Production of nerve growth factor by ?-amyloid-stimulated astrocytes induces p75NTR-dependent tau hyperphosphorylation in cultured hippocampal neurons

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Reactive astrocytes surround amyloid depositions and degenerating neurons in Alzheimer's disease (AD). It has been previously shown that ?-amyloid peptide induces inflammatory-like responses in astrocytes, leading to neuronal pathology. Reactive astrocytes up-regulate nerve growth factor (NGF), which can modulate neuronal survival by signaling through TrkA or p75 neurotrophin receptor (p75NTR). Here, we analyzed whether soluble A? peptide 25-35 (A?) stimulated astrocytic NGF expression, modulating the survival of cultured embryonic hippocampal neurons. Hippocampal astrocytes incubated with A? up-regulated NGF expression and release to the culture medium. A?-stimulated astrocytes increased tau phosphorylation and reduced the survival of cocultured hippocampal neurons. Neuronal death and tau phosphorylation were reproduced by conditioned media from A?-stimulated astrocytes and prevented by caspase inhibitors or blocking antibodies to NGF or p75NTR. Moreover, exogenous NGF was sufficient