Chronic kidney disease: targeting prostaglandin E2 receptors

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Nasrallah R, Hassouneh R, Hébert RL. Chronic kidney disease: targeting prostaglandin E2 receptors. Am J Physiol Renal Physiol 307: F243–F250, 2014. First published June 25, 2014; doi:10.1152/ajprenal.00224.2014.—Chronic kidney disease is a leading cause of morbidity and mortality in the world. A better understanding of disease mechanisms has been gained in recent years, but the current management strategies are ineffective at preventing disease progression. A widespread focus of research is placed on elucidating the specific processes implicated in kidney disease intervention strategies. This review summarizes the major pathogenic mechanisms contributing to initiation and progression of chronic kidney disease, emphasizing the role of hyperglycemia, hypertension, inflammation, and oxidative stress. We have long recognized the multifaceted role of PGs in both the initiation and progression of chronic kidney disease, yet studies are only now seriously contemplating specific EP receptors as targets for therapy. Given the plethora of renal complications attributed to PG involvement in the kidney, this review highlights these pathogenic events and emphasizes the PGE2 receptor targets as options available to complement current therapeutic strategies.

chronic kidney disease; diabetic kidney; EP receptors; prostaglandin E2

CHRONIC KIDNEY DISEASE (CKD) is defined by decreased kidney function and/or damage for 3 mo or more. The leading causes worldwide are hypertension and diabetes, and the aims of therapy are to prevent kidney failure and limit extrarenal complications (42). Diabetic nephropathy accounts for 30–40% of end-stage renal disease (ESRD) requiring replacement therapy in North America, and along with cardiovascular disease causes a great deal of morbidity and mortality (6, 98). CKD is characterized by a progressive nature, the evolution varies considerably, and despite all research efforts the exact pathogenesis remains unclear. All three renal compartments are implicated in the initiation of disease processes, with vascular, glomerular, and tubular events playing various roles (5, 33, 100). In the diabetic kidney, the ultimate decline in renal function is multifactorial. Although current intervention strategies targeting glycemic and blood pressure control can delay renal injury, they fail at preventing the disease course (74), and various add-on therapies to the standard renin-angiotensin-aldosterone system (RAAS) inhibition are now being considered (31, 38, 41, 51, 60, 71, 99).

The main renal changes associated with diabetic nephropathy comprise an initial hyperfiltration with preferential vaso-dilatation of the afferent arteriole, followed by a decline in renal function, hypertrophy of the glomerulus and tubular structures, podocyte injury, expansion of the mesangial matrix leading to glomerular sclerosis, tubulointerstitial fibrosis, and tubular lesions and atrophy. Although glucose is the main determinant, many other factors are involved (12, 33). A number of injurious mechanisms have been delineated, including altered growth responses (proliferation, hyper trophy, and senescence); cell death (apoptosis, necrosis); fibrosis (epithelial-myofibroblast transdifferentiation); and altered transport processes. Several detailed reviews highlight these various pathomechanisms (12, 14, 16, 30, 33, 68, 76, 79, 83, 94, 101). There is a recent emphasis on inflammation and oxidative stress as culprits leading to glomerular scarri ng and tubulointerstitial fibrosis; and the role of hyperglycemia, hypertension, oxidative stress, and inflammation are summarized below.

The role of hyperglycemia in CKD is quite complex. Kanwar et al. (33) provide an extensive review of the various hyperglycemia-induced responses. While glucose can have detrimental effects on cells by initiating various pathogenic responses, i.e., accumulation of advanced glycosylation end products (AGEs), activation of PKC and MAPK, as well as the polycystic kidney pathway, the role of hyperglycemia in disease progression may be less important (103); and tight glycemic control does not always prevent further injury and evolution to ESRD (109). The sustained responses to glucose are more likely mediated by other factors like transforming growth factor-β (TGF-β) and the renin-angiotensin aldosterone system (RAAS). Activation of the renal RAAS is central in the pathogenesis of CKD, altering both renal function and inducing injury, and the main target for therapy (37). TGF-β is the main regulator of the renal fibrotic process, which is a common feature of CKD characterized by cytoskeletal reorganization, matrix changes, and scarring (14, 33, 44, 100, 119).
CKD causes hypertension, but an important pathogenic factor in the progression of CKD is hypertension. The kidney plays a key role in the long-term regulation of blood pressure, especially mediated by the pressure-natriuresis response in the healthy state. Renin is released from the macula densa to produce angiotensin II and aldosterone, which in turn have a number of systemic and renal effects to regulate blood pressure via modifying vascular tone and sodium and water balance. The detailed mechanisms are beyond the scope of this review, but they are clearly delineated in a number of reviews (15, 25). The RAAS is the most significant physiological regulator of blood pressure, and the main target of current therapies to stop renal disease progression, either through inhibition of angiotensin converting enzyme (ACE inhibitors) or angiotensin AT1 receptor blockers (113, 118). The RAAS has been shown to contribute to all aspects of diabetic nephropathy, glomerular filtration rate (GFR), proteinuria, and kidney injury (76). The role of ACE2, angiotensin 1–7, and the Mas receptor in CKD was also recently reviewed (82), but the nature of their involvement remains debatable.

