

Molecular Mechanisms of Renal Blood Flow Autoregulation

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Abstract: Diabetes and hypertension are the leading causes of chronic kidney disease and their incidence is increasing at an alarming rate. Both are associated with impairments in the autoregulation of renal blood flow (RBF) and greater transmission of fluctuations in arterial pressure to the glomerular capillaries. The ability of the kidney to maintain relatively constant blood flow, glomerular filtration rate (GFR) and glomerular capillary pressure is mediated by the myogenic response of afferent arterioles working in concert with tubuloglomerular feedback that adjusts the tone of the afferent arteriole in response to changes in the delivery of sodium chloride to the macula densa. Despite intensive investigation, the factors initiating the myogenic response and the signaling pathways involved in the myogenic response and tubuloglomerular feedback remain uncertain. This review focuses on current thought regarding the molecular mechanisms underlying myogenic control of renal vascular tone, the interrelationships between the myogenic response and tubuloglomerular feedback, the evidence that alterations in autoregulation of RBF contributes to hypertension and diabetes-induced nephropathy and the identification of vascular therapeutic targets for improved renoprotection in hypertensive and diabetic patients.

Keywords: Afferent arteriole, glomerulus, kidney, myogenic response, tubuloglomerular feedback.

INTRODUCTION

Renal blood flow (RBF) autoregulation is a vital homeostatic mechanism that protects the kidney from elevations in arterial pressure that would be transmitted to the glomerular capillaries and cause injury. It also allows the kidney to maintain a relatively constant blood flow and glomerular filtration rate (GFR) necessary for the clearance of metabolic wastes while maintaining efficient recovery of filtered electrolytes and nutrients by the renal tubules. Two mechanisms contribute to autoregulation of RBF. The first is the myogenic response of preglomerular arterioles. Elevations in transmural pressure induce contraction of preglomerular arterioles, predominantly at the level of afferent arterioles. The other mechanism is tubuloglomerular feedback which acts in concert with the myogenic response. It senses changes in the concentration of sodium chloride in the tubular fluid reaching the macula densa cells in the distal tubule and adjusts the diameter of the afferent arteriole accordingly [1, 2]. Tubuloglomerular feedback serves as an effective autoregulatory mechanism because the sodium chloride concentration of the fluid reaching the macula densa is dependent on flow rate, which in turn, is related to the GFR and glomerular capillary pressure.

As is presented in (Fig. 1), RBF remains relatively constant in normal rats over a range of mean arterial pressures between 90 and 150 mmHg and from 70 to 130 mmHg in humans. The myogenic response of the afferent arterioles accounts for most of the rapid compensation to changes in arterial pressure in the range of 0.1 to 0.3Hz (3-10 secs).

Tubuloglomerular feedback acts more slowly, and contributes more to the compensation to slow changes in arterial pressure in the range of 0.05Hz (>20 seconds) [3-8]. In general, the available evidence indicates that the myogenic response is most important in protecting the glomerular capillaries against rapid elevations in arterial pressure, while tubuloglomerular feedback is more involved in maintaining RBF and GFR in response to sustained reductions in arterial pressure [9-13].

Elevations in vascular resistance, especially in the renal circulation, are characteristic of hypertension. There is also generalized endothelial dysfunction associated with diminished vasodilatory responses to shear stress and other stimuli. In the spontaneously hypertensive rat (SHR) and angiotensin II dependent models of hypertension and in patients with mild or moderate hypertension, there is an elevation in renal vascular resistance that is in general appropriate for the degree of hypertension, so baseline RBF and GFR remain in the normal range and renal damage is minimal [14, 15]. However, the range of autoregulation of RBF is shifted to higher pressures and the magnitude of the shift is dependent on the severity and duration of the hypertension [16, 17] (Fig. 1), which is largely due to hypertrophy and thickening of the wall of the preglomerular arterioles [18], and potentiation of myogenic responsiveness [19-22]. In patients with moderate hypertension, the shift in the autoregulatory relationship is not severe and arterial pressure can still be lowered into the normotensive range with antihypertensive therapy without compromising renal function. In more malignant forms of hypertension, however, the hypertrophy of the vascular wall narrows the lumen of preglomerular arterioles sufficiently to lower baseline RBF and GFR and it is often not possible to lower blood pressure into the normotensive range without a decline in renal function [23]. Under these conditions, a gradual reduction in blood pressure is recommended.

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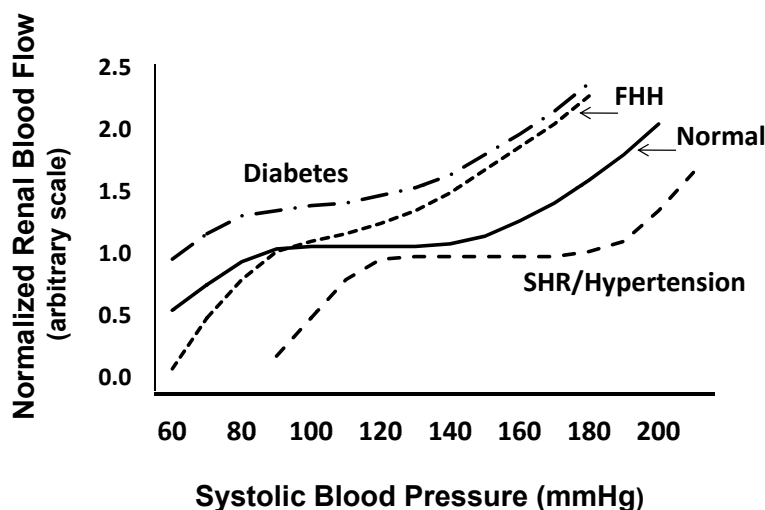


Fig. (1). Autoregulation of renal blood flow in normal and hypertensive individuals. Blood flow in normal subjects is maintained nearly constant over a range of arterial pressures from 70 to 120 mm Hg. The autoregulatory range is shifted to higher pressures in mild to moderate hypertensive patients and animal models of hypertension such as SHR and angiotensin II infused hypertensive rodents due to elevations in preglomerular vascular tone and structural changes in the microcirculation. Renal vascular resistance is reduced in diabetes and the efficiency of autoregulation is impaired. The fawn hooded hypertensive (FHH) rat exhibits a lack of a myogenic response in the preglomerular vasculature and impaired autoregulation of RBF and they develop severe glomerulosclerosis. Autoregulation is also impaired in salt sensitive forms of hypertension (Dahl salt sensitive rats, mineralocorticoid hypertension and reduced renal mass) and all are susceptible to glomerulosclerosis.

