

Presence of enzyme may worsen effects of spinal cord injury and impair long-term recovery

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Traumatic [spinal cord](#) injury (SCI) is a devastating condition with few treatment options. Studies show that damage to the barrier separating blood from the spinal cord can contribute to the neurologic deficits that arise secondary to the initial trauma. Through a series of sophisticated experiments, researchers reporting in *The American Journal of Pathology* suggest that matrix metalloproteinase-3 (MMP-3) plays a pivotal role in disruption of the brain/spinal cord barrier (BSCB), cell death, and functional deficits after SCI. This link also presents new therapeutic possibilities.

"Matrix metalloproteinases (MMPs) are enzymes known to degrade the extracellular matrix and other extracellular proteins and are essential for remodeling of the extracellular matrix and wound healing. Excessive proteolytic activity of MMPs can be detrimental, leading to numerous pathological conditions, including [blood brain barrier](#) (BBB)/BSCB disruption after injury," explains Tae Young Yune, PhD, of the Department of Biochemistry and Molecular Biology, School of Medicine, Kyung Hee University, Seoul, Korea. Although other MMPs have been linked to SCI (i.e. MMP-2, MMP-9, and MMP-12), there has been no previous direct evidence of a similar role for MMP-3.

By comparing mice that underwent spinal cord injury to a control group, investigators found that both MMP3 messenger RNA (mRNA) and MMP-3 protein levels in spinal cord segments were increased after SCI,

peaking one day after surgery in the experimental group, whereas no changes were seen in the controls. MMP-3 immunoreactivity was detected in cells within the lesion site, invading neutrophils, and blood vessel endothelial cells in the area outside of the initial injured area (the penumbra).

Another series of experiments focused on the role of MMP-3 in BSCB permeability, using dye to visualize leakage through the BSCB. Similar to MMP-3 mRNA and protein levels, dye leakage reached a maximum one day after SCI. Leakage was lower in *Mmp3* knockout mice that were genetically altered to be deficient in MMP-3 as well as in mice injected with either *Mmp3* small interfering RNA (siRNA) or a general MMP inhibitor. Injection of MMP-3 into normal spinal cord also significantly increased dye leakage.

MMP-3 was found to contribute to the degradation of tight junction proteins that are responsible for maintaining the integrity of the BSCB barrier. In addition, the researchers reported that MMP-3 induced blood cell infiltration and hemorrhage after SCI in wild-type mice, but not in *Mmp3* knockout mice. MMP-3 also mediated activation of other MMPs (MMP-2 and MMP-9) that are up-regulated after SCI. "This is the first study to demonstrate that MMP-3 is involved in MMP-9 activation in central nervous system injury," says Dr. Yune.

A significant finding was that mice deficient in MMP-3 showed significantly better functional recovery 14 and 28 days after injury than non-deficient mice. Histological analysis showed that after SCI the mice deficient in MMP-3 had smaller volumes of injured tissue and more healthy axons than non-deficient wild-type mice.

"The evidence suggests that BBB/BSCB disruption plays a pivotal role in acute and chronic neurological disorders. The inhibition of MMP-3 may be a promising therapeutic target for human central nervous system

disease, including SCI," notes Dr. Yune.

More information: "Matrix metalloproteinase-3 promotes early blood-spinal cord barrier disruption and hemorrhage and impairs long-term neurological recovery after spinal cord injury," by Jee Youn Lee, Hae Young Choi, Hyun-Jong Ahn, Bong Gun Ju, and Tae Young Yune. ([DOI: 10.1016/j.ajpath.2014.07.016](https://doi.org/10.1016/j.ajpath.2014.07.016)). The article appears online ahead of *The American Journal of Pathology*, Volume 184/Issue 11.

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