Inhibition of BACE1 for benefiting Alzheimers patients

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Principal Investigators

YAN, RIQIANG

Institution

CLEVELAND CLINIC LERNER COM-CWRU

Contact information of lead PI
Country

USA

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Inhibition of BACE1 for benefiting Alzheimers patients

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NIH (NIA)

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4

The project/programme is most relevant to:

Alzheimer's disease & other dementias

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Research Abstract

DESCRIPTION (provided by applicant): Abnormal accumulation of amyloid-ß peptide (Aß), which is generated from amyloid precursor protein (APP) through two sequential proteolytic cleavages by BACE1 and ?-secretase, is widely regarded as having a causal role in the development of Alzheimer's disease (AD). Individuals with Down syndrome (DS), due to an extra copy of chromosome 21 in which APP is located at 21q21, develop age-related cognitive decline and AD dementia by 30-40 years earlier than in the general population, and their brains invariantly develop amyloid plaques. Since cleavage of APP by BACE1 initiates the production of Aß, inhibition of BACE1 activity should decrease the formation of Aß and is therefore a therapeutic target for AD. For the safe use of BACE1 inhibitors in humans, it is very important to fully understand the biological functions of BACE1 in the adult. Notably, neonatal BACE1-null mice have reduced body sizes and survival rates when compared to their age-matched wild-type littermates. However, the death rate is significantly decreased if BACE1-null mice can survive beyond postnatal day 10 and the differences in body weight become much smaller between BACE1-null and wild-type mice over time. In the adult, BACE1-null mice are fertile but do develop multiple mild to moderate phenotypes such as increases in the incidence of epileptic seizures, schizophrenia-like behaviors, retinal pathology, deficits in activity-dependent CA3 synaptic transmission, defects in axonal guidance and impaired myelination in BACE1-null mice. One potential explanation for these phenotypes in BACE1-null mice is the carryover effect from early developmental defects. To determine whether BACE1 is required for normal functions in adult mice, we have generated conditional BACE1 knockout mice and will delete BACE1 in the adult mouse. This new mouse model will allow us to answer questions such as whether inhibition of BACE1 activity in adult is safe and whether BACE1 inhibition at late ages will still e effective in removing preexisting amyloid plaques. This model will also be practical to answer the question of whether BACE1 inhibition in the adult will ameliorate tau pathology. Our central hypothesis in this proposal is that controlled inhibition of BACE1 activity will have optimal effecs on reducing or reversing AD pathologies. By testing our hypothesis, we will perform experiments in three specific aims. Aim 1: To characterize BACE1 conditional KO mice and to determine whether induced BACE1 deficiency will lead to phenotypic changes similar to those observed in BACE1-null mice. Aim 2: To determine whether induced BACE1 deficiency can reverse pre-formed amyloid plaques in AD transgenic mouse brains. Aim 3: to examine whether BACE1 inhibition will impact cognitive function in the Ts65Dn Down syndrome mouse model. The knowledge gained from this study will allow us to answer many unmet questions such as whether a significant reduction of BACE1 in the adult would have beneficial effects for reducing or eliminating AD and DS pathologies.

Lay Summary

PUBLIC HEALTH RELEVANCE: Extracellular neuritic (senile) plaques and intraneuronal neurofibrillary tangles are two known pathological hallmarks in brains of patients with Alzheimer's disease (AD). Although the causal factor for AD remains to be established, large amount of studies suggest that formation of extracellular amyloid plaques occur before the intracellular neurofibrillary tangles. Abnormal accumulation of amyloid peptides (Aß), the major component in the plaques, leads to the formation of Aß and subsequent formation of amyloid plaques. Hence, inhibition of Aß generation is an important AD therapeutic strategy. BACE1 is a critical enzyme for the generation of Aß; compounds that can inhibit BACE1 activity are being developed for AD therapy. For the safe use of BACE1 inhibitors in human, we aim to investigate whether conditional deletion of BACE1 in adult mice will prevent formation of amyloid plaques and remove the pre-formed plaques. In addition, Individuals with DS develop age-related

cognitive decline and AD dementia by 30-40 years earlier than in the general population. AD and DS share certain molecular changes in related to the formation of amyloid deposition. Hence, our model will be applied to the study in the Down syndrome mouse model and we will also explore the beneficial effect of BACE1 inhibition in Down syndrome (DS) patients. Our study will also reveal whether significant inhibition of BACE1 will cause abnormal effects. The knowledge gained from this study will have timely and important guidance for the use of BACE1 inhibitors in human.

Further information available at:

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