The role of inflammation in CKD has received overwhelming recognition in recent years. Several reviews describe the plethora of pathways involved (7, 57, 75, 106, 111). Inflammatory changes are detected in the initial stages of kidney disease, and controlling inflammatory responses is key to preventing or delaying further injury. A number of inflammatory cytokines are involved like tumor necrosis factors (TNF-α), IFN-γ, and interleukins (IL-1β, IL-6, IL-18), by activating a number of signaling pathways such as NF-κB, MAPK, PKC, cyclooxygenase (COX)-2, and nitric oxide (7, 14, 50, 57, 96, 111). Macrophage infiltration and increased monocyte chemoattractant protein-1 and intercellular adhesion molecule-1 can recruit inflammatory cells and affect cellular integrity, contributing to renal injury in diabetes (27, 100). Macrophage infiltration is also associated with mesangial expansion and podocyte injury in diabetes (61, 95), and suppression of inflammation alleviates glomerular lesions and tubulointerstitial fibrosis (14, 32).

Reactive oxygen species (ROS) regulate glomerular hemodynamics as well as tubular transport properties. However, when production becomes excessive, as seen in CKD, the outcome is detrimental to the cell (34, 73). Small et al. (84) provide a recent review of the role of oxidative stress in CKD: altering growth responses, promoting apoptotic signals, increasing matrix deposition, and inducing epithelial-to-myofibroblast transformation. A number of signaling pathways are activated by oxidative stress, leading to kidney injury. NADPH oxidase 4 (NOX-4) has received substantial interest lately, with respect to diabetic and other chronic kidney diseases, but the involvement is controversial both contributing to and protecting against renal injury (reviewed in Ref. 14). We recently reviewed the role of various NADPH oxidases in renal ROS production and their role in kidney diseases like diabetic nephropathy (81).

COXs, PGE2, and EP Receptors

PGs are produced by cyclooxygenases and specific synthases, which metabolize arachidonic acid into five major products; PGE2 being the major renal metabolite. The COX cascade is illustrated in Fig. 1, highlighting the multiple signaling pathways triggered by PGE2 in the kidney. We have previously provided an exhaustive review of the major renal prostanooid systems and the enzymes involved in their synthesis (53). All renal cell types can synthesize PGE2, but the highest production is seen in the glomeruli and collecting ducts. To date, three PGE2 synthases have been identified in the kidney: microsomal PGE synthase 1 and 2 (mPGES-1, mPGES-2) and cytosolic PGE synthase (cPGES). Very little is known about their respective roles. The more abundant renal form is mPGES-1, and it has been shown to couple to both COX-1 and COX-2 to...
produce PGE2, whereas cPGES mainly couples to COX-1 in the collecting duct (62). The role of mPGES-1 in CKD was recently reviewed (70), highlighting the contribution of mPGES-1 to reductions in renal function and urine concentrating ability, as well as elevations in blood pressure. The author also emphasizes the usefulness of targeting mPGES-1 instead of COX-2 in CKD, to reduce cardiovascular complications. The role of PGE2 in the kidney has been extensively studied, contributing to homeostasis and disease, by activating four G protein-coupled receptors, namely EP1-4.

