eIF2alpha Phosphorylation in Synaptic Plasticity, Memory, and Brain Disorders

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Country

USA

Title of project or programme

eIF2alpha Phosphorylation in Synaptic Plasticity, Memory, and Brain Disorders

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,710,701.83

Start date of award

01/05/1995

Total duration of award in years

1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Alzheimer's disease model, Brain Diseases, Synaptic plasticity, Memory impairment, eIF-2 Kinase

Research Abstract
DESCRIPTION (provided by applicant): There is a general lack of understanding concerning the

molecular signaling pathways that are altered in Alzheimer’s disease (AD), and whether dysregulation of these pathways contributes to impairments in synaptic plasticity and memory deficits associated with AD. The studies in this competing renewal are focused on the phosphorylation of the translation initiation factor eIF2¿ and the protein kinases that phosphorylate it. eIF2¿ has four known protein kinases: the general control non-derepressible-2 (GCN2), the double-stranded RNA activated protein kinase (PKR), heme-regulated inhibitor (HRI), and the PKR-like endoplasmic reticulum (ER) resident protein kinase (PERK). The phosphorylation of eIF2¿ on serine 51 causes a decrease in general translation initiation, but it also selectively increases the translation of a subset of mRNAs that contain upstream open reading frames (uORFs) in their 5? untranslated region (UTR). Previous studies showed that eIF2¿ phosphorylation increased in the brains of AD model mice and postmortem brains from AD patients, suggesting that increased eIF2¿ phoshorylation decreases general translation and upregulates the translation of mRNAs with uORFs in their UTRs in AD. Consistent with this notion, in the previous funding period we found that genetic deletion of PERK prevents decreases in general translation, increased expression of ATF4 (whose mRNA contains a uORF), impairments in synaptic plasticity, and memory deficits in AD model mice. Based on these observations, we have formulated a central hypothesis, which is that elevated eIF2¿ phosphorylation in AD via activation of multiple eIF2¿ kinases results in impaired synaptic plasticity and memory deficits due to differential mRNA translation and protein expression. To test this hypothesis, we will 1) determine whether genetic deletion of GCN2 and PKR prevents altered translational control and amyloidogenesis in AD model mice, 2) determine whether genetic deletion of GCN2 and PKR prevents aging-related impairments in synaptic plasticity and memory deficits displayed by AD model mice, and 3) determine the identity of proteins with altered synthesis and expression in AD model mice and in eIF2¿ kinase mutant mice. These studies will provide important information concerning whether reduction of eIF2¿ phosphorylation via deletion of GCN2 and/or PKR can correct dysregulated translation, impaired synaptic plasticity, and memory deficits in AD model mice in a manner similar to the deletion of PERK, and whether these eIF2¿ kinases might be suitable therapeutic targets for AD. Moreover, these studies have the potential to identify additional targets by identifying the proteins with dysregulated translation in the brains of AD mice, as well as the proteins whose translation is regulated by each eIF2¿ kinase.

Lay Summary

PUBLIC HEALTH RELEVANCE: Phosphorylation of the translation initiation factor eIF2? has been shown to regulate protein synthesis during long-lasting synaptic plasticity and long-term memory, and is dysregulated in multiple brain disorders, including Alzheimer’s disease (AD). We have proposed experiments to determine whether genetically removing two protein kinases that phosphorylate eIF2? can correct altered protein synthesis, impaired synaptic plasticity, and memory deficits in AD model mice. Thus, our studies have the potential to provide insight into the role of eIF2? phosphorylation in synaptic dysfunction and memory deficits associated with AD, and to identify new therapeutic targets for the treatment of brain disorders associated with dysregulated eIF2? phosphorylation.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

Diseases:
Alzheimer's disease & other dementias

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