ACAT inhibitors regulate palmitoylated APP and Abeta production

https://neurodegenerationresearch.eu/survey/acat-inhibitors-regulate-palmitoylated-app-and-abeta-production/

Principal Investigators

TANZI, RUDOLPH EMILE

Institution

MASSACHUSETTS GENERAL HOSPITAL

Contact information of lead PI
Country

USA

Title of project or programme

ACAT inhibitors regulate palmitoylated APP and Abeta production

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,677,911.93

Start date of award

23/09/2002

Total duration of award in years

4

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Sterol O-Acyltransferase, Abeta synthesis, Amyloid beta-Protein Precursor, Membrane Microdomains, palmitoylation

Research Abstract

DESCRIPTION (provided by applicant): Enzymes in the cholesterol pathway have emerged as effective drug targets for the prevention and treatment of Alzheimer’s disease (AD). Although

statins reduced beta-amyloid (A?) in cells and animal models, so far yielded disappointing results in phase III clinical trials for AD. A cholesterol-modifying enzyme named acyl-coenzyme A: cholesterol acyltransferase (ACAT) is becoming an exciting target for AD therapy and atherosclerosis. All three classes of existing ACAT inhibitors, knockdown of ACAT in cells and in AD mouse models reduce A? production. We have recently made considerable progress toward understanding the mechanism by which ACAT inhibition decreases A? levels. Specifically, we have found that the amyloid precursor protein (APP) is modified by the addition of a fatty acid in a process called palmitoylation. We were able to show that palmitoylation of APP is highly regulated by ACAT activity. In addition, we have identified a series of novel ACAT inhibitors. The overarching goal of this application is to elucidate the precise mechanism of action and therapeutic efficacy of ACAT inhibitors in AD, with particular focus on our novel compounds. To this end, we propose to use an integrated approach of cell biology and in vivo animal models. We will identify the palmitoylating enzyme of APP and ask whether ACAT inhibitors affect its expression or localization. We will also study how palmitoylated APP gives rise to A? and how ACAT inhibitors specifically reduce this process. Lastly, we will test the therapeutic potential of our novel ACAT inhibitors in animal models of AD and how ACAT inhibition regulates palmitoylated APP in vivo. Collectively, the goal of these experiments is to provide the necessary mechanistic and in vivo data for further development of ACAT inhibitors as a therapeutic strategy for AD and perhaps cardiovascular disease.

Lay Summary
Cholesterol-based Ab-lowering agents are emerging as attractive therapeutic strategies for AD. This proposal directly tests the mechanism of established and novel ACAT inhibitors in reducing beta-amyloid levels in neurons and AD animal models. These studies will greatly facilitate the understanding and development of cholesterol-based therapies for the prevention and treatment of Alzheimer’s disease and perhaps cardiovascular disease.

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