Cyclooxygenases, the Kidney, and Hypertension

Hui-Fang Cheng, Raymond C. Harris

Abstract—Selective cyclooxygenase (COX)-2 inhibitors that are in widespread clinical use were developed to avoid side effects of conventional NSAIDs, including gastrointestinal and renal toxicity. However, COX-2 is constitutively expressed in the kidney and is highly regulated in response to alterations in intravascular volume. COX-2 metabolites have been implicated in maintenance of renal blood flow, mediation of renin release, and regulation of sodium excretion. COX-2 inhibition may transiently decrease urine sodium excretion in some subjects and induce mild to moderate elevation of blood pressure. Furthermore, in conditions of relative intravascular volume depletion and/or renal hypoperfusion, interference with COX-2 activity can have deleterious effects on maintenance of renal blood flow and glomerular filtration rate. In addition to physiological regulation of COX-2 expression in the kidney, increased renal cortical COX-2 expression is seen in experimental models associated with altered renal hemodynamics and progressive renal injury (decreased renal mass, poorly controlled diabetes), and long-term treatment with selective COX-2 inhibitors ameliorates functional and structural renal damage in these conditions. (Hypertension. 2004;43:1-6.)

Key Words: COX-2 ▪ COX-1 ▪ hypertension ▪ renin ▪ sodium ▪ glomerular filtration rate ▪ kidney

In the kidney, prostaglandins are important mediators of vascular tone, salt and water balance, and renin release. The rate-limiting enzyme, cyclooxygenase (prostaglandin synthase G/H2) initiates the metabolism of arachidonic acid to prostaglandin (PG) G2 and subsequently to PGH2, which is then further metabolized by tissue-specific isomerases to PGs and thromboxane. There are at least two distinct cyclooxygenases, COX-1 and COX-2, that share ~60% homology1 but are the products of different genes and have distinct patterns of expression and regulation. COX-1 has been termed “constitutive,” because of its wide tissue distribution, while COX-2 has been designated as “inducible” because of its more restricted basal expression and its upregulation by inflammatory and/or proliferative stimuli and its central role in mediation of inflammatory conditions and malignancies.

In human genomic clones. Therefore, it remains uncertain whether COX-3 is present in the macrophage and the macrophage target of the kidney.

Inhibition of COX activity by NSAIDs has been widely used for the treatment of pain and inflammation. Because prostanoids are involved in renal function, nonselective NSAIDs exhibit adverse effects, including salt retention and decreases in glomerular filtration rate (GFR), which may elevate blood pressure (BP) or make pre-existing hypertension worse.3 Based on the hypothesis that COX-1 performs cellular “housekeeping” functions for normal physiological activity and COX-2 acts at inflammatory sites, it was hypothesized that the renal effects of NSAIDs might be linked to COX-1 inhibition. With the advent of selective COX-2 inhibitors, increasing experimental and clinical evidence has also indicated important roles for COX-2 metabolites in physiological and pathophysiologic modulation of renal function.

Expression of COX-1 and COX-2 in the Kidney

COX-1 is expressed constitutively in the kidney and has been localized to mesangial cells, arteriolar endothelial cells, parietal epithelial cells of Bowman’s capsule, and cortical and medullary collecting ducts.4 COX-2 mRNA and immunoreactive protein are present at low but detectable levels in normal adult mammalian kidney. In the renal cortex, there is localized expression of COX-2 mRNA and immunoreactive protein in the cells of the macula densa and in scattered cells in the cortical thick ascending limb (cTAL) cells immediately adjacent to the macula densa (MD).5 In human kidney, COX-2 expression has also been noted in podocytes and arteriolar smooth muscle cells.4 COX-2 is expressed in the MD/cortical thick ascending limb Henle (cTALH) region of the kidney of a wide variety of mammals, including mouse, rat, rabbit, and dog.5,6 Furthermore, despite initial controversy regarding COX-2 localization in primate and human kidney,4,6 more recent studies confirm a similar distribution of COX-2 in MD, especially in the elderly and in patients with
Renal Cortical COX-2

