nature publishing group

Distinct Roles of Central and Peripheral Prostaglandin E_2 and EP Subtypes in Blood Pressure Regulation

Tianxin Yang[1,2] and Yaomin Du[3]

Prostaglandin E_2 (PGE_2) is a major prostanoid with a wide variety of biological activities. PGE_2 can influence blood pressure (BP) both positively and negatively. In particular, centrally administered PGE_2 induces hypertension whereas systemic administration of PGE_2 produces a hypotensive effect. These physiologically opposing effects are generated by the existence of multiple EP receptors, namely EP_{1-4}, which are G protein-coupled receptors with distinct signaling properties. This review highlights the distinct roles of PGE_2 in BP regulation and the involvement of specific EP receptor subtypes.

Keywords: *blood pressure; brain; EP receptors; hypertension; kidney; mPGES-1; prostaglandin E2*

American Journal of Hypertension, advance online publication 14 June 2012; doi:10.1038/ajh.2012.67

Prostaglandins (PGs) are formed by a sequential series of three enzymatic reactions: release of arachidonic acid (AA) from membrane phospholipids by phospholipases, conversion of AA to an unstable endoperoxide intermediate PGH_2 by cyclooxygenase (COX), and, finally, isomerization of PGH_2 to bioactive prostanoids, including prostaglandin E_2 (PGE_2), prostacyclin (PGI_2), Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), Prostaglandin D_2 (PGD_2), and thromboxane A_2 (TXA_2), by distinct terminal synthases. COX is best known as the molecular target of nonsteroidal anti-inflammatory drugs such as aspirin.[1] These drugs have been used traditionally as analgesics for centuries and are some of the world's most widely used drugs. The seminal work by Sir John Vane delineated the mechanism by which aspirin exerts its anti-inflammatory, analgesic, and antipyretic actions.[1] COX-2 exists in two isoforms, the constitutive COX-1 and the inducible COX-2; the two forms share 66% homology in amino acid sequence and similar enzymatic properties, but differ markedly with respect to cellular expression pattern and regulation.

Among terminal PG synthases, PGE synthase (PGES) specifically catalyzes the conversion of PGH_2 to PGE_2. To date, at least three major forms of PGES have been identified. They are designated membrane-associated PGES (mPGES)-1, mPGES-2, and cytosolic PGES (cPGES). mPGES-1 was cloned from human cells as microsomal glutathione S-transferase 1-like 1 (MGST1-L1) whose PGE synthesis activity was dependent on glutathione.[2] mPGES-1 couples with COX-2 to mediate PGE_2 production in response to inflammatory stimuli and mPGES-1 deletion blunts pain and inflammatory responses. The established role of mPGES-1 in the inflammatory response has prompted interest in development of mPGES-1 inhibitors as the next generation of analgesics.[3,4] Besides inflammatory cells, mPGES-1 is constitutively expressed in a variety of tissues, including adipose tissues, stomach, spleen, and kidney. Increasing evidence suggests a potential role of this enzyme in regulation of sodium and water balance and vascular tone.[5–9] A number of studies examine the effect of mPGES-1 deletion on angiotensin II (Ang II)-induced hypertension and yield variable results. mPGES-$1^{-/-}$ mice on a mixed background and an inbred C57/BL6 background develop accelerated hypertensive response to chronic Ang II infusion.[7] However, another study using the same C57 background observes no impact of mPGES-1 deletion on the blood pressure (BP) response.[10] Facemire *et al.* generated mPGES-$1^{-/-}$ mice on two inbred backgrounds, DBA/1lacJ and 129/SvEv.[11] On the 129 background, BP was significantly higher in mPGES-$1^{-/-}$ mice than wild type controls at baseline and also during Ang II infusion. In contrast, on the DBA background, mPGES-$1^{-/-}$ mice have normal baseline BP and also similar hypertensive response to Ang II infusion as compared with wild type controls. The data clearly suggest that mPGES-1 modifies Ang II-induced hypertension depending on the genetic background. Along this line, mPGES-1 deletion impairs aldosterone escape[12] and exacerbates the hypertensive response to deoxycorticosterone acetate-salt.[6]

mPGES-2 is a second mPGES that was originally purified from bovine heart and subsequently cloned. It is a 43-kDa protein containing a unique N-terminal hydrophobic domain, which determines the association with Golgi membrane; proteolysis leads to a mature, N-terminally truncated form of 33 kDa. A third enzyme is cPGES that was originally identified from rat brain as a cytosolic glutathione-dependent

[1]Institute of Hypertension, Sun Yat-sen University Zhongshan School of Medicine, Guangzhou, China; [2]Department of Internal Medicine, University of Utah and Veterans Affairs Medical Center, Salt Lake City, Utah, USA; [3]Department of Internal Medicine, Guangdong Provincial People's Hospital, Guangzhou, China. Correspondence: Tianxin Yang (yangtianxin@mail.sysu.edu.cn) or Yaomin Du (duyaomin12345@163.com)

Received 20 November 2011; first decision 23 December 2011; accepted 17 April 2012.

PGES. It is identical to p23, which is a steroid hormone receptor/hsp90-associated protein. Both mPGES-2 and cPGES possess PGES activity *in vitro*. However, neither mPGES-2 nor cPGES deletion results in a measurable decrease in PGE_2 levels in tissues known to express these enzymes.[13–15] These findings do not support the contention that mPGES-2 or cPGES is a PGE_2 synthase. Thus, it appears likely that mPGES-1 may represent the only enzymatic pathway capable of producing PGE_2 *in vivo*.

The biologic action of PGE_2 is mediated by G protein-coupled E-prostanoid receptors designated EP_1, EP_2, EP_3, and EP_4. These four subtypes of EP receptors couple to distinct signaling pathways. In general, the EP_1 receptor signals via intracellular Ca^{2+} and phosphatidylinositol-bisphosphate hydrolysis, whereas the EP_2 and EP_4 receptors are coupled to Gs and signal by intracellular cAMP. The EP_3 receptor is more complex in that it exists in multiple splice isoforms, which display differential coupling to distinct signaling mechanisms via Gi (inhibition of cAMP formation), Gs (stimulation of cAMP formation), and Gq (stimulation of intracellular Ca^{2+} release).[16] In general, EP_1/EP_3 receptors are vasoconstrictive and prohypertensive whereas EP_2/EP_4 receptors are vasodilatory and antihypertensive.

