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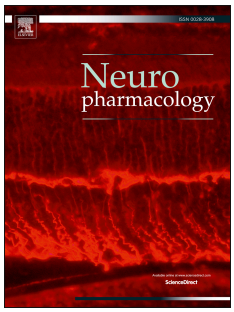

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Crosstalk between endoplasmic reticulum stress and brain inflammation in Alzheimer's disease

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Abstract

While most often noted for its cognitive symptoms, Alzheimer's disease (AD) is, at its core, a disease of protein misfolding/aggregation, with an intriguing inflammatory component. Defective clearance and/or abnormal production of the amyloid-β peptide (Aβ), and its ensuing accumulation and aggregation, underlie two hallmark features of AD: brain accumulation of insoluble protein deposits known as amyloid or senile plaques, and buildup of soluble Aβ oligomers (AβOs), diffusible toxins linked to synapse dysfunction and memory impairment. In neurons, as in typical eukaryotic cells, the endoplasmic reticulum (ER) serves as a main compartment for the folding, maturation, trafficking and quality control of newly synthesized proteins. The ER lumen, a calcium-rich, oxidizing environment, provides favorable conditions for these physiological functions to occur. These conditions, however, also favor protein aggregation. Several stressors, including metabolic/nutrient stress and certain pathologies, may upset the ER homeostasis, e.g., by affecting calcium levels or by causing the accumulation of unfolded or misfolded proteins. Whatever the underlying cause, the result is what is commonly known as "ER stress". This, in turn, triggers a conserved cellular response mechanism known as the "unfolded protein response" (UPR). The UPR comprises three pathways involving transcriptional or translational regulators aimed at normalizing ER function, and each of them results in pro-inflammatory signaling. A positive feedback loop exists between ER stress and inflammation, with clear implications for neurodegeneration and AD. Here, we explore recent findings on the role of ER stress and the UPR in inflammatory processes leading to synapse failure and memory impairment in AD.

Keywords: Alzheimer's disease; Endoplasmic reticulum stress; Unfolded protein response; Inflammation

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