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REVIEW ARTICLE

Cell Degeneration Induced by Amyloid-β Peptides

Implications for Alzheimer's Disease

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Abstract

Extracellular accumulation of amyloid-β (Aβ) peptide and death of neurons in brain regions involved in learning and memory, particularly the cortex and the hippocampus, are central features of Alzheimer's disease (AD). Neuronal Ca^{2+} overload and apoptosis are known to occur in AD. Aβ might play a role in disrupting Ca^{2+} homeostasis, and this AD-associated amyloidogenic peptide has been reported to induce apoptotic death in cultured cells. However, the specific intracellular signaling pathways by which Aβ triggers cell death are not yet well defined. This article provides evidence for the involvement of mitochondrial dysfunction in Aβ-induced toxicity and for the role of mitochondria in apoptosis triggered by Aβ. In addition, the endoplasmic reticulum (ER) seems to play a role in Aβ-induced apoptotic neuronal death, the ER stress being mediated by the perturbation of ER Ca^{2+} homeostasis. It is likely that a better understanding of how Aβ induces neuronal apoptosis will lead to the identification of potential molecular targets for the development of therapies for AD.

Index Entries: Alzheimer's disease; amyloid-β peptide; apoptosis; mitochondria; endoplasmic reticulum; Ca^{2+} homeostasis.

Alzheimer's Disease and Amyloid-β Peptide

Alzheimer's disease (AD) is the most common form of dementia in the elderly, the prevalence of which increases exponentially with aging. Clinically, this neurodegenerative disease of the central nervous system is characterized by the progressive loss of memory, by cognitive and language impairment, and also by behavioral disturbances. These clinical features are accompanied by characteristic histological changes in the brain (especially in the cerebral cortex), which include the presence of extracellular senile plaques, intraneuronal neurofibrillary tangles mainly composed of hyperphosphorylated tau, and the loss of synapses and neurons (Yankner, 1996). The amyloid-β (Aβ) peptide is a major component of the extracellular senile plaque, which naturally arises from the metabolic processing of the amyloid precursor protein (APP) in the endoplasmic reticulum (ER), the Golgi apparatus, or the endosomal-lysosomal pathway and is normally secreted as a 40 (Aβ1-40)- or 42 (Aβ1-42)-amino-acid peptide (Haass and Selkoe, 1993). Amyloid precursor protein (APP) is initially cleaved by either β- or α-secretases, leading to the generation of C-terminal membrane-bound fragments, which are immediate substrates for cleavage by γ-secretase to liberate Aβ (β- and γ-secretase) or a smaller peptide termed p3 (α- and γ-secretase cleavage). The Aβ1-40 and Aβ1-42

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