

*Overall research theme:*

**Studies on the pathogenesis and pathophysiology of hypertensive lesions in brain, kidney and peripheral circulation**

*Latest update:*

November 25, 2002

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*Characteristics of the research group:*

The research group combines clinical and experimental research interest and competence in the fields of hypertension, the renin-angiotensin system, the pathophysiology and treatment of chronic renal disease and the physiology and pathophysiology of the cerebral circulation.

Studies on renal disease are carried out at the department of nephrology, Herlev University Hospital (SS, AHN and ALK), while studies of the cerebral circulation are carried out at the Neurobiology Research Unit, Rigshospitalet, University Hospital, Copenhagen (SS, AHN, OBP).

*Running projects: Title and abstract:*

#### **The renin-angiotensin system and autoregulation of cerebral blood flow**

We have previously shown that ACE-inhibitors and the angiotensin II subtype 1 receptor antagonist candesartan shift the limits of CBF autoregulation towards lower pressure in rats, while the angiotensin II subtype 2 receptor blocker PD 123319 did not influence the limits of autoregulation. In a current series of studies in rats, the lower limit of autoregulation has been studied in bilaterally nephrectomized Sprague Dawley rats, kept alive by peritoneal dialysis for 48 hours, pending disappearance of renin from the circulation. Nephrectomy in itself did not influence the lower limit when compared to sham nephrectomy. In nephrectomized animals, though, captopril shifted the lower limit of autoregulation to lower pressures. It is thought that this is due to an effect of the renin-angiotensin system within the vessel wall, possibly with a contribution of bradykinin accumulation. It is planned to investigate the effect of candesartan or another angiotensin II subtype 1 receptor blocker on the limits of autoregulation in the nephrectomized dialysed rat and in control animals, and also to investigate the effect of bradykinin blockade. With these coming studies it is aimed to obtain a more complete understanding of by which mechanisms the renin-angiotensin system influences the cerebral circulation. In this context, it is interesting that in the recently published LIFE-study, it was found that the angiotensin II subtype 1 receptor blocker losartan protects against stroke when compared to the same degree of blood pressure reduction obtained with a beta-blocker.

#### **Effect of blockage of the renin-angiotensin system on the progression of chronic nephropathy**

Our group at Herlev University Hospital was among the first to show that disease progression in chronic non-diabetic renal disease can be impaired by treatment with an ACE-inhibitor. In recent studies, we have shown that standard doses of the ACE-inhibitor enalapril in patients with impaired renal function may be associated with very high plasma concentrations of enalaprilat, apparently without untoward effects. In a controlled trial in patients with chronic renal disease, we have subsequently shown that high and low dosing of enalapril have the same blood pressure lowering and antiproteinuric effect when added to combinations of other antihypertensive drugs and diuretics. This argues against contemporary arguments for "the higher the better" dosing of ACE-inhibitor and angiotensin II antagonists in chronic renal disease. In another study, the renal effect is examined of combination of ACE-inhibitor and angiotensin II antagonist versus dose increase of the ACE-inhibitor.

#### **The NO system in polycystic kidney disease**

We have demonstrated an impaired endothelium-mediated vasodilatation in small resistance vessels from young normotensive patients with polycystic kidney disease and a normal renal function. We found a similar change in resistance vessels in rats with polycystic kidney disease. In such rats, we also found a reduced expression of NOS

isoenzymes in renal tubular epithelium and cyst walls. It thus appears that impairment of the NO system plays a role in the pathogenesis of hypertension and cyst development in polycystic kidney disease. This opens the potential for novel therapeutic intervention in the early phase of the disease .

#### **Pulse wave velocity in chronic renal disease**

An increased velocity of the pulse wave is a marker of vessel stiffness and a predictor of a poor prognosis in chronic renal disease. Pulse wave velocity can be measured non-invasively with the Sfygmocor equipment developed by O'Rourke and coworkers. A study is planned at Herlev to investigate whether various drug regimes may lower pulse wave velocity and hence possibly reduce vessel stiffness and improve prognosis.

#### *Recent publications related to the projects described above:*

Fischer Pedersen, T, Paulson OB, Høj Nielsen A & Strandgaard S: Effect of nephrectomy and captopril on autoregulation of cerebral blood flow in rats. *J Cereb Blood Flow Metab*, submitted 2002

Fischer Pedersen T, Paulson OB, Høj Nielsen A & Strandgaard S: Nephrectomy and peritoneal dialysis eliminates renin and controls uremia in rats. *J Renin Angiotensin Aldosterone System* 2002;3:130-134

Fischer Pedersen T: Modulation of cerebral blood flow and its autoregulation by the renin-angiotensin system in nephrectomized rats. PhD thesis, University of Copenhagen 2002

Elung-Jensen T: ACE-inhibition in progressive chronic nephropathy. The importance of dosage. PhD-thesis, University of Copenhagen 2002

Elung-Jensen T, Heisterberg J, Kamper A-L, Sonne J & Strandgaard S: Blood pressure response to conventional and low dose enalapril in chronic renal failure. *Brit J Clin Pharm*, in press

Elung-Jensen T, Heisterberg J, Kamper A-L, Sonne J, Strandgaard S & Larsen NE: High serum enalaprilat in chronic renal failure: Measurements of through concentrations. *J Renin Angiotensin Aldosterone System* 2001;2:240-245

Estrup TM, Høj Nielsen A, Strandgaard S & Paulson OB: Angiotensin II AT2 receptor antagonist PD 123319 and cerebral blood flow autoregulation in spontaneously hypertensive rats. *J Renin Angiotensin Aldosterone System* 2001;2:188-192

Wang D, Iversen J & Strandgaard S: Endothelium-dependent relaxation of small resistance vessels is impaired in autosomal dominant polycystic kidney disease. *J Amer Soc Nephrol* 2000;11:1371-1376

Wang D, Iversen J & Strandgaard S: Contractility and endothelium-dependent relaxation of resistance vessels in polycystic kidney disease rats. *J Vasc Res* 1999;36:502-509

Vraamark T, Waldemar G, Strandgaard S & Paulson OB: The effect of the angiotensin II-receptor antagonist CV-11974 (candesartan) on cerebral blood flow autoregulation. *J Hypertens* 1995;13:755-761