DEPRESSOR ACTION OF PGE_2

General vasodilator action of PGE_2

PGE_2 is a potent vasodilator, although in some circumstances it can be a vasoconstrictor. At whole organism level, intravenous administration of PGE_2 and PGE analogs produces a hypotensive effect. This effect is rapid and is observed within 20 s of drug infusion; it is also transient and mean arterial pressure recovers to baseline within 170 s after PGE_2 administration.[17] This short duration of action is due to the efficient metabolism of PGE_2 in the venous blood of the lung. In many vascular preparations including rabbit saphenous vein, mouse aortic ring, hamster uterus, piglet saphenous vein, rabbit ductus arteriosus, human pulmonary vein, human middle cerebral artery, and rabbit ear artery, PGE_2 directly relaxes the tissues preconstricted with KCl or norepinephrine, with a potency almost two orders of magnitude higher than that of the activation of PGI_2 (IP) or PGD_2 (DP) receptors."[18–23] The vasodilatory action PGE_2 is also observed in resistance vessels such as pig pial arterioles[24] and canine renal juxtamedullary arterioles.[25] However, in other vascular beds PGE_2 induces vasoconstriction. In rings of human internal mammary arteries, which are frequently used for coronary artery bypass graft surgery, PGE_2 induces vasoconstriction via EP_3 receptors.[26] This study suggests that EP_3 antagonism may offer a new therapeutic intervention to increase vascular graft patency. In addition, PGE_2 is shown to induce smooth muscle contraction in rat mesentery artery.[27]

RENAL ACTION OF PGE_2

PGE_2 regulation of renal hemodynamics

The status of the intrarenal circulation is an important determinant of body fluid and BP homeostasis. It is known that COX inhibiting nonsteroidal anti-inflammatory drugs do not produce major disturbances in renal blood flow and glomerular filtration rate at basal condition. However, under certain pathophysiological conditions, such as congestive heart failure, cirrhosis with ascites, and nephrotic syndrome, these drugs can cause a catastrophic decrease in glomerular filtration rate in these patients.[28–31] The vascular action of PGE_2 intrarenally depends on the type of blood vessels with vasodilatory action in the preglomerular afferent arterioles, distal interlobular arteries, and medullary vasa recta but contrasting to little action in the postglomerular arterioles;[32,33] in some instances, PGE_2 causes vasoconstriction. The overall vasodilatory action of PGE_2 may help sustain renal hemodynamic function under certain pathological conditions.

The microcirculation of the renal medulla plays a pivotal role in the long-term control of BP, although it represents only a small fraction of the total renal blood flow. For example, nitric oxide (NO) can exert a profound influence on BP control by modulation of renal medullary blood flow. The reduction of renal medullary blood flow by chronic intramedullary infusion of L-NAME leads to sodium retention and salt-sensitive hypertension.[34] Conversely, the elevation of renal medullary blood flow by chronic intramedullary infusion of NO synthase (NOS) substrate L-arginine prevents the development of salt-sensitive hypertension in the Dahl salt-sensitive rat.[35–37] Emerging evidence suggests that PGE_2, similarly to NO, may regulate renal medullary blood flow, thereby determining salt sensitivity. Chronic salt loading induces a marked increase in COX-2 expression in the rat medulla and chronic intramedullary infusion of COX-2 inhibitor leads to salt-sensitive hypertension.[38] Further evidence supports PGE_2 as an important mediator of the antihypertensive action of renal medullary COX-2. PGE_2 attenuates the constriction in isolated perfused vasa recta preconstricted with endothelin or Ang II.[39,40] In anesthetized uninephrectomized mice, acute intramedullary PGE_2 infusion increases urine volume and urine sodium excretion.[41] This natriuretic response is likely the result of increased renal medullary blood flow, although the contribution from the direct tubular effect is possible.

PGE_2 regulation of tubular transport

Intravenous PGE_2 administration to healthy dogs increases renal blood flow and induces a significant increase in urinary sodium excretion.[42] When PGE_2 and PGI_2 were infused into the renal artery of dogs, both compounds elevated renal blood flow to a similar extent, but PGE_2 induced a much larger increase in urinary sodium excretion than PGI_2.[43]

These findings suggest that PGE_2 may have a direct action on tubular function in addition to affecting renal hemodynamics. A significant number of microperfusion studies demonstrate that PGE_2 directly inhibits NaCl reabsorption in the collecting duct (CD) and the thick ascending limb,[44,45] although other investigators were unable to demonstrate an effect on the thick ascending limb or the CD in the similar setting.[46] Most of these studies use the basolateral application of PGE_2. Interestingly, luminal application of PGE_2 produces a similar inhibitory effect on sodium transport in isolated perfused rabbit CD.[47] This finding appears to be physiologically or pathologically relevant since PGE_2 is present in the urine in nanomolar concentrations and its excretion is increased in the states of sodium loading and congestive heart failure.

PGE_2 regulation of renal nerve activity

It is increasingly recognized that renal sympathetic nerve plays a pivotal role in fluid and BP homeostasis. Renal denervation reduces arterial pressure in various animal models of hypertension.[48] More importantly, bilateral renal denervation in patients with resistant hypertension results in a long-term reduction in arterial pressure.[49] In addition to a rich supply of sympathetic nerves, the kidney has abundant afferent sensory innervation, located primarily in the renal pelvic wall. A series of studies by Kopp *et al.* demonstrate that afferent renal nerve activity interacts with efferent renal sympathetic nerve activity, forming a feedback system termed the renorenal reflexes that have become an integrative part of the renal nerve circuit for the control of sodium balance and BP.[50–53] The functional interaction between the two types of nerve fibers is supported by the anatomic evidence that sympathetic efferent nerve fibers and afferent sensory nerve fibers often run separately but intertwined in the same nerve bundles in the renal pelvic wall. In a simplest form, the feedback system exists in such a way that increased efferent renal sympathetic nerve activity or increasing renal pelvic pressure leads activation of afferent renal nerve activity that in turn limits the increase of efferent renal sympathetic nerve activity so that efferent renal sympathetic nerve activity can be maintained at low level. PGE_2 has been implicated to serve as an important activator of afferent renal nerve activity. Increasing renal pelvic pressure or bradykinin activates protein kinase C, which leads to increases in renal pelvic release of PGE_2 via induction of COX-2. PGE_2 activates the AC/cAMP/PKA transduction pathway, with a resultant increase in substance P release and increases in afferent renal nerve activity.[54,55]

PRESSOR ACTION OF PGE_2

Central PGE_2 and sympathoactivation

In a sharp contrast to the above-described vasodilator and antihypertensive action of intravenously administered PGE_2, centrally administered PGE_2 via injection or infusion to the cerebral ventricles in anesthetized or awake rats elicits dramatic pressor responses accompanied by tachycardia, hyperthermia, and antidiuresis and causes increases in plasma norepinephrine and epinephrine, plasma renin activity (PRA), and plasma vasopressin (AVP).[56–60] Increasing evidence suggests that the hypertensive effect of central PGE_2 is mediated by the sympathetic nervous system. In this regard, the pressor response is significantly attenuated by pretreatment with phenoxybenzamine and by cervical section of the spinal cord.[58] In line with the changes in plasma catecholamines, recordings of splanchnic nerve activity demonstrate increased sympathetic neural firing following intracerebroventricular (ICV) PGE_2.[58] In contrast, a large body of evidence demonstrates that PGE_1 and PGE_2 inhibit the release of norepinephrine from sympathetic nerve endings and also suppresses the constrictor response of the effector cells to nerve stimulation, and may serve as a break against sympathoactivation in the peripheral tissues.[61,62] Therefore, the E series of PGs can exert either positive or negative influence on sympathoactivation depending on the type of tissues.

