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EP1c Times for Angiotensin: EP1 Receptors Facilitate Angiotensin II-induced Vascular Dysfunction

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A relatively recent concept is that vascular dysfunction plays a key role in cognitive impairment, as well as stroke. Impaired neurovascular coupling, probably in part through activation of the angiotensin-1 (AT1) receptor, is central to cerebrovascular dysfunction.[1] Reactive oxygen species (ROS) clearly are important mediators of the deleterious vascular effects of angiotensin II. The evidence seemed to favor the concept that angiotensin II, perhaps through activation of NAD(P)H oxidase, releases superoxide, which scavenges nitric oxide to produce cerebral vascular dysfunction.[1]

But just when we thought that we understood mechanisms by which angiotensin II produces cerebrovascular dysfunction, Capone *et al*. in this issue present compelling evidence that products of cyclooxygenase (COX) metabolism are important facilitating factors for angiotensin II signaling in cerebral blood vessels. The authors report that prostaglandin E_2 (PGE_2) and the type 1 PGE_2 (EP1) receptor, are required for endothelial dysfunction and impaired neurovascular coupling induced by acute administration of angiotensin II.[2] Because the hypothesis is novel and important for our understanding of angiotensin II effects, it is desirable to have multiple lines of evidence to support the conclusion. This indeed the authors have accomplished, as they use several genetically altered mice and pharmacological inhibitors to build their case.

EP1 Receptors and COX-1 in angiotensin II-induced vascular dysfunction

COX-1 is involved in synthesis and release of an endothelium-derived contracting factor.[3] Pressor responses to angiotensin are attenuated in COX-1 knockout mice and in mice treated with a COX-1 inhibitor, whereas opposite effects (augmentation of responses to angiotensin) are found with COX-2 inhibitors.[4] Interestingly, angiotensin increases COX-1 and decreases COX-2 expression in murine mesenteric arteries, through an ROS-independent mechanism.[5] These findings suggest that a product of arachidonic acid metabolism, through COX-1, interacts with angiotensin to induce hypertension.

Similarly, several studies have implicated a prostanoid receptor in vascular dysfunction produced by angiotensin. SQ29548, a thromboxane A and EP1 receptor antagonist,

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attenuates vascular dysfunction induced by angiotensin.[5] Moreover, in mice deficient in thromboxane or EP1 receptors, mortality and the pressor response to infusion of angiotensin are attenuated.[6,7]

Capone *et al*.[2] demonstrates that COX-1-dependent formation of PGE_2 and the EP1 receptor are necessary for angiotensin II-induced impairment in neurovascular coupling and cerebrovascular dysfunction. The authors demonstrated that COX-1 and the EP1 receptor are expressed in microglia and blood vessels respectively. Cerebrovascular dysfunction and impaired neurovascular coupling after an acute infusion of angiotensin II are attenuated in mice treated with a COX-1 inhibitor, but not a COX-2 inhibitor, and in mice deficient in COX-1. Angiotensin II did not increase PGE_2 synthesis in brain, but PGE_2 superfusion restored susceptibility of cerebral vessels to angiotensin II-induced dysfunction after COX-1 inhibition.

In addition, effects of angiotensin II are reduced in mice treated with an EP-1 receptor antagonist and in EP-1 knockout mice. EP1 receptors are also required for angiotensin II-induced increase of ROS. Therefore, PGE_2 (a COX-1 product) and EP1 receptors are required for deleterious effects of angiotensin II in the cerebral circulation.

EP1 receptors are important for the vascular effects of angiotensin II, but what is the mechanism?

Several concurrent mechanisms may explain the crosstalk between EP1 and angiotensin II receptors (Fig. 1). First, Capone *et al*.[2] propose that EP1 receptor activation may increase intracellular calcium concentrations and facilitate activation of the NAD(P)H oxidase. Different results have been published before, where PGE_2 attenuated the increase in intracellular calcium induced by angiotensin II in smooth muscle cells from rat preglomerular arterioles[8]. Second, activation of EP1 receptors may modulate the activity of regulatory kinases or regulators of G protein signaling (RGS proteins) to facilitate intracellular signaling in response to angiotensin II. Thus, angiotensin II may work synergistically with prostaglandins to induce vascular dysfunction. Third, we speculate that EP1 receptors may physically regulate the activity of AT1 receptors through heterodimerization. Both angiotensin and PGE_2 receptors are G protein-coupled receptors (GPCR), and it is now known that heterodimerization of GPCRs alters the trafficking and activity of receptors at the plasma membrane.[9] For example, AT1 and EP1 heterodimerize and modulate the activity of β adrenergic receptors.[9] It is not known, however, if angiotensin II receptors dimerize with EP1 receptors. Finally, it is possible that facilitation of angiotensin II signaling by PGE_2 exists only in the context of increased blood pressure.[10] It would be of interest to know if EP1 receptor facilitation of angiotensin II-induced vascular dysfunction is present in the absence of hypertension, for example, during non-pressor doses of angiotensin II in vivo.

Is prostaglandin signaling detrimental for cerebral vascular function?

