Review article

Renal Effects of Prostaglandins and Cyclooxygenase-2 Inhibitors

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Prostaglandins (PGs) with best-defined renal functions are PGE_2 and prostacyclin (PGI_2). These vasodilatory PGs increase renal blood flow and glomerular filtration rate under conditions associated with decreased actual or effective circulating volume, resulting in greater tubular flow and secretion of potassium. Under conditions of decreased renal perfusion, the production of renal PGs serves as an important compensatory mechanism. PGI_2 (and possibly PGE_2) increases potassium secretion mainly by stimulating secretion of renin and activating the renin-angiotensin system, which leads to increased secretion of aldosterone. In addition, PGE_2 is involved in the regulation of sodium and water reabsorption and acts as a counterregulatory factor under conditions of increased sodium reabsorption. PGE_2 decreases sodium reabsorption at the thick ascending limb of the loop of Henle probably via inhibition of the Na^+-K^+-$2Cl^-$ cotransporter type 2 (NKCC2). Cyclooxygenase inhibitors may enhance urinary concentrating ability in part through effects to upregulate NKCC2 in the thick ascending limb of Henle's loop and aquaporin-2 in the collecting duct. Thus, they may be useful to treat Bartter's syndrome and nephrogenic diabetes insipidus.

Key Words : prostaglandins; kidney; sodium; kidney concentrating ability

Introduction

Prostaglandins (PGs) regulate vascular tone and salt and water homeostasis in the mammalian kidney and are involved in the mediation and/or modulation of hormonal action. Cyclooxygenase (COX; prostaglandin G_2/H_2 synthase) is the enzyme responsible for the initial rate-limiting step in the metabolism of arachidonic acid to the PGs, yielding PGH_2 in a two-step reaction. PGH_2 is subsequently metabolized by several distinct enzymes to the primary bioactive prostaglandins, including PGE_2, PGI_2, PGD_2, $PGF_{1\alpha}$, and thromboxane A_2[1].

Sir John Vane's seminal observation that COX was the target of aspirin[2] provided confirmation that PGs are local mediators of inflammation and modulators of physiological functions, including the maintenance of gastric mucosal integrity, the modulation of renal microvascular hemodynamics, renin release, and tubular salt and water reabsorption. The pharmaceutical industry subsequently developed a number of non-steroidal anti-inflammatory drugs (NSAIDs), whose mechanism of action involves competitive or non-competitive inhibition of COX activity.

The PGs that are most important in the kidney are PGE_2 and prostacyclin (PGI_2). These vasodilatory PGs increase renal blood flow and glomerular filtration rate (GFR) under conditions associated with decreased actual or effective circulating volume. In addition, PGE_2 is involved in the regulation of sodium and water reabsorption and PGI_2 increases potassium secretion mainly by stimulating secretion of renin.

Received February 11, 2008. Accepted April 1, 2008.
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Synthesis and cellular actions of prostagladin E_2 and prostagladin I_2 in the kidney

PGE_2 and PGI_2 are widely synthesized in the kidney where they regulate hemodynamics and tubular transport[3]. Tubules produce primarily PGE_2 but also PGI_2. PGE_2 is the major prostaglandin synthesized in the medulla, whereas PGI_2 is the major prostaglandin synthesized by renal vessels and glomeruli[3, 4]. PGI_2 is synthesized predominantly in glomerular endothelial and epithelial cells, whereas PGE_2 is synthesized predominantly in mesangial cells.

The most abundant PG receptors in the kidney are those for PGE_2[5]. Four seven-transmembrane-spanning domain prostaglandin E (EP) receptor subtypes have been cloned from the mouse kidney. Collecting ducts express the EP1 receptor, glomeruli express the EP2 receptor, and tubules of the outer medulla and cortex express the EP3 receptor. The medullary thick ascending limb (mTAL) expresses high levels of EP3 receptor mRNA and the glomerulus expresses high levels of EP4 receptor mRNA[5, 6].

The EP1 receptor has the highest affinity for PGE_2[5]. Its activation stimulates Ca^{2+} mobilization[5]. Activation of the EP1 receptor by PGE_2 is followed by contraction of vascular smooth muscle cells, increases in intracellular Ca^{2+} in mesangial cells[3, 5], and inhibition of Na^+ absorption by rabbit collecting ducts[5].

