Adenosine mediates tubuloglomerular feedback

JURGEN SCHNERMANN
National Institute of Diabetes, Digestive, and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892

VARIATIONS of NaCl concentration in the macula densa region of the tubule between -20 and 60 mM/l cause inverse changes in glomerular filtration rate (GFR) that, for the most part, are the result of a progressive increase in afferent arteriolar resistance and a subsequent fall in glomerular capillary pressure (5). The reductions in capillary pressure and GFR are rapidly inducible and rapidly reversible. They are restricted to the perturbed nephron, although electronic coupling of smooth muscle cells can transmit an attenuated constrictor response to a neighboring nephron. The sensing step at the level of the macula densa cells is linked to some consequence of activation of NKCC2-mediated NaCl uptake (5). It is the premise of this discussion that graded increments in NaCl concentration, normally produced by increments in loop of Henle flow, cause a graded activation of NKCC2. Through a number of intermediate steps, this is followed by the NaCl concentration-dependent appearance of a humoral mediator within the juxtaglomerular interstitium whose interaction with its receptors on afferent arteriolar smooth muscle cells causes progressive vasoconstriction.

A tubuloglomerular feedback (TGF) mediator that fulfills all theoretical requirements for an extracellular paracrine transmitter, analogous to those defined earlier for synaptic transmission, has not been identified to date. On the basis of the available data and their interpretation, different investigators have suggested different agents or combinations of agents as TGF mediators (3, 5). The present essay takes the position that the preponderance of all experimental evidence supports the notion that TGF-mediated vasoconstriction is caused by a single vasoactive mediator and that this mediator is adenosine (4).

Evidence in support of this notion comes from the recent use of mouse strains with knockout mutations in the adenosine 1 receptor (A1AR) gene generated by two independent groups of investigators (1, 7). Adenosine involved in TGF mediation is likely to act through A1AR, because only this receptor subtype mediates vasoconstriction. Both studies show complete absence of TGF responsiveness using either stop-flow pressure or nephron filtration rate as the TGF end point. Adenosine as the natural ligand of A1AR is therefore an obligatory component of the TGF pathway. In the absence of a satisfying alternative explanation for this complete dependence of TGF on functional A1AR, we would argue that this finding, together with the additional evidence discussed below, strongly indicates that adenosine acts as the final mediator of the TGF vasomotor response. TGF inhibition in A1AR-knockout mice cannot be explained by low blood pressure, volume expansion, low levels of renin, or a disturbed kidney structure.

Evidence that variations in adenosine levels are required for normal TGF responsiveness has furnished another strong argument for adenosine being a TGF mediator. Preventing variations in adenosine levels and A1AR activation by exogenous administration of an A1AR agonist and an inhibitor of 5'-nucleotidase caused a reduction in TGF responsiveness (8). This permits the conclusion that the mere presence of adenosine is insufficient, but that adenosine levels must be able to fluctuate for TGF to operate normally, supporting the notion that adenosine is a TGF mediator.

Studies in A1AR-deficient mice for the most part corroborate earlier attempts to establish a role of adenosine in TGF by using specific and nonspecific pharmacological inhibitors of adenosine receptors (5). Luminal or systemic administration of the adenosine receptor blockers theophylline (nonselective), 3-isobutyl-1-methylxanthine (nonselective), 1,3-dipropyl-8-cyclopentylxanthine (DPCPX; A1AR selective), 1,3-dipropyl-8-sulfophenylxanthine (slightly A1AR selective), FK838 (A1AR selective), CVT-124 (A1AR selective), and KW-3902 (A1AR selective) caused inhibition or reduction of TGF responses in vivo and in vitro, although in one study no effect of an intravenously administered nonspecific inhibitor was found (2). The experiments with genetic ablation of A1AR circumvent three major problems...
inherent in the use of pharmacological receptor inhibitors in vivo: specificity of the drug, completeness of the inhibition, and accessibility of the receptor.

Inasmuch as the luminal administration of native adenosine, in contrast to stable analogs, had no effect on TGF responses, A1AR involved in TGF mediation are not located on macula densa cells. Direct proof for an extratubular location of A1AR is the ability to induce TGF blockade by administering the A1AR-selective inhibitor DPCPX into the lumen of a neighboring nephron or into peritubular blood (6). This conclusion is fully supported by in situ hybridization evidence showing the strongest renal expression of A1AR mRNA at the glomerular vascular pole, presumably on afferent arterioles (9). Furthermore, A1AR activation by high nanomolar to low micromolar concentrations of adenosine was found to cause vasoconstriction of both superficial and juxtamedullary afferent arterioles in a number of different in vivo and in vitro microvessel preparations (3).

In summary, experimental evidence collected over several decades has established that adenosine plays an important role in the TGF pathway. In our view it is justified to conclude that this role is that of the final extracellular mediator of the TGF response. We believe that other flow-dependent events are also involved but that these events converge on the generation of adenosine. Further experimental effort needs to be directed toward identifying these upstream events.

REFERENCES