Aging in the Brain: Role of the Fibrous Proteins

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Country

USA

Title of project or programme

Aging in the Brain: Role of the Fibrous Proteins

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NIH (NIA)

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30

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Alzheimer's disease & other dementias

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Research Abstract

DESCRIPTION (provided by applicant): Research focused on disease has often identified genes whose existence and physiology were previously unknown. In the example of Alzheimer’s disease (AD), the genes encoding APP, Presenilin and Nicastrin were all discovered because of

interest in the protein biology of the disorder. APP and its homologues stand out as highly conserved in metazoan evolution, ubiquitously expressed and abundant in neurons. APP mutations or duplications cause rare but mechanistically important forms of AD, and its Ass product accumulates in all AD patients. Although APP is among the most studied gene products in biology, most work has centered on its role in AD; its normal physiology has been less studied and has led to an array of complex, sometimes conflicting findings. The advent of human trials of agents that chronically inhibit APP processing makes it even more urgent to clarify its normal functions. Here, we propose new concepts and approaches regarding APP physiology that are based on strong productivity in the current MERIT Award period and preliminary data which make our multifaceted aims both compelling and technically feasible. A key approach to gene function is to understand its role during early development and then search for related activities in adults. Under this grant, we uncovered a critical function of APP n the development of the mammalian cerebral cortex. To pursue this and other discoveries, we propose three interrelated Aims. First, we seek to determine the molecular mechanism by which holoAPP is required for correct migration of neuronal precursors into the cortical plate and how DISC1 (which we found to interact with the APP cytoplasmic domain) works with DAB1, Fe65 and other factors in this migratory function. We will then ask whether APP plays a related role in neuronal or glial migration in the adult brain. Second, we will use primary neuronal co-culture assays to systematically confirm or deny numerous reported ligands of the APP ectodomain as well as certain novel ligands, e.g., the Pancortins, that have emerged from an unbiased screen. We will also search for cooperative binding of APP to proteoglycans and protein ligands (e.g., Reelin) as regards the regulation of its ectodomain shedding. Third, we will validate a new cell biological model of APP secretase processing, based on our recent identification of a multi-protein complex that appears to contain ?-, ß- and ?-secretases, enabling rapid and efficient substrate processing. We will search for and analyze protein partners of this putative “”sheddasome””, particularly the tetraspanins, and learn if this model applies broadly to other intramembrane proteases and their sheddases: S1P and S2P, and SP and SPP. Together, our aims address a working hypothesis of APP function in neurons: that holoAPP interacts with extracellular factors on neurons, glia and the matrix to activate intracellular signaling pathways (via DAB1, DISC1 and Fe65), and that a spatially and temporally integrated ?/? -secretase complex terminates holoAPP function and initiates alternate signaling by APPs?.

Lay Summary

Intensive research on Alzheimer’s disease enabled the cloning of the ss-amyloid precursor protein (APP) and has recently led to human trials of drugs that chronically inhibit its processing. Nevertheless, the normal function of this conserved and abundant protein remains to be clarified. Based on extensive preliminary data, we propose to define in molecular detail the role of APP in the normal development of the mammalian cerebral cortex and study its protein partners in this function, especially Reelin, Disc1 and DAB1. We will also systematically confirm or invalidate numerous putative ligands of APP from the literature and study a new ligand family we’ve recently identified, the Pancortins. Then, we will explore a new model for the normal processing of APP and many other proteins throughout life: a single complex of its three major cleaving enzymes – ?, ß and ?-secretase. Deciphering APP’s normal function is both meaningful for developmental biology and important for the safe treatment of Alzheimer’s disease.

Further information available at:

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