Active immunization with amyloid-beta 1-42 impairs memory performance through TLR2/4-dependent activation of the innate immune system.

Active immunization with amyloid-β (Aβ) peptide 1-42 reverses amyloid plaque deposition in the CNS of patients with Alzheimer's disease and in amyloid precursor protein transgenic mice. However, this treatment may also cause severe, life-threatening meningoencephalitis. Physiological responses to immunization with Aβ(1-42) are poorly understood. In this study, we characterized cognitive and immunological consequences of Aβ(1-42)/CFA immunization in C57BL/6 mice. In contrast to mice immunized with myelin oligodendrocyte glycoprotein (MOG)(35-55)/CFA or CFA alone, Aβ(1-42)/CFA immunization resulted in impaired exploratory activity, habituation learning, and spatial-learning abilities in the open field. As morphological substrate of this neurocognitive phenotype, we identified a disseminated, nonfocal immune cell infiltrate in the CNS of Aβ(1-42)/CFA-immunized animals. In contrast to MOG(35-55)/CFA and PBS/CFA controls, the majority of infiltrating cells in Aβ(1-42)/CFA-immunized mice were CD11b(+)CD14(+) and CD45(high), indicating their blood-borne monocyte/macrophage origin. Immunization with Aβ(1-42)/CFA was significantly more potent than immunization with MOG(35-55)/CFA or CFA alone in activating...
macrophages in the secondary lymphoid compartment and peripheral tissues. Studies with TLR2/4-deficient mice revealed that the TLR2/4 pathway mediated the Aβ(1-42)-dependent proinflammatory cytokine release from cells of the innate immune system. In line with this, TLR2/4 knockout mice were protected from cognitive impairment upon immunization with Aβ(1-42)/CFA. Thus, this study identifies adjuvant effects of Aβ(1-42), which result in a clinically relevant neurocognitive phenotype highlighting potential risks of Aβ immunotherapy.