In addition to the sympathetic nervous system activation, the increased AVP release may also contribute to the hypertensive effect of ICV PGE_2. In the perfused ventriculo-cisternal system of anaesthetized dogs, PGE_2 infusions elevate plasma AVP levels; in additional experiments, ICV injection of indomethacin decreased the plasma AVP concentration by ~50%.[63] The observations that hypophysectomy and the AVP antagonist, d(CH2)5Tyr(Me) AVP both effectively attenuate the pressor response to ICV PGE_2 suggest a role of AVP.[59] Interestingly, the pressor response is completely abolished by the combination of the AVP antagonist and phenoxybenzamine, suggesting that the pressor effect of ICV PGE_2 is the result of increased sympathetic nervous system activity and AVP release. The elevated PRA in response to ICV PGE_2 may suggest the involvement of the renin–angiotensin system. However, pretreatment with captopril is without an effect, thus ruling out Ang II-dependent rise in BP.[59]

PGE_2 and renin

PGE_2 has been implicated to play a role in the pathogenesis of renin-dependent hypertension such as renovascular hypertension (RVH) by mediating the renin response to renal ischemia. Imanish *et al.* examined the effect of aspirin on BP in patients with unilateral RVH vs. those with essential hypertension.[64] These investigators found that in patients with RVH, PGE_2 concentration in the renal vein plasma from the stenotic kidney was elevated compared with the concentration from the normal kidney or in the aortic plasma; PRA was changed in parallel with the PGE_2 levels. In contrast, PGE_2 levels were similar between the left and right renal veins in patients with

essential hypertension. Intravenous administration of aspirin lowered BP by 10 mm Hg, accompanied with parallel suppression of PGE_2 and PRA levels at all sites in patients with RVH. Conversely, aspirin treatment did not improve, but deteriorate BP control in patients with essential hypertension.[64]

The above-mentioned clinical observations are supported by some animal studies demonstrating BP lowering effects of nonsteroidal anti-inflammatory drugs in rats with RVH. Indomethacin decreased BP and PRA in the rat model of RVH produced by complete ligation between the origin of renal arteries and it had no effect on BP when the left kidney was removed at the time of ligation.[65] In two kidneys, one clip hypertensive (2K1C) rats, COX-2 was upregulated in both kidney, but to a greater extent in the clipped kidney.[66] Moreover, COX-2 deletion or COX-2 inhibitors reduce renin secretion in response to maneuvers including low-salt intake, angiotensin-converting enzyme inhibition, angiotensin AT1 receptor antagonism, and reduced renal perfusion pressure.[67–72] However, functional studies using COX-2 inhibitors in 2K1C hypertensive rats have yield conflicting results. The selective COX-2 inhibitor SC58236 decreased renin production and release and lowered BP in RVH.[73] In contrast, another selective COX-2 inhibitor celecoxib failed to affect BP or urinary aldosterone levels in this model despite the improvement of renal interstitial fibrosis.[74]

Among the five major prostanoids, PGE_2, and PGI_2 were shown to directly stimulate renin secretion in isolated juxtaglomerular cells through elevation of intracellular cAMP, the major signaling mediator of renin expression and secretion.[71,72] Evidence is also available to support an *in vivo* role of PGE_2 in regulation of renin secretion. In this regard, exogenous PGE_2, when chronically infused to the dog kidney, induced increases in PRA and BP; the hypertension induced by intrarenal PGE_2 infusion was renin-dependent since the BP was remarkably reduced by saralasin or an angiotensin-converting enzyme inhibitor.[75]

The characterization of mPGES-1 allows investigations of the role of endogenously produced PGE_2 in renin regulation. Anatomic evidence is available to suggest colocalization of mPGES-1 with COX-2 in the cortical thick ascending limb and the macula densa, raising a possibility that mPGES-1 may functionally couple with COX-2 to produce PGE_2 in the juxtaglomerular apparatus for regulation of renin secretion.[76] Moreover, expression of macula densa mPGES-1, similarly to COX-2, was greatly increased in response to low-salt diet and angiotensin I-converting enzyme inhibition in rabbit kidneys.[77] However, unlike COX-2 deletion, mPGES-1 deletion has failed to affect the renin response to furosemide, which is known to stimulate renin secretion via inhibition of Na^+-K^+-$2Cl^-$ cotransporter type 2 in the macula densa.[9] This observation argues against a functional role of mPGES-1 in renin regulation although more thorough investigations of this topic are apparently needed in the future studies.

In addition to renin regulation, abundant evidence demonstrates that PGE_2 at nanomolar concentrations stimulates aldosterone release from cultured adrenal zona glomerulosa cells almost at the similar potency as Ang II.[78] The stimulation of aldosterone release in response to PGE_2 arises from the increased conversion of cholesterol to pregnenolone in the early step of aldosterone biosynthesis. The detailed signaling mechanism responsible for PGE_2 regulation of aldosterone release is unclear, but appears to involve cAMP-mobilizing EP_2 or EP_4 receptors.[78,79]

ROLES OF EP_1/EP_3 RECEPTORS IN BP REGULATION

The EP_1 receptor was originally described as a smooth muscle constrictor.[80] This receptor is generally coupled to an intracellular calcium signal, a common pathway leading to vasoconstriction by Ang II, endothelin-1, and TXA_2. In some vascular beds, such as tail artery and mesenteric arteries, and cerebral arteries, concomitant activation of EP_1 and EP_3 receptors is responsible for PGE_2-induced constriction via phosphatidylinositol pathway.[81–83] Consistent with the vasoconstrictive property, the $EP1^{-/-}$ mice exhibit a blunted pressor response to acute or chronic Ang II infusion.[84] In this study, the effect of an EP_1 selective antagonist SC51322 on hypertension was also tested in spontaneously hypertensive rats (SHR). The EP_1 antagonism not only reduced BP in SHR but also blocked the acute pressor effect of the EP_1/EP_3 agonist sulprostone in mice.[84] The consistent results obtained using genetic and pharmacological approaches demonstrate an overall prohypertensive role of the EP_1 receptor. A recent study also suggests that activation of EP_1 receptors is responsible for the increased vascular tone and the development of hypertension in db/db mice.[85] However, the selective EP_1 antagonist ONO-8713 failed to affect BP in stroke-prone spontaneously hypertensive rats (SHRSP) despite improvement of renal injury.[86]

Contrary to the above-described vasoconstrictive and prohypertensive action of EP_1 receptors, the direct tubular action of EP_1 receptor activation is natriuretic and therefore is antihypertensive. In isolated, perfused rabbit cortical CD, PGE_2 inhibits sodium transport via elevated intracellular cytosolic calcium[87] and this action is largely ascribed to activation of EP_1 receptors.[45] The physiological significance of natriuretic action of renal EP1 receptors in the context of the overall prohypertensive action of this subtype remains elusive.

