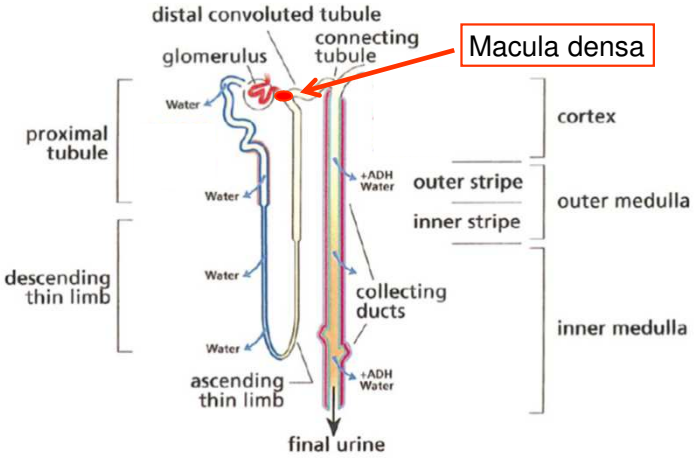

HOMER W. SMITH AWARD LECTURE

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The Juxtaglomerular Apparatus: From Anatomical Peculiarity to Physiological Relevance

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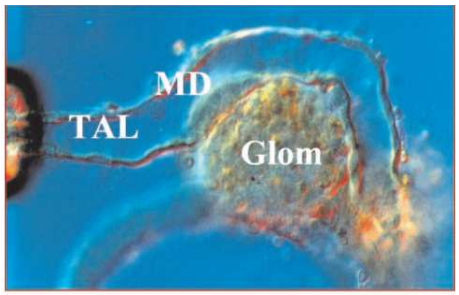

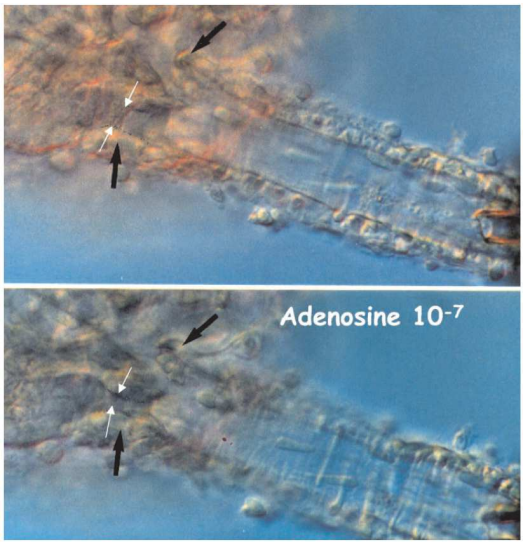

Changes of NaCl and perhaps KCl concentrations at the macula densa serve as the luminal signal that ultimately results in activation of vascular smooth muscle or granular cells. An increase in luminal NaCl concentration initiates an epithelial cell response that consists of NKCC2-mediated cell swelling, depolarization, and an increase of cytosolic calcium. These or some other consequences of NKCC2 activation cause the appearance in the juxtaglomerular interstitium of adenosine, and the suppression of the release of PGE2. Adenosine activates A1 adenosine receptors on vascular smooth muscle and/or extraglomerular mesangial cells, and this activation results in Gαi-dependent activation of phospholipase C, depolarization, activation of voltage-dependent Ca channels, and contraction (Figure 7). A de-

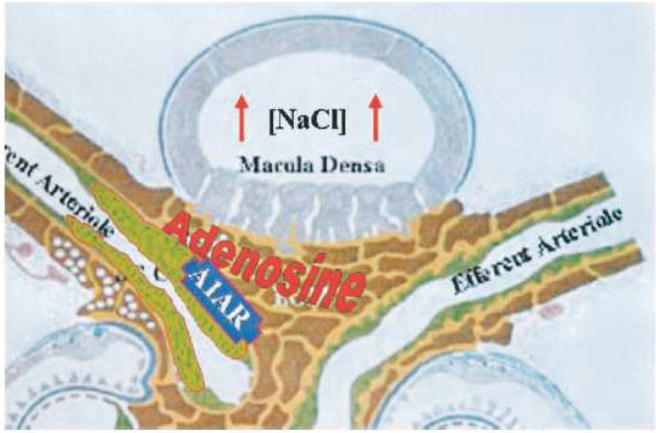

Figure 7. The effect of elevating NaCl at the macula densa is shown schematically to consist of an increase in the levels of adenosine in the juxtaglomerular apparatus (JGA) interstitium and adenosine 1 receptors (A1AR)–mediated constriction of the afferent arteriolar smooth muscle cells.

