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Prevention and Regression of Chronic Kidney Disease and Hypertension

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1. Introduction

Chronic kidney disease (CKD) is a disease which is characterized by the presence of renal damage or decreased GFR for at least 3 months. The prevalence of CKD in the US has been reported to be 3.3% (stage 1), 3.0% (stage 2), 4.3% (stage 3), 0.2% (stage 4), and 0.1% (stage 5) (Levey et al., 2003; 2002). Because of the increasing elderly population in industrial countries, the development of new strategies for the prevention and regression of CKD is important.

Clinical studies have suggested that renin-angiotensin system (RAS) inhibitors can exert a renoprotective effect independent of blood pressure, and attenuate the progression of renal dysfunction (Bakris, 2010; Berl, 2009; Stojiljkovic et al., 2007). Recent studies have suggested that the use of RAS inhibitors, when combined with other treatment modalities such as aggressive blood pressure control, lowering of blood lipids, tight glucose control for diabetics, and lifestyle changes may cause remission of albuminuria, and stabilization or even reversal of the decline in GFR, i.e. regression of CKD in some patients (Aros et al., 2002; Macconi, ; Ruggenenti et al., 2008).

These early clinical findings are important, because they suggest that appropriate interventions may be effective for causing an improvement in renal function, which raises the hope that a 'cure' for CKD may eventually be found in the future. In our laboratory, we have been examining the molecular mechanisms involved in the pathogenesis of CKD and hypertension. Our underlying concept is that both these diseases are highly related, and share common pathophysiological mechanisms, including the abnormal accumulation of extracellular matrix proteins in the kidney. The result is glomerulosclerosis, when the matrix accumulates in the renal glomeruli, and renal arteriosclerosis, when the matrix is deposited in the renal arterioles and small vessels. In this chapter, we will review the evidence from our and other laboratories that these processes may be reversed in animal models, and possibly in humans.

2.1 Studies on CKD prevention

Regardless of the initial injury, most causes of CKD (including diabetic nephropathy, and chronic glomerulonephritis) share several common pathological features, one of which is the development of glomerular scarring or glomerulosclerosis.

Stage	Description	GFR
1	Kidney damage with normal or ↑GFR	≥ 90
2	Kidney damage with mild ↓GFR	60-89
3	Moderate ↓GFR	30-59
4	Severe ↓GFR	15-29
5	Kidney failure	<15 or dialysis

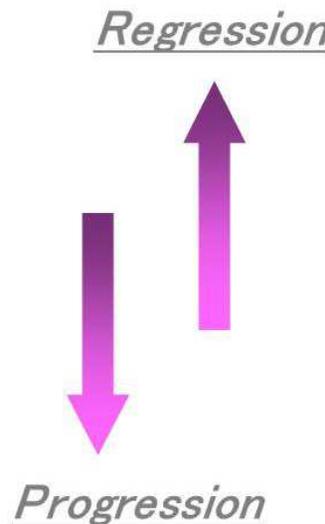


Fig. 1. Relationship between progression and regression of chronic kidney disease.

Glomerulosclerosis occurs because of the excessive deposition of components of the extracellular matrix (ECM) in the glomeruli, resulting in changes in glomerular integrity and albuminuria. This process is triggered by increased synthesis of ECM components, and decreased degradation of ECM components, resulting in net accumulation of ECM (Ma et al., 2007). It is thought that, once renal function declines below a 'point of no return', the decline in glomerular function continues inexorably due to the continuous accumulation of ECM and progression of glomerulosclerosis. Glomerular hypertension has been suggested to play an important role in this process, because the decrease in glomerular filtration leads to a compensatory increase in glomerular hypertension, resulting in a vicious cycle which causes progression of glomerular injury and loss of renal function (Neuringer et al., 1992).

Because of the progressive nature of CKD, one of the optimum strategies for reducing CKD would be to find interventions to prevent new-onset CKD. Multiple clinical studies have shown that the use of RAS inhibitors in patients with and without diabetes can cause a decline in the progression of CKD, which may be mediated, at least in part, by a blood pressure-independent mechanism (Bakris, 2010; Berl, 2009; Stojiljkovic et al., 2007). More recently, several studies have suggested that the use of RAS inhibitors may also be effective in preventing new-onset CKD, especially in patients with diabetes. In particular, Ruggenenti et al. showed in the BENEDICT trial that, in hypertensive patients with type 2 diabetes and no microalbuminuria at baseline, the angiotensin-converting enzyme (ACE) inhibitor trandolapril significantly decreased the risk of developing microalbuminuria compared with conventional therapy (Ruggenenti et al., 2008). Similarly, in the recent ROADMAP study, the use of the ARB olmesartan was associated with a delayed onset of microalbuminuria (Haller et al.). These results are important, because they suggest that diabetic nephropathy can be prevented or at least delayed by appropriate intervention (Remuzzi et al., 2006).

At present, it is unclear from clinical studies whether these measures may be effective for prevention of new-onset CKD in non-diabetic patients. However, the data from animal studies are encouraging, and suggest that early intervention with a RAS inhibitor may be effective for the prevention of renal injury due to hypertension (Ishiguro et al., 2007; Nakaya et al., 2001), salt-loading (Nakaya et al., 2002), or irradiation (Moulder et al., 1996).

