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The binding of small carbazole derivative (P7C3) to protofibrils of the Alzheimer's disease and β-secretase: Molecular dynamics simulation studies

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ABSTRACT

The molecular basis of Alzheimer's disease (AD) is a critical aspect for understanding the role of Aβ fibrils in neurotoxicity and for designing therapeutic strategies against AD. Molecular insight into the prevention of Aβ peptide aggregates in the presence of P7C3, a derivative of dibromocarbazole, molecule is presented for the first time. P7C3 protects newborn neurons from apoptotic cell death, but mechanistic details are lacking. The ability of P7C3 to prevent the onset or to slow the progression of the Alzheimer's disease was studied by using molecular dynamics (MD) simulations. Two different mechanisms were considered: the disruption of Aβ aggregation by direct binding of P7C3 to Aβ and alterations in amyloid precursor protein processing through the inhibition of β-secretase. The results indicate that P7C3 molecule can efficiently bind to the β-secretase active site. The direct interactions of P7C3 with Aβ peptide are also important but in a lesser extent.

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1. Introduction

Alzheimer's disease (AD) is a debilitating neurodegenerative disorder characterized by the formation and deposition of amyloid fibrils. Aggregation of Alzheimer's β-amyloid peptides (Aβ) ranging from 39 to 43 residues are primary components of extracellular senile plaque of AD. Aggregated forms of these proteins are ubiquity present in Alzheimer's patients [1] and leads to neuronal cell death [2,3] while the monomeric form has little apparent toxicity [4]. The Aβ peptide is the product of a hydrolytic cleavage of the amyloid precursor protein (APP) which catalyzed by a tandem of two proteases identified as β- and γ-secretases. It has been demonstrated that β-secretase participates in the rate-limiting step of the hydrolytic process that leads to the APP fragments. Consequently, recent efforts have focused on identifying compounds that inhibit the formation of fibrils or oligomers [5,6]. Many recent studies have concentrated on designing inhibitors of β-secretase, a key enzyme in the pathomechanism of Alzheimer's disease [7].

Despite the agreement on the role of Aβ peptides aggregates in many protein-misfolding diseases, there is a discrepancy about the mechanism of Aβ aggregation. Some investigations have been indicated that hydrophobic stretches are responsible for aggregation and fibrillogenesis [8,9]. In contrast, some studies have suggested the π-stacking of aromatic residues as a key feature promoting the assembly of polypeptides into amyloid structures [10]. Understanding the mechanism by which amyloid-forming peptides form protofibril is essential for designing effective drugs to stop the formation of toxic aggregated Aβ [11].

A class of inhibitors is made up of polyphenols, which are thought to interact with amyloidogenic proteins via aromatic π–π interactions, though the precise mechanism is an issue still under debate [12]. Ono et al. [13] used fluorescence spectroscopy with thioflavin T and electron microscopy to examine the effects of small polyphenolic molecules on the formation, extension, and destabilization of β-amyloid fibrils *in vitro*. They indicated that all examined polyphenols dose-dependently inhibited formation of β-amyloid fibrils from fresh $A\beta_{1-40}$ and $A\beta_{1-42}$, as well as their extension.

Recently, MacMillan et al. [14] discovered the synthetic molecule, named P7C3, which protects newborn neurons from apoptotic cell death, and thus promotes neurogenesis in mice and rats in the subgranular zone of the hippocampal dentate gyrus, the site of normal neurogenesis in adult mammals. It is nontoxic, orally

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bioavailable, metabolically stable, and able to cross the blood–brain barrier [14]. P7C3 contains a dibromocarbazole connected to an aniline with a 2-hydroxypropyl linker (see Fig. 1). The bromines on the carbazole appear particularly important, as the derivatives with dichloro and parent carbazole did not appear active at the concentrations tested. In the results section, we present the quantum mechanical calculations on the interaction energies of dibromo and dichloro carbazol derivatives with Phe amino acid, with the aim to find a reason for the better activity of P7C3 in comparison to dichloro derivative.

In silico molecular simulation experiments, which provide results being complementary to those obtained from *in vivo* and/or *in vitro* experiments, have been used from coarse-grained models to atomistic simulations, to examine the aggregation of Aβ peptides [15,16]. *Ab initio* calculations are also used to investigate the binding affinity and the specific interactions between Aβ monomers to elucidate which Aβ residues contribute to the dimerization [17].

Convertino et al. [18] studied the interactions of aromatic inhibitors with monomeric Aβ_{12-28} point to a common mechanism of action by performing atomistic molecular dynamics simulations at equilibrium. The authors found that the small molecules have different affinities for Aβ_{12-28} that can be partially rationalized by the balance of aromatic and charged moieties constituting the molecules. They concluded that intrinsic disorder of Aβ persists at the level of binding small molecules and that inhibitors can significantly alter properties of monomeric Aβ via multiple routes of differing specificity.

