BMP9 as a juvenile protective factor in cognitive aging

https://www.neurodegenerationresearch.eu/survey/bmp9-as-a-juvenile-protective-factor-in-cognitive-aging/

Principal Investigators

BLUSZTAJN, JAN KRZYSZTOF

Institution

BOSTON UNIVERSITY MEDICAL CAMPUS

Contact information of lead PI
Country

USA

Title of project or programme

BMP9 as a juvenile protective factor in cognitive aging

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,530,144.04

Start date of award

01/06/2014

Total duration of award in years

3

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)... Basic Behavioral and Social Science... Behavioral and Social Science... Brain Disorders... Dementia... Neurodegenerative... Neurosciences... Prevention

Research Abstract

DESCRIPTION: Aging is frequently associated with a decline in multiple cognitive functions. In particular, the ability to form memories of recent events and assimilate new and complex information tends to diminish. Moreover, these cognitive defects are hallmarks of devastating, age-associated dementias such as Alzheimer's disease (AD). Due to their high prevalence and the lack of any effective therapies, the development of prevention measures and treatment strategies for these conditions constitutes one of the highest priorities of the biomedical sciences. The concept of utilizing juvenile protective factors for this purpose is an attractive on – however, it presents two central challenges: 1) the identification and characterization of a candidate factor, and 2) the utilization of its potential for therapeutic benefit. The proposed studies focus on a compelling candidate molecule – growth and differentiation factor 2 (GDF2), more commonly referred to as bone morphogenetic protein 9 (BMP9), and its actions on critical neuronal systems that underlie cognition. One of the key components of the neuronal circuitry necessary for learning, memory and attention is the innervation of the hippocampus and cerebral cortex by basal forebrain cholinergic neurons (BFCN), which provide modulatory input mediated by the neurotransmitter, acetylcholine (ACh). A decline in BFCN function and diminished cholinergic marker expression is apparent in aged humans and animal, in AD patients, and in animal models of AD. Thus, it has been postulated that dysfunction and/or degeneration of BFCN contributes to the memory deficits seen in advanced age and in AD. We have obtained evidence that BMP9 is a key differentiating factor for BFCN during development and, when infused intracerebroventricularly in mice with experimental injury to these neurons, prevents BFCN loss. Moreover, our preliminary data show that BMP9 infusion reverses the downregulation of BFCN markers seen in a transgenic mouse model of AD and ameliorates amyloidosis. These data indicate that BMP9 is sufficient to support BFCN differentiation and function in the adult brain; however we do not yet know to what extent BMP9 is necessary for cholinergic neuron biology. In aim 1 this central question will be addressed by loss-of-function studies on Bmp9 knockout mice. In aim 2 we will test the utility of BMP9 as a therapeutic agent for age-associated cognitive and BFCN dysfunction, with the focus on AD, using transgenic mouse models. In aim 3, we will explore the hypothesis that BMP signaling may be abnormal in the brains of aging humans and AD patients, using post-mortem brain samples from a unique collection of cases with a thorough cognitive and histopathological assessment, available through the Framingham Heart Study.

Lay Summary

PUBLIC HEALTH RELEVANCE: Aging is associated with a decline of multiple cognitive functions and this decline is particularly devastating in Alzheimer's disease (AD). We propose to provide a comprehensive characterization of the molecular phenotype of basal forebrain cholinergic neurons (BFCN) that are crucial for normal memory processing and that are vulnerable to deterioration in AD. We have identified bone morphogenetic protein 9 (BMP9) as a factor that protects BFCN from damage and we will determine if BMP9 has a similar efficacy in a mouse model of AD with the ultimate goal to develop a thorough understanding of BFCN biology and to develop growth- factor replacement strategies that could protect BFCN in people from age- and/or AD-evoked dysfunction.

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