2.2 Studies on CKD regression

Although it has been widely accepted that established sclerosis is irreversible, recent studies have emerged to challenge this concept and to focus on developing new therapies to cause regression or reversal of established glomerulosclerosis (Ma et al., 2007), (Ruggenenti et al., 2001). In particular, studies have suggested that treatment with high-dose RAS inhibitor may be effective in causing regression of glomerular lesions in animal models (Ma et al., 2005), (Teles et al., 2009), (Macconi et al., 2009).

Recently, we reported that transient treatment with an angiotensin receptor blocker (ARB) at a 50-100 times the normal dose in rodents causes regression of glomerulosclerosis in mice (Hayashi et al., 2010). In this study, the effects of treatment with different doses of ARB on established lesions of glomerulosclerosis were examined in the adriamycin nephropathy model, with a focus on whether the regression was sustained after cessation of the ARB treatment. Furthermore, the involvement of matrix metalloproteinase (MMP)-2 in the mechanism of glomerulosclerosis regression were examined both *in vitro* and *in vivo*, using a non-specific MMP inhibitor (doxycycline), and knockout (KO) mice with targeted deletion of MMP-2.

The principal findings of the study are shown in Fig. 2. and Fig. 3. It was found that transient treatment for two weeks with the ARB candesartan caused a regression of established glomerulosclerosis, which was clearly evident with the high doses of ARB and was sustained 6 months after cessation of all treatments. Moreover, the ARB treatment

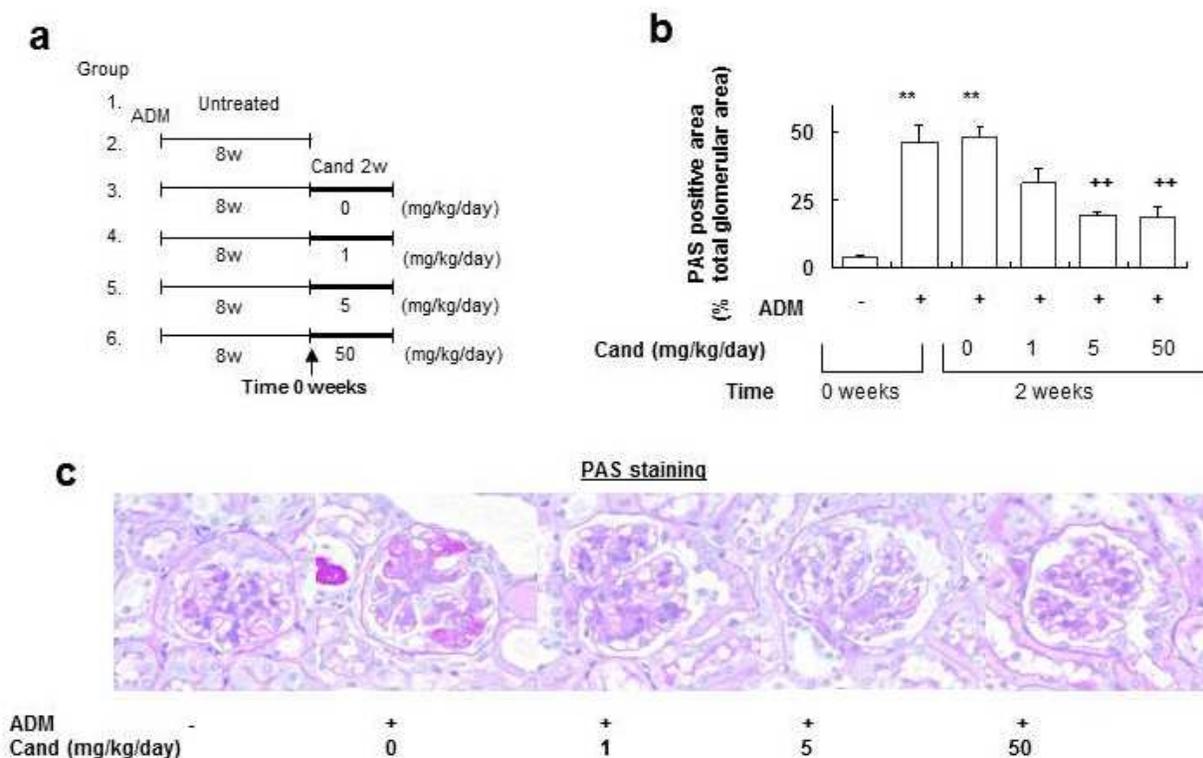


Fig. 2. Effects of different doses of ARB (candesartan) on regression of glomerulosclerosis in the adriamycin-nephropathy model. (a) Experimental protocol (b) Effects on glomerular sclerosis (c) Representative photomicrographs. Reproduced with permission from Hayashi et al. *Kidney Int* 78:69-78, 2010.

caused a dose-dependent increase in glomerular MMP-2 activity and decrease in type IV collagen accumulation. The ARB-induced regression of glomerulosclerosis was attenuated by pretreatment with the MMP inhibitor doxycycline, as well as in mice with targeted deletion of the MMP-2 gene, suggesting the possibility that increased expression of MMP-2 may contribute to the regression of glomerulosclerosis and type IV collagen deposition seen in the high-dose ARB-treated groups.

