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Prostaglandin E_2 modulation of blood pressure homeostasis: studies in rodent models

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Abstract

Hypertension is a well established risk factor for cardiovascular diseases such as stroke and is the leading cause of chronic kidney failure. Although a number of pharmacologic agents are available for the treatment of hypertension including agents that affect the renin-angiotensin-aldosterone system (RAAS), unmet needs in the treatment of hypertension suggest that identification of novel pharmacological targets would be an important healthcare goal. One potential target is prostaglandin E_2 (PGE_2), a potent lipid mediator with a diverse and sometimes opposing range of biological effects. PGE_2 signals through four subtypes of G-protein coupled receptors designated EP1 through EP4. PGE_2 functions primarily as a vasodepressor; under certain conditions PGE_2 administration mediates vasopressor activity. This review focuses on the current understanding of the roles of PGE_2 receptors in vascular reactivity, hypertension and end-organ damage.

Keywords

Prostaglandin E_2; hypertension; GPCR; mouse; rat

Introduction

Hypertension increases the risk of stroke, heart attack and end-organ damage including kidney failure. Current therapies to reduce blood pressure and diminish the incidence of complications include blockade of the renin-angiotensin-aldosterone axis, calcium channels, and beta adrenergic receptors. Nonetheless there is significant unmet need for novel therapeutic agents [1].

Prostaglandins (PGs) are cyclooxygenase metabolites of arachidonic acid, and mediate an array of physiologic functions including the regulation of systemic blood pressure. Prostaglandin E_2 (PGE_2) is a major prostanoid contributing to this regulation of blood pressure, where it can exert either vasopressor or vasodepressor effects depending upon the setting [2,3,4]. These physiologically opposing effects can be explained in part by the

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existence of four PGE_2 receptors, designated the E-Prostanoid (EP) receptors EP1 through EP4. Previous studies have determined that the EP1 and EP3 receptors primarily mediate the pressor response, while the EP2 and EP4 receptors mediate the depressor response [2,5,6,7,8,9,10].

The role of PGs in the regulation of blood pressure is highlighted by the pro-hypertensive action of non-steroidal anti-inflammatory drugs (NSAIDs) which inhibit cyclooxygenase mediated prostanoid production, suggesting that overall prostaglandins have an anti-hypertensive role [11]. However, under certain conditions NSAIDs can also have hypotensive effects [12]. The balance of functionally antagonistic prostaglandin action fine-tunes blood pressure homeostasis. The remainder of this review will focus on the actions of PGE_2 and its receptors in blood pressure regulation and its impact on downstream consequences of blood pressure dysregulation.

Isomerization of PGH_2 to PGE_2 by microsomal PGE synthase (mPGES) plays a key role in the regulation of blood pressure by regulating vascular tone, sodium balance and/or renin release [13]. Inhibitors of mPGES are currently being pursued for treatment of cancer, pain and inflammation; however, unwanted pro-hypertensive effects may result from this strategy. In rodents, deletion of mPGES-1 has been shown to further increase blood pressure in several models of hypertension, including deoxycorticosterone-salt water-induced hypertension and acute or chronic treatment with angiotensin II [14,15,16]. In humans, where there is a great deal of phenotypic heterogeneity, the contribution of PGE_2 towards hypertension is more controversial. In some cases, patients with essential hypertension have been shown to have low urinary excretion of PGE_2; however, in other cases patients have been shown to have high urinary PGE_2 excretion [17]. This inter-patient variability may result in a wide range of untoward side effects for mPGES inhibitors. In order to gain a better understanding of the effects of PGE_2 on blood pressure homeostasis, attention has been focused on the actions of its receptors using knockout mouse models.

