Uncovering the molecular mechanism behind synapse loss in Alzheimer's disease

February 24 2021

Credit: Unsplash/CC0 Public Domain

Korea Brain Research Institute (KBRI, Pann-Ghill Suh (President)) announced that Dr. Kea Joo Lee and Dr. You-Na Jang of the Neural Circuits Research Group have identified the mechanism causing synaptic

loss in Alzheimer's disease as the aberrant expression of RAPGEF2, a synaptic protein.

The results were published on January 2021, in the online early view of *Neuropathology and Applied Neurobiology*. RAPGEF2 mediates oligomeric Aβ-induced synaptic loss and cognitive dysfunction in the 3xTg-AD mouse model of Alzheimer's disease

Alzheimer's disease (AD) accounts for about 75% of dementia cases and is the most common type of degenerative brain disease. AD is a devastating because disease progression can cause memory loss, mood disorder, slurred speech, confusion, and impaired movement.

With the conventional treatment available today, AD patients may expect to see some temporary improvement of symptoms, but nothing exists at the moment that can halt or reverse the progression. Instead, preventive strategies are emphasized, with health care professionals commonly suggesting physical exercise and continued learning programs as options.

AD is a tricky condition that has constantly thwarted the best efforts to unravel the inner workings of the disease. In the leading hypothesis, abnormal aggregation of amyloid beta (Aß) and tau proteins are identified as a possible cause of the illness. Amyloid beta is known to degrade synapses and drive cognitive impairment such as memory loss.

In their work unveiling the complex processes by which amyloid beta brings about synaptic loss, Dr. Kea Joo Lee and his team have been studying the brain tissue of both deceased Alzheimer's patients and genetically modified mouse models for the disease, and have found "RAPGEF2 protein overexpression" to be the common phenomenon.

RAPGEF2(Rap guanin nucleotide exchange factor 2) is an essential

protein involved in multiple critical biological pathways such as synaptic remodeling, neural plasticity, and embryo neural development—employing various neurobiological methodologies that utilize neuronal cell culture models and brain tissue from mouse models of Alzheimer's, the researchers arrived at the conclusion that "amyloid beta facilitates the overexpression of the RAPGEF2 protein," and "the RAPGEF2 protein, in turn, activates downstream effectors RAP2 and JNK to ultimately induce synaptic loss."

Intriguingly, electron microscopy and behavioral tests conducted by the team showed the silencing of RAPGEF2 as having a preventive effect on synapse loss and cognitive impairment even in the presence of increased amyloid beta.

The potential significance of these findings is great. Having a detailed understanding of the molecular mechanisms behind synaptic damage that occurs in the early stages of the Alzheimer's disease can be invaluable in developing treatments for neurodegenerative diseases such as dementia which have continued to plague humanity despite scientific advancement.

More information: You-Na Jang et al, RAPGEF2 mediates oligomeric Aβ-induced synaptic loss and cognitive dysfunction in the 3xTg-AD mouse model of Alzheimer's disease, *Neuropathology and Applied Neurobiology* (2020). DOI: 10.1111/nan.12686

Provided by Korea Brain Research Institute