Role of CK2 in NMDAR trafficking during development and in Alzheimers disease

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Role of CK2 in NMDAR trafficking during development and in Alzheimers disease

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Alzheimer's disease & other dementias

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Research Abstract

DESCRIPTION (provided by applicant): N-methyl-D-aspartate receptors (NMDARs) play a central role in development, learning, memory, and in many neurological disorders. In cerebral cortex NMDARs are mainly composed of two GluN1 and two GluN2A or GluN2B subunits. Many functional properties of NMDARs are determined by GluN2 subunits, so they are subjected to strict control mechanisms. My long-term research objective is to understand the role that glutamate receptors dysregulation (in particular, NMDARs) plays in the development of Alzheimer's disease (AD) and other age-related neurodegenerative diseases. Therefore, the goal of this K99/R00 award proposal is to define the precise molecular mechanisms that regulate synaptic GluN2 composition during the switch from GluN2B to GluN2A that occurs during synaptic maturation and to determine if they are involved in synaptic dysfunction in AD. Specifically, the role of casein kinase 2 (CK2) in these processes will be analyzed, since I have previously demonstrated that CK2 regulates GluN2 synaptic composition by phosphorylating the PDZ binding domain of GluN2B (S1480) and that CK2 activity is required for the GluN2 subunit switch. Although synaptic CK2 has been shown to be important, how synaptic activity regulates this kinase remains obscure, since CK2 is considered a constitutively active kinase and it is not regulated by calcium. Specific Aim 1 will test the hypothesis that synaptic recruitment of CK2 by CaMKII is a key step for GluN2B S1480 phosphorylation, with CaMKII acting as a scaffolding protein to link GluN2B and CK2 after NMDAR activation. Therefore, GluN2B S1480 phosphorylation will be determined after disruption of the GluN2B/CaMKII/CK2 complex, using biochemistry and immunofluorescence microscopy. My central hypothesis is that the GluN2 subunit switch is a process with two sequential and coupled steps, in which the synaptic removal of GluN2B by CK2 phosphorylation is required to allow synaptic incorporation of GluN2A. This will be tested using biochemical and electrophysiological approaches in the Specific Aim 2, analyzing the synaptic GluN2 composition after the replacement of endogenous GluN2B by mutated GluN2B with defective S1480 phosphorylation (GluN2B E1479Q). Several molecular genetic approaches will be used for this replacement including lentivirus infection and the generation of a genetically-altered mouse line expressing GluN2B E1479Q. Recent reports support a role for extrasynaptic NMDARs overactivation in AD. Therefore, using the data and tools generated in my two previous Aims I will analyze if Abeta oligomers, main neurotoxins in AD, leads to a redistribution in GluN2B subunit (from synaptic to extrasynaptic sites) via aberrant CK2 overactivation (Specific Aim 3). The successful completion of this proposal will have a significant positive impact by elucidating the mechanisms regulating GluN2 subunit composition during development and identifying a potential new pharmacological target in AD.

Lay Summary

NMDA receptors (NMDARs) are a subtype of ionotropic glutamate receptors, which play critical roles in development, learning and memory. Therefore, expression of NMDARs at synapses is strictly regulated and, for example, it is well established that a switch in NMDAR subunit composition (from GluN2B to GluN2A) occurs during development. This K99/R00 proposal will investigate the role of GluN2B S1480 phosphorylation by casein kinase 2 (CK2) in this switch and how CaMKII regulates S1480 phosphorylation. Finally, the effect of Abeta oligomers, major pathological agents in Alzheimer's disease (AD), on synaptic CK2 will be analyzed, therefore exploring a new mechanism of synaptic dysregulation in AD and a potentially new pharmacological target for its treatment.

Further information available at:

Types:

Investments > €500k

Member States:
United States of America

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Alzheimer's disease & other dementias

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