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Review

Kidney and Hypertension: Role of the Juxtaglomerular Apparatus

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Ito, S. *Kidney and Hypertension: Role of the Juxtaglomerular Apparatus.* Tohoku J. Exp. Med., 1997, **181** (4), 411-429 —— The kidney plays an important role in the pathophysiology of hypertension. Recent studies suggest that glomerular hemodynamics may be critically involved not only in the pathogenesis of hypertension but also in the mode of progression of renal dysfunction. The juxtaglomerular apparatus (JGA), constisting of the glomerular afferent and efferent arterioles and the specialized tubular epithelial cells called the macula densa, plays a central role in the regulation of glomerular hemodynamics and renin release. This article reviews the mechanism by which the JGA controls renin release and glomerular hemodynamics as well as its relevance in the pathogenesis, pathophysiology and treatment of hypertension. ———— afferent arteriole; macula densa; renin; tubuloglomerular feedback

In each nephron of mammalian kidney, the tubule returns to the parent glomerulus, forming the juxtaglomerular apparatus (JGA). The JGA displays a unique arrangement of the glomerular afferent and efferent arteriole, extraglomerular mesangial cells and a plaque of specialized tubular epithelial cells called the macula densa. In the media of the distal afferent arteriole are the granular juxtaglomerular cells containing renin. The JGA has long been known as the site of regulation of renin release and glomerular hemodynamics (Keeton and Campbell 1981), and thereby playing an important role in the control of systemic blood pressure. Recently, the microdissection and perfusion methods have been applied sucussfully to direct assessment of the function of the JGA, significantly contributing to our understanding of the mechanism that controls renin release and glomerular hemodynamics. This review summarizes results obtained from such studies together with other relevant literature and discusses the role of the JGA in hypertension. Only a limited number of references is given.

Hypertension and renal hemodynamics

The kidney plays an important role in the control of systemic blood pressure by regulating the composition of body fluid and electrolytes as well as producing

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and releasing various vasoactive substances. It is well known that in various renal diseases, systemic blood pressure becomes higher as renal function deteriorates, while systemic hypertension aggravates renal dysfunction. Studies have now provided clear evidence that the kidney is important not only as a target organ of hypertension but also as a possible organ that may cause hypertension. Many investigators have demonstrated that when genetically hypertensive animals are nephrectomized bilaterally and transplanted with a kidney from normotensive control animals, they become normotensive. Conversely, when normotensive animals receive a kidney of hypertensive animals, they become hypertensive (Uber and Retting 1996). Moreover, Curtis et al. (1983) reported that hypertension seen in patients with chronic renal failure caused by essential hypertension was cured, when they were transplanted with kidneys from normotensive donors without family history for hypertension. These studies suggest that the kidney plays an essential role in the long-term control of systemic blood pressure.

In the isolated perfused kidney, an increase in perfusion pressure has been shown to promote natriuresis and diuresis, a phenomenon called "pressure-natriuresis" (Guyton 1980). This would predict that an increase in NaCl intake should be associated with an elevation in renal perfusion pressure (systemic blood pressure) in order to achieve a stady state condition. In normal subjects, however, chronic manipulation of dietary sodium intake has little effect on systemic blood pressure, rendering the slope of the pressure-naturesis curve very steep (Fig. 1). According to the chronic pressure-natriuresis curve, hypertensive subjects can be classified as salt-sensitive and non-salt-sensitive based on their responses to dietary sodium loading. Thus, a parallel rightward shift of the curve and a depression of the slope are the two basic abnormalities seen in the pressure-natriuresis relationship in hypertension, with each representing a different pathophysiology, particularly in terms of renal hemodynamics. A typical example of

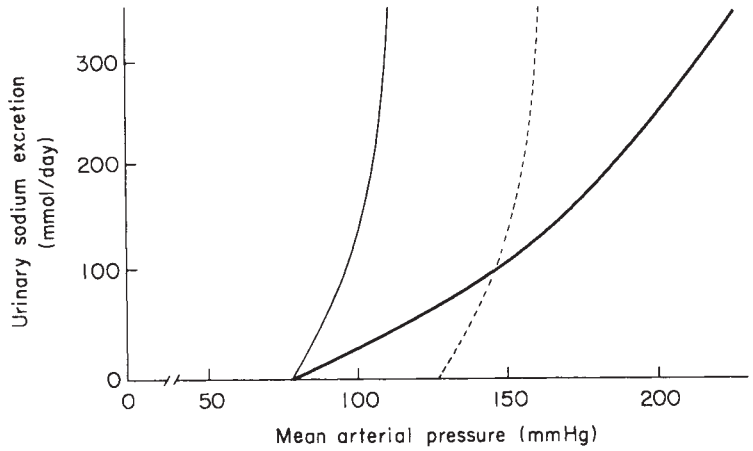

Fig. 1. Pressure-natriuresis relationship. — normal; - - - non-sodium sensitive; — hypertension sodium sensitive.

non-salt sensitive hypertension is essential hypertension without organ damages. In this type of hypertension, renal blood flow and the glomerular filtration rate (GFR) remain within a normal range despite a high systemic blood pressure, indicating an elevated renal vascular resistance. Micropuncture studies in the spontaneously hypertensive rat (SHR), and its normotensive control, Wistar Kyoto (WKY) rat have demonstrated that glomerular capillary pressure is the same despite a higher systemic blood pressure in SHR (Arendshorst and Beierwaltes 1979). Thus an increased vascular resistance is localized only to the preglomerular vasculature. Calculation of glomerular capillary pressure using the Gomez's equation also suggests that in human essential hypertension glomerular capillary pressure is within the normal range, with increased preglomerular resistance (Kimura et al. 1991). Among various preglomerular vascular segments, the afferent arteriole is likely to be the major contributor to the elevated vascular resistance.

The issue of whether increases in afferent arteriolar resistance can cause hypertension remains still unanswered. Using the F_2 generation of cross-bred of SHR and WKY, Nørrelund et al. (1994) examined relationship between afferent arteriolar diameter of one kidney removed at the age of 7 weeks and systemic blood pressure measured at the age of 23 weeks in the same animals. They found that the smaller the diameter at 7 week, the higher the blood pressure measured at 23 week. These data suggest that constriction of afferent arteriole may indeed be involved in (or, at least a predictor of) later development of systemic hypertension.