Renal cells simultaneously express several EP receptors, and their relative levels determine the overall cellular response. The localization of COX and EP receptors along the nephron are depicted in Fig. 2, showing the main effects of PGE2 on hemodynamic responses, transport properties of the proximal tubule, thick ascending limb, distal tubule, and collecting duct, as well as macula densa renin secretion. Binding of PGE2 to EP1 activates Goq protein and increases intracellular Ca2+ through PLC. The highest levels of EP1 are observed in the collecting duct (89), but EP1 is also detected in glomerular mesangial cells (29, 67), podocytes (3, 85), and proximal tubule cells (Nasrallah R and Hébert RL, unpublished data). Despite the natriuretic response to EP1 activation in the collecting duct, genetic disruption of EP1 does not impair sodium excretion; however, EP1 null mice display elevated renin and aldosterone levels consistent with sustained activation of the RAAS (87), and an impaired pressor response to angiotensin II (23). The EP2 receptor stimulates adenylate cyclase and is mainly found in vascular and interstitial compartments of the kidney. EP2 knockout mice develop salt-sensitive hypertension, supporting its role in the kidney (35). In addition, EP2-mediated sodium excretion is elevated in response to a high-salt diet (7). Renal EP3 is most recognized for its pressor effects and its diuretic role opposing vasopressin. It is highly expressed in the distal nephron and most abundant in the cortical and medullary collecting duct. EP3 splice variants are detectable in the kidney, inhibiting adenylate cyclase via pertussis toxin-sensitive Gs protein, activating intracellular calcium and the G12/G13 pathway, which activates Rho kinase (recently reviewed in Ref. 62). Basal urine osmolality was similar in EP3 null and wild-type mice; however, after inhibition of endogenous PGE2 production by indomethacin, urine osmolality decreased by 10.220.33.1 on October 29, 2017

osmolality increased in wild-type but not EP3 null mice (20). Olesen and Fenten (62) provide an intricate review of the collecting duct water transport system, highlighting the contribution of each EP receptor, the interaction with vasopressin signaling responses, and the relevance to various disease states like lithium-induced and postobstructive polyaemia. Finally, EP4 is abundant in the afferent arteriole, but also detected in almost all renal cell types. The Gαs-coupled EP4 receptor directly activates adenylate cyclase, increasing cAMP, but can also activate phosphoinositide 3-kinase (22, 114). EP4 also stimulates AMP-activated protein kinase in the mouse podocyte (18). Glomerular size is reduced in EP4 null mice (also in EP1 and EP4 null mice), emphasizing the importance of EP4 in the early postnatal period (21). In EP4 knockout mice and in response to EP4 antagonism, the low-salt stimulatory effect on kidney and plasma renin levels is attenuated (65).

**Contribution of PGE2/EP Receptors to Renal Disease Processes**

PGs maintain renal function, i.e., glomerular hemodynamics, renin secretion, and tubular transport, but their role in CKD is controversial. COX-2 and PGE2 are consistently elevated in both rodent and human diabetes (9–11, 53, 55, 56), and renal EP1, EP4 receptor subtypes are altered (57, 93). Although differences were observed in the pattern of EP receptor mRNA changes between B6-Ins2Akita and streptozotocin diabetic mice, both models display similar overall alterations: cortical EP1 increased but both EP1 and EP3 increased in the medulla, and other EP receptors were unchanged. In the streptozotocin diabetic rat cortex, EP2 and EP3 were elevated but EP4 protein levels were reduced (93). Figure 3 illustrates the various disease processes linked to each EP receptor.

**PGE2/EP and diabetic renal function.** In addition to regulating filtration barrier function and glomerular permeability, PGE2/EP receptors can influence vascular tone and renal hemodynamics, as well as systemic blood pressure. Swan and Breyer (90) provide a detailed review of the contribution of PG/EP receptors to the regulation of blood pressure and its injurious consequences in various organs. In the rat afferent arteriole, PGE2 elicits a vasodilatory effect via EP4-cAMP (92). The same effect was obtained in rat pregglomerular microvessels (66). The contribution of EP4 to the vasodilatory response of the tubuloglomerular feedback mechanism was confirmed using a specific EP4 antagonist (72). PGE2 also constricts the rat afferent arteriole via EP3 (80, 92). In contrast, EP2 receptors cause vasodilation of mouse afferent arterioles, and buffer vasoconstrictor effects via EP1 and EP3 (28). However, baseline hemodynamics (renal blood flow and vascular resistance) were unchanged in mice lacking EP2 receptors, but mice lacking EP3 receptors had increased renal blood flow and decreased resistance (1). Altogether, PGE2 acting on EP receptors can cause vasodilatory or vasoconstrictor responses and influence renal blood flow and hemodynamics, but the overall effect is dependent on many factors: relative expression of EP receptors; the presence of other hormonal signals, e.g., endothelin, angiotensin II, and nitric oxide; or the cell context (health vs. disease). PGE2 acting on EP4 can also regulate systemic blood pressure by stimulating macula densa renin release (59) to increase angiotensin II, which construcks the efferent arteriole (26). Considering these hemodynamic effects of PGE2, it is not unforeseen that in later stages of the disease, when GFR is already low, NSAIDs exacerbate the decline in renal function. On this note, a differential effect of the COX-2 inhibitor celecoxib in hyperfiltration vs. normofiltering diabetics was observed, with reductions in GFR when kidneys are hyperfiltrating but an opposite effect when GFR is normal (9). COX-2 inhibition also antagonized angiotensin II-mediated declines in GFR in females (11). It was also recently observed that EPs in the thick ascending limb regulate COX-2 by feedback inhibition (104), further emphasizing the
potential of targeting EP3 to modify both renin release and tubuloglomerular feedback responses.

