Impact of Ambient Ultrafine Particle Exposures on Alzheimers Disease Progression

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Country

USA

Title of project or programme

Impact of Ambient Ultrafine Particle Exposures on Alzheimers Disease Progression

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,565,669.72

Start date of award

09/09/2013

Total duration of award in years

1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

particle exposure, ultrafine particle, Alzheimer's Disease, Disease Progression, Aerosols

Research Abstract
DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is a devastating neurodegenerative disorder associated with progressive functional decline and dementia.

Sporadic AD cases are believed to arise from a combination of genetic susceptibility and environmental factors. Inflammatory processes are thought to be integral for initiating and/or propagating AD-associated pathology within the brain and a number of environmental triggers are associated with increased AD risk. Research Plan: We hypothesize that inhalation exposures to ultrafine particle-enriched ambient air pollution (HUCAPS) aerosols will accelerate AD-associated pathology and that early life exposures will lead to more severe pathology than exposures that occur in late adulthood. Moreover, given the link between inflammation and AD-related pathogenesis, we further hypothesize that antagonism of a key inflammatory regulator, namely tumor necrosis factor (TNF)-a, will lessen exposure-related pathology. We will test our hypothesis using a well-characterized genetic mouse model of AD (3xTg-AD) that develops progressive human-like beta-amyloid and tau tangle pathology. Mice will be exposed to traffic-related aerosols that have been enriched for ultrafine particles using a unique stationary concentrator system (HUCAPS). We will evaluate the impact of genetic background, developmental age, and post-exposure time on the disposition of inhaled tracer nanoparticles in the central nervous system (CNS), lung and neuroinflammatory processes, severity and progression of AD-related pathology, and functional learning and memory behaviors. Our objectives will be met with the following three specific aims to test our hypotheses: 1) define changes in the regional accumulation and retention of tracer particles in the CNS following HUCAPS exposure as a function of age and AD pathology status; 2) determine the age-related impact of HUCAPS aerosol exposures on the progression of CNS neuroinflammatory processes, AD-related pathology and cognitive decline in 3xTg-AD mice; and 3) investigate the role of TNF in HUCAPS aerosol-induced inflammatory and pathological CNS changes in 3xTg-AD mice following central or peripheral TNF blockade. Expected Results: These collaborative studies will leverage the collective expertise of two laboratories with established research programs in the fields of particulate air pollution, lung biology, neuroinflammation, and AD. These new studies are designed to learn how ambient air pollution exposures impact brain neuroinflammatory processes and AD pathogenesis and will, thus, lead to a better understanding of the effects that environmental exposures have during normative aging and in the setting of chronic neurodegeneration. The findings will have profound implications for public health policy and will enable the development of therapeutic interventions for this debilitating and costly disease.

Lay Summary
PUBLIC HEALTH RELEVANCE Alzheimer’s disease (AD) is a devastating illness, with the hallmark feature being a progressive loss of cognitive function. The diagnosis of AD and effective intervention strategies are both hampered by an inadequate understanding of how the brain pathology develops. We focus here on the impact of an environmental trigger – namely ambient ultrafine particle-containing air pollution – on disease severity and progression in an animal model of AD with the aim of finding therapeutic or other interventions that can improve the quality of life for AD victims.

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