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Alzheimer fibrils at atomic resolution

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Elongated fibres (fibrils) of the beta-amyloid protein form the typical senile plaque present in the brains of patients with Alzheimer's disease. A European research team, working in conjunction with a team from the United States, has now succeeded in explaining the structure of the beta-amyloid peptide 1–42, which is the most important to the illness, at atomic resolution. This simplifies the targeted search for medicinal products to treat Alzheimer's dementia.

Alzheimer's disease is responsible for at least 60 percent of dementia cases worldwide. It causes enormous human suffering and is associated with high costs. A cure or causal therapy are not yet available. The reason for this, among other things, is because the exact course of the illness in the brain at a molecular level has not yet been adequately clarified.

We do know that the beta-amyloid protein plays an important role. This is a peptide that is 39 to 42 amino acids long, toxic to nerve cells and is able to form elongated fibrils (fibres). Beta-amyloid peptide 1–42 and beta-amyloid peptide 1-40 are the two main forms that appear in senile plaques. We do not know why these lead to the decay of nerve cells in the brain, but it is very interesting for the development of medications to treat Alzheimer's disease.

In a joint project between the Swiss Federal Institute of Technology in Zurich, University of Lyon, and the Goethe University in Frankfurt am Main, and in cooperation with colleagues at the University of Irvine and Brookhaven National Laboratory, researchers have succeeded in

clarifying the structure of a beta-amyloid peptide 1–42 fibril at an atomic resolution. This fibril presents the greatest danger in this disease. The researchers also furthered the work done at the University of Chicago involving the structure of beta-amyloid monomers. Further immunological examinations prove that the investigated form of the fibrils is especially relevant to the illness.

Protein fibrils are in fact visible in electron microscope images (fig. 1), but it is very difficult to go down to an atomic level of detail. The conventional structural-biological methods required to achieve this assume that the macromolecule is present as an extremely regular crystal or in the form of individual molecules that are dissolved in water. However, fibrils are elongated structures that adhere to each other and neither form crystals, nor able to be dissolved in water.

Only solid-state nuclear magnetic resonance spectroscopy (solid-state NMR) is capable of offering a view at the atomic level in this case. New developments in methods are facilitating measurement of a network of distances between the atoms in the protein molecules that make up a fibril (Fig. 2). Extensive calculations enabled the atomic structure of the fibril to be reconstructed from these measurements.

The main part of the beta-amyloid 1-42 peptide is shaped like a double horseshoe (fig. 3). Two of the same molecules at one level are stacked onto each other to form a long fibril. Numerous oxygen bridge connections parallel to the long axis lend the fibrils their high stability.

"The structure differs fundamentally from earlier model studies, for which barely any experimental measurement data was available." explains Prof Peter Güntert, a professor of computer-aided structural biology at Goethe University.

The publications released by these European and American teams, which

confirm each other, have caused great excitement in expert circle, as they have enabled a targeted, structure-based search for medicinal products that will attack the beta-amyloid fibrils. The researchers hope that the horror of this scourge of old age, first described 110 years ago by a Frankfurt-based doctor Alois Alzheimer, will finally be rendered harmless over the next one or two decades.

More information: Marielle Aulikki Wälti et al. Atomic-resolution structure of a disease-relevant Aβ(1–42) amyloid fibril, *Proceedings of the National Academy of Sciences* (2016). DOI: 10.1073/pnas.1600749113

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