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Elucidating the 3D structures of Al(III)–Aβ complexes: a template free strategy based on the pre-organization hypothesis†

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Senile plaques are extracellular deposits found in patients with Alzheimer's Disease (AD) and are mainly formed by insoluble fibrils of β-amyloid (Aβ) peptides. The mechanistic details about how AD develops are not fully understood yet, but metals such as Cu, Zn, or Fe are proposed to have a non-innocent role. Many studies have also linked the non biological metal aluminum with AD, a species whose concentration in the environment and food has been constantly increasing since the industrial revolution. Gaining a molecular picture of how Al(III) interacts with an Aβ peptide is of fundamental interest to improve understanding of the many variables in the evolution of AD. So far, no consensus has been reached on how this metal interacts with Aβ, partially due to the experimental complexity of detecting and quantifying the resulting Al(III)–Aβ complexes. Computational chemistry arises as a powerful alternative to investigate how Al(III) can interact with Aβ peptides, as suitable strategies could shed light on the metal–peptide description at the molecular level. However, the absence of any reliable template that could be used for the modeling of the metallopeptide structure makes computational insight extremely difficult. Here, we present a novel strategy to generate accurate 3D models of the Al(III)–Aβ complexes, which still circumvents first principles simulations of metal binding to peptides of Aβ. The key to this approach lies in the identification of experimental structures of the isolated peptide that are favourably pre-organized for the binding of a given metal in configurations of the first coordination sphere that were previously identified as the most stable with amino acid models. This approach solves the problem of the absence of clear structural templates for novel metallopeptide constructs. The posterior refinement of the structures *via* QM/MM and MD calculations allows us to provide, for the first time, physically sound models for Al(III)–Aβ complexes with a 1 : 1 stoichiometry, where up to three carboxylic groups are involved in the metal binding, with a clear preference towards Glu3, Asp7, and Glu11.

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Introduction

The quest for cures of neurodegenerative diseases has become a vital field of research in our modern societies and many directions are considered to fight against them, from genetic to pharmacological approaches. Whatever the strategy, decoding key cellular and molecular mechanisms of sickness represents a fundamental objective in this field. Amongst the molecular aspects shared by most neurodegenerative diseases is the formation of insoluble peptide aggregates. These species are formed through the association of soluble protein fragments known as amyloids. About twenty proteins are already known to form such amyloids as Aβ in Alzheimer's disease (AD) or α-synuclein in Parkinson's disease (PD).

In AD, two main types of deposits are found: senile plaques and neurofibrillary tangles. The former contains insoluble filaments made of β-amyloid fragments and the latter consists of hyperphosphorylated tau proteins. The γ-secretase enzyme acts on the Amyloid Precursor Protein (APP) membrane protein to produce the $A\beta_{1-40}$ and $A\beta_{1-42}$ fragments that are found in senile plaques. Despite the fact that the formation of these peptides is a normal process in healthy people, several factors may prompt an imbalance in their concentration and so favoring and accelerating the aggregation in the unhealthy ones. The aggregation is a complex process in which species

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