Molecular aspects of copper and zinc binding to the prion protein

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Contact information of lead PI
Country

USA

Title of project or programme

Molecular aspects of copper and zinc binding to the prion protein

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,333,700.00

Start date of award

01/03/2002

Total duration of award in years

1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Prions, Copper, Zinc, Prion Diseases, PrP

Research Abstract

? DESCRIPTION (provided by applicant): This research program focuses on copper and zinc uptake by the prion protein (PrP), and the role of metal binding in PrP structure, regulation,

homeostasis, and neurodegenerative diseases. Brain deposits of misfolded PrP are responsible for a remarkable class of neurodegenerative diseases termed the Transmissible Spongiform Encephalopathies (TSEs). TSEs share pathologies with prevalent, age-related, neurodegenerative illnesses including Alzheimer’s and Parkinson’s disease. Although originally recognized for its role in neurodegenerative disease, it is now clear that PrP is essential for sustaining neuron function. PrP takes up both copper and zinc at sites that are essential for PrP activity. Through previous funding periods, this program fully elucidated the structure and thermodynamics of the copper and zinc binding sites. Most recently, a fundamentally new Zn2+ promoted interaction was discovered in which the metal ion drives contact between PrP’s N-terminal and C-terminal domains. This finding suggests that many inherited prion diseases may arise from a weakening of this newly identified structure. Also in the last funding period, new mechanisms and sites for a- cleavage were identified, fundamentally modifying concepts in PrP regulation. The proposed work will build on these findings with the following three aims. 1) New structural studies will examine how copper influences PrP tertiary contacts, how familial mutations modulate this interaction, and whether the PrP N-terminus contributes to metal ion promoted stabilization. 2) New findings in the study of neurodegeneration suggest that PrP is a primary receptor for Abeta oligomers, implicated in Alzheimer’s disease. Interestingly, the Abeta binding site is proximal to the PrP segment susceptible to a-cleavage. This project will further examine how ?-cleavage is regulated and whether toxic species, such as Abeta, occlude enzymatic access to the cleavage sites. 3) Early stage cellular damage arises from unregulated transmembrane currents caused by PrP. Work from several labs suggests that these currents arise from a poorly regulated PrP N-terminal domain. This will be examined collaboratively using whole cell patch clamp electrophysiology to determine the influence of PrP structure, a-cleavage and Abeta binding. Together, these experiments will test a model in which PrP must be tightly regulated in metal ion homeostasis, and how loss of regulation might contribute to prion and Alzheimer’s disease.

Lay Summary
PUBLIC HEALTH RELEVANCE: Copper and zinc are essential micronutrients in the brain. This program will examine the interplay among these metal ions and proteins implicated in neurodegenerative disease, specifically the prion and Alzheimer’s diseases. Concepts emerging from the planned projects on prion protein structure and regulation will identify new pathways and targets for treating neurodegeneration.

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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