Accumulating evidence suggests an important role played by EP_3 receptor in mediating the sympathetic responses to central PGE_2. Ariumi *et al.* examined the effects of ICV administration of PGE_2 and selective agonists of $EP_{1–4}$ receptors on central cardiovascular and renal sympathetic nerve activity. Among the four EP agonists tested, only ICV infusion of the

EP_3 agonist ONO-AE-248 resulted in an increase in RSNA with pressor and tachycardia responses, mimicking the effect of ICV PGE_2 infusion.[88] This observation has been extended by Zhang *et al.* who tested the effects of central administration of various EP antagonists in a similar experimental setting.[89] PGE_2-elicited cardiovascular and renal sympathoexcitatory responses were significantly reduced by pretreatment with the EP_3 antagonist; the EP_1 and EP_4 antagonists had little or no effects. The independent studies respectively using EP agonists and antagonists consistently demonstrate that EP_3 receptor is a dominant EP subtype responsible for the central sympathoexcitatory effect of PGE_2. In a general agreement with this notion, $EP_3^{-/-}$mice show reduced brain injury after cerebral ischemia.[90] Together, these results suggest that EP_3 receptor activation may largely account for the pressor effect of central PGE_2 via eliciting the sympathoexcitatory response and that EP_3 inhibitors may hold promise to develop into novel therapies for the management of hypertension and stroke. Of note, the pressor action of EP_3 receptors also occurs in peripheral vascular beds including rat mesentery artery, rat tail artery, guinea-pig aorta, human pulmonary artery, and murine renal vasculature.[27,91–94] The relative contribution of peripheral versus central action of EP_3 receptors to increased BP is unclear.

Within the kidneys of rabbits and mice, EP_3 receptors are abundantly detected in the renal medulla and localized to medullary thick ascending limb and the CD, the two important nephron sites for the natriuretic and diuretic actions of PGE_2. Activation of EP_3 receptors also inhibits AVP-induced cAMP accumulation. However, EP_3 receptor deletion in mice does not produce a major influence on renal function or BP.[92]

ROLES OF EP_2/EP_4 RECEPTORS IN BP REGULATION

The increase of intracellular cAMP through a Gs coupled pathway is a classical mechanism for vasorelaxation. EP_2/EP_4 receptors via this pathway have the potential to control vascular tone and BP. An important role of EP_2 receptors in BP regulation is suggested by the hypertensive phenotype of $EP_2^{-/-}$ mice at baseline and following a high-salt diet. While $EP_2^{-/-}$ mice had a modest increase of BP at baseline, these animals developed profound hypertension when fed a high-salt diet. Moreover, the hypertension was quickly reversed by switching to normal salt diet and is re-established by resumption of the high-salt diet, establishing salt sensitivity.[95] In light of the well recognized vasodepressor action of EP_2 receptors, it is conceivable that the loss of this action may account for the hypertensive phenotype in $EP_2^{-/-}$ mice. This notion is supported by the observation that in response to acute PGE_2 infusion, $EP_2^{-/-}$ mice developed hypertension rather than hypotension seen the wild-type mice. It is somewhat puzzling, however, that evidence from studies using the aortic ring preparation suggests a primary role of the EP_4, but not the EP_2 receptor in mediating PGE_2-induced relaxations.[21] Since conduit vessels were used in these preparations, a possibility still exists that EP_2 receptor may be more important in resistance vessels. Recently, Chen *et al.* examined the role of EP_2 in the natriuretic response to intramedullary infusion of PGE_2 in mice.[41] Intramedullary, PGE_2 infusion to anesthetized, uninephrectomized mice produced natriuresis and diuresis, an effect that was recapitulated by intramedullary infusion of the EP_2 agonist butaprost. Strikingly, the natriuresis was absent in $EP_2^{-/-}$ mice.[41] These results underscore an important role of the EP_2 receptor in mediating the renal natriuretic action of PGE_2. It is unknown whether the natriuretic effect of EP_2 receptor activation is the result of altered renal medullary blood flow or tubular sodium transport.

As discussed above, *in vitro* evidence supports an essential role of EP_4 receptors in mediating PGE_2-elicited vasodilation in isolated aortic rings.[21] The dilator action of EP_4 receptor activation is dependent on endothelium derived NO production via increased eNOS activity as a result of dephosphorylation at Thr^{495}. NO results in guanylyl cyclase-dependent accumulation of cGMP that leads to vasorelaxation in aortic rings. This study also presents *in vivo* evidence that the hypotensive response to acute PGE_2 infusion is blunted in $eNOS^{-/-}$ mice. However, despite the well-defined vasodepressor action of EP_4 receptors, the underlying signaling mechanism and the functional role of this subtype in long-term BP regulation *in vivo* remains unclear.

PGE_2 INACTIVATION

The steady-state level of active prostanoids is determined by the relative rates of biosynthesis and inactivation. Thus, it is equally important to understand PG-degrading processes. PGs are rapidly cleared in a single passage through any of the vascular beds, including those of lung. This may serve as a key mechanism to ensure that PGs act in the vicinity of the site of synthesis, exerting autocrine, or paracrine functions. In this way, the local determination of the signal can prevent undesired action at a distance. Compared with the overwhelming information regarding the PG biosynthesis pathway, much less is known about the inactivation pathway. The inactivation of PGs has been proposed to involve two major steps: (i) selective uptake across plasma membrane via PG transporter (PGT) and (ii) oxidation inside the cell via NAD^+-dependent 15-hydoxyprostaglandin dehydrogenase).[96–99] PGT is broadly expressed in many cell types with most abundant expression in the lung, suggesting that this transporter may be responsible for the single-pass metabolic clearance of PGs through that vascular bed in the lung. Recently, a structurally distinct PG-specific organic transporter (OAT-PG) in the OAT group of the SLC22 family has been identified.[100,101] OAT-PG has high affinity and selectivity for PGE_2, similar to PGT. Unlike

PGT, however, OAT-PG is exclusively expressed in the kidney and further localized to the basolateral membrane of proximal tubules where 15-hydoxyprostaglandin dehydrogenase is expressed mostly in the cytosol.[100] This anatomic evidence suggests functional coupling between transporters and metabolic enzymes in the clearance of extracellular PGs in the kidney.