The MMP family constitutes a multigene family of zinc- and calcium-dependent endopeptidases which play a major role in the degradation of collagen and other ECM components (Woessner, 1991), (Baramova et al., 1995), (Sasamura et al., 2005). MMP-2 (also known as gelatinase A) is a MMP which is found in the conditioned media of cultured fibroblasts, and is involved in the cleavage of multiple ECM proteins including type IV collagen (Woessner, 1991), (Baramova et al., 1995). In contrast to gelatinase B (MMP-9), MMP-2 is not highly expressed in normal or diseased glomeruli (Urushihara et al., 2002). However, it has been shown that renal MMP-2 expression and activity are upregulated by ACE inhibitors in rats with diabetes (McLennan et al., 2002), (Sun et al., 2006). Moreover, Turkay et al reported that the ACE inhibitor enalapril also increased hepatic MMP-2 expression in rats with experimental hepatic fibrogenesis (Turkay et al., 2008), while Westermann et al. showed that the ARB irbesartan increased MMP-2 activity in the hearts of mice with cardiomyopathy (Westermann et al., 2007), suggesting that the RAS plays a key role in regulation of MMP-2 expression in the kidney and other tissues.

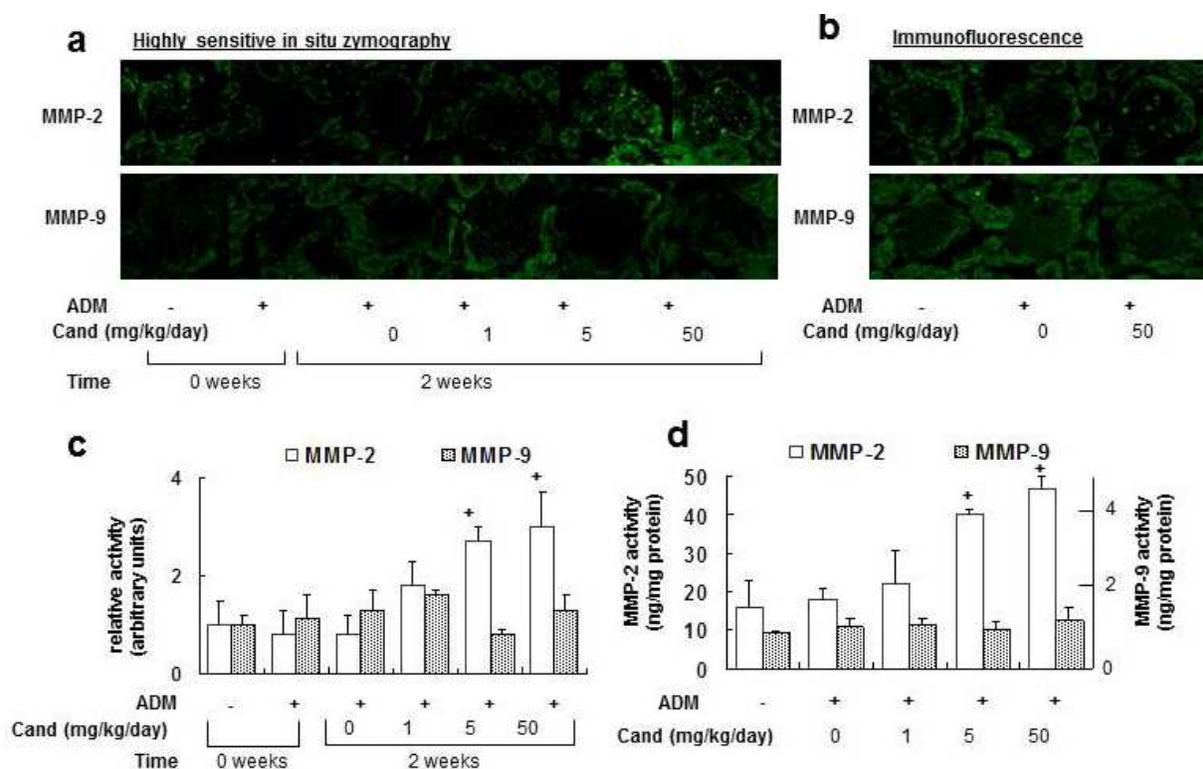


Fig. 3. Effects of different doses of ARB (candesartan) on glomerular MMP-2 and MMP-9 activity and expression in the adriamycin-nephropathy model. Representative results of (a) highly-sensitive in situ zymography (b) immunofluorescence. Quantification of glomerular MMP activity by (c) in situ zymography (d) ELISA. Reproduced with permission from Hayashi et al. *Kidney Int* 78:69-78, 2010.

As shown in Fig. 3, the results of highly-sensitive *in situ* zymography and immunofluorescence suggested that MMP-2 might be upregulated in glomerular podocytes, but this could not be determined accurately because of the relatively low expression of MMP-2 protein. Therefore, to further characterize the mechanisms of the ARB-induced increase in glomerular MMP-2 activity, we examined the effects of ARB treatment in cultured podocytes. These experiments revealed that ARB treatment of podocytes resulted in a dose-dependent increase in MMP-2 activity in the supernatant. Podocytes are known to express components of the RAS, including renin, angiotensinogen, angiotensin-converting enzyme, and AT1 and AT2 receptors (Durvasula et al., 2006), (Durvasula et al., 2008), (Liebau et al., 2006). Moreover, functional expression of the renin-angiotensin system has been documented in both mouse and human podocytes (Durvasula et al., 2008), (Liebau et al., 2006). To examine the possibility that the effects of ARB were mediated through inhibition of the RAS, further studies were performed using an ACE inhibitor, and a non-peptide Ang II antagonist (Saralasin). The use of these different RAS inhibitors yielded similar results, suggesting that the effects of ARB were mediated by inhibition of the intrinsic RAS in podocytes.

