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REGULATION OF NMDA RECEPTOR ACTIVITY BY AMYLOID BETA OLIGOMERS IN NEURONS

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Alzheimer disease is the most frequent cause of progressive cognitive decline in the aged population. Several studies have demonstrated that amyloid beta peptides (Aβ) have a causal role in its pathogenesis altering glutamatergic transmission and inhibiting synaptic plasticity. In addition, diverse lines of evidences suggest that Aβ involves the activation of Src tyrosine Kinase family, which presumably leads to the phosphorylation of the NMDA receptor subunits, causing an increased Ca++ influx. Accordingly, we have studied whether amyloid beta oligomers induce changes on NMDA receptor expression and function and the mechanisms by which Aβ affects the NMDA receptor signaling on cortical primary cultured neurons. We found that short and long-term treatment of neurons with Aβ oligomers differentially regulates the NMDA receptor activity. First, we found that Aβ caused a sustained Src protein phosphorylation and specific pharmacological inhibition reduced Aβ-induced neuronal cell death. Next, we analyzed the role of Aβ in the regulation of mRNA transcription and protein expression of NMDA receptor subunits in cultured neurons. Here, we found that a chronic exposure of Aβ oligomers (1uM for 24h) significantly increased the mRNA levels expression of NR1, NR2A and NR2B subunits. Western blot analysis further confirmed the increase of NR1 protein levels after Aβ treatment. Then, we examined the effect of Aβ oligomers on glutamate-induced neurotoxicity and Ca++ permeability and we found that long-term Aβ exposure (1uM for 24h) significantly increases glutamate induced neurotoxicity but short-term Aβ exposure (1uM for 30') protects neurons against glutamate-induced cell death and reduces the glutamate-induced increase in intracellular Ca++ concentration. Overall, these results suggest that Aβ oligomers activate Src-like kinases and modulate the NMDA receptor expression and function of cortical primary cultured neurons.