ON THE ORIGIN OF FLUORESCENCE ENHANCEMENT OF NIAD-4 UPON INTERACTION WITH AMYLOID FIBRILS

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Alzheimer's disease, a progressive disorder of the central nervous system, shows several pathological hallmarks, including plaques caused by aggregation of the peptide amyloid-β (Aβ) into fibrils.[1] An early diagnosis of the disease requires the fast and accurate detection of such aggregates in vivo. Among the several techniques that are available, fluorescence imaging offers important advantages in terms of cost, speed and level of toxicity over nuclear techniques such as PET and SPECT. [2] The fluorescent marker NIAD-4, synthetized in 2005 by Nesterov et al., [3] is a promising Aβ marker due to its high emission at high wavelength (> 600) nm and its ability to rapidly cross the blood-brain barrier and target Aβ deposits. Furthermore, it shows very different photophysical properties in aqueous solution and when bound to amyloid fibrils, which is essential for attaining a good imaging contrast. The present work analyzes the photophysics of NIAD-4, using a pool of computational (TD-DFT and post Hartree-Fock calculations, ab-initio molecular dynamics and fit induced docking) and UV-Vis spectroscopic techniques with the ultimate goal of understanding the origin of the fluorescence enhancement observed upon binding to amyloid fibrils. Computational and experimental results show that neither variation in polarity nor in hydrogen bond donor/acceptor capabilities of the surrounding medium is responsible for such a difference. Concentration-dependent absorption spectra and fluorescence excitation spectra in aqueous solution, on the other hand, indicate that NIAD-4 aggregates in aqueous solution already at very low concentrations, which accounts for the lack of fluorescence emission observed in this medium. Furthermore, the computational exploration of NIAD-4 binding to different models of Aβ fibers shows that the interaction is mainly driven by dispersion forces and that the marker is preferentially accommodated at the hydrophobic core of the fibril. These binding sites are accessible by the monomeric form of the marker only, thus suggesting that disaggregation and diffusion into the hydrophobic amyloid voids is the main reason for the strong fluorescence enhancement of NIAD-4 upon binding to Aβ deposits.

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