2-Hydroxybenzylamine for the prevention of Alzheimers disease: Initial evaluation in humans

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Country

USA

Title of project or programme

2-Hydroxybenzylamine for the prevention of Alzheimers disease: Initial evaluation in humans

Source of funding information

NIH (NIA)

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€ 1,244,143.12

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30/09/2016

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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)... Brain Disorders... Clinical Research... Clinical Research - Extramural... Dementia... Neurodegenerative... Neurosciences...

Prevention... Translational Research

Research Abstract

Approximately 5.2 million Americans are affected by Alzheimer’s disease (AD), and up to 13 million will be affected by 2050. At present, there is no preventive or curative treatment for AD or in age-related cognitive decline and clinical trials of cognitive-modifying compounds have not succeeded in identifying an effective treatment. Despite a lot of efforts, no candidates are available to slow down the development or even cure this devastating disease. Although most of the efforts are focusing on the amyloid and the tau pathways, we have taken a different approach and targeted oxidative stress. Oxidative stress is a major pathogenic mechanism that underlies both the pre-clinical development and subsequent progression of AD, and one that could potentially be targeted preventively as well as therapeutically. Levels of reactive oxygen species (ROS) increase during inflammation, mitochondrial dysfunction, and metal redox cycling catalyzed by A?, all processes associated with AD development. ROS-catalyzed lipid peroxidation generates bifunctional electrophiles (BFEs). We have shown that BFEs generated by oxidative stress accelerate Aß oligomerization, generating oligomers that have similar neurotoxicity and immunoreactivity as the amyloid-derived diffusible ligands. They inhibit proteosomal activity, cause mitochondrial dysfunction, and promote dendritic cell activation of T cells. Importantly, we have shown that levels of BFE adducts on proteins are significantly elevated in hippocampus of AD post mortem human brains, and correlate positively with both the CERAD plaque score and the Braak stage. We have found that 2-hydroxybenzylamine (2-HOBA) reacts 1,600-fold faster with BFEs than lysine, preventing protein modification in vitro and in vivo. Importantly, in hApoE4 transgenic mice, 2-HOBA inhibits all the effects of BFEs described above, and prevents working memory deficit. 2-HOBA, a natural product present in buckwheat seeds, has been developed for use in humans by Metabolic Technologies, Inc. (MTI, Ames, IA). The chemical, manufacturing and control data have been generated and pre-clinical pharmacology and toxicology data are currently being collected. In this project, we propose to do single and multiple escalation dose studies necessary to characterize pharmacokinetics, metabolism, and safety of 2-HOBA. We also propose to establish brain penetrance of 2-HOBA and to determine whether it reduces blood and CSF markers of oxidative modification of proteins.

Lay Summary

Alzheimer’s disease is the 5th cause of death for people over 65, and over 5 million Americans suffer from it. If no treatment is developed to slow down or even cure the disease, it is estimated that over 13 million Americans will have AD by 2050. The goal of our proposed research is to perform human studies for a natural occurring small molecule that will be effective in arresting the progression of AD and could help target the mechanism of tissue injury that occurs at all stages of AD development and with of age-related cognitive decline in healthy adults.

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