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

John D. Imig
Vascular Biology Center, Department of Physiology, Medical College of Georgia, Augusta, Georgia 30912-2500

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 electrolyte balance and ultimately arterial blood pressure contribution that contributes to the long-term regulation of fluid and electrolyte homeostasis. Pressure natriuresis is a renal phenomenon that contributes to the long-term regulation of fluid and electrolyte homeostasis. Pressure natriuresis is a renal phenomenon that contributes to the long-term regulation of fluid and electrolyte homeostasis.
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 PGE2 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 PGE2 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 PGE2 synthesis (23). This EET stimulation of PGE2 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-PGE2 (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 vasculatures (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


