The killing of neurons by β-amyloid peptides, prions, and pro-inflammatory cytokines[§]

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Abbreviations: Aβ, β-amyloid; AD, Alzheimer's disease; APP, amyloid precursor protein; BH_4, tetrahydrobiopterin; CASR, calcium-sensing receptor; DD, death domain; ECD, extracellular domain; JICD, juxtamembrane intracellular domain; MAPKs, mitogen-activated protein kinases; MBP, myelin basic protein; NAHA, normal adult human astrocytes; NO, nitric oxide; NOS-2, NO synthase-2; PARP, nuclear poly-(ADP-ribose) polymerase; $p75^{NTR}$, p75 neurotrophin receptor; ROS, reactive oxygen species.

SUMMARY

Reportedly, β-amyloid peptides ($A\beta_{40}$ and $A\beta_{42}$) induce the neurodegenerative changes of Alzheimer's disease (AD) both directly by interacting with components of the cell surface to trigger apoptogenic signaling and indirectly by activating astrocytes and microglia to produce excess amounts of inflammatory cytokines. A possible cell surface target for Aβs is the p75 neurotrophin receptor ($p75^{NTR}$). By using SK-N-BE neuroblastoma cells without neurotrophin receptors or engineered to express the full-length $p75^{NTR}$ or various parts of it, we have proven that $p75^{NTR}$ does mediate the Aβ-induced cell killing via its intracellular death domain (DD). This signaling via the DD activates caspase-8, which then activates caspase-3 and apoptogenesis. We also found a strong cytocidal interaction of direct $p75^{NTR}$-mediated and indirect pro-inflammatory cytokine-mediated neuronal damage induced by Aβ. In fact, pro-inflammatory cytokines such as TNF-α and IL-1β from Aβ-activated microglia potentiated the neurotoxic action of Aβ mediated by $p75^{NTR}$ signaling. The pro-inflammatory cytokines probably amplify neuronal damage and killing by causing astrocytes to flood their associated neurons with NO and its lethal oxidizing $ONOO^-$ derivative. Indeed, we have found that a combination of three major pro-inflammatory cytokines, IL-1β+IFN-γ+TNF-α, causes normal adult human astrocytes (NAHA) to express nitric oxide synthase-2 (NOS-2) and make dangerously large amounts of NO via mitogen-activated protein kinases (MAPKs). Soluble $A\beta_{40}$, the