In contrast to the increase in renal vascular resistance and augmented myogenic autoregulatory responses observed in SHR and in patients with essential hypertension, autoregulation of RBF is impaired in Fawn Hooded Hypertensive (FHH) rats [24, 25], Dahl salt-sensitive rats [26-28], rats with mineralocorticoid induced hypertension [29, 30] and in animals with reduced renal mass [31] (Fig. 1). The impairment of RBF autoregulation leads to increased glomerular capillary pressure and glomerular injury with the development of proteinuria, glomerulosclerosis and renal fibrosis in Dahl salt sensitive [32], FHH [25, 33-35] and in hypertensive rats treated with deoxycorticosterone acetate (DOCA) and a high salt diet. A similar abnormality in glomerular capillary hemodynamics is thought to contribute to the rapid development of glomerulosclerosis in hypertensive African American patients [36] who are four times more likely to develop chronic kidney disease than caucasian patients [37-41]. Alterations in renal hemodynamics is also thought to play a critical role in the initiation and progression of diabetic nephropathy [42]. Hypertension and diabetes now accounts for 67% of new cases of end-stage renal disease with total estimated cost in 2007 of \$35.3 billion (\$23.9 billion in Medicare costs alone) for the treatment of an estimated 500,000 patients in the US [43]. Thus, new therapies for slowing the development and progression of glomerulosclerosis in diabetic and hypertensive patients is of utmost importance. A better understanding of the molecular mechanisms underlying renal autoregulation is key to someday achieving this goal.

MYOGENIC RESPONSE

The myogenic response is an intrinsic property of vascular smooth muscle (VSM) that allows arterioles to constrict in response to elevations in transmural pressure. The myogenic response can be readily demonstrated in de-endothelialized

arterioles *in vitro* devoid of endothelial or parenchymal influences [44-46]. Despite intensive investigation, identification of the mechanosensors responsible for initiating the myogenic response and many aspects of the signaling pathways remain uncertain. The myogenic response involves stretch activation of mechanosensitive ion channels resulting in depolarization of VSM cells and calcium influx through L-type voltage-gated calcium channels (VGCC), Ca^{2+} /calmodulin-dependent phosphorylation of myosin light chain kinase and sensitization of actinomyosin-based contractile mechanisms [47, 48]. There is evidence that the initial mechanotransduction event involves an interaction of cell surface integrins with extracellular matrix proteins such as fibronectin and actin filaments in the cytoskeleton, since blockade of integrins with integrin binding peptide inhibits Ca^{2+} currents and myogenic tone of skeletal muscle arterioles [47-49]. There is also evidence that β and γ subunits of epithelial sodium channels (ENaC) are expressed in vascular smooth muscle cells and that they play some role in the mechanotransduction event since administration of blockers of ENaC; benzamil and amiloride, impair the myogenic response of isolated vessels [50-53]. Several investigators have identified non-selective cation channels in vascular smooth muscle cells that are activated by membrane stretch [54-56]. These channels were initially thought to be directly activated by membrane stretch to promote Na^+ or Ca^{2+} entry which depolarizes VSM cells and facilitates Ca^{2+} entry through VGCC to initiate the myogenic response. However, more recent evidence indicates that the stretch-activated cation channels are likely transient receptor potential melastatin 4 (TRPM4) and transient receptor potential canonical 6 (TRPC6) channels that respond to stretch through activation of second messenger signaling pathways rather than direct mechanical activation [57-59]. In support of this view, Early and Brayden have shown that both TRPM4 and TRPC6 channels are expressed in VSM cells and knockdown of the

expression of these channels impairs the myogenic response in cerebral arteries [58, 59]. Similar studies in renal afferent arterioles have yet to be performed.

More recent data have indicated that the stretch activation of the TRP channels in cell systems requires co-expression of the channels with Gq dependent receptors, such as the angiotensin type 1, endothelin, vasopressin or histamine receptors [57]. An emerging view summarized in (Fig. 2) is that membrane stretch causes this class of receptors to interact with Gq proteins in the membrane to activate phospholipase C (PLC) and increase the production of diacylglycerol (DAG) and inositol trisphosphate (IP3) [60]. IP3 then promotes the release of Ca²⁺ from the sarcoplasmic reticulum near the membrane such that local Ca²⁺ concentration can reach levels sufficient to activate TRPM4 channels to allow Na⁺ entry and depolarize the membrane [58]. DAG can also directly activate TRPC6 channels [57] and protein kinase C (PKC) which phosphorylates and sensitizes TRPM4 channels to increases in intracellular Ca²⁺ and enhances the degree of depolarization sufficiently to allow Ca²⁺ entry through VGCC. The activation of PKC also has additional

actions to enhance the depolarization and activation of vascular smooth muscle. In this regard, PKC is known to phosphorylate the VGCC to enhance the voltage sensitivity of this channel to facilitate Ca²⁺ entry [61]. Indeed, there are studies indicating that inhibitors of PLC [62] and PKC [63, 64] block the myogenic response of renal and cerebral arteries.

Activation of non-selective cation channels (NSCC) such as TRPM4 or TRPC6 and subsequent local increases in intracellular Ca²⁺ also activate large conductance potassium channels, (BK) [65-67] (Fig. 2). BK channels are also activated by the transient calcium release (Ca²⁺ sparks) through ryanodine receptors located in the sarcoplasmic reticulum and in close proximity to these channels. In VSM cells, Ca²⁺ sparks give rise to spontaneous transient outward K⁺ currents (STOCs) that hyperpolarize the cells [68]. The magnitude and frequency of STOCs can be increased by membrane depolarization, sarcoplasmic reticulum Ca²⁺ release, and Ca²⁺ influx through VGCC [69]. The interplay between the activation of NSCC, Ca²⁺ sparks and activation of BK channels oppose depolarization of VSM cells and inhibit myogenic

