Resolving Factors in Alzheimers Disease

https://neurodegenerationresearch.eu/survey/resolving-factors-in-alzheimers-disease/

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Research Abstract

DESCRIPTION (provided by applicant): Inflammation with aging is a systemic event which affects physiological correlates of aging in the brain. Inflammatory pathways are closely linked to Alzheimer’s disease (AD), and are strongly suggested to partake in the pathological disease process, even though clinical trials using anti-inflammatory agents have not been promising. Although it may not be possible to prevent inflammatory processes in AD, it may instead be possible to stimulate the resolution of the inflammatory cascade. In the last stage of

inflammation, specialized pro-resolving mediators (SPMs) are actively involved in down-regulation of the inflammatory response. Albeit fairly well studied in the peripheral immune system, the SPMs have only recently been detected in brain tissue. Our findings suggest significant alterations in SPMs and their synthetic enzymes and receptors, both in cerebrospinal fluid (CSF) of patients with AD, and in postmortem tissue from the hippocampus. However, the specific influence of the resolving cascade on AD neuropathology, or its potential correlation with cognitive decline have not been explored. The CSF data clearly indicate a significant reduction in SPMs with AD, in a step-wise manner from non-impaired, MCI and AD patients, and a strong staining pattern for SPM receptors in the hippocampus formation in patients with AD. We are the first to report both distribution and levels of the SPM pathway components in AD and age-matched control human samples. In this revised proposal, we wish to examine the role of the resolving cascade, in CSF and plasma from humans with different levels of cognitive impairment (Aim 1) and in postmortem tissue (Aim 2) to determine whether the resolving cascade can serve as an early biomarker for AD, and whether resolving stimulating agents can enhance the outcome of AD or reduce conversion of MCI to AD. The overall hypothesis of this proposal is: SPMs and their receptors are dys-regulated in the brain of AD patients and correlate with degree of dementia. Measurements of SPMs in CSF or in plasma can be used as a viable biomarker for AD degeneration and dementia in the brain. We have proposed two specific aims: In Aim 1, CSF and plasma levels of inflammation resolving factors will be correlated with specific cognitive and neuropathological measures in SCI, MCI, and AD patients, and in Aim 2, we propose to examine whether SPMs and associated molecules correlate with amyloid plaque load and/or tangle formation in vulnerable areas of the brain in elderly individuals with or without AD. CSF and plasma samples will be correlated with cognitive performance in a cohort of patients from the Karolinska memory clinic (Schultzberg laboratory) and double labeling coupled with stereological cell counts in postmortem tissue (Granholm Laboratory) from the two brain banks involved will generate sufficient data to determine whether evaluating the resolving cascade warrants further in depth experiments in humans or mouse models of AD.

Further information available at:

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