Moreover, it was observed *in vitro* that the increase in MMP-2 activity was greatest at the high doses of candesartan (greater than 0.1 $\mu\text{mol/L}$), whereas maximum plasma concentrations in humans administered a standard dose of candesartan are below the nanomolar range (Pfister et al., 1999). Assuming that local (glomerular) concentrations of ARB will be greatest with the high-doses of ARB, these *in vitro* results are consistent with the *in vivo* observation that the glomerulosclerosis regression was maximal with the high doses of ARB.

In humans, it is known that MMP-1 (collagenase-1) also plays a major role in the breakdown of collagens, in particular type I and type III collagen. It has been reported that rodents lack the human MMP-1 gene, and MMP-13 (collagenase-3) is the main collagenase in mice (Henriet et al., 1992), (Parks et al., 2000.). When the possibility that MMP-13 may also contribute to the observed changes was examined, it was found that ARB treatment did not increase glomerular MMP-13 activity, but rather decreased the activity, suggesting that increased MMP-13 activity did not contribute to the observed regression of glomerulosclerosis in the adriamycin nephropathy model (Hayashi et al., 2010).

We also examined whether the effects of ARB could be attenuated by pretreating the mice with doxycycline, or by performing studies on mice with a deletion of the MMP-2 gene. It was found that neither inhibition of MMP nor deletion of MMP-2 completely abolished the effects of high-dose ARB, suggesting that other mechanisms may be involved, including the involvement of other proteases such as the serine protease plasminogen activator inhibitor-1 (PAI-1) (Ma et al., 2005). Other studies have suggested that regeneration of glomerular podocyte function may also play a role in the regression of glomerulosclerosis by RAS inhibitors (Macconi et al., 2009).

It should be noted that the effects of ARB on regression may differ widely in different animal models. In particular, the effects of ARB on regression were less marked in the 5/6 nephrectomy model (Ma et al., 2005). This may be because the adriamycin model relies on a single (acute) injury to the glomeruli, whereas the injury in the 5/6 nephrectomy model is a continuous process. In the studies on the adriamycin nephropathy model, it was found that

MMP-2 activity decreased to baseline after the ARB treatment was discontinued. The transient increase in MMP-2 was probably sufficient to permanently reverse the glomerulosclerosis in that model, but its effect in other disease states is unclear.

Interestingly, clinical studies using different ARBs (Rossing et al., 2005), (Hollenberg et al., 2007), (Burgess et al., 2009) also suggest that high-dose ARB treatment may have a greater beneficial effect on the kidney compared to standard doses. One potential reason may be that standard doses of ARB do not fully suppress the RAS in the kidneys. Another possibility is that mechanisms unrelated to RAS inhibition may be involved, for example an antioxidant action independent of AT1 receptor blockade (Chen et al., 2008). Currently, we are performing further studies to examine why high-dose ARB is particularly effective in ameliorating glomerular injury.

2.3 Clinical studies of CKD regression

The clearest clinical demonstration of glomerulosclerosis regression was provided by Fioretto et al., who showed that pancreas transplantation in patient with type 1 diabetes caused regression of established lesions of glomerulosclerosis in patients with type 1 diabetes (Fioretto et al., 1998).

There are also several studies which examined the effect of RAS inhibition on structural changes in diabetic and non-diabetic CKD. In the study on type 1 diabetic patients with microalbuminuria, treatment with enalapril, perindopril, or metoprolol resulted in a decrease in glomerular basement membrane thickness after 3-4 years of follow-up (Nankervis et al., 1998) (Rudberg et al., 1999). Other studies have suggested that glomerular volumes may be reduced by RAS inhibition, however the contribution of changes in blood pressure is unclear (Perrin et al., 2008). On the other hand, a recent study by Mauer et al. did not detect a statistical difference in mesangial fractional volume in patients treated with placebo, ARB, or ACEI (Mauer et al., 2009). In the ESPRIT study, 3-year treatment with enalapril or nifedipine did not cause a significant change in renal structural abnormalities (2001).

In the case of type 2 diabetes, the study by the Diabiopsies group suggested that treatment with perindopril resulted in stabilization of the percentage of sclerosed glomeruli, but this could not be confirmed by electron microscopy (Cordonnier et al., 1999). In the case of non-diabetic CKD, Ohtake et al. reported that treatment of 15 patients with mild to moderate IgA and non-IgA mesangial proliferative glomerulonephritis with an ARB for an average of 28 months caused a decrease in mesangial matrix expansion and interstitial fibrosis (Ohtake et al., 2008). In summary, although there is encouraging evidence that RAS inhibition can cause regression of glomerular structural changes in humans, the clinical data are not as clear as the data from animal experiments, possibly because the human studies have not focused on the use of high-dose RAS inhibitors.

2.4 The search for clinical biomarkers of disease regression

One of the reasons that there are relative few large-scale studies on CKD regression is that demonstration of resolution of glomerular lesions requires repeat kidney biopsies, which may not be feasible in large populations. One potential way to overcome this problem is to find surrogate biomarkers of disease regression in the serum and urine of patients with early (stage 1-2) CKD, using the new science of metabolomics (Hayashi et al., 2011).

