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HYPERPHOSPHORYLATION OF TAU BY GSK-3β IN ALZHEIMER'S DISEASE: THE INTERACTION OF Aβ AND SPHINGOLIPID MEDIATORS AS A THERAPEUTIC TARGET

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the extracellular deposits of β amyloid peptides (Aβ) in senile plaques, and intracellular aggregates of hyperphosphorylated tau in neurofibrillary tangles (NFT). Although accumulation of Aβ has been long considered a leading hypothesis in the disease pathology, it is increasingly evident that the role hyperphosphorylation of tau in destabilization of microtubule assembly and disturbance of axonal transport is equally detrimental in the neurodegenerative process. The main kinase involved in phosphorylation of tau is glycogen-synthase kinase 3-beta (GSK-3β). Intracellular accumulation of Aβ also likely induces increase in hyperphosphorylated tau by a mechanism dependent on GSK-3β. In addition, Aβ affects production of ceramides, the major sphingolipids in mammalian cells, by acting on sphingomyelinases, enzymes responsible for the catabolic formation of ceramides from the sphingomyelin. Generated ceramides in turn increase production of Aβ by acting on β-secretase, a key enzyme in the proteolytic processing of the amyloid precursor protein (APP), altogether leading to a ceramide-Aβ-hyperphosphorylated tau cascade that ends in neuronal death. Modulators and inhibitors acting on members of this devastating cascade are considered as potential targets for AD therapy. There is still no adequate treatment for AD patients. Novel therapeutic strategies increasingly consider the combination of multiple targets and interactions among the key members of implicated molecular pathways. This review summarizes recent findings and therapeutic perspectives in the pathology and treatment of AD, with the emphasis on the interplay between hyperphosphorylated tau, amyloid β, and sphingolipid mediators.

Keywords

• Alzheimer's disease • Tau hyperphosphorylation • Glycogen-synthase kinase 3β • Amyloid β • Sphingolipids

Abbreviations

Aβ	- Amyloid β protein
AD	- Alzheimer's disease
AICD	- APP intracellular domain
APP	- Amyloid precursor protein
BACE1	- β-secretase
BDNF	- Brain-derived neurotrophic factor
Cer	- Ceramides
Cdk5	- Cyclin-dependent kinase 5
GSK-3β	- Glycogen synthase kinase-3β
NFT	- Geurofibrillary tangles
PA	- Palmitic acid
PHF	- Paired helical filaments
PI3-K	- Phosphatidylinositide 3-kinase
PP2A	- Protein phosphatase 2A
NFT	- Neurofibrillary tangles
SM	- Sphingomyelinase
SPT	- Serine palmitoyltransferase

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A link between hyperphosphorylated tau, Aβ, and lipids

Alzheimer's disease (AD) is a chronic progressive neurodegenerative disorder and the leading cause of dementia syndrome in elderly people. Existing treatments for AD do not delay or modify progression of the disease, and the number of affected people is estimated to rise to 100 million worldwide by 2050 without new effective therapy [1]. Besides age that is considered the most significant risk factor for AD, epidemiological studies indicate that a high-fat diet might contribute to its development, the degree of saturation of fatty acid being the most important factor determining risk [2,3]. In fact, white matter from AD brain is characterized by increased fatty acid content, although the cholesterol levels are decreased in comparison to healthy subjects [4,5]. Hence, understanding the etiopathological processes of AD, particularly in respect of lipid contributions, is of major importance for the development of novel therapeutic strategies that will reverse or slow down progression of the disease.

The most researched neuropathological hallmarks found in AD brains are extracellular senile plaques containing neurotoxic amyloid β-peptide (Aβ) derived from the amyloid precursor protein (APP), and intracellular aggregates of abnormally phosphorylated tau protein that form paired helical filaments (PHF). They associate and build up densely packed networks of neurofibrillary tangles (NFT) [6-8]. Besides AD, phosphorylation of tau protein is also implicated in the pathogenesis of several related disorders called tauopathies [9,10].