It has been found in animal experiments that COX-2 expression increases at the MD/cTAL region in response to a salt-deficient diet and decreases in response to a high-salt diet, whereas in the medulla, COX-2 expression decreases with salt depletion and increases with a high-salt diet. Increased COX-2 activity may promote organic osmolyte accumulation and adaptation of renal medullary interstitial cells to hypertensive stress.8

In the mammalian kidney, the MD is involved in regulating arterial tone and renin release by sensing alterations in luminal chloride via changes in the rate of Na+/K+/2Cl− cotransport.9 Studies in vivo, in isolated perfused kidney, and in isolated perfused juxtaglomerular preparations have all shown that administration of non-specific cyclooxygenase inhibitors will blunt increases in renin release mediated by MD sensing of decreases in luminal NaCl (reviewed in10). High renin states, as are seen with salt deficiency, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers, diuretic administration, or experimental renovascular hypertension lead to increased MD/coTALH COX-2 expression.5,11–14 The in vivo studies with ACEIs and angiotensin II receptor blockers and in vitro studies using cultured cortical cTALH cells suggest a feedback inhibition of COX-2 expression by angiotensin II and/or mineralocorticoids.13

Previous studies demonstrated that alterations in intraluminal chloride concentration are the signal for MD regulation of tubuloglomerular feedback (TGF) and renin secretion, with high chloride stimulating TGF and low chloride stimulating renin release. Ion substitution experiments of tubular perfusate demonstrated that substitution of other cations for sodium did not affect renin secretion, whereas substitution of other anions for chloride led to increased renin secretion.15 Angiotensin II directly stimulates MD Na+2Cl−K cotransporter via apical AT1 receptors.16 The Na+/K+/2Cl− cotransporter possesses a high affinity for Na+ and K+, such that minimal alterations in transport occur with physiological changes of Na+ or K+ concentrations; however, the affinity for chloride is lower and falls within the range of loop chloride values, thereby resulting in an uptake mechanism that is very sensitive to any change in luminal chloride.17 When cultured cTALH or MD cells were incubated in media with selective substitution of chloride ions, COX-2 expression and prostaglandin production were significantly increased,18,19 mediated by transcriptional and posttranscriptional mechanisms.20

Most but not all experimental studies have supported a role for COX-2 in MD mediation of renin release.14,19,21–25 In isolated perfused glomerular preparations, renin release induced by MD perfusion with a low chloride solution was inhibited by a COX-2 inhibitor but not a COX-1 inhibitor.22 In vivo studies in rats indicated that increased renin release in response to low-salt diet, ACEI, loop diuretics, or aortic coarctation could be inhibited by administration of COX-2–selective inhibitors.13,14,19,23,26–27

In mice with genetic deletion of COX-2, ACEIs or low-salt diet failed to increase renal renin expression, although renin significantly increased in wild-type mice.28 In contrast, in COX-1 null mice there were no significant differences in ACEI-stimulated level of renal renin activity from plasma or renal tissue compared with wild-type mice.29

Furthermore, the COX-2 inhibitor, SC58236, blocked ACEI-induced elevation in renin activity to a similar degree in wild-type and COX-1 knockout mice, further confirming that metabolites of COX-2 rather than COX-1 mediate ACEI-induced renin increases.