Salt-sensitive hypertension is characterized by the inability of the kidney to excrete unnecessary amounts of sodium loaded to the body. This may be caused by 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 glomerular capillary pressure and therefore an increase in the GFR. With such increases in GFR, more sodium is loaded to the tubules, maintaing sodium balance. Thus in salt-sensitive hypertension, glomerular hypertension is a common feature regardless of the cause of hypertension, such as diabetic nephropathy, primary aldosteronism, chronic glomerulonephritis and essential hypertension seen in black populations (Kimura et al. 1994). Since glomerular hypertension contributes significantly to glomerular damages, renal function declines more rapidly in salt-sensitive types of hypertension than non-salt-sensitive types in which glomerular capillary pressure is normal. Taken together, those and other studies indicate that glomerular hemodynamic are important not only for the genesis of hypertension but also for the mode of progression of renal dysfunction.

JGA and renal hemodynamics

It is now clear that the JGA plays a central role in the control of glomerular

hemodynamics by regulating resistance of the afferent and efferent arterioles as well as renin release. Four mechanisms operate at the JGA to control glomerular hemodynamics: 1) myogenic response, 2) tubuloglomerular feedback (TGF), 3) the sympathetic nervous system and 4) various systemic and local hormones. In the absence of systemic hemodynamic changes, selective constriction of the afferent arteriole would not only decrease the rate of plasma flow entering the glomerulus, but also pressure within the glomerulus, a primary physical force for glomerular ultrafiltration. On the other hand, constriction of the efferent arteriole would increase glomerular capillary pressure, hence the glomerular filtration fraction (FF), calculated as GFR/renal plasma flow. In addition, the GFR can rise even in the absence of changes in glomerular capillary pressure when glomerular plasma flow is increased, as seen with balanced dilation of the afferent and efferent arteriole (Dworkin and Brenner 1992). Thus the balance of vascular tone of the afferent arteriole and efferent arteriole would critically affect the GFR and, hence, renal excretory function.

The GFR and renal blood flow are maintained at a constant level over a wide range of renal perfusion pressure (autoregulation). Such stability of GFR seems to be the basic requirement for a complex tubular system to function in a well-integrated manner and hence maintain homeostasis of body fluid and electrolytes. The myogenic response and TGF are the two intrinsic mechanisms for renal autoregulation. Micropuncture studies have demonstrated that changes in the composition of tubular fluid in the distal nephron affect the rate of glomerular ultrafiltration at the level of single nephron, a phenomenon called the TGF (Thurau et al. 1982). Indeed, when the distal Cl^- concentration and the proximal tubular pressure, an index of single nephron GFR were measured simultaneously,

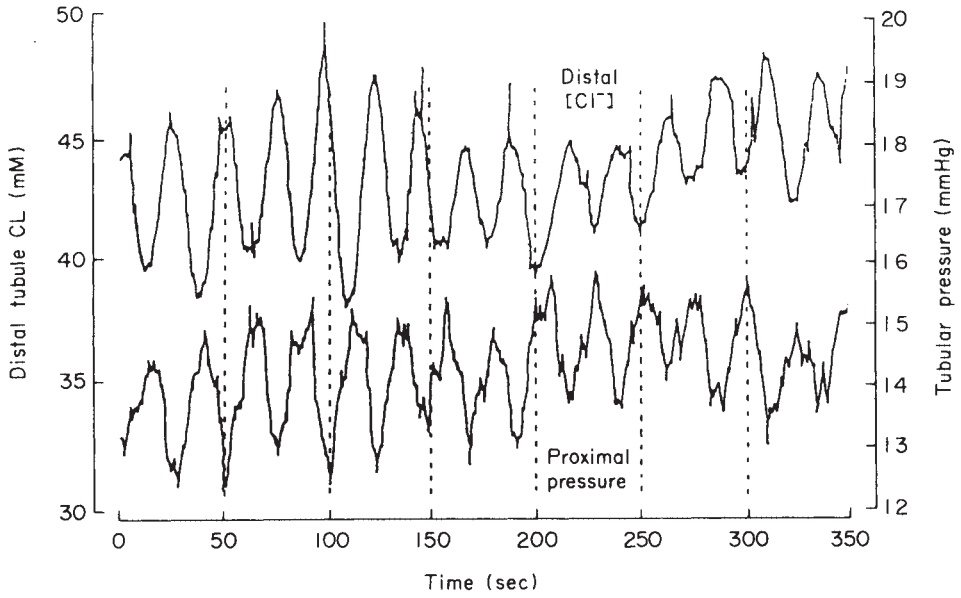

Fig. 2. Simultaneous measurement of early distal tubule Cl^- concentration and proximal tubule hydrostatic pressure in the same nephron.

they were found to oscillate synchronously, with an increase in the Cl^- being associated with an decrease in the pressure (Fig. 2) (Holstein-Rathlow and Marsh 1989). Thus it appears that the TGF is an exquistly intricate mechanism for maintaining the constant GFR at the single nephron level. In the myogenic response, the afferent arteriole responds to changes in perfusion pressure per se, with increased pressure causing constriction which prevents a rise in glomerular capillary pressure. It should be noted that the myogenic response exists only in the afferent arteriole but not in the efferent arteriole. It has been proposed that stretch-activated calcium channels are involved in the myogenic response.