Metabolomics is a discipline dedicated to the global study of metabolites, their dynamics, composition, interactions, and responses to interventions or to changes in their environment (Oresic, 2009), and the recent development of metabolome analysis technology allows the global 'metabolome' to be assessed comprehensively in individual patients. An important advantage of metabolome analysis is the potential to identify new and unidentified metabolites which could have important pathophysiological functions. In a recent study, we obtained serum and urine samples from 15 patients and 7 healthy volunteers, and compared the metabolome profiles of the two groups. Serum or urine samples (100 ul) were added to methanol (900 ul) containing internal standards, deproteinised, and subjected to anionic and cationic capillary electrophoresis time-of-flight mass spectrometry (CE-TOFMS) analysis

The results of our metabolome analysis suggested that serum and urine levels of several amino acid, nucleic acid, and carbohydrate metabolites were altered in patients from an early stage of CKD (Hayashi et al., 2011). We also found evidence for the presence of several novel metabolites which were markedly increased or decreased in the patients with CKD compared to controls. We are performing further studies to examine the structure of these unidentified products, with the final aim to find new biomarkers of disease regression which may be utilized in clinical studies.

3.1 Prevention of hypertension

It has been recognized that the kidney plays an important role in the control of systemic blood pressure, and is involved in the pathogenesis of hypertension, which is a major risk factor for cardiovascular disorders such as stroke, heart failure, vascular disease, and end-stage renal disease, and an important cause of morbidity and mortality. Similar to CKD, the development of hypertension appears to be progressive: the systolic blood pressure of an individual patient rises progressively over time, so that median values of systolic blood pressure in the population increases at every age (Qureshi et al., 2005).

In our laboratory, we have been studying the use of RAS inhibitors to prevent the development of hypertension, using the spontaneously hypertensive rat (SHR) and other animal models of hypertension. Previous studies by Harrap et al. demonstrated that treatment of SHR from age 6 to 10 weeks with an angiotensin-converting enzyme (ACE) inhibitor resulted in the sustained suppression of hypertension at age 25 weeks (Harrap et al., 1986), (Harrap et al., 1990). Studies from the group of Berecek et al. suggested that these results could result from a decrease in arginine vasopressin (AVP) levels (Lee et al., 1991), (Zhang et al., 1996). Similar findings have been reported by other laboratories, using both ACE inhibitors (Giudicelli et al., 1980), (Christensen et al., 1989) and ARBs (Morton et al., 1992), (Gillies et al., 1997).

In our laboratory, it was found that treatment of stroke-prone SHR (SHRSP) with an ACE inhibitor from age 3 to 10 weeks resulted in a sustained suppression of blood pressure, whereas such an effect was not found with the vasodilator hydralazine (Nakaya et al., 2001). The same results were found with an ARB, suggesting that this effect could be explained by the inhibitory actions of ACE inhibitors and ARB on the RAS. Importantly, it was also found that the development of renal injury was also suppressed in this model.

To examine if the effects of RAS inhibitors to suppress the development of hypertension was specific to the SHR and its related strains, studies were performed on the Dahl salt-sensitive

rat, which is a model of salt-sensitive hypertension with a low renin profile (Nakaya et al., 2002). These studies revealed that treatment of Dahl salt-sensitive rats with an ARB during the same 'critical period' (age 3 to 10 weeks) prevented the later development of salt-induced hypertension in this model even when the ARB treatment had been discontinued, and also a partial attenuation of renal injury induced by salt loading.

To examine the mechanisms of these long-lasting effects of RAS blockade, further studies were performed using the SHR/L-NAME model, which is a model of accelerated hypertension characterized by marked renal injury (Ishiguro et al., 2007). SHR were treated with a RAS inhibitor (ACE inhibitor or ARB), or a vasodilator (hydralazine), or a calcium channel blocker (CCB, nitrendipine) during the 'critical period' from age 3 to 10 weeks. Medications were discontinued at age 10 weeks, and the rats observed without treatment for two months. At age 18 weeks, the rats were administered the NO synthase inhibitor L-NAME in the drinking water for 3 weeks to induce renal injury, and sacrificed at age 21 weeks. Interestingly, the rats treated with a RAS inhibitor had reduced vascular injury (arterial hypertrophy, endothelial thickening, and lumen narrowing) compared to vasodilator- or CCB-treated rats, and reduced renin mRNA, probably due to attenuation of the intrarenal vascular injury and renal ischemia induced by L-NAME. To explain all these experimental findings, we proposed a 'reno-vascular amplifier' mechanism for the development of hypertension and renal injury in this model (Fig. 4). High blood pressure is known to cause vascular hypertrophy in the resistance vessels, which consists predominantly of inward 'eutrophic' remodeling. When this remodeling is accentuated, as in the SHR/L-NAME model, glomerular perfusion decreases, which results in increased synthesis of renin and activation of the RAS. These changes cause a further increase in the blood pressure, resulting in a vicious cycle which causes accelerated hypertension. RAS inhibitors can block this vicious cycle by attenuating both the increase in blood pressure, and importantly, by decreasing the vascular hypertrophy of the resistance arteries.