Randomized crossover studies in healthy humans administered furosemide and/or low-sodium diet have also demonstrated inhibition of renin release by the COX-2 inhibitor, rofecoxib.30 In addition, in patients with hyperprostaglandin E syndrome/antenatal Bartter syndrome who have genetic abnormalities in thick limb/MD NaCl reabsorption, rofecoxib administration suppresses hyperreninemia as effectively as indomethacin, further supporting a role for COX-2 metabolites in mediation of renin release.30

Studies of prostanooid-dependent control of renal blood flow and GFR by the MD indicate vasodilator and vasoconstrictor prostanooids may contribute to regulation of TGF. Vasodilatory PGs appear to maintain renal blood flow and GFR in the face of vasoconstrictors, such as angiotensin II or norepinephrine, by blunting constriction of the afferent arteriole. Some studies suggest that COX-2–derived prostanooids are predominantly vasodilators,31 and a recent study by Peri-Peterdi et al has directly demonstrated COX-2 –derived PGE2 release by MD.32 By inhibiting the production of PGs that contribute to maintenance of vasodilation of adjacent afferent arterioles, COX-2 inhibition may contribute to the decrease in GFR observed in patients using NSAIDs or selective COX-2 inhibitors.32

The effect of COX-2–specific inhibitors on renal hemodynamics has been investigated in recent years. In anesthetized dogs, nimesulide infusion had no effects on arterial pressure or renal hemodynamics but did reduce urinary sodium excretion, urine flow rate, and fractional lithium excretion during normal sodium intake. In contrast, nimesulide administration increased arterial pressure and decreased renal blood flow, urine flow rate, and fractional lithium excretion during low sodium intake.33 Roig et al showed that COX-2–derived metabolites play a more important role in the long-term regulation of renal hemodynamic when sodium intake is low.34 In healthy human subjects on normal diets, COX-2 inhibitors have minimal effects on renal hemodynamics.35 However, COX-2 inhibitors decrease GFR in salt-depleted subjects or elderly.36–38
Therefore, COX-2 expression in the renal cortex seems to be inhibited by angiotensin II and stimulated under conditions of low sodium intake or diuretic administration. If the activity of the renin-angiotensin system is diminished or insufficient to maintain electrolyte balance, then, at least in some circumstances, increased COX-2 expression and synthesis of PGs activate expression and release of renin, leading to increased activity of angiotensin II and aldosterone and resulting in increased tubule reabsorption, thereby facilitating reestablishment of intravascular volume homeostasis. Once this is achieved, the expression of COX-2 is reduced through inhibition by angiotensin II, decreasing a stimulus for renin production and release.\footnote{9,40} Thus, PGs facilitate the TGF response to low salt delivery to MD by increasing angiotensin II levels and by preventing angiotensin II from decreasing GFR. COX-2–derived PGs may be involved in maintaining sodium excretion, GFR and renal blood flow, especially in elderly and/or patients with decreased circulating volume. In states of relative or absolute intravascular volume depletion, COX-2 inhibitors may exert deleterious effects on renal function. Caution should be made in individuals with volume depletion or decreased organ perfusion, such as those with chronic heart failure, hepatic cirrhosis, chronic renal disease, protracted dehydration, or in the elderly.\footnote{41}

### Renal Medullary COX-2

Medullary PGE\textsubscript{2} plays an important role in regulating NaCl and water reabsorption in the medullary thick ascending limb and collecting duct. Sodium retention is a well-recognized side effect of nonselective NSAIDs.\footnote{42} Because COX-1 is abundantly and constitutively expressed in cortical and medullary collecting duct, COX-1–derived prostaglandins appear to be involved in the natriuretic response. In this regard, acute increase in renal interstitial hydrostatic pressure by direct renal interstitial volume expansion is known to increase sodium excretion, and infusion of non-selective NSAIDs, but not COX-2 inhibitors, will blunt this natriuretic response.\footnote{43} Furthermore, in a rat model of cirrhosis and ascites, a COX-1 selective inhibitor but not a COX-2 selective inhibitor decreased sodium excretion and impaired the diuretic and natriuretic responses to furosemide.\footnote{44}