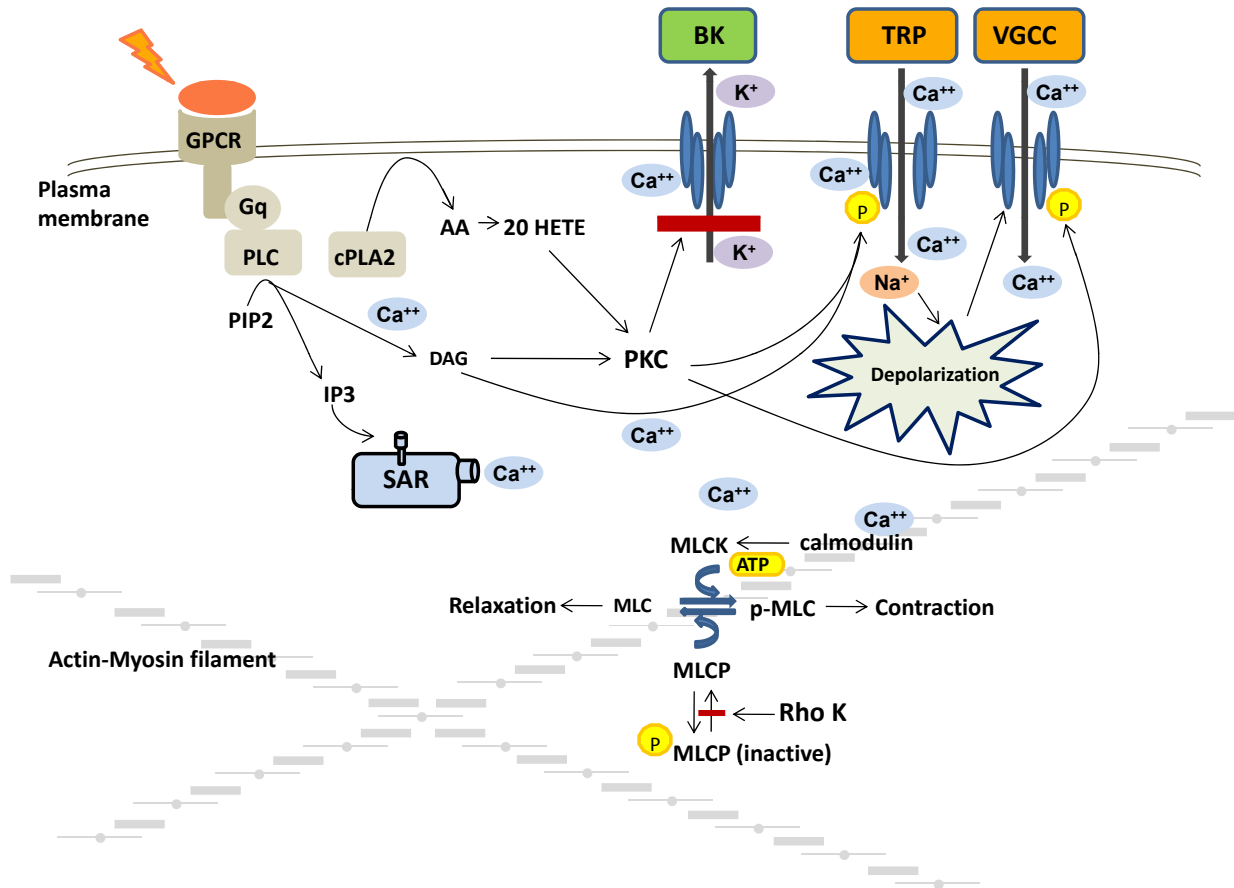


Fig. (2). Mechanisms involved in myogenic response of preglomerular renal arterioles. Stretch activation of Gq dependent receptors activates phospholipase C (PLC) and increases the production of diacylglycerol (DAG) and inositol trisphosphate (IP3). IP3 promotes the release of Ca²⁺ from the sarcoplasmic reticulum (SR) to increase local Ca²⁺ concentration sufficiently to activate transient receptor potential melastatin 4 (TRPM4) channels. DAG activates transient receptor potential canonical 6 (TRPC6) channels and protein kinase C (PKC) which phosphorylates and sensitizes TRPM4 channels to depolarize the membrane sufficiently to allow Ca²⁺ entry through voltage gated calcium channels (VGCC). The activation of PKC also blocks calcium activated large conductance potassium (BK) channel activity to enhance the degree of depolarization and phosphorylates the VGCC to enhance the voltage sensitivity and facilitate Ca²⁺ entry. The rise in intracellular Ca²⁺ initiates the contraction and is followed by activation of additional mechanisms that enhance the sensitivity of the contractile mechanism to Ca²⁺.

responsiveness [65, 66]. Thus, there must be mechanisms in place to blunt the opening of BK channels. In this regard, there is evidence that PKC phosphorylates and inhibits activation of BK channels [65, 66]. There is also considerable evidence that a cytochrome P450 metabolite of arachidonic acid, namely 20-hydroxyeicosatetraenoic acid (20-HETE), plays a key role in augmenting the myogenic response by blocking BK channels [63, 64, 70, 71]. In this regard, the rise in intracellular Ca^{2+} following stretch of VSM cells activates phospholipase A2 which stimulates the release of arachidonic acid (AA). AA has been shown to be avidly converted to 20-HETE by cytochrome P450 enzymes of the 4A family expressed in renal afferent arterioles [72]. 20-HETE is a potent constrictor of renal arterioles [73, 74] that activates PKC [63, 64, 75], mitogen activated protein kinase [76, 77], src-type tyrosine kinase [78] and rho kinase [79]. 20-HETE potentiates the myogenic response by activating PKC which has been shown to phosphorylate and inhibit BK channels thereby allowing for sustained depolarization of VSM cells [64, 70, 71, 80]. 20-HETE also augments activation of TRPC6 channels enhancing depolarization and increasing activity of L-type calcium channels [81]. Indeed, elevations of transmural pressure increase 20-HETE levels in isolated arterioles [82] and inhibitors of the synthesis of 20-HETE block the myogenic response in isolated renal [83] and cerebral arteries [82] *in vitro* and impair autoregulation of renal [84] and cerebral blood flow [82] *in vivo*.

