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The Proliferative Changes of Renal Afferent Arteriolar Walls and Renin-Angiotensin-Aldosterone System Inhibitors

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Abstract

Our group has studied the morphological influences of Renin-Angiotensin-Aldosterone System (RAAS) inhibitors on the renal afferent arterioles. Studies were performed using Angiotensin II type1 Receptor Blockers (ARBs), an Angiotensin Converting Enzyme inhibitor (ACEi), and a Direct Renin Inhibitor (DRI) with several strains of rats. The same results were found in these experiments except DRI. The long-term administration of ARBs or ACEi both induced unusual severe proliferative changes of the renal afferent arteriolar walls and narrowed the lumens. The smooth muscle cells (SMCs) of the proliferative arteriolar walls were considered to be de-differentiated SMCs, which were originally renin cells. The renin granules were evidently increased in the juxtaglomerular apparatus cells by all the RAAS inhibitors. The increased renin granules were also found in the outer layers of SMCs in the treatment of ARBs/ACEi, and sometimes extended from the entrance of the glomeruli to the bifurcation of the interlobular arteries. Our group found the same results in humans by the treatment of ARB and/or ACEi.

The RAAS inhibitors are widely known to have the potential to influence the intra-glomerular hemodynamics and the organ-protective effects in essential hypertension or secondary hypertension. However, the long-term administration of ARB and/or ACEi include the ability to affect the afferent arteriolar walls in the kidney. It is necessary to give serious attention to the influences and the results of the blockade of the RAAS cascade in the kidney. Further studies on the beneficial methods of using these agents for the kidney are needed.

Keywords: Angiotensin II type1 receptor blocker, RAAS inhibitors, Renal afferent arteriole, Morphology

The hyperfiltration theory of Brenner et al. in 1982 [1], is widely recognized and studied closely as a final common pathway of kidney function deterioration from some point to the irreversible end-stage by any first kidney insult. In the paper, the deterioration of kidney function is induced because of the glomerular hemodynamics, glomerular hyperfiltration, and glomerular hypertension. These are caused by the overload of remaining glomeruli from any kidney insult that is associated with the decrease in the number of glomeruli [2-4]. In glomeruli, the increase of blood flow in each glomerulus occurs when afferent arterioles dilate, such as diabetes [5,6] or obesity [7], and occurs when blood flow is relatively higher in the afferent than in the efferent arterioles. The glomerular blood flow and transglomerular pressure are regulated by afferent and efferent arteriolar constriction or dilation. The blood flow fluctuates in order to preserve intraglomerular pressure from the renal interlobular, arcuate, interlobar arteries, and through the renal arteries directly reflected by central blood pressure [8].

Arterial and arteriolar constriction are known to be induced by vaso-constrictive substances, especially the strong vasoconstrictor angiotensin II, through the stimulation of the angiotensin II receptor type 1 in vessels. Then, after the publishing of the glomerular hyperfiltration theory, the role of activation in the renal Renin-Angiotensin-Aldosterone system (RAAS) was remarkably focused on the progression to the end-stage renal disease (ESRD) [3-5].

Essential hypertension is known to be induced by the morphologic changes of vessels in many organs, especially intrarenal arteries and arterioles. The morphological changes of the interlobular arteries and the bigger size intrarenal arteries (arcuate, interlobar, renal artery, and its branches)

were fibroelastic intimal thickening with reduplication of the internal elastic lamina which is the same as atherosclerosis. The media thickened in small arteries and/or arterioles reflecting hypertrophy, hyperplasia, or remodeling. Arterioles commonly affected by hyaline arteriolosclerosis [9]. In contrast, in the vessels of malignant hypertension and angiitis, the characteristic necrotic changes, endothelial damage, and/or inflammatory cell infiltrations are shown in the vessel [9,10]. Those morphological findings previously mentioned, frequently shown in the process of progression of the kidney function deterioration, attenuate lumens of vessels gradually and lead to ESRD as a result. However, the glomerular blood supply in kidney needs to be maintained in any condition of acute change of blood pressure to protect the kidney function in order to regulate body fluid. So, oxygen supply to the tissue of main organs should be indispensable [11].

