Nonhuman/Target identification and validation studies: Inflammation and innate immunity

The novel omega-6 fatty acid docosapentaenoic acid positively modulates brain innate immune response for resolving neuroinflammation at early and late stages of humanized APOE-based Alzheimer’s disease models

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Abstract

Background: Neuroinflammation has been well established to play a crucial role in the pathogenesis and progression of Alzheimer’s disease (AD), and strong epidemiological studies have shown clear evidence of nonsteroidal anti-inflammatory drugs (NSAIDs) for preventing the onset of AD in middle-aged people, but NSAIDs and all other anti-inflammatory drugs such as selective cyclooxygenase 2 (COX2) inhibitors have failed to treat moderate to severe or early stage AD in clinical trials. In this study, we report the mechanism and efficacy of omega-6 fatty acid linoleic acid (LA) on the reduction and resolution of neuroinflammation at early and late stages of humanized APOE-based AD models. We found that the novel LA metabolite docosapentaenoic acid (DPAn-6) has robust anti-inflammatory and neuronal protective effects in old ApoE4x5FAD mice with pre-existing severe amyloid burden, gliosis, behavior deficits and neurodegeneration.

Method: Two different ages of ApoE4x5FAD animals were used for the study. First, 3 to 4-month-old adult ApoE3x5FAD and ApoE4x5FAD were treated by dietary linoleic acid for four months. Secondly, 11 to 14-month-old ApoE4x5FAD mice were treated by oral DPAn-6 for three weeks. Treatment efficacy was analyzed by novel object recognition, ELISA, RNAseq and immunohistochemistry.

Result: We found that dietary LA reduced proinflammatory cytokines and COX2 gene expression and resolved neuroinflammation evidenced by reduced IL1&beta and IL6 but increased anti-inflammatory IL-10 in adult ApoE3x5FAD and ApoE4x5FAD mice. In this study, the high LA diet increased its CNS metabolite DPAn-6 greater with ApoE4. Thus, we further tested DPAn-6 in old ApoE4x5FAD administering by gavage for three weeks. DPAn-6 significantly reduced microgliosis, astrogliosis, innate immune inflammatory and caspase gene expression. In parallel, DPAn-6 coordinately increased BDNF, VGF, ADCYAP1 and neuronal pentraxin 2 expression, indicating increased...
neurotrophin and plasticity-related gene expression relevant to novel object memory improvement. In addition, COX expression was also reduced by LA or DPAn-6 in vivo and in vitro amyloid-β42 oligomer-challenged microglial BV2 cells.

**Conclusion:** Taken together, we demonstrated that a novel n-6 fatty acid docosapentaenoic acid modulated innate immune responses to resolve neuroinflammation at early and late stages of AD models with or without ApoE4. This was accompanied by synaptic, neuronal and cognitive benefits.