The initial rise in intracellular calcium concentration following activation of the myogenic response is transient, generally falling to levels near or slightly elevated from baseline, whereas the vasoconstrictor response is sustained. This indicates that there must be an increase in the Ca^{2+} sensitivity of contractile apparatus that plays a key role in the response. As seen in (Fig. 2), the rise in intracellular Ca^{2+} is thought to activate myosin light chain kinase via a Ca^{2+} -calmodulin dependent process and phosphorylate the 20 kD regulatory subunit of myosin light chain. This permits the myosin light chain to more effectively bind to actin and hydrolyze ATP to enhance cross bridge formation and cycling. Myosin light chain phosphatase normally dephosphorylates the light chain to limit cross bridge formation and allow for diminished tone [85]. Recent studies indicate that the sustained activation of vascular smooth muscle cells is related not only to increased myosin light chain kinase activity but also to inhibition of myosin light chain phosphatase activity. This is due to the increase in PKC activity induced by DAG, [86, 87] and 20-HETE that activate a rho-A sensitive kinase that phosphorylates and inhibits the activity of myosin light chain phosphatase [79]. In summary, the myogenic response involves stretch activation of ion channels, depolarization and Ca^{2+} influx through VGCC that initiates contraction that is followed by other mechanisms that enhance the Ca^{2+} sensitivity of the contractile mechanism that are essential for the sustained contractile response.

TUBULOGLOMERULAR FEEDBACK

The other mechanism contributing to autoregulation of RBF is tubuloglomerular feedback [1, 2, 88]. This mechanism senses increases in the concentration of sodium chloride (NaCl) in tubular fluid reaching the macula densa cells of the distal nephron which then acts to decrease the diame-

ter of the juxtaposed afferent arteriole. Tubuloglomerular feedback serves as a negative feedback loop to stabilize GFR to enable excretion of metabolic waste and to prevent transmission of elevations in arterial pressure from being transmitted to the glomerular capillaries and damaging the glomerulus. A summary of the proposed mechanism of tubuloglomerular feedback is presented in (Fig. 3). Increases in arterial pressure, that are not fully compensated via the myogenic response, increase glomerular capillary pressure and GFR and inhibit Na^+ reabsorption in the proximal tubule via the mechanism of pressure natriuresis [89, 90]. This leads to an increase in the concentration of NaCl delivered to the distal nephron which increases Na^+ uptake by the Na-K-2Cl co-transporter in the apical membrane of the macula densa. The essential role of Na^+ transport via the Na-K-2Cl cotransporter in triggering tubuloglomerular feedback is based on the observations that inclusion of loop diuretics in the tubular perfusate nearly completely blocks the tubuloglomerular feedback response [91-93] and the observation that targeted knockout of the Na-K-2Cl, A or B genes, impairs the tubuloglomerular feedback response in mice [94, 95]. The uptake of Na^+ via the Na-K-2Cl transporter is thought to increase intracellular Na^+ concentration and the activity of Na K-ATPase and increase intracellular Ca^{2+} levels in the macula densa [96]. This is associated with increased release of ATP from the basolateral membrane of macula densa cells through a maxi anion channel [97, 98].

There still remains some controversy regarding whether the ATP that is released from the macula densa then acts directly on the afferent arteriole to elicit vasoconstriction through stimulation of the ATP P2X receptors or whether it is degraded by ecto-ATPases and nucleotidases to adenosine that constricts the afferent arteriole through activation of the adenosine $\text{A}_{1\text{A}}$ receptor [99-104]. The evidence supporting the role for ATP in mediating tubuloglomerular feedback is that administration of the P2X₁ receptor antagonist, NF-279, impairs the response of afferent arterioles to elevations in perfusion pressure in the isolated perfused juxtamedullary nephron preparation [105]. Similarly, knockout of the P2X₁ receptor in mice impairs the response of afferent arterioles to elevations in perfusion pressure in the isolated perfused juxtamedullary nephron preparation [105, 106] and autoregulation of RBF *in vivo* [107] but tubuloglomerular feedback responses to increases in tubular flow to the macula densa *in vivo* are not significantly altered [108].

Two independent laboratories have reported that tubuloglomerular feedback responses are completely absent in adenosine $\text{A}_{1\text{A}}$ receptor knockout mice and this is associated with impaired autoregulation of RBF and GFR especially in response to reductions in renal perfusion pressure [109-111]. Similarly, tubuloglomerular feedback responses are impaired in mice with deletion of the NTPDase1 gene, an extracellular ATPase that dephosphorylates ATP to ADP or ADP to AMP by deletion of ecto-5'-nucleotidase cd73 [99, 102]. Adenosine has a direct effect to constrict isolated perfused afferent arterioles and this effect is blocked by an adenosine $\text{A}_{1\text{A}}$ receptor antagonist and in vessels obtained from $\text{A}_{1\text{R}}$ knockout mice [104, 112]. As presented in (Fig. 3), previous studies have indicated that the vasoconstrictor response to adenosine in the afferent arteriole is mediated by G_i -dependent activa-

