Summary

The role of the endothelin system in development of hypertension and hypertensive end-organ damage in Ren-2 transgenic rats

Endothelin-1 (ET-1) has been described as one of the most powerful vasoconstrictors, that also play a role in the regulation of renal hemodynamics. ET system plays an important role in the pathogenesis of salt-sensitive models of hypertension. The beneficial effects of ET receptor blockers in modulating target-organ damage arise from their antiproliferative action. There is, however, a large discrepancy in the effect of ET between various models of hypertension.

The hypertensive rat strain transgenic for the mouse Ren-2 (TGR) renin gene is a valuable monogenetic model of renin-dependent and thus angiotensin II(Ang II) – dependent hypertension, which exhibits typical signs of fulminant hypertension,i.e. reduced glomerular filtration rate and proteinuria associated with glomerulosclerosis. Moreover, it carries a salt-sensitive component.

We have recently found that nonselective endothelin ET_A/ET_B receptor blockade markedly improves survival rate and ameliorates end-organ damage in maleTGR without lowering blood pressure. Because activation of the ET_A receptor may be responsible for the detrimental effects of ET in the development of hypertension, our study was performed to determine whether ET_A/ET_B or rather ET_A receptor blockade exerts these beneficial effects. The antihypertensive therapy in general is known to be more efficient when started at early age and our study was performed to determine whether onset of ET receptor blockade at a later age in animals with established hypertension will have similar protective effects as does early-onset therapy. Proteinuria may be caused by defects of podocytes that maintain intact filtration barrier and control glomelur basement membrane. Only a few studies explored the involvement of podocyte damage in experimental hypertensive glomerulopathy.

Our data indicate that the ET system, especially via ET_A receptors, plays an important role in the development of hypertensive end-organ damage and confirm the concept that the predominant role of ET_B receptors within the peripheral vasculature is to mediate the vasorelaxant actions of ET-1. They also demonstrate that selective blockade of ET_A receptors with atrasentan is superior to nonselective ET_A/ET_B in attenuating hypertension, hypertensive organ damage and survival rate. Our data indicate that in homozygous TGR ET receptors play an important role also in established hypertension. Chronic selective ET_A blockade starting at the time of established hypertension in homozygous TGRs on a high salt diet proved to have substantial protective effects on survival rate and growth with a transient attenuation of the rise in BP. Our results also show that ultrastructural changes of podocytes preceded light microscopic histological disturbances and closely correlate with survival rat. Thay can, therefore, serve as a marker of future injury long before manifestation of proteinuria.