The Cdk5/35 Kinase

https://neurodegenerationresearch.eu/survey/the-cdk5-35-kinase/

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Country

USA

Title of project or programme

The Cdk5/35 Kinase

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,717,715.60

Start date of award

01/04/1996

Total duration of award in years

1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Cyclin-Dependent Kinase 5, tau Proteins, Phosphotransferases, neuroinflammation, Calpain

Research Abstract

Cyclin-dependent kinase 5 (Cdk5) is a fascinating and enigmatic enzyme necessary for neuronal migration, synapse development, and synaptic homeostasis. To date, a large body of literature also supports the role of Cdk5 in numerous phenotypes associated with neurodegenerative disorders, including Alzheimer’s disease (AD). Cdk5 is not catalytically active unless it is associated with a regulatory activator, such as p35 or p39. We and others

showed that p35 can be cleaved by calpain under neurotoxic conditions, which leads to the generation of the p25 peptide. Various transgenic p25 mouse models exhibit neurodegeneration phenotypes such as Tau hyperphosphorylation, increased amyloid beta (A?), neuroinflammation, synaptic loss, neuronal loss, and memory impairments, demonstrating that the activity of the p25/Cdk5 kinase can be neurotoxic. In our last grant period, we created a mouse model harboring a calpain-resistant version of p35 (the ?p35KI mouse), and found that blocking p25 production abolished AD phenotypes in vivo. In this application, using the ?p35KI mouse model, we aim to determine the role of p25 generation in Tau-mediated neurodegeneration, as well as its role in neuroinflammation mediated by microglia. Furthermore, using genome editing in human induced pluripotent stem cells (iPSCs), we will determine whether p25 generation mediates AD-related pathology, including amyloid and Tau pathology, synaptic deficits, DNA damage, epigenetic dysregulation, endosome defects, and neuronal survival in human neurons. The overall hypothesis to be tested in this application is that p25-mediated Cdk5 dysregulation plays key roles in AD-like neurodegeneration.

Lay Summary
Current treatment approaches for Alzheimer’s disease (AD) and other age-related neurodegenerative disorders, have led to failed drug trials, discouraged researchers, and an increasing sense of desperation in a vulnerable aging population. In combating neurodegenerative disease, it is imperative that we understand the multiple pathologies that lead to brain dysfunction, which include neuroinflammation, in addition to amyloid and Tau pathology, and synaptic dysfunction. In the current application, we explore the role of aberrant p25/Cdk5 signaling in both neuroinflammation and Tau pathologies, in novel mouse models as well as neural cells derived from isogenic lines of patient-derived induced pluripotent stem cells (iPSCs).

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