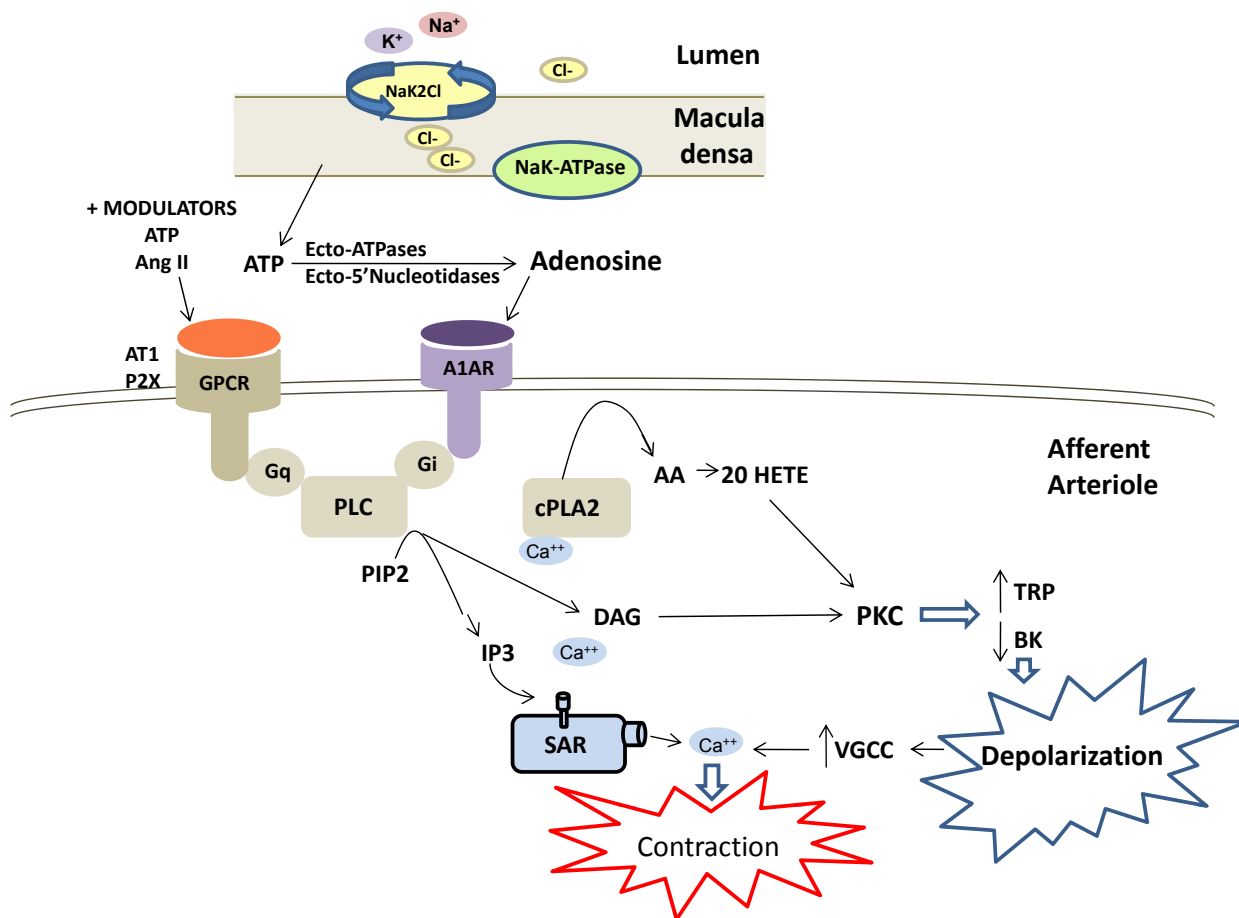


Fig. (3). Mechanisms involved in tubuloglomerular feedback control of renal vascular tone. Tubuloglomerular feedback is initiated when the filtered load of sodium chloride is increased to the macula densa resulting in increases of; sodium reabsorption via the sodium potassium 2 chloride exchanger (NaK2Cl), intracellular Na⁺, sodium potassium ATPase (NaK-ATPase) activity and intracellular Ca²⁺. These events trigger the release of ATP from the macula densa cells. ATP is converted to adenosine extracellularly and then acts on adenosine 1A receptors (A1AR) in the adjacent afferent arteriole to promote vasoconstriction. A1AR activates phospholipase C (PLC) via a GTP binding protein (Gi), the release of inositol trisphosphate (IP₃) and diacylglycerol (DAG). The subsequent activation of cytosolic phospholipase A₂, formation of arachidonic acid (AA) and 20-HETE, as well as activation of protein kinase C (PKC), alters transient receptor potential channel (TRPC) and large conductance calcium activated potassium channel (BK) activities resulting in depolarization and activation of voltage gated calcium channels (VGCC) and Ca²⁺ influx. The increase in intracellular Ca²⁺ initiates contraction of the afferent arteriole, reduction in glomerular capillary pressure and filtered sodium chloride load. Activation of the angiotensin II receptor type I (AT₁R) stimulates a similar transduction pathway to that shown in (Fig. 2) for the myogenic response. In addition, ATP and angiotensin II have been shown to be positive modulators of tubuloglomerular feedback through activation of G-protein coupled receptors, specifically purinergic receptor 2X (P₂X) and angiotensin 1 receptor (AT₁) via G_q to modulate PLC activity.

tion of PLC via the β subunit [113, 114] followed by release of DAG and IP₃, the release of Ca²⁺ from intracellular stores, activation of PKC, depolarization of the membrane and Ca²⁺ influx in a manner analogous to the activation of the myogenic response by stretch or the vasoconstrictor response to angiotensin II via the angiotensin II receptor type I (AT₁R) and G_q dependent pathways. Similarly, there is evidence that ATP, and possibly adenosine as well, stimulate the formation of 20-HETE in the afferent arteriole [115] and that 20-HETE may contribute to the vasoconstrictor response to these agonists by inhibiting BK channels and enhancing calcium influx [70]. In this regard, inhibitors of the formation of 20-HETE have been reported to impair autoregulation of tubuloglomerular feedback responses in the rat *in vivo* [116].

INTERACTIONS BETWEEN G-PROTEIN COUPLED VASOCONSTRICTORS, MYOGENIC RESPONSE AND TUBULOGLOMERULAR FEEDBACK MECHANISMS IN THE AUTOREGULATION OF RBF AND GLOMERULAR CAPILLARY PRESSURE

An examination of the pathways summarized in (Figs. 2 and 3) illustrates that elevations in transmural pressure (Fig. 2) and tubuloglomerular feedback (Fig. 3) activate the same second messenger signal transduction cascade characterized by activation of PLC, increases in DAG and IP₃, cellular depolarization and influx of intracellular calcium. Moreover, this same pathway is involved in the response of the afferent arteriole to vasoconstrictor agonists acting via the AT₁, P₂X and endothelin ETA receptors [1, 117-119]. Given the convergence of these second messenger pathways, it is not sur-

prising that the myogenic response, tubuloglomerular feedback and G protein coupled vasoconstrictor pathways interact synergistically to regulate the tone of the afferent arteriole. For example, Inoue *et al.* [81] recently demonstrated that membrane stress/pressure induced responses were synergistically augmented in A7r5 cells and mesenteric arteries that normally respond poorly to membrane stress/stretch after low level Gq-receptor activation. They further demonstrated that the synergism was linked to increased production of 20-HETE. Other studies have indicated that activation of the angiotensin II AT₁ or adenosine A_{1A} receptor augments the myogenic response [104, 110, 114, 120, 121]. Similarly, blockade of the renin angiotensin system with angiotensin converting enzyme (ACE) inhibitors or AT₁ receptor blockers (ARBs) attenuate tubuloglomerular feedback responses and shift the relationships between flow to the macula densa and stop flow pressure, and index of glomerular capillary pressure to the right [122, 123]. Although there is little direct data to support this hypothesis, one would also expect that increases in arterial pressure and myogenic tone would increase tubuloglomerular feedback responsiveness. Moreover, elevations in perfusion pressure should potentiate the dose response relationship to vasoconstrictor agonists, and suppressor levels of angiotensin, adenosine and endothelin should potentiate myogenic and tubuloglomerular feedback responsiveness. These types of interactions have been postulated to play a role in the enhanced myogenic responsiveness and elevated renal vascular resistance seen in angiotensin II models of hypertension and in the SHR, in which the kidney is generally protected from the development of glomerular injury until late in the disease process when arterial pressure rises beyond the reset autoregulatory range.