The EP3 receptor is expressed predominantly in the mTAL and cortical collecting ducts[5]. There are a number of splice variants yielding different isoforms[5, 6]. The EP3 receptor signals by way of a pertussis toxin-sensitive Gi leading to inhibition of adenylate cyclase[5]. The expression of EP3 receptors in the mTAL, but not the cortical thick ascending limb (cTAL), may account for why PGE_2 inhibits Cl^--transport in the rabbit selectively in the mTAL[6]. The EP3 receptor mediates the inhibition of arginine vasopressin-stimulated water permeability by PGE_2 in the cortical collecting duct[6].

EP2 and EP4 receptors share similar signaling mechanisms and physiologic characteristics. Their stimulation activates Gs coupled to adenylate cyclase and elevates levels of cyclic adenosine 3'5'-monophosphate (cAMP)[3, 5]. EP2 receptors and cAMP accumulation mediates the effect of PGE_2 to vasodilate in blood vessels[3] and decrease water reabsorption in the cortical collecting duct[6].

The IP receptor is activated by PGI_2. It is distributed throughout the renal cortex and medulla[5]. This seven-transmembrane-spanning receptor is coupled to generation of cAMP. It is activated selectively by cicaprost and iloprost[3, 5], which vasodilate renal arterioles and inhibit water permeability of the cortical collecting ducts[5].

Physiologic roles of prostagladin E_2 and prostagladin I_2 in the kidney

PGE_2 and PGI_2 mediate several natriuretic responses. The natriuresis that accompanies an increase in renal perfusion (pressure natriuresis) or interstitial pressure is dependent on PGs[3]. Because intrarenal infusion of PGE_2, but not PGI_2, restores the pressure natriuresis during COX inhibition[7], PGE_2 is probably the primary vasodilator PG responsible.

PGE_2 decreases sodium reabsorption at the thick ascending limb of the loop of Henle probably via inhibition of the Na^+-K^+-$2Cl^-$ cotransporter type 2 (NKCC2)[8]. COX inhibitors enhance urinary concentrating ability, in part, through effects to increase the NKCC2 abundance in the thick ascending limb of Henle's loop[9].

PGI_2 stimulates renin release, which in turn increases aldosterone[10, 11]. Aldosterone increases sodium reabsorption and potassium secretion at the distal nephron. Prostacyclin is also a potent vasodilator that maintains GFR and renal blood flow in patients with decreased actual or effective circulating volume[10, 11]. In healthy individuals, the vasodilatory role of PGI_2 is not operative and has little importance in renal hemodynamics.

Arginine vasopressin releases kinins into the distal nephron and renal interstitial space where they enhance PGE_2 synthesis in the collecting ducts. The increase in PGE_2 inhibits the hydroosmotic effect of vasopressin and increases the medullary blood flow[12]. Therefore, PGE_2 is an important buffer of vasopressin-induced free water absorption. PGs also buffer the renal vasoconstrictor and

antidiuretic actions of angiotensin II[3, 13].

Vasodilator PGs increase renal blood flow and GFR[3]. Urinary sodium excretion is decreased by the PGI_2 mimetic, iloprost, but is increased by PGE_2, probably secondary to an increase in renal interstitial hydrostatic pressure[12]. In contrast, the EP2 and EP3 receptor agonist, misoprostol, causes vasoconstriction and a decrease in GFR in humans[3]. Thus, the multiple EP receptors located throughout the nephron have complex and even antagonistic effects on hemodynamics and NaCl transport.

Efficient renal autoregulation is dependent on tubuloglomerular feedback (TGF) and myogenic responses. Whereas COX metabolites do not appear essential for autoregulation, they do modulate TGF responses[3, 14]. COX inhibition with indomethacin blunts TGF responses[3, 15], but these recover before there is a return of PG excretion[3]. However, the effects of indomethacin do appear to be due to inhibition of PG synthesis because local microperfusion of PGs into the macula densa restores TGF responses in indomethacin-treated rats[14]. The reason for these discrepancies has not been resolved. Endogenous generation of vasoconstrictor PGs and TxA_2 enhance the sensitivity and responsiveness of TGF[14]. Therefore, COX metabolites are important positive and negative modulators of TGF.

