

1,2,3,4,6-penta-O-galloyl- β -D-glucopyranose binds to the N-terminal metal binding region to inhibit amyloid β -protein oligomer and fibril formation



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ABSTRACT

The early oligomerization of amyloid β -protein ($A\beta$) is a crucial step in the etiology of Alzheimer's disease (AD), in which soluble and highly neurotoxic oligomers are produced and accumulated inside neurons. In search of therapeutic solutions for AD treatment and prevention, potent inhibitors that remodel $A\beta$ assembly and prevent neurotoxic oligomer formation offer a promising approach. In particular, several polyphenolic compounds have shown anti-aggregation properties and good efficacy on inhibiting oligomeric amyloid formation. 1,2,3,4,6-penta-O-galloyl- β -D-glucopyranose is a large polyphenol that has been shown to be effective at inhibiting aggregation of full-length $A\beta_{1-40}$ and $A\beta_{1-42}$, but has the opposite effect on the C-terminal fragment $A\beta_{25-35}$. Here, we use a combination of ion mobility coupled to mass spectrometry (IMS-MS), transmission electron microscopy (TEM) and molecular dynamics (MD) simulations to elucidate the inhibitory effect of PGG on aggregation of full-length $A\beta_{1-40}$ and $A\beta_{1-42}$. We show that PGG interacts strongly with these two peptides, especially in their N-terminal metal binding regions, and suppresses the formation of $A\beta_{1-40}$ tetramer and $A\beta_{1-42}$ dodecamer. By exploring multiple facets of polyphenol-amyloid interactions, we provide a molecular basis for the opposing effects of PGG on full-length $A\beta$ and its C-terminal fragments.

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1. Introduction

Extracellular deposits of amyloid β -protein ($A\beta$) in the brain are a pathological hallmark of Alzheimer's disease (AD), the most common type of dementia, which is characterized by neuronal cell loss leading to cognitive impairment [1–8]. $A\beta$ proteins are derived from sequential endoproteolytic cleavage of the amyloid precursor

protein (APP) by β - and γ -secretase [9–12] to generate alloforms of 37–43 amino acid. $A\beta_{1-40}$ and $A\beta_{1-42}$ (Scheme 1) are the dominant forms and the main targets in the amyloid cascade hypothesis. $A\beta_{1-40}$ is the main constituent of all $A\beta$ species present in the body (~90%), while $A\beta_{1-42}$ (9%) is the more toxic form and has a higher aggregation propensity [13,14]. Compelling evidence has shown that the early, soluble amyloid oligomers are the primary pathologic agents in AD. Some of these amyloid oligomers are highly neurotoxic and accumulate inside neurons, causing a decline in synaptic functions [1,15–21].

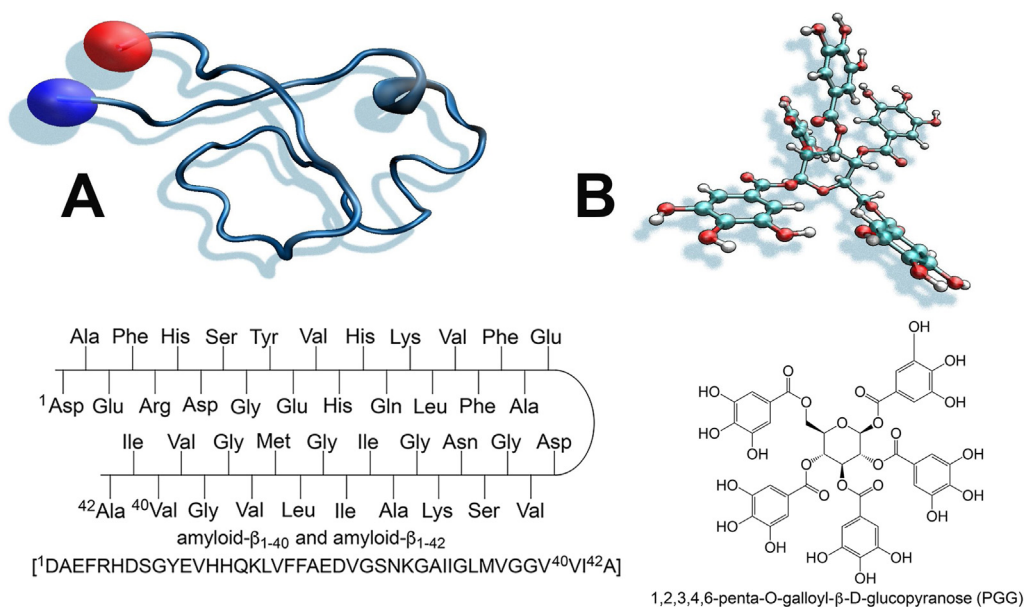
Soluble oligomers are produced and accumulated during the conversion of soluble, non-toxic $A\beta$ monomers to benign fibrils [22]. They exist in equilibrium with other species, and may have relative short lifetimes; as a result, they are difficult to isolate and characterize. Of note, previous studies by IMS-MS show that $A\beta_{1-40}$ and $A\beta_{1-42}$ follow different pathways *en route* to fibrils.

