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A new cell type is implicated in epilepsy caused by traumatic brain injury

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Traumatic brain injury is a risk factor for epilepsy, though the relationship is not understood. A new study in mice, published in *Cerebral Cortex*, identifies increased levels of a specific neurotransmitter as a contributing factor connecting traumatic brain injury (TBI) to post-traumatic epilepsy. The findings suggest that damage to brain cells called interneurons disrupts neurotransmitter levels and plays a role in the development of epilepsy after a traumatic brain injury.

The research team, led by David Cantu and Chris Dulla, studied the effect of traumatic brain injury on the levels of the neurotransmitter gamma-aminobutyric acid (GABA) in the cerebral cortex, the portion of the brain associated with higher level functions such as information processing.

Normally, GABA inhibits neurotransmission in the brain, while its precursor, glutamate, stimulates neurotransmission. When the cortex is damaged by brain injury, however, the cells that create GABA, called interneurons, die. This leads to a toxic buildup of glutamate, which overstimulates brain activity. The study identifies this disrupted balance of GABA and glutamate as a factor in increased epileptic brain activity. The findings suggest that traumatic brain injuries cause damage to the interneurons responsible for creating GABA.

"If we can preserve these important cells, we may be able to decrease the negative impacts of traumatic brain injury," said first author David Cantu, Ph.D., a postdoctoral scholar at Tufts University School of

Medicine, and member of the NIH-funded Institutional Research Career and Academic Development Awards (IRACDA) Program, Training in Education and Critical Research Skills (TEACRS), at the Sackler School of Graduate Biomedical Sciences at Tufts. "Interneurons play a critical role in preventing seizures from starting."

"This research increases our basic understanding of the effects of head trauma, particularly for those severe single injuries that can and do happen in military service and contact sports," said Naomi Rosenberg, Ph.D., dean of the Sacker School and vice dean for research at Tufts University School of Medicine. "The IRACDA program provides transformational experiences to outstanding post-doctoral researchers, like David, who want to combine training in research with training in teaching at institutions serving under-represented minorities."

Epilepsy affects more than 2.3 million Americans, according to estimates by the Centers for Disease Control and Prevention. The Epilepsy Foundation estimates that 15 to 34 percent of TBI patients have post-traumatic epilepsy while the rate of post-traumatic epilepsy rises to as high as 52 percent among TBI patients who have served in active military roles.

"Millions of Americans experience a TBI every year, often with devastating and life-altering results. A TBI can cause issues with walking, talking, and living independently. Brain injury is the 'signature injury' of those in the military who have served in Iraq and Afghanistan. There are also many sports-related brain injuries. Fall-related injuries can disrupt the brain development of children, and upset the delicate brain systems among the elderly," said senior author Chris Dulla, Ph.D. He is an assistant professor of neuroscience at Tufts University School of Medicine, and member of the Cell, Molecular & Developmental Biology, and Neuroscience program faculties at the Sackler School.

"Our study is an important step in identifying the mechanistic relationship between TBI and post-traumatic epilepsy. The study describes a potential outline of what happens after brain injury to trigger epilepsy, but the neurological causes of how TBI kills interneurons specifically after the initial injury are still unknown. Understanding how brain injury disrupts normal brain function will allow scientists and physicians to develop new treatments and therapies to help people recover from post-traumatic epilepsy," said Cantu.

The work was done in collaboration with Giuseppina Tesco, M.D., Ph.D., associate professor of neuroscience at Tufts and member of the neuroscience graduate program faculty at the Sackler School. It is part of the team's larger effort to understand brain injury and epilepsy.

More information: Cantu D, Walker K, Andresen L, Taylor-Weiner A, Hampton D, Tesco G, Dulla C. "Traumatic brain injury increases cortical glutamate network activity by compromising GABAergic control." *Cerebral Cortex*. Published online Mar 7, 2014: DOI: 10.1093/cercor/bhu041

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