PGs regulate release of renin[3, 16]. PGI_2 or PGE_2 stimulates renin release and COX inhibition suppresses it[16, 17]. COX inhibition in the rabbit isolated perfused juxtaglomerular apparatus nearly abolishes renin release in response to decreased luminal concentration of NaCl[17]. Because COX-2, but not COX-1, can be expressed in the macula densa or adjacent TAL cells of the rat and mouse nephron[16], it may be the isoform responsible for mediation of macula densa-dependent renin release in these species.

Expression of clyclooxygenase-1 and clyclooxygenase-2 in the kidney

COX-1 is expressed constitutively in the kidney and has been localized to mesangial cells, arteriolar smooth muscle and endothelial cells, parietal epithelial cells of the Bowman's capsule, and cortical and medullary collecting ducts[18]. COX-2 is inducible in most tissues in response to injury or inflammation, but COX-2 mRNA and immunoreactive protein are present at detectable levels in normal adult mammalian kidneys. In the renal cortex, there is localized expression of COX-2 mRNA and immunoreactive protein in the cells of the macula densa (MD) and in scattered cells in the cortical thick ascending limb immediately adjacent to the MD[16, 19, 20]. In the human kidney, COX-2 expression also has been reported to be present in podocytes and arteriolar smooth muscle cells[18, 21].

COX-2 expression is also abundant in the lipid-laden medullary interstitial cells in the inner medulla and papilla[16, 19]. Some investigators have reported that COX-2 may also be expressed in inner medullary collecting duct cells or intercalated cells in the renal cortex[22]. Nevertheless constitutively expressed COX-1 is clearly the most abundant isoform in the collecting duct, so the expression and physiologic significance of COX-2 co-expression in these cells remains uncertain. A recent report in the human kidney has suggested that there is also significant COX-2 expression in the medullary vasa recta[21].

Regulation of clyclooxygenase-2 in the kidney

PG generation is enhanced by angiotensin II, which occurs during dietary salt restriction[23]. 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[16]. Increased COX-2 activity may promote organic osmolyte accumulation and adaptation of renal medullary interstitial cells to hypertonic stress[24].

In lithium-induced polyuria, COX-2 expression was reported to be decreased in the inner medulla and increased in cortex and outer medulla[25]. Studies in vivo, in the 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[26]. High renin states, as are seen

with salt deficiency, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers, diuretic administration, or experimental renovascular hypertension lead to increased MD/cTALH COX-2 expression[16, 27, 28]. The in vivo studies with ACEIs and angiotensin II receptor blockers and in vitro studies using cultured cortical cTAL cells suggest a feedback inhibition of COX- 2 expression by angiotensin II and/or mineralocorticoids[28].

Medullary PGE_2 plays an important role in regulating NaCl and water reabsorption in the medullary thick ascending limb and collecting duct. Salt loading downregulates COX-2 expression in the renal cortex, but upregulates its expression in the renal medulla[29]. The increased COX-2-derived PGs may mediate natriuresis especially when dietary sodium intake is high. Recent compelling evidence indicates that the renal medulla is a critical site of intrarenal COX-2 activity's protection against the development of systemic hypertension during high-salt intake[30], because selective intramedullary infusion of a COX-2 inhibitor or COX-2 antisense oligonucleotides caused animals to develop hypertension when they were placed on a high-salt diet.

Effect of clyclooxygenase-2 inhibitors on salt and water homeostasis

Nonselective NSAIDs have been reported to induce peripheral edema in up to 5% of the general population[10]. COX-2 inhibitors will cause sodium retention occasionally in humans without renal impairment[31, 32], and in balanced studies that were performed in a clinical research center environment, administration of COX-2 inhibitors consistently decreased urinary sodium excretion for the first 72 hours of administration[33, 34]. The relative amount of lower extremity edema has been documented to be greater with 25 mg/d rofecoxib than with 200 mg/d of celecoxib[35].

Nonselective NSAIDs may elevate blood pressure (BP) and antagonize the BP-lowering effect of antihypertensive medications, including diuretics, angiotensin-converting enzyme (ACE) inhibitors, and β blockers, to an extent that may potentially increase hypertension-related morbidity[36]. COX-2 inhibitors also have been shown to affect BP. In studies that involved experimental animals, rofecoxib was shown to significantly elevate systolic BP in SHR or WKY rats that were fed a normal-salt or high-salt diet but not a low-salt diet, which suggests that the hypertension that is induced by COX-2 inhibition can occur independent of a genetic predisposition to hypertension and can be prevented by salt deprivation[37]. In mice, COX-2 inhibition enhances the pressor effect of angiotensin II[38].

