Renoprotection of angiotensin receptor blockers: beyond blood pressure lowering

Toshio Miyata¹ and Charles van Ypersele de Strihou²

¹Institute of Medical Sciences and Division of Nephrology, Hypertension and Metabolism, Tokai University School of Medicine, Kanagawa, Japan and ²Service de Nephrologie, Université Catholique de Louvain, Brussels, Belgium

Keywords: advanced glycation end products; blood pressure; chronic hypoxia; diabetic nephropathy; oxidative stress; PAI-1; renin-angiotensin system

In pioneering studies, Mogensen [1] and Parving et al. [2] have demonstrated that anti-hypertensive treatment slowed the decline of renal function in hypertensive patients with diabetic nephropathy. These observations were subsequently extended to other types of hypertensive renal diseases. No attention was paid to the type of the utilized anti-hypertensive drug: blood pressure lowering was the main goal.

Several clinical studies, mainly but not exclusively in diabetic patients, have subsequently suggested that anti-hypertensive agents inhibiting the renin–angiotensin system (RAS), such as angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II type 1 receptor blockers (ARBs), achieved better renoprotection than other anti-hypertensive drugs [3–7]. Inhibitors of the RAS not only protected renal function, but also lowered proteinuria even at the level of microalbuminuria [6,7]. Microalbuminuria emerged as an important independent risk factor not only for end-stage renal failure but also for cardiovascular disease [8]. As a result, ARBs and ACEIs are now part of the standard treatment of patients with diabetic nephropathy, regardless of the presence of systemic hypertension.

Renoprotection is partially independent of blood pressure lowering

Clinical studies had already suggested that RAS inhibitors provide renoprotection independently of blood pressure (BP) lowering [3–7]. More recently, Weinberg et al. [9] gave patients with heavy proteinuria increasing doses of candesartan up to 96 mg/kg/day, doses far above those for which the drug is licenced and which are accepted in clinical practice. Proteinuria fell progressively throughout the dosage range, although BP did not decrease beyond the maximal recommended dose of 32 mg/day. Parving and his colleagues [10] reported a similar dissociation between BP and renoprotection in several patients given increasing doses of candesartan.

However, as yet, no systematic, prospective study has evaluated separately the dose of ARB needed for optimal BP control and that providing a maximal reduction of proteinuria. Indeed, in most clinical studies, the dose used to assess the decrease in proteinuria had remained within the range providing a dose-dependent BP reduction. We therefore utilized a hypertensive, type 2 diabetic rat model to compare the BP and proteinuria lowering effect of increasing doses of valsartan [11]. Different animal groups received various doses of valsartan (4–160 mg/kg/day) for 8 weeks. No additional decrease in BP was observed above 120 mg/kg/day, suggesting that the optimal dose for BP lowering was between 80 and 120 mg/kg/day. In contrast, proteinuria fell in a dose-dependent fashion, without evidence of any ceiling. Clearly, renoprotection was dissociated from BP lowering.

Extrapolation of these experimental findings to humans suggests that the dosages of ARB used in clinical studies are below those needed to obtain a maximal BP reduction. They remain within the range in which BP and proteinuria fall in parallel. A combination of ACEIs and ARBs (reviewed in [12]) is, therefore, expected to improve proteinuria without postulating a synergistic effect due to each drug’s individual RAS target.

Pleiotropic benefits of ARBs beyond BP lowering

The dissociation between BP and renoprotection has been interpreted within the RAS inhibition
hypothesis as a consequence of the substantially higher angiotensin II concentrations within the kidney than in the systemic circulation [13].

Recent studies offer, however, an alternative view, implying at least in part an RAS independent effect of ARBs. Miyata et al. [14] and Forbes et al. [15] previously demonstrated that in vitro ARBs and ACEIs inhibit the formation of advanced glycation end products (AGEs), in diabetic or uraemic serum, i.e. independently of BP or RAS levels. The finding is of interest because AGEs have previously been implicated in the genesis of diabetic complications and atherosclerosis [16]. Inhibition of the formation of AGEs by ARBs is linked to a common core structure, 5-(4’-methylbiphenyl-2-yl)-1H-tetrazol. Therefore, we are dealing with a class effect. In contrast, no common core structure could be identified for ACEIs. Further in vitro studies revealed that ARBs also inhibit oxidative stress (i.e. by scavenging hydroxyl radicals and by chelating transition metals involved in the Fenton reaction) [17]. Compared with calcium channel blockers and beta blockers, only ARBs inhibit simultaneously advanced glycation and oxidative stress [17].

The in vivo relevance of these in vitro results was tested in hypertensive, type 2 diabetic rats with nephropathy, spontaneously hypertensive/NIH-corpulent rat SHR/NDmc-cp [18]. Three types of anti-hypertensive agents (i.e. olmesartan, nifedipine and atenolol) were compared. Despite similar BP lowering effects, only olmesartan significantly reduced proteinuria and prevented glomerular and tubulointerstitial damage (i.e. mesangial activation, podocyte injury, tubulointerstitial injury, inflammatory cell infiltration). Intra-renal AGE formation decreased in parallel: proteinuria was tightly correlated with the renal content of pentosidine, an AGE moiety [17–19]. Interestingly, the fall in intra-renal AGEs was accompanied by a decreased expression of haem-oxygenase (HO)-1 and of p47phox (a subunit of NADPH-oxidase), two enzymes involved in the defence against oxidative stress [17].

