Interactions between the sympathetic nervous system and renin-angiotensin system in heart failure
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Chapter 9

Summary & Conclusions

Interaction between the sympathetic nervous system and renin-angiotensin system in part relate to their common role in regulation of hemodynamics. Besides these hemodynamic related interactions, some evidence was provided for direct receptor mediated interactions between these systems. These direct interactions are possibly involved in early compensated stages of heart failure. In Part A the direct interactions between the sympathetic nervous system and renin-angiotensin system were further evaluated.

Chapter 2 presents the development and validation of a method that enables study of these local interactions. This so called ‘microdialysis’ method is generally accepted in experimental studies of the central nervous system. In this chapter local norepinephrine release in the rat left ventricle was monitored, in vivo, without affecting hemodynamics. Several experiments were performed to validate whether the detected norepinephrine concentration was actually released from sympathetic nerve endings. This, by means of locally applied type I or type II reuptake inhibition using desipramine or cocaine respectively, inhibition of stress induced catecholamine release by the voltage gated Na⁺ channel blocker tetrodotoxin, or monitoring of infused norepinephrine. The results show, that the norepinephrine detected in these experiments was indeed released by sympathetic nerve endings.

In chapter 3 the newly developed cardiac microdialysis method was employed to further evaluate the direct interaction between the sympathetic nervous system and renin-angiotensin system. This study shows that increasing doses of exogenous angiotensin II stimulates endogenous norepinephrine release. Moreover, this angiotensin II-induced norepinephrine release was significantly reduced by local administration of losartan. Consequently these experiments indicate that the renin-angiotensin system is able to regulate sympathetic activation directly, involving AT₁ receptors.

In Part B1, the relative role of the sympathetic nervous system in heart failure was studied by evaluating the effects of dopaminergic agonists. These compounds were found potentially useful in the treatment of heart failure, since on the one hand they are able to reduce the sympathetic drive, involving presynaptic D₂-like
receptors, while on the other hand they are able to induce direct vasodilation, involving postsynaptic D₁-like receptors. However, although stimulation of dopaminergic receptors may be favourable in the treatment of heart failure, at higher doses these compounds often also activate non-dopaminergic receptors, such as α- and β-adrenoceptors. Stimulation of these receptors has known adverse effects. Since heart failure may be accompanied by accumulation of drugs, this non-dopaminergic receptor profile may be of particular importance for the total effect of treatment with dopaminergic agonists.

In chapter 4 the effects of several dopaminergic agonists on human artery rings were studied, in vitro. This, to illustrate the potential favourable- and unfavourable effects of these compounds. The data show that these dopaminergic agonists induce direct dilatation, when other interacting receptors are blocked. However, when these interacting receptors were not blocked, ibopamine and dopamine induced contraction, whereas Z1046 did not. This contraction of ibopamine and dopamine was mediated by α₁-adrenoceptor stimulation. The data show that, in contrast to ibopamine and dopamine, Z1046 inhibited α₁-adrenoceptor. In conclusion, the study shows that the selectivity of these compounds should be further improved, before use in treatment of heart failure. Since it may be difficult to reach absolute selectivity for dopaminergic receptors, the total receptor profile of these compounds is of particular importance. In this respect Z1046 may be useful, although the effect of this compound should be thoroughly tested, particularly under different physiological conditions before use in heart failure patients.

Chapter 5 evaluates the effects of relative selective dopaminergic receptor stimulation on ventricular remodeling after experimental myocardial infarction in rats. In line with the previous chapter, this study addresses the issue of whether the receptor profiles of ibopamine and Z1046 are appropriate to treat heart failure. Although there were no large differences between treatment with ibopamine and Z1046, there was a tendency to a further reduction of remodeling, and a preservation of cardiac function after treatment with Z1046. Therefore, these data further establish the potential beneficial effects of Z1046. Unfortunately, however, further development of this compound was stopped, since the interest in the dopaminergic concept declined after the finding that mortality in heart failure patients increased after ibopamine treatment.

