Structural-dynamic studies of D3-peptide interaction with membrane bound Aβ-peptide precursor

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Alzheimer's disease (AD) is a devastating neurodegenerative disease resulting in severe dementia. Despite huge efforts to combat the problem currently, there is no appropriate treatment of the disease. Amyloid Aβ-peptides forming plaques in brain during AD are the products of sequential cleavage of amyloid precursor protein (APP). Recently we developed D3-like peptides, which destroy the Aβ-aggregates, inhibiting AD, and currently one of them is about to undergo a phase II clinical trial. Here, we report that D3-peptide directly interacts with Aβ precursor, transmembrane APP fragment 672-726 (APPmc), solubilized in membrane-mimicking DPC micelles and studied by means of protein engineering, microscale thermophoresis and high-resolution NMR. Molecular Dynamics relaxation of the D3/APPmc-complex in explicit lipid bilayer revealed that D3-peptide can fold into a nascent helix and stabilize juxtamembrane helical region of APP in a manner of so-called IDP-IDP (intrinsic disorder-based protein) interactions. Also, we find that AD familial mutations (D693N and E694G) placed in the C-terminus of APP juxtamembrane helix are considerably decrease the strength of D3/APPmc-interactions, specifying the hotspot of APPmc/D3-interaction and assuming the importance of local Coulomb contacts in the complex formation. The structural data in agreement with ELISA and Western-blot analyzes, which did not reveal any influence of D3 on the APP cleavage by the secretases, which is consistent with the flexible IDP/IDP nature of the D3/APP interactions. The data suggest that D3 can recognize the amyloidogenic region of APP before its processing, restricting conformational diversity generally favoring its α-helicity via prevention of intermolecular hydrogen bond formation, inhibiting early steps of Aβ conversion into β-conformation that precedes toxic oligomerization, thus targeting early stages of AD development. This work was supported by the Russian Science Foundation (project 20-64-46027).