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Specific organ protection by blocking the renin–angiotensin system

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Introduction—the role of the RAS in progressive renal disease

Since renal disease is characterized by sodium/volume retention and elevated blood pressure (BP) one would expect suppression of the renin–angiotensin system (RAS) in renal patients, but inappropriate activity of the RAS has been documented even in early stages of renal diseases, i.e. when glomerular filtration rate (GFR) and BP are in the normal range.

The activation of the RAS has been attributed to a faulty sensing by the baroreceptor because of luminal narrowing and altered wall texture of afferent glomerular arterioles. Consequently, despite hypertension, the juxtaglomerular apparatus senses low BP and secretes inappropriate amounts of renin. It has become evident that this is not the only mechanism of inappropriate activation of the RAS. In several studies renin production outside of the juxtaglomerular apparatus could be demonstrated.

Activation of the RAS has been documented by measurements of plasma renin activity (PRA), which is inappropriately high in relation to BP and sodium status. PRA is mostly (pseudo) normal or slightly elevated. Low PRA is common in elderly diabetic patients.

The most convincing evidence for a pathogenetic role of the RAS in progression has come from intervention studies following the report of Anderson *et al*. [1] that the ACE-inhibitor enalapril abrogates proteinuria and glomerulosclerosis more than equipotent lowering of BP by alternative hypertensive agents. This has been confirmed in many models of renal disease and in clinical trials [2–4].

It is also evident that the nephroprotective effect of ACE-inhibitors and angiotensin II (Ang II) receptor blockers is not only mediated via their renal haemodynamic effects, but also through non-haemodynamic mechanisms.

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Involvement of local *vs* systemic RAS in renal disease

There are several examples that pharmacological blockade of the RAS is paradoxically effective although circulating PRA is low, e.g. in the elderly and in diabetes mellitus. This has been shown both in experimental studies and in human beings [2,5]. As an example we discuss the human evidence in diabetes. Price *et al*. [6] looked at the increment in renal plasma flow (RPF) after administration of the Ang II receptor antagonist irbesartan in patients with type 2 diabetes. They noted that although PRA was lower than in healthy subjects (0.58 ± 0.14 *vs* 1.58 ± 0.28 ng/l), RPF increased more in response to irbesartan in type 2 diabetes (714 ± 83 to 931 ± 116 ml/min) than in normal subjects (624 ± 29 to 772 ± 49 ml/min). The authors hypothesized that there was activation of the local RAS, which would explain the paradoxical contrast between suppressed renin in the circulation and the exaggerated renal vasodilator response to irbesartan, as well as therapeutic effectiveness of pharmacological blockade of the RAS [2]. The question arises: which signal activates the local RAS? Miller [7] examined patients with early type 1 diabetes under two conditions: euglycaemia and hyperglycaemia. The increment of RPF after losartan was seen only in hyperglycaemic, but not in normoglycaemic patients. This raises the issue whether hyperglycaemia *per se* activates the RAS possibly in sites outside of the juxtaglomerular apparatus. Indeed, recent evidence documents local synthesis of angiotensinogen and other components of the RAS in proximal tubular epithelial cells. Wang *et al.* [8] found that in opossum kidney cells as a model of proximal tubular cells, hyperglycaemia upregulated expression of the angiotensinogen gene, presumably because of a glucose responsive element in the 5′-flanking region of the angiotensinogen gene. In agreement with this hypothesis of a local activation of the RAS, Wagner *et al.* [9] found lower mRNA for the AT1-subtype of the Ang II receptor mRNA in kidney biopsy samples of diabetic compared to non-diabetic patients; this was interpreted as a reflection of homogenous receptor downregulation.

The idea that local activation of the RAS in the proximal tubular cells may be generalized to apply to non-diabetic renal disease as well is illustrated by the study of Gilbert *et al*. [10]. They found marked expression of renin and Ang II (predominantly in tubular epithelial cells) by *in-situ* hybridization and immunostaining in the subtotally nephrectomized rat. Upon administration of the ACE-inhibitor perindopril renin expression in the juxtaglomerular apparatus increased (as one would anticipate because of interruption of the short feed-back loop), whilst expression of renin and Ang II in the proximal tubular cells decreased. This illustrates that the juxtaglomerular and extra-juxtaglomerular systems are not controlled by the same regulatory mechanisms.

Clinical evidence for the importance of local RAS

Today there is no good clinical evidence available that clearly documents BP-independent effects of ACE-inhibitors on progression of renal damage, despite some tantalizing findings pointing towards this direction, particularly the dissociation between the BP-lowering and the antiproteinuric effect [4,5].

In this context, it is rewarding to discuss the results of the HOPE study [11]. This study examined patients at high cardiovascular risk without evidence of heart failure, almost 50% of whom were normotensive. They were given either 10 mg/day of ramipril or placebo. Ramipril caused a remarkable reduction of death from cardiovascular causes (−26%), myocardial infarction (−20%), stroke (−32%), death from any cause (−16%) revascularization procedures (−15%), cardiac arrest (−38%), heart failure (−23%), and complications related to diabetes (−16%). In parallel, progression of microalbuminuria to more advanced stages of diabetic nephropathy was also reduced [12].

What is the explanation for this BP-independent cardiovascular benefit from ACE-inhibition? There have been many recent reports on accumulation of ACE within coronary artery plaques in humans, specifically in macrophages. Ang II presumably enhances the expression of IL-6, stimulates the NADPH/NADH dehydrogenases, increases reactive oxygen species and acts as a signal to induce an inflammatory phenotype. Due to space limitation, we cannot discuss other potential mechanisms of Ang II-induced vascular/renal damage, particularly activation of TGF-α, which undoubtedly also plays an important role. It is logical to assume (but currently still hypothetical) that the beneficial effect of ACE-inhibition in cardiovascular protection studies is mediated via such non-haemodynamic mechanisms.

Clinical consequences and conclusion

In the past, ACE-inhibitors and Ang II receptor blockers have been dosed according to their antihypertensive action. If indeed local RASs are involved (as one may conclude from the above evidence) the question arises whether the antihypertensive dose is identical with the dose conferring maximal benefit from blockade of these non-classical systems. As to the kidney, there are suggestions that when BP is maximally lowered by ACE-inhibitors or Ang II receptor blockers, a further increase of dose may reduce proteinuria despite no further change in BP. In a recent study [13] increasing doses of enalapril and losartan, which were clearly higher than those required to control BP in rats with mesangioproliferative glomerulopathy, caused progressively more marked reduction in glomerulosclerosis and transcription of TGF-α despite no further lowering of BP.

There is some human evidence for this phenomenon in patients with IgA-glomerulopathy. Palla *et al.* [14] examined 16 proteinuric patients with IgA-glomerulopathy and normal GFR and BP. The patients received 5, 10, 15, and 20 mg lisinopril/day for 4-week periods, respectively. Between each dose increment a 3-week wash-out period was interposed. BP decreased by 22% with the lowest dose and no further decrease was seen with the higher doses. Yet, proteinuria progressively decreased by 39, 44, 61, and 67% with the increasing doses of lisinopril.

Would this indicate that one should dose ACE-inhibitors or Ang II receptor blockers according to reduction in proteinuria? In the REIN study it was indeed noted that the initial (4 weeks) reduction in proteinuria was predictive for the long-term attenuation of the rate of GFR [4]. As a practical consequence of the above considerations, it follows that urinary protein excretion should be routinely monitored in renal patients receiving ACE-inhibitors or Ang II receptor blockers. If no satisfactory decrease of proteinuria is noted, more rigorous sodium depletion and increase of the dose of the ACE-inhibitor are indicated.

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