Aβ1-6A2V(D): a bio-inspired peptide as potential multitarget treatment for tauopathies

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Alzheimer's disease (AD), the most common form of tauopathy, is a double proteinopathy characterized, in addition to tau deposition, also by amyloid-β (Aβ) misfolding, resulting in the formation of neurofibrillary tangles and amyloid plaques in specific regions of the brain. Despite enormous efforts in the last decades, no effective therapies are available for the treatment of AD. The approaches followed so far focused solely on Aβ or tau protein. This study aimed to investigate the mechanism of action of a bio-inspired all-D-isomer synthetic peptide Aβ1-6_{A2V}(D). This peptide stems from the clinical discovery that the presence of the A2V mutation in the N-terminal region of Aβ plays a protective role against amyloidogenesis in heterozygous carriers suffering from AD (Di Fede G et al. (2009) Science, 323,1473-1477). Previous observations from our group demonstrated that $Aβ_{1-6}$A2V(D) interacts with Aβ, reducing oligomer generation and fibril formation, and interferes with Aβ-dependent neurotoxicity *in vitro* and *in vivo* (Di Fede G et al. (2012) Prog Neurobiol 99, 281-292). We here investigated if $Aβ_{1-6}$A2V(D) could also interact with tau. In-depth biochemical studies involving thioflavin T fluorescence assay, circular dichroism, and structural studies demonstrated that $Aβ_{1-6}$A2V(D) peptide can interfere with the aggregation and stability of tau. Additional analysis indicates that the peptide increased the susceptibility of tau to degradation by proteases, significantly reducing the tau protein level without affecting the fraction of insoluble tau (Diomede L et al. (2023) Mol Psychiatry 28, 2433-2444). These findings confirm that this peptide interferes with Aβ and tau aggregation propensity and proteotoxicity, providing proof of concept for developing and optimizing multitarget treatments for tauopathies.