CONCLUSION

PGE_2 plays a diverse role in BP regulation depending on the site of action. Rodent studies demonstrated that centrally administered PGE_2 elevates BP, but systemically administered PGE_2 produces a hypotensive effect; PGE_2 also modulates BP via affecting renin secretion. In most cases, the net effect of PGE_2 is determined by the balance between the pressor action of EP_1/EP_3 receptors and the depressor action of EP_2/EP_4 receptors. The preferential activation of a particular EP subtype relies on the setting of BP regulation. For example, EP_3 receptors play a dominant role in hypertension development induced by central PGE_2 infusion through sympathoactivation whereas EP_1 receptors mediate increased BP in response to Ang II infusion and in SHR via vasoconstriction. On the other hand, the EP_2 receptor deficiency leads to salt-sensitive hypertension due to impaired renal natriuresis. An in-depth understanding of PGE_2 signaling pathway will offer unique opportunity for development of novel antihypertensive interventions targeting specific EP receptors in a specific setting.

Acknowledgments: This work was supported by the National Basic Research Program of China 973 Program 2012CB517600 (No. 2012CB517602), the National Institute of Diabetes and Digestive and Kidney Diseases DK079162, and VA Merit Review. T.Y. is an Established Investigator from American Heart Association and Research Career Scientist in Department of Veterans Affairs.

Disclosure: The authors declared no conflict of interest.

1. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature New Biol* 1971; 231:232–235.
2. Jakobsson PJ, Thorén S, Morgenstern R, Samuelsson B. Identification of human prostaglandin E synthase: a microsomal, glutathione-dependent, inducible enzyme, constituting a potential novel drug target. *Proc Natl Acad Sci USA* 1999; 96:7220–7225.
3. Chang HH, Meuillet EJ. Identification and development of mPGES-1 inhibitors: where we are at? *Future Med Chem* 2011; 3:1909–1934.
4. Chi Y, Min J, Jasmin JF, Lisanti MP, Chang YT, Schuster VL. Development of a high-affinity inhibitor of the prostaglandin transporter. *J Pharmacol Exp Ther* 2011; 339:633–641.
5. Jia Z, Wang H, Yang T. Mice lacking mPGES-1 are resistant to lithium-induced polyuria. *Am J Physiol Renal Physiol* 2009; 297:F1689–F1696.
6. Jia Z, Aoyagi T, Yang T. mPGES-1 protects against DOCA-salt hypertension via inhibition of oxidative stress or stimulation of NO/cGMP. *Hypertension* 2010; 55:539–546.
7. Jia Z, Guo X, Zhang H, Wang MH, Dong Z, Yang T. Microsomal prostaglandin synthase-1-derived prostaglandin E2 protects against angiotensin II-induced hypertension via inhibition of oxidative stress. *Hypertension* 2008; 52:952–959.
8. Jia Z, Yan G, Liu H, Wang Z, Jiang P, Shi Y. The optimization of wireless power transmission: design and realization. *Int J Med Robot* 2012.
9. Francois H, Facemire C, Kumar A, Audoly L, Koller B, Coffman T. Role of microsomal prostaglandin E synthase 1 in the kidney. *J Am Soc Nephrol* 2007; 18:1466–1475.
10. Harding P, Yang XP, He Q, Lapointe MC. Lack of microsomal prostaglandin E synthase-1 reduces cardiac function following angiotensin II infusion. *Am J Physiol Heart Circ Physiol* 2011; 300:H1053–H1061.
11. Facemire CS, Griffiths R, Audoly LP, Koller BH, Coffman TM. The impact of microsomal prostaglandin e synthase 1 on blood pressure is determined by genetic background. *Hypertension* 2010; 55:531–538.
12. Jia Z, Aoyagi T, Kohan DE, Yang T. mPGES-1 deletion impairs aldosterone escape and enhances sodium appetite. *Am J Physiol Renal Physiol* 2010; 299:F155–F166.
13. Jania LA, Chandrasekharan S, Backlund MG, Foley NA, Snouwaert J, Wang IM, Clark P, Audoly LP, Koller BH. Microsomal prostaglandin E synthase-2 is not essential for ***in vivo*** prostaglandin E2 biosynthesis. *Prostaglandins Other Lipid Mediat* 2009; 88:73–81.
14. Nakatani Y, Hokonohara Y, Kakuta S, Sudo K, Iwakura Y, Kudo I. Knockout mice lacking cPGES/p23, a constitutively expressed PGE2 synthetic enzyme, are peri-natally lethal. *Biochem Biophys Res Commun* 2007; 362:387–392.
15. Lovgren AK, Kovarova M, Koller BH. cPGES/p23 is required for glucocorticoid receptor function and embryonic growth but not prostaglandin E2 synthesis. *Mol Cell Biol* 2007; 27:4416–4430.
16. Sugimoto Y, Narumiya S. Prostaglandin E receptors. *J Biol Chem* 2007; 282:11613–11617.
17. Zhang Y, Guan Y, Schneider A, Brandon S, Breyer RM, Breyer MD. Characterization of murine vasopressor and vasodepressor prostaglandin E(2) receptors. *Hypertension* 2000; 35:1129–1134.
18. Lydford SJ, McKechnie KC, Dougall IG. Pharmacological studies on prostanoid receptors in the rabbit isolated saphenous vein: a comparison with the rabbit isolated ear artery. *Br J Pharmacol* 1996; 117:13–20.
19. Lawrence RA, Jones RL. Investigation of the prostaglandin E (EP-) receptor subtype mediating relaxation of the rabbit jugular vein. *Br J Pharmacol* 1992; 105:817–824.
20. Coleman RA, Grix SP, Head SA, Louttit JB, Mallett A, Sheldrick RL. A novel inhibitory prostanoid receptor in piglet saphenous vein. *Prostaglandins* 1994; 47:151–168.
21. Hristovska AM, Rasmussen LE, Hansen PB, Nielsen SS, Nüsing RM, Narumiya S, Vanhoutte P, Skøtt O, Jensen BL. Prostaglandin E2 induces vascular relaxation by E-prostanoid 4 receptor-mediated activation of endothelial nitric oxide synthase. *Hypertension* 2007; 50:525–530.
22. Foudi N, Kotelevets L, Louedec L, Leséche G, Henin D, Chastre E, Norel X. Vasorelaxation induced by prostaglandin E2 in human pulmonary vein: role of the EP4 receptor subtype. *Br J Pharmacol* 2008; 154:1631–1639.
23. Davis RJ, Murdoch CE, Ali M, Purbrick S, Ravid R, Baxter GS, Tilford N, Sheldrick RL, Clark KL, Coleman RA. EP4 prostanoid receptor-mediated vasodilatation of human middle cerebral arteries. *Br J Pharmacol* 2004; 141:580–585.
24. Francois H, Facemire C, Kumar A, Audoly L, Koller B, Coffman T. Role of microsomal prostaglandin E synthase 1 in the kidney. *J Am Soc Nephrol* 2007; 18:1466–1475.
25. Matsuda H, Hayashi K, Arakawa K, Kubota E, Honda M, Tokuyama H, Suzuki H, Yamamoto T, Kajiya F, Saruta T. Distinct modulation of superficial and juxtamedullary arterioles by prostaglandin in vivo. *Hypertens Res* 2002; 25:901–910.
26. Foudi N, Kotelevets L, Gomez I, Louedec L, Longrois D, Chastre E, Norel X. Differential reactivity of human mammary artery and saphenous vein to prostaglandin E(2): implication for cardiovascular grafts. *Br J Pharmacol* 2011; 163:826–834.
27. Kobayashi K, Murata T, Hori M, Ozaki H. Prostaglandin E2-prostanoid EP3 signal induces vascular contraction via nPKC and ROCK activation in rat mesenteric artery. *Eur J Pharmacol* 2011; 660:375–380.
28. Arisz L, Donker AJ, Brentjens JR, van der Hem GK. The effect of indomethacin on proteinuria and kidney function in the nephrotic syndrome. *Acta Med Scand* 1976; 199:121–125.
29. Walshe JJ, Brentjens JR, Costa GG, Andres GA, Venuto RC. Abdominal pain associated with IgA nephropathy. Possible mechanism. *Am J Med* 1984; 77:765–767.
30. Antillon M, Cominelli F, Lo S, Moran M, Somberg K, Reynolds T, Zipser RD. Effects of oral prostaglandins on indomethacin-induced renal failure in patients with cirrhosis and ascites. *J Rheumatol Suppl* 1990; 20:46–49.
31. Huerta C, Rodríguez LA. Incidence of ocular melanoma in the general population and in glaucoma patients. *J Epidemiol Community Health* 2001; 55:338–339.
32. Edwards RM. Effects of prostaglandins on vasoconstrictor action in isolated renal arterioles. *Am J Physiol* 1985; 248:F779–F784.

