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Prostanoids and blood pressure: which way is up?

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Commentary

Members of the family of prostanoids, made up of prostaglandins and thromboxanes, are generated via COX-mediated metabolism of arachidonic acid. These lipid mediators exhibit wide-ranging biological actions that include regulating both vasomotor tone and renal sodium excretion. As COX inhibition is often associated with sodium retention leading to edema and hypertension, prostanoids appear to have a role in preventing the development of high blood pressure. On the other hand, prostaglandin E_2 (PGE_2) and PGI_2 have also been implicated as determinants of renin secretion. A new study suggests that PGI_2 plays a critical role in stimulating renin release and promoting hypertension following renal artery stenosis.

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Prostanoids and blood pressure: which way is up?

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Members of the family of prostanoids, made up of prostaglandins and thromboxanes, are generated via COX-mediated metabolism of arachidonic acid. These lipid mediators exhibit wide-ranging biological actions that include regulating both vasomotor tone and renal sodium excretion. As COX inhibition is often associated with sodium retention leading to edema and hypertension, prostanoids appear to have a role in preventing the development of high blood pressure. On the other hand, prostaglandin E_2 (PGE_2) and PGI_2 have also been implicated as determinants of renin secretion. A new study suggests that PGI_2 plays a critical role in stimulating renin release and promoting hypertension following renal artery stenosis (see the related article beginning on page 805).

Prostanoids are generated by COX-mediated metabolism of arachidonic acid. These lipid mediators have a myriad of biological actions (1, 2). A role for prostanoids in the regulation of blood pressure was originally suggested by early observations that prostaglandins and thromboxanes affect vascular tone and renal excretory functions (3). Later, the impact of prostanoids upon blood pressure in humans was clearly demonstrated through clinical experiences with NSAIDs. NSAIDs, among the most widely prescribed drugs worldwide, act by inhibiting COX enzymes and hence blocking prostanoid production. Sodium retention leading to edema and hypertension is often observed in patients treated with NSAIDs (4, 5). However, increased blood pressure after treatment with NSAIDs is observed primarily in patients with preexisting hypertension (6–8), suggesting a compensatory role for the prostanoid system in attenuating or preventing the development of high blood pressure.

Data from clinical trials suggest that nonselective NSAIDs, which inhibit both COX isoforms (COX-1 and -2), and selective COX-2 inhibitors (9–12) have similar propensities to cause hypertension. The theory that COX-2–dependent prostanoids resist the development of hypertension is further supported by experiments showing that COX-2 inhibitors or the genetic absence of COX-2 markedly augment the vasoconstrictor actions of Ang II (13). Among the prostanoids, prostaglandin E_2 (PGE_2) and PGI_2 are potent vasodilators that promote renal sodium excretion and thus are logical candidates to mediate these counter-regulatory functions. In this regard, studies in humans suggest that COX-2 may be specifically linked to the generation of PGI_2 in the systemic circulation (14). The predominant inhibition of PGI_2 by COX-2 inhibitors has been posited as an explanation for putative associations between COX-2 inhibitors and the development of cardiovascular complications (15), including hypertension (16, 17).

Prostanoids and renovascular hypertension

In this issue of the *JCI*, Fujino and associates show that the absence of the receptor for PGI_2 (the I-prostanoid [IP] receptor) confers substantial resistance to the development of renovascular hypertension (18). Based on the discussion above, these findings may seem surprising.

Nonstandard abbreviations used: EP, E-prostanoid; IP, I-prostanoid; JGA, juxtaglomerular apparatus; NKCC2, Na-K-2Cl cotransporter 2; PGE_2, prostaglandin E_2.

