Pulling the plug on brain injury: Manipulating fluid flows could save lives, improve recovery post-TBI

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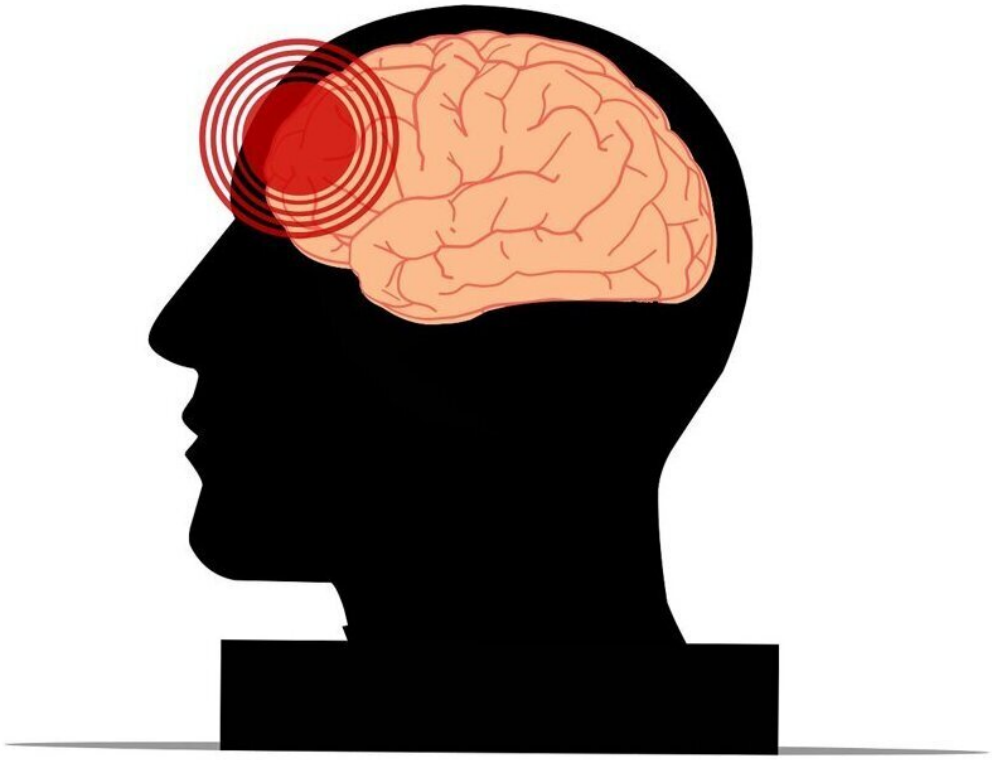

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Cerebral edema, the dangerous brain swelling that occurs after traumatic brain injury (TBI), can increase risk of death 10-fold and significantly

worsen prospects for recovery in brain function. In extreme cases, surgeons will remove a portion of the skull to relieve pressure, but this has significant risks and is not viable for the vast majority of TBI cases.

Physicians have very few tools at their disposal that are effective in treating cerebral edema, which is one of the leading causes of in-hospital deaths, and is associated with long-term neurological disability.

New research appearing in the journal *Nature* could change all that, showing that a cocktail of drugs already approved to treat high blood pressure quickly reduces brain swelling and improves outcomes in animal models of brain injury.

"Our research shows that cerebral edema is the consequence of impaired fluid flow through the glymphatic system and its associated lymphatic drainage," said Maiken Nedergaard, MD, DMSc, co-director of the University of Rochester Center for Translational Neuromedicine and senior author of the study.

"This impairment is under adrenergic control, and can therefore be rescued pharmacologically by broadly inhibiting adrenergic receptors. Because these drugs are already being used clinically and have observed neurological benefits, there is the potential to move quickly to clinical studies to confirm these findings."

Manipulating fluid flows in the brain to release post-TBI brain pressure

The glymphatic system was first described by Nedergaard's lab in 2012 as the brain's unique waste removal process. Since then, a growing understanding of the mechanics of the system–aided by advanced imaging technologies and AI-driven models of fluid dynamics—has

allowed researchers to better predict and manipulate the movement of cerebrospinal fluid (CSF) in the central nervous system.

This research has opened new possibilities to treat Alzheimer's and other neurological disorders and more effectively deliver and distribute drugs in the central and peripheral nervous system, including the inner ear.

The new study points to the potential to repurpose the glymphatic system to act as an emergency pressure release valve. Cerebral edema is a common consequence of moderate and severe cases of TBI.

"In other parts of the body, edema helps with tissue repair, but because of the skull, the brain has limited capacity for expansion. As a result, pressure increases, blood supply decreases, and debris and toxic proteins are trapped at the injury site, compounding the damage and impairing recovery," said Rashad Hussain, Ph.D., an assistant professor in the Center for Translational Neuromedicine and first author of the study.

One of the main triggers of cerebral edema is noradrenaline, a neurotransmitter that floods the brain immediately after TBI. Noradrenaline is typically associated with the flight-or-fight response, but in TBI this "adrenergic storm" impairs the flow of CSF in and out of the brain.

The researchers describe how noradrenaline interferes with the function of the glymphatic system. Specifically, it restricts the movement of fluid through the section of the system's plumbing where CSF drains from the brain and flows into the meningeal and cervical lymph nodes in the neck. This observation led the team to speculate whether reopening these gates to the lymph nodes could flush excess CSF from the brain, thereby relieving pressure.

Blood pressure medications suppress adrenaline

'storm' and restart fluid flow

To accomplish this, the team used a cocktail of drugs, including prazosin, atipamezole, and propranolol. This combination of alpha- and beta-blockers collectively suppress the different receptors used by cells to take up noradrenaline. Previous research in Nedergaard's lab has shown that this combination of drugs ramps up the glymphatic system, replicating the level of activity experienced when we sleep, which is when the system is most efficient in manipulating CSF flow to remove waste.

In the new study, the same drug cocktail was administered to mice soon after TBI. Using fluorescent microspheres, the researchers traced CSF originating from the site of the swelling as it exited in bulk from the brain via lymphatic vessel, carrying with it debris from the injury to the lymph nodes. The result was an almost immediate elimination of cerebral edema and a sustained return to normal intracranial pressure in the animals. The treatment resulted significant recovery of cognitive, behavioral, and motor function.

"These findings show that the adrenergic storm, the resulting edema and intracranial pressure, and retention of neural debris, can all be reversed by broad adrenergic inhibition, with subsequent improvement in recovery in injured mice," said Nedergaard.

The authors point to several clinical studies that demonstrate the safety profiles and observed neurological benefits of these drugs, early indications that this approach could also benefit humans. Atipamezole reduces post-traumatic seizures, prazosin is effective in treating the post-traumatic stress associated with TBI, and beta-blockers reduce in-hospital mortality and improve functional outcome of TBI patients.

Additionally, Nedergaard and her colleagues at the University of

Copenhagen have shown that individuals who take beta-blockers for hypertension are at lower risk for Alzheimer's.

More information: Maiken Nedergaard, Potentiating glymphatic drainage minimizes post-traumatic cerebral oedema, *Nature* (2023). DOI: 10.1038/s41586-023-06737-7. www.nature.com/articles/s41586-023-06737-7

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