Epigenetic and phenotypic effects of arsenic: impacts on cognition and AD

https://neurodegenerationresearch.eu/survey/epigenetic-and-phenotypic-effects-of-arsenic-impacts-on-cognition-and-ad/

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Country

USA

Title of project or programme

Epigenetic and phenotypic effects of arsenic: impacts on cognition and AD

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 2,354,088.99

Start date of award

19/09/2014

Total duration of award in years

1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Arsenic, Cognition, Liver X Receptor, Epigenetic Process, Alzheimer's Disease

Research Abstract

DESCRIPTION (provided by applicant): The only risk factor identified so far for sporadic late onset AD (LOAD) is aging. The inheritance of APOE?4 allele of apolipoprotein E is the major

genetic risk factor for LOAD but molecular mechanisms underlying this susceptibility are unknown. It is possible that similar to other multifactorial (systemic) diseases, the underlying quantitative variation in susceptibility to develop LOAD is probably controlled by multiple genes. The role of environmental factors in the risk and pathogenesis of AD has been increasingly appreciated. In this regard, the research on epigenetic reprogramming inflicted by exposure to environmental factors, strongly suggests that changes induced at certain chromatin marks during the development and postnatal life can influence development of dementia and AD progression. We are proposing investigation in animal models to advance the understanding of the role of environmental arsenic (As) exposure in the etiology and progression of AD. We capitalize on the results generated with the support of our ongoing NIEHS R21: 1) exposure of adult mice, with already developed AD phenotype, to human relevant As concentrations (100 ?g/ml) in drinking water further deteriorates their cognitive performance, increases amyloid plaques and reactive astrocytosis in hippocampus; the expression of nuclear liver X receptors (LXR) and important target genes, is decreased. 2) Young mice exposed to as are cognitively impaired and the expression level of and activity dependent transcription factor EGR1 (Early growth response 1), implicated in memory formation and cognitive performance is lower. 3) prenatal exposure to As and high fat diet (HFD) causes global hypoacetylation at Lysine 9 of histone 3 (H3K9) and alterations in acetylation pattern of genes, components of Polycomb Repressive Complexes PRC1 and PRC2, that modulate gene expression genome-wide through changes in histone modifications. We hypothesize that prenatal, perinatal and postnatal as exposure impairs cognitive reserve and inhibits adaptive capacity of the adult organism to environmental insults (e.g. HFD). The outcome is a predisposition to AD or aggravated existing AD phenotype, with the APOE genetic background significantly impacting the pathology. We are proposing that histone modifications, including those catalyzed by PRC2 and loss of essential transcriptional programs (e.g. LXR and EGR1) are molecular mechanisms underlying as effects. To test the hypothesis we will accomplish two Specific Aims: Aim 1. To elucidate the effects of as exposure on the development of AD-like phenotype in AD model mice. Aim 2: To identify epigenetic molecular mechanisms underlying changes in cognitive performance and AD phenotype in response to as exposure.

Lay Summary

PUBLIC HEALTH RELEVANCE: The impact of environmental factors on Alzheimer’s disease and impaired cognition is under realized and there are many gaps in understanding how environmental factors cause or promote neurodegenerative disease. These studies will elucidate the molecular mechanisms for epigenetic regulation of cognitive impairment and AD phenotypes caused by environmental as exposure and will implicate these mechanism in enhancing AD pathology from combined environmental and nutritional exposures. The findings may aid in developing interventions to prevent, delay or reverse the devastating cognitive effects of As exposure, and may contribute to identifying molecular targets for therapeutic strategies to slow AD progression.

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

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