Role of sphingosine-1-phosphate in the renal medulla

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FOR MORE THAN A CENTURY FOLLOWING the discovery of sphingolipids, biochemists viewed these ubiquitous phospholipids as pharmacologically silent structural elements of the cell membrane. After the identification of G protein-coupled receptors for sphingosine-1-phosphate (S1P) (1, 8, 10), researchers began to recognize the importance of sphingolipid-mediated cell signaling, and this recognition led to discoveries of roles for S1P signaling in numerous physiological systems. In this regard, a seminal article in this issue of the Am J Physiol Renal Physiol by Zhu and co-workers (11) no doubt will focus the attention of renal physiologists on the role of sphingolipids in regulating renal excretory function and will inspire a new area of kidney research.

Readers not familiar with S1P might find a brief description of sphingolipid metabolism useful for understanding this emerging field. Sphingomyelinases hydrolyze sphingomyelin (component of cell membranes), a reaction that releases ceramide, and ceramidases then in turn hydrolyze ceramide to form sphingosine (7). Sphingosine kinase (SphK), an enzyme that comes in two different forms (SphK1 and SphK2), phosphorylates sphingosine to produce S1P, and specific S1P transmembrane transporters permit S1P manufactured inside the cell to reach the extracellular compartment (7).

There exist at least five known S1P receptors (S1P1–5) (5). The expression of S1P1, S1P2, and S1P3 receptors occurs in many cell types, whereas the expression of S1P4 and S1P5 receptors is concentrated in lymphoid tissue and brain/spleen, respectively (5). S1P2 receptors couple exclusively to Gi/o and activate Akt and Rac, and although S1P2 and S1P3 receptors can partner with several G proteins, S1P2 and S1P3 receptors couple most efficiently to G12/13 (leading to Rho activation) and Gq (leading to the activation of the inositol-1,4,5-trisphosphate/calcium pathway), respectively (5). S1P4 and S1P5 receptors appear to signal primarily via Gq, Gi/o, and G12/13 (5). This elaborate differential receptor-subtype coupling allows S1P to exert an array of physiological effects based on not only the receptor activated but also the coupled G protein that can be cell-type specific.

Despite more than 2,700 publications on S1P, the role of S1P in renal physiology is barely explored. Some of the earliest pioneers are Bischoff et al. (2) whose work demonstrates that S1P constricts isolated renal microvessels and intravenuous and intrarenal arterial administration of S1P causes renal vasoconstriction (3). Additional studies by these investigators (4) demonstrate that intravenous infusions of S1P cause natriuresis despite a reduction in renal blood flow. The fact that infusions of S1P into the renal vasculature increase salt excretion while despite a reduction in renal blood flow.

Discoveries in pharmacology often provide novel tools that enable new insights into physiological mechanisms. This is certainly the case for S1P in which enthusiasm for S1P receptor modulators for the treatment of several diseases (case in point, the FDA recently approved FTY720 for multiple sclerosis) has led to the availability of agonists and antagonists selective for S1P receptor subtypes (5, 7).

Taking advantage of these opportunities, Zhu et al. (11) report in an issue of the American Journal of Physiology-Renal Physiology that S1P, acting via S1P1 receptors, importantly regulates sodium excretion by affecting transport mechanisms in the renal medulla, possibly via modulating the activity of the epithelial sodium channel (ENaC). Measuring both mRNA (real-time RT-PCR) and protein (Western blotting and immunohistochemistry), Zhu et al. demonstrate that in a rat model 1) S1P receptors (S1P1, S1P2, and S1P3) are expressed more in the renal medulla than the cortex, with localization mainly to the collecting ducts; 2) intramedullary delivery of a S1P receptor agonist markedly increases sodium excretion with only minor effects on medullary blood flow (slight vasodilation); 3) the natriuretic effects of a S1P receptor agonist are blocked by selective antagonism of S1P1, but not S1P2 or S1P3, receptors; 4) S1P1 receptor antagonism per se reduces sodium excretion; and 5) the natriuretic effects of a S1P receptor agonist are additive with inhibition of the Na+/K+–cotransporter (hydrochlorothiazide), Na+/K+–Cl– cotransporter (furosemide), and Na+/H+ exchanger (amiloride), but not with inhibition of ENaC (amiloride). The proposition that S1P regulates sodium excretion by affecting transport mechanisms in the renal medulla gives significance to the recent report by Facchini et al. (6) that SphK1 activity is highest in the renal medulla.

Studies by Synder et al. (9) demonstrate that cAMP, by activating protein kinase A, promotes phosphorylation (and thus inhibition) of Nedd4–2, an E3 ubiquitin–protein ligase that targets ENaC for degradation. Because S1P regulates sodium handling in the renal medulla via the S1P1 receptor, which is negatively coupled to adenyl cyclase via Gi, the concept that S1P increases sodium excretion by inhibiting ENaC is a reasonable hypothesis.

The finding that S1P modulates sodium transport in the renal medulla raises a number of interesting and important questions: 1) What are the mechanisms by which S1P modulates sodium reabsorption in the renal medulla? 2) What regulates the levels of S1P in the renal medulla and what cell types give rise to renal medullary S1P? 3) Does salt intake alter the renal medullary S1P system to stabilize body fluid volumes and blood pressure in the face of changes in the amount of dietary sodium? 4) Do alterations in the renal medullary S1P system participate in the pathophysiology of hypertension and edema secondary to kidney, heart, and liver diseases? 5) Can S1P receptor modulators be used to manage edema or hypertension.
Regulation of sodium transport in the collecting duct is a key mechanism for adjustment of body fluid volumes and electrolyte composition and for long-term regulation of arterial blood pressure. The study by Zhu et al. (11) marks the beginning of an exciting research program rich with opportunities to better understand the intricacies of how the collecting duct performs its functions. Exploration of the role of S1P in the collecting duct doubtless will yield long-term payoffs, both in terms of new insights into kidney physiology and better treatments for cardiorenal diseases.

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DISCLOSURES

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REFERENCES