In order to study the myogenic response and TGF directly, we developed in

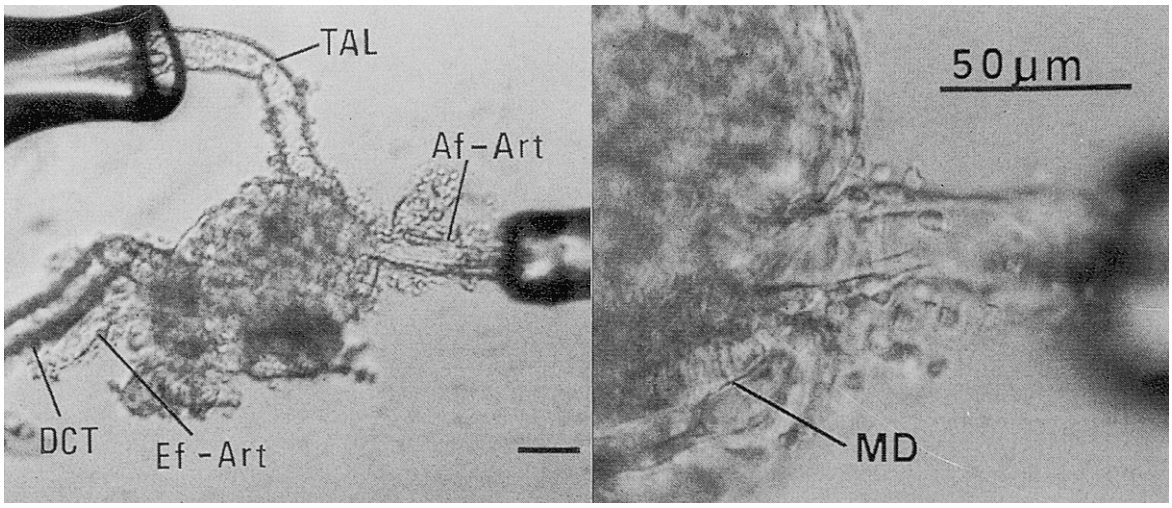

Fig. 3. (a) Simultaneous perfusion of an afferent arteriole (Af-Art) and attached macula densa (MD). Ef-Art, efferent arteriole; DCT, distal convoluted tubule; TAL, thick ascending limb of loop of Henle. (b) After perfusion has been established, both the MD and distal Af-Art can be visualized.

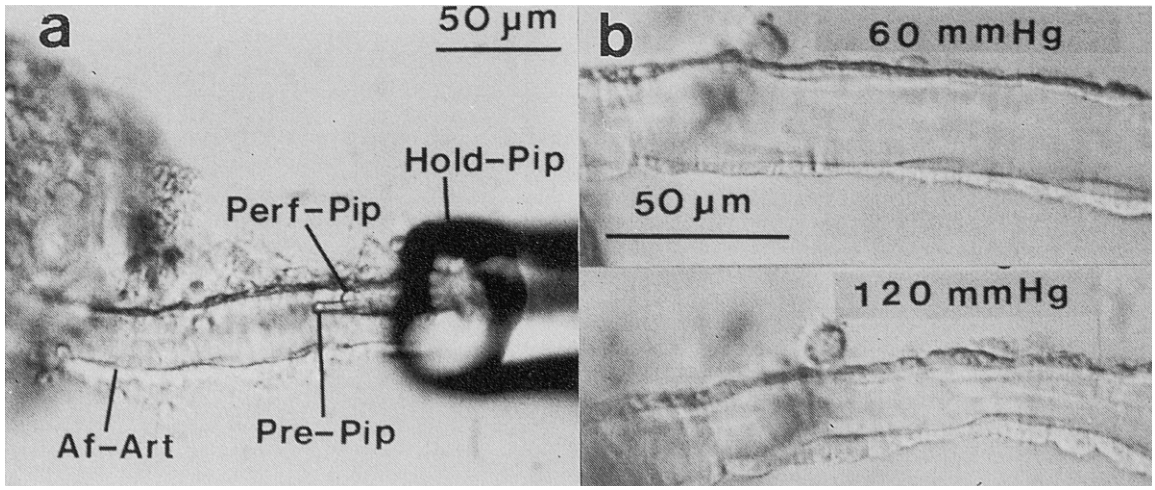

Fig. 4. Isolated microperfused afferent arteriole (Af-Art) (a) and myogenic response (b). Hold-Pip, Holding pipette; Perf-Pip, Perfusion pipette; Pre-Pip, Pressure pipette.

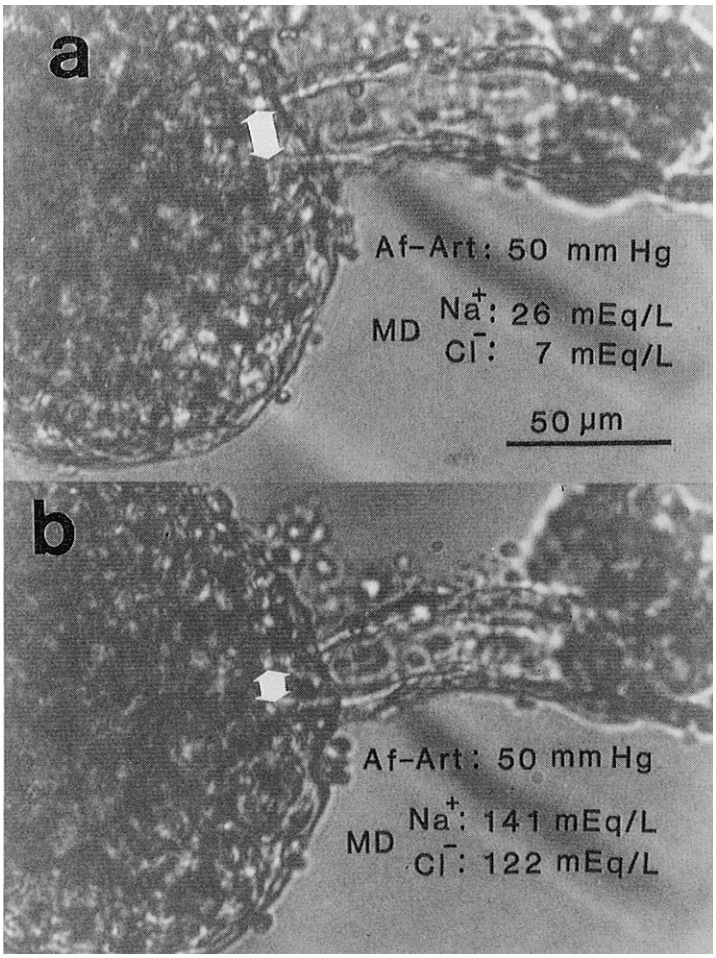

Fig. 5. Afferent arteriolar constriction induced by high NaCl at the macula densa (MD). When Na^+ and Cl^- concentrations at the MD were increased from 26 and 7 mEq/liter (a) to 141 and 122 mEq/liter (b) respectively, the distal segment of the afferent arteriole constricted significantly.

vitro preparations in which microdissected afferent arterioles are perfused either alone or together with the attached macula densa simultaneously (Figs. 3 and 4) (Ito and Carretero 1990; Ito et al. 1992). We found that afferent arterioles become constricted significantly when either intraluminal pressure of the afferent arteriole or NaCl concentration at the macula densa was elevated (Figs. 3 and 5), demonstrating the myogenic response and the TGF, respectively. Of note is the fact that the myogenic response and the TGF exist in series along the afferent arteriole, with the former being in the more proximal and the latter in the terminal segment. Thus the myogenic response is the first to respond to changes in renal perfusion pressure in order to prevent changes in glomerular capillary pressure, while any changes in GFR that are not prevented by the myogenic response are reflected as changes in NaCl concentration at the macula densa, with the subsequent tuning of the distal segment by TGF. Such interactions of the myogenic response and TGF enable the kidney to achieve the most efficient autoregulation as compared with any other organs in the body.

