Role of COX-2 in unilateral ureteral obstruction: what is new?

Tianxin Yang1,2 and Chunling Li2
1Department of Medicine, University of Utah and Veterans Affairs Medical Center, Salt Lake City, Utah; and 2Institute of Hypertension, Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, China

Submitted 3 November 2015; accepted in final form 2 December 2015

PROSTANOIDS are metabolites of arachidonic acid through the activity of cyclooxygenase (COX). COX exists in two major isoforms: constitutive COX-1 and inducible COX-2. PGE2 is the major prostanooid produced in the kidney, and it induces biological function by binding to four G protein-coupled receptors (EP1-EP4), which each couple to a distinct signaling pathway. COX-derived prostanooids affect a wide spectrum of renal function in health and disease (2).

Obstructive nephropathy is a common cause of chronic kidney disease in both children and adults. In addition, unilateral ureteral obstruction (UUO) readily induces tubulointerstitial fibrosis, a common pathophysiology of chronic kidney disease, irrespective of the causes, which leads to the 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 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 is increased in response to pressure, dependent on the endogenous production of ROS (3, 11). ROS dependence of COX-2 induction was also observed in rats subjected to UUO (11). A number of studies using pharmacological inhibitors of COX-2 have attempted to address the functional role of COX-2 in UUO but have yielded inconclusive results. UUO-induced renal fibrosis, as assessed by the expression of collagen types I, III, and IV, was exaggerated by the administration of celecoxib, a specific COX-2 inhibitor (8). In parallel, mRNA expression of transforming growth factor-β, a major profibrogenic factor, also increased in the celecoxib-treated group compared with the vehicle-treated control group (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 using a genetic approach.

In a recent issue of the American Journal of Physiology-Renal Physiology, Nilsson et al. (9a) used COX-2 knockout (KO) mice to clarify the role of COX-2 in the development of several injurious indexes induced by UUO. The authors were aware of the pathological changes in the COX-2 KO kidney, a developmental phenotype that may confoundingly influence obstruction-induced kidney injury. Accordingly, the authors chose COX-2 KO mice on a mixed 129/C57 background at the age 10–14 wk in this study since these animals did not exhibit differences in blood pressure, urine concentrating capability (14), or indexes of oxidative stress, apoptosis, or tubular injury under basal conditions compared with wild-type (WT) control mice. 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 [heme oxygenase (HO)-1, SOD1, and SOD2], apoptosis (TUNEL staining and caspase-3), and tubular injury (histology and kidney injury molecule-1) were determined. Consistent findings showed the indexes of these three 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, SOD1, and SOD2 has been determined to indirectly reflect ROS production. Direct measurement of ROS production using methods such as the electron paramagnetic resonance 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, SOD1, and SOD2 compared with WT control kidneys 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 was elevated accompanied with increased PGE2 levels (7). Inhibition of prostaglandin synthase by celecoxib or meloxicam or by microsomal prostaglandin synthase-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 has been shown to mediate renal inflammation, oxidative stress, and apoptosis (13). In this study, a novel technique involving the use of chitosan/small interfering RNA nanoparticles was successfully used 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 the 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.

EP2 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 the PGE₂/EP₄ pathway (Fig. 1). COX-2 inhibitors should be used with caution in patients with this disease.

REFERENCES


