Steroids rapidly restore blood-brain barrier function after blast

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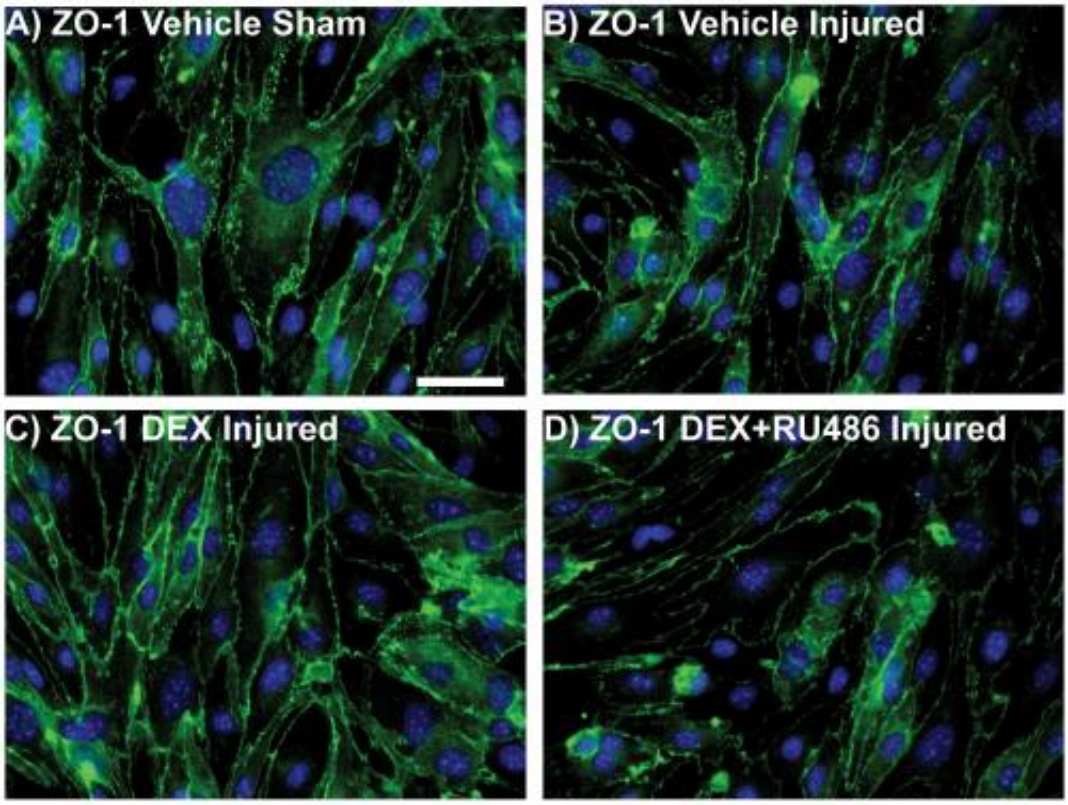

This image shows increased tight junction immunostaining 1 day after blast injury due to dexamethasone (DEX) treatment. (A) Characteristic staining of the ZO-1 tight junction protein in untreated controls. (B) Reduced ZO-1 staining in untreated injured cultures after blast exposure. (C) Stronger ZO-1 tight junction staining in DEX-treated injured cultures. (D) Reduced ZO-1 staining in injured cultures treated with DEX and RU486 (mifepristone), inhibiting effects of DEX treatment alone. Credit: Image courtesy of Barclay Morrison III/Columbia Engineering

Barclay Morrison III, associate professor of biomedical engineering at Columbia Engineering, has led the first study to determine underlying biological mechanisms that promote functional recovery of the blood-brain barrier (BBB) after blast injury. The research demonstrates that treatment with the glucocorticoid, dexamethasone, after primary blast injury promotes rapid recovery of an in vitro model of the BBB, a highly restrictive semi-permeable barrier whose primary function is to maintain the brain's microenvironment and protect it from potentially toxic substances. The study is published in the March 11 Advance Online Publication of the *Journal of Cerebral Blood Flow & Metabolism*.