EP Receptors in blood pressure homeostasis

PGE_2 signals through four subtypes of G-protein coupled receptors designated EP1–EP4, each having distinct tissue localization and signal transduction properties [7,18]. EP1 couples to G_q-proteins, mobilizes intracellular calcium, and stimulates phosphoinositide turnover activating protein kinase C. EP1 receptors were originally defined as constrictor receptors in smooth muscle. EP1 receptor mRNA is ubiquitously expressed; in a recent report, mRNA was detected in all 41 tissues assayed including kidney, lung and adrenal gland. This is consistent with EP1 expression throughout the vasculature [19]. EP1 receptors function as constrictors in the smooth muscle of the trachea, gastrointestinal tract, bladder and uterus. EP2 and EP4 couple to G_s-proteins, activate adenylate cyclase and increase intracellular cAMP ($[cAMP]_i$). The EP2 receptor was initially described as a smooth muscle relaxant receptor. EP2 mRNA is most abundantly expressed in the lung, spleen and ovary while EP4 mRNA is predominantly localized the uterus, thymus, ileum, lung, spleen, adrenal gland, and kidney. EP3 couples to G_i-proteins, inhibits adenylate cyclase and decreases intracellular $[cAMP]_i$. EP3 receptor expression is widespread, and it is found in the kidney, uterus, pancreas, stomach, thymus, spleen, smooth muscle of the gastrointestinal tract, vasculature, and CNS. In the brain, EP3 receptor mRNA has been observed in the hippocampus, preoptic area, hypothalamus, locus coeruleus and raphe nuclei (For reviews, see [7,18,20]). Although the EP receptors were initially described by their ligand binding selectivity and coupling to these well-characterized heterotrimeric G-protein mediated signaling pathways, they are now appreciated to couple to other signal transduction pathways as well, including arrestin-mediated signaling pathways [21,22]. Overall, the principal vasodepressor actions of PGE_2 are mediated via the EP2 and EP4 receptors,

whereas the vasopressor actions are mediated by activation of the EP1 and EP3 receptors [2,5,6,7,8,9,10] (Fig. 1).

Vasodepressor Receptors

Upon acute infusion, PGE_2 is a vasodepressor in both humans and mice [2,5,23]. This observation underscores the pro-hypertensive effects of blockade of all prostaglandin production and subsequent receptor activation by NSAIDs [11,24,25,26,27] consistent with the loss of a tonic vasodepressor PG effect. Although no selective EP2 antagonists are available, the pharmacology of EP vasodepressor response has been addressed with EP2 knockout mice. It has been shown that the depressor effect is primarily due to the activation of the EP2 receptor. When the EP2 receptor is deleted, the depressor response to PGE_2 is lost. Moreover, the loss of the depressor response unmasks a PGE_2 pressor response [2]. In addition, EP2 −/− mice fed a high-salt diet experienced an increase in blood pressure consistent with a protective role for EP2 activation in salt-sensitive hypertension [2]. Intravenous infusion of the EP2 agonist ONO-AE1-259 into Wistar rats increases retinal arteriolar and venous diameter and substantially reduces mean arterial pressure [28]. EP2 and EP4 receptors evoke an increase in $[cAMP]_i$ through a G_s coupled pathway, a classical mechanism for smooth muscle relaxation. Hristovska et al. demonstrated a dose-dependent relaxation in response to PGE_2 in aortic rings which was lost in tissue from EP4 −/− mice but remained intact in EP2 −/− tissue. The EP4 dilator effect was dependent upon endothelium-derived nitric oxide production via eNOS [29]. Acute blood pressure studies are challenging in EP4 −/− mice because the mice exhibit near complete perinatal lethality in inbred strains as a result of persistent patent ductus arteriosus [30]. Analysis of studies performed with surviving EP4 −/− animals on a mixed-strain background may not be straightforward as their survival may be dependent on modifier genes. Nonetheless, deletion of EP4 resulted in a diminished vasodepressor response to PGE_2 [5]. In rats, infusion of the EP4 selective agonist ONO-AE1-329 significantly reduces blood pressure; it does not alter retinal vessel diameter [28]. Taken together is consistent with EP4 vasodilator action in a subset of vascular beds.

Vasopressor Receptors

As described above, the pressor effects of systemic PGE_2 infusion are only observed in the absence of the predominant depressor receptor EP2 [2]. In contrast, infusion of EP3 receptor selective agonists such as sulprostone, MB28767 or SC46275 in wildtype mice results in an acute and substantial rise in mean arterial pressure [8]. It would be of interest to determine the result of systemic EP3 agonists on heart rate, as presynaptic inhibitory EP3 receptors are believed to mediate the reduced release of norepinephrine by PGE_2 [31]. The EP3 mediated pressor effect undergoes desensitization with repeated administration of EP3 agonists. In EP2 −/− mice after desensitization of EP3 responses, the depressor action of EP4 in response to PGE_2 infusion is then apparent [8]. Thus, upon systemic infusion of PGE_2 in mice the depressor action of EP2 predominates, followed by the pressor action of EP3, and then the depressor action of EP4. Importantly, the order of expression of EP receptor mRNA does not mirror the phenotypic effects of the EP receptors. RNA levels determined by RNAse protection identified expression levels of EP3>>EP4>EP1≥EP2 in both renal resistance vessels and the aorta [8]. It is unclear whether changes in EP receptor density underlie changes in vascular tone in the hypertensive state. Because messenger RNA levels do not correlate with receptor function, and anti-receptor antibodies are of questionable value, this remains an important unanswered question.

