Role of BACE in the pathogenesis of Alzheimers disease after head trauma

https://www.neurodegenerationresearch.eu/survey/role-of-bace-in-the-pathogenesis-of-alzheimers-disease-after-head-trauma/

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Contact information of lead PI
Country

USA

Title of project or programme

Role of BACE in the pathogenesis of Alzheimers disease after head trauma

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NIH (NIA)

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01/09/2015

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3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

beta-site APP cleaving enzyme 1, Craniocerebral Trauma, Alzheimer's Disease, Traumatic Brain Injury, Caspase

Research Abstract

? DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is a complex disease

influenced by the actions of multiple genes, their interactions with each other and with the environment. Traumatic brain injury (TBI) is one of the most robust environmental risk factors for AD. TBI has been suggested to accelerate the onset of AD and the severity of the injury positively correlates with increased risk. Compelling evidence is mounting that a single TBI event is associated with increased levels of A? and amyloid deposition both in humans and animal models. We, and others, have demonstrated that BACE1 levels are increased following experimental TBI suggesting that BACE1 elevation may be responsible for increased A? production following head trauma. However the molecular mechanisms responsible for this post-injury elevation of BACE1 remain largely unknown. We have previously shown that BACE1 increases following cerebral ischemia in rodents and proposed that caspase-mediated depletion of the BACE1 interacting molecule GGA3 (Golgi-localized ?-ear-containing ARF binding protein 3) is the underlying mechanism of BACE1 elevation. We have determined that GGA3 is a caspase-3 substrate and that GGA3 depletion stabilizes BACE1 by impairing its sorting to lysosomes where it is normally degraded. We also reported that levels of GGA3 are decreased and inversely correlated with BACE1 levels in post-mortem AD brains. More recently, we reported that GGA3 and its homologue GGA1 are depleted while BACE1 levels increase in the acute phase post-injury in a mouse model of TBI and in post-mortem AD brains. We further demonstrated the role of GGA3 in the regulation of BACE1 in vivo by showing that BACE1 levels are increased in the brain of GGA3 null mice. Moreover, extensive behavioral analysis of GGA3 null mice has revealed that genetic deletion of GGA3 produces a behavioral phenotype suggesting a specific role for GGA3 in the brain. We have also determined that ectopic expression of GGA3 decreases levels of BACE1 and A? in vitro. Thus, we propose: 1) to determine the extent to which the behavioral phenotype of GGA3 null mice depends on BACE1 elevation in specific region of the brains; 2) to determine the extent to which the over-expression of GGA3 reduces levels of BACE1 and A? in a caspase-dependent fashion in vivo; 3) to determine the extent to which depletion of GGA1 and GGA3 increases levels of BACE1 and A? in a mouse model of TBI.

Lay Summary

PUBLIC HEALTH RELEVANCE: It has been known for several years that traumatic brain injury (TBI) can increase the risk of developing Alzheimer’s disease (AD), but the mechanism underlying that increased risk has not been understood. Our work shows that head trauma, can trigger a series of biochemical events that increase the production of beta- amyloid, the toxic peptide that accumulates in the brain of AD patients, by elevating BACE1, one of the enzymes responsible for the production of beta-amyloid. Thus, we propose to use mouse models to determine the extent to which the depletion of the trafficking molecules GGA3 and GGA1 is the underlying mechanism of BACE1 elevation following TBI. Overall, the outcome of this study will help to identify novel therapeutic targets to prevent the development of AD in subjects affected by TBI.

Further information available at:

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United States of America

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Alzheimer's disease & other dementias

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