Targeted oxidation-blocker prevents secondary damage after traumatic brain injury

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Treatment with an agent that blocks the oxidation of an important component of the mitochondrial membrane prevented the secondary damage of severe traumatic brain injury and preserved function that would otherwise have been impaired, according to a research team from the University of Pittsburgh School of Medicine, Graduate School of Public Health and Department of Chemistry in a report published online today in *Nature Neuroscience*.

Annually, an estimated 1.7 million Americans sustain a traumatic brain injury (TBI) due to traffic accidents, falls, assaults and sports participation, said the study's senior author Hülya Bayır, M.D., associate professor, Department of Critical Care Medicine, University of Pittsburgh School of Medicine. She added that 52,000 of those injured die, and 85,000 are left with significant disability.

"We don't yet have a specific therapy for TBI, but can provide only supportive care to try to ease symptoms," Dr. Bayır said. "Our study drug shows promise as a neuroprotective agent that might help address this important public health problem."

For the study, the research team conducted a global assessment of all the phospholipids in rat brain cells. This revealed that damage from TBI was nonrandom and mostly involved cardiolipin, a phospholipid that is found in the membranes that form mitochondria, the cell's powerhouse. They

noted that in the healthy animal, only 10 of the 190 cardiolipin species were modified by oxygen, but after a brain injury, the number of oxidized species rose many-fold.

The researchers then developed an agent, called XJB-5-131, which can cross the blood-brain barrier and prevent the oxidation of cardiolipin. Using an established research model of severe TBI, the agent or a placebo was injected into the bloodstream of rats five minutes and again 24 hours after head injury.

In the weeks that followed, treated animals performed akin to normal on tests of balance, agility and motor coordination, learning, and object recognition, while placebo-treated animals showed significant impairment. The results indicate that blocking cardiolipin oxidation by XJB-5-131 protected the brain from cell death.

"The primary head injury might not be that serious," Dr. Bayır noted. "But that initial injury can set into motion secondary cellular and molecular events that cause more damage to the brain and that ultimately determine the outcome for the patient."

She added that a targeted oxidation-blocker might also be beneficial in the treatment of other neurological disorders, such as Parkinson's disease, amyotrophic lateral sclerosis, or ALS, and stroke.

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