ABSTRACT
An important measure of cardiovascular health is obtained by evaluating the global cardiovascular risk, which comprises a number of factors, including hypertension and type 2 diabetes, the leading causes of illness and death in the world, as well as the metabolic syndrome. Altered immunity, inflammation, and oxidative stress underlie many of the changes associated with cardiovascular disease, diabetes, and the metabolic syndrome, and recent efforts have begun to elucidate the contribution of PGE2 in these events. This review summarizes the role of PGE2 in kidney diseases.21 In fact, a lack of EP1 or EP4 antagonism protects against hyperfiltration, albuminuria, and markers of injury in diabetic mouse models21,26 or spontaneously hypertensive mice.31 Our group recently reported that EP1 mediates reactive oxygen species and fibronectin induction in PGE2-stimulated cultured mouse proximal tubules.20 A protective role for EP1 was described in glomerulonephritic mice32 but the reason for this discrepancy is unclear. EP2 is mainly found in vascular and interstitial compartments of the kidney, and EP2 knockout mice develop salt-sensitive hypertension.33 The contribution of EP2 to renal disease is unknown, but it may have a role in cyst formation in polycystic kidney disease.34 EP3 is mainly associated with water balance, mediating pathologic polyuria and tubular injury in postobstructive35 and lithium-induced nephropathies27,36 and diabetes insipidus.37

PGE2, Kidney Disease, and Cardiovascular Risk: Beyond Hypertension and Diabetes
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Accelerated cardiovascular disease is the leading cause of mortality in patients with kidney disease.1,2 This implies that kidney disease has a major effect on global cardiovascular risk, affecting fluid (volume, BP), electrolyte, and acid base balance, among many other cardiovascular risk factors. In fact, renal transplantation ameliorates cardiovascular risk, improves quality of life, and reduces mortality.2 PGs are important homeostatic regulators of kidney function. PGE2 is the major product of cyclooxygenase (COX)-2 and microsomal PGE synthase 1 (mPGES1), and both of these enzymes are elevated in renal diseases.3–10 PGE2 binds four EP receptors (EP1–4) to activate G protein signaling responses. Figure 1 illustrates the COX pathway leading to PGE2, as well as its target receptors. These receptors are often coexpressed in cells and usually have opposing effects (protective and harmful). PGE2 acting on EP can alter vascular tone and influence renal blood flow and hemodynamics.11–15 PGE2 also stimulates the macula densa to activate the renin-angiotensin-aldosterone system, a key mediator of kidney injury.16–19 Inflammatory, immune, and oxidative stress responses are influenced by PGE2, which are reported to alter growth, fibrosis, and apoptosis in renal cells.20–26 PGE2 also contributes to disturbances in collecting duct salt and water transport in polyuric diseases,19,27–29 and β cell defects in sodium and potassium handling associated with type I diabetic renal tubule acidosis.30 PGE2/EP4 also compensates for the loss of vasopressin V2 receptors in mouse diabetes insipidus.28 Although attempts to block PGE2 using COX-2 or mPGES1 inhibitors have failed, selective inhibition of EP receptors may prove to be quite useful in controlling the deleterious effects of COX-2/mPGES1/PGE2, while leaving the protective responses intact. EP1 mediates many of the pathologic effects of PGE2 in kidney diseases.21 In fact, a lack of EP1 antagonism protects against hyperfiltration, albuminuria, and markers of injury in diabetic mouse models21,26 or spontaneously hypertensive mice.31 Our group recently reported that EP1 mediates reactive oxygen species and fibronectin induction in PGE2-stimulated cultured mouse proximal tubules.20 A protective role for EP1 was described in glomerulonephritic mice32 but the reason for this discrepancy is unclear. EP2 is mainly found in vascular and interstitial compartments of the kidney, and EP2 knockout mice develop salt-sensitive hypertension.33 The contribution of EP2 to renal disease is unknown, but it may have a role in cyst formation in polycystic kidney disease.34 EP3 is mainly associated with water balance, mediating pathologic polyuria and tubular injury in postobstructive35 and lithium-induced nephropathies27,36 and diabetes insipidus.37

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Our group confirmed that EP₄ contributes to diabetic dysfunction and injury in mice, including hyperfiltration, hypertension, polyuria, and albuminuria (unpublished data). The protective nature of EP₄ was demonstrated in EP₄ null mice subjected to unilateral ureteral obstruction, with augmented fibrosis and inflammatory/fibrotic markers of injury. EP₂/EP₄ also maintains podocyte integrity and reduces the onset of proteinuria in diabetes, and EP₄ agonism was beneficial in 5/6 nephrectomy. EP₄ is also harmful in other studies; for instance, EP₄ antagonism antagonism promoted glomerulosclerosis. Clearly targeting EP receptors may be advantageous in the treatment or prevention of kidney disease outcomes, but more work is needed to clarify the controversies and gain insight into the precise contribution of each receptor subtype. Figure 2 illustrates the contribution of PGF₂/EP to kidney disease processes (insufficiency and injury) that affect cardiovascular risk.

