Learning from simulations

Birgit Strodel explains how her research group employs molecular simulations aiming to reveal details about the aggregation of the Alzheimer's peptide amyloid-ß into toxic oligomers

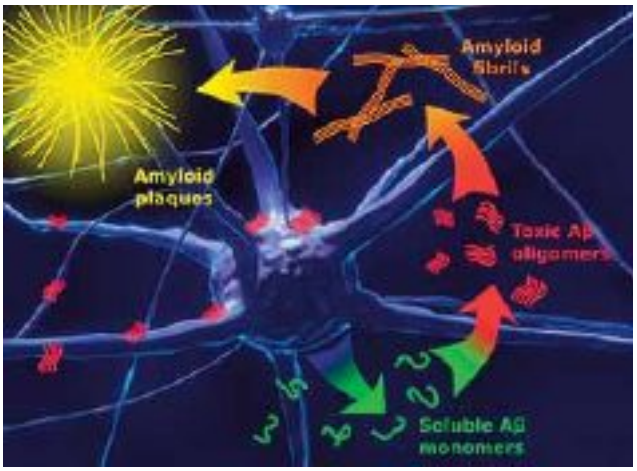
Alzheimer's disease (AD) is the most common form of dementia in the elderly. Currently, one in eight persons above the age of 65 is suffering from this disorder and it is expected that there will be 100 million persons affected by 2040. In AD, the small molecular weight amyloid-ß peptide (Aß) has been identified as a clinical hallmark in disease development and progression.

Amyloid-ß

Aß is the main component of the amyloid plaques found in the brains of AD patients. These amyloid plaques were identified for the first time in 1906 by Alois Alzheimer, who, after the death of his patient suffering from a particularly rapid decay of her mental powers accompanied by pronounced impairments of language and practical skill, decided to thoroughly study her brain. Besides a general loss of cerebral tissue, he found plaques which he interpreted as the incorporation of a peculiar substance into the cerebral cortex. Today, we know that the 'peculiar' substance is Aß, which derives from the amyloid precursor protein and can exist in different lengths ranging from 36 to 43 amino acids. The most common of these peptides is Aß40 while Aß42 is the most toxic. Monomers of Aß are soluble in water, yet at sufficiently high concentrations or as a result of modifications to external conditions, such as changes of the pH or metal ion concentration in the brain, Aß can undergo a dramatic structural change to form a ß sheet-rich structure that aggregates into amyloid fibrils, which in turn clump together to form the senile plaques.