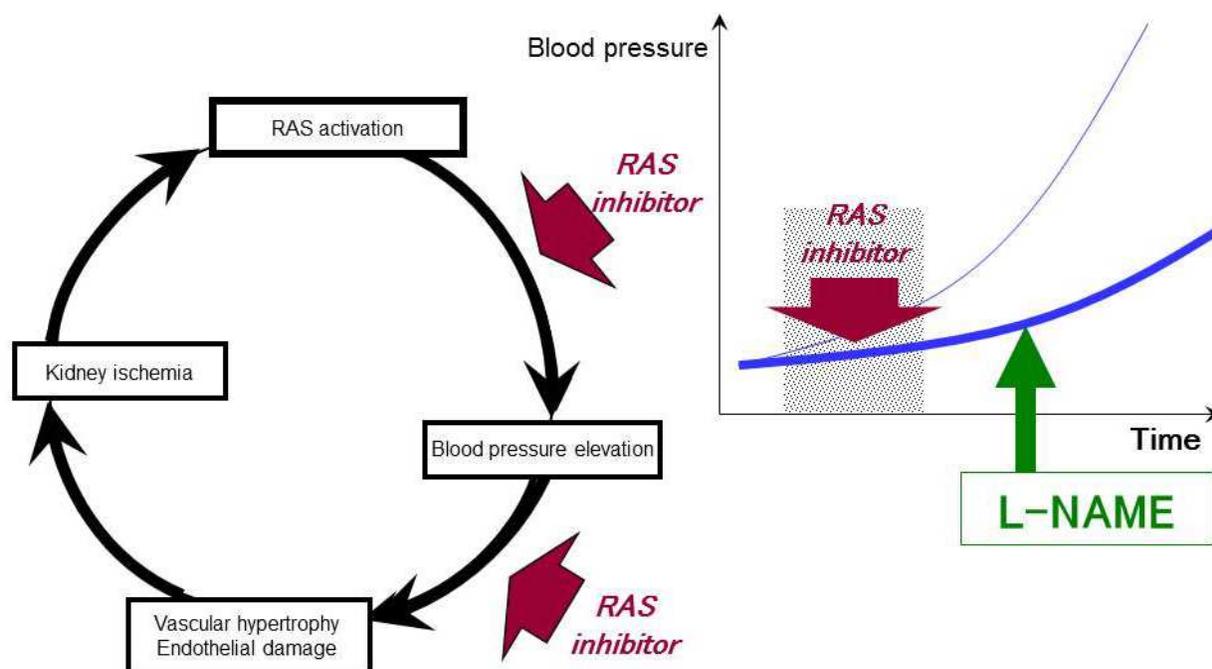


Fig. 4. Inhibition of the 'reno-vascular amplifier' as a proposed mechanism for prevention of hypertension in the SHR/L-NAME model.

This hypothesis was supported by experiments in which the agonist angiotensin II was administered during the 'critical period' from age 4 to 8 weeks, after which all treatments were discontinued. Rats which had been transiently exposed to angiotensin II during this period were found to have elevated values of blood pressure which were 10-20 mmHg higher than rats which had been exposed to saline vehicle. Moreover these rats were more susceptible to the subsequent development of renal vascular injury, and increased renin synthesis at a later time point (age 18 weeks), and to have a much higher mortality after L-NAME administration (Ishiguro et al., 2007). Thus, the effects of angiotensin II administration were the opposite of the effects of ARB, and were found to cause an acceleration of the 'reno-vascular amplifier' in this model of accelerated hypertension and renal injury.

The results of animal studies on hypertension prevention have been supported clinically by the TROPHY study (Julius et al., 2006). In this prospective, randomized, multi-center study designed by Julius et al., patients with prehypertension and systolic blood pressure of 130-139 mmHg and/or diastolic blood pressure of 85-89 mmHg were randomized to placebo or the ARB candesartan cilexetil (16 mg/day) for two years, then both groups were switched to placebo for the next two years. The primary end-point was the development of hypertension. As in the animal studies, the treatment with ARB caused a suppression of the development of hypertension, not only during the active treatment period (first two years), but even after the active treatment had been discontinued. The absolute risk reduction at the end of two or four years was 26.8 % and 9.8 % respectively, whereas the corresponding values of relative risk reduction (when relative risk is defined as the frequency of events in the treated group divided by the events in the placebo group) were 66.3 % and 15.6 %, respectively. Changes in the systolic blood pressure at the end of the study were small (2 mmHg), but statistically significant.

3.2 Regression of hypertension

Hypertension is associated with increased peripheral arterial resistance, and most of the resistance develops in the resistance arteries of the microvasculature, which includes both arterioles and small arteries with diameters < 400 μm . The importance of the microvasculature in the pathogenesis and maintenance of hypertension was originally proposed by Folkow, who pointed out that a vicious cycle exists between increased blood pressure and vascular hypertrophy (Folkow, 1990). According to this hypothesis, hypertension may be initiated by a specific fast-acting pressor mechanism (e.g. angiotensin II) that increases blood pressure and initiates a positive feedback loop that induces vascular hypertrophy and maintains the hypertension. The hypothesis was later refined by Lever and Harrap, who proposed further elements: an abnormal or 'reinforced' hypertrophic response to pressure, and an increase of a humoral agent that causes hypertrophy directly (Lever et al., 1992). Animal studies have provided evidence to support the hypothesis that arteriolar restructuring may act as a primary accelerator of hypertension and provide a driving force for the progression of hypertension (Feihl et al., 2006; Intengan et al., 2001; Skov et al., 2004)). In particular, increased renal vascular resistance has been well documented in the SHR model of hypertension (Dilley et al., 1984), and morphometric studies on the afferent arteriole of SHR and Wistar-Kyoto rats (WKY) have confirmed that afferent arteriolar diameters are smaller in SHR compared to WKY (Kimura et al., 1989) (Gattone et al., 1983). Importantly, these differences are already seen in the 4-week-old SHR, even before blood pressure is significantly increased compared to WKY controls (Kimura et al., 1989).