However, COX-2–derived prostaglandins also appear to be involved in modulating sodium excretion. Salt loading downregulates COX-2 expression in renal cortex but upregulates its expression in renal medulla.\footnote{45} The increased COX-2–derived PGs may mediate natriuresis. Infusion of the COX-2 inhibitor, nimesulide, in dogs reduced urinary sodium excretion.\footnote{46} COX-2 inhibitors have also been shown to cause sodium retention in a small percentage of human subjects without renal impairment.\footnote{47,48,49} and decreased urinary sodium excretion for the first 72 hours of administration of COX-2 inhibitors is seen in subjects with salt depletion\footnote{50} or in elderly subjects on a normal-salt diet.\footnote{51,52,53} When renal cortical blood flow (CBF) and medullary blood flow (MBF) were selectively measured in mice, it was found that acute infusion of a COX-1 selective inhibitor did not affect either cortical blood flow or medullary blood flow. In contrast, a COX-2 selective inhibitor significantly reduced medullary blood flow without altering cortical blood flow.\footnote{54}

### COX-2 Inhibitors and Hypertension

NSAIDs may elevate BP and antagonize the BP-lowering effect of antihypertensive medication to an extent that may potentially increase hypertension-related morbidity.\footnote{49} COX-2 inhibitors may also affect BP (Figure). Rofecoxib significantly elevated systolic BP (SBP) in SHR or WKY rats with normal-salt or high-salt diet, but not in rats on low-salt intake, which suggested that the hypertension induced by COX-2 inhibition can occur independently of a genetic predisposition to hypertension and can be prevented by salt deprivation.\footnote{50} In mice COX-2 inhibition enhanced the pressure effect of angiotensin II.\footnote{51}

In double-blind, randomized, controlled, clinical trials, conflicting results have been obtained about the influence of COX-2 inhibitor treatment on BP. It is somewhat difficult to compare these trials, because there are variations in design, subject characteristics, endpoints, COX-2 inhibitors investigated, and methods of BP measurement. In this regard, in the two large trials designed to investigate the safety of COX-2 inhibitors, the Celecoxib Long-Term Arthritis Safety Study (CLASS) study (celecoxib) and the Vioxx Gastrointestinal Outcomes Research Study (VIGOR) study (Rofecoxib) both found evidence for increased BP in a minority of subjects less than or equal to (CLASS) or greater than (VIGOR) the NSAID comparators.\footnote{52-54} In a review of clinical studies involving more than 13 000 subjects, Whelton et al found that the overall incidence of renal adverse events induced by celecoxib was greater than seen with placebo and similar to NSAIDs.\footnote{55} The Successive Celecoxib Efficacy and Safety Studies (SUCCESS) VI\footnote{55} and VII\footnote{56} studies compared the renal safety in older hypertensive OA patients (890 and 1092 patients in VI or VII, respectively) and found that at week 6, rofecoxib was more likely to increase the SBP than celecoxib. Rofecoxib caused the greatest increase in SBP in patients receiving ACE inhibitors or \(\beta\)-blockers, whereas those on calcium channel antagonists or \(\beta\)-blockers receiving either celecoxib or rofecoxib showed no significant effect of inhibition of COX-2 on BP.\footnote{57} RAS indicates renin-angiotensin system; ET, endothelin.
increases in BP. However, in a randomized, double-blind, placebo-controlled, parallel-group, clinical trial involving 178 patients with essential hypertension, using 24-hour ambulatory recordings, high doses (400 mg per day, twice the recommended dose) of celecoxib did not show significant alteration of the antihypertensive effect of the ACEI, lisinopril during a 4-week period.56 The effects of most antihypertensive agents, except calcium channel blockers and angiotensin II receptor antagonists, require the synthesis of vasodilator PGs;3,41 recent studies have suggested that at least one COX-2 inhibitor, rofecoxib, appears to interfere with antihypertensive effects of ACEIs and β-blockers, but not calcium channel blockers.55 The Table indicates clinical studies that have examined the effect of COX-2 inhibitors on BP.

