Role of COX-2 in Unilateral Ureteral Obstruction: What Is New?

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Prostanoids are metabolites of arachidonic acid (AA) through the activity of cyclooxygenase (COX). COX exists in two major isoforms, the constitutive COX-1 and inducible COX-2.

Prostaglandin E2 (PGE2) is the major prostanoid produced in the kidney and it induces biological function by binding to four G-protein coupled receptors (EP1-4), each of which couples to a distinct signaling pathway. COX-derived prostanoids affect a wide spectrum of renal function in health and disease (2).

Obstructive nephropathy is a common cause of chronic kidney disease (CKD) in both children and adults. In addition, unilateral ureteral obstruction (UUO) readily induces tubulointerstitial fibrosis, a common pathophysiology of CKD, irrespective of the causes, which leads to end stage of renal disease (1). Accordingly, UUO in rodents is a widely used experimental model of renal fibrosis. It has been reported that PGE2 generation is elevated in the obstructed kidneys (10, 12). The heightened PGE2 synthesis is associated with increased COX-2 expression in the UUO model (4, 8). In vitro evidence demonstrates that COX-2 expression in renal medullary interstitial cells (RMICs) is increased in response to pressure, dependent of endogenous production of reactive oxygen species (ROS) (3, 11). ROS dependence of COX-2 induction was also observed in rats subjected to UUO (11). A number of studies employing pharmacological inhibitors of COX-2 attempted to address the functional role of COX-2 in UUO but yielded inconclusive results. UUO-induced renal fibrosis as assessed by the expression of collagen typ1 I, III, and IV is exaggerated by administration of celecoxib, a specific COX-2 inhibitor (8). In parallel, mRNA expression of TGF-β, a major profibrogenic factor, is also increased in the celecoxib group as compared with the vehicle control (8). These results suggest a protective role of COX-2 against tubulointerstitial fibrosis during UUO. Conversely, inhibition of COX-2 with meloxicam attenuated extracellular matrix protein syntheses in
stretched fibroblasts and tubulointerstitial fibrosis in UUO (5, 15). While celecoxib is more selective than meloxicam, the conflicting results obtained with the two inhibitors obviously necessitates validations by using a genetic approach.

In this issue of *American Journal of Physiology-Renal Physiology*, Nilsson et al. employed COX-2 KO mice to clarify the role of COX-2 in the development of several injurious indices induced by UUO. The authors were aware of the pathological changes in the COX-2 KO kidney, a developmental phenotype that may confoundingly influence the obstruction-induced kidney injury. Accordingly, the authors chose COX-2 KO mice on a mixed 129/C57 background at the age 10-14 weeks in this study since these animals did not exhibit differences in blood pressure, urine concentrating capability (14), or indices of oxidative stress, apoptosis, or tubular injury at basal condition as compared with their WT controls. It is known that the renal phenotype in COX-2 KO mice is dependent on genetic background and age (14). COX-2 KO and WT mice underwent UUO for 3 and 7 days and parameters of oxidative stress (HO-1, SOD1&2), apoptosis (TUNEL staining, caspase-3) and tubular injury (histology, KIM-1) were determined. Consistent findings showed the indices of these 3 categories of tissue injury were induced by UUO in WT mice, all of which were exaggerated in COX-2 KO mice. These results represent the first genetic evidence to prove a protective role of COX-2 against renal injury in UUO.

This study has a number of limitations. ROS have been postulated to be a major molecular target of COX-2-derived prostaglandins in UUO. However, the assessment of ROS production in the obstructed kidney is insufficient. The expression level of HO-1, SOD-1 and -2 is determined to indirectly reflect ROS production. The direct measurement of ROS production using methods such as the EPR spin-trapping technique will be extremely helpful. The COX-2 KO kidney exhibits a greater increase in the expression of antioxidant genes such as HO-1,
SOD-1 and -2 as compared with WT controls after UUO. However, the causal relationship between COX-2 deletion and the antioxidant gene upregulation is unclear. The detailed mechanism of how COX-2-derived prostaglandins affect a specific antioxidant gene awaits further investigations.

In a sharp contrast to the protective role of COX-2 in UUO as described above, COX-2 plays a pathogenic role in other models of kidney injury such as cisplatin nephropathy. In a mouse model of cisplatin nephrotoxicity, renal expression of COX-2 and microsomal prostaglandin synthase-1 (mPGES-1) is elevated accompanied with increased PGE\(_2\) levels (7). Inhibition of prostaglandins synthesis by celecoxib, meloxicam, or by mPGES-1 deletion consistently attenuated cisplatin-induced renal dysfunction, oxidative stress, and inflammation (6, 7). It is interesting to note that even in the same model of UUO, macrophage COX-2 is shown to mediate renal inflammation, oxidative stress, and apoptosis (13). In this study, a novel technique involving the use of chitosan/siRNA nanoparticles was successfully employed to achieve macrophage-specific knockdown of COX-2 (13). This technique helps address the pathogenic role of macrophage COX-2 during UUO and also represents a novel intervention for management of obstructive nephropathy. This study also brings up a question as to the cell type responsible for the protective role of COX-2, which should be distinct from macrophages.

EP\(_4\) has been shown to mediate the protective role of COX-2 against UUO-induced tubulointerstitial fibrosis (9). It will be interesting to determine the EP subtype responsible for the pathogenic role of COX-2 in kidney injury.

In summary, COX-2 deletion in mice exacerbates obstruction-induced renal oxidative stress, apoptosis, and tubular injury. These results represent a strong genetic evidence supporting a protective role of COX-2 against obstructive nephropathy. Such protective action of COX-2 is
likely mediated by PGE$_2$/EP$_4$ pathway (Fig. 1). COX-2 inhibitors should be used with caution in patients with this disease.

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Conflict of Interest

None.

References


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**Figure Legend**

Fig. 1. Illustration of the protective role of COX-2 in obstructive nephropathy. In UUO model, ROS play a central role in mediating obstruction-induced apoptosis, fibrosis, and inflammation. On the other hand, ROS also activate protective COX-2/PGE2/EP4 pathway that mitigates oxidant induced tissue damage.
Obstruction

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ROS

Apoptosis, fibrosis, inflammation

COX-2/PGE₂/EP₄

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Tissue remodeling