Moreover, when SHR and normotensive rats were crossbred to form second generation hybrids, a narrowed afferent arteriole lumen diameter at 7 weeks was found to be a predictor of the later development of hypertension (Skov et al., 2004).

In our laboratory, the morphological effects of treatment with an ARB or CCB during the 'critical period' on renal small artery structure were examined in SHR. SHR were treated with an ARB or CCB from age 3 to 10 weeks, and sacrificed at age 10 weeks. The arteriolar hypertrophy was significantly reduced in the ARB-treated rats compared to the CCB-treated rats, despite similar reductions in blood pressure. These results were consistent with reports from other groups using RAS inhibitors in both animal models (Freslon et al., 1983), (Christensen et al., 1989) and humans (Schiffrin et al., 1994), (Thybo et al., 1995).

Recently, we reported that treatment of SHR with established hypertension with high-dose ARB (at 50-100 times the normal dose in rodents) resulted in a sustained decrease in hypertension, suggesting that regression of hypertension is feasible in this model (Ishiguro et al., 2009). Similar results were reported previously by Smallegange et al. using an ACE inhibitor combined with a low-salt diet (Smallegange et al., 2004). Examination of the effects of transient high-dose ARB therapy on renal arteriolar structure revealed a remarkable reversal of the arteriolar hypertrophy found in SHR treated with ARB, whereas this effect was not seen with CCB (Fig. 5). Interestingly, these findings were particularly noticeable in the small arteries (diameter 30-100 μ m) and arterioles in the kidney, compared to small arteries from other vascular beds, such as the brain, heart, and mesentery.

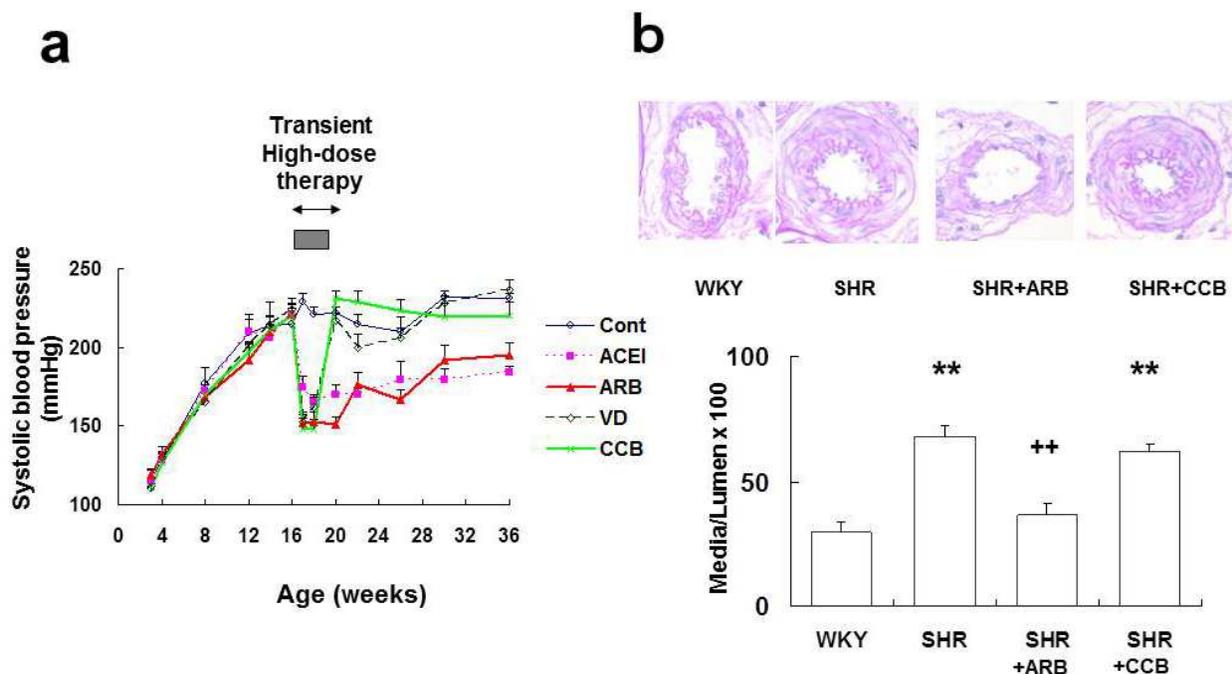


Fig. 5. Regression of hypertension in the SHR model by transient high-dose ARB treatment. (a) Effects on blood pressure (b) Effects on renal arteriolar media/lumen ratios. Reproduced with permission from Ishiguro/Hayashi et al. *Hypertension* 53:83-89, 2009.

To examine potential mechanisms of these changes, the gene expression profile of kidneys treated with ARB were compared with the kidneys treated with CCB. Using the Affymetrix rat 230 2.0 gene expression array, it was found that 1,345 genes were elevated in the ARB-

treated rats compared to CCB-treated rats, while 5,671 were reduced. Several ECM-related genes were elevated in the ARB-treated rats, while MMP-9, TIMP-2, and TIMP-3 gene expressions were decreased in the ARB-treated group. These differences were also confirmed by real time RT-PCR. To examine if these changes in MMP expression could be involved in the observed reversal of renal arteriolar hypertrophy by ARB, the activities of different MMPs in the renal microvasculature were examined using a highly sensitive in situ zymography method. It was found that MMP-13 activity was markedly increased by ARB but not by CCB (Ishiguro et al., 2009). These results are compatible with a role for MMPs in the actions of ARB to cause reversal of renal arteriolar hypertrophy, and subsequent remodeling of the renal microvasculature (Fig.6).

