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Viability of primary hippocampal neurons cultured from different knockouts of tumor necrosis factor receptor subtypes

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Abstract

Tumor necrosis factor (TNF)-α is a major component of the inflammatory process responsible for neuronal cytotoxicity in Alzheimer's disease (AD); however, the specific mechanisms of TNF-α-induced neurotoxicity and neuroprotection are still unclear. TNF-α signaling through TNF receptor (TNFR) type 1 (TNFR1) and TNFR type 2 (TNFR2) has been reported to be involved in amyloid-β peptide (Aβ)- and glutamate-induced neurotoxicity. In the present study, we aimed to evaluate whether the TNFR subtypes differentially contribute to neuronal death induced by soluble $A\beta_{1\text{-}42}$ oligomers and L-glutamate using primary cultures of hippocampal neurons from TNFR1 knockout (TNFR1 –/–), TNFR2 knockout (TNFR2 –/–), and wild-type mice. Morphological evaluation of neurons under a phase-contrast microscope and an assay for LDH release from neurons revealed that, with exposure to $A\beta_{1\text{-}42}$ oligomers or L-glutamate, primary neurons from the TNFR1 –/– mouse hippocampus grew more healthily than those from the wild-type mouse hippocampus, and primary neurons from the TNFR2 –/– mouse hippocampus grew less healthily than those from the wild-type mouse hippocampus. Our present results suggest that TNFRs have some relationship with the processes of neuronal death induced by $A\beta_{1\text{-}42}$ oligomers and L-glutamate, and that the receptor subtypes differentially contribute to the processes; that is, Aβ- and glutamate-induced signaling pathways are thought to cooperate with the signaling pathways activated by binding of TNF-α to TNFR1 to promote neuron death, whereas the signaling pathways mediated by TNFR2 counteract the Aβ- and glutamate-induced neurotoxicity. Two types of TNFRs are therefore potential targets for treating Aβ- and glutamate-induced AD pathologies. Tottori J. Clin. Res. 6(1), 49-59, 2014

Key Words

Tumor necrosis factor (TNF)-α, TNF receptors (TNFRs), neuron cultures, amyloid-β peptide (Aβ), lactate dehydrogenase (LDH) release assay, glutamate neurotoxocity

Introduction

TNF-α is a major component of the inflammatory process responsible for neuronal cytotoxicity, dysfunction and protection in a wide range of neurodegenerative disorders such as AD; however, the specific mechanisms underlying this process are still unclear[1, 2)]. TNF-α is a pleiotropic pro-inflammatory cytokine that exerts multiple biological effects[3)]. The diverse regulatory functions of TNF-α are explained by the fact that it can bind to two structurally distinct membrane receptors expressed on many types of cells[1, 4–6)]. In