AMYLOID-B PROTEIN INDUCES CASPASE-12 DEPENDENT SYNAPTOTOXICITY IN ISOLATED NERVE ENDINGS

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Synaptic loss is one of the pathological hallmarks of Alzheimer’s disease (AD). In fact this event may exceed neuronal death and appear to underlie memory dysfunction. Emerging evidence suggests the involvement of the internal Ca²⁺ stores in the pathophysiology of neurodegeneration in AD. Some evidences support the notion that certain events that trigger neuronal death in AD can initiate with the local activation of caspases into the synaptic compartment. Caspase-12 is located in ER and can be specifically activated during ER-stress, suggesting the participation of caspase-12 in ER- and Aβ-mediated apoptosis. The current study has been conducted to explore the presence and local activation of the ER-associated caspase-12 in synaptosomes from rat cortex and hippocampus in the presence of Aβ and ryanodine. Under these conditions we found synaptosomal mitochondrial dysfunction accompanied by a reduction in the content of actin protein concomitant with local caspase-12 activation. The reduction in the content of actin was prevented in the presence of specific inhibitors Z-ATAD-FMK for caspase-12. In the same way the calpain inhibitor MDL 28170 was able to prevent caspase-12 activation. Other caspases also were tested without observed their activation under this condition. These results support the activation of synaptic apoptotic mechanisms by caspase-12 after ER stress-mediated Aβ toxicity.