Amyloid ?-peptide oligomers stimulate RyR-mediated Ca2+ release inducing mitochondrial fragmentation in hippocampal neurons and prevent RyR-mediated dendritic spine remodeling produced by BDNF

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Soluble amyloid ?-peptide oligomers (A?Os), increasingly recognized as causative agents of Alzheimer's disease (AD), disrupt neuronal Ca2+ homeostasis and synaptic function. Here, we report that A?Os at sublethal concentrations generate prolonged Ca2+ signals in primary hippocampal neurons; incubation in Ca2+-free solutions, inhibition of ryanodine receptors (RyRs) or N-methyl-d-aspartate receptors (NMDARs), or preincubation with N-acetyl-l-cysteine abolished these signals. A?Os decreased (6<h) RyR2 and RyR3 mRNA and RyR2 protein, and promoted mitochondrial fragmentation after 24<h. NMDAR inhibition abolished the RyR2 decrease, whereas RyR inhibition prevented significantly the RyR2 protein decrease and mitochondrial fragmentation induced by A?Os. Incubation with A?Os (6<h) eliminated the RyR2 increase induced by brain-derived nerve factor (BDNF) and the dendritic spine remodeling induced within minutes by BDNF or the RyR agonist caffeine. Addition of BDNF to neurons incubated with A?O