In contrast to the depressor effects of systemic administration, when PGE_2 is administered intracerebroventricularly (ICV) a rise in mean arterial pressure occurs, accompanied with tachycardia and enhanced renal sympathetic nerve activity [32]. These effects were ascribed

to the EP3 receptor using ICV infusion of subtype selective EP receptor agonists [32]. Taken together, these data demonstrate that the centrally mediated pressor actions of PGE_2 are EP3-mediated.

Although the EP1 receptor does not appear to play a significant role in the blood pressure effects of systemically administered PGE_2, it has been shown to be a significant contributor to hypertension, particularly in cases with enhanced renin-angiotensin system activity. Genetic deletion of the EP1 receptor in mice has been shown to significantly decrease systolic blood pressure, an effect amplified when mice are fed a low sodium diet [33]. Importantly, EP1 −/− mice have blunted pressor responses to both acute and chronic angiotensin II administration [10]. In isolated vascular preparations of preglomerular arterioles and mesenteric arteries, pre-treatment with SC51322, an EP1/3 antagonist, was able to abolish any angiotensin II-mediated vasoconstriction [10]. Furthermore, treatment of spontaneously hypertensive rats, a multifactorial model of essential hypertension, with SC51322 significantly reduces blood pressure [10], indicating the EP1 receptor and/or EP3 receptor may be novel targets for the treatment of hypertension.

Consequences of hypertension

Hypertension is an established risk factor for cardiovascular diseases including stroke, myocardial infarction, heart failure, arterial aneurysm and is the leading cause of chronic kidney failure. Current anti-hypertensive therapies reduce the risk of the related cardiovascular sequelae, though not to baseline risk observed in normotensive subjects. There is an unmet need for treatment which will reduce blood pressure and maximize target organ protection [1]. In considering whether PGE_2 and its receptors make viable drug targets for hypertension, determination of their ability to reduce end-organ damage will be important. While it has been shown that genetic deletion of mPGES-1 in mice results in increased blood pressure [14,15,16], deletion of mPGES-1 has also been shown to protect against aortic aneurysm formation and vascular injury [34,35]. Angiotensin II infusion into hyperlipidemic mice produced fewer and less severe aneurysms, and reduced oxidative stress on a mPGES-1 −/− background compared to wildtype mice [36]. However, these results were complicated by the observed increase in PGI_2 and PGD_2 production accompanying the reduction in PGE_2 [36]. It is yet to be determined whether potentially beneficial substrate diversion is a consequence specific to genetic mPGES-1 deletion, or would be recapitulated with chronic use of an mPGES inhibitor.

Blockade of individual PGE_2 receptors might result in a reduction in end-organ damage while being less likely to produce unwanted side effects. In addition, GPCRs are demonstrably “druggable” and are one of the most common targets of currently developed therapeutic agents. Antagonism of EP1 receptors has been shown to preserve renal function, reducing tubulointerstitial damage, proliferative lesions, fibrotic area and proteinuria in stroke-prone spontaneously hypertensive rats [37], as well as cerebrovascular dysfunction induced by angiotensin II [38], making the EP1 receptor a potential target for treatment of hypertension and protection from end-organ damage. In the study performed in stroke-prone hypertensive rats tail cuff blood pressure was modestly reduced two weeks post-treatment with an EP1 antagonist, but this reduction was not maintained past five weeks of treatment. Nonetheless treatment with the EP1 antagonist provided end-organ protection. In contrast to the deleterious actions of the EP1 receptor, EP2 and EP4 receptors have been shown to be cardioprotective; it would seem important to maintain function of these receptors. For example, deletion of the EP4 receptor in a mouse model of ischemia reperfusion of the heart significantly increased infarct size, while treatment of wildtype mice with an EP4 agonist, ONO-4819, reduced infarct size [39]. Therefore, EP4 agonists could be useful for reducing blood pressure and afford cardioprotective benefits. Selective blockade of EP1 and/or EP3

receptors, while EP2 and EP4 signaling remains intact may be preferable to the loss of signaling in all four receptors resulting from inhibition of PGE_2 ligand production.

Conclusions

In summary, PGE_2 plays a dynamic role in regulation of blood pressure homeostasis. The existence of multiple receptors with diverse signaling abilities allows for modulation both positively and negatively. The development and availability of additional highly selective agonists and antagonists for EP receptors is fundamental to the advancement of the field. Unwanted side effects resulting from inhibition of the cyclooxygenase enzymes upstream of prostanoid production demonstrated the value of selective targeting as proximal to the pathophysiological action as possible. Development of new therapeutics targeting specific PGE_2 receptors could reduce blood pressure and provide end-organ protection, while minimizing side effects.

