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On the mechanism of the renoprotective action of ace-inhibition

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In many patients with chronic renal disease, progressive loss of renal function occurs despite absence of overt activity of the underlying disorder. The hypothesis that this progressive renal function loss reflects a final common pathway of renal damage was fuelled by several observations. First, by the linear renal function deterioration that occurs in many patients irrespective diagnosis. Second, by the similarity of the histopathology of end-stage kidneys across most renal disorders. Important evidence was furthermore provided by the fact that risk factors for progressive long term renal func-tion loss tend to be similar for different renal diseases. Systemic and glomerular hypertension, glomerular protein leakage and systemic factors like hyperlipidemia all appear to be involved, in a process that also involves mutual interactions.

Remuzzi and Bertani hypothesized a central role for glomerular protein leakage in this multifactorial process of progressive long term renal damage. They identify two basic mechanisms underlying increased glomerular protein leakage. First, an increased intraglomerular hydrostatic pressure, and second altered permeability characteristics of the glomerular basement membrane, for instance due to toxins or an immunological reactions. In both situations the increased renal protein load is assumed to be the mediator of the ensuing renal glomerular and interstitial damage, thus constituting a final common pathway for the progression of renal function loss.

This placed focus on proteinuria as a mediator of progressive renal function loss. Clearly, this might have implications for renoprotective intervention therapy. As to renoprotective intervention the last decade emphasis has been on two major strategies, i.e antihypertensive treatment and dietary protein restriction. Considering the alleged role of proteinuria, it is of interest that both reduction of blood pressure and an effective reduction of dietary protein intake result in a reduction of proteinuria. This is consitent with the assumption that reduction of proteinuria as such might be a mediator of renoprotection, by different interventions.

Interestingly, previous investigations found ACE-inhibitors to exert a more pronounced antiproteinuric effect than conventional antihypertensives with a similar effect on blood pressure. Later studies showed their efficacy in providing protection against long term renal function loss in experimental animals and in man, illustrating their potency as a class of drugs of proven renoprotective potential. Yet renoprotection afforded by ACE inhibition is not complete, and it would be useful to unravel their mechanism of action, in order to guide the development of more effective renoprotective strategies. Our studies aimed to elucidate the mechanisms of the antiproteinuric and renoprotective action of ACE inhibition, by studying the effects of ACE inhibition in adriamycin-induced proteinuria in the rat.

Adriamycin-induced proteinuria is a well-established normotensive rat model for proteinuria-induced progressive renal damage. However, at the onset of our studies its suitability as a tool for intervention studies was still disputed. Therefore, we had to investigate and validate its properties as a tool for renoprotective intervention studies (Chapters I and II). To this purpose we deliberately refrained from a common practice in intervention studies in experimental renal disease, i.e. a study design where intervention starts before, or at the time of disease induction. By contrast, we investigated the properties of the model in a setting that more closely resembles the treatment conditions in clinical practice. That is, treatment was started not until proteinuria was well-established.

Chapter I

In this chapter we tested the hypothesis that in adriamycin-induced proteinuria, like in Human renal disease, dietary sodium restriction potentiates the effects of ACE inhibition on blood pressure and proteinuria. Sodium intake per se did not affect blood pressure or the severity of proteinuria. The ACE-inhibitor lisinopril reduced blood pressure as well as proteinuria. In accord with our hypothesis, these effects were potentiated by dietary sodium restriction.

Chapter II

Adriamycin nephrosis has been used by many different laboratories. It is induced by a single or a double dose of adriamycin with doses that vary considerably between investigators, from 2 to 7,5 mg/kg. Intervention studies with ACE-inhibitors in this model have provided conflicting results. We hypothesized that these discrepancies might be related to the dose of adriamycin used to induce proteinuria. To test this hypothesis we compared the effects of three different doses of adriamycin (1, 2 and 3 mg/kg) on proteinuria and glomerulosclerosis and on the therapeutic efficacy of ACE-inhibition on these parameters. We found that indeed the dose of adriamycin used to induce proteinuria was crucial for the properties of the model. It appeared to be an important determinant not only of the eventual severity of glomerulosclerosis, but notably also of the responsiveness to ACE-inhibition. Despite a more or less similar proteinuria in the 3 mg/kg animals as compared to the 2 mg/kg animals, the therapy response to ACE inhibition was markedly different, with a clearcut response in the 2 mg/kg animals, and a virtually absent response in the 3 mg/kg animals. Thus, in the interpretations of findings in this model the dose of adriamycin used should be carefully considered. Under the experimental conditions of our laboratory in the Wistar rat strain (Harlan) 2 mg/kg adriamycin appeared to be the most appropriate dose. We want to note, however, that the optimal dose may not necessarily be similar for different experimental settings as the susceptibility to adriamycin toxicity may vary across different rat strains and depend on experimental conditions.