The myogenic response and TGF are found to be altered in various forms of

hypertension. The myogenic response is attenuated in Dahl salt-sensitive rats and in diabetic rats, permitting transmission of systemic blood pressure to the glomerulus and causing glomerular hypertension (Hayashi et al. 1992; Takenaka et al. 1992). On the other hand, we (Ito and Carretero 1990) and Hayashi et al. (1989) reported that the myogenic response is exaggerated in SHR. The TGF has also been shown to be exaggerated in SHR and Milan hypertensive rats, so that at a same NaCl concentration reaching the macula densa, the single nephron GFR becomes less due to stronger constriction of the afferent arteriole as compared with their normotensive controls (Leyssac and Holstein-Rathlow 1989; Brannstrom et al. 1996; Thorup and Persson 1996). Together with the exaggerated myogenic response, such alterations in the TGF may contribute to the elevated preglomerular vascular resistance seen in SHR.

Role of nitric oxide and angiotensin II in renal hemodynamics

Nitric oxide (NO) and angiotensin II (Ang II) play important roles in the control of the renal functions. Infusion of Ang II or inhibition of its action in the kidney has been shown to result in an increased or decreased filtration fraction, respectively (Davalos et al. 1978; Kastner et al. 1984). Thus it has been postulated that sensitivity to Ang II is higher in the efferent than afferent arterioles. Indeed, using in vitro microperfusion methods, we and others has demonstrated that sensitivity to Ang II is much higher or exclusively present in efferent arterioles (Edwards 1983; Yuan et al. 1990; Ito et al. 1993). The mechanism for such differences in the sensitivity seems to be that both endogenous NO and prostaglandins (PGs) modulate Ang II action much stronger in the afferent than efferent arterioles (Schor et al. 1980; Ito et al. 1993; Arima et al. 1994). However,

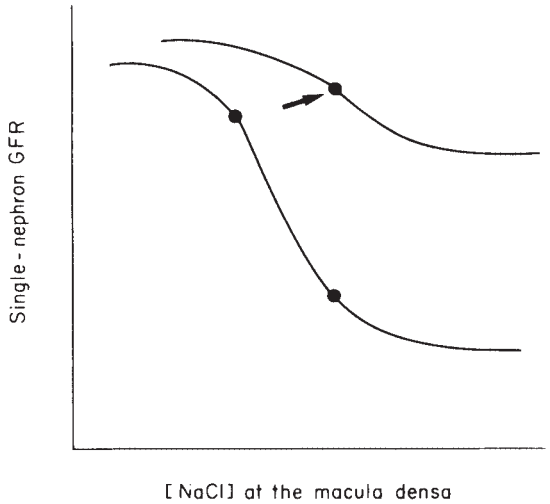

Fig. 6. Tubuloglomerular feedback. When the NaCl concentration at the macula densa increases, the single-nephron glomerular filtration rate decreases, primarily due to constriction of the afferent arteriole. Volume expansion shifts the tubuloglomerular feedback response curve to the right.

there may be a significant interaction between PGs and NO in modulating Ang II action, since there was no additional effect over inhibiting either one alone (Arima et al. 1994).

Experiments have shown that during volume expansion, the tubulogomerular feedback response curve shifts to the right (Fig. 6) and renin release decreases (Haberle and David 1984). As the efferent arteriole is more sensive to Ang II than the afferent arteriole, decreased Ang II dilates it preferentially, thereby increasing RBF and decreasing the filtration fraction. This results in decreased oncotic pressure and increased hydrostatic pressure in peritubular capillaries, which in turn inhibits fluid reabsorption (Wilcox et al. 1992b). In addition, decreased Ang II attenuates Na reabsorption in the proximal tubule. As a result, Na reabsorption in the tubular segments proximal to the macula densa decreases, resulting in increased NaCl delivery to the macula densa, which in turn would constrict the afferent arteriole. However, owing to the rightward shift of the tubuloglomerular feedback response curve (Fig. 6), the GFR does not change significantly, allowing continued excretion of NaCl. While the mechanism of such resetting is not completely understood, evidence suggest that both Ang II and NO may be important (Navar and Rosivall 1984; Schnermann and Briggs 1986; Wilcox et al. 1992a). Indeed, microperfusing both the afferent arteriole and the macula densa simultaneously, we have shown that selective inhibition of NO within the macula densa augments vasoconstriction induced by high NaCl at the macula densa (Fig. 7) (Ito and Ren 1993), while afferent arteriolar constriction induced by Ang II is much weaker when NaCl at the macula densa was low (Fig.

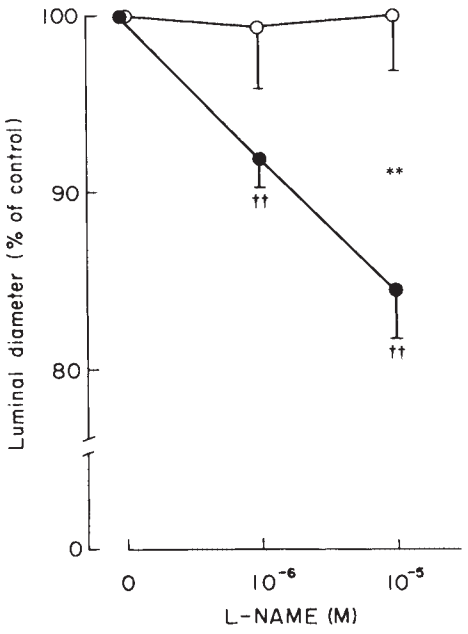

Fig. 7. Changes in afferent arteriolar diameter induced by NG-nitro-L-arginine methyl ester (*L-NAME*), an inhibitor of NO synthase, added to high-NaCl (●, $n=10$) or low- NaCl macula densa perfusate (○, $n=7$). $^{**}p<0.01$ compared with low NaCl; $\dagger\dagger p<0.01$ compared with control.

