PrPC- and NOX-dependent signaling in dementia

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USA

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PrPC- and NOX-dependent signaling in dementia

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2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Dementia... Neurodegenerative... Neurosciences

Research Abstract

? DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is the only leading cause of

death with no effective means of slowing its progression. Varying models predict the involvement of diverse neurodegenerative stresses, including amyloid beta (Aß) peptides, proinflammatory cytokines, oxidative stress, and energetic stress in mediating the pathogenesis of both familial (FAD) and sporadic (SAD) forms of the disease. In spite of decades of active research and a deep molecular understanding of many of the major molecular players in the progression of dementia, there are many areas of confusion. For example, there is good agreement on the fact that excess production of amyloid-ß is a causative or major contributing factor to the initiation of dementia and most mouse models to study AD utilize the expression of human amyloid precursor protein (APP) with early onset AD mutations (usually along with other mutant human proteins) to generate mice that develop cognitive deficits and at least some aspects of human AD pathology. However, there is still much debate over the actual form of the Aß that induces the synaptic deficits. In addition, a plethora of neuronal proteins with totally unrelated functions that interact with human Aß have been identified and elimination of any one of these binding partners alone was sufficient to reduce or eliminate the cognitive deficits when these mice were crossed with an AD mouse model over producing Aß. No current model can explain how single elimination of the different Aß binding partners protects against development of Aß-induced cognitive deficits. We recently showed that very active forms of soluble Aß consisting of dimers and trimers (Aßd/t), as well as proinflammatory cytokines (TNFa, IL-1ß, IL-6) stimulate NADPH oxidase (NOX) and production of reactive oxygen species (ROS) in neurons through a cellular prion protein (PrPC)-dependent pathway. This pathway stimulated the formation of rod-shaped bundles of 1:1 cofilin:actin (rods), which cause synaptic dysfunction. Formation of rods requires activation (dephosphorylation) of the actin binding protein cofilin as well as its oxidation to form intermolecular disulfide bonds. Rods do not form i response to Aß or proinflammatory cytokines in PrPC-null neurons, but surprisingly, over expression of PrPC alone is sufficient to induce rods at much higher levels than are induced by Aß of proinflammatory cytokine treatment. Thus, we have proposed a new model in which multiple receptors can contribute to NOX activation and ROS production through PrPC-interactions in enlarged membrane domains. The triggering of cofilin oxidation to form rods is dependent on achieving a threshold level of ROS and this is why coalescence of many different receptors into signaling complexes contributes to achieving this ROS level. Rods sequester cofilin and can occlude neurites, blocking transport, either of which inhibit normal synaptic function. Using cultured primary neurons and several knock-out or transgenic mouse lines, we propose to determine (1) if the relative rod-inducing activities of different forms of Aß relate t their direct affinity for PrPC, (2) if specific proinflammatory cytokine receptors are required for their rod induction through the PrPC- dependent pathway, (3) if the PrPC-pathway functions in both axons and dendrites and if mislocalization of rod signaling components occurs between compartments, and (4) the role in cofilin activation played by three likely components of the cytoplasmic domain of PrPC-signaling complexes.

Lay Summary

PUBLIC HEALTH RELEVANCE: Proinflammatory cytokines and the most synaptotoxic form of amyloid-ß (SDS-stable dimers/trimers) utilize a common signaling pathway dependent upon the cellular prion protein (PrPC) and NADPH oxidase to induce cofilin activation, oxidation and formation of cofilin-actin rods, a major brain pathology in dementia. Rods sequester cofilin from dendritic spines and occlude neurites causing synaptic dysfunction. Here we will determine if there is a PrPC- dependent signaling complex utilized by many functionally diverse neuronal amyloid-ß binding partners that can explain synaptic loss in dementia through a common rod-

forming mechanism and whether or not this pathway operates similarly within axons and dendrites.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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2016

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