"Our research should stimulate renewed clinical interest in developing glucocorticoid therapies to treat blast-induced traumatic brain injury (bTBI) and other disorders of the central nervous system," Morrison says. His findings also hold important implications for military personnel exposed to blast injury. "We may be able to improve outcomes in brain-injured soldiers and civilians," he continues, "and reduce the length of their mandatory rest periods before returning to duty, making the difference between requiring only days rather than weeks or longer to recover."

This improvement could be a significant result, as there are currently no approved pharmaceutical therapies for traumatic brain injury (TBI), and recently completed clinical trials have not demonstrated any benefit of other tested neuro-protective interventions. For patients with head injuries (non-blast related) and brain edema, doctors have been prescribing glucocorticoids, a class of steroid hormones, as standard treatment for the past 30 years. These drugs are also frequently used to manage central nervous system (CNS) disorders associated with a pathologically permeable BBB, such as with brain tumors and multiple sclerosis.

"But there have been mixed reports about the effectiveness of

glucocorticoids after traumatic insult and their use in the clinic for TBI is controversial, partly due to side effects associated with high doses and long durations of treatment," Morrison notes. "Our study's positive results may lead the way to developing a more targeted therapy using steroids to quickly restore the integrity and function of the BBB after bTBI."

The U.S. Department of Defense has recorded more than 300,000 cases of TBI between 2000 and 2014, most caused by explosive blast. The prevalence of bTBI is largely due to the development of improved personal protective armor that has led to increased survival of military personnel who sustain injuries from blast. There are four types of blast trauma injury: 1) primary injury caused directly by the pressure wave, which can travel through tissue at velocities close to that of sound in water, 2) secondary injury caused by objects put in motion by the blast, 3) tertiary injury caused by an individual thrown into motion by the blast and hitting surrounding objects, and 4) quaternary injury caused by burns, explosion-related injuries, illnesses and diseases not attributed to the other three blast trauma types.

"Primary blast injury is a biomechanically distinct phase of bTBI that remains the least understood by researchers," explains Christopher Hue, Morrison's PhD student and lead author of the study. The shock wave that emanates from an explosion source as compressed and rapidly expanding gases can occur in milliseconds or less. Given the fine structure of the BBB—nearly every neuron has its own blood supply—primary blast can incur major damage. And damage to the BBB would allow potentially harmful blood constituents to flood the brain, and that, in turn, could wreak havoc on the neurons that make up the brain.

So, says Hue, "Speeding blood-brain barrier recovery is an important therapeutic target for developing new treatments for victims of bTBI."

Working in Morrison's Neurotrauma and Repair Laboratory at Columbia Engineering, the team developed a blast injury model using a shock tube and custom-designed sample receiver to simulate a primary blast event and applied it to an isolated, living model of the BBB that consisted of brain endothelial cells. The shock tube was designed to recapitulate blasts by generating shock waves with pressure histories similar to explosions from improvised explosive devices in open environments (i.e. a 105 mm mortar shell). They were able to test separate components of the central nervous system, including the BBB, in isolation, which gave them precise control over the mechanical "insult," and eliminated potentially confounding effects of inertial injury that are often present when studying the effects of blast in pre-clinical models.

"Our in vitro experimental strategy had a big advantage in that separate components of the CNS, including the BBB, can be tested in isolation from others," Morrison says. "We were the first to use our blast injury model to precisely control the biomechanical initiators of injury and measure subsequent changes to BBB function more directly than in vivo."

The study showed that treatment with dexamethasone resulted in full recovery of BBB function one day after injury, as opposed to three days in untreated samples. Morrison and his team are hoping next to translate their in vitro findings in vivo.

"The combination of in vitro and in vivo experimental models to understand the biophysical and molecular mechanisms of primary blast injury and the effects of treatment on the BBB offer a powerful set of tools to guide the development of novel therapeutic strategies to mitigate the consequences of bTBI," says Morrison. "Accelerating BBB recovery after blast exposure represents an important advance in addressing the multifaceted, short- and long-term complications associated with bTBI."

Hue adds, "We're especially excited about our results because our research may pave a way to help protect those men and women who put themselves in harm's way in the service of our country."

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