Scientists demonstrate means of reducing Alzheimer's-like plaques in fly brain

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Neuroscientists at Cold Spring Harbor Laboratory (CSHL) are part of a collaboration that has succeeded in demonstrating that overexpression of an enzyme in the brain can reduce telltale deposits causally linked with Alzheimer's disease.

CSHL Professor Yi Zhong, Ph.D., whose lab studies genetic mechanisms involved in neurodegenerative illnesses, helped develop a line of transgenic fruit flies that was central in the experiments. Transgenic organisms express genes that occur naturally in other species. In this instance, the fruit flies were engineered to express a human gene that codes for the production of an enzyme called neprilysin, or NEP.

Beta amyloid and the pathology of Alzheimer's

NEP enzymes are known from prior experiments to degrade protein deposits in the brain that are characteristic of Alzheimer's . The protein clumps -- sheet-like plaques between brain cells called beta amyloid deposits -- have been found in the autopsied brains of human Alzheimer's patients.

Two types of beta amyloid sheets are associated with Alzheimer's plaques. Scientists have suspected that so-called Aβ42 plaques -- those structurally composed of 42-amino acid beta amyloid peptides -- are involved in the genesis of the illness. "But the mechanism by which Aβ42 reaches pathological levels in the brains of late-onset patients is

not well understood," Dr. Zhong explained.

Past experiments in transgenic mice expressing human beta amyloid had shown that a deficiency of NEP caused a series of serious problems. The deficiency accelerated the formation of amyloid plaques, caused dysfunction in the synapses, or gaps, across which nerve cells in the brain communicate, and caused memory defects.

Reversing the process: mixed results

In new experiments, Dr. Zhong and other team members, who include Kanae Iijima-Ando, Ph.D., of the Farber Institute for Neurosciences and neuroscientists from Thomas Jefferson University in Philadelphia, sought to turn the tables. If NEP deficiency caused pathology, what would happen if NEP enzymes were expressed in above-normal amounts in brain cells affected by beta amyloid plaques?

Using transgenic fruit flies, the team found that by overexpressing human NEP in fly neurons, accumulation of Aβ42 inside the neurons was reduced. The scientists also observed that outright death of neurons due to Aβ42 plaques was suppressed.

At the same time, the experiment produced results that were not at all encouraging. Although NEP overexpression fought off plaques, chronic overexpression in the fly brain caused age-related degeneration of the axons that connect nerve cells, and also shortened the lifespan of the flies. The team believes that this effect was caused by the unintended impact of chronic NEP activity upon a critical gene-regulating protein, a transcription factor called CREB.

The team wants to test whether the life-shortening impact of NEP overexpression upon CREB occurs in transgenic mammals -- for instance, in mice, which are genetically closer to humans than flies.

"We have succeeded in demonstrating both protective and detrimental aspects of high NEP activity in the fly brain," Dr. Zhong said. "We also noted a reduction of NEP activity in fly brains that correlates with age. These are intriguing clues about mechanisms that contribute to the causation of Alzheimer's.

"We must now seek additional knowledge about the physiological mechanisms that underlie age-dependent downregulation of NEP in flies. This is a powerful genetic model system that we hope will lead us to discover novel therapeutics to combat Alzheimer's, a disease that devastates so many people every year."

Citation: "Overexpression of Neprilysin Reduces Alzheimer Amyloid-â42 (Aâ42)-induced Neuron Loss and Intraneuronal Aâ42 Deposits but Causes a Reduction in cAMP-responsive Element-binding Protein-mediated Transcription, Age-dependent Axon Pathology, and Premature Death in Drosophila" appears in the *Journal of Biological Chemistry*, and can be viewed online at: doi:10.1074/jbc.M710509200. The compete citation is: Kanae Iijima-Ando, Stephen A. Hearn, Linda Granger, Christopher Shenton, Anthony Gatt, Hsueh-Cheng Chiang, Inessa Hakker, Yi Zhong, and Koichi Iijima.

Source: Cold Spring Harbor Laboratory