**COX-2 Expression in Hyperfiltering States**

In a rat model of subtotal renal ablation, selective increases in renal cortical COX-2 expression can be detected in the region of the MD without significant alterations in COX-1 expression.57 In addition, there was detectable COX-2 immunoreactivity in some glomeruli from remnant kidneys, with increased expression in podocytes and mesangial cells.57 Of interest, COX-2 expression has been reported in podocytes of human kidney.4 Isolated glomeruli from remnant kidneys also demonstrated selective increases in COX-2 immunoreactivity and increased PGE2 production in response to exogenous arachidonic acid, which was inhibited by a COX-2 selective inhibitor.57

In addition to the remnant model, increased MD COX-2 expression is also seen in rats with streptozotocin-induced diabetes.58,59 Komers et al found that in rats with moderately controlled streptozotocin-induced diabetes, GFR was increased and acute administration of a selective COX-2 inhibitor returned the GFR to control levels.58 In hyperfiltering states, TGF is reset at a higher distal tubular flow rate, and there is decreased myogenic tone of the afferent arteriole, which is corrected by inhibition of cyclooxygenase activity.60 Although we have not yet determined the signals mediating increased COX-2 expression in this diabetic model, it is worth noting that recent studies have indicated that glomerular hyperfiltration in diabetic rats occurs as compensation for increased proximal fractional reabsorption and a decrease in electrolyte load to the distal nephron, resulting in resetting

