Research suggests new therapeutic approach for spinal cord injury

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A new study suggests that administering FTY720, an oral drug that has shown promise in trials for human multiple sclerosis, significantly improves locomotor recovery in mice with spinal cord injury (SCI). The research suggests a possible new avenue to counteract the degeneration of the spinal cord in human SCI. The study will be published in the April 2012 issue of The *American Journal of Pathology*.

Beyond the initial tissue damage, much of the degradation of the spinal cord in SCI is due to a cascade of secondary injuries, including neuronal and glial apoptosis, inflammation, glial scar formation, local edema and ischemia, and oxidative stress. The aim of current SCI treatment is to counteract the mechanisms of secondary injury and prevent their pathological consequences, because central nervous system (CNS) neurons have very limited capacity to self-repair and regenerate.

Researchers from the Jichi Medical University School of Medicine and the Graduate School of Medicine at the University of Tokyo had previously shown that the concentration of the lysophospholipid mediator, sphingosine 1-phosphate (S1P), was significantly increased in the location of a contusion injury, triggering the migration of neural progenitor/stem cells to the site of the injury. They hypothesized that targeting S1P receptors may become a candidate therapy for various refractory central nervous system disorders, including SCI.

FTY720 acts as a broad S1P receptor modulator. Its efficacy in central nervous system disorders is believed to derive from immunomodulation.

Researchers found that orally administering FTY720 to mice shortly after contusion SCI significantly improved motor function recovery. Importantly, they found that the therapeutic effects of FTY720 were not solely dependent on immune modulation. The administration of FTY720 induced lymphopenia, clearing lymphocytes from the blood, and reduced T-cell infiltration in the spinal cord. But it did not affect the early infiltration of neutrophils and activation of microglia, and it did not reduce plasma levels and mRNA expression of inflammatory cytokines in the spinal cord. Tests in mice with severe combined immunodeficiency (SCID mice) with SCI found that FTY720 significantly improved recovery of hind limb motor function.

"These data clearly indicate the importance of immune-independent functions of FTY720 in the amelioration of functional deficits after SCI in mice," explains lead investigator Yoichi Sakata, MD, PhD, Research Division of Cell and Molecular Medicine, Center for Molecular Medicine, Jichi Medical University School of Medicine.

Dr. Sakata notes that S1P receptors exist in many types of cells and play a role in many cellular processes. "We observed that FTY720 decreased vascular permeability and astrocyte accumulation in injured spinal cord. These changes were also noted in SCID mice, suggesting they are not dependent on lymphocyte function. Increased vascular permeability can lead to destruction of the blood-brain barrier in spinal cord, and astrocyte accumulation is the main cellular component of glial scar after CNS injury. FTY720 might counteract these secondary injuries and thereby prevent their pathological consequences."

"Our data suggest that targeting S1P receptors with FTY720 is an attractive therapeutic approach for SCI," Dr. Sakata concludes. "However, further evaluation utilizing larger animals such as non-human primates will be necessary to confirm its efficacy in treating SCI. Further, strategies targeted at modulating the SIP concentration in

injured CNS may lead to new therapeutic approaches towards repairing various CNS disorders."

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