

Molecular Mechanisms of ER Stress and UPR in the Pathogenesis of Alzheimer's Disease

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Alzheimer's disease (AD) is a progressive neurodegenerative disease involving aggregation of misfolded proteins inside the neuron causing prolonged cellular stress. The neuropathological hallmarks of AD include the formation of senile plaques and neurofibrillary tangles in specific brain regions that lead to synaptic loss and neuronal death. The exact mechanism of neuron dysfunction in AD remains obscure. In recent years, endoplasmic reticulum (ER) dysfunction has been implicated in neuronal degeneration seen in AD. Apart from AD, many other diseases also involve misfolded proteins aggregations in the ER, a condition referred to as ER stress. The response of the cell to ER stress is to activate a group of signaling pathways called unfolded protein response (UPR) that stimulates a particular transcriptional program to restore ER function and ensure cell survival. ER stress also involves the generation of reactive oxygen species (ROS) that, together with mitochondrial ROS and decreased effectiveness of antioxidant mechanisms, producing a condition of chronic oxidative stress. The unfolded proteins may not always produce a response that leads to the restoration of cellular functions, but they may also lead to inflammation by a set of different pathways with deleterious consequences. In this review, we extensively discuss the role of ER stress and how to target it using different pharmacological approaches in AD development and

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Alzheimer's disease

Amyloid ?

Endoplasmic reticulum

Tau

Unfolded protein response

activating transcription factor 4

activating transcription factor 6

ADAM10 endopeptidase

adenosine triphosphatase (calcium)

amyloid beta protein

amyloid precursor protein

anthra[1,9 cd]pyrazol 6(2h) one

beta secretase 1

calcium calmodulin dependent protein kinase II

dibenzoylmethane derivative

glucose regulated protein 78

glutathione

glycogen synthase kinase 3 inhibitor

growth arrest and DNA damage inducible protein 153

gsk 2606414

initiation factor 2

initiation factor 2alpha

inositol 1,4,5 trisphosphate receptor

pancreatic ER kinase

protein disulfide isomerase

protein IRE1

protein kinase

protein tyrosine kinase inhibitor

reactive oxygen metabolite

resveratrol

tau protein

transcription factor Nrf2

trazodone

unclassified drug

unindexed drug

X box binding protein 1

Alzheimer disease

apoptosis

autophagy (cellular)

brain mitochondrion

calcium signaling

endoplasmic reticulum

endoplasmic reticulum stress

gene expression

gene overexpression

hippocampus

human

hyperphosphorylation

immunohistochemistry

nerve cell necrosis

nonhuman

oxidative stress

pathogenesis

phosphorylation

protein aggregation

protein degradation

protein expression

protein folding

protein phosphorylation

protein protein interaction

Review

temporal cortex

unfolded protein response

upregulation

Western blotting