Highlights

- PGE_2 receptors are key modulators of blood pressure control, where EP receptors have functionally antagonistic actions
- Activation of EP2 and EP4 receptors generally lowers blood pressure
- Activation of EP1 and EP3 receptors generally raises blood pressure
- Systemic infusion of PGE_2 leads to a fall in mean arterial pressure by activation of the EP2 receptor
- Intracerebroventricular infusion of PGE_2 leads to a rise in mean arterial pressure by activation of the EP3 receptor

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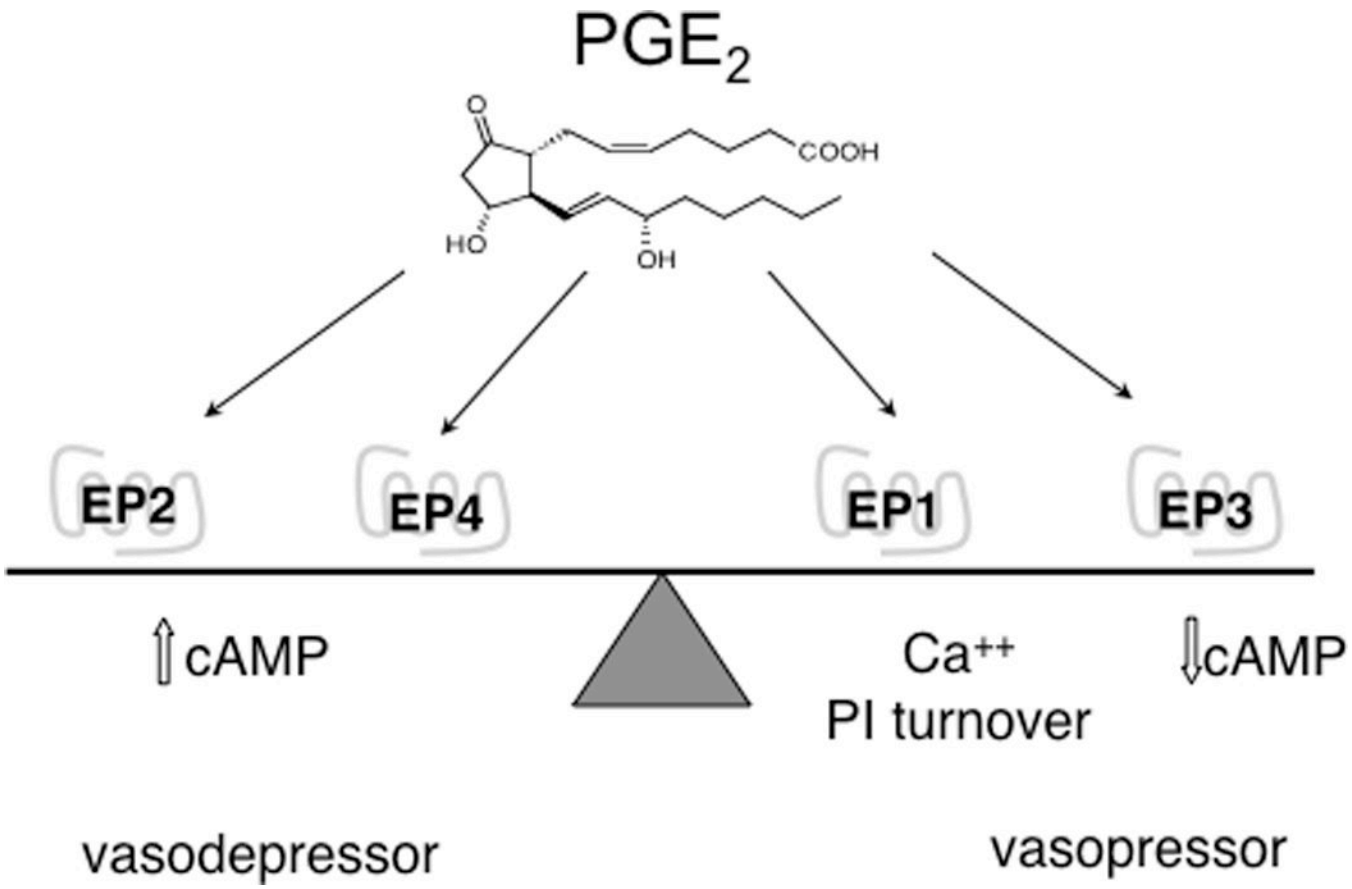

Figure 1.
The role of EP receptors as regulators of blood pressure. The vasodepressor EP2 and EP4 receptors are functionally antagonistic to the pressor EP1 and EP3 receptors.