dependent Ca channels, and contraction (Figure 7). A decrease in luminal NaCl concentration initiates an epithelial response that consists of activation of multiple MAP kinases and stimulation of COX-2 activity and induction of COX-2 expression. This is followed by the appearance in the juxtaglomerular interstitium of PGE2 and the suppression of adenosine. PGE2 activates EP4 receptors on granular cells, and this results in Gαs-mediated adenylate cyclase activation and PKA-mediated renin secretory and transcriptional activation (Figure 8). Or, maybe more provocatively, one could envisage two extreme states in which the macula densa cells exist: one when the luminal NaCl is extremely low, or when NaCl uptake is pharmacologically inhibited. In this situation, the MD cell is a PGE2-producing cell through the activation of COX-2. On the other hand, when the NaCl concentration and therefore NKCC2-mediated uptake is maximal, the MD cell is an ATP/adenosine-releasing cell.

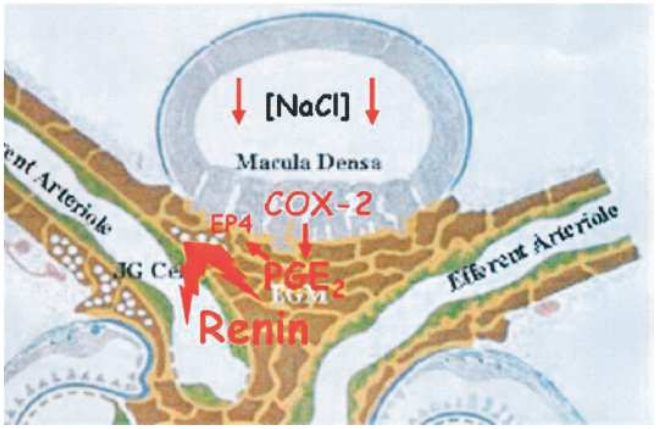

Figure 8. The effect of decreasing NaCl concentration at the macula densa is schematically shown to cause an increase of PGE2 in the JGA interstitium and an EP4-mediated release of renin from granular cells.

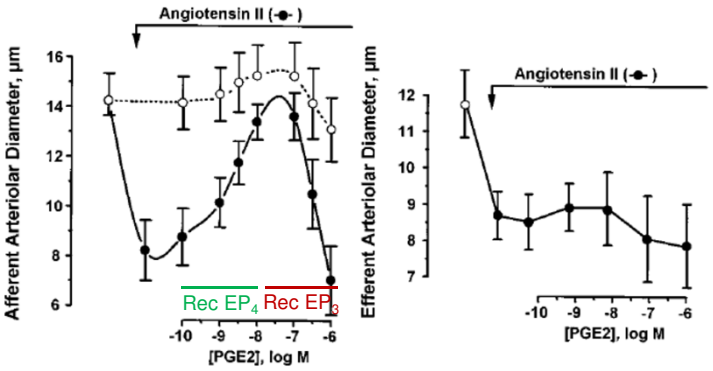

Figure 2. Effects of PGE_2 on afferent arteriole (top) during Ang II–induced vasoconstriction (0.1 nmol/L, ●, n=8) and during control (○, n=8). Right , Lack of effect of PGE_2 on reactivity of the efferent arteriole to Ang II (n=7).

Tang et al. (2000) Circ. Res. 86, 663-670

Biphasic Actions of Prostaglandin E_2 on the Renal Afferent Arteriole

Role of EP_3 and EP_4 Receptors

Lilong Tang, Kathy Loutzenhiser, Rodger Loutzenhiser

Abstract—Prostaglandin (PG) E_2 is an important modulator of the actions of angiotensin (Ang) II. In the present study, we investigated the renal microvascular actions of PGE_2 and the EP receptor subtypes involved. Ibuprofen potentiated Ang II–induced vasoconstriction in in vitro perfused normal rat kidneys and augmented afferent arteriolar, but not efferent arteriolar, responses in the hydronephrotic rat kidney model. This preglomerular effect of endogenous prostanoids was mimicked by exogenous PGE_2, which reversed Ang II–induced afferent arteriolar vasoconstriction at concentrations of 0.1 to 10 nmol/L without affecting the efferent arteriole. The PGE_2-induced vasodilation was potentiated by the phosphodiesterase inhibitor Ro 20-1724 and was mimicked by 11-deoxy-PGE_1 (0.01 to 1 nmol/L). Butaprost, which acts preferentially at EP_2 receptors, was relatively ineffective. Whereas 0.1 to 10 nmol/L PGE_2 elicited vasodilation, higher concentrations (1 to 10 µmol/L) restored Ang II–induced afferent arteriolar vasoconstriction. This response was blocked by pertussis toxin (200 µg/mL) and was mimicked by the EP_1/EP_3 agonist sulprostone (1 to 300 nmol/L). Reverse transcription–polymerase chain reaction of individually isolated afferent arterioles revealed the presence of message for EP_4 and all 3 EP_3 splice variants (α, β, and γ) but not EP_1 or EP_2. Our findings thus indicate that PGE_2 elicits both vasodilatory and vasoconstrictor actions on the afferent arteriole. The vasodilation is mediated by EP_4 receptors coupled to cAMP, presumably via G_{as}. The vasoconstriction is mediated by an EP_3 receptor coupled to G_{ai} and appears to reflect a functional antagonism of the EP_4-induced vasodilation. (*Circ Res.* 2000;86:663-670.)

