Kidney and Hypertension

Shuji Arima

Division of Nephrology, Department of Internal Medicine, Kinki University Faculty of Medicine, Osakasayama, Osaka 589-8511, Japan

Abstract

The kidney plays an important role in the control of systemic blood pressure by regulating the composition of body fluid and electrolytes and by producing and releasing various vasoactive substances. Thus, normal renal function is required for the precise blood pressure control and kidney plays a pivotal role in the pathogenesis of hypertension. Three major renal mechanisms have been proposed which lead to the development of hypertension; an increased pre-glomerular vascular resistance, a decreased whole kidney ultrafiltration and an increased tubular sodium reabsorption. This review summarizes the pathological role of renal abnormalities, with a special attention to the renal microcirculation, in the development of hypertension.

Key words: glomerular hemodynamics, afferent arterioles, efferent arterioles, macula densa, salt-resistant hypertension, salt-sensitive hypertension

Introduction

Studies suggest that renal microcirculation (glomerular hemodynamics) is critically involved not only in the pathogenesis of hypertension but also in the mode of progression of renal dysfunction. The juxtaglomerular apparatus (JGA, Fig 1), consisting of the glomerular afferent and efferent arterioles as well as the specialized tubular epithelial cells called macula densa, plays a critical role in the regulation of glomerular hemodynamics and renin release. Kimura and Brenner proposed three major renal mechanisms leading to the development of hypertension: increased pre-glomerular vascular resistance, a decreased whole kidney ultrafiltration and an increased tubular sodium reabsorption. To date, it has been demonstrated that pre-glomerular vasoconstriction causes salt-resistant hypertension, whereas a reduced renal mass and alterations of renal sodium handling result in the development of salt-sensitive forms of hypertension. Moreover, it has been suggested that salt sensitivity is associated with an increased glomerular capillary pressure (P_{GC}), and hence a higher risk of developing glomerulosclerosis and chronic renal failure.

PGC and clinical pictures

There is substantial evidence that P_{GC} greatly influences the rate of the progression of renal dysfunction. The P_{GC} is found to be normal in salt-resistant essential hypertension, whereas it is elevated in such cases as diabetes mellitus, various renal diseases and salt-sensitive (essential) hypertension.

Micropuncture studies in the spontaneously...
hypertensive rats (SHR), a model of human essential hypertension, and its normotensive control Wistar-Kyoto rats (WKY) have revealed that despite a significant difference in systemic blood pressure and renal vascular resistance (RVR), Pgc is the same in both strains. This demonstrates that in SHR, RVR is high due to a strong constriction of the pre-glomerular vessels. Calculation of Pgc according to Gomez’s equation suggests that in human essential hypertension Pgc is also within the normal range with increased pre-glomerular resistance, whereas post-glomerular efferent arteriolar resistance remains essentially unchanged. Among various pre-glomerular vascular segments, the afferent arteriole is likely to be the major contributor to the elevated vascular resistance. Such functional alterations are reflected in the histology of human kidneys; because of the strong constriction of afferent arterioles (and distal segment of interlobular arteries), the glomerulus is protected from systemic hypertension, thereby maintaining a relatively normal architecture. In contrast, afferent arterioles and interlobular arteries show hypertrophy and sclerotic changes due to a long-lasting pressure overload. The increased afferent arteriolar resistance with normal Pgc is also reflected in clinical pictures. Namely, compared to renal parenchymal diseases, there would be less proteinuria and the progression of renal dysfunction would be slow because of the normal Pgc. However, progressive luminal narrowing of afferent arterioles and a subsequent fall in glomerular blood flow would induce glomerular ischemia, ultimately leading to the renal failure. Alternatively, long-lasting pressure overload can damage the autoregulatory vasoconstrictor behavior of afferent arterioles (see below), which permits the direct transmission of elevated systemic pressure to the glomerulus and facilitates glomerular hypertension leading to a glomerular structural injury and a progressive loss of renal function. Although elevated pre-glomerular vascular resistance protects the glomerulus from systemic hypertension, this compensation impairs the ability of the kidney to excrete salt and water, and contributes to the inappropriate retention of extracellular fluid and the development of salt-sensitive hypertension. Elevated pre-glomerular vascular resistance also contributes to the development of salt-sensitive hypertension.

The strong constriction of afferent arterioles may be important in the pathogenesis of hypertension. Norrelund et al measured afferent arteriolar diameter in one kidney removed at the age of 7 week from F2 generation of SHR and WKY, and kept these uninephrectomized rats until the age of 23 weeks. They found that rats which had smaller afferent arteriolar diameter at 7 week developed hypertension, whereas those with larger diameter remained normotensive. In addition, these authors have shown that when the young rats were given anti-hypertensive drugs, treatments associated with increased afferent arteriolar diameter resulted in lower systemic blood pressure in adulthood even after the cessation of the therapy. These results suggest that exaggerated afferent arteriolar constriction may be essential for the future development of hypertension.

