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Tubuloglomerular feedback responses of the downstream efferent resistance: Unmasking a role for adenosine?

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This Commentary aims to integrate or interrelate the available *in vivo* data with the *in vitro* study by Ren and co-workers, which comes to the somewhat surprising conclusion that tubuloglomerular feedback activation vasodilates the efferent arteriole by an adenosine-dependent mechanism.

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Blood flow and glomerular filtration rate are highly regulated in the kidney by several factors: (1) a balance of neurohormonal vasodilator and vasoconstrictor molecules, (2) an efficient autoregulation of blood flow in response to variations in systemic blood pressure, and (3) activity of the tubuloglomerular feedback (TGF) system. The critical vascular resistances that participate in the tight control of blood flow and glomerular filtration rate have been fairly well defined in the case of hormonal and neural influences. Autoregulation to variations in blood pressure has been primarily localized to the afferent arteriole and preglomerular vascular resistances, and there is little doubt that the primary site for the effector response of TGF resides within the afferent arteriole. However, the specific response of the efferent arteriole has been less well defined. Ren and co-workers[1] (this issue) now supply valuable information regarding *in vitro* activation of TGF in a preparation with simultaneous microperfusion of the macula densa segment and the efferent arteriole. Their studies come to the somewhat surprising conclusion that TGF activation (in addition to afferent arteriolar vasoconstriction) vasodilates the efferent arteriole, the latter being also the consequence of TGF-induced adenosine generation and activity.[2] These results are not parochial and irrelevant to clinical nephrology, as maintenance of glomerular filtration rate under a variety of conditions is best understood if we understand the vascular contributions of TGF in detail, which include the behavior of both arterioles, together constituting approximately 80% of renal vascular resistance. To a great extent, the magnitude of the changes in resistance and the ratio of changes in afferent (R_A) and efferent (R_E) arteriolar resistances dictate the capacity to maintain glomerular capillary hydraulic pressure (P_{GC}) and glomerular plasma flow, both critical determinants of glomerular ultrafiltration.

In normal *in vivo* conditions, how does the efferent arteriole behave in relationship to associated changes in the afferent arteriole? There are actually considerable data on this issue. We and others, using measurements of glomerular hemodynamics, have examined the changes in R_E in association with R_A changes and have found a remarkable parallelism in the directional changes in the resistances.[3] There are a very few physiologic and pathophysiologic exceptions to this general relationship. In multiple studies, vasoconstrictors such as adrenergic nerves or angiotensin II and vasodilators such as prostaglandins or nitric oxide generally demonstrated parallel effects on R_A and R_E, resulting in a trend for P_{GC} to remain relatively constant across a wide range of glomerular flows and resistances, such that filtration fraction remained relatively stable. Administration of benzolamide, a carbonic anhydrase inhibitor that inhibits proximal reabsorption, may induce whole-kidney activation of TGF. We found that benzolamide induced largely parallel increases in R_A and R_E, constancy of glomerular capillary pressure, and a flow-dependent reduction in single-nephron glomerular filtration rate (SNGFR).[4] Considering the overall impact of the TGF system, the current results of Ren and co-workers[1] seem somewhat surprising and deserve further analysis of studies using TGF-specific regulation of R_A and R_E.

Despite the overall interest in TGF mechanisms, few studies have attempted to localize the sites of the TGF effector by directly assessing aspects of glomerular hemodynamics during microperfusion of Henle's loop *in vivo*. Some of these studies are not in complete agreement with regard to the responses in P_{GC} during TGF activation, and together the available studies provided no definitive answer as to the role of the efferent arteriole. In a study in hydropenic rats, Ichikawa[5] observed that directly measured P_{GC} did not change, whereas SNGFR decreased in response to TGF activation. Ichikawa concluded that the reduction in SNGFR was due to parallel increases in both R_A and R_E and possibly a reduction in the ultrafiltration coefficient.[5] Briggs and Wright[6] concluded that the effector response of TGF resulted primarily from afferent arteriolar constriction, in part due to the observed major reductions in P_{GC} during TGF activation. R_E was not determined in that study, but the authors estimated its potential role in TGF by relating the range of possible values for filtration fraction to possible changes in R_A and R_E. They concluded that the results gave no