Chapter III

Reduction of proteinuria might play a role in the renoprotective effect of ACE-inhibition. If so, an effective antiproteinuric response to ACE-inhibition would predict subsequent protection against renal structural damage. This hypothesis was tested in 96 male Wistar rats with established adriamycin nephrosis. Reduction in proteinuria was achieved by lisinopril (0, 2, 5 and 10 mg/kg/24h) on two different sodium intakes: normal sodium (0,3% NaCl) and restricted sodium (0,05% NaCl). Therapy started six weeks after the induction of the disease and was continued for six weeks. Lisinopril reduced blood pressure by 32±4% and proteinuria by an average of 72±7% with stabilization after two weeks. Considerable interindividual differences in antiproteinuric response were found. Glomerulosclerosis score was significantly reduced. Sodium restriction in itself did not affect blood pressure, proteinuria and glomerulosclerosis score, but the effects of ACE-inhibition on blood pressure and proteinuria were enhanced by dietary sodium restriction. Interestingly, the more proteinuria was reduced initially in an individual rat the less sclerosis was found on the long term. Thus, the individual short-term antiproteinuric effect predicts protection against ultimate glomerular
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Chapter IV

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Chapter V

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against ultimate glomerular damage. These findings support the hypothesis that reduction of proteinuria is a mechanism by which ACE-inhibition exerts renoprotection.

Chapter IV

ACE-inhibition not only decreases the formation of angiotensin II, but also interferes with the breakdown and inactivation of bradykinin. In the studies described in this chapter we aimed to differentiate between these two possible mediating pathways. Four series of chronic experiments in established adriamycin nephrosis were performed. In the first series lisinopril reduced blood pressure and proteinuria after two weeks of treatment. Subsequent continuous intraperitoneal infusion of angiotensin-II for two weeks partially restored proteinuria whereas blood pressure increased to almost pretreatment levels. Subsequent withdrawal of angiotensin-II restored the antiproteinuric effect of lisinopril, whereas subsequent withdrawal of ACE-inhibition restored proteinuria to pre-ACE-inhibition levels. In the second series an angiotensin-II antagonist reduced blood pressure and proteinuria, similar to the effect of lisinopril. In the third series lisinopril reduced blood pressure and proteinuria. Subsequent intraperitoneal infusion of a bradykinin antagonist for two weeks had no effect on blood pressure or on proteinuria. In the fourth series a continuous two weeks infusion of exogenous bradykinin was used to mimic decreased bradykinin breakdown. This had no effect on proteinuria but did induce a fall in blood pressure. The blood pressure lowering effect of exogenous infused bradykinin was completely reversed by one week of bradykinin antagonist infusion while proteinuria remained unchanged. Thus, the antiproteinuric effect of ACE-inhibition appears to be independent of bradykinin effects in this model, supporting a main role for reduction of angiotensin-II in the antiproteinuric action of ACE-inhibition.

Chapter V

This chapter explores one of the possible mechanisms of the antiproteinuric effect of ACE-inhibition. Reduction of systemic and intraglomerular pressure have been stated to be involved in the antiproteinuric effect. However, at the onset of ACE-inhibition all hemodynamic effects are immediately apparent whereas the antiproteinuric effect has a more gradual onset of action. This suggests involvement of additional factors such as renal structural alterations improving the glomerular permselectivity. Heparan-sulfate proteoglycans play a crucial role in the permselective properties of the glomerular basement membrane. We therefore investigated the effects of ACE inhibition on proteinuria, focal glomerulosclerosis and heparan-sulfate proteoglycan staining in adriamycin nephrosis. Adriamycin nephrosis was associated with impairment of heparan-sulfate side-chain staining preceding focal glomerulosclerosis. When focal glomerulosclerosis ensued, both heparan-sulfate side-chain and heparan-sulfate proteoglycan core-staining were impaired. Interestingly, this impairment was significantly less severe in the lisin-opril treated rats. The latter finding is consistent with the assumption that structural effects on the glomerular basement membrane contribute to the renoprotective effects of ACE-inhibition in this model.

Chapter VI

In contrast to the previous chapters in this last chapter we return to the clinical setting, reviewing the predictive value of the short term antiproteinuric effect of ACE-inhibition for subsequent renoprotective efficacy in patients with non-diabetic renal disease. The reviewed studies demonstrate that a more effective early reduction of proteinuria consistently predicts a more favorable course of long term renal function during therapy. This relationship is apparent for between-group studies comparing the renoprotective efficacy of different therapeutic regimens as well as for within-group comparisons for patients on a single regimen. This relationship shows a remarkable parallel with the evidence for a better renal prognosis after spontaneous remission of proteinuria. Taken together these findings support the assumption that proteinuria might be a mediator of long term renal function loss. As to the mechanism by which ACE-inhibitors afford long term renoprotection the predictive value of the short term reduction in proteinuria, as opposed to the lack of a predictive value of the blood pressure response, supports the assumption that specific renal effects are involved in long term renoprotection. The findings reviewed suggest that the investigation of treatment regimens aimed at aggressive reduction of proteinuria might provide a strategy to further enhance the potency of long term renoprotection.

For the moment, despite the advancements of the last decade, proteinuric renal disease is still essentially a progressive condition with a grim long term prognosis for most patients. If titration for reduction of proteinuria could further ameliorate long term GFR decline, this would not only provide evidence for proteinuria as a mediator of renal damage, it might also improve the outlook for the patient with chronic renal failure.