Substantial differences in renal hemodynamic adaptation to a high salt intake are evident between salt-sensitive and salt-resistant hypertensive patients. During a low salt diet both salt-sensitive and salt-resistant patients have similar mean arterial pressure, glomerular filtration rate (GFR), effective renal blood flow (RBF) and filtration fraction (FF). On the other hand, during a high salt intake effective RBF increases in salt-resistant but decreases in salt-sensitive patients without any change in GFR in either group; FF and Pgc decrease in salt-resistant but increase in salt-sensitive patients. Salt-sensitive hypertension is characterized by an inability of the kidney to excrete unnecessary amounts of sodium loaded into the body. This is likely due to either a decreased ultrafiltration coefficient or increased tubular reabsorption. When dietary sodium intake is increased under such abnormalities, body fluid volume, and hence systemic blood pressure increase, leading to an elevated Pgc and therefore an increase in the GFR. With such increased GFR, more sodium is loaded to the tubules to maintain sodium balance. Thus, in salt-sensitive hypertension, glomerular hypertension is a common feature regardless of the cause of hypertension, such as diabetes, primary aldosteronism, chronic glomerulonephritis and essential hypertension in black populations. Regardless of initial insults, however, glomerular hypertension causes endothelial, mesangial and podocyte injuries, which ultimately results in glomerulosclerosis. This decreases the number of functioning nephrons and further elevates Pgc, thereby resulting in a vicious cycle. Thus, clini-
cal pictures of glomerular hypertension would be the presence of more proteinuria from an early stage, faster decline in renal function, and glomerulosclerosis but not arteriosclerosis seen in essential hypertension. Glomerular hemodynamics is important in the pathophysiology of hypertension, particularly it greatly influences the mode of progression of renal dysfunction. It is therefore important to understand first the basic mechanisms that regulate glomerular hemodynamics, second alterations and possible mechanisms that lead to progression of renal dysfunction.

**Mechanisms that control the glomerular hemodynamics**

The $P_{GC}$ is controlled very precisely by well balanced constriction and dilation of the afferent and efferent arterioles. Four mechanisms, namely sympathetic nervous system, myogenic response (Fig 2), macula densa-mediated tubuloglomerular feedback (TGF, Fig 3) and various local hormones, operate at the JGA to control the $P_{GC}$. Among these, two intrinsic mechanisms, the myogenic response and TGF, operate mainly the afferent arteriolar vascular resistance. (In addition, presence of connecting tubular glomerular feedback (CTGF), which precisely tunes TGF-induced afferent arteriole constriction by sensing NaCl concentration at the connecting tubule has recently been demonstrated. In order to study the myogenic response and TGF in detail, we have developed preparations of isolated microperfused afferent arteriole alone, or together with the macula densa. We have found that increasing luminal pressure of the afferent arteriole caused constriction at the proximal segment (myogenic response), while increasing NaCl concentration at the macula densa caused constriction at the terminal segment of the afferent arteriole (TGF). Indeed, when the Cl$^-$ concentration near the macula densa and the proximal tubular pressure (an index of single nephron GFR) were measured simultaneously in the same nephron, it was found that they oscillate in a synchronous fashion at a rate of 2 times per minute, and that any small changes in Cl$^-$ concentration are immediately followed by changes in pressure in an opposite direction. This is most likely due to a fine tuning of afferent arteriolar resistance at the distal end. Thus, the myogenic response and the TGF exist in serieses along the afferent arteriole. The myogenic response is the first to respond to changes in systemic pressure, and any changes that cannot be prevented by the myogenic response are now well compensated by the TGF in a single cycle. This perhaps is the reason why the kidney exhibits very efficient autoregulation over a wide range of systemic blood pressure.

On the other hand, efferent arteriole does not exhibit myogenic response, and there are uncertainties about the role of macula densa in the regulation of efferent arteriolar resistance (although Ren et al have provided some data suggesting it). Possible important mechanisms
are autocoids, among which angiotensin II (Ang II) is well-known and studied extensively. When we studied the effect of Ang II in isolated afferent and efferent arterioles, we found stronger constriction in the efferent than in the afferent arteriole. The higher sensitivity of efferent arteriole to Ang II may be due, at least in part, to the lack of modulation by nitric oxide (NO), since L-NAME (an inhibitor of NO synthase; NOS), enhanced Ang II action only in the afferent arteriole. Indeed, it was recently shown that NADPH oxidase (NOX; the main source of superoxide (O$_{2}^{-}$) in vascular tissue) 2 is necessary for the full vasoconstrictor actions of Ang II on afferent arteriole.