One of the common important complications of hypertension is known as benign nephrosclerosis. Recently nephrosclerosis with ESRD patients that required hemodialysis are the second most common among the primary and secondary hemodialytic ESRD patients in Japan [12]. Therefore, all generalists and specialists, such as nephrologists, cardiologists, endocrinologists and neurologists, who treat hypertension as clinicians have to select antihypertensive agents not only for lowering blood pressure but also for organ-protective effects in each agent [13]. The reno-protective effects of antihypertensive agents with the potential to cause the glomerular hemodynamic changes, are considered to be most important in any kidney disease. The effects of some kinds of antihypertensive agents on glomerular hemodynamics are regarded to be valuable to prevent the deterioration of kidney function. This is one of the options of the treatments for kidney diseases [14,15].

These days, antihypertensive agents commonly used are divided into five major kinds as follows: Calcium Channel Blockers (CCB), RAAS inhibitors, Diuretics, α blockers, and β blockers.

Almost all CCB are known to be strong dilators of the peripheral vessels resulting in lower blood pressure. CCB often induce glomerular hyperfiltration in the kidneys, except efonidipine and barnidipine [16]. Nifedipine, which has been commonly used for a long time, was found to dilatate the afferent arterioles much larger than the efferent arterioles and accelerate glomerular hyperfiltration [17]. Many investigators stated that CCB is not appropriate to treat patients with type 2 diabetes mellitus. Since the glomerular hyperfiltration is commonly found from the early phase of diabetes mellites, it accelerates diabetic nephropathy. The afferent arteriolar dilatation and the increase of the glomerular blood flow are known to be commonly induced by hyperinsulinemia in the early phase [18,19].

On the other hand, RAAS inhibitors, such as Angiotensin Converting Enzyme inhibitors (ACEi) and Angiotensin II type1 receptor blockers (ARB), were both studied by many investigators about the influence on the glomerular hemodynamics [20,21]. ACEi reduces conversion of angiotensin I to II, resulting in the decrease of the production of angiotensin II [22].

ARB is prohibiting angiotensin II from attaching to the receptor, and stimulating the angiotensin II type 1 receptor on vessels. Through the inactivation of angiotensin II, the strong vasoconstrictor and the one of the steps of the RAAS cascade, lose their vasoconstrictive effect [22]. Moreover, ARB was reported to dilate the efferent arterioles but not dilate the afferent arterioles, resulting in a protective effect of glomeruli; which is recognized as reducing the glomerular hypertension and glomerular hyperfiltration in many studies [23,24]. Razga et al. found angiotensin II type 1 receptors existed more abundantly in the afferent arterioles than in the efferent arterioles using immuno-electron microscopic study [25]. Papers were published one after another suggesting that ARB decreased the intraglomerular mesangial cell proliferation [26] and interstitial fibrosis [27]. Thereafter, ARB was considered to be a very effective reno-protective agent.

There are only a few clinical markers of kidney function. Serum creatinine levels are not quickly paired with an increase of kidney injury, such as glomerular damage, tubular atrophy, and interstitial fibrosis because of the remaining healthy parts of the kidney compensate for the lost functions. Moreover, clinicians are not able to perform renal biopsy repeatedly and safely in many occasions, they also just speculate the extent of damages in the whole kidney from small specimens of limited size. The amount of urinary protein, macro- or micro-, is considered to be a marker of kidney damage. Then we regard the amount of urinary protein or albumin as a convenient clinical marker of activity of kidney disease. However, sometimes it changes without any relation to the real tissue damage of kidneys.

In many studies, the reno-protective effects related to ARB are estimated using serum creatinine levels, estimated Glomerular Filtration Rate (eGFR), doubling of serum creatinine levels, and the number of patients requiring hemodialysis. The decrease in the amount of macro- or micro- urinary protein excretion is also used for estimation of reno-protective effect.