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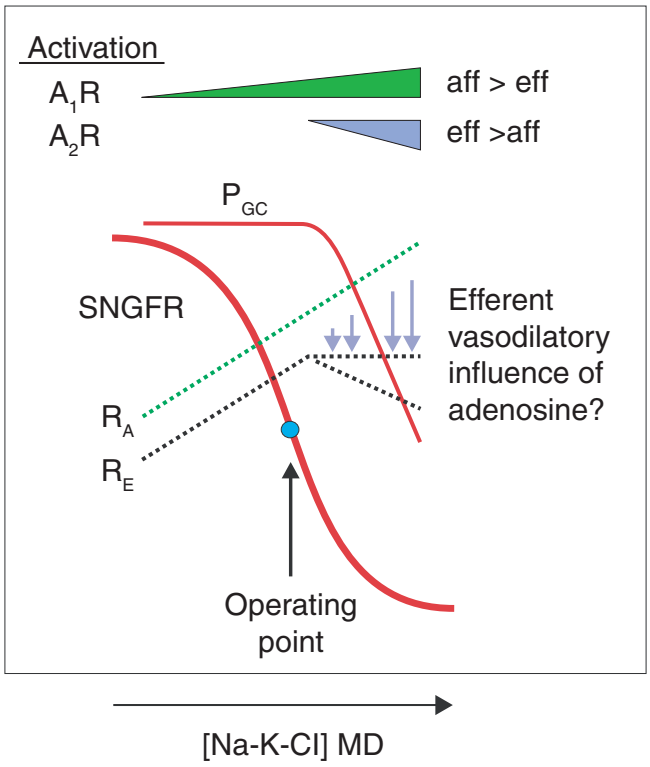

Figure 1 | Asymmetry of tubuloglomerular feedback effector response: potential role of an efferent vasodilatory influence of adenosine. See text for details. A_1R, adenosine A_1 receptor; A_2R, adenosine A_2 receptor; aff, afferent arteriole; eff, efferent arteriole; [Na-K-Cl] MD, tubuloglomerular feedback signal at macula densa; P_{GC}, glomerular capillary hydraulic pressure; R_A, afferent arteriolar resistance; R_E, efferent arteriolar resistance; SNGFR, single-nephron glomerular filtration rate.

indication that the observed TGF-induced changes in P_{GC} and SNGFR depend on a net change in efferent resistance, but they suggested that more direct measurements be taken in order to answer this question more certainly.[6] The studies described above examined the TGF responses at only very low and maximal TGF signals. A study from our laboratory by Thomson *et al.* examined both the vasodilatory and the vasoconstrictor sides of TGF, measuring online tubular flow rate and P_{GC} in response to modest additions and subtractions of fluid from free-flowing nephrons.[7] These closed-loop assessments concluded that the TGF responses were asymmetric: small perturbations from the operating point lowered or increased SNGFR by parallel increases or decreases in R_A and R_E, such that P_{GC} was unchanged, indicating that TGF-induced SNGFR changes were entirely the consequence of changes in nephron plasma flow. In contrast, raising the TGF stimulus significantly above normal flow rates lowered both SNGFR and P_{GC}, a response that could be perfectly explained by further afferent arteriolar constriction in the absence of further increases in R_E, although an actual reduction in the latter was not ruled out. In summary, none of the published *in vivo* single-nephron studies observed convincing evidence or required net efferent arteriolar vasodilation to explain the observed TGF-induced reductions in SNGFR, but a possible contribution of an efferent vasodilating influence in response to large increases in the TGF signal could not be absolutely ruled out.

It may be possible to integrate or interrelate all of these seemingly disparate findings when one considers the different experimental conditions. Because the preparation by Ren and co-workers[1] is in a bath, the normal pressure volume constraints and the local hormonal milieu may differ substantially from those in the glomerular arterioles and connected tubule *in vivo*. Moreover, the basal status of the efferent arteriole may have an important conditioning influence on the magnitude and even the direction of the response. This seems to be the case during autoregulation, whereby the efferent arteriole may vasodilate initially and then vasoconstrict with progressive reductions in systemic blood pressure.[8] Studies from our laboratory examined the TGF responses of SNGFR and glomerular capillary pressure in normal rats and during simultaneous blockade of angiotensin II and prostaglandin activities.[9] In normal rats, increasing late proximal perfusion decreased SNGFR and P_{GC}, although the turning point for pressure changes always appeared at higher flows. After blockade, the SNGFR response remained intact, but no changes in P_{GC} were observed. This we attributed to the efferent arteriolar vasodilation achieved after combined hormonal blockade, leading to additional vasoconstrictor reserve of the efferent arteriole, which allowed for maintenance of P_{GC}. In the *in vitro* study by Ren and co-workers,[1] prior vasoconstriction with norepinephrine could have changed the baseline conditions, which in turn may limit capacities for vasoconstriction, biasing toward a vasodilatory response, and unmasking the vasodilatory influence of adenosine on the efferent arteriole during TGF activation.

