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Study outlines how stroke, head injury can increase risk of Alzheimer's disease

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Researchers from the MassGeneral Institute for Neurodegenerative Disorders (MGH-MIND) have discovered how the death of brain cells caused by a stroke or head injury may cause generation of amyloid-beta protein – the key component of senile plaques seen in the brains of patients with Alzheimer's disease. Their report appears in the June 7 issue of the journal *Neuron*.

“We have discovered how a stroke can trigger a series of biochemical events that increase amyloid-beta production in the brain,” says Giuseppina Tesco, MD, PhD, of the MGH-MIND Genetics and Aging Research Unit, the paper’s lead author. “These findings raise the prospect of novel therapies that could interfere with this process and reduce the risk of Alzheimer’s disease in stroke or head trauma patients.”

It has been known for several years that strokes and head injuries can increase the risk of Alzheimer’s disease, but the mechanism underlying that increased risk has not been understood. Alzheimer's disease is characterized by plaques within the brain of amyloid-beta protein, which is toxic to brain cells. Amyloid-beta is formed when the larger amyloid precursor protein (APP) is clipped by two enzymes – beta-secretase, also known as BACE, and gamma-secretase – which releases the amyloid-beta fragment. The usual processing of APP by an enzyme called alpha-secretase produces an alternative, non-toxic protein.

The MGH-MIND team previously reported that cellular BACE levels are normally controlled by the enzyme’s breakdown in compartments called

lysosomes, a process that is disrupted if a molecular signal on the enzyme is altered. That signal binds to GGA proteins, which are required for the transport of several types of enzymes into lysosomes. One of these proteins, GGA3, can be degraded by caspase, an enzyme takes part in the cell-death process called apoptosis.

In a series of experiments the MGH-MIND researchers revealed how cell death caused by a brain injury, including a stroke, can lead to the production of amyloid-beta. Damaged brain cells undergo apoptosis, releasing caspase which also breaks down GGA3. Without enough GGA3 to help transport BACE to lysosomes, levels of BACE rise and lead to increased amyloid-beta production. Amyloid-beta itself is toxic to brain cells, so it may cause further apoptosis, leading to a vicious cycle of continued cell death and amyloid-beta production.

The importance of GGA3's control of BACE levels was supported by the observation that, in brain tissue from Alzheimer's patients, reductions in GGA3 corresponded with elevations in BACE, particularly in those areas most affected by the disease.

"Our findings also shed new light on how the aged brain becomes more vulnerable to AD, since any insult to the brain – head injury, stroke, or the mini-strokes called TIAs – can set off this process and turn up BACE activity," says Rudolph Tanzi, PhD, director of the Genetics and Aging Research Unit and senior author of the Neuron paper. "Therapies that protect GGA3 from caspase cleaving might be able to reduce the risk of AD or the more transient type of dementia that can occur after such injuries." Tanzi is a professor of Neurology at Harvard Medical School, where Tesco is an assistant professor.

Source: Massachusetts General Hospital

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