White matter repair and traumatic brain injury

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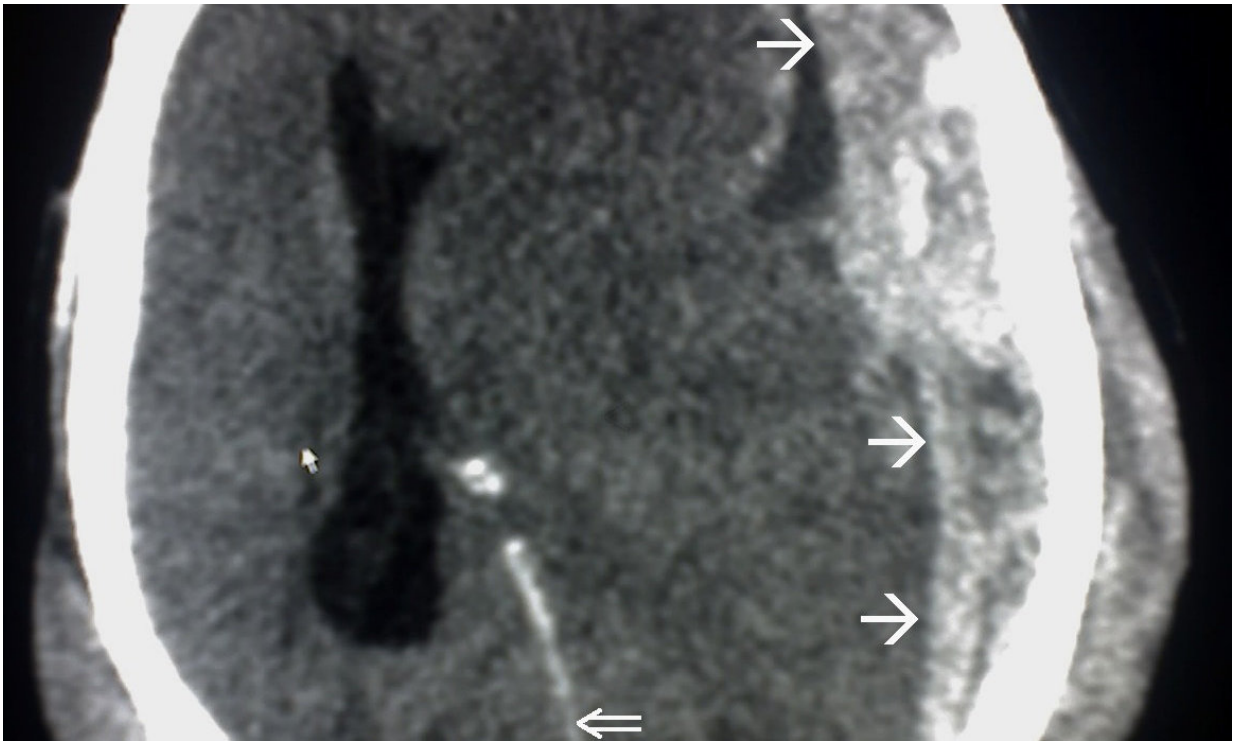

This CT scan is an example of Subdural haemorrhage caused by trauma. Single arrows mark the spread of the subdural haematoma. Double arrows mark the midline shift. Credit: Wikipedia Commons

Traumatic brain injury (TBI) is a leading cause of death and disability in the U.S., contributing to about 30 percent of all injury deaths, according to the CDC. TBI causes damage to both white and gray matter in the

brain, but most research to date has focused on protecting neuronal cell bodies in gray matter, and thus far, has yielded few promising clinical trials. But damage to white matter in TBI, which occurs in the corpus callosum, internal capsule and corticospinal tracts, is also significant. Executive function and memory are particularly dependent on intact white matter tracts, and, compared with focal lesions, white matter disruption is known to be a superior predictor of long-term clinical outcomes in TBI.

Seeking to better understand the role of white matter, and particularly axonal injury and regeneration in TBI, a group of investigators from the University of Pittsburgh, Duquesne University, the Albert Einstein College of Medicine, and the Veterans Administration undertook a study involving tissue plasminogen activator (tPA) in a murine model of TBI.

