Response to A. Nishiyama and L. G. Navar: ATP mediates tubuloglomerular feedback

DIsCRIMINATION BETWEEN ATP and adenosine as mediators of TGF is made difficult by the fact that the actions of these two agents in the preglomerular renal vascular bed are similar to some extent. Both adenosine and ATP are vasoconstrictors of afferent arterioles, elevate cytosolic Ca in afferent arteriolar smooth muscle cells, and blunt tubuloglomerular feedback (TGF) responses when administered in saturating concentrations.

Most of the discriminating evidence discussed by Nishiyama and Navar (6) deals with the potential role of ATP in the autoregulatory vasomotor response rather than in the TGF response itself. Nishiyama and Navar acknowledge that TGF is responsible for only a fraction of autoregulation, and it is thus not a priori clear which of the autoregulatory mechanisms is affected by ATP. As has been discussed by Inscho et al. (3) inhibition of autoregulation by the ATP receptor blockers PPADS or suramin is consistent with a role for ATP in either the myogenic or TGF components of autoregulation. The demonstration that interstitial ATP concentrations change parallel to autoregulatory resistance changes is intriguing (5). It is to be noted, however, that dialysate-based measurements of ATP, if taken at face value, are problematic, because these concentrations are in the order of only 5 nM/l, at least two orders of magnitude lower than the ATP concentrations required to cause vasoconstriction of renal resistance vessels (4).

More importantly, the underlying premise that release of ATP from macula densa cells determines overall interstitial fluid ATP concentrations seems questionable in view of the small tissue mass of macula densa cells compared to other sources of ATP such as nerve endings, endothelial cells, and tubules. In the context of autoregulation, it is of particular relevance that endothelial cells of various origins have consistently been shown to release ATP in response to increased flow, pressure, or shear stress (2). Thus it is highly likely that shear stress-related release of ATP from the endothelial lining of renal blood vessels is mainly responsible for the relation between arterial blood pressure and renal interstitial ATP concentrations. In fact, release of ATP from endothelial cells and its interaction with underlying smooth muscle cells may be a TGF-independent autoregulatory mechanism.

Finally, Nishiyama and Navar suggest that the release of ATP from macula densa cells shown recently by Bell et al. (1) supports a role for ATP as a TGF mediator. However, ATP release by macula densa cells is not incompatible with a role of adenosine as the final TGF mediator. It is conceivable that the released ATP is converted to adenosine by ecto-ATPases, ATP diphosphohydrolases, and 5’-nucleotidases, all enzymes with a wide tissue distribution. Thus ATP might be one of the upstream factors that converge on the production of adenosine, a notion that would be consistent with all currently available evidence.

REFERENCES


J. Schnermann

Response to J. Schnermann: Adenosine mediates tubuloglomerular feedback

SCHNERMANN MAKES several strong points in his article “Adenosine mediates tubuloglomerular feedback responses” (19). We completely agree that the data provided by two independent laboratories demonstrating that tubuloglomerular feedback (TGF) responses to increases in distal perfusion rate are not observed in adenosine A1-receptor-deficient mice are consistent with the hypothesis that the adenosine A1 receptor plays a critical role in maintaining the integrity of the TGF mechanism (2, 21). However, we wish to emphasize that there are other observations that are not consistent with the hypothesis that adenosine is released from the macula densa cells into the interstitium in response to increases in distal flow and signals the glomerular microvasculature to cause selective afferent arteriolar vasoconstriction.

As indicated by Schnermann, the TGF mediator must exert selective actions on preglomerular arterioles (11, 12, 16). However, several studies demonstrated that adenosine or adenosine agonists evoke both afferent and efferent arteriolar constriction (3, 4, 7, 13). The response is complex because adenosine also causes afferent and efferent vasodilation via A2 receptors.
tors. As the concentration of adenosine increases, the vasodilatory stimulus becomes predominant (7, 13). It is also recognized that TGF-mediated changes in afferent arteriolar resistance are sustained for long periods (12, 16, 23, 24). In contrast, adenosine elicits transient vasoconstriction in the kidney that spontaneously abates within a few minutes (1, 9, 12, 17, 22). Thus adenosine as the predominant TGF mediator would be in a precarious role, because its effects would wane as the TGF signal intensity increased. Also, the in situ hybridization studies cited, although demonstrating a significant expression of adenosine A1 receptor in the vicinity of the juxtaglomerular apparatus (25), do not appear to clearly demonstrate that the receptors are selectively expressed in the preglomerular renal vasculature.

Schnermann points out that adenosine receptor antagonists interfere or block TGF responses (5, 8, 10, 20). However, these studies have shown that extremely high concentrations of adenosine A1-receptor antagonists were required to inhibit the TGF response (5, 8, 10, 20). In some studies, systemic administrations of adenosine A1-receptor antagonists fail to inhibit the TGF response (5, 8, 10).

Another critical issue involves the role of adenosine in mediating renal autoregulatory responses. Because the TGF mechanism participates in the autoregulatory responses of the arteriolar vasculature to changes in perfusion pressure, it follows that the mediator of the TGF mechanism must also contribute to the changes in renal vascular resistance (RVR) associated with autoregulatory responses (12, 16). However, the data have failed to show that adenosine A1-receptor antagonists impair renal autoregulatory responses. Ibarrola et al. (6) and others (12, 18) demonstrated that adenosine receptor antagonists do not elicit any perceptible effects on renal blood flow and glomerular filtration rate autoregulatory responses to changes in renal arterial pressure. More recently, we performed experiments using the juxtamedullary nephron preparation to determine if afferent arteriolar responses to increasing renal perfusion pressure are impaired by selective blockade of adenosine A1 receptors (Nishiyama et al., unpublished data). We used a highly selective adenosine A1-receptor antagonist, 8-noradaman-3-yl-1,3-dipropylxanthine (KW-3902, 10 μmol/l), which prevents afferent arteriolar vasoconstriction induced by exogenously administered adenosine (13). Basal afferent arteriolar diameter at 100 mmHg averaged 16.0 ± 1.1 μm (n = 5), and the vasoconstrictor responses to increasing perfusion pressure to 135 and 170 mmHg averaged 8.3 ± 1.1 and 17 ± 2.2%, respectively. Neither basal diameters nor vasoconstrictor responses to the increase in perfusion pressure were altered after treatment with KW-3902 (135 mmHg: 8.2 ± 1.4% and 170 mmHg: 19.5 ± 2.8%). The absence of any effect of adenosine receptor blockade on autoregulatory responses suggests that either the TGF mechanism is not involved in mediating autoregulatory responses or that adenosine is not the TGF mediator.

As previously described (16), 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 RVR. In our recent studies evaluating the renal interstitial concentrations of adenosine and ATP, we demonstrated that renal interstitial adenosine concentrations remain stable within the autoregulatory range and do not show any significant relationship with either the autoregulatory or TGF-related changes in RVR (14, 15). In contrast, ATP clearly demonstrated such a relationship as discussed in the initial essay (16).

In summary, the collective data obtained in different laboratories using various approaches support the concept that adenosine serves as an important modulator rather than mediator of the TGF mechanism. We emphasize, however, that we clearly recognize the importance of the recent elegant work reported by Schnermann in demonstrating that the adenosine A1 receptors are an essential component needed for the manifestation of TGF responses.

REFERENCES