$A\beta_{1-40}$ initially forms dimers and tetramers, whereas $A\beta_{1-42}$ forms hexamers and dodecamers [9,13]. Among these oligomeric

Abbreviations: AD, Alzheimer's disease; $A\beta$, amyloid β -protein; $A\beta_{1-11}$, amyloid β -protein (1–11); $A\beta_{11-22}$, amyloid β -protein (11–22); $A\beta_{12-22}$, amyloid β -protein (12–22); $A\beta_{25-35}$, amyloid β -protein (25–35); $A\beta_{36-42}$, amyloid β -protein (36–42); $A\beta_{1-40}$, amyloid β -protein (1–40); $A\beta_{1-42}$, amyloid β -protein (1–42); Ala, alanine; APP, amyloid precursor protein; Arg, arginine; Asp, aspartic acid; ATD, arrival time distribution; CCS, collision cross sections; His, histidine; Ile, isoleucine; IMS-MS, ion mobility spectrometry coupled to mass spectrometry; Lys, lysine; MD, molecular dynamics; PGG, 1,2,3,4,6-penta-O-galloyl- β -D-glucopyranose; Phe, phenylalanine; TEM, transmission electron microscopy; Val, valine.

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Scheme 1. (A) Primary sequence of Aβ₁₋₄₀ and Aβ₁₋₄₂ and three dimensional structure of Aβ₁₋₄₂ (B) chemical structure of 1,2,3,4,6-penta-O-galloyl-β-D-glucopyranose (PGG).

species, appearance of the dodecamer (56 kDa) has been linked to cognitive decline in both human AD brains and transgenic mice [23,24]. However, the etiology of AD is presently not well understood and no effective treatment is available. Current approved drugs for AD show only meager efficacy at mitigating disease progression.

An attractive therapeutic approach for AD treatment is to remodel the Aβ assembly pathway in a way that attenuates the neurotoxicity of the transient, early-stage soluble Aβ oligomers [9,13,25–28]. In this context, many polyphenolic compounds have shown promise as potential therapeutic agents for AD treatment and prevention [29–32]. This class of compounds is plentiful in nature; many can be extracted from plants and herbs [32,33]. More specifically, 1,2,3,4,6-penta-O-galloyl-β-D-glucopyranose (PGG) (Scheme 1), a large tannin-type polyphenol found in the traditional medicinal herb *Paeonia suffruticosa*, has been shown to be potent inhibitor for both Aβ₁₋₄₀ and Aβ₁₋₄₂ aggregation [34]. Paradoxically, this same polyphenol has been recently shown to be an aggregation agonist for Aβ₂₅₋₃₅, a cytotoxic fragment of Aβ, by promoting the formation of extended Aβ₂₅₋₃₅ conformations [35]. This discrepancy may be due to a mismatch between the size and shape of PGG and its amyloid targets; however, supporting evidence for this model remains inadequate.

