ATP mediates tubuloglomerular feedback

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THE MACULA DENSE CELLS COMPRISE the sensing component of the tubuloglomerular feedback (TGF) mechanism and respond to changes in tubular fluid composition by transmitting signals to the afferent arterioles thus regulating the preglomerular vascular resistance and filtered load to the tubules (14, 15). This intriguing mechanism has remained under intensive investigation, and the accrued evidence indicates that there are multiple interacting paracrine agents involved in the communication pathway between the macula densa cells and the vascular smooth muscle cells. The macula densa cells are thought to produce and release ATP, adenosine, arachidonic acid metabolites, and nitric oxide. Some of these serve to modulate the sensitivity of the TGF mechanism, and it has remained a formidable challenge to discriminate between the powerful modulators and the specific mediator that respond to the acute changes in distal tubular fluid composition. Perhaps the single most important criterion distinguishing between the mediator and modulators is that there should be a direct relationship between the change in the macula densa stimulus and the change in the release or concentration of the TGF mediator associated with the change in renal vascular resistance (RVR).

Because the TGF mechanism participates in the autoregulatory responses of the arteriolar vasculature to changes in perfusion pressure, it is also recognized that the mediator of the TGF mechanism contributes to the changes in RVR associated with autoregulatory responses (15, 20, 22). Thus one would expect a certain internal consistency in the evidence regarding the mechanism that mediates the TGF mechanism and the mechanism that mediates autoregulatory responses. Considering that the TGF mechanism is a major mediator of renal autoregulatory responses and primarily serves to regulate afferent arteriolar resistance (9, 15, 20), it is surprising that no consensus has emerged regarding the nature of the signaling mechanism that links macula densa function with the changes in afferent arteriolar resistance. Nevertheless, analysis of the available data provides strong support for the hypothesis that ATP, rather than adenosine, serves as the actual mediator of TGF mechanism. Our analysis is based on the following criteria.

Criterion 1. The TGF mediator must exert selective actions on preglomerular arterioles (15) to stimulate Ca²⁺ influx in afferent arteriolar renal vascular smooth muscle cells via activation of L-type voltage-dependent Ca²⁺ channels in the afferent arterioles (5, 15).

Criterion 2. Saturation of the renal interstitial fluid (RIF) with the TGF mediator would interfere with the ability of the afferent arteriolar smooth muscle cells to respond to either TGF or autoregulatory responses.

Criterion 3. Blockade of the vascular smooth muscle receptors that respond to the TGF mediator would also interfere with TGF and autoregulatory responses.

Criterion 4. The mediator must be released from macula densa cells into the renal interstitium to exert its actions on the afferent arteriolar vascular smooth muscle cells. Furthermore, there should be a relationship between changes in TGF or autoregulation dependent alterations in RVR and the interstitial fluid concentration of the mediator.

Considerable investigative efforts have been directed toward determining how close some of the putative TGF mediators fit the requirements of the hypothesis described above. It is also recognized that the recent reports showing an absence of TGF responses in the adenosine A₁-receptor knockout mouse (2, 19) support an important role for adenosine A₁ receptors in the TGF mechanism (2, 19). Nevertheless, we feel that there is compelling evidence from whole kidney and microcirculatory experiments in dogs and rats strongly supporting the participation of ATP as an important mediator of the TGF mechanism. The following points are submitted for consideration.

Point 1. ATP selectively constricts the afferent arterioles. Studies using the juxtamedullary nephron prep-
vascular smooth muscle cells. ATP and P2X agonists, such as α,β-methylene-ATP, activate Ca\(^{2+}\) influx pathways in freshly isolated vascular smooth muscle cells obtained from preglomerular microvessels (5, 6). These actions of ATP and of slowly metabolizable analogs of ATP are sensitive to blockade of L-type calcium channels (5, 10).

Point 3. Autoregulatory-mediated afferent arteriolar vasoconstrictor responses are prevented by P2 receptor saturation or desensitization (8). Micropuncture and microperfusion experiments demonstrated that stop-flow pressure TGF responses to increases in peritubular capillary infusion with saturating doses of ATP or slowly metabolizable analogs (9, 13). P2 receptor saturation at the whole kidney level by intrarenal arterial infusion of high doses with ATP resulted in marked impairment of renal blood flow and glomerular filtration rate autoregulatory efficiency (12).

Point 4. P2 receptor blockade blocks afferent arteriolar autoregulatory responses. Suramin and pyridoxal phosphate-6-azophenyl-2′,4′-disulfonic acid (8) and a more selective P2\(_{\text{x}}\) receptor antagonist, NF-279 (7), have all been shown to prevent afferent arteriolar autoregulatory responses to increases in perfusion pressure.

Point 5. Macula densa cells secrete ATP. Although the macula densa cells have abundant mitochondria, they have reduced levels of Na\(^{+}\)–K\(^{+}\)-ATPase, making the macula densa cells good candidates for a source of extracellular ATP (18). Recent studies by Bell et al. (1) demonstrated that the macula densa cells have a Maxi-chloride channel that is permeable to ATP and that increases in luminal NaCl concentrations result in the release of ATP from macula densa cells.

Point 6. RIF concentrations of ATP are closely associated with autoregulatory TGF-mediated changes in RVR. With the use of microdialysis probes, the RIF ATP concentrations were shown to decrease consistently in response to reductions in renal arterial pressure. Furthermore, there was a highly significant relationship between RIF ATP and autoregulatory associated alterations in RVR (16, 17). Whole kidney stimulation of the TGF mechanism elicited by administration of a carbonic anhydrase inhibitor, acetazolamide, to inhibit proximal reabsorption rate and increase distal volume delivery (20, 21) led to increases in RIF ATP concentrations, whereas furosemide treatment reduced RIF ATP concentrations (16, 17). The association between the autoregulatory adjustments in RVR and RIF ATP concentrations is enhanced after treatment with acetazolamide, whereas furosemide abolished the relationship between RVR and RIF ATP (17).

In summary, the collective data obtained in different laboratories using various approaches strongly support the hypothesis that renal interstitial ATP, derived from macula densa cells, serves as the major paracrine agent mediating TGF signals to regulate afferent arteriolar resistance.

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