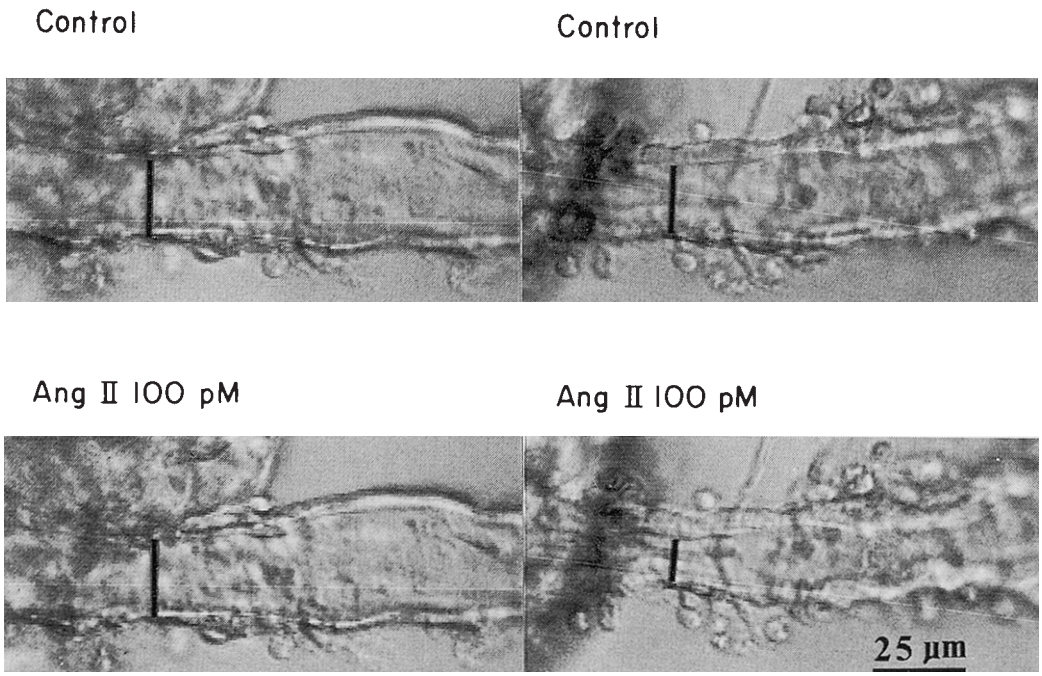

Fig. 8. Afferent arteriolar constriction induced by 100 pmol/liter Ang II with low (left) or high (right) NaCl concentration at the macula densa (MD). Note that 100 pmol/liter Ang II caused stronger constriction of the afferent arteriole with high NaCl at the macula densa.

8) (Ren et al. 1996).

In order to study the roles of luminal flow, the endothelium, NO and PGs in the myogenic response and Ang II action, we perfused two afferent arterioles simultaneously, one with free flow and the other without (Fig. 9) (Juncos et al. 1995a, b). We found both the myogenic response and Ang II action were significantly weaker in the presence of luminal flow, with the differences beeing abolished by either removing the endothelium (Fig. 10) or inhibiting NO synthesis. Indomethacin was found to be without effect on the myogenic response, whereas it augmented Ang II action significantly. These results suggest that flow stimulates the endothelium to release NO, which in turn attenuate both myogenic response and Ang II action in the afferent arteriole.

Since NO attenuates both TGF and the myogenic response, it may be predicted that inhibition of NO synthesis would decrease RBF and GFR to a greater extent when renal perfusion pressure is high. However, most studies have found that autoregulation is well maintained (but at a lower RBF) during NO synthesis inhibition (Majid and Navar 1992). While the reason for this discrepancy is unknown, other compensatory mechanisms may be capable of maintaining RBF in vivo in normal animals. It may be that due to possible modulation of the glomerular-tubular balance and increased sodium reabsorption by tubular segment proximal to the macula densa, sodium chloride concentration at the macula densa may fall significantly, so that tubuloglomerular feedback contributes less to renal autoregulation. On the other hand, the importance of flow- or

