-natriuretic response, this finding is consistent with the antinatriuretic and prohypertensive vascular actions described for 20-HETE (12, 20). It has been very difficult to investigate and separate 20-HETE’s antinatriuretic vascular actions and the natriuretic tubular actions given the current methodology.

What is the evidence that 20-HETE or EETs contribute to regulation of proximal tubule sodium transport and pressure natriuresis? Unfortunately, the epithelial cell activities of the hydroxylase and epoxyxygenase metabolites make both 20-HETE and EETs viable candidates for contributing to the increase in urinary sodium excretion in response to an increase in renal perfusion pressure. 20-HETE and EETs are produced by the proximal tubule and inhibit sodium reabsorption (13, 20). 20-HETE inhibits renal Na+/K+-ATPase activity and this appears to be due to stimulation of protein kinase C (PKC) to phosphorylate the α-subunit of the Na+/K+-ATPase (19). 20-HETE has also been shown to inhibit Na+/H+ exchange in cultured proximal tubule cells (20). Likewise, EETs have been reported to inhibit Na+/H+ exchange in cultured rabbit proximal tubule cells and isolated rat proximal tubules (13). Therefore, the possibility remains that 20-HETE and/or EETs are stimulated by an increase in renal interstitial hydrostatic pressure and act at the proximal tubule to increase sodium excretion.

Does the involvement of CYP450 metabolites to the pressure-natriuretic response extend beyond the proximal tubule segment? A segment of the nephron that was not evaluated in the current study is the thick ascending limb of the loop of Henle (TALH) segment. Na+ transport in the TALH segment of the nephron is decreased after elevations in renal perfusion pressure (8). Again, 20-HETE and EETs have actions on TALH cells that would decrease sodium reabsorption (13, 20). 20-HETE appears to be the primary arachidonic acid metabolite produced by TALH cells. Inhibition of the Na+/K+-2Cl− cotransporter by 20-HETE is due to the fact that 20-HETE blocks an apical membrane 70-pS K+ channel that limits the availability of K+ for the TALH Na+/K+-2Cl− cotransporter (26). The ability of EETs to inhibit renal epithelial cell Na+/K+-2Cl− cotransport has also been established (13). A recent study demonstrated that nitric oxide-mediated inhibition of Na+/K+-2Cl− cotransport in a renal epithelial cell line (MMDD1) involves stimulation of a CYP450 pathway (11).

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14,15-EET inhibited apical and basolateral cotransport of sodium in this renal epithelial cell line (11). It should be noted that nitric oxide participation in the pressure natriuresis is supported by a plethora of studies; however, nitric oxide effects on Na\(^+\) transport occur in distal nephron segments and appear to serve as a modulator of the vascular and tubular aspects of the pressure-natriuretic response (17). 20-HETE and/or EETs actions at the TALH cells or other nephron segments to increase sodium excretion remain unexplored.

Other possibilities for arachidonic acid metabolite contribution to pressure natriuresis are the involvement of cyclooxygenase (COX) metabolites, EET-stimulated PGE\(_2\) production, and metabolism of 20-HETE by COX enzymes. As for COX enzymes, COX-2 is located in the cortical TALH and macula densa cells that are known to play important roles in regulating sodium and water reabsorption (4, 10, 24). COX-2 metabolites appear to be involved in maintaining sodium excretion and glomerular filtration rate in cases of decreased circulating plasma volume (10). COX-1 and COX-2 are also abundantly expressed in the renal medulla with COX-1 predominating in the medullary collecting duct cells and COX-2 being expressed in medullary interstitial cells (4, 10, 24). The COX metabolite PGE\(_2\) contributes importantly to the regulation of salt and water reabsorption in the medullary TALH cells and collecting duct (10). Intriguingly, a nonselective COX inhibitor but not a COX-2 selective inhibitor blunts the increase in sodium excretion after an acute increase in renal interstitial hydrostatic pressure (9). This would implicate a COX-1 metabolite as contributing to the pressure-natriuretic response. There are at least two ways that COX metabolites could be linked to CYP450 metabolites in the renal medulla. First, 5,6-EET inhibits sodium reabsorption in cortical collecting duct cell by stimulating PGE\(_2\) synthesis (23). This EET stimulation of PGE\(_2\) could contribute to natriuresis and a similar scenario is possible in other nephron segments. Second, increased COX-2 expression in segments of the kidney appears to coincide with increased CYP4A expression and 20-HETE formation (5, 7). This coordinated regulation of COX-2 and CYP4A occurs in the renal microcirculation in response to salt deprivation, and COX-2 metabolizes 20-HETE to form 20-hydroxy-PGE\(_2\) (5). These findings support the possibility that COX and CYP450 pathways may be regulated in a coordinated fashion that contributes to pressure natriuresis.

Another missing piece to this puzzle is the link between increased renal interstitial hydrostatic pressure and increased CYP450 metabolite production. One possibility is that an increase in renal interstitial hydrostatic pressure could be transmitted to surrounding cells in the medulla to release CYP450 metabolites from cell membrane phospholipids. This would be more likely for EETs because previous studies demonstrated that epoxygenase metabolites are stored and released in response to stimuli from cell membranes (3, 25). Another likelihood is that an increase in renal interstitial hydrostatic pressure is sensed as an extracellular mechanical force that via cytoplasmic connection with the cytoskeleton results in increased CYP450 metabolite formation. Stretch-sensitive mechanisms are known to exist and can trigger the vascular myogenic mechanism. Interestingly, 20-HETE has been implicated as a contributing signaling mechanism to the myogenic response in the afferent arteriole and other vascularatures (12, 20). Thus there are plenty of unexplored possibilities that could link an increase in renal interstitial hydrostatic pressure to CYP450 metabolites.

The significance of the findings dos Santos et al. (6) relate to the central importance of the pressure-natriuretic response to the long-term control of blood pressure. The present study places 20-HETE and/or EETs as essential components in the kidney’s natriuretic response to an increase in renal perfusion pressure. Recent studies suggested that 20-HETE does not properly regulate sodium excretion in humans with salt-sensitive hypertension and there may be a connection to obesity (14, 15). Obesity and type II diabetes are other clinically relevant areas that dysregulation of tubular transporters and the pressure-natriuretic response occur (2). Although the present finding that a CYP450 metabolite contributes to pressure natriuresis by inhibiting Na\(^+-\)K\(^+-\)ATPase activity and internalizing the NHE3 protein from the brush border of the proximal tubule is clinically relevant, a primary question still remains: which CYP450 arachidonic acid metabolite regulates proximal tubule transporters and contributes to pressure natriuresis?

REFERENCES