When the remarkable proliferative changes in the afferent arteriolar walls were first found in an experiment for the another purpose which planned on feeding Zucker fatty rats with ARB or without ARB [28]. Those randomly numbered rats were morphologically investigated under microscopy by two pathologists independently. The rats with ARB showed the evident afferent arteriolar wall proliferation and their blood pressure was lower than that of rats without ARB. The urinary protein excretion in the rats with ARB was lesser than that of the rats without ARB. The morphologically proliferative

changes of the afferent arteriolar walls were remarkably found and they narrowed the arteriolar lumens. The abundant renin granules were found in hyperplastic juxta glomerular apparatus (JGA) cells, also the granules extended from the entrance of the glomerulus along the outer layers of the arteriolar smooth muscle cells (SMCs) to the bifurcation of the interlobular arteries [28].

Many experiments were performed, such as with or without lowering blood pressure, using other strains of rats (Zucker, Wistar rats, Spontaneous Hypertensive Rats, etc.), or different aged rats (juveniles, aged), but the results were the same [28.29]. Those effects with or without lowering blood pressure reduced the urinary protein excretion, completely matching the effects of ARB that were published by the other researchers up until that time.

Until the morphological findings were found, the glomerular hemodynamic changes induced by ARB were imagined only as functional, not structural. However, if the severe morphological changes lasted for a long time, those changes could accelerate the attenuation of the lumens in the afferent arterioles to lead to a decrease of the intraglomerular blood flow. That also could decrease the efferent arteriolar blood flow and lose blood flow that connected to the post glomerular capillaries as a result. Tubules which are supplied oxygen by the post glomerular capillary perfusion fell into a state of hypoxia [30]. In the hypoxic state, the tubular cells transform into fibroblasts [31], they could induce interstitial fibrosis and that accelerates the decrease of the interstitial oxygen diffusion. This is a vicious cycle of the process in the progression to ESRD. In 2006, the review published by Nangaku, stated that the chronic hypoxia in the tubulointerstitium as a common final pathway to the progression to ESRD [32].

Patients treated with ARBs sometimes have an increase in the serum creatinine levels in spite of a decrease in the urinary protein excretion. The reason for deterioration of kidney function in the hypertensive patients has been recognized as a progression of arterio- and/or arteriolosclerosis. They are associated with the narrowing of the intrarenal arterial and arteriolar lumens. The stenotic or obstructive changes of vessels are commonly induced by the long-term hypertension, the inappropriate control of hypertension, aging and kidney diseases.

However, several papers [33,34] published that the cessation of the treatment of RAAS inhibitors in chronic kidney disease (CKD) patients induced the preservation or improvement in the deteriorated kidney function. Bhandari et. al. in NDT in 2016 reported the same results, clearly showing that ARB treatment affected the deterioration of kidney function in CKD patients [35].

The extremely proliferative thickening of the renal afferent arteriolar walls, induced by ARB/ACEi, has not been reported in humans. The morphological findings of the arterioles detected in autopsies or biopsies were overlooked as a part of hypertensive nephrosclerosis or aging nephrosclerosis, or affected vessels of patients with renal diseases. Several experimental results about the evident proliferative changes of afferent arteriolar walls caused by ARB/ACEi treatments have been published [28,29,36,37]. Due to the widespread use of ARB/ACEi for many organ-protective effects, those papers were not considered to have relation to or have an important role in the progression of the deterioration of kidney function. There have been a few more papers published containing the same morphological changes in animal experiments [38,39].

Then these findings are needed to confirm that human kidneys were treated with ARB/ACEi, and the specimens were studied using healthy parts of uni-nephrectomized kidneys because of malignancy, picked up from hypertensive patients. The morphological and immunohistochemical studies were performed and clinical features were also estimated. The hypertensive patients were divided into the two groups. The one group with antihypertensive agents, which included ACEi/ARB and the second group did not use RAAS inhibitors. Both groups were compared with the normotensive group [40]. In the study, we found the extreme proliferative changes of afferent arteriolar walls, have narrowing arteriolar lumens in specimens of patients treated with antihypertensive agents, including ARB or ACEi, that was the same as the results of the animal experiments. Abundant renin granules were found in the hypertrophic JGA cells, and afferent SMC walls that increased its layers, and with the proliferation of SMC cells [40].

