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# Cyclooxygenase-2 in the kidney

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In the mammalian kidney prostaglandins are important mediators of physiologic processes, including modulation of vascular tone and salt and water. Prostaglandins arise from enzymatic metabolism of free arachidonic acid, which is cleaved from membrane phospholipids by phospholipase $A_2$activity.The cyclooxygenase enzyme system is a major pathway for metabolism of arachidonic acid in the kidney. Cyclooxygenases (COX) are the enzymes responsible for the initial conversion of arachidonic acid to prostaglandin $G_2$and subsequently to prostaglandin $H_2$, which serves as the precursor for subsequent metabolism by prostaglandin and thromboxane synthases. In addition to high levels of expression of the constitutive rate-limiting enzyme responsible for prostanoid production, cyclooxygenase-1 (COX-1), the "inducible isoform of cyclooxygenase, COX-2, is also constitutively expressed in the kidney and is highly regulated in response to alterations in intravascular volume.Prostaglandins and thromboxane A2 exert their biological functions predominantly through activation of specific 7-transmembrane G protein coupled receptors.COX metabolites have been shown to exert important physiologic functions in maintenance of renal blood flow, mediation of renin release and regulation of sodium excretion. In addition to physiologic regulation of prostanoid production in the kidney, increases in prostanoid production are also seen in a variety of inflammatory renal injuries, and COX metabolites may serve as mediators of inflammatory injury in renal disease.

Inhibition of prostaglandin production by either non-selective or selective inhibitors of cyclooxygenase-2 (COX-2) activity can induce or exacerbate salt-sensitive hypertension. The mechanism has been previously attributed to inhibition of intrinsic renal COX-2 activity, leading to increased sodium retention by the kidney. We have found that selective inhibition of COX-2 in medullary interstitial cells can induce salt-sensitive hypertension. In addition, we have found that macrophages isolated from kidneys of high salt-treated wild type mice express increased COX-2 and mPGES-1. Furthermore, bone marrow transplantation (BMT) from either $COX\text{-}2^{-/-}$or $mPGES\text{-}1^{-/-}$mice into wild type mice or selective deletion of the macrophage prostaglandin $E_2$type 4 receptor ($EP_4$) induced salt-sensitive hypertension and increased phosphorylation of the renal sodium chloride cotransporter, NCC. Kidneys from high salt-treated $COX\text{-}2^{-/-}$-WT BMT mice had increased macrophage and T cell infiltration and increased M1/Th1 markers and cytokines. Skin macrophages from high salt-treated mice with either genetic or pharmacologic inhibition of the COX-2 pathway expressed decreased M2 markers and VEGF-C production and exhibited aberrant lymphangiogenesis. Therefore, these studies indicate that COX-2-derived $PGE_2$in hematopoietic cells plays an important role in both kidney and skin in maintaining homeostasis in response to chronically increased dietary salt and that inhibiting COX-2 expression or activity in these cells can predispose to salt-sensitive hypertension.