New mechanism for amyloid beta protein's toxic impact on the Alzheimer's brain

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Scientists have uncovered a novel mechanism linking soluble amyloid -- protein with the synaptic injury and memory loss associated with Alzheimer's disease (AD). The research, published by Cell Press in the June 25 issue of the journal *Neuron*, provides critical new insight into disease pathogenesis and reveals signaling molecules that may serve as potential additional therapeutic targets for AD.

Amyloid beta protein plays a major pathogenic role in AD, a devastating neurodegenerative disorder characterized by progressive cognitive impairment and memory loss. "Given the mounting evidence that small soluble A-beta assemblies mediate synaptic impairment in AD, elucidating the precise molecular pathways by which this occurs has important implications for treating and preventing the disease," explains senior study author, Dr. Dennis Selkoe from the Center for Neurologic Diseases at Brigham and Women's Hospital and Harvard Medical School.

Dr. Selkoe, Dr. Shaomin Li, and colleagues examined regulation of a cellular communication phenomenon known as long-term synaptic depression (LTD). LTD has been linked with neuronal degeneration, but a role for A-beta in the regulation of LTD has not been clearly described. The researchers found that soluble A-beta facilitated LTD in the hippocampus, a region of the brain intimately associated with memory. The enhanced synaptic depression induced by soluble A-beta was mediated through a decrease in glutamate recycling at hippocampal synapses.

Excess glutamate, the major excitatory neurotransmitter in the brain, is thought to contribute to the progressive neuronal loss characteristic of AD. The researchers went on to show that A-beta-enhanced LTD was mediated by glutamate receptor activity and that the LTD could be prevented by an extracellular glutamate scavenger system. A very similar enhancement of LTD could be induced by a pharmacological blocker of glutamate reuptake. Importantly, soluble A-beta directly and significantly decreased glutamate uptake by isolated synapses.

"Our findings provide evidence that soluble A-beta from several sources enhances synaptic depression through a novel mechanism involving altered glutamate uptake at hippocampal synapses," concludes Dr. Selkoe. "These results have both mechanistic and therapeutic implications for the initiation of hippocampal synaptic failure in AD and in more subtle forms of age-related A? accumulation." Future studies are needed to determine precisely how soluble A-beta protein physically interferes with glutamate transporters at the synapse.

Source: Cell Press (news : web)