Hypertension and Cyclooxygenase-2 Inhibitors
Target: The Renal Medulla

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Cyclooxygenase (COX)-inhibiting NSAIDs are widely prescribed to treat arthritis, exerting analgesic and antiinflammatory effects via their capacity to block endogenous prostaglandin synthesis. Unfortunately, their widespread use has been associated with an increased risk of developing hypertension, and clinical experience with COX-2 selective inhibitors suggests they similarly predispose hypertension.

The physiological mechanisms through which COX-2 inhibitors increase blood pressure are gradually being elucidated. Experimental evidence from animal models suggests an important vasodilator role for endogenous COX-2-derived prostaglandins, reducing the systemic pressor effects of angiotensin II. These findings underscore the importance of COX-2 activity in regulating the tone of peripheral resistance vessels. COX-2, but not COX-1, inhibition also reduces renal medullary blood flow and urine salt excretion, which is in agreement with clinical studies in humans showing COX-2 inhibition impairs renal salt excretion. As a consequence of COX-2 inhibition, the combined increase in peripheral activity of pressors (like angiotensin II) and reduced renal salt excretion likely conspire to predispose humans to hypertension.

The precise cellular sources of the COX-2–derived products promoting vascular dilator tone and renal salt excretion remain uncharacterized. In the kidney, COX-2 expression is restricted to 2 main cellular compartments: the macula densa with surrounding cortical thick ascending limb and renal medullary interstitial cells. In this issue of Hypertension, Zewde and Mattson provide evidence that focuses attention on the renal medulla as the important intrarenal site of endogenous COX-2 activity protecting against the development of systemic hypertension. These investigators report that when animals were placed on a high-salt diet, selective intramedullary infusion of a COX-2 inhibitor or COX-2 antisense oligonucleotides caused animals to develop hypertension. Because renal medullary COX-2 is primarily expressed in medullary interstitial cells, the study by Zewde and Mattson also implies a critical role for the medullary interstitial cell in maintaining systemic blood pressure.

Renal medullary interstitial cells (RMICs) represent a unique stromal cell residing between tubule epithelial cells of thick limbs and collecting ducts and vasa rectae in the renal medulla. RMICs are thus positioned at a nexus of physiological control, potentially impacting the tone of the vasa recta as well as epithelial salt absorption. RMICs are morphologically distinct by the presence of abundant lipid-rich intracellular droplets comprising long-chain unsaturated fatty acids, including arachidonate. Muirhead and colleagues showed transplanted renal medulla, but not renal cortex elaborated substances capable of reducing blood pressure in animal models of hypertension and subsequently reported the source of these antihypertensive lipid substances as RMICs. The precise identities of the antihypertensive substances elaborated by RMICs remain incompletely characterized; however, PGE2 was identified as an important component of this activity. In the context of the current knowledge, COX-2 would appear to be a critical source for PGE2 and possibly other vasodepressors derived from RMICs as well.

High-salt diet markedly increases medullary COX-2 expression, both in vivo and in vitro, where increased extracellular salt potently augments RMIC COX-2 expression. When considered with studies showing COX-2 inhibition reduces urine salt excretion and the present findings of the hypertensive effects of intramedullary COX-2 inhibition, a physiological feedback system can be constructed whereby increased salt intake augments RMIC COX-2 expression and prostaglandin production, thereby promoting increased renal salt excretion. Whether this system also includes elaboration of a renal medullary COX-2–dependent systemic vasodepressor activity remains to be clarified. The identity of these antihypertensive products and the receptors controlling the tone of vascular tissue and promoting renal salt excretion remains to be established.

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References


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