EP1 null mice are hypertensive (87), and the same antihypertensive effect of EP1 antagonism was observed in diabetic (77) or spontaneously hypertensive rats (23). EP1 receptors may also contribute to the vasoconstrictor effects of angiotensin II (64) to modulate glomerular hemodynamics. In a recent study, it was shown that diabetic EP1 null mice are protected from diabetic injury, with reduced diabetic hyperfiltration, albuminuria, and markers of injury (97). This protective response was also previously demonstrated by EP1 antagonism in diabetic (46) and spontaneously hypertensive rats (88). However, using SC51322, an EP1 receptor blocker, and sulprostone, an EP2/EP3 receptor agonist, van Rodijnen et al. (102) demonstrated that EP3 vasoconstricts rat proximal interlobular arteries, suggesting it may protect the kidney during states of diabetic hyperfiltration. Furthermore, EP3 agonism decreased perfusion of the cortex and medulla in rats. Combining the EP3 agonist with a RAAS blocker confirmed that the vasoconstrictive effect in the rat cortex is mediated by EP3 independently of RAAS activation (2). In addition to modulating vascular responses, PGE2/EP receptors can contribute to tubular transport anomalies in CKD. For example, PGE2 acting on P2 and/or EP2 receptors plays a key role in ß-irradiated cell defects in sodium and potassium handling associated with type I distal renal tubule acidosis (24). Also, EP3-mediated collecting duct responses likely contribute to lithium-induced polyuria (117). EP4 receptors also regulate sodium and water transport, and in a model of mouse diabetes insipidus, EP4 agonism compensates for the loss of vasoressin V2 receptors (43). There remain many unanswered questions regarding the involvement of PGE2/EP responses in the altered transport behavior along the nephron in CKD.

Renal PGE2/EP and diabetic injury. Although both COX-1 and COX-2 maintain renal homeostatic function, PGE2 is the main product of COX-2 in CKD, mediating renal injury. Proximal tubule injury was attributable to COX-2-PGE2-mediated inflammatory responses in netrin-1-deficient mice (49). However, in a number of kidney disease models COX-2 inhibitors reduce hyperfiltration, proteinuria, glomerulosclerosis (13, 39, 78, 107, 112), structural damage (78), interstitial fibrosis (47), disturbances in salt and water balance (58), macrophage infiltration (63), and biochemical markers of injury: TGF-ß, plasminogen-activator inhibitor-1, and fibronectin levels (8). In contrast we recently demonstrated that chronic high-dose COX-2 inhibition with celecoxib exacerbated glomerular injury, but ibuprofen (a nonselective COX inhibitor) was more detrimental (53).

EP1 receptors can affect injurious responses in glomerular cells. For example, PGE2 increases the cyclin-dependent kinase inhibitor p27 in rat mesangial cells, causing cell cycle arrest via EP1 (67), and EP1 antagonism reduces mesangial expansion (46). Similarly, altered renal function and markers of injury were attenuated in diabetic EP1 null mice (97). In contrast, EP1 deletion caused severe renal impairment in glomerulonephritic mice (69) with no difference in the level of proteinuria. The reason for this discrepancy has not yet been addressed. PGE2 regulates growth, cell fate, and fibrosis under a number of conditions in different renal cells, and our group recently showed that PGE2 acting on EP1 receptors promotes fibronectin and ROS generation in proximal tubule cells (Nasrallah R and Hébert RL, unpublished data) Not much is known about the role of EP2 receptors in mediating renal injury in CKD, but an antiapoptotic role of EP2 receptors has implicated this receptor in the development of renal cysts in polycystic kidney disease (17).