The efferent arteriole resides within the mesangium at the confluence of the glomerular capillaries and could function as a passive waterfall resistor, the resistance of which varies inversely with the pressure gradient from glomerular capillary to mesangial interstitium. A primary increase in R_A, mediated by TGF, would immediately dissipate this gradient because of reductions in intraluminal glomerular pressure, tending to collapse the efferent arteriole and thereby producing an increase in R_E.[7] In this way, TGF could effect changes in R_E in the absence of direct humoral communication between the macula densa and efferent arteriole. Because of the study design, this parallel linkage of changes in R_A and R_E was excluded in the current study, which also may have unmasked the vasodilating influence of adenosine on the efferent arteriole during TGF activation, and this may have been further facilitated by the use of rather large TGF stimuli.

On the basis of the outlined *in vivo* studies, the current study by Ren and co-workers,[1] and the established vascular renal effects of adenosine,[10] a concept could be envisioned in which small perturbations of the TGF signal from the operating point trigger parallel changes in local adenosine concentrations that induce primarily afferent arteriolar vasoconstriction via adenosine A_1 receptors and efferent vasoconstriction due to passive interactions with R_A (see above) and/or due to some coactivation of adenosine A_1 receptors on the efferent arteriole such that P_{GC} remains unchanged. In comparison, more excessive TGF signals trigger larger local adenosine concentrations that in addition induce a vasodilating influence on the efferent arteriole via adenosine A_2 receptors, which attenuates or prevents a further rise in R_E and thus lowers P_{GC} (Figure 1).

In summary, the basal conditions, the co-response of the afferent arteriole, and the strength of TGF stimuli applied may dictate the net magnitude and even the direction of the efferent arteriolar response. The study by Ren and co-workers[1] has defined an important influence, which tends to reduce R_E during TGF activation, and this appears to be another important effect of local adenosine. From a teleological standpoint, a TGF-induced adenosine-mediated efferent vasodilatory influence would be appealing especially in deep nephrons, where the postglomerular blood flow is nutritive for the medulla and thus consistent with a proposed role of adenosine in metabolic control of kidney function.[10]

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Diabetes: Caught in the Akt?

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One complication of diabetes is a pronounced renal cellular hypertrophy, inevitably resulting in chronic fibrotic changes. Chuang and colleagues demonstrate that hypertrophy *in vitro* is dependent on an increased phosphoinositide 3-kinase (PI3K) activity and is correlated with increased levels of $p21^{WAF1/Cip1}$, a cell-cycle regulator that was previously associated with renal fibrosis and sclerosis from nondiabetic causes.

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The response of hypertrophy occurs in organs, such as heart, lungs, and kidneys, usually in reaction to a demand for increased work load. This reaction, in which there is an increase in total cell volume without a similar increase in total cell number, has been suggested in older literature to be maladaptive.[1] Renal hypertrophy is found in several different disorders and is associated with a progressive loss of kidney function and eventual glomerular and tubulointerstitial fibrosis. Although hypertrophy may be accompanied or preceded by a period of hyperplasia,[2–4] chronic fibrotic changes in the kidney are preceded by hypertrophic growth.[5] Several *in vivo* models, such as the rodent models of streptozotocin-induced diabetes and renal ablation, mimic clinically observed kidney and systemic changes. A similar hypertrophic response was also observed *in vitro* when kidney cells were cultured in high-glucose-containing medium.[6–8]

The commitment to hypertrophic growth by kidney cells in reaction to diabetes or ablation has recently been approached by the use of gene knockout studies. Early evidence had shown that proteins associated with cell-cycle regulation and inhibition were increased in the kidney after both acute and chronic stress,[9,10] and that these inhibitors, transduced into kidney proximal tubular cells, caused hypertrophy.[11] In knockout models of one of these proteins, the p21 cyclin-dependent kinase inhibitor, hypertrophy, glomerulosclerosis, and interstitial fibrosis did not develop after partial renal ablation,[4] and glomerular hypertrophy did not occur in streptozotocin-treated mice.[12] Thus it may be concluded that the hyperplastic increase in kidney cells observed in these models was not detrimental, but that hypertrophic

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