While recombinant tPA is an effective stroke drug that is thought to have pleiotropic effects on the brain beyond thrombolysis of blood clots, its role in TBI cases is not well understood. Existing data even suggest that tPA may actually play a harmful role in models of acute brain injury. Some studies have implicated tPA in cortical tissue injury, edema and brain hemorrhage when used to treat TBI. To further confuse things, tPA is naturally expressed in the vascular system as well as in the brain, where it promotes synaptic plasticity and axon growth. Here, it is thought to have a protective effect for neurons and white matter.

To examine the effect of both endogenous and exogenous tPA on white matter in TBI, the investigators conducted a two-part experiment involving mice. For the first part, knockout mice lacking the gene coding for endogenous tPA (tPA-KO) and wild type (WT) mice underwent either TBI or sham surgery. Over a 35-day period, the four groups of mice performed several physical tests, including the rotarod, cylinder and Morris water maze to measure sensorimotor and cognitive function. The sham WT and tPA-KO mice performed normally on these tests,

whereas both groups of TBI mice performed relatively poorly, demonstrating sensorimotor, learning and memory deficits. Performance deficits were even more pronounced in the tPA-KO subgroup of TBI mice.

At 35 days, the researchers performed diffusion tensor imaging (DTI) and immunostaining on samples from all groups to evaluate the extent of white matter damage. As might be expected, imaging showed both TBI groups with significant loss of white matter integrity, while the white matter damage was markedly more pronounced in the tPA-KO mice. Immunostaining to assess myelin integrity in several regions of the brain likewise showed little damage in the sham group and the WT TBI group, whereas damage was significantly worse for the KO-tPA TBI group. The immunostain results for this group correlated with those of the physical tests described previously.

These longer-term data from 35 days led the investigators to suspect that tPA deficiency would also manifest early in TBI in the form of axonal damage. Immunuofluorescent staining and measurement of evoked compound action potentials at three days post-TBI bore this out. "[E]ndogenous tPA mitigates both acute and chronic white matter damage after TBI at the histological and functional levels," the investigators concluded.

For the second part of the experiment, the investigators tested whether or not exogenous, intranasally administered tPA would improve the neurological deficits observed in the KO-tPA group post TBI. The sham group of both WT and tPA-KO mice were treated with phosphate buffered saline (PBS), while the TBI group of WT and tPA-KO mice were treated with either PBS or 0.5 mg of tPA two hours after injury and then every other day for two weeks. The sham group showed no sensorimotor deficits. However, after treatment with intranasal tPA, the tPA-KO mice showed sensorimotor function equivalent to WT mice.

Though tPA treatment did not improve spatial learning significantly in these mice, it did improve long-term spatial memory, which was equivalent to that exhibited by the PBS-treated WT mice. So treatment with recombinant tPA in the knockout mice after TBI brought their neurological function up to the level of wild type mice.

As per the first experiment, histologic and electrophysiologic criteria were used to assess white matter disruption and axonal conduction. While differences between the sham injury and TBI groups were apparent, tPA-KO mice treated with intranasal tPA and WT mice showed similar results, indicating that recombinant tPA treatment makes up for a lack of endogenous tPA and prevents long-term demyelination and axonal damage.

This study also demonstrated that electrophysiologic measures are a good post-TBI predictor of functional performance. Importantly, the investigators also found that that the administration of recombinant tPA in wild type mice after TBI failed to increase brain hemorrhage, while the knockout mice, in comparison, showed no decrease in bleeding. Additionally, the investigators found that mice treated with recombinant tPA showed improved neurologic outcomes in terms of axonal sprouting as measured in a tract-tracing test, and that the epidermal growth factor receptor (EGFR) plays a role in mediating axon growth.

This study demonstrates that tPA, whether endogenously produced or exogenously administered, plays an important role in the brain's recovery from TBI. Additionally, the interplay of tPA, white matter and axonal growth, particularly as they relate to functional performance, contribute to a better understanding of the pathophysiology of TBI.

The study authors conclude: "Our findings suggest that the roles of the pleiotropic tPA-encoding gene to protection of neuronal network communication and improvement in of functional outcomes in acute and

chronic phases of TBI." Their findings regarding the risk of cerebral hemorrhage also suggest that "low-dose, recombinant forms of tPA should continue to be tested for their potential to preserve or rescue white matter tracts and improve long-term functional recovery after acute brain injuries."

More information: Yuguo Xia et al. Tissue Plasminogen activator promotes white matter integrity and functional recovery in a murine model of traumatic brain injury. *Proc Natl Acad Sci*. 2018 Sep 10. pii: 201810693. DOI: 10.1073/pnas.1810693115 . [Epub ahead of print]