Modulation of renal microvascular function by adenosine

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RENAL DAMAGE, AS A CONSEQUENCE of hypertension, is well established. Chronic elevation of arterial blood pressure results in a steady decline in the number of functional glomeruli, leading to a reduction in renal filtering capacity (6, 19, 23). Evidence indicates that a significant portion of hypertension-associated renal damage occurs as a consequence of inappropriately low preglomerular resistance, allowing glomerular capillary pressure to rise above normal (6, 34). Direct assessment of afferent arteriolar responses to elevations in renal perfusion pressure clearly demonstrates impaired autoregulatory capability in kidneys from hypertensive rats compared with kidneys from normotensive controls (2, 5, 10–12, 14, 16, 27, 33). Impairment of autoregulatory capability reflects an intrinsic change within the kidney of hypertensive animals, because autoregulatory behavior was not restored by perfusion with blood from normotensive donors and thus could not be attributed to a humoral factor present in the blood of hypertensive donors (14). Therefore, chronic elevation of arterial pressure produces a functional alteration in the afferent arteriole or in arteriolar signaling pathways, which reduces or abolishes autoregulatory control of glomerular capillary pressure. This phenomenon cannot be attributed to a generalized reduction in preglomerular responsiveness to vasoactive stimuli, because many investigators have reported exaggerated responsiveness to vasoactive agents such as angiotensin II, norepinephrine, and endothelin (12, 27). Pathological alterations in the actions or release of locally generated regulators of vascular resistance have not been heavily investigated but do represent a significant target for explaining inappropriate renal vascular control.

Regulation of renal blood flow and renal vascular resistance is accomplished by the interaction of numerous intrarenal and extrarenal influences (27). Certainly ambient blood pressure, sympathetic nerve activity, and circulating vasoactive substances are major extrarenal determinants. However, the kidney produces a multitude of locally generated substances, including ATP, adenosine, and angiotensin II, that also contribute to the regulation of renal vascular resistance (1, 13, 18, 24, 26, 27, 37, 45). As these influences converge on the renal vasculature, their respective contributions primarily focus on setting preglomerular resistance. The afferent arteriole is the primary resistance element responsible for controlling glomerular capillary pressure and accounts for between 80 and 90% of renal vascular resistance. Exactly how locally produced vasoactive substances regulate afferent arteriolar function continues to be clarified. Significant roles are emerging for constitutive contributions by the tissue renin angiotensin system (26), cytochrome P-450 metabolites of arachidonic acid (24, 32), release of nitric oxide and products of oxidative stress by endothelium and tubular epithelia (5, 27, 44, 45), local activation of the P2 receptor system by paracrine release of ATP (1, 13, 29), and the regional influences of the ubiquitous product of tissue metabolism, adenosine (3, 37, 40). Although the relative importance of each of these systems is still enthusiastically debated, there is a general consensus that each plays an important physiological role in setting ambient renal vascular resistance. Furthermore, the potential exists for more sophisticated levels of regulatory control, when one considers the impact of complex interactions between these systems and pathways.

A major property by which the kidney sets and regulates glomerular capillary pressure and renal blood flow is known as autoregulation. Autoregulatory control is intrinsic to the kidney and functions in the absence of sympathetic nerve activity and in the absence of blood and circulating vasoactive substances. It is a collective manifestation of myogenic influences, inherent to all vascular smooth muscle, and the added level of control contributed by the tubuloglomerular feedback mechanism. Together, they control preglomerular and thus glomerular hemodynamics. Today, the major hypotheses offered to explain the mechanisms of autoregulatory control center on P2X receptor activation by ATP (1, 13, 30) and A1 receptor activation by adenosine (3, 36, 37, 40). The most recent evidence in support of these respective hypotheses comes from the work of Bell and colleagues (1). In those studies, initiation of tubuloglomerular feedback (TGF) responses by macula densa cells was associated by ATP release from the basolateral surface via activation of a large-conductance anion channel. In a more recent report, Inscho et al. (15) reported that mice lacking P2X1 receptors exhibit impaired autoregulatory responses but retain responsiveness to adenosine (15). The alternative hypothesis is supported by two recent reports that mice lacking adenosine-sensitive A1 receptors also lack TGF responses (3, 40). This topic was debated in a series of opinion articles published in this publication (30, 36).

