Membrane-anchored amyloid peptides in Alzheimers disease

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Research Abstract

? DESCRIPTION (provided by applicant): Cerebral plaques composed of the amyloid ?-peptide (A?) and neurofibrillary tangles composed of the microtubule-associated protein tau are pathological hallmarks of Alzheimer’s disease (AD). The discovery that dominant missense mutations in the amyloid precursor protein (APP) and presenilin-1 and -2 (PS1 and PS2) cause

early-onset familial AD (FAD) cemented the idea that altered A? production alone could trigger a cascade of events leading to clinical AD. The single-pass membrane protein APP is the substrate from which A? is produced by the sequential proteolytic action of ?-secretase and ?-secretase, and presenilin is the catalytic component of the membrane-embedded ?-secretase complex. FAD mutations alter A? production to increase total A? production (APP mutations), increasing the aggregation propensity of the peptide (APP mutations), or increasing the proportion of aggregation-prone 42-residue A?42 over that of A?40 (presenilin mutations). Other than onset in midlife and the completely hereditary nature of the disease, FAD and the much more prevalent late-onset sporadic AD (SAD) are pathologically and clinically virtually identical, following similar progressions of molecular, cellular and behavioral changes, strongly suggesting shared pathological pathways. However, the identities of the responsible A? form(s) and associated toxic mechanism(s) remain unclear. In recent years, we and others have found that FAD presenilin mutations do not only change the proportion of secreted, aggregation-prone A?42 but substantially increase the proportion of membrane- anchored forms of A? that are 45-49 residues long. ?-Secretase initially cleaves the transmembrane region of APP substrate near the cytosolic interface, producing either A?49 or A?48, which are subsequently trimmed roughly every 3 amino acids via a carboxypeptidase function of ?-secretase. This specific proteolytic function of ?-secretase is dramatically decreased by FAD presenilin mutations. If long forms of A? are indeed pathogenic, a fundamental restructuring of the amyloid hypothesis would be in order, shifting the focus away from plaques, soluble oligomers or their major component (A?42) and toward membrane-anchored forms that are well positioned to trigger neurotoxic signals. It is essential to AD research that this possibility be either confirmed or denied. The overarching goal of this proposal is to test the hypothesis that presenilin mutations cause FAD through production of long, membrane-anchored A? peptides. Toward this end, the following questions will be addressed: (1) Are long, membrane-anchored A? peptides neurotoxic? (2) Are long, membrane-anchored A? peptides present in brain?

Further information available at:

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