Lemkul and Bevan [19] have used extensive explicit-solvent, atomistic MD simulations to describe the interactions of the flavonoid morin with monomeric and dimeric Aβ_{1-40} and Aβ_{1-42} in an attempt to understand the means by which this compound inhibits Aβ aggregation. They have found that binding of morin to monomeric Aβ alters the free energy surface defined by tertiary interactions within the peptide, altering its ability to collapse and form a stable hydrophobic nucleus. They have concluded that dimerization was not prevented by the administration of morin, but the structure of newly formed Aβ dimers was affected by the binding location of morin, either at the dimerization interface or the surface of the aggregate.

The molecular target of P7C3 is not known. Therefore, this study is conducted for the first time to give additional insight into the specific mechanism by which P7C3 exert its potential neuroprotective actions in the brain of Alzheimer's disease patients. First, we have studied the intermolecular interactions of different residues in Aβ fibrils in the presence or absence of P7C3 small molecules. Then, we have evaluated the capability of P7C3 as a probe for β-secretase inhibition. Finally, we have compared the data to support one mechanism over the other.

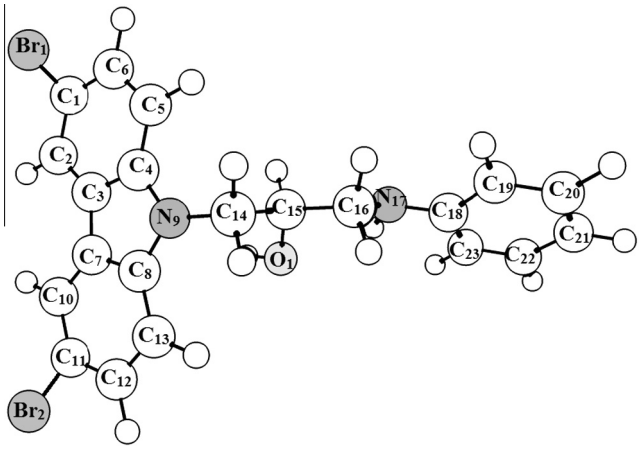

Fig. 1. The optimized structure and atom labeling of P7C3 at B3LYP/6-311++G(d,p) level of theory.

2. Methods and simulation setup

2.1. Initial structures

The initial conformation of the Aβ_{1-40} was taken from PDB (ID: 2LFM) and is shown in Fig. 2a. This structure is partially folded and differs substantially from previously reported NMR studies of Aβ_{1-40} and Aβ_{1-42} in solution. The central hydrophobic region of the peptide in this structure forms a 3_{10} helix from H_{13} to D_{23} and the N and C-termini collapse against the helix due to the clustering of hydrophobic residues [20]. The starting structure of Aβ fibril is a pentapeptide segment of the Aβ protofilament, as extracted from solid-state NMR (PDB ID: 2BEG; Fig. 2b) [21]. The N-terminus was capped by an acetyl group and the C-terminus was left ionic. This region of Aβ_{42} (residues 17–42) is principally responsible for the stability of the mature fibril, and thus this core region, lacking the 16 N-terminal residues, serves as a suitable model of the full-length fibril [22,23]. β-secretase crystal structure in a flap-closed conformation (PDB ID: 1W51; Fig. 2c) was downloaded from the Protein Data Bank [24].

MD simulations were performed using the GROMACS 4.5.5 package [25,26] utilizing the GROMOS force field 53A6. This force field has previously been successfully employed to produce the structures of the Aβ peptide which are compatible with experimental observations. Olubiyi and Strodel indicated that the GROMOS 53A6 force field properly reproduce experimental NMR shifts of Aβ [27]. Also, this force field has been used for the simulation of Aβ protofibrils by Lemkul and Bevan over the past several

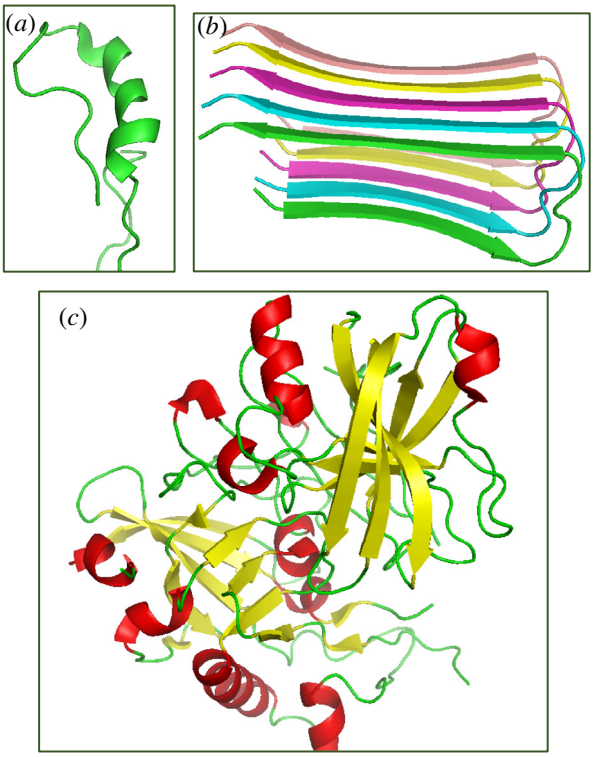

Fig. 2. Cartoon plots showing (a) the high-resolution NMR structure of Aβ_{1-40}. (b) Structure of the Aβ protofibril (c) β-secretase crystal structures in a flap-closed conformation.

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