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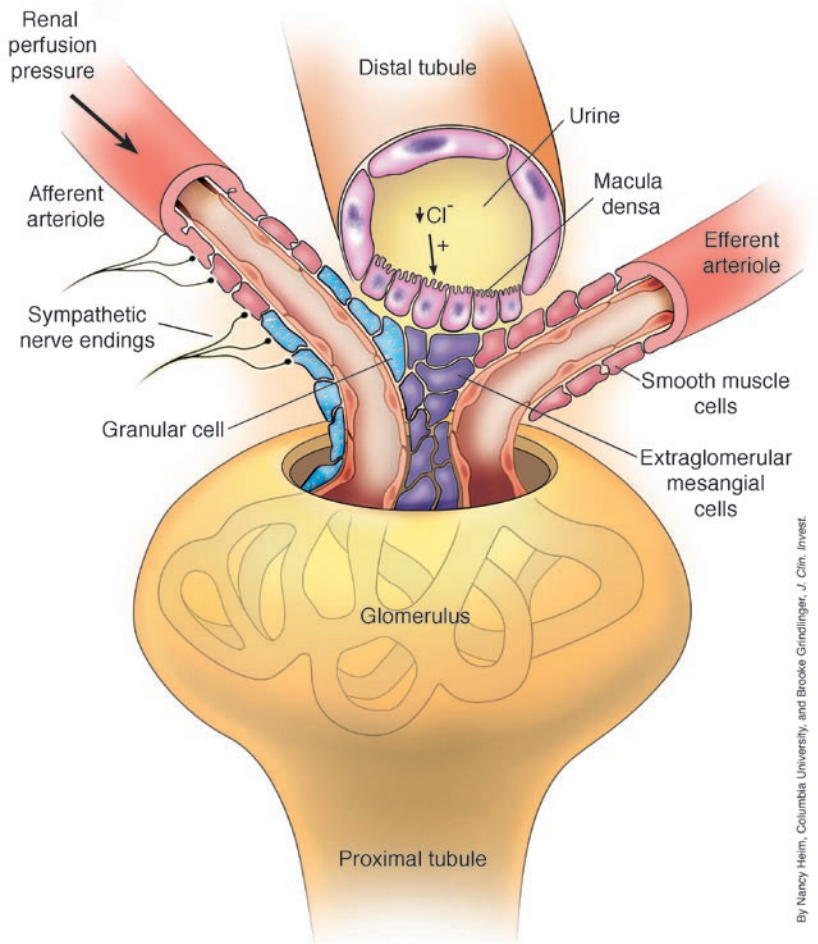

Figure 1
The juxtaglomerular apparatus. Integration of the regulated secretion of renin is carried out at the JGA. There are three major pathways regulating the secretion of renin by granular cells at the JGA: the baroreceptor, the macula densa mechanism, and direct stimulation by the sympathetic nervous system. The renal baroreceptor monitors renal perfusion pressure and signals an increase in renin when renal perfusion pressure falls. In the macula densa mechanism, macula densa cells sense the decrease in chloride ions in the filtrate in the distal tubule, thereby stimulating release of renin. Increased activity of renal sympathetic nerves directly stimulates renin release via activation of β adrenergic receptors. Sympathetic innervation also modulates both the baroreceptor and macula densa mechanisms.

However, along with the well-characterized effects of prostanoids on vascular tone, the role of prostanoids in the regulation of renin release has long been recognized For example, studies dating back to the 1970s have documented potent actions of both PGE_2 and PGI_2 in stimulating renin secretion (19). These actions depend on the intracellular generation of cAMP. In this regard, the IP receptor, along with the E-prostanoid 2 (EP2) and EP4 receptors for PGE_2, signal via G_s protein activation of adenyl cyclase (20). To test the role of individual prostanoid receptors in renovascular hypertension, Fujino et al. evaluated blood pressure and renin responses in mice lacking the IP receptor or one of the 4 individual EP receptors using a Goldblatt kidney model wherein a stenosis is created in one renal artery. The consequent reduction in renal blood flow stimulates synthesis and release of renin by granular cells of the juxtaglomerular apparatus (JGA) (Figure 1). The resulting generation of Ang II promotes vasoconstriction and impaired sodium excretion by the kidney. In the mice lacking IP receptors, stimulation of renin by renal artery stenosis and the subsequent development of hypertension were markedly attenuated.

