Structural SAXS Studies of the Human Amyloid Precursor Protein

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The amyloid precursor protein (APP) gives rise to the β-amyloid peptide, considered to be a causal factor for Alzheimer's disease. The soluble extracellular domain of APP released by α-secretase cleavage (sAPPα) has several important physiological functions. Several APP fragments have been structurally characterized at atomic resolution, but the structures of APP and full-length sAPPα have not been determined. In this work, *ab initio* reconstruction of molecular models from solution X-ray scattering (SAXS) data for the two main isoforms of sAPPα (sAPPα$_{695}$ and sAPPα$_{770}$) provided models with enough resolution to identify distinct domains. Using the *ab initio* models and molecular docking tools, the fragments whose structures are known at the atomic level were optimally fit within the models of full-length sAPPα, allowing localization of important functional sites (glycosylation, protease inhibition and heparin-binding sites). Furthermore, SAXS and analytical ultracentrifugation (AUC) results indicate that both sAPPα isoforms are monomeric in solution. AUC measurements further show that sAPPα$_{695}$ forms a 2:1 complex with heparin, in agreement with SAXS results. Possible implications of such complex formation for the dimerization of sAPPa and biological signalling are discussed in terms of the structural models proposed.
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