Agonizing EP3 receptors in Madin-Darby canine kidney cells (distal nephron epithelial cells) in hypertonic media lead to increased cell survival, independently of reduced cAMP production, suggesting that EP3 may regulate hemodynamics and tubular transport via changes in the thick ascending limb (36). Also, using a selective EP3 agonist resulted in recovery from acute nephritis in mice as evidenced by normalized blood urea nitrogen, normalized glomerular cell numbers, restored synaptopodin distribution and F-actin filament arrangement in glomeruli (40).

PGE2 acting on EP4 receptors can alter growth responses, matrix turnover, and fibrotic responses, as well as apoptosis in renal cells. A recent study by Mohamed et al. (48) indicates that a selective EP4 agonist promotes glomerulosclerosis and tubulointerstitial fibrosis in streptozotocin-diabetic mice. They attribute these findings to an induction of a novel EP4 pathway mediated by interleukin-6. Similarly, EP4 receptor deletion from podocytes ameliorated the kidney anomalies induced by % nephrectomy (86). In direct contrast, a number of studies underline the potential role of PGE2 in protecting against injurious processes in the kidney via the EP4 receptor. In cultured mouse podocytes exposed to mechanical stretch, PGE2 acting on EP4 receptors attenuates AKT and MAPK pathways to maintain podocyte integrity and reduce the onset of proteinuria in diabetic kidneys (19). Interestingly, a recent study in cultured mouse podocytes and hyperfiltered oligosyndactyly mice (OS/+ ) demonstrated that EP2 and not EP4 receptors mediate injurious responses to fluid shear stress (85). In distal nephron Madin-Darby canine kidney cells, PGE2 derived from COX-2 reduced the epithelial-to-mesenchymal transition (EMT) by inhibiting TGF-ß-induced oxidant production and promoting hepatocyte growth factor-induced antiinflammatory response (116). The EP2-ßAMP pathway may mediate these effects, although the responses were not thoroughly characterized. The same reduction in EMT was observed in cisplatin-induced injury in rats, whereby EP4 agonism stimulates proliferation and decreases apoptosis in renal epithelial cells (110). Similarly, EP4 receptors could suppress inflammatory responses in mesangial cells and prevent mesangial cell injury (115). The same anti-inflammatory effect of renal EP4 was shown to prevent tubulointerstitial fibrosis in mice subjected to unilateral ureteral obstruction, with augmented fibrosis and inflammatory/fibrotic markers of injury in EP4 null mice, which was prevented by EP4 agonism (52). This same beneficial response to EP4 agonism was observed in the % nephrectomy model of chronic renal failure (105). Another recent study reports the therapeutic potential of EP4 antagonism to prevent abnormalities in epithelial proliferation and chloride transport associated with autosomal dominant polycystic kidney disease (45). The protective nature of EP4 in the kidney is reviewed by Boor (4).

Summary: Modified CKD Intervention Strategies Targeting EP Receptors

CKD is on the rise. Despite the overwhelming efforts being made to find alternative therapeutics that will more specifically target different aspects of kidney disease, and slow its progression, the search for better alternatives/additives to the conventional RAAS interventions remains unsuccessful. Recent re-
search efforts have emphasized the possibility of targeting various levels of the COX/PG system for disease intervention. Prior views only considered the glomerulus and the mesangial cell as the keys to the pathogenesis of diabetic nephropathy. The understanding of CKD has taken a spin, and we now see a drastic rise in research interests looking for novel therapeutic targets to slow glomerular and proximal tubule injury, and limit oxidative stress and inflammatory responses. Antagonizing PGE₂ EP₁ receptors or agonizing EP₂/EP₃ may hold promise to prevent renal injury (reducing growth/apoptosis, inflammation, oxidative stress, and fibrosis) and control its dysfunction (preventing hyperfiltration, renin secretion, altered sodium and water transport) in diabetes, altogether decreasing the need for renal replacement therapy.

AUTHOR CONTRIBUTIONS

Author contributions: R. Nasrallah drafted manuscript; R. Nasrallah and R. Hassounen prepared figures; R. Nasrallah, R.L. Hébert, and R. Hassounen edited and revised manuscript; R. Nasrallah, R.L. Hébert, and R. Hassounen approved final version of manuscript.

DISCLOSURES

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