33. Imig JD, Breyer MD, Breyer RM. Contribution of prostaglandin EP(2) receptors to renal microvascular reactivity in mice. *Am J Physiol Renal Physiol* 2002; 283:F415–F422.
34. Mattson DL, Lu S, Nakanishi K, Papanek PE, Cowley AW Jr. Effect of chronic renal medullary nitric oxide inhibition on blood pressure. *Am J Physiol* 1994; 266:H1918–H1926.
35. Mattson DL, Lu S, Cowley AW Jr. Role of nitric oxide in the control of the renal medullary circulation. *Clin Exp Pharmacol Physiol* 1997; 24:587–590.
36. Mattson DL, Meister CJ. Renal cortical and medullary blood flow responses to L-NAME and ANG II in wild-type, nNOS null mutant, and eNOS null mutant mice. *Am J Physiol Regul Integr Comp Physiol* 2005; 289:R991–R997.
37. Nakanishi K, Mattson DL, Cowley AW Jr. Role of renal medullary blood flow in the development of L-NAME hypertension in rats. *Am J Physiol* 1995; 268:R317–R323.
38. Ye W, Zhang H, Hillas E, Kohan DE, Miller RL, Nelson RD, Honeggar M, Yang T. Expression and function of COX isoforms in renal medulla: evidence for regulation of salt sensitivity and blood pressure. *Am J Physiol Renal Physiol* 2006; 290:F542–F549.
39. Pallone TL. Vasoconstriction of outer medullary vasa recta by angiotensin II is modulated by prostaglandin E2. *Am J Physiol* 1994; 266:F850–F857.
40. Silldorff EP, Yang S, Pallone TL. Prostaglandin E2 abrogates endothelin-induced vasoconstriction in renal outer medullary descending vasa recta of the rat. *J Clin Invest* 1995; 95:2734–2740.
41. Chen J, Zhao M, He W, Milne GL, Howard JR, Morrow J, Hébert RL, Breyer RM, Chen J, Hao CM. Increased dietary NaCl induces renal medullary PGE2 production and natriuresis via the EP2 receptor. *Am J Physiol Renal Physiol* 2008; 295:F818–F825.
42. Elsner D, Müntze A, Kromer EP, Riegger GA. Prostaglandin I2 versus prostaglandin E2 in dogs with and without low cardiac output. Differential effects on renal function. *Am J Hypertens* 1992; 5:175–179.
43. Jones RL, Watson ML, Ungar A. A comparison of the effects of prostaglandins E2 and I2 on renal function and renin release in salt-loaded and salt-depleted anaesthetized dogs. *Q J Exp Physiol* 1981; 66:1–15.
44. Stokes JB, Kokko JP. Inhibition of sodium transport by prostaglandin E2 across the isolated, perfused rabbit collecting tubule. *J Clin Invest* 1977; 59:1099–1104.
45. Guan Y, Zhang Y, Breyer RM, Fowler B, Davis L, Hébert RL, Breyer MD. Prostaglandin E2 inhibits renal collecting duct Na+ absorption by activating the EP1 receptor. *J Clin Invest* 1998; 102:194–201.
46. Fine LG, Trizna W. Influence of prostaglandins on sodium transport of isolated medullary nephron segments. *Am J Physiol* 1977; 232:F383–F390.
47. Sakairi Y, Jacobson HR, Noland TD, Breyer MD. Luminal prostaglandin E receptors regulate salt and water transport in rabbit cortical collecting duct. *Am J Physiol* 1995; 269:F257–F265.
48. DiBona GF. Sympathetic nervous system and the kidney in hypertension. *Curr Opin Nephrol Hypertens* 2002; 11:197–200.
49. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambar S, Abraham WT, Esler M. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 2009; 373:1275–1281.
50. Kopp UC, Cicha MZ, Smith LA, Ruohonen S, Scheinin M, Fritz N, Hökfelt T. Dietary sodium modulates the interaction between efferent and afferent renal nerve activity by altering activation of a2-adrenoceptors on renal sensory nerves. *Am J Physiol Regul Integr Comp Physiol* 2011; 300:R298–R310.
51. Kopp UC, Grisk O, Cicha MZ, Smith LA, Steinbach A, Schlüter T, Mähler N, Hökfelt T. Dietary sodium modulates the interaction between efferent renal sympathetic nerve activity and afferent renal nerve activity: role of endothelin. *Am J Physiol Regul Integr Comp Physiol* 2009; 297:R337–R351.
52. Kopp UC, Cicha MZ, Smith LA. Differential effects of endothelin on activation of renal mechanosensory nerves: stimulatory in high-sodium diet and inhibitory in low-sodium diet. *Am J Physiol Regul Integr Comp Physiol* 2006; 291:R1545–R1556.
53. Kopp UC, Cicha MZ, Smith LA, Ruohonen S, Scheinin M, Fritz N, Hokfelt T. Dietary sodium modulates the interaction between efferent and afferent renal nerve activity by altering activation of alpha2-adrenoceptors on renal sensory nerves. *Am J Physiol Regul Integr Comp Physiol* 2011; 300:R298–R310.
54. Kopp UC, Cicha MZ. PGE2 increases substance P release from renal pelvic sensory nerves via activation of N-type calcium channels. *Am J Physiol* 1999; 276:R1241–R1248.
55. Kopp UC, Cicha MZ, Smith LA. PGE(2) increases release of substance P from renal sensory nerves by activating the cAMP-PKA transduction cascade. *Am J Physiol Regul Integr Comp Physiol* 2002; 282:R1618–R1627.
