# Novel Mechanisms of Synaptic Dysfunction and Neuroprotection in Alzheimer's Disease

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**INTRODUCTION**. Alzheimer's disease (AD) is a neurodegenerative disorder characterized by brain amyloid deposition, synaptic failure and memory loss. Accumulating clinical and experimental evidence has implicated amyloid-β oligomers (AβOs), whose levels are increased in AD brains, as culprits of synapse and cognitive dysfunction. However, the underlying molecular mechanisms still remain to be fully determined. **OBJECTIVES:** Here we aimed to identify novel mechanisms of synapse and memory dysfunction triggered by AβOs in experimental models of AD, as well as potential neuroprotective strategies. **MATERIALS AND METHODS:** Our experimental models consisted of wild-type mice and non-human primates given intracerebroventricular injections of AβOs, the APP/PS1 mouse model of AD and hippocampal neurons exposed to AβOs. To determine mechanistic routes, knock-out animals and pharmacological approaches were used. Biochemical and morphological outcomes were determined by immunofluorescence, ELISA and Western blotting. Behavioural tests, such as novel object recognition and fear conditioning, were also used. **DISCUSSION AND RESULTS**: We described a novel mechanism of AβO-induced synapse and memory loss that depends on tumor necrosis factor α (TNF-α) signaling and phosphorylation of eIF2α (eIF2α-P) induced by activation of stress-sensitive kinases in the hippocampus. In line with the notion that such mechanisms are similar to those operating in peripheral metabolic disorders, such as diabetes, we found that anti-diabetic agents blocked such aberrant pathways and cognitive impairment in AD models. We next investigated potential neuroprotective properties of FNDC5/irisin, an exercise-induced hormone whose brain actions are still poorly understood. Results demonstrated that AD brains present reduced levels of FNDC5/irisin, and that such reduction is sufficient to promote memory loss in mice. FNDC5/irisin blocked AβO-dependent eIF2α-P in hippocampal neurons and remarkably protected against synapse failure and cognitive damage in AD mice. **CONCLUSAO:** Our findings uncover new potential neuroprotective approaches acting through attenuation of pathways that drive synapse and memory impairment. Such body of evidence could contribute to identify novel therapeutic targets in AD.

Palavra chave: Alzheimer's disease, neuroprotection, synapses.
Patrocínio: FAPERJ, CNPq, HFSP and INNT