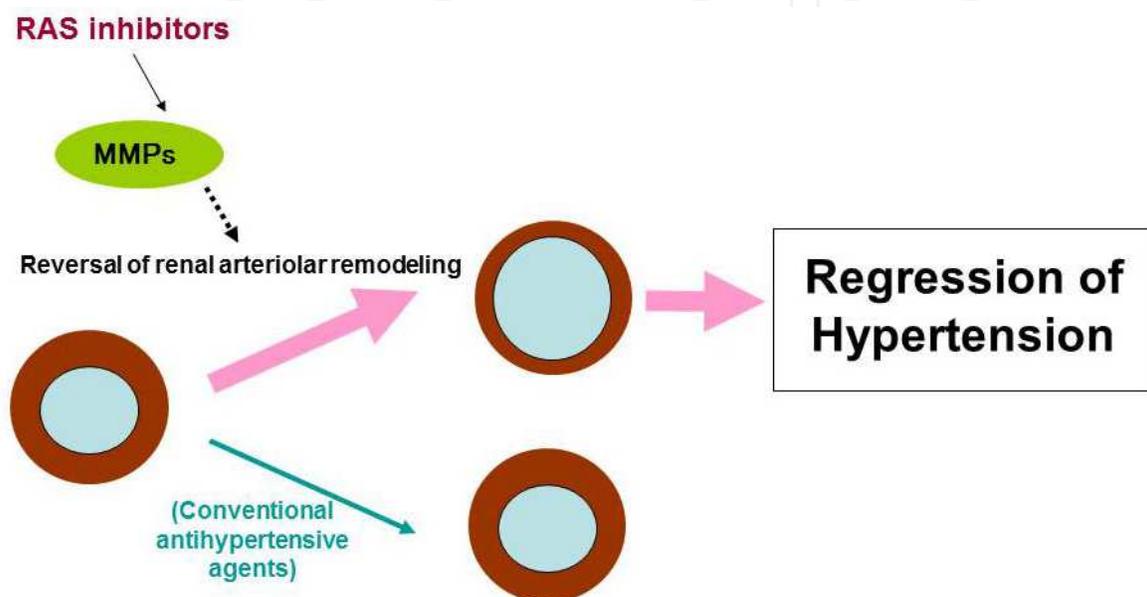


Fig. 6. Proposed hypothesis for the mechanism of regression of hypertension by high-dose renin-angiotensin inhibitors.

To our knowledge, there have been no clinical studies which were specifically designed to address the question whether regression of hypertension (i.e. reversal of Grade 1 hypertension to high-normal blood pressure) is feasible in humans. For this reason, we are currently performing a prospective, multi-center study (STAR CAST) study to examine the effects of one-year treatment with an ARB or CCB on regression of hypertension (Sasamura et al., 2008). In this study, patients aged 30-59 with newly diagnosed hypertension and a positive family history of hypertension are randomized to treatment for one year with either an ARB (candesartan) or CCB (nifedipine XL). After one year, the patient's antihypertensive drug dose will be reduced, then withdrawn. The antihypertensive drug withdrawal success rate will be compared between the two antihypertensive agents, as an index of the regression of hypertension in the two groups. Because of safety concerns, the patients' home blood pressure will be monitored in real time using a home blood pressure monitoring system (i-TECHO). Although this study is being performed using standard doses of ARB, it is hoped that this trial will provide information concerning whether RAS inhibitors are indeed different from other antihypertensive agents in terms of long-term effects on blood pressure. If the results are encouraging, we hope to perform further clinical studies on CKD and hypertension regression, using high or even ultrahigh doses of ARB.

4. Conclusion

The increasing evidence from laboratory and clinical studies on chronic kidney disease and hypertension suggest that effective interventions at an early stage may be beneficial in preventing the development of both these disorders. Because of the high prevalence of both chronic kidney disease and hypertension amongst the general population, further research on the development of methods to induce regression of these conditions may be expected to result in widespread health benefits.

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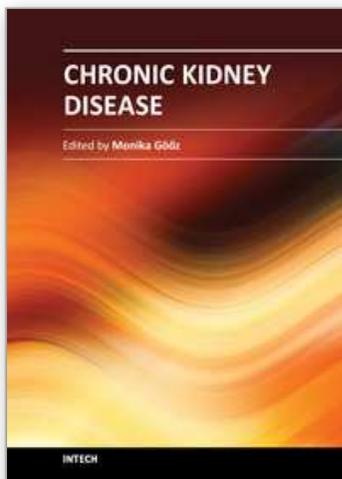
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Chronic kidney disease is an increasing health and economical problem in our world. Obesity and diabetes mellitus, the two most common cause of CKD, are becoming epidemic in our societies. Education on healthy lifestyle and diet is becoming more and more important for reducing the number of type 2 diabetics and patients with hypertension. Education of our patients is also crucial for successful maintenance therapy. There are, however, certain other factors leading to CKD, for instance the genetic predisposition in the case of polycystic kidney disease or type 1 diabetes, where education alone is not enough.

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