Neuroinflammatory and cognitive consequences of losing cholinergic anti-inflammatory tone in the forebrain

https://neurodegenerationresearch.eu/survey/neuroinflammatory-and-cognitive-consequences-of-losing-cholinergic-anti-inflammatory-tone-in-the-forebrain/

Principal Investigators

CUNNINGHAM, COLM

Institution

TRINITY COLLEGE DUBLIN

Contact information of lead PI
Country

USA

Title of project or programme

Neuroinflammatory and cognitive consequences of losing cholinergic anti-inflammatory tone in the forebrain

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NIH (NIA)

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01/09/2016

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1

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)... Basic Behavioral and Social Science...

Behavioral and Social Science... Brain Disorders... Dementia... Mental Health... Neurodegenerative... Neurosciences

Research Abstract
Project Summary (complete rewrite) Acute cognitive dysfunction (including delirium) is a highly prevalent neuropsychiatric complication of systemic inflammation in the elderly and, in particular, in those with dementia. As well as extending hospital stays, acute systemic inflammatory episodes also increase the risk for subsequent dementia and accelerate existing dementia. Despite these economic and public health imperatives, the pathophysiological mechanisms of systemic inflammation- induced acute cognitive dysfunction and lasting brain injury are poorly understood. We have previously demonstrated that systemic inflammation, when superimposed on existing neurodegenerative pathology, produces acute, fluctuating and reversible impairments in cognitive domains relevant to delirium (Davis et al., 2015) and accelerates the trajectory of long-term decline (Cunningham et al, 2009). Acetylcholine (ACh) is a neuromodulator with important roles in attention and cognitive function and the cholinergic neurons of the basal forebrain degenerate significantly in Alzheimer's disease. We have recently demonstrated that existing neurodegeneration in the basal forebrain cholinergic system leads to more severe acute cognitive dysfunction after systemic administration of bacterial endotoxin (LPS; Field et al., 2012). Macrophage lineage cells can also be modulated by ACh and here we highlight that loss of cholinergic forebrain ennervation leads to a priming of the forebrain microglial population to show exaggerated IL-1? responses to subsequent inflammatory stimulation. We propose that this cholinergic and consequent inflammatory predisposition significantly impacts on the short-term cognitive/neurophysiological, and long-term cognitive and neuropathological, outcomes of systemic inflammation. We will address this hypothesis directly by administering LPS or poly-microbial sepsis (cecal ligation and puncture; CLP) to mice with immunotargeted degeneration of the basal forebrain cholinergic system. In AIM1 we will demonstrate exaggered microglia, astroglial and neuronal responses to systemic inflammation and probe the role of nicotinic receptors in these effects. In AIM 2 we will use both LPS and CLP coupled with unique real-time in vivo brain monitoring of acetylcholine and of key determinants of neuronal function: oxygen, glucose, lactate, time-synced to behavioral testing to interrogate the neurophysiological underpinning of acute cognitive changes and the mechanisms of brain injury leading to long-term cognitive impairment. In AIM3 we will examine differential effects (on hypocholinergic versus normal mice) of some pharmacological interventions typical of the acute medical setting. Together we believe that these studies will significantly contribute to our understanding of acute cognitive dysfunction occurring during systemic inflammation and the exacerbation of ongoing cognitive decline relevant to aging and dementia.

Lay Summary
Project Narrative Systemic inflammation can trigger acute cognitive dysfunction (including delirium) as well as accelerating long-term cognitive decline (including dementia) and this occurs with high prevalence in the aging population. It is accepted that prior neurodegeneration increases the risk of these adverse health outcomes but this is poorly understood and we now propose that loss of anti-inflammatory acetylcholinergic tone predisposes to exaggerated brain inflammatory responses to systemic inflammatory insults, resulting in excessive inflammatory mediator release and contributing to acute cognitive dysfunction and lasting brain injury. In the current proposal we will use p75NTR-saporin to produce partial and selective degeneration of basal forebrain cholinergic neurons, and will induce systemic inflammation with bacterial

endotoxin or polymicrobial sepsis, in order to study the influence of pre-existing hypocholinergia on acute illness-induced brain inflammation, changes in brain energy metabolism and neurophysiology (time-synchronized to behaviour) and new brain injury leading to long-term cognitive decline.

Further information available at:

Types:
Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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