

Differential expressions of type 1 and 2 receptors for TNF- α in neurons and microglia from Alzheimer's disease and normal healthy elderly control brains

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Abstract

It is believed that tumor necrosis factor (TNF)- α is centrally involved in the pathogenesis of Alzheimer's disease (AD). Although TNF- α signals exert bidirectional effects of being destructive and protective, increasing evidence that elevated levels of TNF- α in AD provides a rationale for clinical trials of anti-TNF- α agents, such as etanercept, for AD therapy; however, the molecular mechanisms underlying the effects of etanercept on TNF- α signaling through TNF receptors (TNFRs) in AD remain unclear. To address this issue, it should be clarified which effect, toxic or trophic, in the pathological course of AD, is predominant and which receptor, TNFR type 1 (TNFR1) or TNFR type 2 (TNFR2), plays a major role in the involvement of TNF- α signaling in the AD pathogenesis. In the present study, we demonstrate differential expression levels of mRNA and protein of TNFR1 and 2 in neurons and microglia, both of which were from AD and nondemented healthy elderly control (ND) brains. Primary neurons and microglia were obtained from autopsied human brains with short postmortem intervals (PMIs) (<4 hours), and total RNA and protein were extracted for subsequent reverse transcription (RT)-PCR and immunocytochemistry for TNFR1 and 2. First, exposure to β -amyloid peptide (A β) induced opposite reactions in TNFR expression between AD and ND neurons: A β enhanced mRNA expression levels of both TNFRs in AD neurons, while it inhibited both in ND neurons. Second, outcomes of the changes in TNFR mRNA seemed to head toward the same destination in TNFR1 and 2, suggesting that, in chronic neuropathological processes such as AD, the two types of TNFRs may cooperate to lead respective TNF- α -induced signaling pathways to the same destination. Third, in these primary AD neurons under exposure to A β , TNFR1 protein levels were higher than those of TNFR2. AD neurons with exposure to A β expressed TNFR1 to some extent either enough to induce cell damage or to protect cells, while slightly expressed TNFR2 not enough to either impair or protect cells. Fourth, microglia exposed to A β further expressed TNFR2, regardless of the disease state (AD and ND), although no expression of TNFR1 was observed despite the disease state or A β exposure, suggesting that all TNF- α signaling to microglia is mediated through TNFR2, probably switching to a trophic pathway in microglia, leading to their proliferation and activation; however, it remains unclear whether such microglia are detrimental or beneficial to neurons. Experiments using AD transgenic mice lacking both TNFRs may answer this issue. To further understand the roles of TNFR1 and 2 in the AD pathogenesis, it is necessary to investigate the activation states of molecules involved in the downstream signaling pathways for cell damage and protection. Tottori J. Clin. Res. 5(2), 143-153, 2013

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β -amyloid peptide ($A\beta$)