**Abstract of thesis: Agonist and antagonist interaction with $AT_1$ subtype angiotensin II receptors**

The octapeptide angiotensin II is the main peptide hormone of the renin-angiotensin system (RAS) and is known to be involved in the physiological and pathological regulation of blood pressure and cardiovascular function by stimulating $AT_1$ receptors. Therapeutic agents that block the production of angiotensin II or inhibit its interaction with the receptor have been proven to be highly efficient in reducing the pathological effects. The $AT_1$ receptor blockers are widely and effectively used for the treatment of hypertension and congestive heart failure. In this study, the molecular interaction between $AT_1$ receptors and their ligands as well as the pharmacological characterization of two newly developed $AT_1$ receptor blockers were investigated on intact CHO-K1 cells transiently and stably transfected with human $AT_1$ receptors. Rather than the former notion of two receptor conformations, an active and an inactive one, the present study argues in favour of multiple ligand-stabilized receptor conformations.

In the first part, agonist and antagonist interactions to $AT_1$ receptor were compared between the wild type and mutated human $AT_1$ receptors by radioligand binding and functional studies. This provides information about the structural requirements for AT1 receptor binding and activation by angiotensin II and its peptide fragments. Based on our findings, a multi-step model for $AT_1$ receptor activation was proposed in which the receptor activation by angiotensin II occurs in at least two steps involving a pre-activated and a fully active state. According to this model, amino acid residues at the N-terminal part of angiotensin II play a key role in the pre-activation process, which is initiated by the breaking of constraining intramolecular interactions within the receptor. Subsequently the C-terminal part of this hormone is necessary to drive the receptor into a fully active state.

In the second part, we investigated the pharmacological properties of the recently developed non-peptide antagonists, olmesartan and telmisartan, by studying their interaction with the $AT_1$ receptor stably expressed in CHO-K1 cells. Using well characterized *in vitro* methods, we found that both olmesartan and telmisartan are competitive antagonists and that they displayed high affinity, slow dissociation, and a high degree of insurmountability for the $AT_1$ receptor. Our studies provide detailed information about the molecular action mechanism of non-peptide antagonists and, most importantly, that their interaction with the receptor is also a multi-step process. A "two-state, two-step" model was proposed, in which the initial antagonist-receptor interaction yields a fast reversible complex (i.e. surmountable state) and then subsequently a more stable, tight binding antagonist-$AT_1$ receptor complex (i.e. insurmountable state).

Finally, we found that the binding and functional properties of the human $AT_1$ receptor differed when comparing stably and transiently transfected CHO-K1 cells. This may result from differences in receptor reserve (which was exclusively found in the transiently transfected cells) and/or the receptor maturation. It is therefore pertinent to take these issues into consideration when characterizing ligand-$AT_1$ receptor interaction using the transient receptor expression system.