Regardless of the identity of the signaling molecules responsible for autoregulatory adjustments in afferent arteriolar resistance, adenosine remains an important modulator of renal microvascular function. There is clear evidence for the involvement of A1 and A2a recep-
tors in renal function (17, 25, 27, 35); however, the role of $A_{2b}$ and $A_3$ receptors in regulating renal vascular and tubular function is less clear. The renal vasculature expresses both $A_1$ and $A_{2a}$ receptors, and both likely participate in regulating renal microvascular function (17, 25, 27, 35). Different tubular segments also express adenosine receptors where they may affect regulation of tubular transport (17, 25, 27, 35). The influence of adenosine on renal hemodynamics is complex. Typically, intrarenal infusion of adenosine results in a transient reduction in renal blood flow followed by a sustained increase (17, 20, 25, 27, 35). It is believed that the initial renal vasoconstriction involves activation of preglomerular $A_1$ receptors followed by a postglomerular vasodilation, mediated by $A_2$ receptors (17). Indeed, the prevailing view is that vasodilation of the postglomerular circulation, particularly in the inner cortex, redistributes blood flow from the cortex to the medulla (8, 21, 22, 38, 42). Direct appraisal of microvascular function, however, corroborates only the preglomerular $A_1$ receptor-mediated vasoconstriction and does not substantiate postulated vasodilation of postglomerular vessels. Two reports evaluated efferent arteriolar responses to adenosine in the inner cortex (4, 28). In both studies, 10 $\mu$M adenosine vasoconstricted juxtamedullary afferent and efferent arterioles. Greater adenosine concentrations reversed the vasoconstriction and returned arteriole diameters to near control values. Selective blockade of $A_1$ receptors with KW-3902 resulted in marked adenosine-mediated vasodilation of afferent and efferent arterioles, whereas selective blockade of $A_{2a}$ receptors with KW-17837 significantly augmented adenosine-mediated vasoconstriction in both arteriolar segments (28). These data demonstrate that vasoconstriction is the principal response evoked by adventitial administration of adenosine to afferent and efferent arterioles of the inner cortex and are at variance with the postulate that adenosine vasodilates the inner cortical microvasculature. It should be noted, however, that adenosine may provide an important vasodilatory influence in the medullary circulation. Zou et al. (46) reported that blockade of medullary $A_2$ receptors, with the $A_2$ receptor antagonist 3,7-dimethyl-1-propargylyxanthine (DPCPX) decreased outer and inner medullary blood flow, as measured using laser-Doppler flowmetry. In contrast, $A_1$ receptor blockade with 8-cyclopentyl-1, 3-dipropylxanthine (DPCPX) or $A_3$ receptor blockade with N$^\ominus$-benzyl-5'-[(N-ethylcarboxamido)adenosine left medullary blood flow unchanged. Thus, whereas the inner cortical microvasculature does not exhibit adenosine-mediated vasodilation until $A_1$ receptors are blocked, or until local adenosine concentration exceeds 10 $\mu$M, it is possible that resistance elements of the medullary circulation respond to endogenous adenosine with $A_2$ receptor-mediated vasodilation.

Investigations into the mechanisms by which adenosine influences renal vascular resistance have led to the speculation that a significant interaction exists between adenosine and angiotensin II (4, 7, 9, 31, 39, 41). $A_1$ receptor blockade with DPCPX significantly reduced angiotensin II-mediated vasoconstriction of isolated rabbit afferent arterioles (43). Whole kidney studies suggest that ambient adenosine concentrations reset renal microvascular reactivity and modulate preglomerular responsiveness to angiotensin II (9). More recent studies using mice deficient in AT$_1$A receptors, reveal that adenosine-mediated preglomerular vasoconstriction is markedly attenuated compared with heterozygote or wild-type mice (41). Finally, in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, Hansen et al. (9a) report that chronic deficiency of the adenosine $A_1$ receptor modestly attenuates the ability of angiotensin II to vasoconstrict renal resistance vessels. This basic observation was obtained using whole kidney approaches as well as isolated afferent arterioles from wild-type and $A_1$ receptor-knockout mice. These observations are consistent with an interaction between adenosine and angiotensin to regulate preglomerular vascular resistance. However, not all studies support such an interaction. Direct assessment of microvascular responses to angiotensin II indicates that preglomerular vasoconstriction can occur independent of adenosine receptor activation (7). $A_1$ receptor blockade with DPCPX had no significant effect on angiotensin II-mediated vasoconstriction of afferent or efferent arterioles (7). Furthermore, no significant interaction was found in studies evaluating the role of endogenous adenosine to serve as an essential cofactor in facilitating angiotensin II-mediated vasoconstriction of juxtamedullary afferent or efferent arterioles (4). In those studies, pharmacological blockade of adenosine receptors or exposure to exogenous adenosine did not alter angiotensin II-mediated vasoconstrictor responses compared with untreated control kidneys. Taken together, the issue of whether or not the renal microvascular response to angiotensin II and adenosine is significant, or importantly, altered by an interaction between the angiotensin and the purine nucleoside adenosine remains unresolved.

REFERENCES
