Alzheimer's disease therapeutic prevents long-term damage from TBI in pre-clinical studies

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A class of Alzheimer's disease drugs currently studied in clinical trials appears to reduce damage caused by traumatic brain injury in animals, researchers at Georgetown University Medical Center report in an upcoming advance online publication of *Nature Medicine*.

They say the results suggest that this class of drugs could potentially do something no other drug has been able to do-- prevent the long-term and continuing damage that often follows a serious injury to the brain.

That is because the agents, known as gamma secretase inhibitors, are designed to prevent build-up of amyloid, a toxic peptide found in the brain. This peptide clogs the brains of Alzheimer's patients but it is has also been found in people who have died from traumatic brain injury, says the study's lead author, neuroscientist Mark Burns, PhD, an assistant professor at GUMC.

"No one knows why it occurs, but abnormal amounts of amyloid plaque have been found during an autopsy in about a third of brain injury victims, some of whom were children who would ordinarily never have had these deposits," says Burns. "Remarkably, these deposits may occur in less than one day after injury."

There is another connection between traumatic brain injury and Alzheimer's disease, he says - it is known that people who suffered a brain injury had a 400 percent increased risk of developing the disorder.

"But up until now, these were just interesting observations," Burns says. "In this study we show that the same pathways activated chronically in Alzheimer's disease are activated acutely in traumatic brain injury and that they appear to play a very important role in secondary injury."

Severe brain injury usually produces an immediate "necrotic" death of nerve cells, but this damage is often followed by a secondary wave of injury that can last weeks, months, and even years, Burns says. This damage comes from apoptosis, which is a different form of cell death, and can result in large holes in brain tissue that cause lasting neurological effects. To date, there has been no way to prevent or treat this damage, he says.

In this study, the investigators sought to understand if amyloid peptide contributed to secondary injury. Amyloid peptides are produced when a long protein in the brain known as the amyloid precursor protein (APP) is cut in two by the enzyme beta secretase, and then cut into smaller pieces by a second enzyme, known as gamma secretase.

The researchers went on to test Alzheimer's disease amyloid-busting agents as a brain injury treatment. It worked. "By using a gamma secretase inhibitor, we prevented much of secondary traumatic brain injury in mice in our experiments," he says.

To look at the role of amyloid in brain injury, the researchers used two different approaches to blocking activation of the pathway that produces amyloid peptide. They used a group of mice that were genetically altered so that they did not produce any beta secretase, which meant they were incapable of producing amyloid.

They also treated "normal" mice with the experimental agent DAPT, one of the first gamma secretase inhibitors developed and the model upon which some Alzheimer's disease drugs now in clinical testing are based.

As a result, amyloid peptide production was substantially reduced in this group.

They first showed that in a group of normal control mice, brain injury produced substantially more amyloid peptide, and that the brain region known as the hippocampus, which is also affected in Alzheimer's disease, was substantially damaged.

They then followed the groups of reduced amyloid mice after injury, and found that three weeks after initial trauma, both groups performed almost equally well on learning tests. Magnetic resonance imaging scans of the mice showed that these two groups of mice did not have "nearly the same amount of damage in the hippocampus of their brain as control mice did," Burns says.

"The experiment with the genetically altered mice shows that amyloid peptide contributes to the secondary damage seen in traumatic brain injury," he says. "If injured mice that cannot develop amyloid demonstrate reduced signs of secondary trauma, that points to amyloid peptide as a cause of this continuing damage."

The study using DAPT then proved that in mice able to produce amyloid, a gamma secretase inhibitor reduced amyloid peptide production, and significantly improved learning, Burns says. "This is an exciting finding that we hope can be readily tested in patients with traumatic brain injury," he says.

Source: Georgetown University Medical Center