Cardiorenal interaction
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CARDIORENAL INTERACTION

Chronic kidney disease is a major cause of morbidity and mortality worldwide, leading to end-stage renal disease with the need for dialysis and renal transplantation. Prevention of further progression of renal disease is of utmost importance to postpone these undesired events. Recent studies have disclosed a complex relationship between cardiovascular and renal disease. Enhanced progressive renal damage was described in a model of cardiorenal interaction elicited by myocardial infarction in unilateral nephrectomized rats. In chapter 2 we confirmed this detrimental cardiorenal interaction and we showed that it can be attenuated by treatment with an angiotensin converting enzyme inhibitor (ACEi) with substantial beneficial effects on kidney and heart. ACEi therapy interference was effective in the prevention of enhanced renal damage caused by myocardial infarction. Interestingly, cardiac function showed a more favorable outcome in the ACEi group compared to the vehicle group at the end of the study. In view of these findings, it is likely that the RAAS is of significant importance in this cardiorenal interaction model.

In chapter 3 we explored the hypothesized vicious circle between the heart and the kidneys in animals with already decreased renal function, and therefore high serum creatinine levels caused by 5/6 nephrectomy (5/6NX), by investigating the long term renal effect of cardiac function loss caused by myocardial infarction (MI). Moreover, protective effects of ACEi in combined severe cardiac and renal damage were established trying to break through this vicious circle. The main finding of this study is that the cardiorenal interaction model, comprising of 5/6NX + MI, features specific additional hemodynamic damage to both kidney and heart compared to 5/6NX or MI alone, although no increase in proteinuria and focal glomerulosclerosis. Moreover, treatment with an ACEi effectively attenuates these specific features of cardiorenal interaction in the rat.

The cardiorenal interaction leads to a decreased cardiac output and cardiac remodeling. This process of cardiac remodeling shows similarities with features of cardiac aging. In chapter 4 we investigated if cardiac remodeling, due to renal function loss caused by 5/6NX, is associated with cardiac telomeric shortening as a measure of aging. Telomeres form the end of chromosomes and prevent the loss of genetic information. We found in rats with severe renal failure shortening of telomere lengths, while such changes were absent in rats with only mild renal function loss. The changes in cardiac telomere length in severe renal function loss were even comparable to the changes measured in rats that underwent myocardial infarction. The combination of severe renal damage and myocardial infarction did not lead to an excess in shortening of telomeres compared to sole 5/6NX and MI. From these results we conclude that in animals with renal failure, cardiac aging was present in comparable amount as after myocardial infarction, although in animals with both renal and cardiac damage, cardiac aging was comparable to aging in sole cardiac and renal damage.

THERAPEUTIC PERSPECTIVES

Not all patients with chronic renal failure benefit optimally from ACE inhibitors, though to the large inter-individual variation in therapy response to these drugs. Because the amount of proteinuria reduction is correlated to renal prognosis, it is of utmost importance to reduce proteinuria to the lowest possible level. Beside the RAAS, there are other hormone/peptide systems influencing these disease processes. Insight into the effect of these peptide systems on the progression of renal damage could give insight in how to optimize ACEi therapy.
In chapter 2 we investigated the hypothesized additive effect of neutral endopeptidase inhibition (NEPi) to ACEi in a cardiorenal interaction model. No additional protective effect of ACE/NEPi over ACEi was observed on renal damage in the present study. This leaves only little evidence for a discernible beneficial effect of increased natriuretic peptide levels of beyond concurrent RAAS inhibition and associated blood pressure reduction in this cardiorenal model with short-term pharmacological intervention. Our data does however not exclude ACE/NEPi to still have an important clinical contribution in both ‘renal’ or ‘cardiac’ patients, since ACE/NEPi has proven to be effective in more isolated renal and cardiovascular disease.

Beside combination therapy of ACE and NEP, the inhibition of the natriuretic peptide system could be combined with inhibition of the endothelin system as well. In chapter 5 we investigated the pharmacological effects of ECE/NEPi in advanced renal damage after 5/6NX. We showed that ECE/NEPi did not affect the already developed proteinuria and focal glomerulosclerosis in this rat model for renal impairment. In contrast, ACEi effectively reduced proteinuria and slightly prevented focal glomerulosclerosis. Beneficial cardiovascular effects of ECE/NEPi have been shown in different animal models of heart failure. In the time frame we used, ECE/NEPi was not effective on cardiovascular parameters.

An other vasoactive peptide playing an important role in the pathogenesis of several cardiovascular diseases such as heart failure, hypertension, and chronic renal failure is vasopressin. In chapter 6 we compared early and late intervention with a Vasopressin1a-receptor antagonist in the 5/6 nephrectomy model for renal damage. It was shown that the V1a-receptor antagonist protected against the early progression of renal injury, whereas its effectiveness seems limited in established renal damage.

A large interindividual variation in therapy response to ACEi is observed in patients. In chapter 7 we investigated if ACE inhibitor therapy responsiveness on proteinuria in 5/6 nephrectomized rats is caused by a variation in pharmacokinetic or -dynamic effects of the ACE inhibitor lisinopril. As a pharmacodynamic cause, we found that high renal ACE activity and ACE protein expression might account for therapy resistance of ACEi. As a pharmacokinetic cause we found a correlation between antiproteinuric response and inter-individual variation in lisinopril excretion. It seems that a combination of pharmacodynamic and -kinetic variation could account for the inter-individual differences in antiproteinuric response in 5/6 nephrectomized rats.

Because increased renal ACE expression could account for therapy resistance, optimizing ACEi therapy could be established by targeting ACEi to the exact location were renal ACE is localized: the brush boarders of the tubular cells. In chapter 8 we investigated whether an inferior response to ACEi under high sodium condition may be attenuated by targeting the drug to the kidney. Therefore, we studied the effect of captopril-lysozyme conjugate on adriamycin induced proteinuria in rats fed with a high sodium diet. In these rats, captopril-lysozyme conjugate significantly reduced the proteinuria without affecting blood pressure. In contrast, captopril treated animals displayed the opposite effect, i.e. a reduction in blood pressure without any effect on proteinuria. Although captopril-lysozyme conjugate was administered in a dose five times lower than captopril, even higher captopril levels were found in the kidneys. These results demonstrate the working profile of the captopril-lysozyme conjugate to be reno-selective up to an extent that antiproteinuric effects were observed, without any effect on blood pressure in nephrotic rats on high sodium diet.
CONCLUSION
The aim of this thesis was to get more insight in the mechanism behind the cardiorenal interaction and in the pharmacological approach to optimize therapy response to interfere in the negative spiral of cardiorenal interaction. From the first part of this thesis we can conclude that in our cardiorenal interaction model RAAS activation is an important mechanism leading to an increase in renal and probably also cardiac damage. Especially in animals with only mild renal function loss, RAAS activation could account for an increase in renal damage after myocardial infarction. In rats with already high plasma creatinine levels, inhibiting this RAAS activation with an ACEi showed to be effective in neutralizing this cardiorenal interaction: the increase in renal and cardiac damage caused by a myocardial infarction was counteracted by ACEi.

From the second part of this thesis we can conclude that in the animal models we used and in the time span in which therapy was applied, ACEi showed to be at least comparable or even preferable to the studied interventions in the other hormone/peptide systems. The beneficial therapy response to ACEi is highly variable between different individuals. This response variation could be explained by a difference in both pharmacodynamic and pharmacokinetic alterations of the ACEi. A strategy to optimize a blunted therapy response to ACEi by high sodium diet is to specifically target the ACEi to the kidney.