56. Kondo K, Okuno T, Saruta T, Kato E. Effects of intracerebroventricular administration of prostaglandins I2, E2, F2 alpha and indomethacin on blood pressure in the rat. *Prostaglandins* 1979; 17:769–774.
57. Hoffman WE, Schmid PG. Cardiovascular and antidiuretic effects of central prostaglandin E2. *J Physiol (Lond)* 1979; 288:159–169.
58. Takahashi H, Buñag RD. Pressor responses to centrally-administered prostaglandin E2 in spontaneously hypertensive rats. *Hypertension* 1981; 3:426–432.
59. Okuno T, Lindheimer MD, Oparil S. Central effects of prostaglandin E2 on blood pressure and plasma renin activity in rats. Role of the sympathoadrenal system and vasopressin. *Hypertension* 1982; 4:809–816.
60. Feuerstein G, Adelberg SA, Kopin IJ, Jacobowitz DM. Hypothalamic sites for cardiovascular and sympathetic modulation by prostaglandin E2. *Brain Res* 1982; 231:335–342.
61. Westfall TC. Local regulation of adrenergic neurotransmission. *Physiol Rev* 1977; 57:659–728.
62. Medina P, Segarra G, Mauricio MD, Vila JM, Chuan P, Lluch S. Role of Ca(2+)-activated K(+) channels and Na(+),K(+)-ATPase in prostaglandin E(1)- and E(2)-induced inhibition of the adrenergic response in human vas deferens. *Biochem Pharmacol* 2011; 82:65–71.
63. Yamamoto M, Share L, Shade RE. Vasopressin release during ventriculo-cisternal perfusion with prostaglandin E2 in the dog. *J Endocrinol* 1976; 71:325–331.
64. Imanishi M, Kawamura M, Akabane S, Matsushima Y, Kuramochi M, Ito K, Ohta M, Kimura K, Takamiya M, Omae T. Aspirin lowers blood pressure in patients with renovascular hypertension. *Hypertension* 1989; 14:461–468.
65. Jackson EK, Oates JA, Branch RA. Indomethacin decreases arterial blood pressure and plasma renin activity in rats with aortic ligation. *Circ Res* 1981; 49:180–185.
66. Bivol LM, Hultström M, Gudbrandsen OA, Berge RK, Iversen BM. Tetradecylthioacetic acid downregulates cyclooxygenase 2 in the renal cortex of two-kidney, one-clip hypertensive rats. *Am J Physiol Regul Integr Comp Physiol* 2008; 295:R1866–R1873.
67. Yang T, Endo Y, Huang YG, Smart A, Briggs JP, Schnermann J. Renin expression in COX-2-knockout mice on normal or low-salt diets. *Am J Physiol Renal Physiol* 2000; 279:F819–F825.
68. Ahn KO, Lim SW, Yang HJ, Li C, Sugawara A, Ito S, Choi BS, Kim YS, Kim J, Yang CW. Induction of PPAR gamma mRNA and protein expression by rosiglitazone in chronic cyclosporine nephropathy in the rat. *Yonsei Med J* 2007; 48:308–316.
69. Cheng HF, Wang JL, Zhang MZ, Wang SW, McKanna JA, Harris RC. Genetic deletion of COX-2 prevents increased renin expression in response to ACE inhibition. *Am J Physiol Renal Physiol* 2001; 280:F449–F456.
70. Castrop H, Schweda F, Schumacher K, Wolf K, Kurtz A. Role of renocortical cyclooxygenase-2 for renal vascular resistance and macula densa control of renin secretion. *J Am Soc Nephrol* 2001; 12:867–874.
71. Schnermann J, Briggs JP. Synthesis and secretion of renin in mice with induced genetic mutations. *Kidney Int* 2012; 81:529–538.
72. Castrop H, Höcherl K, Kurtz A, Schweda F, Todorov V, Wagner C. Physiology of kidney renin. *Physiol Rev* 2010; 90:607–673.
73. Wang JL, Cheng HF, Harris RC. Cyclooxygenase-2 inhibition decreases renin content and lowers blood pressure in a model of renovascular hypertension. *Hypertension* 1999; 34:96–101.
74. Richter CM, Godes M, Wagner C, Maser-Gluth C, Herzfeld S, Dorn M, Priem F, Slowinski T, Bauer C, Schneider W, Neumayer HH, Kurtz A, Hocher B. Chronic cyclooxygenase-2 inhibition does not alter blood pressure and kidney function in renovascular hypertensive rats. *J Hypertens* 2004; 22:191–198.
75. Hockel GM, Cowley AW Jr. Effect of chronic intrarenal prostaglandin E2 infusion and angiotensin II blockade on arterial pressure in the dog. *Adv Prostaglandin Thromboxane Res* 1980; 7:1061–1065.
76. Câmpean V, Theilig F, Paliege A, Breyer M, Bachmann S. Key enzymes for renal prostaglandin synthesis: site-specific expression in rodent kidney (rat, mouse). *Am J Physiol Renal Physiol* 2003; 285:F19–F32.
77. Fuson AL, Komlosi P, Unlap TM, Bell PD, Peti-Peterdi J. Immunolocalization of a microsomal prostaglandin E synthase in rabbit kidney. *Am J Physiol Renal Physiol* 2003; 285:F558–F564.
78. Csukas S, Hanke CJ, Rewolinski D, Campbell WB. Prostaglandin E2-induced aldosterone release is mediated by an EP2 receptor. *Hypertension* 1998; 31:575–581.
79. Muro S, Tanaka I, Usui T, Kotani M, Koide S, Mukoyama M, Fukata J, Itoh H, Narumiya S, Kawata M, Nakao K. Expression of prostaglandin E receptor EP4