In Part B2, the relative role of the renin-angiotensin system in progression of heart failure was evaluated by comparing the effects of different intervention strategies in the REN-2 transgenic rat model, in which the local renin-angiotensin system...
Summary & Conclusions

In Chapter 6, the protective effects of different intervention strategies on cardiovascular end-organ damage were described. In order to do so, a comparison was made between treatment with the angiotensin converting enzyme (ACE) inhibitor, quinapril, the angiotensin II AT_1 receptor antagonist, losartan, the mixed α/β-antagonist, carvedilol, and the nonselective vasodilator, hydralazine. Losartan and quinapril fully normalized blood pressure and prevented end-organ damage. In contrast, carvedilol and hydralazine did not prevent end-organ damage, despite reduction of blood pressure. However, in these later treatment groups blood pressure was not fully normalized. Therefore, we concluded that end-organ damage dissociates from blood pressure reduction when the latter is not fully normalized. Furthermore, no important differences were found between treatment with losartan or quinapril. Accordingly, this suggests that the end-organ damage in this model was primarily related to increased angiotensin II concentrations. The data do not exclude possible involvement of other pathways that are regulated by angiotensin II, such as the sympathetic nervous system. It is concluded that treatment of hypertension should not be focused merely on reduction of blood pressure, but also on the underlying mechanism responsible for this phenomenon.

Chapter 7 evaluates the effects of treatment with quinapril, losartan and hydralazine on cardiac hypertrophy and β-adrenergic neuroeffector mechanisms again in these hypertensive REN-2 rats. The study shows that part of the effects of quinapril and losartan are mediated by preventing deterioration of the sympathetic innervation, since these compounds prevent a reduction of myocardial norepinephrine content, as measured indirectly by determining co-transmitted neuropeptide-Y concentrations. Furthermore, desensitization of the β-adrenoceptor-G-protein-adenyl cyclase complex was prevented by treatment with both quinapril and losartan. Since treatment with losartan and quinapril was equally effective, it was concluded that there were no important additional effects of bradykinin accumulation, prostaglandin production or alternative formation of angiotensin II. Furthermore, the limited effect of hydralazine treatment was related both to the moderate hemodynamic effects, and to the limited neuroendocrine inhibitory properties.

In Part C, the possible synergistic effects of combined inhibition of both the sympathetic nervous system and renin-angiotensin system were studied. In order to do so, the neurohormonal consequences of β-blocker treatment as adjunct to

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In Part C, the possible synergistic effects of combined inhibition of both the sympathetic nervous system and renin-angiotensin system were studied. In order to do so, the neurohormonal consequences of β-blocker treatment as adjunct to
ACE-inhibition were evaluated. Rational for this study lies in the fact that recent clinical trials reported significant reduction in mortality after β-blockade against placebo, in patients that were almost all treated with ACE-inhibitors. The explanation for these beneficial effects were focussed primarily on improved hemodynamic and not neurohormonal consequences of adjunctive β-blockade. In chapter 8 these neurohormonal effects of β-blockers in patients with advanced heart failure were studied. In order to do so, we compared the neurohormonal profiles of patients treated without β-blockers or ACE-inhibitors, and patients treated with ACE-inhibitors either with or without adjunctive β-blocker treatment. We found that plasma renin-concentrations were significantly higher after ACE-inhibition when compared to patients not on ACE-inhibition. In contrast, plasma renine levels were not increased after combined β-blockade and ACE-inhibition. The fact that plasma renin levels were low despite chronic β-blockade (in this study for an average period of 3.8 years), suggest that renine release was not accompanied by formation of alternative routes of release. Although actual angiotensin II concentrations were not measured in this study, it is tempting to speculate that reduced renine release may be accompanied by lower angiotensin II concentrations. This, since renin is one of the rate limiting steps of the renin-angiotensin cascade. This hypothesis was supported by the plasma aldosterone and endothelin I concentrations, since these neurohormones that are regulated in part by angiotensin II show tendency to further reduction after adjunctive β-blocker treatment when compared to patients only on ACE-inhibitors. Further study of actual angiotensin II concentration is needed to establish the theory.

**In conclusion:** The present thesis supports the concept that inhibition of the sympathetic nervous system and the renin-angiotensin system is important in reducing both development and progression of heart failure. Although inhibition of either pathway was effective in treating heart failure, inhibition of both pathways was even more effective. The beneficial effects of combined treatment may result from direct interactions between these pathways. As a consequence, combined inhibition may be more effective in restoration of the disturbed neurohormal balance. However, extensive research after all physiological and clinical consequences of the interactions between these pathways is needed to confirm this hypothesis.