Although the observation that PGE_2 contributes to angiotensin-induced cerebral vascular dysfunction is convincing,[2] several other lines of evidence point towards a beneficial role of PGE_2 and EP1 receptors in vascular function. Mice deficient in microsomal PGE_2 synthase have a profound pressor response and increased oxidative stress in aorta after treatment with non-pressor doses of angiotensin.[10] Moreover, PGE_2 evoked dilation of mouse basilar artery, *ex vivo*.[11] EP1 receptors also facilitate NO release during neurogenic vasodilation in porcine basilar arteries.[12] Finally, in a rat model of hypertension associated with increased formation of angiotensin II, COX 1 inhibition did not attenuate vascular dysfunction or hypertension.[13] The conflicting results may be explained by differences in model (*in vivo* vs.

ex vivo preparations), vascular bed (cerebral cortical vessels vs. basilar arteries or systemic vessels), and duration of treatment (acute vs. chronic). Therefore, studies are needed to clarify the protective or deleterious effects of different isoforms of PGE_2 synthase and EP1 receptors in function of cerebral and other vessels during chronic infusions of angiotensin II.

Perspective

Capone *et al*.[2] provide evidence for a crucial role of prostanoid metabolism and signaling in regulation of cerebrovascular function. Inhibition of COX-1 or EP1 receptors attenuated the deleterious vascular effects of angiotensin II. Development of specific PGES inhibitors might be a therapeutic target for cerebrovascular disease. It will be of interest to clarify mechanisms responsible for crosstalk between prostaglandin and angiotensin II pathways especially in chronic hypertension.

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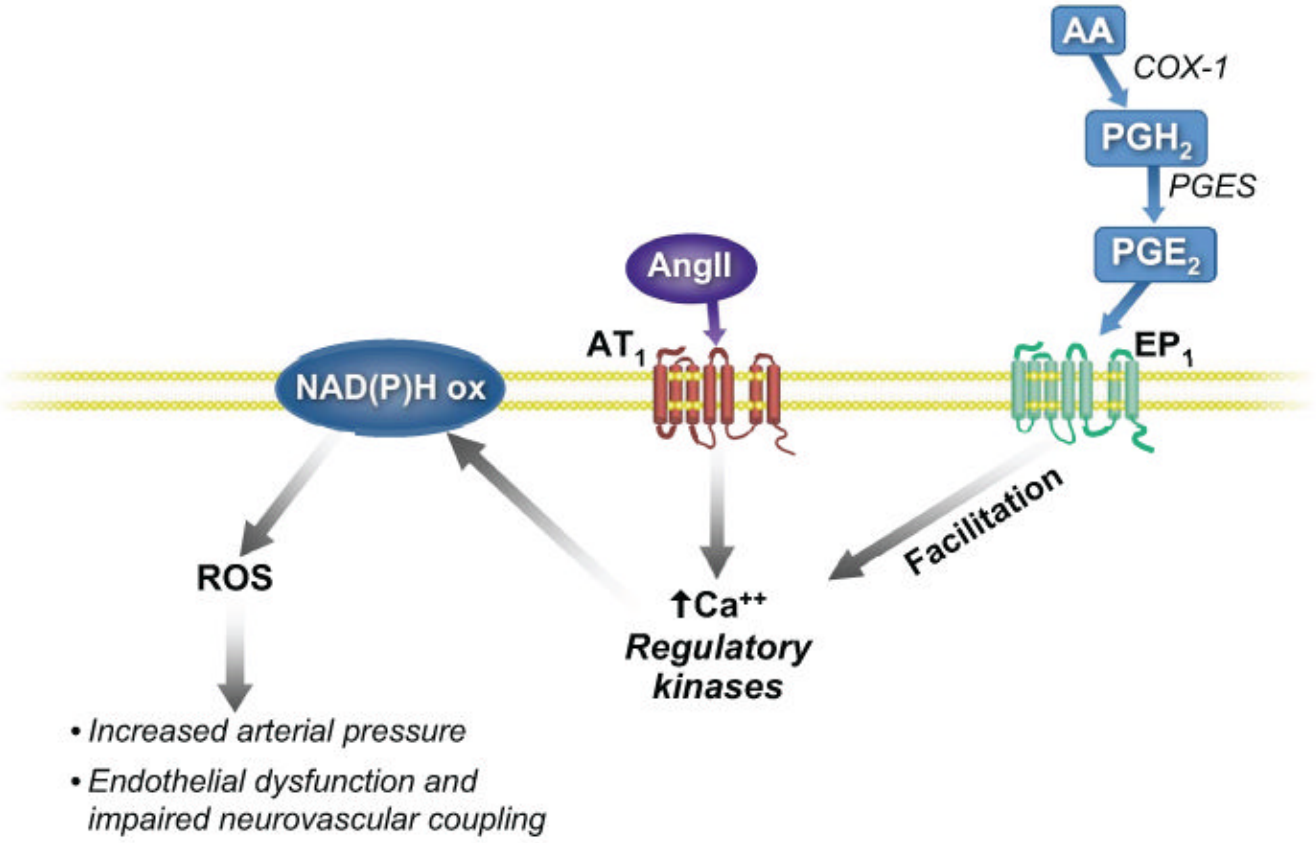

Figure 1.

Prostaglandin E_2 (PGE_2) is a product of metabolism of arachidonic acid (AA) by cyclooxygenase I (COX-1) and the prostaglandin E synthase (PGES), perhaps in microglia. Activation of prostaglandin EP1 receptors by PGE_2 on cerebral blood vessels, may increase the intracellular concentrations of calcium (Ca^{++}) or facilitate the activation of regulatory kinases by angiotensin II (Ang II) type I (AT_1) receptors, which are required for activation of the NAD(P)H oxidase. Reactive oxygen species (ROS) derived from the active NAD(P)H oxidase, are associated with increased arterial pressure, endothelial dysfunction, and impaired neurovascular coupling.