MODULATORS OF MYOGENIC RESPONSE AND TUBULOGLOMERULAR FEEDBACK RESPONSIVENESS

Shear stress is directly dependent on the velocity of flow in a vessel and is inversely proportional to vascular diameter. Shear stress stimulates the release of endothelial-derived relaxing factors that act as negative modulators of autoregulatory responses. Following activation of myogenic or tubuloglomerular feedback, the decrease in the diameter of the afferent arteriole increases shear stress which stimulates the release of vasodilator mediators from the endothelium that oppose further vasoconstriction. The mediators that are released include, nitric oxide, prostaglandin E₂, prostacyclin, epoxyeicosatrienoic acids (EETs) which dilate vessels by opening potassium channels which hyperpolarize vascular smooth muscle cells and oppose calcium influx [88, 124-126]. Each uses a different signal transduction pathway. Nitric oxide stimulates the formation of cGMP [127] and binds heme in CYP450 enzymes to inhibit the formation of 20-HETE in vascular smooth muscle cells [71, 128]. Both of these effects open potassium channels to hyperpolarize the cell and diminish calcium entry through voltage sensitive channels [129]. Prostacyclin and prostaglandin E₂ act on receptors to promote vasodilation via cAMP-dependent pathway [125]. EETs are metabolites of arachidonic acid formed by cytochrome P450 enzymes of the 2C family that are produced by the endothelium. They are potent vasodilators that open BK channels in renal vascular smooth muscle cells by stimulating the formation

of cAMP [130, 131] and/or c-AMP ribose [126, 132, 133]. In many vascular beds EETs have been identified as an endothelial derived hyperpolarizing factor that mediates the response to endothelial dependent vasodilators following blockade of nitric oxide synthase (eNOS) and cyclooxygenase [134].

Nitric oxide (NO) and arachidonic acid metabolites also play very important roles in modulating the activity of tubuloglomerular feedback [135]. Neuronal nitric oxide synthase (nNOS) is expressed in macula densa cells and NO is released following activation of tubuloglomerular feedback [96, 136-138]. Blockade of the formation of NO in the macula densa by administration L-NAME or more selective inhibitors of nNOS to the tubular perfusate markedly enhances the tubuloglomerular feedback response.

More recently, Ren *et al.* and Wang *et al.* [139, 140], have identified another important pathway that decreases the sensitivity of the tubuloglomerular feedback mechanism. They reported that increased flow in the connecting tubule of the distal nephron stimulates the production and release of both prostaglandin E₂ and EETs and that both of these compounds diffuse to the juxtaposed afferent arteriole to promote vasodilation and oppose vasoconstriction. Again, the physiologic significance of this modulatory pathway remains to be determined but it is likely a compensatory mechanism that allows the kidney to rapidly increase sodium excretion without reducing GFR following elevations in sodium intake. Moreover, upregulation of the formation of NO by the macula densa or the connecting tubule in diabetes and various forms of hypertension may oppose both myogenic and tubuloglomerular feedback responsiveness, leading to elevations in glomerular capillary pressure, which promotes the development of proteinuria and glomerular injury.

ROLE OF IMPAIRED AUTOREGULATORY MECHANISMS IN THE PATHOGENESIS OF GLOMERULOSCLEROSIS AND CHRONIC KIDNEY DISEASE

Although the range of autoregulation may be shifted toward higher pressures, autoregulatory mechanisms are intact in most patients with essential hypertension and they do not develop proteinuria or significant renal injury [141, 142]. Similar renoprotection is seen in the SHR model of hypertension [15] in which the myogenic response of the preglomerular vasculature is enhanced [14, 143] perhaps due to elevated production of 20-HETE [73]. Recent studies have indicated that renal vascular resistance is also markedly elevated in the angiotensin II infused mouse model of hypertension which develops ischemic renal injury to the glomerulus rather than proteinuria, mesangial matrix expansion and focal glomerular sclerosis [144].

In contrast, renal autoregulation is impaired in patients with diabetes, other forms of proteinuric chronic kidney disease (CKD) and in African Americans with low renin forms of hypertension. These patients exhibit increased susceptibility to the development of progressive glomerulosclerosis in response to even modest elevations in pressure [9]. Indeed, this is the reason for the recommendation for strict control of blood pressure in patients with diabetes and CKD and it underlies the rationale for the use of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) that lower systemic pressure and reduce glomerular capillary pressure.

The increased susceptibility to renal injury observed in patients with diabetes and chronic kidney disease, as well as work done in wide variety of animal models of hypertension and diabetes, suggest that impairments in renal autoregulatory mechanisms leading to elevation in glomerular capillary pressure trigger the development of proteinuria and glomerulosclerosis. Work done in the 5/6 nephrectomy model of chronic kidney disease indicates that the remaining glomeruli hypertrophy and autoregulatory mechanisms are impaired. These animals exhibit hyperfiltration and elevated glomerular capillary pressure [9, 31, 145, 146]. With time these animals develop progressive proteinuria and glomerular sclerosis. Further support for a key role of alterations in renal hemodynamics in the development of renal injury are the findings that administration of calcium channel blockers, that further impair renal autoregulation, markedly accelerate the progression of renal disease in the 5/6 remnant kidney model [147-149].