The macula densa is worth its salt

Commentary

See related article in this issue, pages 1149–1158.

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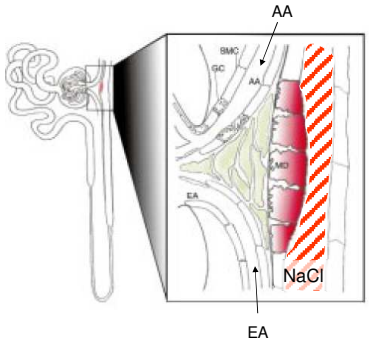
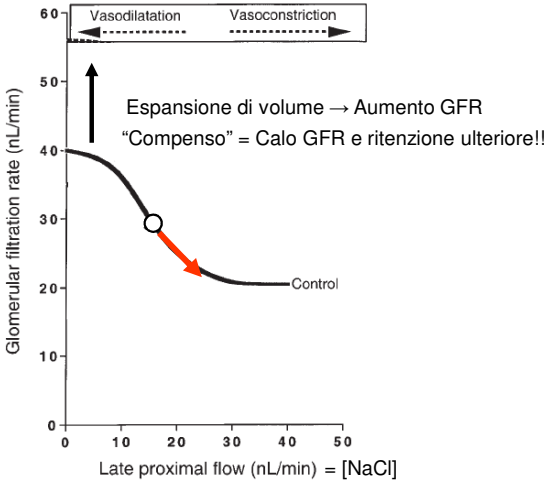
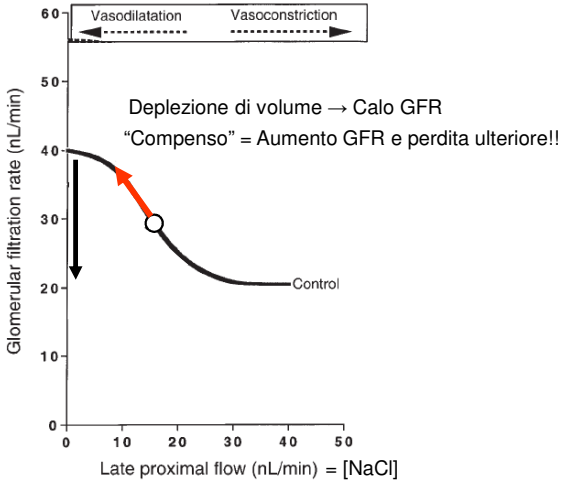
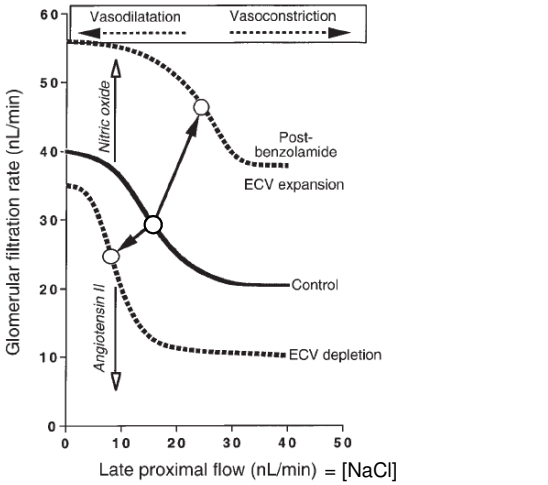


Figure 1
Schematic drawing of the architecture of a nephron, showing the position of the macula densa in the nephron and its relationship to the glomerulus of origin. A magnified view of the contact area of the macula densa with the glomerulus is shown on the right. MD, macula densa; AA, afferent arteriole; EA, efferent arteriole, GC: granular cell, SMC: smooth muscle cell.







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