Cholesterol Metabolizing P450s; structure and function

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Contact information of lead PI
Country

USA

Title of project or programme

Cholesterol Metabolizing P450s; structure and function

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,425,045.87

Start date of award

01/05/2001

Total duration of award in years

5

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Cytochrome P450, efavirenz, Cholesterol, Hydroxycholesterols, 27-hydroxycholesterol

Research Abstract

? DESCRIPTION (provided by applicant): Cytochrome P450 enzymes 46A1 (CYP46A1) and 27A1 (CYP27A1) act on the same substrate, cholesterol, but metabolize it to different products, 24-hydroxycholesterol (24HC) and 27-hydroxycholesterol (27HC), respectively. CYP46A1 is

mainly expressed in neural tissues, the brain and retina, whereas CYP27A1 is ubiquitous. Enzymatic reactions catalyzed by CYPs 46A1 and 27A1 serve two main purposes: cholesterol elimination and cellular regulation. 24HC and 27HC (also called oxysterols) represent transport forms of cholesterol to the liver, and are also regulatory molecules modulating a variety of cellular processes. Animal studies demonstrate that elevated 24HC levels enhance memory and learning and diminish the development of amyloid plaques, a hallmark of Alzheimer's disease (AD). Elevated 27HC levels, however, are deleterious in post-menopausal women as indicated by epidemiologic studies showing that this population group has increased risk of coronary heart disease and the progression of estrogen-receptor positive breast cancer. The involvement of 24HC and 27HC in normal and pathological processes make CYP46A1 and CYP27A1, which produce these oxysterols, potential targets for therapeutic treatments. The challenge is that enzymatic activity of CYP46A1 should be stimulated, which is difficult to accomplish post-translationally, whereas enzymatic activity CYP27A1 should be inhibited but only partially. We found a number of drugs on the US market that have unanticipated binding to either CYP46A1 or CYP27A1 and modulate the activities of these P450s in mice. Pharmacologic stimulation of CYP46A1 has never been accomplished before and opened a totally new area of investigation, which we began to develop. We selected efavirenz (an anti-HIV drug), which at tiny doses activates CYP46A1 and cholesterol turnover in mouse brain, and began drug treatments of 5XFAD mice, a model of AD. We also tested CYP46A1 for activation by endogenous compounds, such as neurotransmitters, and discovered that some of them activate CYP46A1 in vitro. Our pilot investigation of CYP27A1 demonstrated that this P450 is a druggable target and can partially be inhibited by some of the marketed medications both in vitro and in mice. In this competing renewal we propose to continue our ongoing studies. The Specific Aims are: 1) to ascertain the effects of long-term efavirenz treatments on cholesterol homeostasis and pathological processes in the brain of a mouse model of AD; 2) to generate a model of CYP46A1 activation by neuroactive compounds; 3) to identify more drugs on the market that partially inhibit CYP27A1. We will obtain principally new information about the role of cholesterol metabolism in normal and disease-affected brain and whether efavirenz should be tested on humans as a new anti-AD drug. We will also identify additional medications for potential off label use in post-menopausal women with atherosclerosis or breast cancer. Collectively, the proposed research will significantly advance our understanding of the role of cholesterol metabolism in different organs and how to control this process pharmacologically.

Lay Summary
PUBLIC HEALTH RELEVANCE: This research will facilitate the development of new therapeutic approaches for treatment of Alzheimer's disease and breast cancer and lead to safer drugs on the market.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

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