Tranthyretins Regulatory Role in Beta-Amyloid Aggregation and Toxicity

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USA

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Tranthyretins Regulatory Role in Beta-Amyloid Aggregation and Toxicity

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NIH (NIA)

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7

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)... Bioengineering... Biotechnology... Brain Disorders... Dementia... Nanotechnology... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): Beta-amyloid (Aß) is the primary protein component of

Alzheimer’s disease (AD) amyloid plaques, and there is substantial evidence to support the hypothesis that soluble Aß aggregates are neurotoxic. Transgenic mice expressing the Swedish mutation of the human Aß precursor protein (APPSw) produce high levels of Aß and develop amyloid plaques, but surprisingly they do not suffer the extensive neuronal cell death characteristic of AD. Recent studies have uncovered a possible explanation: APPSw mice upregulate synthesis of transthyretin (TTR), a transport protein found in plasma and cerebrospinal fluid, and TTR appears to protect the mice from the neurotoxic effects of Aß. The long-term goals of this project are to answer three questions that arise from this intriguing discovery: (1) how does TTR exert its protective activity? (2) why does this natural protective activity fail in AD? (3) can it be restored or replaced? In aim 1, the specific residues on TTR involved with binding to Aß will be identified. From mass spectrometry analysis coupled with peptide array binding studies, residues on the G strand and near the EF helix of TTR were implicated. Further definition of the binding site will be obtained by screening for Aß binding to peptide library derived from overlapping sequences of TTR, and by targeted alanine mutagenesis. Compounds that mimic the TTR binding sites will be synthesized and tested for Aß binding as well as inhibition of in vitro toxicity. In aim 2, the effect of TTR and variants on Aß aggregation will be characterized. Preliminary data show that TTR quaternary structure and stability, oxidation, and binding of natural ligands all influence the extent of Aß binding to TTR. The greatest Aß binding is observed at intermediate aggregation states. Put another way, TTR may be a natural scavenger for the most toxic Aß aggregates. Aggregation of Aß in the presence of TTR will be characterized by a combination of dynamic and static light scattering, and nanoparticle tracking. These complementary methods, which are particularly suited for examining soluble aggregates, will yield data on aggregate size, size distribution, number, morphology, and aggregation rate. Synthetic mimics, developed in aim 1, will also be characterized for their effect on Aß aggregation. In aim 3, further validation of TTR’s neuroprotective action will be sought. Astrocytes will be transfected to secrete TTR (wt and monomeric), and inhibition of Aß toxicity will be tested in vitro with mixed cortical cultures, or y adding medium from secreting astrocytes to highly enriched cortical neurons. Transgenic mice that overexpress TTR in astrocytes on an APP/PS1 background will be generated, and pathological endpoints will be evaluated to ascertain the level of in vivo protection afforded by TTR. Finally, initial screening of promising TTR mimics from Aim 1 will be tested in a stereotactic injection assay. These studies, which integrate chemical, biophysical, and biological approaches, will provide a rational basis for developing novel pharmacological approaches to preventing AD by enhancement of TTR’s natural defenses.

Lay Summary

Alzheimer’s disease has been linked to deposition of beta-amyloid plaques in the brain and subsequent death of neurons. Studies with transgenic mice suggest that a normal protein, transthyretin may provide some protection against the neuronal cell death caused by beta-amyloid. This investigation will provide a rational basis for elucidating why this protective action of TTR is lost and for developing novel pharmacological approaches to preventing Alzheimer’s disease by restoration or replacement of the natural defenses provided by transthyretin.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

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2016

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