Molecular-Modeling Experiments Towards an Understanding of Alzheimer's Disease

Alzheimer's disease (AD) is strongly connected to the failure of the cholinergic synapses and a continuous neuronal degeneration. In the present work mechanistic features of two key proteins the acetylcholine receptor (AChR) and the acetylcholinesterase (AChE) have been studied using different computational chemistry methods. In particular we have investigated

- structural models of the extracellular part of the AChR,
- the AChE induced aggregation of β-amyloid peptides, and
- the folding processes of the β-amyloid peptides during plaque formation.

In addition, a biophysical assay was established that can be used to study the process of β-amyloid-aggregation. The results foster our understanding of mechanisms underlying the AD and help to develop new symptomatic and causal AD-therapies.

For the modeling studies concerning AChR new homology models of the extracellular part of the receptor were built, which are in good agreement with known experimental data, and which were utilized in docking studies to predict the binding site for allosteric potentiating ligands (APL). These models provide for the first time three-dimensional information of the APL binding site. On the basis of these results candidate residues of AChR were suggested for mutational studies. These studies then have been carried out in close cooperation with the group of Prof. Maelicke at the University of Mainz, Germany. As a result we are now able to define single amino acids that are essential for the allosteric effect and for channel activation, respectively. On the other hand, a number of residues was shown to have no effect on either of these activities. Our findings are of great importance for the symptomatic therapy, because they open up new ways for a structural design towards new lead compounds.

The modeling studies on AChE were focused on inhibitors for the AChE induced β-amyloid aggregation process. In this respect we have developed an efficient scoring method which was applied in a series of docking studies with bis-galanthamine ligands to predict a bis-functional galanthamine derivative that simultaneously can block the esterase activity and the deposition of β–amyloids at the AChE peripheral anionic site. To better understand the aggregation process, the interaction between the AChE and the β-amyloid peptides has been studied in detail by computational chemistry methods, including the dynamic behavior of the monomeric β-amyloid peptide. Particularly our molecular dynamics investigations yield an insight into the folding pathway of the peptide, which is essential for the understanding of the early onsets of the aggregation process. In addition a biophysical assay, based on multi-angle-light-scattering, has been established which allows us to follow the aggregation process over time and to estimate structural features of the aggregates.