Our group considered the proliferative cells in the afferent arterioles to be SMC cells. However, these days it is known that renin cells in embryonic or early neonatal period differentiate to the SMCs of the afferent arteriolar walls in adults [41]. In 2021, Watanabe et al. found the deletion of renin cells or inhibition of RAAS lead to the concentric thickening of the intrarenal arteries and arterioles in mice and humans. They reported that the SMCs, originally renin cells, proliferated in the afferent arteriolar walls and narrowed its lumens by inhibition of the RAAS inhibition [42].

ARB blocks the angiotensin II type1 receptor of RAAS cascade on vessels. In the endocrinal stream the feedback system of RAAS starts to activate. Then renin production, which is the first substance of the upstream of RAAS, increases. That is a natural reaction of the system. A surprising increase of the renin granules was found in the extremely increased layers of SMC walls of the afferent arterioles by PAM-HE (Periodic Acid Silver-Methenamine -Hematoxylin-Eosin) stain and electron-microscopy in ARB treated rats' kidney [28,29,36]. An increase of the renin granules and renin-producing cells was caused by the feedback system of RAAS. The SMCs are considered to be dedifferentiated SMCs, because myosin patches were found in each cell by electron microphotograph [28,29]. This finding is being used for the identification of SMC. The expression

of anti-smooth muscle myosin isoform 2 (SM2) monoclonal antibody disappeared in the thickened afferent arteriolar walls. This is positively expressed only in mature SMCs, evident by the immunohistochemistry [43]. These show as the same results of the mature SMCs dedifferentiaing to the immature renin cells reported by Watanabe et. al.

Aliskiren, direct renin inhibitor (DRI), induced the extreme increase of renin granules in JGA and in the entrance SMCs of the glomeruli, though SMCs with the abundant renin granules does not extend to the outer SMC layers in rats. The concentric afferent arteriolar proliferation was not found as well [44]. The difference between AEi/ARB and DRI is the activation or lack of activation of the renin/prorenin receptors. These are the start point of the RAAS cascade in the kidney vessel walls. There might be data of Mineral corticoid Receptor Antagonists (MRA), but the results on the afferent arteriolar walls should not be the same as ARB/ACEi.

In the other organs, ARB/ACEi is well known to have organ-protective effects. The protective effect on arteriosclerosis of coronary arteries of ARB. An example that has been reported is a decrease in the remodeling of vessels [45]. The cardiac arteriolar morphological changes were not found in rats which have evident renal arteriolar proliferative changes induced by ARB (unpublished data).

The duration of the experiment using rats was 12 weeks, which is not long-term for humans. The proliferative afferent arteriolar walls were more frequently seen in the juvenile rats than in the adult rats [29]. The juvenile Wister rats were studied after the cessation of diet with ARB, and followed with normal diet for several weeks. In the study, a decrease of the degree and frequency of pathological arteriolar changes and renin granules were found. However, the findings were different for each rat (unpublished data). It is difficult to identify when treatment started and the amount of dosage throughout duration of the administration of ARB/ACEi in the retrospective study of humans. The many patients with essential hypertension or hypertensive renal diseases have renal arteriosclerosis and/or arteriolosclerosis in a wide range of severity. The severe changes of the renal vessels narrow the lumens of renal arteries and arterioles. The obstructive or stenotic changes of lumens accelerate with ARB/ACEi over a long-term treatment. This leads to a lesser glomerular blood flow and possibly to tissue hypoxia.

As mentioned above, the cessation of ARB/ACEi was clinically reported to preserve or improve the kidney function deterioration of CKD. However, it needs careful exchange of ARB/ACEi as antihypertensive agents. Due to the renal histological changes, the afferent arteriolar changes, and the numbers of renin-producing cells do not decrease quickly, although they might be reversible until some point. DRI or MRIA should be used in those cases instead of ARB/ACEi, or the dosage of ARB/ACEi should decrease to a minimal amount.

The treatment of RAAS inhibitors, especially ARB and ACEi, have many organ-protective effects. However, ARB/ACEi include the ability to affect the afferent arterioles in the kidney. These agents can induce renin production increase and SMCs on the arteriolar walls to change to the de-differentiated original renin cells in the kidney. It is necessary to give the serious attention to the influences and the results of the blockade of the RAAS cascade in the kidney. Further studies on the beneficial methods of using these agents for the kidney are needed.

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