Phenylethanoids can modulate Amyloid-β Aggregation Associated with Alzheimer’s Disease
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Alzheimer’s Disease (AD) is a common neurodegenerative disease and the 6th leading cause of death in the US. One neurological marker of AD is the deposition of extracellular plaques composed of aggregates of the amyloid-β (Aβ) protein. Aβ aggregation follows a nucleation-dependent pathway, beginning with monomer forming nuclei that grow into soluble aggregates and proceed to form the insoluble fibrils deposited in AD brain. As such, many therapeutic treatments target the inhibition of Aβ aggregation. It is hypothesized that compounds containing a phenol structure can interrupt aggregate β-sheet formation by disrupting π-π stacking at phenylalanine residues in the core of the protein. In this study, the phenylethanoid oleuropein, along with metabolites hydroxytyrosol and tyrosol, were studied for their effect on Aβ aggregation.

Segregation of SEC-purified Aβ was initiated via agitation in the presence of a 5-fold excess of compound and monitored using thioflavin-T to detect aggregate β-sheet structure. To examine the earliest stages of aggregation, oligomerization was induced by combining DMSO-solubilized Aβ with a 10-fold excess of inhibitor and diluting into PBS. Oligomer formation was monitored via SDS-PAGE and Western blotting to quantify oligomer size.

Distinct correlations were observed between compound structure and the effect on oligomer size and the formation of larger aggregates. Hydroxytyrosol, a metabolite of oleuropein, exhibited the most effective inhibition among these compounds in aggregation and oligomerization. Thus, effectiveness of phenylethanoid compounds in Aβ inhibition is influenced by the substituents present on the ring. In contrast, the structure with only one hydroxyl group, tyrosol, has little effect. Further study will elucidate the effect that these changes in Aβ aggregation have upon Aβ neurotoxicity.

Probing the Role of Cytoglobin’s Extended Termi
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Cytoglobin (hCyg) is an α2-haemocyanin-based protein that is expressed ubiquitously in vertebrate tissues. The physiological function of Cygb remains unknown; however it has been proposed to have a role in oxygen sensing, lipid peroxidation and NO metabolism. Structurally, Cygb has a unique feature among vertebrate globins including extended, disordered N- and C-termini. Although the function of the terminal extensions remains to be determined, their role in promoting intracellular interactions has been proposed. In order to probe the impact of the N- and C-terminal on the functional and structural properties of Cygb, human Cygb (hCyg) with truncated N-terminal (hCyg ΔN), C-terminal (hCyg ΔC) and N- and C- termini (hCyg ΔNΔC) were studied using various spectroscopic techniques. The presence of the N- termini increases the stability of Cygb by 13°C. In addition, all studied forms of Cygb bind 1-anilino-8-naphthalene sulphonate hydrophobic probe, although the affinity for 1,8-ANS increases in the absence of the N- and C-termi suggesting that the deletion of the N- and C-termi leads to the exposure of the hydrophobic sites on the protein surface. Furthermore, the impact of the extended N- and C- termini on Cygb interactions with small gaseous ligands will be discussed.

Protein Assemblies I

Statistical Thermodynamics of One-To-Many Molecular Recognition Accompanied by Partner-Dependent Folding: In the Case of a Tumor Suppressor Protein p53
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A tumor suppressor protein p53 recognizes over 100 biomolecules. Here we investigate the mechanism of its molecular recognition accompanied by partner-dependent folding of its partial peptide, the p53 C-terminal domain (p53-CTD). The p53-CTD lacks a well-defined tertiary structure without a partner, form a helix in binding to S100bβ, a sheet in binding to sirtuin, and a coil with two distinct backbone conformations in binding to CBP or cyclin A. We calculate changes in thermodynamic quantities upon these binding processes using a statistical-mechanical approach combined with molecular models for water. The hydration entropy is calculated by our hybrid method in which the angle-dependent integral equation theory applied to a multipolar water model is combined with the morphometric approach. The three-dimensional reference interaction site model theory is employed for calculation of the hydration energy. This approach is the cutting edge of studies on the biomolecule hydration and on a variety of biological self-assembly processes. It is shown that a common driving force for the p53-CTD binding is a large gain of the water entropy, which originates primarily from an increase in the total volume available to the translational displacement of water molecules in the system and the reduction in the water crowding. We discuss the several characteristics of the one-to-many molecular recognition by p53-CTD from the viewpoint of hydration thermodynamics.