**PGE₂ IN HYPERTENSION AND DIABETES**

Inappropriate immune responses, chronic low-grade inflammation, and oxidative stress are important in the development and progression of target organ damage associated with both hypertension and diabetes. A comprehensive listing of the various systemic and metabolic factors involved (environmental/genetic, immune, hypertensive mechanisms were not fully explored but seem to be associated with oxidative stress responses in the kidney. PGE₂ is an important modulator of BP, acting at various levels (central and peripheral responses, renal hemodynamics, and salt and water balance). Yang and Du provide an intricate overview of the PGE₂/EP pathways that act both centrally and peripherally to elicit hypertensive and hypotensive effects. We recently reviewed the role of renal PGE₂/EP receptors in the development of hypertension, affecting renal hemodynamics, renin release, and salt and water transport in the nephron. Overall PGE₂ is an important antihypertensive agent under basal conditions, because of its potent diuretic and natriuretic roles in the kidney mediated by all four EP receptors as well as its systemic depressor effect mediated by EP₃, which predominates in basal states. In the absence of this depressor response, a pressor effect of EP₃ was revealed. EP₃ is also implicated in the central regulation of BP, stimulating sympathetic responses. Moreover, pulmonary hypertension was attenuated in complex interplay, and cardiovascular consequences that arise have been thoroughly reviewed. Despite their obvious involvement, strategies to halt the mediators of these pathogenic mechanisms remain unsuccessful at managing disease progression. Because COX-2/mPGES1/PGE₂/EP receptors are implicated in many of the disturbances associated with diabetes and hypertension, many efforts are aimed at deciphering the exact role, to identify alternate targets for therapy.

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit COX, and mostly have hypertensive effects, especially with prolonged use (recently reviewed by Khatchadourian et al.). This response depends on the relative selectivity for each COX isoform, but both chronic high-dose ibuprofen (nonselective) and celecoxib (COX-2 inhibitor) increased systolic BP in diabetic mice. However, deoxycorticosterone acetate–salt hypertension was attenuated in mice lacking mPGES1, which otherwise displayed a 5-fold increase in PGE₂ levels. The mechanisms were not fully explored but seem to be associated with oxidative stress responses in the kidney. PGE₂ is an important modulator of BP, acting at various levels (central and peripheral responses, renal hemodynamics, and salt and water balance). Yang and Du provide an intricate overview of the PGE₂/EP pathways that act both centrally and peripherally to elicit hypertensive and hypotensive effects. We recently reviewed the role of renal PGE₂/EP receptors in the development of hypertension, affecting renal hemodynamics, renin release, and salt and water transport in the nephron. Overall PGE₂ is an important antihypertensive agent under basal conditions, because of its potent diuretic and natriuretic roles in the kidney mediated by all four EP receptors as well as its systemic depressor effect mediated by EP₃, which predominates in basal states. In the absence of this depressor response, a pressor effect of EP₃ was revealed. EP₃ is also implicated in the central regulation of BP, stimulating sympathetic responses. Moreover, pulmonary hypertension was attenuated in complex interplay, and cardiovascular consequences that arise have been thoroughly reviewed. Despite their obvious involvement, strategies to halt the mediators of these pathogenic mechanisms remain unsuccessful at managing disease progression. Because COX-2/mPGES1/PGE₂/EP receptors are implicated in many of the disturbances associated with diabetes and hypertension, many efforts are aimed at deciphering the exact role, to identify alternate targets for therapy.

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mice lacking EP3 receptors.48 It had long been recognized that prostacyclin analogs are beneficial in pulmonary hypertension, but their use is limited by the presence of vasoconstrictor EP3. Accordingly, antagonizing EP3 may prove useful in preventing vessel injury and remodeling in response to chronic hypoxia. Better control of PGE2-mediated BP effects would be achieved by directly targeting EP-specific responses. In addition to conventional regulators of BP, new evidence of a more complex nature is emerging, with mechanisms involving the skin, the gut and mouth microbiome, and dietary nitrates in hypertension.49–56 Future exploration of these avenues may unveil novel roles for PGE2.

