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Johannes Stegbauer, Thomas M. Coffman

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Commentary

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Skin tight: macrophage-specific COX-2 induction links salt handling in kidney and skin

Johannes Stegbauer¹ and Thomas M. Coffman^{2,3}

¹Division of Nephrology, Medical Faculty, University Hospital Düsseldorf, Düsseldorf, Germany. ²Cardiovascular and Metabolic Disorders Program, Duke-NUS Graduate Medical School, Singapore.

³Division of Nephrology, Department of Medicine, Duke University and Durham VA Medical Centers, Durham, North Carolina, USA.

The relationship between dietary salt intake and the associated risk of hypertension and cardiovascular disease is an important public health concern. In this issue of the *JCI*, a study by Zhang and associates shows that consumption of a high-sodium diet induces expression of cyclooxygenase-2 (COX-2) in macrophages, resulting in enhanced levels of prostaglandin E₂ (PGE₂), autocrine activation of the macrophage E-prostanoid 4 (EP4) receptor, and subsequent triggering of parallel pathways in the kidney and in skin that help dispose of excess sodium. The authors found that blockade or genetic elimination of the COX-2/PGE₂/EP4 receptor pathway in hematopoietic cells causes salt-sensitive hypertension in mice. These studies illuminate an unexpected central role for the macrophage in coordinating homeostatic responses to dietary salt intake and suggest a complex pathophysiology for hypertension associated with NSAID use.

Roles for prostaglandins in cardiovascular disease and hypertension

Prostaglandins or prostanoids are generated through the cyclooxygenase (COX) pathway of arachidonic acid metabolism and have a wide range of biological functions. Prostaglandins have relatively short half-lives; therefore, these compounds typically act locally in the tissues where they are synthesized and their actions are mediated by specific receptors belonging to the large family of G-protein-coupled, 7-transmembrane (7-TM) receptors (1). NSAIDs, among the most widely used medications worldwide, act by inhibiting COX enzymes and thereby broadly attenuate the production of prostanoids. There are two COX isoforms: COX-1, which is constitutively expressed at relatively low levels in many cell lineages, and COX-2, which has a more restricted expression profile, but can be induced to very high levels in response to inflammation or injury (2,

3). Clinical use of COX-2-specific inhibitors has been associated with increased risk for cardiovascular disease, highlighting the powerful impact of prostanoids on heart and vascular functions (4).

Administration of COX inhibitors has also been associated with fluid retention and exacerbation of hypertension (5). Likewise, genetic elimination of the major microsomal prostaglandin E (PGE) synthase-1 (mPGES-1) or the prostacyclin receptor (IP) causes hypertension in mice (6, 7). The COX isoforms and a range of prostanoid receptors are expressed in the kidney (8). Moreover, PGE₂ promotes natriuresis and inhibits sodium reabsorption by renal tubules (2). Accordingly, it has been suggested that hypertension associated with the use of COX inhibitors is caused by inhibition of prostanoid synthesis within the kidney, with consequent impairment of sodium excretion and increased blood pressure, consistent with tenets of Guyton's hypothesis (9).

Macrophages and salt-sensitive hypertension

As the prevailing dogma is that COX inhibition in the kidney promotes hypertension, the findings of Zhang and associates are unexpected and interesting (10). These authors convincingly show that COX-2 expression in macrophages plays a critical role in protecting against the development of hypertension induced by consumption of a high-sodium diet. In human hypertension, exaggerated fluctuation of blood pressure with high-salt feeding, so-called sodium sensitivity, is a common phenotype and sodium sensitivity itself is linked to increased cardiovascular risk (11). Furthermore, a modest reduction of salt intake substantially reduces cardiovascular mortality and medical costs, indicating the critical importance of dietary salt and its associated homeostatic responses to long-term health (12).

Zhang et al. show that high-salt feeding enhances expression of both COX-2 and mPGES-1 in macrophages, whereas transfer of COX-2-deficient bone marrow-derived hematopoietic cells to WT mice was sufficient to cause salt-sensitive hypertension (10). Moreover, elimination of mPGES-1 from bone marrow or macrophage-specific deletion of the gene encoding the PGE₂ receptor E-prostanoid 4 (EP4) also resulted in salt-sensitive hypertension. Together, these results indicate that COX-2-dependent PGE₂ synthesis by macrophages acts in an autocrine manner via EP4 receptors to attenuate blood pressure increases associated with high-salt feeding (Figure 1). Conversely, these data suggest inhibition of this pathway may be a major mechanism that underlies NSAID-induced hypertension.