**Mechanisms for altered glomerular hemodynamics in hypertension**

1. **Salt-resistant hypertension**

   Consistent with micropuncture studies in SHR, the estimated $P_{oc}$ is within the normal range in human salt-resistant hypertension. It has been reported that during the developmental phase of hypertension in SHR both the myogenic response and the TGF are exaggerated, contributing to the elevated afferent arteriolar resistance. It has recently been demonstrated that activation of NOX and increased superoxide (O$_{2}^{-}$) production contribute to the exaggerated myogenic response during development of hypertension. In addition, cytochrome P-450 (CYP-450)-dependent metabolites of arachidonic acids may also be involved. Imig et al.

   Thus, it is possible that altered CYP-450-dependent metabolism of arachidonic acids may play a role in the exaggerated myogenic response in SHR during development of hypertension.

   On the other hand, Ang II, neuronal NOS (nNOS) and oxidative stress at the macula densa have been implicated in the exaggerated TGF response in SHR. In addition to these factors, Brannstrom and Arendshorst have demonstrated the involvement of thromboxane A$_{2}$ (TxA$_{2}$), which is increased in SHR kidney, in the enhanced TGF activity in young (7-week old) SHR. They found that synthesis inhibition or receptor blockade of TxA$_{2}$ attenuates the enhanced TGF activity close to that observed in normal rats. Thus, increased endogenous TxA$_{2}$ is likely to contribute to the enhanced TGF activity in young SHR, promoting the development of hypertension. It may also be possible that TxA$_{2}$ mediates Ang II-induced enhancement of TGF activity, since Ang II stimulates the renal production of TxA$_{2}$. In addition to such alterations in intrinsic mechanisms, renal vascular response to Ang II is known to be exaggerated during the development of hypertension in SHR. Such exaggerated responses to Ang II may be responsible, at least in part, for the elevated pre-glomerular vascular resistance in young SHR. The increased endogenous TxA$_{2}$ is likely to contribute to the enhanced TGF activity in young SHR, promoting the development of hypertension. It may also be possible that TxA$_{2}$ mediates Ang II-induced enhancement of TGF activity, since Ang II stimulates the renal production of TxA$_{2}$.

   In addition, increased renal production of TxA$_{2}$ has been demonstrated in SHR afferent arterioles before the development of hypertension (4- to 5-week old) compared with age-matched WKY. It is unlikely that increased AT$_{1}$ receptor levels can be responsible for the exaggerated afferent arteriolar Ang II responsiveness because upregulation of renal vascular AT$_{1}$ receptors was not observed in SHR. Instead, exaggerated Ang II reactivity in SHR has been attributed to an impaired buffering capacity of prostaglandins (PGs) associated with a decreased cAMP production. Arrendshorst et al.

   Cyclooxygenase inhibition with indomethacin abolished the strain differences in Ang II action between SHR and WKY, and suggested an involvement of impaired buffering effect of vasodilator PGs. On the other hand, we have previously demonstrated an impaired function of the AT$_{2}$ receptor in SHR afferent arterioles before the development of hypertension. Since activation of AT$_{2}$ receptor in afferent arterioles causes endothelium-dependent vasodilation by stimulating the release of EETs and modulates the vasoconstrictor actions of Ang II mediated by AT$_{1}$ receptor, impaired function of AT$_{2}$ receptor would account, at least in part, for the difference in Ang II action between SHR and WKY afferent arterioles. In addition, we have also suggested a possibility that in the afferent arterioles activation of AT$_{1}$ receptor stimulates the production of 20-HETE, which in turn mediates the vasoconstrictor action of Ang II on this vascular segment. Thus, increased renal
production of 20-HETE (during development of hypertension) may also be responsible for the exaggerated vasoconstrictor action of Ang II in SHR afferent arterioles.

2. Salt-sensitive hypertension

The glomerular hypertension seen in diabetes and renal diseases can be due to either decreased afferent arteriolar resistance or increased efferent arteriolar resistance, or both. In diabetes, the pathogenesis of glomerular hemodynamic abnormalities that cause glomerular hypertension is multifactorial. Elevated efferent arteriolar resistance may be due to an increased intrarenal renin-angiotensin system or decreased vasodilator substances such as NO or PGs. On the other hand, impaired calcium/potassium channels in vascular smooth muscle cells, several humoral factors (such as atrial natriuretic peptide, NO or insulin) and attenuated intrinsic mechanisms (myogenic response and TGF) are thought to be involved in the decreased afferent arteriolar resistance.

