Synaptic Dysfunction Affecting DNA Integrity in Alzheimers Disease

https://neurodegenerationresearch.eu/survey/synaptic-dysfunction-affecting-dna-integrity-in-alzheimers-disease/

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Country

USA

Title of project or programme

Synaptic Dysfunction Affecting DNA Integrity in Alzheimers Disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 2,079,115.60

Start date of award

01/09/1992

Total duration of award in years

22

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)... Brain Disorders... Dementia... Genetics... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): This grant focuses on Alzheimer’s disease (AD), the

most frequent neurodegenerative condition, and on the question of how elevation of amyloid-beta (A-beta) levels in the brain contributes to its pathogenesis. Recently, we discovered that exploration of a novel environment causes putative DNA double strand breaks (DSBs) in neurons of wildtype (WT) mice. The DSBs were most abundant in memory centers and were repaired within 24 hours. Transgenic mice with neuronal expression of familial AD-mutant forms of the human amyloid precursor protein (hAPPFAD mice), which simulate several aspects of AD, had increased neuronal DSBs at baseline and more severe and prolonged DSBs after exploration. Treatment with the anti-epileptic drug levetiracetam suppressed aberrant network activity, normalized levels of DSBs and improved synaptic functions as well as learning and memory in hAPPFAD mice. In primary neuronal cultures from WT mice, exposure to human A-beta oligomers increased DSBs, and this effect was prevented by blocking NR2B-containing NMDA-type glutamate receptors. Thus, A-beta may exacerbate and prolong activity-related increases in neuronal DSBs, possibly as a result of synaptic and network dysfunction. By changing the expression of genes involved in cognitive functions and the regulation of neuronal activities, this process could promote a vicious cycle and contribute to the pathogenesis of AD. To test these hypotheses, we will (1) further characterize the nature and causes of neuronal DSBs in WT and hAPP-J20 mice, (2) determine the mechanisms by which levetiracetam counteracts A-beta-induced increases in neuronal DSBs, (3) determine whether neuronal DSBs and the associated histone variant YH2A.X specifically affect learning/memory and related gene expression, and (4) validate key findings in other mouse models and in humans with AD. The most novel aspects of this proposal include the hypotheses that physiological brain activity causes transient neuronal DSBs that DNA integrity in neurons is regulated by the activity of NR2B-containing glutamate receptors, and that pathologically elevated levels of A-beta alter these processes by changing the activities of synapses and neuronal networks. Innovative approaches include the use of chromatin immunoprecipitation and massively parallel DNA sequencing to identify the genes affected and the use of a novel APP knockin mouse that overproduces Aß but not APP. Investigational anti-A-beta treatments have been associated with serious side effects that were probably unrelated to the reduction of A-ß levels per se. It is therefore desirable to identify alternative or complementary therapeutic strategies to make the brain more resistant to A-beta-induced neuronal dysfunction. Protecting the neuronal genome against A-beta’s adverse effects could be particularly critical in this regard.

Lay Summary

PUBLIC HEALTH RELEVANCE: Amyloid-beta (A-beta) peptides and neuronal DNA damage may causally contribute to Alzheimer’s disease (AD), the major cause of dementia in the elderly. Because investigational anti-A-beta treatments have been associated with serious side effects, it is desirable to identify alternative or complementary strategies to make the brain more resistant to A-beta-induced neuronal dysfunction. The current proposal aims to elucidate the relationship between A-beta-induced DNA damage and neuronal dysfunction, to block the disease-causing processes involved, and to normalize the expression of genes required for effective learning and memory.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

Database Tags:
N/A