Over the past decade, emerging data have highlighted a role for immune and inflammatory pathways in hypertension pathogenesis (13). For example, studies by Harrison and colleagues clearly demonstrate a role for T cells and cytokines,

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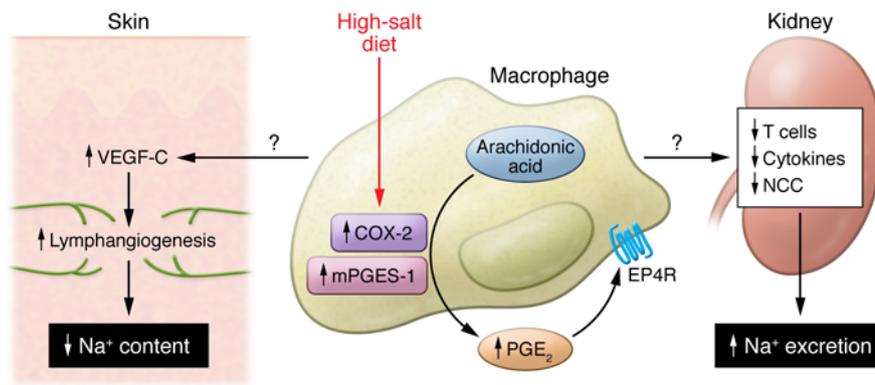


Figure 1. The COX-2/mPGES-1/EP4 receptor pathway in macrophages maintains sodium homeostasis by influencing salt secretion in the kidney and extrarenal sodium storage. In this issue, Zhang and colleagues demonstrate that a high-salt diet induces expression of COX-2, thereby enhancing PGE₂ production and autocrine EP4 receptor (EP4R) signaling. In mice lacking the COX-2/mPGES-1/EP4 receptor pathway in hematopoietic cells, extrarenal salt storage and sodium secretion by the kidney are dysfunctional, resulting in the development of hypertension.

including IL-17, in hypertension responses (14, 15). Recent studies have suggested that sodium chloride levels can directly control the character of T cell responses and that high-salt feeding can modulate the course of autoimmune diseases (16). The finding that COX-2 expression in macrophages is triggered by high-salt feeding and participates in blood pressure homeostasis is consistent with this larger body of work. Moreover, the data of Zhang and associates suggest that COX-2 expression by macrophages may influence blood pressure in part by affecting T cell migration and function. In this regard, previous studies in experimental models of hypertension have shown that blood pressure elevation is associated with accumulation of T lymphocytes and other inflammatory cells within the kidney, where these effectors may influence epithelial functions, including sodium reabsorption, directly or through generation of cytokines (17, 18). Indeed, Zhang et al. demonstrated that, compared with control animals, mice lacking COX-2 in bone marrow-derived cells or EP4 receptors in macrophages exhibit increased T cell accumulation in kidneys (10). Moreover, expression of several cytokines was also increased, consistent with previous data showing that, among the 4 receptors for PGE₂, the EP4 receptor is primarily responsible for attenuating cytokine release (19). Zhang et al. also showed that increased kidney inflammation was associated with enhanced abundance of the thiazide-sensitive sodium

chloride cotransporter (NCC), implicating direct stimulation of renal sodium reabsorption via NCC as a mechanism that causes salt-sensitive hypertension in this setting (Figure 1).

COX-2/mPGES-1/EP4 receptor pathway influences extrarenal salt disposition

Along with the modulatory effects on renal sodium reabsorption, the impact of the COX-2/mPGES-1/EP4 receptor pathway in hematopoietic cells on sodium homeostasis appears to be more wide ranging and also involves control of extrarenal sodium disposition. Titze and colleagues have previously established a role for the skin as a physiological storage compartment for sodium in a hypertonic state without concomitant accumulation of water (20, 21). This storage mechanism is activated by high-salt intake and is characterized by infiltration of macrophages into skin and stimulation of the tonicity enhancer binding protein (TonEBP)/VEGF-C axis, which induces structural remodeling, including lymphangiogenesis, which in turn facilitates sodium clearance. Blocking or disrupting this axis decreases lymphangiogenesis and triggers salt-sensitive hypertension. Zhang et al. show that macrophage-derived COX-2 and EP4 receptors are required for the normal operation of this pathway, as pharmacological inhibition of COX-2, absence of COX-2 in bone marrow-derived cells, or the absence of EP4 receptors on

macrophages each was associated with decreased VEGF-C expression, impaired lymphangiogenesis, and increased salt content in skin (10). Thus, disruption of this homeostatic pathway in skin may be another mechanism underlying hypertension caused by COX-2 inhibition.

Conclusions

The study by Zhang and associates illuminates a novel role for macrophage-generated COX-2 in sodium homeostasis at two different sites — the kidney and the skin — and suggests a complex pathophysiology for sodium sensitivity and hypertension caused by COX-2 inhibition (Figure 1). The study also raises a number of interesting questions for future investigation. For example, this work does not distinguish the relative contribution of each pathway, skin versus kidney, in the development of hypertension. In addition, the mechanism by which increased dietary sodium intake triggers COX-2 expression is not clear. Furthermore, how the COX-2/PGE₂/EP4 receptor pathway modulates NCC expression is not defined and would also be of considerable interest. A better understanding of the distal molecular pathways that link COX-2 inhibition to adverse cardiovascular consequences, such as hypertension, should facilitate the development of new and safer approaches to antiinflammatory and analgesic therapy.

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Address correspondence to: Thomas M. Coffman, Dean's Office, Duke-NUS Graduate Medical School, 8 College Road, Singapore 169857. Phone: 65.6601.1069; E-mail: tcoffman@duke.edu.

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