Summary

Renin-angiotensin and endothelin system play important role in blood pressure regulation. In order to determine the contribution of an interaction between ET-1 and ANG II to the development of hypertension and related end-organ damage in an ANG II-dependent model of hypertension, we utilized a rat strain transgenic for the mouse Ren-2 renin gene (TGR; strain name TGR(mRen2)27).

All our experimental studies have confirmed the crucial effect of increased natrium intake in a diet on development of arterial hypertension and hypertensive end-organ damage (especially kidneys and heart) in this model of arterial hypertension.

Previous studies have demonstrated the presence of several types of endothelin system receptors - ET_A and ET_B receptors with two subtypes- ET_{B1} and ET_{B2}. Our study has brought a new knowledge of physiologic and pathophysiologic function of these receptors. The non- selective blockade of ET_A and ET_B receptors by Bosentan, improves survival rate of both homozygous and heterozygous transgenic animals, declines extent of hypertensive cardiac end-organ damage and reduce proteinuria and glomerulosclerosis.

However, this positive effect of nonselective endothelin blockade is not caused due to decrease of arterial blood pressure. The reason for this fact is probably in various effects of different subtypes of endothelin receptors and their unequal distribution in whole organism. The activation of ET_A receptors evokes vasoconstriction, ET_{B1} causes through release of NO and prostaglandines vasodilatation and ET_{B2} receptors, localized on vascular smooth muscle cells, causes non-ET_A mediated vasoconstriction. The result of non-selective blockade is then produced by combination of all these mechanisms.

The vasoconstrictive effect of ET_A activation has been confirmed in our experimental study (see section II.C). In this study we have clearly demonstrated the positive effect of selective ET_A receptor blockade using Atrasentan – arterial blood pressure has been significantly decreased in experimental animals, the overall mortality has been decreased and proteinuria levels, heart hypertrophy and glomerulosclerosis index have been significantly reduced. This effect comparing to non-selective blockade was more significant. Thus, selective ET_A receptor blockade could bring a new possibility to the treatment of salt sensitive arterial hypertension in the future.

In clinical part of this work arterial hypertension was demonstrated as a frequent complication in children after renal transplantation, which is associated with high prevalence of hypertensive end-organ damage, mainly left ventricular hypertrophy of the heart.Our cross-sectional study has shown, that the use of ACE- inhibitors is inadequately low in the antihypertensive treatment of children after renal transplantation. This is one of the main reasons for unsatisfactorily poor control of high blood pressure in these patients. Our two-year interventional trial has shown, that arterial hypertension in children after successful kidney transplantation is not resistant to the treatment, as some previous studies speculated, but that increased use of antihypertensive drugs, especially ACE inhibitors, can lead to the better control of arterial hypertension.