Diets rich in palmitate increase Alzheimers disease risk by activating CHOP gene

https://neurodegenerationresearch.eu/survey/diets-rich-in-palmitate-increase-alzheimers-disease-risk-by-activating-chop-gene/

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USA

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Diets rich in palmitate increase Alzheimers disease risk by activating CHOP gene

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2

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Alzheimer's disease & other dementias

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Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Dementia... Genetics... Neurodegenerative... Neurosciences... Nutrition

Research Abstract

DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is a complex disorder that affects memory and progresses to a debilitating dementia. Evidence shows that the nature of our dietary intake influences both epigenetic changes and disease-related genes, thus potentially increasing or reducing our risks of developing diseases such as AD. This application examines novel mechanisms that link a specific dietary agent (palmitate) to a specific transcription factor (CHOP) that may work in concert to cause AD-like pathology in mice. Characterization of such mechanisms may help identify new etiological factors and targets for drug discovery for AD in humans. CHOP (C/EBP-homologous protein) is expressed in the cytoplasm at low levels in normal conditions and is specifically overexpressed following sustained stress to the endoplasmic reticulum (ER). Various agents including environmental (chemical or dietary), genetic, and pathological factors can induce ER stress. The objective of this proposal is to test the hypothesis that the saturated free fatty acid palmitate triggers or exacerbates AD-like pathology by mechanisms involving the activation of the transcription factor CHOP; inhibiting CHOP precludes palmitate-induced AD-like pathology. Our hypothesis is formulated based on our recently published data and preliminary results showing that (i) a palmitate-enriched diet triggers AD hallmarks in wild type mice and exacerbates AD-like pathology in the triple transgenic mouse model for AD (3xTg-AD); (ii) CHOP levels are increased in postmortem brain tissue from humans with AD, in vivo in the 3xTg-AD, and ex vivo in mouse hippocampal slices incubated with palmitate; and that (iii) deleting CHOP gene abrogates palmitate-induced AD hallmarks. In the light of our postmortem, in vivo, and ex vivo results, we propose that determining the particular functional link between the common dietary agent palmitate and the transcription factor CHOP is extremely important to the continuing effort of identifying new etiological agents and genes that may be relevant to the pathogenesis of AD. We propose the following Specific Aims to test our hypothesis: Aim 1: Characterize the functional relationship between palmitate feeding and the triggering of AD-like pathology in mouse models. Aim 2: Determine the role of CHOP in the progression of AD-like pathology in mouse models. Aim 3: Determine the extent to which available drugs that inhibit CHOP prevent or delay AD-like pathology in mice. Completion of the proposed studies may show that the saturated free fatty acid palmitate promotes AD- like pathology in mice through CHOP activation. This is important to identifying etiological factors and genes related to the pathogenesis of AD in humans. Using existing drugs or designing new agents that inhibit CHOP might be promising targets for determining their translational potential in reducing the progression of AD.

Lay Summary

PUBLIC HEALTH RELEVANCE: Alzheimer’s disease (AD) is becoming a worldwide public health crisis and only a disease- modifying therapy can limit the progression of the disease. A major problem behind the current unavailability of AD therapies is the lack of identification of factors and mechanisms by which these factors cause AD. This proposal aims to demonstrate that the dietary saturated fatty acid palmitate activates the transcription factors CHOP and may increase the risk for AD in animal models.

Further information available at:

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Investments > €500k

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United States of America

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