Molecular insight into amyloid beta peptide heterogeneity: a biophysics and in silico approach.

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Abstract: The β-amyloid peptide (Aβ) is related to neurotoxicity in Alzheimer disease (AD). The two most abundant alloforms of the peptide co-exist under normal physiological conditions in the brain in an Aβ1-42: Aβ1-40 ratio of 1:9 spiked with low concentrations of Aβ1-38 and Aβ1-43. The Aβ1-42:Aβ1-40 ratio is often shifted to a higher percentage of Aβ1-42/Aβ1-43 in brains of patients with familial AD and we have shown this to lead to increased synaptotoxicity [1]. Current therapeutic approaches under development for Alzheimer disease include γ-secretase modulation which aims at increasing the production of Aβ1-38 and Aβ1-40 at the cost of longer Aβ peptides. We investigated the impact of such a shift in peptide production on aggregation and toxicity of the total peptide pool using a biophysical and in silico approach combined with toxicity read-outs. Aβ1-38 and Aβ1-43 demonstrate aggregation profiles similar to Aβ1-40 and Aβ1-42, respectively [2,3], but variation is observed in kinetics of assembly and toxicity possibly as a result of differences in short timescale conformational plasticity as revealed by molecular dynamics approaches [2]. The finding that these Aβ variants co-occur in the brain motivated us to investigate how peptide heterogeneity affects disease-related parameters. We show that Aβ1-40 and Aβ1-42 interact as well as modify the behaviour of the other [4]. The structures of monomeric and fibrillar assemblies formed from Aβ1-40 and Aβ1-42 mixtures do not differ from those formed from either of these peptides alone. Instead, the co-assembly of Aβ1-40 and Aβ1-42 influences the aggregation kinetics by altering the pattern of oligomer formation as evidenced by a combination of solution nuclear magnetic resonance spectroscopy, high molecular weight mass spectrometry, and cross-seeding experiments. We relate these observations to the observed enhanced toxicity of relevant ratios of Aβ1-42: Aβ1-40 in synaptotoxicity assays [1] and in AD patients.

References

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