Beyond cyclooxygenase

Real estate agents are known to regale prospective buyers with the maxim “Location! Location! Location!” The same mantra should be kept in mind when considering the action of prostanoids. As opposed to circulating hormones, such as insulin and vasopressin, which act upon tissues distant from their site of production, prostanoids are rapidly metabolically degraded, limiting their effects to the immediate vicinity of their synthetic site. This circumstance dictates that the entire enzymatic machinery required for production of a specific prostanoid be localized at its site of action and, furthermore, that the receptor(s) mediating the action of this prostanoid be locally available.

Prostanoids are composed of a diverse group of unsaturated, oxygenated fatty acids, derived from the enzymatic metabolism of arachidonic acid, by cyclooxygenase-1 (COX-1) or cyclooxygenase 2 (COX-2). Both cyclooxygenase isoforms convert arachidonate to the same product, the bioactive but unstable prostanoid precursor, prostaglandin H2 (PGH2). Once formed, PGH2’s fate is determined by further metabolic processing via a set of enzymatic synthases, yielding either prostaglandin E2 (PGE2), prostaglandin F2α (PGF2α), prostaglandin D2 (PGD2), thromboxane A2, or prostacyclin. The effects of each these prostanoids is, in turn, mediated by a family of G protein-coupled transmembrane receptors that possess both ligand and signaling specificity.

It is now well established that COX-1 and COX-2 are differentially expressed along the nephron. Whereas COX-1 is highly expressed in the collecting duct [1, 2], COX-2 expression is restricted to the cortical thick ascending limb, specifically in cells associated with the macula densa [2–4]. COX-2 is also highly expressed in medullary interstitial cells [2, 5]. The significance of this distinct isoform localization appears to be more than a mere curiosity since selective COX-2 inhibition accentuates the pressor effects of angiotensin II, whereas COX-1 inhibition reduces its pressor effect [2]. One possible explanation for these observations is that COX-1 activity primarily yields a pressor such as thromboxane A2, whereas COX-2 mediates the production of a vasodepressor like prostacyclin [6, 7]. This implies that distinct enzymatic machinery is co-expressed with COX-1 versus COX-2, thereby limiting the end product formation and the physiologic consequences of PGH2 formation.

Whether a cell synthesizes thromboxane A2, PGE2, or prostacyclin depends almost entirely on the accessibility of the specific prostanoid synthase that metabolizes PGH2. Thus, platelets express abundant thromboxane synthase and primarily produce thromboxane A2 [8–10]. Similarly, smooth muscle and endothelial cells express abundant prostacyclin synthase, corresponding to their high rate of prostacyclin synthesis [11]. What, then, are the main prostanoid synthases localized together with COX-1 and COX-2 in the kidney?

In this issue of *Kidney International*, Vitzhum et al further define the distribution of mRNAs for prostanoid synthases along the nephron [12]. These studies used reverse transcription-polymerase chain reaction (RT-PCR) on microdissected nephron segments to confirm the previously described differential expression of COX-1 and COX-2 along the nephron. In addition, these investigators described the expression pattern of the associated prostanoid synthases. In agreement with earlier studies of Farman, Pradelles and Bonvalet [13], and more recent studies of microsomal PGE synthase expression in mouse kidney [14], these investigators found the highest expression of microsomal PGE synthase in the collecting duct.

Just because an enzyme possesses the capacity to metabolize PGH2 to a specific prostanoid in vitro, does not mean that this is its role in the intact organism. Indeed, the existence of another enzyme catalyzing PGE synthesis has been reported [15]. Thus, it is reassuring that disruption of the gene for this microsomal PGE synthase completely blocked lipopolysaccharide stimulated PGE2 production in mice [16]. Taken together, these studies define microsomal PGE synthase as an enzyme downstream of renal COX-1 and possibly responsible for PGE2 synthesis by the collecting duct. Importantly, the collecting duct also expresses abundant E prostanoid receptors, including EP1, EP3, and EP4 receptors through which PGE2 presumably exerts its natriuretic and diuretic effects [17]. An unanswered question is whether PGE2 derived from collecting duct COX-1 versus interstitial cell COX-2 have differential access to distinct EP receptor subtypes along the collecting duct.

Prostacyclin synthase and thromboxane synthase were also detected in the kidney by RT-PCR. Since prostacyclin synthase was not detected in any of the nephron segments studied, Vitzthum et al infer that it must be ex-
pressed in interstitial or vascular compartments, a conclusion supported by other studies [11]. Thromboxane synthase was only detected in the glomerulus, even after perfusion to eliminate the possibility of contaminating platelets. These findings also support preceding studies pointing to a role for thromboxane in regulating glomerular function [18–20]. Curiously, none of these synthases, including PGE synthase, was detected in the cortical thick limb/macula densa segment, begging the question of the identity of the prostanoid synthesized by COX-2 at this site.

An unexpected finding in the present studies was the renal expression and segmental localization of prostanoid D synthase along the nephron. Two synthase isoforms were mapped: (1) lipocalin-type PGD synthase (L-PGD synthase) and hematopoietic type (PGD synthase). The presence of L-PGD synthase in the proximal tubule, which is devoid of cyclooxygenase, suggests this protein might subserve functions other than PGD synthase. Nevertheless, the investigators provided additional support for the functional significance of these enzymes by showing that PGD2 can be detected in renal homogenates. If the PGD2 detected does indeed arise as a product of PGDS expressed in distal nephron segments, where COX-1 or COX-2 mediate PGH2 synthesis, this finding is particularly intriguing given the apparent lack of D-prostanoid receptor in the kidney [21]. Overlap between L-PGD synthase and the DP receptor has been reported in other tissues [22]. The present observations would then suggest the possibility of novel PGD2 receptors. Recently a new PGD2 receptor, designated CRTH2, has been identified in T cells and eosinophils [23]. Whether this or another type of PGD2 receptor mediates the actions of PGD2 in the kidney remains to be determined. Nonetheless, defining the sites of expression of prostanoid synthases along the nephron must prompt us to identify their relevant “neighbors.” Implicit in this endeavor is the assumption that the pattern of gene expression in the body is, like any well-planned community, highly organized and designed with a purpose.

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