Effects of clyclooxygenase-2 inhibitors on renin and renal hemodynamics

Measurements in vivo in isolated perfused rat kidneys and in isolated perfused juxtaglomerular preparations all indicated that administration of nonspecific COX inhibitors prevents the increases in renin release that are mediated by MD sensing of decreases in luminal NaCl[39]. Studies using experimental animals have indicated that selective COX-2 inhibitors can significantly decrease plasma renin levels, renal renin activity, and mRNA expression under certain high-renin states[40].

Most[28, 41], but not all experimental studies[42] have indicated a role for COX-2 in MD mediation of renin release. Randomized crossover studies in healthy humans who were administered furosemide and/or a low-sodium diet demonstrated inhibition of renin release by the COX- 2 inhibitors rofecoxib and meloxicam. In addition, in patients with hyperprostaglandin E syndrome/antenatal Bartter's 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[43].

Vasodilatory PGs seem to be critical for maintaining renal blood flow (RBF) and GFR during volume-depleted states associated with increased circulating vasoconstrictors, such as Ang II or norepinephrine, by blunting constriction of the afferent arteriole[44]. By inhibiting the production of PGs that contribute to maintenance of vasodilation of adjacent afferent arterioles, COX-2 inhibition may contribute to the decline in GFR that is observed in patients who take NSAIDs or selective COX-2 inhibitors.

When renal cortical blood flow (CBF) and medullary blood flow (MBF) were selectively measured in mice, it was found that acute infusion of COX-1 selective inhibitors did not affect either CBF or MBF. In contrast, COX-2 selective inhibitors significantly reduced MBF without altering CBF; chronic pretreatment with a COX-1 inhibitor did not modify the effect of angiotensin II infusion, whereas angiotensin II significantly reduced MBF in mice that were pretreated with a COX-2 inhibitor or in COX-2 knockout mice[38]. In healthy humans who were on normal-sodium diets, COX-2 inhibitors had minimal effects on renal hemodynamics[31, 33]. However, COX-2 inhibitors significantly decreased GFR in salt-depleted subjects[45]. As further evidence of an important role for COX-2 in regulation of renal hemodynamics and renin production arise, acute ischemic renal insufficiency and hyperkalemia/type 4 renal tubular acidosis are being reported as acute nephrotoxic effects of COX-2 inhibitors, especially in older adults[46].

Use of clyclooxygenase-2 inhibitors in Bartter's syndrome and nephrogenic diabetes insipidus

Bartter syndrome is a genetic renal tubular group of diseases characterized by sodium, potassium, and chloride urinary wasting, hypokalemic metabolic alkalosis with hyperreninemia and hyperaldosteronemia, resistance to the blood pressure-augmenting effect of angiotensin II, and high levels of some urinary prostaglandins. Clinically the patients present with polyuria, polydipsia, failure to thrive, frequent episodes of dehydration, and normal blood pressure. In patients with Bartter syndrome, excessive PGE_2 synthesis and hyperreninemia occurs and is dependent on COX-2 activity. Both indomethacin and rofecoxib can ameliorate clinical symptoms, the typical laboratory findings, and significantly suppressed PGE_2 and its metabolite excretion to normal values[43, 47].

Nephrogenic diabetes insipidus (NDI) is a clinical syndrome in which the kidney is unable to concentrate urine despite normal or elevated concentrations of the antidiuretic hormone arginine vasopressin. For the treatment of NDI, NSAIDs or COX-2 inhibitors have been useful. The oral administration of indomethacin was effective in reducing urine volume in a patient with Li-induced NDI[48]. In a congenital NDI patient, the use of rofecoxib, a COX-2 inhibitor, in combination with hydrochlorothiazide has been shown to maintain normal serum sodium by decreasing urine flow by approximately 72% and decreasing free water clearance by 83% compared with prior combination therapy. Celecoxib, the alternative COX-2 inhibitor, was also effective in lowering urine output in a patient with congenital NDI[49]. We recently reported that treatment of lithium-induced NDI by COX-2 inhibition improved polyuria via upregulation of AQP2 and NKCC2 in the kidney suggesting that the upregulation of AQP2 and NKCC2 in response to the COX-2 inhibition may underlie the therapeutic mechanisms by which NSAIDs or COX-2 inhibitors enhance antidiuresis in patients with NDI[50].

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