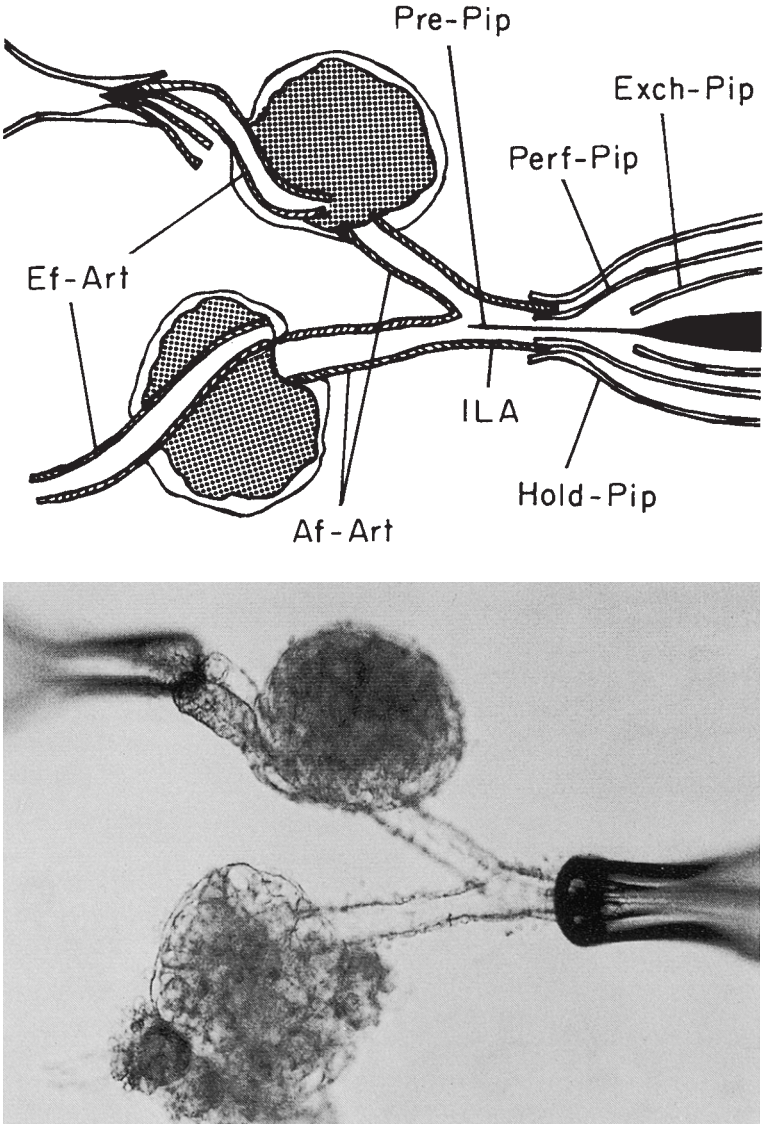

Fig. 9. Schematic representation (top) and photograph (bottom) of the double afferent arteriolar preparation. Hold-Pip, holding pipette; Perf-Pip, perfusion pipette; Exch-Pip, exchange pipette; Pre-Pip, pressure pipette; Af-Art, afferent arteriole; Ef-Art, efferent arteriole; ILA, interlobular artery. Note: Since the arteriolar perfusate contained 5% albumin, oncotic pressure builts up in the glomerulus with the occluded Ef-Art and opposes the force of filtration, resulting in little or no flow through the corresponding afferent arteriole. Perfusion pressure was measured at the bifurcation of the interlobular artery using Landis' technique.

shear stress-associated NO release may become more apparent in pathological conditions such as polycythemia rubra vera. In patients with polycythemia, RBF and GFR are often within the normal range despite high blood viscosity (DeWardener et al. 1951), which if left unopposed, results in increased vascular resistance. Since heightened blood viscosity increases shear stress on the endothelium, NO may play an important role in the maintenance of RBF and GFR. Indeed, Wilcox et al. (1993) reported that L-NAME-induced systemic and renal

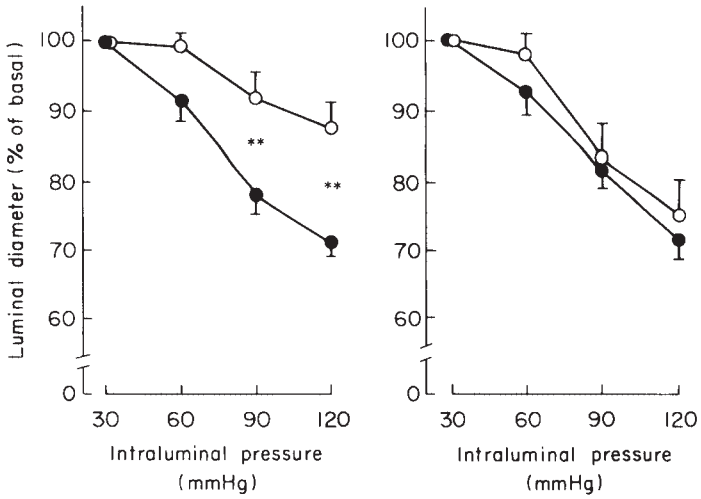

Fig. 10. Pressure-diameter relationships in free-flow (left) and no-flow Af-Arts (right) before (○) and after endothelial disruption (●); $n=7$; $^{**}p<0.01$ for control (○) vs. deendothelialized Af-Arts (●).
Note that endothelial disruption only augmented pressure-induced constriction in free-flow Af-Arts, thus eliminating the difference between free-flow and no-flow Af-Art.

vasoconstriction was greatly augmented in rats with erythropoietin-induced polycythemia.

Renin-angiotensin system

Because of the intimate anatomical relationship between the macula densa

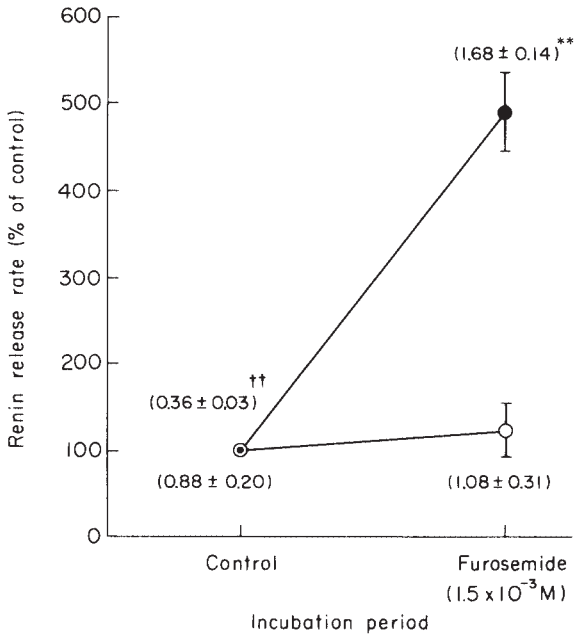

Fig. 11. Effect of furosemide on renin release from afferent arterioles alone (○, $n=6$) and afferent arterioles with macula densa attached (●, $n=7$). Absolute values are presented in parenthesis. $^{**}p<0.01$ compared with control period. $\dagger\dagger p<0.01$ compared with afferent arteriole alone.

and JG cells, it has been proposed that the rate of renin release may somehow be controlled by the ionic composition of the tubular fluid at the macula densa (Goormaghtigh 1945). However, attempts to obtain direct evidence of this have been hindered by the anatomical complexity of the JGA. In order to study the role of the macula densa in renin release, we have developed a unique preparation of microdissected afferent arterioles with or without attached macula densa for the study of renin release (Itoh and Carretero 1985). We found that basal rate of renin release was lower in the afferent arterioles with the attached macula densa than those without, while furosemide stimulated renin release only in the presence of the macula densa (Fig. 11). These findings have demonstrated for the first time that the macula densa indeed participates to the control of renin release. In addition, indomethacin was found to inhibit furosemide-induced and macula densa-mediated renin release in our in vitro preparation. Furthermore, we found that PGE_2 stimulates renin release in the presence but not the absence of the macula densa (Ito et al. 1989). Thus, the renin-stimulating action of furomemide seems to result from a combination of its direct inhibition of Na-K-2Cl co-transporter at the macula densa and increased renal levels of PGE_2 acting within the JGA (Abe et al. 1978). In addition to PGs, adenosine seems to play an important role in the macula densa control of renin release, since the adenosine antagonist theopylline abolished the differences in basal renin release between the presence and the absence of the macula densa in our population (Itoh et al. 1985). The roles of PG and adenosine in the macula densa-mediated renin release have also been demonstrated by other investigators employing the isolated JGA preparation in which the macula densa (but not the afferent arteriole) is perfused (Skott and Briggs 1987; Greenberg et al. 1993; Weihprechet et al. 1990). Finally, we have demonstrated substantial heterogeneities in renin distribution within the kidney in that renin content and release in the superficial nephrons are about 50 $\sim$100 times as much as those seen in the juxtamedullary nephrons in the rabbit (Nushiro et al. 1990; Juncos et al. 1992).

