Chirality, Alzheimer's Disease and Amyloid Beta

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Chirality is of paramount importance to all living systems. It is a property of all principal biomolecular building blocks, i.e., amino acids except glycine, sugars and nucleosides, as well as lipids. Continuous improvement of preparative methodologies meanwhile allows increasingly complex molecules to be synthesized, which includes sophisticated mirror-image biomolecules, such as proteins. [1]

Aggregation-prone (amyloidogenic) polypeptides are produced by living systems, often as cleavage products of substantially larger protein precursors. Whereas their functions in health are challenging to study and not always well understood, it is widely accepted that an imbalance between their production and clearance can trigger a range of pathological conditions, including Alzheimer's Disease (AD / amyloid β, Aβ), Huntington’s Disease (HD / the huntingtin protein) and Type 2 Diabetes (T2D / amylin). [2] A feature that is common to all those peptides is the high polydispersity across both aggregate size and shape, with distinctions frequently made between oligomers, protofibrils and fibrils. [3] In sporadic AD, Aβ oligomers (especially those derived from the 42-amino acid long isoform, Aβ42) are believed to be particularly harmful, whereas fibrils appear to represent an aggregation endpoint that may be relatively benign. [4]

Peptide backbone conformations can be altered through introduction of D-amino acids ("Chiral Editing"), [5] and replacement of L- by D-amino acids across the entire peptide yields mirror image ("D-“)Aβ. Because of the enantiomeric relation, D-Aβ has to possess an identical oligomer-protofibril-fibril distribution to that of the natural ("L-“) stereoisomer. However, all 3D-structural parameters are mirrored in D-Aβ42, including the peptide backbone. Through stereochemical arguments, we envisioned that racemic Aβ42 should exhibit increased fibril formation and reduced toxicity. We synthesized the two enantiomers of Aβ42 and found that their equimolar mixture exhibited pronounced acceleration of fibril formation, as compared to the enantiopure counterparts. This led to substantial suppression of oligomer formation and inhibition of toxicity in model cell-based systems. [6] We termed this the “Chiral Inactivation” effect. [7] The underlying molecular mechanisms that lead to the differences in biophysical and biological properties observed between enantiopure and racemic Aβ42 remain subject of active research in our laboratory.

References