Restoring Brain Functions in Alzheimer Models with Interneuron Transplants

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Country

USA

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Restoring Brain Functions in Alzheimer Models with Interneuron Transplants

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NIH (NIA)

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15/05/2014

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3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

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Research Abstract

DESCRIPTION (provided by applicant): Alzheimer's disease (AD) results in deterioration of cognitive functions and abnormal patterns of neuronal network activity, but the underlying mechanisms are poorly understood. We recently found that reduced levels of the voltage-gated sodium channel Nav1.1 in inhibitory parvalbumin interneurons critically contribute to abnormalities in neuronal network activity and cognitive functions in human amyloid precursor protein (hAPP) transgenic mice (Verret et al., 2012, Cell). Thus, we propose to test the overreaching hypothesis that impaired inhibition and altered oscillatory network activity contribute to synaptic and network impairments in hAPPJ20 mice and possibly in humans with AD. The proposal will investigate a cell-based therapeutic approach to enhanced inhibitory interneuron function and reduce brain network and cognitive abnormalities in hAPP mice by transplanting genetically modified embryonic interneuron precursors. Embryonic precursor cells from the medial ganglionic eminence (MGE) generate large numbers of Nav1.1-postive inhibitory interneurons. MGE-derived interneurons retain a remarkable capacity to migrate and integrate when transplanted into neonatal or adult host brains where they mature into functional and synaptically active inhibitory interneurons. Our preliminary data indicate that MGE-derived inhibitory interneurons reverse behavioral abnormalities in cognitive and emotional domains in hAPPJ20 mice, suggesting that inhibitory dysfunction contributes to these deficits. Interestingly, MGE-derived interneurons overexpressing Nav1.1 were more effective than wildtype MGE-derived interneurons, indicating that genetic manipulations of these precursors might be required to make them more resistant to hAPP/A¿ toxicity. Thus, we propose to manipulate inhibitory cell activity in hAPPJ20 and NTG mice by grafting genetically modified embryonic interneuron precursors with wildtype, high (Nav1.1BAC), and low (Nav1.1R1407X) Nav1.1 levels into host hAPPJ20 and NTG mice. We hypothesize that MGE transplants will increase the number of functional inhibitory cells in hAPPJ20 mice (Aim 1), ameliorate or restore inhibitory and excitatory synaptic activity (Aim 2), and reduce network abnormalities (Aim 3) and cognitive impairments (Aim 4). Thus, this cell- based therapeutic approach will target a key cell type (PV cells) and a key molecular alteration (reduced Nav1.1) that play causal roles in inducing network and cognitive dysfunction in hAPPJ20 mice. In addition, we will investigate approaches to genetically manipulate MGE-precursors to enhance their functions and/or resistance to disease mechanisms of the host brain. Initially, MGE-derived inhibitory cells will be manipulated by altering Nav1.1 levels, which tightly controls cellular excitability. Finally, this experimental approach will allow us to specifically manipulate inhibitory interneurons in different host mice and, therefore, address network and cell-autonomous effects of inhibitory function in great mechanistic detail.

Lay Summary

PUBLIC HEALTH RELEVANCE: Alzheimer's disease (AD) results in deterioration of cognitive functions and abnormal patterns of neuronal network activity, but the underlying mechanisms are poorly understood. We recently found that reduced levels of the voltage-gated sodium channel Nav1.1 in inhibitory parvalbumin interneurons critically contribute to abnormalities in neuronal network activity and cognitive functions in human amyloid precursor protein (hAPP) transgenic mice (Verret et al., 2012, Cell). The proposal will investigate a cell-based therapeutic approach to enhanced inhibitory interneuron function and reduce brain network and cognitive abnormalities in hAPP mice by transplanting genetically modified embryonic interneuron precursors.

Further information available at:

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Investments > €500k

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United States of America

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