Increased susceptibility to the development of proteinuria and focal segmental glomerulosclerosis has been observed in other rat models of hypertension that exhibit impaired autoregulation of RBF. These include the DOCA salt model of hypertension [29, 150] the unclipped kidney of 2 kidney 1 clip Goldblatt hypertensive rats [151, 152] and in the FHH rat [35, 153]. The FHH rat in particular develops proteinuria and focal segmental glomerulosclerosis at a relative young age that progresses to end state renal disease. These rats have little or no myogenic response in preglomerular renal arteries but tubuloglomerular feedback responses are intact [28, 35, 154, 155]. Autoregulation of RBF is markedly impaired in these rats and glomerular capillary pressure increases following elevations in renal perfusion pressure [25, 34, 35]. Similarly, Dahl S rats and Brown Norway rats exhibit impaired dynamic autoregulation of RBF related to a defect in the myogenic control of the renal vasculature [26, 156]. Both of these strains rapidly develop proteinuria and progressive glomerular disease following the development of hypertension [32, 157-159]. Glomerular capillary pressure is also thought to be elevated in African Americans [36, 160] with salt-sensitive forms of hypertension and this is thought to underlie the increased susceptibility to the development of proteinuria and chronic kidney disease.

The mechanisms by which impaired autoregulation of RBF in diabetes, salt-sensitive forms of hypertension and chronic kidney disease promote the development of renal disease remain to be determined. A proposed mechanism is presented in (Fig. 4). The available data suggest that impaired autoregulation of RBF leads to an elevation in glomerular capillary pressure, which increases glomerular expression of transforming growth factor beta (TGF- β) through increases in stretch of the glomerular capillaries and adherent mesangial cells and podocytes [161-164] TGF- β is known to increase the production of collagen and fibronectin in cultured mesangial cells and podocytes [165]. There is also an increase in the renal expression of matrix metalloproteinase 2 (MMP2) which has been shown to increase the release of bound forms of TGF- β [166-168], activate the epidermal growth factor pathway and promote epithelial to mesenchymal transformation [169] which is critical to the development of renal fibrosis [170]. TGF- β has been shown to directly increase the permeability of isolated glomeruli to albumin [171, 172]. Damage to

the glomerular filtration barrier and increased filtration of macromolecules and/or growth factors may trigger a positive feedback loop that further stimulates podocytes, mesangial cells and renal tubular epithelial cells to upregulate the expression of TGF- β , increasing the production of extracellular matrix. This may be one of the pathways for the development of focal glomerulosclerosis, renal interstitial fibrosis and tubular necrosis in hypertensive and diabetic patients. Ultimately, the sustained overexpression of TGF- β stimulates the production of extracellular matrix and leads to the collapse of glomerular capillaries (glomerulosclerosis), renal interstitial fibrosis, loss of nephrons and chronic renal failure.

The mechanism by which TGF- β increases the glomerular permeability to albumin is still unknown. We have reported that TGF- β inhibits the synthesis of 20-HETE in isolated glomeruli and that pretreatment of glomeruli with 20-HETE mimetics opposes the effects of TGF- β to increase the glomerular permeability of albumin [173]. Moreover, inhibitors of the synthesis of 20-HETE mimic the action of TGF- β to increase the albumin permeability of the glomerulus and development of proteinuria [174]. These findings suggest that 20-HETE may also play a role in maintaining glomerular barrier function and that TGF- β may initiate the development of proteinuria and renal disease in part by inhibiting the formation of 20-HETE.

There is also overwhelming evidence that over expression of TGF- β plays a key role in the pathogenesis of renal fibrosis associated with exposure to nephrotoxins, renal ischemia and immune injury, as well as hypertension and diabetic nephropathy. Increased circulating and/or renal concentrations of TGF- β mRNA or protein have been reported in patients with diabetic nephropathy [175-178], following transplant rejection [179] and cyclosporine-induced nephropathy [180] and in various forms of glomerulosclerosis [181, 182]. Increases in renal expression of TGF- β have been reported in every animal model of renal injury examined to date [165]. This includes use of anti-thymocyte or anti-glomerular basement membrane serum and Heyman nephritis [183], cyclosporine and puromycin nephropathies [184, 185], remnant kidney [186, 187], ureteral obstruction [188], chronic allograft rejection [180] and radiation injury [189], as well as animal models of diabetes-induced renal injury including streptozotocin induced rodent models [178, 190], the biobreeding (BB) rat and the non obese diabetic (NOD) mouse model [191]. Hypertension models linked to elevated levels of TGF- β include: L-NAME [192, 193] and angiotensin II treated animals [165, 194], deoxycorticosterone acetate-salt hypertensive rats [150] and genetic models including stroke prone SHR rats [195] and Dahl S rats [172, 196]. Previous studies have shown that treatment of rats and mice with TGF- β 2 induces a renal interstitial fibrosis in the outer medulla resembling that seen in patients with hypertension [197, 198]. Transgenic mice that over express TGF- β also develop glomerular lesions and tubulointerstitial renal disease resembling that seen in patients with hypertension and diabetes [199-203].

The most direct evidence for a role for TGF- β in the pathogenesis of renal disease comes from inhibitor studies. These studies have shown that chronic treatment of rats with

