Neurobiology and Therapeutic Potential of Klotho

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Principal Investigators

MUCKE, LENNART

Institution

J. DAVID GLADSTONE INSTITUTES

Contact information of lead PI
Country

USA

Title of project or programme

Neurobiology and Therapeutic Potential of Klotho

Source of funding information

NIH (NIA)

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€ 3,249,917.43

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01/08/2014

Total duration of award in years

2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Human Amyloid Precursor Protein, Structure of choroid plexus, klotho protein, Neurobiology, N-Methyl-D-Aspartate Receptors

Research Abstract

DESCRIPTION (provided by applicant): Cognitive functions such as learning and memory are of fundamental biological importance and diseases that affect these functions are among the most

challenging biomedical problems of our time. We recently obtained evidence indicating that elevating levels of the pleotropic protein klotho enhances cognitive functions in mice and humans and can prevent synaptic and cognitive impairments in a transgenic mouse model simulating key aspects of Alzheimer's disease (AD). Klotho is a class I transmembrane protein whose ectodomain is released by proteolytic cleavage. In the periphery, it is produced predominantly by the kidney. Within the central nervous system (CNS), it is produced predominantly by the choroid plexus, with lower levels of expression seen in specific neuronal populations, particularly in the hippocampus. While diverse lines of evidence suggest that klotho delays aging and aging-related diseases, the functions it fulfills in the CNS and the roles it migh play in neurological disease are largely unknown. In our preliminary studies, increasing klotho production throughout the body of transgenic mice enhanced learning and memory not only in middle-aged and old mice, but also in young mice. Moreover, heterozygous human carriers of a KLOTHO variant (KL-VS) had elevated levels of klotho in the serum and performed better in a battery of cognitive tests than non-carriers. Again, this klotho effect was seen across a wide age range. Global klotho elevation also prevented AD-related synaptic, neural network and cognitive dysfunctions in human amyloid precursor protein (hAPP) transgenic mice. We hypothesize that klotho improves neural functions in both normal and diseased brains through a mechanism that is independent of aging. We also hypothesize that augmenting klotho or its effects can counteract the pathogenic effects of elevated amyloid-? (A?) levels in the brain and may help prevent AD. To test these hypotheses and help unravel the functions of this fascinating protein in the brain, we propose three specific aims. Aim 1 will explore whether increasing the peripheral production of klotho improves synaptic and cognitive functions or whether klotho levels must be elevated within the blood-brain barrier to achieve these beneficial effects. It will also ascertain the relative importance of secreted klotho released from choroid plexus epithelial cells into the cerebrospinal fluid versus full-length klotho expressed in specific neuronal populations. Aim 2 will examine the functional importance of klotho expression in the CNS at different life stages and define the potential pathogenic impact of klotho depletion from the brain, which occurs with aging and is prominent in humans with AD. Aim 3 will explore potential mechanisms by which increased klotho levels enhance synaptic and cognitive functions, with a particular emphasis on glutamate receptors and related signaling pathways. The proposed studies will fill important knowledge gaps and could provide critical guidance for the development of klotho-related therapeutics in independent projects.

Lay Summary

PUBLIC HEALTH RELEVANCE: Aging is the main risk factor for Alzheimer's disease (AD) and other neurodegenerative disorders, but whether and how master regulators of aging and lifespan such as the protein klotho counteract these diseases is largely unknown. To address this critical question and help unravel the functions of klotho in the brain, we will follow up on promising preliminary data indicating that increasing klotho levels can improve cognitive functions such as learning and memory in healthy or diseased brains at different life stages. We will attempt to unravel the mechanisms underlying these effects and further explore the therapeutic potential of this fascinating protein in mouse models.

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

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