BACE1 in neurodegeneration and neuronal dysfunction

https://www.neurodegenerationresearch.eu/survey/bace1-in-neurodegeneration-and-neuronal-dysfunction/

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Country

USA

Title of project or programme

BACE1 in neurodegeneration and neuronal dysfunction

Source of funding information

NIH (NIA)

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01/05/2011

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5

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

beta-site APP cleaving enzyme 1, Neuronal Dysfunction, jagged1 protein, Neuregulin 1, Nerve Degeneration

Research Abstract

ABSTRACT BACE1 was discovered as the Alzheimer’s ?-secretase for initiating the production of ?-amyloid peptide (A?) from amyloid precursor protein (APP). Abnormal accumulation of A?

in various forms (dimers, trimers, multimers, oligomers) has been linked to impaired synaptic and cognitive functions in Alzheimer’s disease (AD) patients. Reducing A? generation by BACE1 inhibition is therefore an actively investigated area for ameliorating cognitive dysfunction in AD patients. However, BACE1, as a membrane-bound aspartyl protease, can cleave membrane-bound proteins other than APP. Among its identified substrates, the signaling molecule neuregulin-1 (Nrg1) and Notch ligands such as Jagged-1 (Jag1) are important for their roles in neural development and synaptic functions. In this study, we will focus on the roles of BACE1 in processing signaling molecules such as Nrg1 and Jag1. The abolished cleavage of Nrg1 in BACE1-null mice reduces Nrg1 signaling through ErbB receptors and thus impairs myelination during development and remyelination in the adult, and it also induces schizophrenia-like behaviors, including impaired cognitive functions. On the other hand, abolished cleavage of Jag1 in BACE1-null mice likely increases Jag1 signaling on the neuronal surface and activation of its receptor Notch in a paracrine fashion; this increased Jag1-Notch signaling induces astrogenesis and reduces neurogenesis in the subgranular zone (SGZ). Neurogenesis in the SGZ produces dentate granule cells, which are neurons important for long-term potentiation. Hence, BACE1 is required for normal neural development and synaptic functions. We aim to test our central hypothesis that BACE1 cleavage of signaling molecules such as Nrg1 and Jag1 regulates neurogenesis and synaptic functions. Specifically, we will 1) determine the role of BACE1-dependent Nrg1 signaling in the control of synaptic function, and 2) investigate BACE1-dependent Jag1 signaling in astrogenesis and neurogenesis. Our main objectives for accomplishing the proposed studies are to fully understand the in vivo neuronal functions that BACE1 exerts during early development and in the adult brain and to develop strategies for enhancing synaptic functions or neurogenesis to couple with therapeutic strategies of reducing A? through BACE1 inhibition in AD patients.

Lay Summary

Project Narrative Abnormal accumulation of ?-amyloid peptide (A?) in various forms has been linked to impaired synaptic and cognitive functions in Alzheimer’s disease (AD) patients. Hence, AD is also considered as a disease of synaptic dysfunction. Drugs for inhibiting BACE1, also known as Alzheimer’s ?-secretase, are expected to reduce A? in AD patients. It is highly important to ensure that BACE1 drugs will achieve the best clinical endpoints by not only reducing amyloid plaques, but also by enhancing cognitive functions. This study is designed to achieve a molecular understanding of BACE1 in synaptic functions and to explore strategies for enhancing synaptic functions or neurogenesis. The knowledge will guide better BACE1 inhibition in AD patients.

Further information available at:

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Investments > €500k

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United States of America

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