subtype in rat adrenal zona glomerulosa: involvement in aldosterone release. *Endocr J* 2000; 47:429–436.
80. Breyer MD, Breyer RM. Prostaglandin E receptors and the kidney. *Am J Physiol Renal Physiol* 2000; 279:F12–F23.
81. Ren J, Karpinski E, Benishin CG. Prostaglandin E2 contracts vascular smooth muscle and inhibits potassium currents in vascular smooth muscle cells of rat tail artery. *J Pharmacol Exp Ther* 1995; 275:710–719.
82. Bolla M, You D, Loufrani L, Levy BI, Levy-Toledano S, Habib A, Henrion D. Cyclooxygenase involvement in thromboxane-dependent contraction in rat mesenteric resistance arteries. *Hypertension* 2004; 43:1264–1269.
83. Jadhav V, Jabre A, Lin SZ, Lee TJ. EP1- and EP3-receptors mediate prostaglandin E2-induced constriction of porcine large cerebral arteries. *J Cereb Blood Flow Metab* 2004; 24:1305–1316.
84. Guan Y, Zhang Y, Wu J, Qi Z, Yang G, Dou D, Gao Y, Chen L, Zhang X, Davis LS, Wei M, Fan X, Carmosino M, Hao C, Imig JD, Breyer RM, Breyer MD. Antihypertensive effects of selective prostaglandin E2 receptor subtype 1 targeting. *J Clin Invest* 2007; 117:2496–2505.
85. Rutkai I, Feher A, Erdei N, Henrion D, Papp Z, Edes I, Koller A, Kaley G, Bagi Z. Activation of prostaglandin E2 EP1 receptor increases arteriolar tone and blood pressure in mice with type 2 diabetes. *Cardiovasc Res* 2009; 83:148–154.
86. Suganami T, Mori K, Tanaka I, Mukoyama M, Sugawara A, Makino H, Muro S, Yahata K, Ohuchida S, Maruyama T, Narumiya S, Nakao K. Role of prostaglandin E receptor EP1 subtype in the development of renal injury in genetically hypertensive rats. *Hypertension* 2003; 42:1183–1190.
87. Hébert RL, Jacobson HR, Breyer MD. Prostaglandin E2 inhibits sodium transport in rabbit cortical collecting duct by increasing intracellular calcium. *J Clin Invest* 1991; 87:1992–1998.
88. Ariumi H, Takano Y, Masumi A, Takahashi S, Hirabara Y, Honda K, Saito R, Kamiya HO. Roles of the central prostaglandin EP3 receptors in cardiovascular regulation in rats. *Neurosci Lett* 2002; 324:61–64.
89. Zhang ZH, Yu Y, Wei SG, Nakamura Y, Nakamura K, Felder RB. EP3 receptors mediate PGE2-induced hypothalamic paraventricular nucleus excitation and sympathetic activation. *Am J Physiol Heart Circ Physiol* 2011; 301:H1559–H1569.
90. Saleem S, Kim YT, Maruyama T, Narumiya S, Doré S. Reduced acute brain injury in PGE2 EP3 receptor-deficient mice after cerebral ischemia. *J Neuroimmunol* 2009; 208:87–93.
91. Orie NN, Clapp LH. Role of prostanoid IP and EP receptors in mediating vasorelaxant responses to PGI2 analogues in rat tail artery: Evidence for Gi/o modulation via EP3 receptors. *Eur J Pharmacol* 2011; 654:258–265.
92. Audoly LP, Ruan X, Wagner VA, Goulet JL, Tilley SL, Koller BH, Coffman TM, Arendshorst WJ. Role of EP(2) and EP(3) PGE(2) receptors in control of murine renal hemodynamics. *Am J Physiol Heart Circ Physiol* 2001; 280:H327–H333.
93. Jones RL, Woodward DF. Interaction of prostanoid EP3 and TP receptors in guinea-pig isolated aorta: contractile self-synergism of 11-deoxy-16,16-dimethyl PGE2. *Br J Pharmacol* 2011; 162:521–531.
94. Qian YM, Jones RL, Chan KM, Stock AI, Ho JK. Potent contractile actions of prostanoid EP3-receptor agonists on human isolated pulmonary artery. *Br J Pharmacol* 1994; 113:369–374.
95. Kennedy CR, Zhang Y, Brandon S, Guan Y, Coffee K, Funk CD, Magnuson MA, Oates JA, Breyer MD, Breyer RM. Salt-sensitive hypertension and reduced fertility in mice lacking the prostaglandin EP2 receptor. *Nat Med* 1999; 5:217–220.
96. Yao B, Xu J, Harris RC, Zhang MZ. Renal localization and regulation of 15-hydroxyprostaglandin dehydrogenase. *Am J Physiol Renal Physiol* 2008; 294:F433–F439.
97. Nomura T, Chang HY, Lu R, Hankin J, Murphy RC, Schuster VL. Prostaglandin signaling in the renal collecting duct: release, reuptake, and oxidation in the same cell. *J Biol Chem* 2005; 280:28424–28429.
98. Nomura T, Lu R, Pucci ML, Schuster VL. The two-step model of prostaglandin signal termination: ***in vitro*** reconstitution with the prostaglandin transporter and prostaglandin 15 dehydrogenase. *Mol Pharmacol* 2004; 65:973–978.
99. Uchida S, Nonoguchi H, Endou H. Localization and properties of NAD+-dependent 15-hydroxyprostaglandin dehydrogenase activity in the rat kidney. *Pflugers Arch* 1985; 404:278–284.
100. Shiraya K, Hirata T, Hatano R, Nagamori S, Wiriyasermkul P, Jutabha P, Matsubara M, Muto S, Tanaka H, Asano S, Anzai N, Endou H, Yamada A, Sakurai H, Kanai Y. A novel transporter of SLC22 family specifically transports prostaglandins and co-localizes with 15-hydroxyprostaglandin dehydrogenase in renal proximal tubules. *J Biol Chem* 2010; 285:22141–22151.
101. Hatano R, Onoe K, Obara M, Matsubara M, Kanai Y, Muto S, Asano S. Sex hormones induce a gender-related difference in renal expression of a novel prostaglandin transporter, OAT-PG, influencing basal PGE2 concentration. *Am J Physiol Renal Physiol* 2012; 302:F342–F349.