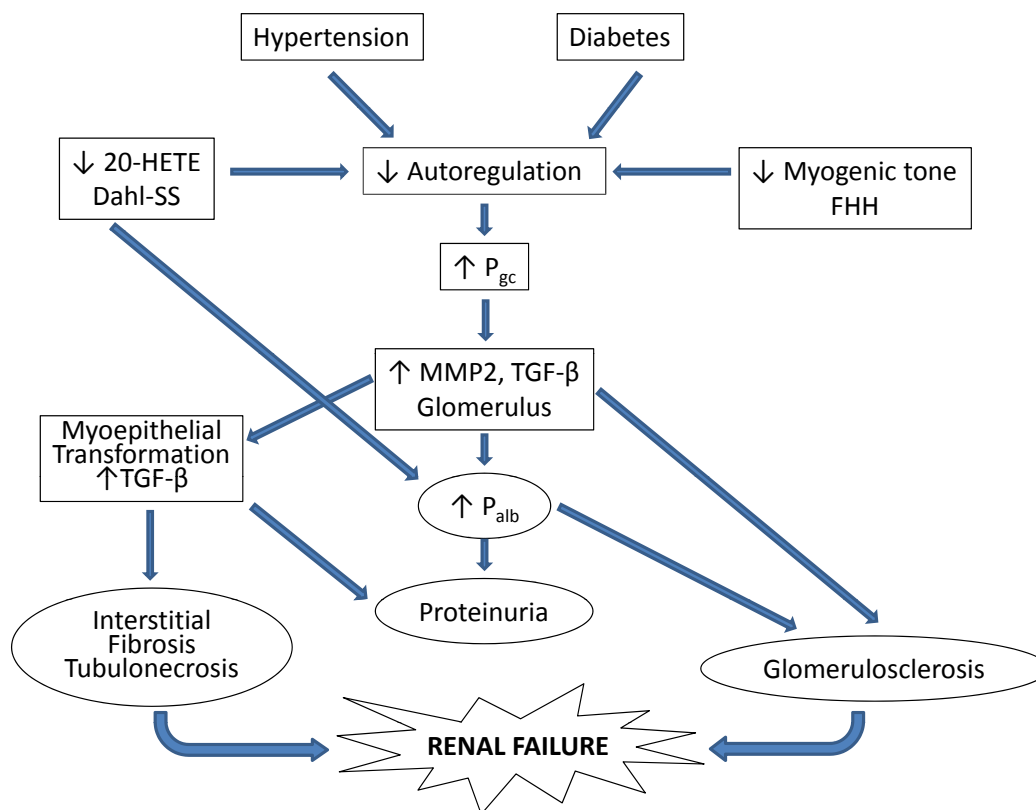


Fig. (4). Proposed mechanisms contributing to the development of diabetic and hypertensive nephropathy. Autoregulation of renal blood flow is impaired in patients with salt sensitive forms of hypertension and diabetes as well as in Dahl salt sensitive (Dahl-SS) and Fawn-hooded hypertensive (FHH) rats. The impaired autoregulation leads to greater transmission of fluctuations in arterial pressure to the glomerulus and increased glomerular capillary pressure (P_{gc}). Elevated P_{gc} results in increased expression of matrix metalloproteases and transforming growth factor beta (TGF- β). Increased TGF- β promotes glomerulosclerosis, increased glomerular permeability to albumin (P_{alb}), myoepithelial transformation, proteinuria and renal interstitial fibrosis.

a TGF- β neutralizing antibody [204], decorin, an endogenous inhibitor of TGF- β [205], or antisense constructs that down regulate the expression of TGF- β or T β RII [193] reduce the degree of glomerulosclerosis in the anti-Thy1 model of glomerulonephritis. Several investigators have reported that knock-down of the production of TGF- β with antisense TGF- β 1 oligodeoxynucleotides or by blocking the actions of the TGF- β with a neutralizing antibody also reduces the degree of proteinuria and glomerular damage in diabetic mice [190, 206-208]. Beneficial effects of TGF- β neutralizing antibodies have also been reported in rats with puromycin nephropathy [185] and in mice with cyclosporin-induced nephropathy [209]. These studies indicate that TGF- β levels are elevated in diabetes, hypertension and following renal injury. They also suggest that TGF- β plays a causal role in the pathogenesis of renal fibrosis associated with these conditions. Sustained overproduction of TGF- β [196] also leads to apoptosis of podocytes [210, 211], mesangial cells [212] and tubular epithelial cells [213, 214], damage to the glomerular filtration barrier, proliferation of mesangial cells, increased deposition of extracellular matrix, and collapse of glomerular capillaries. TGF- β also promotes epithelial-mesenchymal transformation, [169, 170, 215, 216] leading to renal interstitial fibrosis, loss of capillaries and tubular necrosis.

POTENTIAL FOR NEW THERAPEUTIC STRATEGIES FOR IMPROVED RENAL PROTECTION

Overall, there is strong evidence that impaired autoregulation of RBF leading to increased transmission of fluctuations in system pressure to the glomerular capillaries markedly increases the susceptibility to the development of proteinuria, glomerulosclerosis and chronic kidney disease. Much of the work using animal models have indicated that this is largely associated with changes in the myogenic component of renal autoregulation. Examination of the signaling pathways involved indicates that the control of the tone of the afferent arteriole by myogenic, tubuloglomerular feedback and vasoconstrictor agonists activate common signaling pathways involving activation of PLC, IP₃, DAG, release of intracellular Ca²⁺, opening of TRP channels, membrane depolarization, Ca²⁺ entry through VGCC and sensitization of the contractile mechanism to Ca²⁺. There are several potential intervention points that might restore the efficiency of the myogenic autoregulatory mechanisms to protect the glomerulus from barotrauma. These include; TRP channel agonists, BK channel blockers, 20-HETE agonists or CYP4A inducers, L-type calcium channel agonists and rho kinase agonists. Unfortunately, none of these approaches would be selective for increasing the tone of the afferent arteriole and would likely be associated with unacceptable risks and side effects such as the development of hyperten-

sion, cardiac arrhythmias and vasospasm. These same pathways also play a key role in cell growth and proliferation so these drugs may promote the development of vascular hypertrophy and arteriosclerosis or certain forms of cancer. As a result, it appears that the most effective strategy to slow the progression of renal disease for the foreseeable future will remain strict control of diabetes and the associated renal vasodilation and to reduce systemic pressure with ACE inhibitors and ARBs which lower glomerular capillary pressure by dilating the efferent arteriole. This approach may someday be augmented with the emergence of new anti-fibrotic agents that block the actions of TGF- β and matrix metalloproteinase 2. Indeed, recent data have been very promising in experimental animal models of diabetes, hypertension and renal disease. However, none of these compounds have yet entered clinical development for the prevention of hypertension and/or diabetic nephropathy in humans.

CONFLICT OF INTEREST

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LIST OF ABBREVIATIONS

ACE	=	Angiotensin converting enzyme
ARB	=	Angiotensin receptor blocker
BK	=	Large conductance potassium channel
DAG	=	Diacylglycerol
DOCA	=	Deoxycorticosterone acetate
EET	=	Eicosatetraenoic acid
ENaC	=	Epithelial sodium channels
FHH rats	=	Fawn hooded hypertensive
GFR	=	Glomerular filtration rate
IP3	=	Inositol trisphosphate
NOS	=	Nitric oxide synthase
MMP2	=	Matrix metalloproteinase 2
P _{alb}	=	Glomerular permeability to albumin
PLC	=	Phospholipase C
PKC	=	Protein kinase C
RBF	=	Renal blood flow
SHR	=	Spontaneously hypertensive rats
TGF- β	=	Transforming growth factor beta
TRPC6	=	Transient receptor potential canonical 6
TRPM4	=	Transient receptor potential melastatin 4

VGCC	=	Voltage gated calcium channel
VSM	=	Vascular smooth muscle
20-HETE	=	20-hydroxyeicosatetraenoic acid

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