AB INDUCES CASPASE-DEPENDENT LOSS OF PSD-95 AND SYNAPTOPHYSIN THROUGH NMDA RECEPTORS

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Soluble oligomeric amyloid-β (Aβ) is thought to induce synaptic dysfunction during early stages of Alzheimer's disease (AD). In this report, we show that soluble Aβ downregulates the levels of two synaptic proteins, PSD-95 and synaptophysin and that this effect can be blocked by MK-801 (NMDAR antagonist) and ifenprodil (NR2B antagonist). Low (1 µM) and high (10 µM) doses of NMDA, respectively, prevented and potentiated the actions of Aβ. Blockade of NR2A or synaptic NMDAR eliminated the protective effect of 1 µM NMDA, while the effects of 10 µM NMDA were only abolished by ifenprodil. Caspase-8, acting upstream of caspase-3, was found to mediate the synaptotoxic actions of Aβ in an ifenprodil-reversible fashion. Thus, Aβ leads to a loss of synaptic proteins by suppression of NR2A function and activation of NR2B function and subsequent induction of caspase-8 and caspase-3 activities. The identified novel mechanism through which Aβ initiates synaptic dysfunction suggests that selective enhancement of NR2A activity and/or reduction of NR2B activity can halt the manifestation of a key early-stage event in AD.