<table>
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<th>Reference</th>
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<tr>
<td>CLASS46</td>
<td>8059 patients with OA or RA, 6 months</td>
<td>HTN: 1.7% celecoxib (400 mg bid) vs 2.3% ibuprofen (800 mg tid) diclofenac (75 mg bid)</td>
</tr>
<tr>
<td>VIGOR5,52</td>
<td>8076 patients with RA, 9 months</td>
<td>HTN: 10% rofecoxib (25 mg/d), 4.7% rofecoxib (12.5 mg/d)</td>
</tr>
<tr>
<td>Welton et al51</td>
<td>From 50 clinical studies involving more than 13,000 subjects, up to 12 weeks</td>
<td>HTN: 0.8% celecoxib, 0.7% NSAID, 0.3% placebo; 0.6% exacerbation of preexisting HTN, not time-related or dose-related</td>
</tr>
<tr>
<td>White et al56</td>
<td>178 patients with essential HTN; 2.6/1.5+/--0.9/0.6 mm Hg on celecoxib vs (200 mg bid) 87 with placebo</td>
<td>Changes from baseline in the 24-h SBP/DBP on lisinopril, 91 with 1.0/0.3 ±1/0.6 mm Hg on placebo, NS</td>
</tr>
<tr>
<td>Rossat et al 56</td>
<td>40 salt-depleted subjects, 7 days</td>
<td>Celecoxib had no effect on SBP, but transient decreases in RBF and GFR with high dose of 400 mg on day 1</td>
</tr>
<tr>
<td>Emery et al 44</td>
<td>655 patients with RA, 24 weeks</td>
<td>Mean SBP and DBP fell 1–2 mm Hg in celecoxib (200 mg bid) or diclofenac (75 mg bid)</td>
</tr>
<tr>
<td>Catella-Lawson et al55</td>
<td>36 healthy older adults (59–80 years), 2 weeks</td>
<td>BP did not change: 125.2 ±11.2/72.0 ±6.6 mm Hg in placebo; 129.4 ±9.6/75.9 ±5.2 in MK 966; 127.3 ±14.7/71.8 ±7.4 in indomethacin; transient decline of Ua in both; decreased GFR in indomethacin</td>
</tr>
<tr>
<td>Geba et al45</td>
<td>382 patients with OA, 6 weeks</td>
<td>HTN: 1.1% celecoxib (200 mg); 2.1% rofecoxib (12.5 mg); 1.1% rofecoxib (12.5 mg); 3.2% acetaminophen (4 g).</td>
</tr>
<tr>
<td>Simonet et al47</td>
<td>1149 patients with RA, 12 wk</td>
<td>HTN: no significant difference in placebo, 100-, 200-, or 400-mg celecoxib and naproxen (&lt;1/200 in all groups)</td>
</tr>
<tr>
<td>SUCCESS VI and VII45</td>
<td>810 (VI) &amp; 1092 (VII) patients with OA older than 65 y taking antihypertensive drugs, 6 weeks</td>
<td>BP: ±2.6 mm Hg in rofecoxib (25 mgm), −0.5 mm Hg in celecoxib (200 mg); patients increased SBP:14.9 vs 6.9%, respectively</td>
</tr>
<tr>
<td>Collantes et al 46</td>
<td>Conducted at 67 sites in 28 countries, including 1171 long-term NSAD users with RA, 12 weeks</td>
<td>HTN: none in placebo (0/357) or etoricoxib (90 mg) (0/335), only 1/181 in naproxen (1000 mg)</td>
</tr>
<tr>
<td>Dilger et al47</td>
<td>12 normotensive subjects in each, young (mean: 32 years) and elderly (68 years), 2 weeks</td>
<td>Neither in young nor in elderly were significant BP and renal functions affected by short-term treatment with celecoxib (200 mg bid) or diclofenac (75 mg bid)</td>
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<td>Schwartz et al 46</td>
<td>67 healthy elderly subjects on a sodium-replete diet, 4 weeks</td>
<td>Rofecoxib (25 mg/d), celecoxib (200 mg bid) and naproxen (500 mg bid) increased SBP similarly (3.4, 4.3, and 3.1 mm Hg, respectively, vs −1.4 mm Hg for placebo)</td>
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<tr>
<td>Chan et al46</td>
<td>287 patients with OA and ulcer bleeding history for 6 months</td>
<td>HTN: 13.9% celecoxib (400 mg/d); 18.9% diclofenac (150 mg/d)+ omeprazole (20 mg/d)</td>
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HTN indicates hypertension; GFR, glomerular filtration rate; RBF, renal blood flow; SBP, systolic blood pressure; DBP, diastolic blood pressure.
of TGF to a higher single nephron GFR; this increased proximal reabsorption and resultant decrease in distal nephron electrolyte presentation would also be expected to increase MD COX-2 expression. The vasodilatory component of TGF is inhibited by the selective COX-2 inhibition, suggesting that COX-2–mediated prostanoids may be essential for arteriolar vasodilation.64 Long-term administration of a selective COX-2 inhibitor significantly decreased proteinuria and inhibited development of glomerular sclerosis in rats with reduced functioning renal mass.57 These effects were seen in the absence of any detectable changes in SBP, suggesting that any "renoprotective" effects seen with the COX-2 inhibitor were not secondary to modulation of systemic BP.57 These studies confirm and extend the recent findings of Fujihara et al that prolonged treatment with a combination cyclooxygenase inhibitor/nitric oxide donor significantly decreased progression of glomerular injury in rats with remnant kidneys.62

In a model of diabetes with superimposed DOCA-salt hypertension, long-term administration of a selective COX-2 inhibitor also significantly decreased proteinuria and reduced extracellular matrix deposition, as indicated by decreases in immunoreactive fibronectin expression and mesangial matrix expansion. In addition, COX-2 inhibition reduced expression of transforming growth factor-β, plasminogen activator inhibitor-1, and vascular endothelial growth factor in the kidneys of the diabetic hypertensive animals.59

In summary, COX-2 is expressed in the mammalian kidney in a localized distribution, and its expression is physiologically regulated in response to alterations in volume status. The regulation of enzyme expression in response to alterations in extracellular ionic composition indicates potentially important roles in modulation of renal regulation of salt and water homeostasis. Similar to NSAIDs, COX-2 inhibitors may elevate BP in a subset of patients, and caution should be taken when COX-2 inhibitors are prescribed, especially in high-risk patients (including elderly and patients with volume depletion). Finally, recent animal studies have suggested a possible pathophysiologic role for COX-2 in models of progressive renal injury.

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