Hypertension is more prevalent in patients with diabetes, causing target organ damage, especially cardiovascular and renal vascular disease. The associated decline in cardiovascular health accounts for >80% of the mortality.45,57 In addition to cardiovascular disease, the three major microvascular complications of diabetes are retinopathy, neuropathy, and nephropathy. The main trigger is hyperglycemia, with microvascular alterations contributing to progressive injury, but many vasoactive substances are also involved. PGE2, as a major product of COX-2, clearly plays an important role in the end organ damage associated with diabetes. Diabetic retinopathy is the leading cause of blindness and has been associated with a number of injurious responses, with inflammation and oxidative stress as the main features.58 COX-2 has long been implicated in the retinal damage associated with diabetes.59–65 In the earliest stages of
streptozotocin-induced diabetes in rodents, COX-2 and PGE₂ are elevated and COX-2 inhibitors reduce injurious responses to many pathogenic factors, like TNF-α and vascular endothelial growth factor. Although the mechanism appears to involve various second messengers (extracellular-regulated kinases, protein kinase A or C, NFκB), the nature of COX-2, PGE₂, and EP receptor involvement is poorly understood. A pilot study using the COX-2 inhibitor celecoxib to treat diabetic macular edema was inconclusive as a result of a small study group and short duration of the intervention. A more elaborate trial is needed to ascertain the benefits of COX-2 inhibition in preventing blindness owing to macular edema in patients with diabetes. Interestingly, EP₃ has been implicated in ischemic retinopathy by inhibiting thrombospondin 1 and cluster of differentiation 36. However, EP₃ protects against retinal ischemia reperfusion–induced angiogenesis by stimulating neuronal nitric oxide synthase and choline acetyltransferase, whereas EP₄ promotes vascular endothelial growth factor–mediated neovascularization in cultured Müller cells. A better characterization of the specific EP pathways would certainly yield better intervention possibilities in early diabetic retinopathy.

Diabetic neuropathy is another common microvascular complication of diabetes, consisting of progressive nerve dysfunction and damage due to altered blood supply, oxidative stress, and inflammatory injury. A wide range of symptoms arise as a result of the diabetic injury, ranging from an exaggerated perception of sensory stimuli to spontaneous paresthesias and pain, features of both allodynia and hyperalgesia. Recently published studies provide an elaborate review of the pathophysiology underlying the neuropathic pain as well as the detailed mechanisms triggered by hyperglycemia leading to nerve injury. Although hyperglycemia is central to the pathogenesis of diabetic neuropathy, a number of metabolic and vascular factors are involved. Most of the available therapies are symptomatic, including antidepressants, anticonvulsants, topical anesthetics, opioids, and other analgesics. NSAIDs have shown narrow therapeutic benefits, but more work is needed to ascertain their benefits along with other pharmacological agents. As a major inflammatory mediator in the diabetic milieu, COX-2 is implicated in diabetic neuropathy, and a more targeted approach to therapy will certainly prove more effective. Unlike nonselective NSAIDs, COX-2 inhibitors show promise, with protection against nerve dysfunction and nerve fiber loss as well as attenuated mechanical hyperalgesia in experimental diabetes. There may be important considerations regarding therapy; for instance, mechanical allodynia was only prevented by inhibiting spinal COX-2 before established symptoms, otherwise the treatment becomes ineffective. COX-2 is elevated in three diabetic rat models and may be implicated in tactile allodynia in the rat, as well as p38-mediated allodynia in diabetic mice. A couple of studies in diabetic rodents indicate that both COX-2 and PGE₂ are elevated in hyperglycemic conditions as well, and PGE₂ may mediate the bradykinin-induced nociceptor sensitization described in response to hyperglycemic hypoxia in diabetic rats. Although PGE₂ can also modulate nondiabetic pain responses, contributing to heat- and acid-induced nociceptor sensitization, more work in this area is warranted to better clarify the role of PGE₂/EP receptors in diabetic neuropathy.