More recently, the variation between different polyphenols in their inhibitory effects on Aβ oligomerization have been correlated to differences in polyphenol size and shape. For large polyphenolic compounds, hydrophobic interactions with Aβ were stronger than hydrophilic ones. This difference was attributed to incompatibility between the geometry of large polyphenols and intramolecular hydrogen bonds [32]. In contrast, for small polyphenolic compounds both polar and nonpolar interactions were equally involved in the Aβ binding interfaces [32]. Therefore, it is reasonable to propose that large polyphenols (e.g., PGG) are more selective for their targets, and that the inhibitory mechanisms of large polyphenols cannot be extrapolated from previous studies on small polyphenols.

Herein we utilize ion mobility spectrometry-mass spectrometry (IMS-MS) [36,37], transmission electron microscopy (TEM) and molecular dynamics (MD) simulations to characterize the Aβ self-assembly pathways and to determine the structural changes within amyloid systems promoted by PGG. We investigate the effects and binding motifs of this ligand with full-length Aβ₁₋₄₀ and Aβ₁₋₄₂,

focusing on early homo- and hetero-oligomer (Aβ:PGG) formation and structure. Additionally, we evaluate the interactions of PGG with Aβ₁₁₋₂₂ and Aβ₁₁₋₂₂, which taken together with published data on Aβ₂₅₋₃₅ [35], provide insight into the molecular mechanism by which large polyphenols inhibit amyloid aggregation.

2. Results and discussion

2.1. Self-assembly of Aβ₁₋₄₀ and Aβ₁₋₄₂ by IMS-MS and TEM.

The fundamental challenge in studies of transient, early-stage soluble Aβ oligomers is that the conformational transitions are not easily accessible by traditional bulk measurements. In contrast, IMS-MS has been demonstrated to successfully capture transient structural changes accompanying Aβ self-assembly [38–40], as well as to successfully evaluate the efficacy of small-molecule inhibitors of amyloid assembly processes [9,13,31,35,41–44].

IMS-MS experiments with full-length Aβ₁₋₄₀ and Aβ₁₋₄₂ were performed in negative mode polarity because the natural charge states of those species are $z = -3$ (at pH 7). The nano-ESI-Q mass spectrum of pure Aβ₁₋₄₀ (Fig. 1A) reveals the presence of two major peaks at m/z 1081 and 1442, corresponding to Aβ monomers: $[n]^z = [1]^{-4}$ and $[1]^{-3}$, respectively, where n is the oligomer number and z the charge. The two features in the ATDs at m/z 1731 are assigned to the Aβ dimer ($[n]^z = [2]^{-5}$) and tetramer ($[n]^z = [4]^{-10}$) (see Fig. S2, Supporting information). Similarly, the mass spectrum obtained for pure Aβ₁₋₄₂ (Fig. 1C) shows three peaks. The most abundant peaks are at m/z 1504 and m/z 1128 corresponding to the monomers $[n]^z = [1]^{-3}$ and $[n]^z = [1]^{-4}$, respectively. The ATDs obtained for the peak at m/z 1805 (shown in Fig. S5, Supporting information) show four different oligomeric species of Aβ₁₋₄₂: dimer ($[n]^z = [2]^{-5}$), tetramer ($[n]^z = [4]^{-10}$), hexamer ($[n]^z = [6]^{-15}$) and dodecamer ($[n]^z = [12]^{-30}$), as previously reported [38,40].

To analyze the transient soluble Aβ oligomers, the experimental collisional cross sections (CCSs), obtained by measuring ATDs at different pressure/voltage (P/V) ratios (Equations S3 and S4), were compared to the ideal isotropic growth model, which approximates the cross sections (σ) of oligomers that grow equally distributed in all spatial dimensions ($\sigma_n = \sigma_1 \times n^{2/3}$) [45]. From the CCSs obtained for Aβ₁₋₄₀ and Aβ₁₋₄₂ (Fig. 2, panels A and D, and Supporting information, Figs. S2 and S5, Tables S1 and S3), positive deviations from

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