Cyclooxygenases, Prostanoids, and Glomerular Injury: Complex Relationships

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The association of prostanoid production with glomerular injury has been appreciated for more than 20 yr, well in advance of more recent studies that have characterized pathways that are associated with phospholipid hydrolysis and metabolism of free arachidonic acid to prostanoids. Release of arachidonic acid from phospholipids by phospholipase A_{2} generally is the rate-limiting step in the synthesis of prostanoids (1). Free arachidonic acid is metabolized by cyclooxygenases (COX), followed by prostaglandin or thromboxane synthases. There are two COX genes, which result in transcription of COX-1 and COX-2 proteins, as well as COX-3, a splice variant of COX-1 (2). In many tissues, COX-1 is expressed constitutively, whereas COX-2 is induced in disease states, but in certain cells within the kidney, COX-2 also is expressed constitutively (3). Therefore, the view that COX-1 produces prostanoids that are necessary for normal physiologic functions whereas COX-2–derived prostanoids play a pathologic role does not necessarily apply to kidney physiology. Effects of prostanoids are mediated via specific receptors, and many of these have been identified in renal cells (4).

In experimental animal models, administration of nephritogenic toxins or deposition of antibody and complement within glomeruli may induce changes in prostanoid generation by intrinsic glomerular cells. Alternatively, production of glomerular prostanoids may be altered after recruitment of leukocytes. A functional role for prostanoids in glomerular injury first was suggested by studies that showed that nonsteroidal anti-inflammatory drugs can alter glomerular hemodynamics and urinary protein excretion in various proteinuric states. Studies in the 1980s and early 1990s used pharmacologic manipulation of prostanoid synthesis to study changes in glomerular permeselectivity, and some but not all of these studies showed that administration of inhibitors of COX or thromboxane synthase can reduce proteinuria (reviewed in reference [5]). For example, these drugs lowered proteinuria in Adiriamycin nephropathy in rats (a model of minimal-change disease/focal glomerulosclerosis), nephrotic nephritis in rats and mice (anti–glomerular basement membrane disease), passive Heymann nephritis (PHN) in rats (membranous nephropathy), and rat anti–Thy-1 nephritis (mesangioproliferative nephritis). When studied, reduction of proteinuria occurred independent of changes in glomerular hemodynamics. Another approach to modulating prostanoid effects has been to shift production of dienoic prostanoids to inactive trienoic metabolites with diets that are rich in omega-3 fatty acids (e.g., fish oils). These diets have shown beneficial effects on renal function and/or proteinuria in animals with lupus nephritis, nephrotoxic nephritis, PHN, and focal glomerulosclerosis. Fish oil may alter humoral or cell-mediated immune responses or may affect glomerular cell function and permselectivity directly. Together, a number of studies that used distinct experimental approaches support a role for prostanoids in exacerbating proteinuria in various glomerulopathies. It also should be noted that indomethacin was shown to reduce proteinuria in human nephrotic syndrome (6), and a beneficial effect of fish oil diet on the progression of renal failure was reported in IgA nephropathy in humans (7).

Since the late 1990s, a newer generation of studies has addressed the role of COX and prostanoids in glomerular injury. These studies followed the discovery of COX-2, characterization of prostanoid receptors, and the advent of selective inhibitors. For example, glomeruli from rats with PHN express significantly more COX-1 and COX-2 and produce more prostanoids than normal rat glomeruli (8). The increase in prostanoids was attenuated with a COX-2 selective inhibitor (8). In a glomerular epithelial cell (GEC) culture model of PHN, complement increased the expression of COX-2 via activation of protein kinases (9). A COX-2 selective inhibitor reduced proteinuria in PHN but to a lesser extent than indomethacin (nonselective inhibitor), suggesting that inhibition of both COX-1 and -2 was required to achieve a maximum antiproteinuric effect (10). Neither drug affected inulin clearance. In PHN, proteinuria was reduced with other COX-2 inhibitors as well (11). In a distinct proteinuric model (rats with reduced renal mass), a COX-2 selective inhibitor decreased proteinuria and inhibited development of glomerulosclerosis (12).

In this issue of JASN, Cheng et al. (13) use an elegant technique to overexpress COX-2 in podocytes in vivo (nephrin promoter–COX-2 transgene). Overexpression of COX-2 in podocytes in a mouse strain that otherwise is resistant to Adriamycin injury sensitized the podocytes to injury, indicated by foot process effacement and albuminuria. These responses were associated with an increase in endogenous (but not transgenic) podocyte COX-2 expression and a decrease in expression of nephrin, a key component of the filtration slit diaphragm. Chronic treatment with a COX-2 selective inhibitor attenuated the albuminuria and foot process effacement and restored nephrin expression. COX-2 or its metabolites seemed to increase the susceptibility of podocytes to further injury. The authors, however, did not examine whether glomerular COX-2 expression correlated with generation of prostanoids.
or other metabolites, and the amount of proteinuria that was observed in mice was very small. In another recent study, Aoudjit et al. (14) used an analogous model of injury in rats (puromycin amino-nucleoside nephrosis) to show that glomerular COX-2 expression was upregulated. However, an antagonist of the EP4 subtype of prostaglandin E<sub>2</sub> receptor exacerbated proteinuria and glomerular cell apoptosis in this model, suggesting that induction of COX-2 and prostaglandin E<sub>2</sub> production attenuated podocyte injury.

There are several mechanisms by which COX and prostanooids could modulate proteinuria. Prostanoids may contribute toward increasing glomerular capillary pressure, such that proteinuria is increased on a hemodynamic basis (5). Alternatively, COX and prostanooids may modulate proteinuria by targeting podocytes. In cultured GEC, COX inhibition reduced complement-induced cytotoxicity, and this reduction was reversed by a thromboxane A<sub>2</sub> analog, suggesting that production of thromboxane A<sub>2</sub> may exacerbate GEC injury directly (10). Mechanical stretching induced expression of COX-2 and the EP4 receptor in cultured GEC, and in the stretched cells, prostaglandin E<sub>2</sub> induced dissociation of actin stress fibers (15). In other cells, COX-2 was reported to cause lipid peroxidation and DNA damage (16). Together, these studies suggest that signals that are mediated via COX can have a negative impact on podocyte metabolic pathways and the structure/function of lipids and key proteins in the cytoskeleton and slit diaphragm. Alternatively, inducible overexpression of COX-2 in cultured GEC promoted cell survival in association with Akt activation (14). This effect was mimicked by exogenous prostaglandin E<sub>2</sub> and was blocked by an EP4 receptor antagonist. Finally, an additional complexity of signaling by prostanooids is that these compounds may enhance activation or “transactivate” growth factor receptors in cells, including GEC (17,18). One conclusion from all of these studies is that certain effects or products of COX exacerbate glomerular cell injury, whereas other products may be protective. Thus, selective inhibition or activation of prostanooid pathways may be an effective means of modulating proteinuria, perhaps independent of hemodynamic factors; however, the cellular mechanisms still are uncertain and require further study. Successful specific therapy of glomerular diseases likely will depend on concurrent targeting of multiple signaling pathways.

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Disclosures

None.

References


