Memory loss in Alzheimer's disease: are the alterations in the UPR network involved in the cognitive impairment?
Memory loss in Alzheimer’s disease: are the alterations in the UPR network involved in the cognitive impairment?

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Alzheimer’s disease (AD) is a progressive and devastating age-related neurodegenerative disorder, involving memory loss and the extracellular deposition in the brain of misfolded and aggregated amyloid beta (Aβ) peptide (Holtzman et al., 2011). The molecular mechanism that triggers AD is not completely understood. The AD neuropathological process begins many years before the clinical onset with general alterations in protein homeostasis (referred to as proteostasis) among other effects. Recent evidence suggests that disturbances in the normal function of the secretory pathway and the occurrence of endoplasmic reticulum (ER) stress may represent a common pathological feature of familial and sporadic AD (Cornejo and Hetz, 2013). ER stress engages an adaptive reaction known as the unfolded protein response (UPR) which modulates many aspects of ER proteostasis to decrease the unfolded protein load (Walter and Ron, 2011). Under conditions of irreversible or chronic ER stress the UPR shifts its signaling toward induction of apoptosis.

Aβ oligomers are known to induce neuronal loss and dysfunction (Mucke and Selkoe, 2012) and impair synaptic plasticity and memory in animal models of AD (Cleary et al., 2005; Shankar et al., 2008). In this line, whether ER stress causes cognitive impairment remained poorly studied until very recently. Besides, interesting novel concepts are emerging where ER stress may actually operates upstream of the generation of Aβ as part of the etiology of the disease (Yoon et al., 2012). Could these findings provide insights about new points for disease intervention? Many recent studies have developed small molecules and gene therapy strategies to alleviate ER stress in vivo, which offers interesting future applications for the development of clinical trials in AD and other diseases (Hetz et al., 2013).

Medial temporal lobe areas, such as the hippocampus and entorhinal cortex, are the first regions affected during the progression of AD, contributing to the occurrence of dementia in affected patients. Under diverse stress conditions, including ER stress, inhibition of protein synthesis operates as a survival pathway that is mediated by the phosphorylation of eukaryotic translation initiator factor 2 α (eIF2α), referred to as the “integrated stress response.” Of note, the process of memory consolidation and synaptic plasticity involve active protein synthesis, among other events (Costa-Mattioli et al., 2009). In fact, several studies have shown that exacerbated phosphorylation of eIF2α induces cognitive impairment (Costa-Mattioli et al., 2005, 2009; Jiang et al., 2010). In agreement with this findings, an elegant recent study demonstrated that decreasing the expression of two of the eIF2α kinases, double-stranded RNA-activated protein kinase (PKR)-like endoplasmic reticulum kinase (PERK) and General control non-derepressible-2 (GCN2), improve cognitive function and synaptic plasticity in an AD transgenic mouse model (Ma et al., 2013). In addition, targeting another eIF2α kinase termed dsRNA-dependent protein kinase (PKR), can also improve learning and memory processes at basal levels (Zhu et al., 2011), similarly to GCN2 deficient animals. Consistent with these finding, another recent report demonstrated that brain inflammation in AD models engages PKR to induce synaptic loss and memory impairment (Lourenco et al., 2013). In that study the authors also showed that Aβ oligomers alters insulin signaling leading to memory deficits through a mechanism involving the proinflammatory cytokine tumor necrosis factor (TNF)-α. Of note, PERK deficiency in the nervous system did not alter learning and memory-related processes at basal levels, and only impacted cognition in the context of AD models when ER proteostasis is altered (Ma et al., 2013). Importantly, these results solved an important question since they indicated that despite of reducing the adaptive activity of one branch of the UPR on a model of AD, this genetic manipulation improved cognitive aspects of AD without affecting the ability of cells to survive under the stress conditions generated by the accumulation of amyloid beta. Is the phosphorylation of eIF2α a key converging event involved in neuropathology and cognitive impairment in AD? Is this the molecular link between protein misfolding and neuroinflammation? These reports suggest the concept that modulation of protein synthesis through the eIF2α axis is directly involved in memory formation and could be also exploited as a target to reduce synaptic dysfunction in AD.
Advances in this line were provided by a recent study identifying a small molecule called ISRIB that efficiently reduces the consequences of eIF2α phosphorylation and improve learning and memory in wild-type rats (Sidrauski et al., 2013). This potent inhibitor showed promising pharmacokinetic properties, it crossed the blood-brain barrier with no overall adverse effects to the animal. These findings raise the possibility that compounds that inhibit PERK signaling may offer interesting future applications for the development of clinical trials in AD. Fine-tuning the concentrations the compounds will be a challenging issue due to the dual impact of this signaling pathway on cell fate. In this line, PERK inhibitors have been recently shown to revert synaptic dysfunction and neurodegeneration in models of Prion disease (Moreno et al., 2013).

Many important questions are still open in this emerging and growing field: (i) Is the IRE1α network, IRE1α/XBP1 and/or IRE1α/JNK pathways, involved in the consolidation and formation of memory? (ii) Do the activation of these pathways play a functional role in cognitive decline in AD? and, (iii) How is the UPR network as a whole related to the progression and pathogenesis of AD, APP processing and Aβ oligomers generation? Is neuroinflammation also converging into the IRE1α UPR axis? How can we consolidate that PERK signaling may have a dual and opposing activity in AD? All of the available evidence points to the fact that ER disturbances and UPR activation may facilitate and amplify both memory loss and protein aggregation on a vicious cycle that may turn initial adaptive memory loss and protein aggregation on a vicious cycle that may turn initial adaptive memory consolidation in Alzheimer’s disease.

FIGURE 1 | UPR response underling memory consolidation in Alzheimer’s disease. Activation of ER stress signaling by abnormal protein misfolding activates several stress kinases leading to phosphorylation of eIF2α, inhibiting protein synthesis. Phosphorylation of eIF2α impairs synaptic function and cognitive processes. The IRE1α/JNK pathway may feed forward to enhance amyloid deposition and AD process, whereas XBP1 has neuroprotective effects against Aβ toxicity, and controls the expression of a cluster of AD-related genes.
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