The best characterized role for COX-2 and PGE₂ is related to diabetic nephropathy, contributing to hyperfiltration, growth, fibrosis, apoptosis, and altered transport. A number of detailed reviews describe these events from hyperglycemia to altered renal function and kidney injury. Both COX-2 and PGE₂ are consistently elevated in patients with diabetes and in a number of rodent models. Interestingly, despite the many claims that COX-2 mainly couples to mPGES1, a recent study reports that diabetic renal PGE₂ production by COX-2 is independent of mPGES1. In fact, diabetic mice lacking mPGES1 were no different than diabetic wild types with respect to albuminuria and other markers of injury. The authors suggest that another as-yet unidentified synthase may mediate PGE₂ production by the diabetic kidney. Interestingly, in mice with type 2 diabetes, mPGES1 contributed to induction of glomerular PGE₂ synthesis, and the peroxisome proliferator–activated receptor-γ (PPAR-γ) agonist rosiglitazone protected against glomerular injury by targeting the mPGES1/PGE₂/EP₄ pathway. Unfortunately, glomerular COX-2 expression was not directly addressed in this study, but whole-kidney COX-2 was elevated in diabetic mice and was unaffected by rosiglitazone treatment. COX-2 inhibitors may display some protection against diabetic injury, but studies are inconsistent. As discussed above, a new interest has emerged in specifically targeting EP receptors to better control renal complications in diabetes. Diabetic kidney injury is ameliorated by EP₁ antagonism and exacerbated by EP₄ agonism, but the role of EP₄ remains controversial. There is undoubtedly a detrimental role of PGE₂/EP receptors in diabetic nephropathy, but more work is needed to clarify the exact pathways involved, with many controversies awaiting clarification. Our group recently reviewed the role of each EP receptor in the diabetic changes as well as the potential of EP receptors as therapeutic targets, suggesting that overall EP₁ antagonists and/or EP₃/EP₄ agonists may prevent renal injury (reducing growth/apoptosis, inflammation, oxidative stress, and fibrosis) and control kidney dysfunction (preventing hyperfiltration, renin secretion, and altered sodium and water transport) in diabetes. A detailed account is beyond the scope of this review. However, we have new evidence that EP₃ contributes to diabetic dysfunction and injury in mice (unpublished data).

**PGE₂ IN OTHER ASPECTS OF THE METABOLIC SYNDROME**

Obesity is a major factor in the assessment of global cardiovascular risk; like
hypothesis and diabetes, obesity is reaching epidemic proportions, especially in North America. Abdominally distributed adiposity, as measured clinically by waist circumference, is a central component of the metabolic syndrome, both as a direct risk factor and as a contributor to other risk factors such as dyslipidemia, insulin sensitivity, glucose intolerance, and hypertension. The link between obesity and metabolic disturbances leading to diabetes, hypertension, and cardiovascular disease was thoroughly reviewed by Sowers. A better appreciation of peripheral transformation of white-to-brown fat is of great interest, and PPAR-γ is a key regulator of adipose homeostasis, promoting differentiation of both white and brown adipocytes. A regulated coordination between mPGES-1 and PPAR-γ underlies white-to-brown transformations. COX-2 is also involved in the recruitment of brown adipocytes to white adipose tissue, but the nature of the PG involved was not identified. PGE_2 is the main PG secreted by adipose tissue, and EP receptors are expressed in adipocytes, mediating its local responses. EP_4 receptors in adipose tissue reduce chemokine production, by inhibiting IFN-γ and macrophage inflammatory protein 1α. PGE_2/EP_3 increases both leptin secretion and lipolysis in rodent adipocytes, and it regulates adipogenesis. Consistently, mice lacking EP_3 display enhanced night eating behaviors and are obese. Moreover, PGE_2 regulates the transformation of white to beige fat, which protects against obesity and metabolic disease, but whether EP_3 is involved remains unclear. Although very little is known about all of the EP receptor pathways implicated, PGE_2 does inhibit adipogenesis via EP_4. It is also clear that mPGES-1/PGE_2 interact with PPAR-γ, promoting beige adipocyte differentiation in white adipose tissue, which increases energy expenditure and can prevent obesity related comorbidities. Interestingly, the treatment of obesity and related metabolic disturbances by targeting PG reductase-3 (which metabolizes the PPAR-γ ligand 15-keto-PGE_2) to limit PPAR-γ-mediated adipocyte differentiation, was reported. 15-keto-PGE_2 is the product of PGE_2 oxidation; in chronic diseases characterized by a state of increased inflammation (increased COX2-PGE_2) and oxidative stress, this reveals a novel mechanism linking the two environments to regulation of adipogenesis. Therefore, targeting mPGES-1 or specific PGE_2 EP receptors may be important therapeutic avenues to explore in the treatment or prevention of obesity.

