Prefrontal AMPA receptors in FTD Pathogenesis

https://neurodegenerationresearch.eu/survey/prefrontal-ampa-receptors-in-ftd-pathogenesis/

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Country

USA

Title of project or programme

Prefrontal AMPA receptors in FTD Pathogenesis

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,915,200.00

Start date of award

01/04/2016

Total duration of award in years

2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Frontotemporal Dementia, AMPA Receptors, C9orf72, PGRN gene, Prefrontal Cortex

Research Abstract

? DESCRIPTION (provided by applicant): Frontotemporal dementia (FTD) is a fatal disease associated with focal atrophy of the prefrontal and anterior temporal cortex. FTD is the second most common cause of dementia under age 65 (after Alzheimer’s disease), and there is no

cure. Compared to other major neurodegenerative disorders, very little is known about its pathogenic basis at molecular, synaptic, and circuit levels. Behavioral abnormalities, characterized by marked changes in personality and social conduct are hallmarks of FTD. As many as 50% of FTD patients have a family history of the disease, suggesting a strong genetic component. Recent molecular genetic studies have identified a number of FTD-causing genes, including CHMP2B, progranulin (GRN), and C9ORF72, paving the way for in-depth investigation of pathogenic mechanisms of the disease. Interestingly, the clinical outcome in FTD patients carrying different mutations is often strikingly similar, suggesting that the same neural circuits are affected. In an effort to model FTD in animals and elucidate underlying mechanisms, we have generated a conditional transgenic mouse strain that expresses an FTD-causing CHMP2BIntron5 in the forebrain. Mutant mice recapitulate several key features of FTD-associated neurodegeneration phenotypes, including social behavioral impairments. Our studies uncover a marked change in AMPA receptor (AMPAR) composition, leading to abnormal insertion of Ca2+-impermeable AMPARs in synapses of the medial prefrontal cortex (PFC). This AMPAR dysregulation appears to be driven by a loss of the brain-enriched noncoding microRNA miR-124. Importantly, similar changes in miR-124 and AMPARs are also observed in the frontal cortex and iPSC-derived cortical neurons from a subset of patients with behavioral variant FTD (bvFTD). This suggests that miR-124 and AMPAR dysregulation are not limited to CHMP2BIntron5 mutation, and are perhaps a more general pathogenic mechanism for FTD with more common mutations. Based on these results, we propose a novel mechanism of FTD pathogenesis: altered synaptic AMPAR assembly and function in PFC circuits underline the social behavioral impairments in FTD. The goal of this application is to test and establish this “”AMPAR hypothesis of FTD””. We will examine key AMPAR mechanisms and map affected circuits in the medial PFC in an existing (GRN haploinsufficiency) and two newly generated (CHMP2BIntron5 and C9ORF72 AAV transgenic mice with G4C2 repeat expansions) mouse models of FTD (Aim 1), establish the miR-124-AMPAR pathogenic axis and by manipulating this axis, especially CP-AMPARs, restore sociability deficits in mouse models in vivo (Aim 2), and finally, validate the AMPAR hypothesis and explore therapeutic strategies in human patient iPSC-derived cortical neurons harboring different genetic mutations (Aim 3). We will use a multidisciplinary approach combining in vivo gene manipulations, electrophysiology, mouse behavior, and human iPSC technologies. Our results will set the stage for translational studies aimed at developing an AMPAR-based therapeutic strategy for FTD.

Lay Summary
PUBLIC HEALTH RELEVANCE The goals of this multi-PI R01 are to establish that prefrontal AMPA receptor dysfunction represents a pathogenic mechanism underlying social behavioral deficits of frontotemporal dementia (FTD). The studies are fundamentally important, highly significant, and extremely novel because they establish a synaptic basis for social behavior, they advance our understanding of pathogenesis basis of FTD at molecular, synaptic, and circuit levels, and they provide new molecular targets and strategies for treatment of FTD.

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