Rewiring injured neural pathways

Larry Benowitz, PhD
Boston Children's Hospital and Harvard Medical School

Following injury to the central nervous system (CNS), neurons cannot regenerate long-distance connections, and undamaged neurons have only a limited ability to form new connections to compensate for ones that have been lost. Because of these limitations, victims of stroke, spinal cord injury, optic neuropathies, and certain neurodegenerative conditions often suffer irreversible, life-changing losses in sensory, motor, or cognitive functions depending on the extent and location of injury. One agent that has been found to enhance the growth of compensatory connections after CNS damage in animal studies is inosine, a small naturally occurring molecule derived from adenosine. Inosine diffuses into nerve cells and activates Mst3b, an component of the cell-signaling pathway through which many trophic factors promote axon outgrowth (1-3). After a unilateral stroke of the rat motor cortex, intraventricular delivery of inosine enhances the ability of motor neurons on the undamaged side of the brain to sprout axon collaterals into the denervated side of the spinal cord, resulting in improved use of the impaired forepaw. This capacity was strongly enhanced by environmental enrichment or by combining inosine with a peptide antagonist of the Nogo receptor (4, 5). Inosine also promotes the formation of "detour circuits" in the spinal cord after mid-thoracic injury to the corticospinal tract (CST). Inosine enhanced the ability of transected CST axons to sprout collateral branches in the cervical spinal cord that formed synaptic contacts onto interneurons which project to the lumbar level, restoring some volitional control to the hindlimbs (6). Other studies in our lab are using the optic nerve to identify factors that promote long-distance axon regeneration in the CNS. A combination of treatments that activate the intrinsic growth state of retinal ganglion cells, the projection neurons of the eye, enables some of these cells to regenerate injured axons all the way from the eye to the appropriate nuclei in the brain (7). Preventing the accumulation of zinc in synapses after nerve injury represents another way to promote optic nerve regeneration (8). In sum, studies from our lab and many others point to novel ways to improve outcome after CNS damage.

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