PGE_2 can also increase cardiovascular risk by contributing to atherogenesis. Since the introduction of COX-2 inhibitors into the clinical setting, prothrombotic and atherogenic consequences were discovered, mainly owing to the shifting synthesis of PGs to favor thromboxane and PGE_2 while reducing prostacyclin. This same PG profile was observed upon deletion of COX-2. COX-2 null mice actually had the same phenotypic consequence as deletion of the prostacyclin IP receptor, with accelerated atherogenesis. Instead, deletion of vascular mPGES1 limits the atherogenic response and prevents the thrombotic consequences associated with COX-2 selective antagonism. A central role was revealed for mPGES1 from myeloid cells to the atherogenic response in inflammatory states, suggesting that it can be targeted to protect against cardiovascular consequences. The role of COX-2 in the inflammatory response is controversial and it appears that timing is everything, with a dual role as a producer of proinflammatory and proresolving mediators in acute inflammation. PGE_2 plays a central role in the nonresolving inflammatory state associated with the formation of atherosclerotic lesions, and all three EP receptors are somehow implicated in the formation and stabilization of the atherosclerotic lesion. In fact, statins protect against thrombotic events by inhibiting COX-2/mPGES1/PGE_2/EP-mediated instability of carotid plaques, and the expression of EP_1, EP_3, and EP_4 receptors is reduced by atorvastatin in both the plaques and mononuclear cells of patients with carotid atherosclerosis. EP_3 is highly expressed in platelets and is involved in platelet activation. EP_3 null mice displayed increased bleeding times and were less prone to developing thromboembolisms. PGE_2 acting on EP_2 and EP_3 reduces human platelet hyper-reactivity, which is associated with increased cardiovascular risk, and was shown to inhibit mouse platelet aggregation.

PGE_2 also contributes to dyslipidemia and insulin resistance. PGE_2 acting on EP_3 mainly has antilipolytic effects in adipose tissue of both obese and diabetic mice, although mice lacking EP_3 are obese. More work is needed to clarify this contradiction. Interestingly, in diet-induced obesity in rats, rather than PGE_2 from adipocytes, macrophage-derived PGE_2 via EP_3 signals adipocytes to reduce lipolysis, thereby contributing to abdominal adiposity and associated metabolic disturbances (insulin sensitivity, glucose intolerance, and cardiovascular abnormalities). In this regard, PGE_2 also inhibits liver lipolysis, β-oxidation, and very low density lipoprotein synthesis further contributing to obesity, yet the EP receptor is unknown. This lipid-accumulating effect of PGE_2 on hepatic lipid metabolism has been recognized for quite some time; however, it has also been demonstrated that PGE_2 derived from nonparenchymal liver cells attenuates insulin responses in the hepatocyte. COX-2 derived PGE_2 also inhibits pancreatic insulin secretion, and COX-2 inhibitors and EP antagonists improved β-cell function in mice, resulting in enhanced insulin release and glucose tolerance after a glucose challenge. Kimple et al. confirmed that EP3 is elevated in the diabetic pancreas and reduces insulin secretion from diabetic islets. Clearly, EP_3 receptors are involved in many deleterious responses associated with diabetes and the metabolic syndrome, and they prove to be enticing targets for therapeutic interventions.
Figure 3 summarizes the contribution of PGE2/EP receptors to hypertension and diabetes, while depicting the plethora of responses linking PGE2 to cardiovascular risk. PGE2 acting on EP receptors has been implicated in hypertension and diabetes, as well as many other aspects of the metabolic syndrome; as such, PGE2 has a great effect on global cardiovascular risk.

The global effect of hypertension, diabetes, and obesity epidemics is immeasurable. COX-2/mPGES1/PGE2/EP receptors affect the global cardiovascular risk, including the development of hypertension, diabetes (retinopathy, neuropathy, and nephropathy), and other aspects of the metabolic syndrome (adipose homeostasis, dyslipidemia, and atherogenesis). PGE2 is clearly implicated in glucose and lipid metabolism,
vascular remodeling and injury, as well as nerve fiber dysfunction and injury. Because EP receptors are often coexpressed in the same cells and have opposing effects (protective and harmful), it is more promising to explore selective inhibition of EP receptors to modify disease processes. Although our knowledge of the harmful PGE2 EP receptor pathways is expanding, more concerted research efforts are needed to determine the contribution of each EP receptor in these events. These strategies may prove to be quite useful in controlling the deleterious effects of COX-2/mPGES1/PGE2, while leaving the protective EP receptor–mediated responses intact. A better understanding of the underlying mechanisms can lead to more targeted therapies to shrewdly manage disease outcomes.

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DISCLOSURES

None.

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