Prostaglandin and renal hemoydnamics

The prostaglandin system is important in the control of renal functions and systemic blood pressure under certain conditions. It has been shown that non-steroidal anti-inflammatory drugs (NSAIDs) have little effect in normal subjects, whereas they often aggravate renal function and cause hypertension in patients with various renal diseases. In addition, urinary PGE_2 excretion was found to be reduced in patients with essential hypertension, suggesting that renal PGs play a role in the pathophysiology of hypertension (Abe et al. 1979). We further assessed the role of PG in the BP and renin responses to sodium depletion in essential hypertension. We found that sodium-depletion decreased BP in low-renin hypertensive patients, with addition of indomethacin abolishing the hypotensive effect (Fig. 12). On the other hand, in normal-renin hypertensive

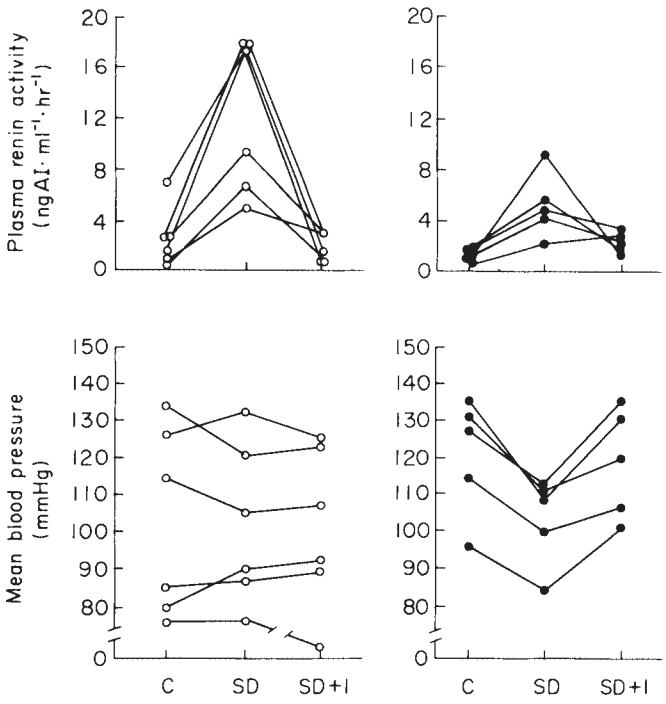

Fig. 12. Effects of sodium depletion (NaCl 90 mEq/day + furosemide 80 mg for three days) and addition of indomethacin (150 mg/day) on blood pressure and plasma renin activity in normal-(○, $n=6$) and low-(●, $n=5$) renin hypertensive patients. C, control period; SD, sodium depletion; SD + I, sodium depletion + Indomethacin.

patients, sodium depletion increased plasma renin activity (PRA) which was returned to basal level upon addition of indomethacin, whereas BP remained unchanged throughout the study. Thus PGs seems to be important in both renin release and pathophysiology of low-renin essential hypertension. However, it is not clear how PGs are involved in the salt-sensitivity of blood pressure. It may be that sodium depletion increases the renal level of PGs, which in turn affect glomerular hemodynamics and tubular functions, resulting in reduced BP. It is interesting to note that in salt-sensitive hypertension in human and animals, renal blood flow does decrease upon salt-loading, which may contribute salt-retention and hypertension (Campese 1994). Such decreases in renal blood flow are associated with increased in glomerular capillary pressure, which are attributed to increased efferent arteriolar resistance.

In order to define the role of PG in glomerular microcirculation, we developed in vitro preparations in which isolated efferent arterioles were pufused either from its distal end (retrograde perfusion) or from the end of the afferent arteriole through the glomerulus (orthograde perfusion) (Arima et al. 1994). Since the efferent arteriolar perfusate passes through the glomerulus only in the orthograde perfusion, vasoactive substances released by the glomerulus could modulate vascular reactivities in the down-stream efferent arteriole (Fig. 13). We found that both Ang II and NE caused much weaker constriction of the efferent arteriole in orthograde than retrograde perfusion, while inhibition of PG synthesis with

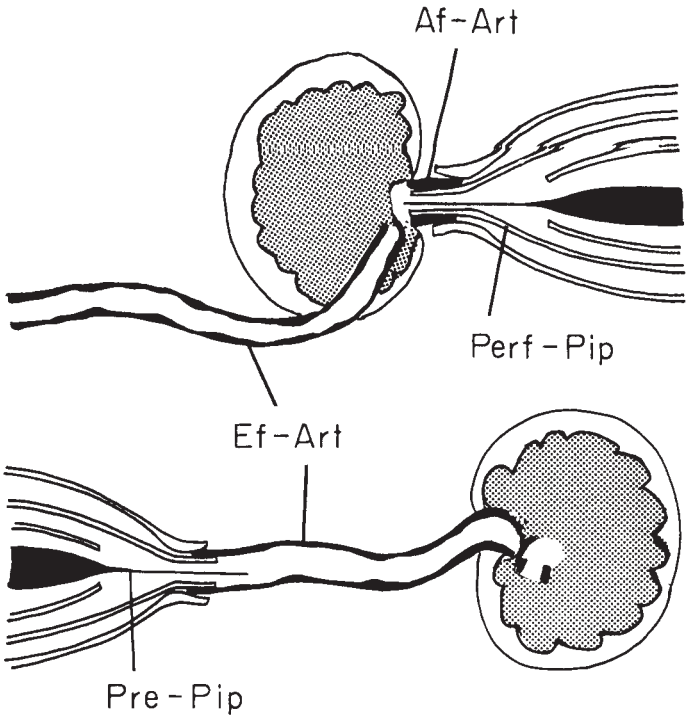

Fig. 13. Schematic illustration of orthograde and retrograde perfusion of the afferent arteriole (Ef-Art). The two filled pipettes (Pre-Pip) are for measurement of pressure. Af-Art, afferent arteriole.

