ESSENTIAL INVOLVEMENT OF OLIGODENDROGLIAS IN THE PATHOGENESIS OF SPORADIC ALZHEIMER’S DISEASE

Yoshitaka Tatebayashi, Naomi Kikuchi-Nihonmatsu, Yoshiki Matsuda, Toshiki Uchihara, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan. Contact e-mail: tatebayashi-ys@igakuen.or.jp

Background: Sporadic Alzheimer’s disease (SAD) is the biggest target of drug development, although its pathological process still has been elusive. It must be promoted (or protected) by genetic factors, however, the research has long been dominated by a single direct causality called the amyloid b (Ab) hypothesis, rejecting alternative ones. Methods: We investigated roles of oligodendrocyte (OL) lineage cells in the pathogenesis of SAD by establishing a method to purify and culture adult OL progenitor cells (aOPCs) from the rat hippocampus and by investigating postmortem human brains. Results: We found novel aOPCs expressing plexin-B3 as Ab secreting cells. A small population of plexin-B3+ aOPCs was persistently cultured in fibroblast growth factor 2 (FGF2) and FGF2 withdrawal increased plexin-B3+ but decreased NG2+ aOPCs, with cored plaque-like morphological changes and increased Ab1-42 secretion greater than that of cultured fetal neurons. They express massive amounts of APP, the components of gamma-secretase, and the receptors of apolipoprotein E. In vivo, plexin-B3+ aOPCs distributed throughout the adult brain and spreading depolarization, a common mechanism of cortical injuries, induced unique delayed cortical gliosis of plexin-B3+ aOPCs whose distribution resembles to that of cored senile plaques. In human AD brains, cortical senile plaques were mostly immunostained with plexin-B3 antibodies. Conclusions: These findings suggest that plexin-B3+ aOPCs play essential roles in the pathogenesis of SAD as Ab secreting cells. Fine control of a SAD-type demyelination in the aged cortex would be a novel, promising and unexplored therapeutic target for SAD.

THE ROLE OF A RECENTLY DISCOVERED ALPHA-7 NICOTINIC ACETYLCHOLINE RECEPTOR ON AMYLOID-BETA PATHOLOGY IN ALZHEIMER’S DISEASE

Grace Williams, and Teresa Murray, Louisiana Tech University, Ruston, LA, USA. Contact e-mail: williams.grace.r@gmail.com

Background: Alzheimer’s disease (AD) is a neurodegenerative disease that affects the hippocampus and cortex of the brain causing irreversible damage. Despite scientific advances, its etiology is not fully understood. The α7β2 nicotinic acetylcholine receptor (nAChR), a recently-discovered neurotransmitter receptor subtype, is expressed in the septum and hippocampus of the brain. Scientists have shown that α7-nAChRs will mediate amyloid-beta peptide (Aβ1-42) internalization. Research also supports Aβ1-42 internalization initiating neuronal death. However, studies have not yet focused on α7β2-nAChR mediated internalization of Aβ1-42. Methods: One of the most commonly studied forms of nAChRs is α7, however α7β2 is suspected to have a higher affinity for Aβ1-42, SH-EP1 human neuroepithelial cell lines stably expressing α7-nAChRs or α7β2-nAChRs, and wild type cells were incubated with oligomeric Aβ1-42, or scrambled peptide followed by incubation with Amylo-Glo® dye (Biosensis). Fluorescence intensity was used to compare relative amounts of Aβ1-42 internalization. Cell death assays were also performed. Results: SH-EP1 cells expressing α7-nAChRs had markedly higher levels of internalized Aβ1-42 compared to the same type of cells incubated with a scrambled peptide sequence (Aβ1-42 scrambled), which did not appear to have internalized the peptide. Cells expressing the α7-nAChRs had a higher fluorescence intensity than cells expressing α7β2-nAChRs when incubated with amyloid beta oligomers. These results suggest that α7-nAChRs have a higher internalization rate than α7β2-nAChRs. Conclusions: This work provides a better understanding of Aβ1-42 cellular mechanisms involved in Aβ accumulation. These findings form a foundation for future research into the mechanisms of cellular dysfunction and cell death caused by intracellular Aβ1-42 accumulation. The α7β2 receptor is expressed in the septum and hippocampus where neuronal death is observed in AD pathology. Because Aβ aggregation is a hallmark of AD pathology that contributes to neurodegeneration, understanding the role of nicotinic acetylcholine receptor,

Sorting Nexin-4 Regulates β-Amyloid Production by Modulating β-Site-Activating Cleavage Enzyme-1

Na-Young Kim1, Mi-Hyang Cho2, 1University of Ulsan College of Medicine, Seoul, Republic of South Korea; 2University of Ulsan College of Medicine, Seoul, Republic of South Korea. Contact e-mail: dya818@hanmail.net

Background: Amyloid precursor protein (APP) is cleaved by β-site APP cleaving enzyme 1 (BACE1) to produce β-amyloid (Aβ), a critical pathogenic marker in Alzheimer’s disease (AD). Dysregulation of the intracellular trafficking of BACE1 may affect Aβ generation, contributing to AD pathology. Sorting nexin-4 (SNX4), a member of the sorting nexin (SNX) family that is involved in the regulation of protein trafficking. Part of sorting nexin-4 (SNX4) regarding AD has not been studied yet. Methods: Human brain and APP/PS1 mouse brain tissue were used to confirm the disease relevance of SNX4. To confirm the role of SNX4 in AD pathogenesis, several experiments were done, such as Western blotting, Immunohistochemistry, Immuno-precipitation, Gradient fractionation. Results: Our results demonstrated that SNX4 protein levels changed in the brains of patients with AD and of APP/PS1 mouse. Overexpression of SNX4 increased the levels of BACE1 and Aβ. Downregulation of SNX4 had the reverse effect. SNX4 interacts with BACE1 and blocks BACE1 trafficking to the lysosomal degradation system, resulting in an increased half-life of BACE1 and increased production of Aβ. Conclusions: Our studies suggest that SNX4 regulates BACE1 trafficking. A novel aspect of SNX4 function is to regulate BACE1-mediated β-processing of APP and subsequent generation of Aβ through its modulation of BACE1 trafficking. Thus, inhibition of BACE1 expression by disturbing other aspects of BACE1 cell biology, such as SNX4, may be a critical strategy in developing AD therapeutics.