Prostanoids and renin release

There are two major physiological controls for stimulating renin in vivo: the baroreceptor and the macula densa mechanisms. It has been suggested that both of these mechanisms depend on prostanoids and can be influenced by sympathetic innervation (21). In renovascular hypertension, the baroreceptor mechanism is the primary mechanism for stimulating renin release. In the presence of a critical stenosis of the renal artery, renal perfusion pressure drops, stimulating renin. The magnitude of renin release is inversely correlated with renal perfusion pressure (22). Although both PGI_2 and PGE_2 have been implicated in the baroreceptor response (23), the study by Fujino et al. (18) indicates that PGI_2, acting through the IP receptor, is primarily responsible for this action. Moreover, a contribution of PGE_2 seems to be clearly excluded as deficiency of any of the individual EP receptors had no impact on the development of hyperreninemia and hypertension (18).

While the baroreceptor mechanism regulating renin release has been localized to the kidney, identification of its precise nature has been elusive. Various models have been proposed to explain the mechanism for pressure sensing and consequent signal transduction, including direct stretch of the juxtaglomerular cells due to transmural pressure across the afferent arteriole (24) or indirect pathways involving secondary release of autocoids (25). Identification of a nonredundant role for IP receptors in the baroreceptor response may provide a means for developing a more explicit characterization of its molecular and cellular mechanisms. Further, these new findings raise a number of interesting questions. How does reduced intrarenal pressure activate COX-2 and enhance synthesis of PGI_2? Which cell lineages are involved? As most studies have failed to identify IP receptor expression in juxtaglomerular cells (26, 27), the cellular targets for IP receptor actions that affect renin release also need to be defined. Because IP receptors are expressed on dorsal root ganglia (27) and renal nerves play a critical role in baroreceptor responses, it is possible that IP receptors may influence renin release by modulating sympathetic nerve activity.

The second major pathway for physiological regulation of renin is the so-called macula densa mechanism whereby cells at the macula densa sense a reduction of chloride ions in the filtrate within the distal tubule, thereby triggering renin release (28). In this circumstance, release of renin and the con-

sequent generation of Ang II is believed to serve as a mechanism for enhancing renal sodium reabsorption in states of fluid volume depletion. The prevailing view of this mechanism has suggested that reduced chloride flux through Na-K-2Cl cotransporter 2 (NKCC2) activates COX-2, thereby generating PGE_2 (29). PGE_2 then activates an EP receptor (probably EP4) on granular cells to stimulate renin release. Previous studies have clearly demonstrated the importance of COX-2 in the macula densa pathway (30). In addition, the activity of various components of this system has been demonstrated in isolated perfused macula densa segments (31) and juxtaglomerular cell lines (32). However, the role of these individual components in regulating renin release in the intact animal has not been unequivocally demonstrated.

Accordingly, Fujino and associates also carried out experiments to test for contributions of the IP and various EP receptors to the macula densa response by placing prostanoid receptor–deficient mice on a low-salt diet and treating them with furosemide, which blocks chloride reabsorption by NKCC2 (18). Once again, stimulation of renin was attenuated in the IP-deficient mice but was unaffected in mice deficient in any of the individual EP receptors. Based on this result, the authors concluded that the IP receptor also delivers a critical signal for renin regulation by the macula densa mechanism. However, because there is no report of blood pressure monitoring in these studies, one must be somewhat circumspect about this conclusion. It is likely that the combination of a low-salt diet and furosemide administration affected blood pressure, potentially activating renin via baroreceptor mechanisms that are independent of the macula densa pathway. As discussed by the authors, there are also issues related to the genetic background of the EP4-deficient animals that may further confound interpretation of this result. Thus, further studies are required to define specific prostanoids and prostanoid receptors mediating renin release by the macula densa mechanism.

Complex actions of prostanoids on blood pressure

Taken together, these studies highlight the paradoxical nature of blood pressure regulation by prostanoids. The consequences of activation of the renin-angiotensin system by COX-2–dependent generation of PGI_2 are in direct opposition to its effects on renal vasculature and epithelia that lead to vasodilation and natriuresis. Moreover, it is not clear whether or how these apparently conflicting actions of PGI_2 are differentially regulated. Normal blood pressure homeostasis clearly involves a balance among these divergent actions. Understanding how these elements are integrated remains a fundamental objective in this field. Characterizing factors affecting this balance should facilitate managing patients at risk for NSAID-induced hypertension and, conversely, may identify patients whose blood pressure control might actually benefit from prostanoid inhibition.

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