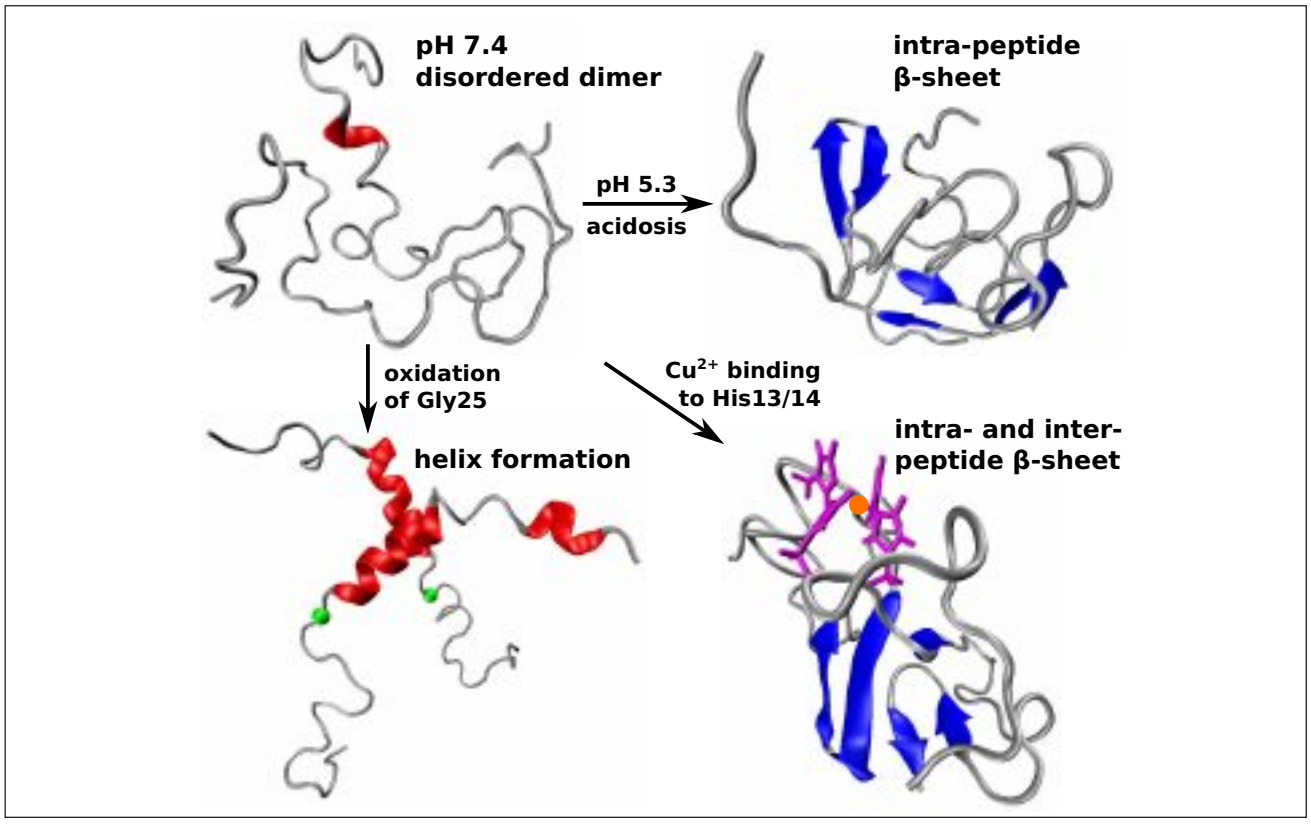
Toxic oligomers

For a considerable period of time, the amyloid cascade hypothesis assuming the plaques to be responsible for the pathology of AD, was accepted by the majority of researchers. However, the lack of correlation between the manifestation of the disease and the plaque burden together with the facts that neuronal death can also occur in brain regions devoid of plaques, and that plaques can also be present in cognitively normal individuals led to the perception that soluble oligomers are the toxic species of Aß. These oligomers are non-fibrillar Aß assemblies that occur during fibril formation, whose toxicity has been demonstrated in various cell studies and animal models. These studies further revealed that the deleterious effects increase with decreasing size of the oligomeric assemblies, which shifts the research focus towards rather small Aß oligomers, such as dimers, hexamers or dodecamers. The strong interest in oligomeric species is also supported by the need for new therapeutic or diagnostic targets in the treatment of AD, for which still no disease-modifying drug is on the market. However, determination of the precise mechanism of Aß oligomer toxicity has been challenging. Reasons for this are the inherent instability of Aß oligomers owing to their high aggregation propensity and also their structural flexibility, making their structural characterisation by experimental techniques difficult.



Oligomers tackled by molecular simulations

Computational studies using the molecular dynamics (MD) technique provide a complementary approach to experiments for studying the aggregation process of Aß. MD simulations provide movies of the biomolecular motions over a time scale of microseconds, with femtosecond time resolution and atomistic spatial resolution. We believe that such MD simulations are one of the key methods to reveal the intricacies of Aß oligomers. Our group was the first one to simulate the oligomer formation of Aß beyond the dimer state at an atomistic level. Our simulations revealed that the shape of the oligomers is decisive for the aggregation pathway and that already at the dimer state Aß40 and Aß42 follow different pathways. Moreover, we were able to provide answers to the, for many years, open questions as to why only two extra residues at the C-terminus of Aß42 lead to a faster aggregation and higher toxicity compared to Aß40. This is because these two extra amino acids cause Aß42 to aggregate into oligomers, which are more hydrophobic on their surface than the Aß40 oligomers, a property which is directly linked to a faster aggregation and higher cytotoxicity. To further understand the origin of amyloid toxicity, we modelled the interactions between Aß and lipid membranes as the plasma membrane of neurons is not only able to stimulate the formation of Aß oligomers, it is also a site of AD toxicity, as Aß has been shown to increase membrane permeability and to form membrane channels that disrupt the Ca^{2+} balance of neurons. Our simulations revealed that oligomers as small as tetramers in a ß-sheet conformation can harm the integrity of the lipid membrane by increasing its water permeability. In order to elucidate the influence of the membrane surface on the aggregation of Aß, we started a rigorous simulation study aiming to delineate the influence of the different molecules composing a neuronal membrane on the aggregation of Aß.



Moreover, we also composed a lipid bilayer mimicking a neuronal membrane, which has not been simulated before.

Metal ions, acidosis and oxidative stress

In addition to lipid membranes, metal ions, inflammation leading to acidosis, and oxidative stress are putative modulators of AD. While Cu^{2+}, Zn^{2+} and Fe^{2+} are crucial for life, AD patients suffer from increased levels of these ions in the brain. They are also concentrated in and around amyloid plaques and, notably, Cu^{2+} binds strongly to Aß. Since we have experience with the modelling of transition metal ions in MD simulations and have probed the roles of Cu^{2+} binding and a low pH mimicking acidosis on monomeric Aß, we are in a good position to now check what effects these external factors on the oligomer formation of Aß have. As for the monomer we find that the structural equilibrium of Aß dimers is shifted towards ß-sheet rich and thus aggregation-prone structures by both Cu^{2+} binding and mild acidic conditions. The latter provides a molecular rationale for the clinical observation that brain inflammation promotes pathological processes leading to AD. Interestingly, when we studied the effects of oxidation of Aß, we did not observe an increase in ß-sheet formation, which suggests that oxidative stress is not directly involved in amyloid aggregation. However, it has been shown that oxidative stress plays a detrimental role in AD. A possible molecular mechanism for this could be that oxidative stress leads to oxidation of Aß, which then transmits the oxidation to lipids, which in turn can lead to cell death.

Finding a drug

Given the overwhelming evidence of the involvement of Aß oligomers in the development of AD, it seems to be desirable to either inhibit the formation of these toxic oligomers or to directly target them by a drug thereby removing their toxicity. The latter approach is followed at the Institute of Complex Systems: Structural Biochemistry headed by Professor Dieter Willbold at Forschungszentrum Jülich. Willbold and co-workers screened thousands of 12-residue peptides for their capability to specifically bind Aß oligomers. This approach led to the identification of a few D-peptide inhibitors, which were shown to reduce Aß's toxicity in a dose-dependent manner. Following administration to transgenic mice as models of AD, these peptides improved the cognitive function of the mice and also reduced their amyloid plaque burden. In my group we performed molecular simulations to elucidate how these D-peptides bind to the Aß oligomers, which helps in the design of improved aggregation inhibitors.

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