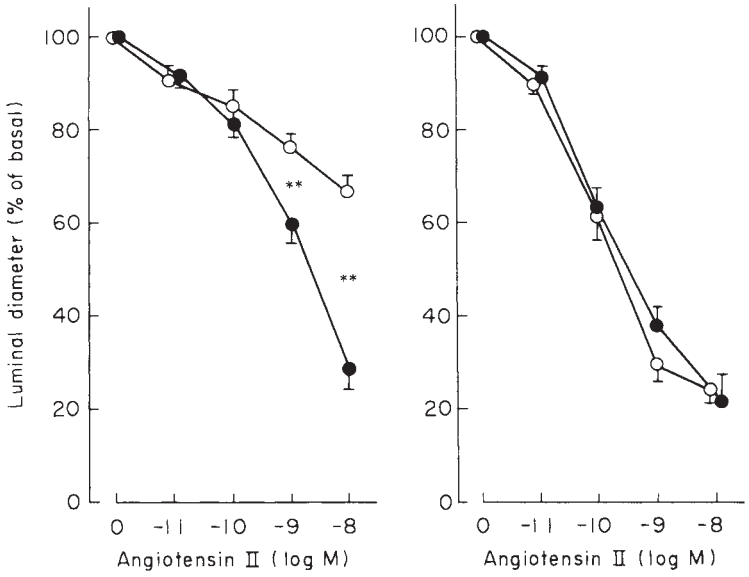

Fig. 14. Effect of angiotensin II in vehicle-treated efferent (○) or indomethacin-treated (●) afferent arterioles with orthograde (left: ○, $n=9$; ●, $n=8$) and retrograde (right: ○, $n=5$; ●, $n=5$) perfusion. $^{**}p<0.01$ compared with vehicle-treated arterioles (○). Note that indomethacin pretreatment significantly augmented angiotensin II-induced vasoconstriction in afferent arterioles with orthograde but not retrograde perfusion.

indomethacin augmented the vasoconstriction only in the orthograde perfusion (Fig. 14). These results suggest that in addition to controlling afferent arteriolar resistance, PGs produced by the glomerulus, can modulate efferent arteriolar resistance. This may be a novel mechanism by which the glomerulus may control its own capillary pressure (and hence the rate of ultrafiltration) by adjusting the resistance of the downstream efferent arterioles. It may be speculated that sodium depletion may increases glomerular synthesis of PGs, which would dilate the efferent arterioles. Such dilation of the efferent arteriole would be strong, particularly in low-renin hypertension, since renin release and hence intrarenal Ang II levels (a predominant regulator of efferent arterioles resistance) are unresponsive to sodium depletion.

Effect of anti-hypertension drugs on renal hemodynamics

Systemic hypertension is often associated with various renal diseases and is a risk factor for renal failure. It is now clear that management of systemic blood pressure is an important means of treating progressive renal disease. When renal injury occurs and the number of functional nephrons decreases, the remaining nephrons undergo a series of compensatory changes (both functional and structural), including hypertrophy and hyperfiltration. Studies have suggested that such adaptational changes are actually linked to progressive loss of renal function. Brenner et al. (1982). have provided evidence that glomerular hypertension may cause glomerular sclerosis, leading to further loss of functional nephrons. These findings suggest that it may be important to treat not only systemic hypertension, but also glomerular hypertension in order to conserve renal function. Thus understanding the mechanism of action of various anti-hypertensive drugs as well as their influences on glomerular hemodynamics is imperative in order to select adequate drugs for the treatment of hypertension with various degrees of renal dysfunction (Ito and Abe 1997).

Clinical studies have proven that angiotensin converting enzyme inhibitors (ACEi) retard the rate of progression of renal function in diabetic nephropathy (Lewis et al. 1993). Recent studies suggest that they may be beneficial in other renal diseases as well (Maschio et al. 1996). ACEi block the conversion of angiotensin I to Ang II, thereby reducing systemic blood pressure. Studies using isolated microperfused afferent and efferent arterioles, have shown that the efferent arteriole is more sensitive to Ang II than the afferent arteriole. Thus, ACEi preferentially dilate the efferent arteriole and hence reduce glomerular capillary pressure. However, the GFR would change much less than would be accounted for by a fall in glomerular capillary pressure, since ACEi increase both renal blood flow and ultrafiltration coefficient. In addition, ACEi inhibit cell proliferation and hypertrophy as well as accumulation of extracellular matrix. Thus, the renoprotective effect of ACEi would be expected independently of the level of systemic blood pressure. Indeed our recent clinical study involving

patients with chronic glomerulonephritis suggests that this is the case (Omata et al. 1996).

Calcium antagonists inhibit calcium influx through voltage-sensitive calcium channels, thereby relaxing vascular smooth muscle cells and reducing systemic blood pressure. It has been shown that voltage-sensitive calcium channels are critically involved in afferent arteriolar constriction induced by virtually all mechanisms, including the myogenic response and TGF. Indeed we have shown that calcium antagonists dilate isolated microperfused afferent arterioles preconstricted with norepinephrine (Arima et al. 1996). Such dilation of the afferent arteriole renders glomerular capillary pressure dependent on systemic blood pressure. Thus glomerular capillary pressure would be reduced or normalized only when systemic blood pressure is well controlled. This may explain the equivocal efficacy of calcium antagonists in conserving kidney function in clinical studies (Maki et al. 1995), even though animal studies suggest that they exert a renoprotective effect by inhibiting hypertrophy (Dworkin et al. 1993). Interestingly, we found that when patients with chronic glomeruler nephritis were treated with calcium antagonists, poor control of systemic hypertension was associated with progression of renal dysfunction, while controlling blood pressure to low normal levels improved renal function (Omata et al. 1996). This results may suggest that renoprotective effect of calcium antagonist is indeed pressure-dependent.

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