The inter-relationship between the reduction of AGEs and of oxidative stress remain to be elucidated. A primary effect on oxidative stress is possible as AGE formation is closely linked to an enhanced oxidative stress [16]. It was previously demonstrated that glomerular damage in diabetic patients required the local association of AGEs with oxidative stress [20]. We assessed three distinct AGE moieties, pentosidine and CML (both of which depend on glycation and oxidation), and pyrraline (the generation of which solely depends on glycation): only the first two AGEs but not the latter accumulated in diabetic glomeruli. These data support Monnier’s contention that AGE accumulation and the resulting pathological consequences may be corrected by agents with potent hydroxyl radical scavenging and transition metal chelating capacities [21]. Alternatively, a primary effect of ARBs on AGE formation with a subsequent change in oxidative stress is also plausible as the interaction of AGEs with a cell surface receptor (RAGE) releases reactive oxygen species [22]. Overexpression of RAGE in mice indeed worsens oxidative stress and diabetic renal damage [23].

Four other features of type 2 diabetic renal damage in rats are improved by ARBs and may contribute to diabetic nephropathy [17]. The first is the chronic tubulointerstitial hypoxia, evaluated by staining with pimonidazole, a cellular marker of hypoxia. Tubulointerstitial hypoxia is crucial in the progression of renal disease [24]. Its causes are multifactorial, including the constriction of efferent arterioles by angiotensin II with an attendant decrease in peritubular capillary flow.

The second is the reduction of interstitial infiltrate of inflammatory cells. It might result from an amelioration of hypoxia or, alternatively, from the correction of an imbalance between helper T cell subsets as observed after angiotensin II infusion in another hypertensive kidney injury model [25].

The third is the disappearance of iron deposits in the rat diabetic kidney. Iron precipitation harms the kidney. The iron content of proximal tubular cells, both in human chronic renal disease and in the rat haemodilution model, correlates with proteinuria but not with glomerular filtration rate [26]. Conversely, the iron chelator, desferrioxamine, prevents iron deposition in tubular cells of rats given angiotensin II and reduces proteinuria [27]. Iron staining might thus provide investigators with an easy tool to ascertain in vivo the renoprotective effects of various treatments. Of note, the parallel between iron deposition in the tubulointerstitium and the infiltration of inflammatory cells suggests that apoptotic degradation of inflammatory cells might release intracellular iron into the interstitial space [17]. However, the precise relationship between in vitro metal chelation, in vivo reduction of iron deposits and direct inhibition of oxidative metabolism remains to be investigated.

The fourth is the lowered intra-renal activity of the plasminogen activator inhibitor (PAI-1), a multifunctional protein. Its activities extend beyond fibrinolysis and include turnover of extracellular matrix and activation of several proenzymes and growth factors [28]. PAI-1 is involved in both glomerulosclerosis and tubulointerstitial fibrosis and facilitates the progression of renal diseases [29].

This rather heterogeneous list of potential determinants or mediators of diabetic nephropathy is tentatively integrated in a hypothetical scheme depicted in Figure 1. Clearly, the inter-relationships between these various elements preclude the identification of a single culprit in the genesis of diabetic kidney lesions. Whatever be these hypotheses, ARBs and probably ACEIs have unique renoprotective properties including certainly a decreased oxidative stress, the correction of chronic hypoxia, and the inhibition of AGE formation, abnormal iron deposition, PAI-1 activity and inflammatory cell infiltration. These experimental observations support clinical studies which have
reported that beta blockers and calcium channel blockers do not provide renoprotection independently of BP lowering.

Therapeutic perspectives

The pleiotropic effects of ARBs have rekindled the search for new targets to prevent diabetic nephropathy and, perhaps, other nephropathies.

For example, we screened in vitro the anti-oxidative and AGE lowering activities of over 1300 compounds contained in our chemical library. Edaravone, a drug used in the treatment of cerebral infarction or vascular disease, was found to be a powerful AGE inhibitor. Its trapping of pyridoxal might, unfortunately, limit its long-term use. We traced this entrapment to an α-methylene group, the deletion of which led to the eventual synthesis of an original compound, TM2002 [30]. In vitro, TM2002 does not trap pyridoxal, but inhibits AGE formation more efficiently than other known inhibitors, such as aminoguanidine, pyridoxamine and ARBs. Furthermore, it inhibits α-tirosine formation mediated by hydroxyl radicals as well as oxidation of ascorbic acid catalysed by the transition metal mediated Fenton reaction. This compound has no affinity for the human angiotensin II receptor, is orally bioavailable and toxicologically safe. In two rat models of renal disease (anti-Thy 1 nephritis and ischaemia-reperfusion), TM2002 (100 mg/kg/day), given for 1–14 days, markedly improved renal lesions without modification of systolic BP and without any adverse effect [30]. The lack of hypotensive effect should prove crucial in the treatment of normotensive or hypertensive patients.

We are also currently testing new small molecule agents targeting the plasminogen activator system or the hypoxia inducible factor (HIF).

To summarize, the discovery of unexpected benefits of ARBs and ACEIs, unrelated to BP lowering, suggests a new paradigm to understand the genesis and progression of renal disease in diabetic and perhaps other patients. Novel therapeutic strategies will, hopefully, ensue.

Conflict of interest statement. None declared.

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Received for publication: 27.12.05
Accepted in revised form: 12.1.06