The Impact Of Surgery-Induced Neuroinflammation On Tau Pathology And Function

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Country

USA

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The Impact Of Surgery-Induced Neuroinflammation On Tau Pathology And Function

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NIH (NIA)

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15/09/2011

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3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

neuroinflammation, tau Proteins, tau phosphorylation, lipoxin A4, Anesthesia procedures

Research Abstract

? DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) remains a major health problem in the U.S., and as life expectancy continues to increase, the number of AD patients presenting for surgery and anesthesia will also rise. The etiology of AD is probably multifactorial however, studies suggest that surgery and anesthesia may contribute to the progression of AD pathology and its related cognitive decline. Recent studies have shown that the resolution of neuroinflammation is impaired in AD. Intraneuronal neurofibrillary tangles, composed of aggregates of hyperphosphorylated tau protein, are one of the main neuropathological hallmarks of AD. However, how impaired resolution physiology impacts the progression of tau pathology following surgery?induced neuroinflammation and anesthesia exposure is unknown. Hence, we now hypothesize that pre?existing tau pathology inhibits the resolution response to surgery?induced neuroinflammation, resulting in increases in hippocampal and cortical tau phosphorylation, neurofibrillary pathology, and neurocognitive impairment. Moreover, these changes are amplified by the presence of anesthetics known to promote tau phosphorylation, yet attenuated by increased Lipoxin A4 signaling. The following aims will test these hypotheses: Specific Aim 1: To confirm that pre?existing impairment of resolution physiology results in increased tau phosphorylation and the exacerbation of tau pathology following surgery?induced neuroinflammation in the absence and presence of anesthetics. Specific Aim 2: To identify the functional and behavioral sequelae as well as the in vivo spatio?temporal distribution of tauopathy?related changes following surgery?induced neuroinflammation. Specific Aim 3: To investigate the impact of increased lipoxin A4 signaling on resolution physiology impairment, tau phosphorylation, and tau pathology following surgery?induced neuroinflammation. Relevance: These studies are unique in that they will use AD transgenic mice expressing non?mutant, human tau (hTau) to investigate the impact of impaired resolution physiology on tau pathology, tau function, and will also establish the impact of these changes on learning and memory. Furthermore, using transgenic reporter mice and biophotonic imaging, we will monitor post?surgical neuroinflammatory changes in real time in vivo and establish spatio?temporal relationships to the longitudinal progression of tau pathology. Lastly, the therapeutic potential o Lipoxin A4 to attenuate the negative effects of surgery?induced neuroinflammation on tau pathology and cognitive decline will be also investigated. This information is critical for attainig the long? term goal of preventing the postoperative acceleration of cognitive decline in the growing number of patients, with or at risk for AD, who require surgery and anesthesia.

Lay Summary

PUBLIC HEALTH RELEVANCE: Alzheimer’s disease (AD) is a major health problem in the elderly population, and as life expectancy continues to increase, the number of AD patients presenting for surgery and anesthesia will also rise. Recent studies suggest that surgey and anesthetics may contribute to the progression of this neurodegenerative disorder; moreover, AD patients are at a higher risk of developing postoperative cognitive complications. The overall goal of this project is to determine and characterize the impact of surgery?induced neuroinflammation, in the absence and presence of anesthesia, on AD?associated tau pathology, which is critical information for improving the perioperative car of this rapidly increasing and vulnerable patient population.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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