Pathogenesis of Postoperative Cognitive Dysfunction

https://neurodegenerationresearch.eu/survey/pathogenesis-of-postoperative-cognitive-dysfunction/

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Country

USA

Title of project or programme

Pathogenesis of Postoperative Cognitive Dysfunction

Source of funding information

NIH (NIA)

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01/09/2012

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4

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Behavioral and Social Science... Biotechnology... Brain Disorders... Dementia... Genetics... Immune System... Mental Health... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): With an increase in the number of aged people, it is predicted that cognitive decline will be one of the most demanding healthcare problems in the near future for both patients and their providers, consuming a growing fraction of healthcare resources. Post-operative cognitive dysfunction or decline (POCD) is one of the most common post-operative complications in older patients, and is associated with substantially increased morbidity, mortality, and cost of care. However, the pathogenesis of POCD is still largely unknown, and this gap in knowledge impedes further studies of POCD. Neuroinflammation includes microglia activation and increases in pro-inflammatory cytokines such as tumor necrosis factor (TNF)-?, interleukin-6 (IL-6), and IL-1ß in the brain. ß-Amyloid protein (Aß) is th key component of senile plaques in Alzheimer's disease (AD) patients, and Aß levels are elevated in the brains of AD patients as well as older adults. Consistent with the notion that neuroinflammation and Aß accumulation are associated with cognitive dysfunction, and that surgery without general anesthesia can also lead to POCD in humans, our Preliminary studies in mice have shown that open abdominal surgery under local anesthesia induced neuroinflammation, Aß accumulation, and neurobehavioral deficits. Thus, the proposed research will extend these studies to define a potential multifactorial model of POCD pathogenesis by testing the hypothesis that: surgery-induced neuroinflammation will interact with the gene mutation- or aging-induced elevation of Aß levels, leading to impairment of learning/memory and attention/executive function. We will employ chemical and genetic tools through both in vitro (neurons) and in vivo (mice) approaches to accomplish three Specific Aims: 1) We will evaluate the time- dependent effects of the surgery on plasma levels of TNF-?, IL-6, and IL-1ß; the brain levels of TNF-?, IL-6, IL- 1ß, phosphorylated eukaryotic translation initiatin factor 2? (eIF2?-P), ß-site APP-cleaving enzyme (BACE)1, Aß, microglia activation, and amyloid plaques; and postoperative behavioral changes in mice. 2) We will dissect the pathways contributing to Aß accumulation following surgery-induced neuroinflammation by investigating the effects of TNF-?, IL-6, and IL-1ß on eIF2?-P-associated Aß generation pathway and potential CD33 (a newly suggested Alzheimer's disease gene)-associated Aß degradation pathway. 3) We will assess whether the knockout of TNF-?, IL-6 or IL-1ß receptor, anti-inflammatory, or anti-Aß accumulation treatment can inhibit the surgery-induced neurotoxicity. We will include wild-type and younger (9 month-old) mice versus age matched AD transgenic and older (18 month-old) mice (with higher baseline Aß levels), and employ Western blot, ELISA, immunohistochemistry, RT-PCR, microdialysis, RNAi, the Fear Conditioning Test, and an intra-dimensional/extra-dimensional digging task. This proposal aims to investigate an understudied topic in an innovative system by testing novel hypotheses. Our efforts would ultimately lead to safer surgical care and better post-operative outcomes for senior patients.

Lay Summary

Post-operative cognitive dysfunction or decline (POCD), one of the most common post-operative complications in geriatric patients, is associated with substantially increased morbidity, mortality, and cost of care. However, its pathogenesis is largely unknown. The proposed research will characterize surgery-induced neurotoxicity, investigate the underlying mechanisms, and define its role in POCD pathogenesis.

Further information available at:

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Investments > €500k

Member States:

United States of America

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Alzheimer's disease & other dementias

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