Among them, Hayashi et al demonstrated an involvement of vasodilator PGs in the pathogenesis of attenuated myogenic responses. Using the isolated perfused hydrenephrotic kidney technique, they found that inhibition of PG synthesis normalized the (attenuated) myogenic response of diabetic afferent arterioles.

Several hormonal and autocrine systems (including the renin-angiotensin and PG systems) have been involved in the pathophysiology of salt sensitivity. Suppression of the renin-angiotensin system is one important mechanism for both the immediate and long-term increase in sodium excretion following the increased sodium intake. Hall et al have demonstrated in the dog that when the activity of the renin-angiotensin system cannot be modulated, blood pressure becomes salt-dependent. In accordance with this finding, several studies have reported that plasma renin activity is inappropriately suppressed in patients whose blood pressure increases on a high sodium diet, and that the blunted renin response correlates with a diminished salt-induced renal vasodilation. In patients with impaired renal function, the rate of sodium excretion per nephron increases, as evidenced by an exaggerated fractional sodium excretion. In addition, the fractional sodium excretion was found to correlate positively with the rate of urinary excretion of PGE\textsubscript{2}, a major cyclooxygenase metabolite of arachidonic acids in the kidney, in patients with chronic glomerulonephritis. This finding suggests that the renal PG system plays an important role in the control of excretory functions of residual nephrons.

This notion is supported by the study of Kennedy et al demonstrating a development of salt-sensitive hypertension in mice with targeted disruption of the EP\textsubscript{2} receptor, which mediate vasodilator actions of PGE\textsubscript{2}. Thus, it is thought that PGE\textsubscript{2} facilitates the ability of the kidney to increase sodium excretion, thereby protecting systemic blood pressure from a high-salt diet, and that impaired function of PG system (especially PGE\textsubscript{2}) contributes to the development of salt-sensitive hypertension.

It may be also possible that sodium depletion increases the renal level of PGs, which in turn affects glomerular hemodynamics and tubular functions, resulting in reduced systemic blood pressure. It is interesting to note that in salt-sensitive hypertension in humans and animals, RBF does decrease upon salt-loading, which may contribute to salt-retention and development of hypertension. Such decreases in RBF are associated with increases in P\textsubscript{CC}, which are attributed to increased efferent arteriolar resistance. In order to define the role of PGs in the control of glomerular microcirculation, we developed in vitro preparations in which isolated effenter arterioles are perfused either from the end of afferent arterioles through the glomerulus (orthograde perfusion, Fig 4 top) or from their distal end (retrograde perfusion, Fig 4 bottom).

Since the efferent arteriolar perfusate passes
through the glomerulus only in orthograde perfusion, vasoactive substances released by the glomerulus could modulate vascular reactivities in the downstream efferent arteriole. We found both Ang II and norepinephrine (NE) cause much weaker constriction of the efferent arteriole in orthograde than in retrograde perfusion, while inhibition of PG synthesis with indomethacin augmented the vasoconstriction only in orthograde perfusion (Fig 5). These results suggest that the glomerulus may control its own capillary pressure (and hence the rate of ultrafiltration) by releasing PGs and thereby adjusting the resistance of the downstream efferent arterioles. Thus, it is speculated that sodium depletion may increase glomerular synthesis of PGs, which in turn dilate the efferent arterioles. Thus, in the setting of salt-sensitive hypertension, Ang II- or NE-induced efferent arteriolar constriction may become stronger because of an impaired buffering effect of PG together with an inappropriate suppression of renal Ang II and an activated sympathetic nervous system.

Conclusion

In conclusion, the glomerular hemodynamics seems to be very important not only for the pathogenesis of hypertension but also the progression of renal dysfunction in various renal diseases. In salt-resistant essential hypertension, P_{GC} is normal with a significant constriction of pre-glomerular arterioles, whereas in various renal diseases P_{GC} is elevated. There is substantial evidence that glomerular hypertension plays an important role in the pathogenesis glomerulosclerosis, thereby contributing to the progressive nature of the decline in renal function in various renal diseases. Since transmission of systemic blood pressure to the glomerulus is facilitated, strict control of systemic blood pressure would be critical in order to prevent the progression of renal dysfunction. In addition, measures to improve autoregulation (low protein diet) and/or dilate efferent arteriole (inhibition of the renin-angiotensin system) would be important. Thus, understanding the mechanism that regulates glomerular hemodynamics as well as its alterations under various pathological conditions would be important not only for the basic or clinical research but also for a good management of patients with hypertension and/or renal diseases.

References

Cyclooxygenase 1 and 2 and thromboxane synthase in kidneys of Lyon hypertensive rats. Am J Hypertension 13: 404-409


