SPINAL CORD INJURY

Environmental enrichment increases neuroplasticity and recovery after SCIHutson et al. *Sci. Transl. Med.* **11**, eaaw2064 (2019)

After spinal cord injury (SCI), axons in the central nervous system of adult mammals do not spontaneously regenerate, leading to permanent neurological impairments. In patients with SCI, rehabilitation interventions such as locomotor training can improve the recovery of sensorimotor functions, notably by promoting neuroplasticity. Research efforts are currently underway to increase our understanding of activity-induced neuronal plasticity and optimize the effectiveness of rehabilitation. A new study shows that housing mice in environmental enrichment (EE) conditions before SCI increases the activity of dorsal root ganglion (DRG) neurons, leading to enhanced neuronal regeneration and functional recovery after SCI. The study also identifies a drug that mimics the effects of EE, opening new therapeutic avenues for neurological recovery after SCI.

“I was looking for robust physiological mechanisms that could stimulate the regeneration of sensory neurons after peripheral and spinal cord injury,” explains lead investigator Simone Di Giovanni from Imperial College London. Sensory DRG neurons are located at the interface between the peripheral and central nervous system and convey information from the periphery to the spinal cord to modulate motor input. Previous work in mouse has shown that DRG sensory feedback is essential for circuit reorganization after SCI and that sensory axon regeneration promotes functional recovery after SCI. Inducing a ‘conditioning’ injury before inducing a second lesion can prime DRG neurons for enhanced regeneration, but this approach cannot be translated to the clinics. “These neurons convey sensory information from the environment and lie at the crossroads between the world around us and the nervous system,” says Di Giovanni. “I thought: what would happen if we enrich sensory stimuli around mice with EE, would it promote plasticity and sensory axon regeneration?”

Mice were housed in EE — housing in larger cage, with increased number of mice, previously unidentified objects, and increased nesting material — or in standard housing (SH) for 1, 3, 6, 10, or 35 days before DRGs were isolated and cultured in a growth-permissive substrate for 12 h. Quantitative imaging showed that

Mice running on the exercise wheel. Credit: Douglas Sacha/Moment/Getty

EE exposure for at least 10 days enhanced neuronal regeneration, even when the mice were returned to SH for up to 5 weeks after EE. The positive response was however abolished when actinomycin-D was added to the culture, indicating that the long-lasting effects of EE on neuronal regeneration are mediated by transcriptional events. Next, mice were exposed to EE or SH for 10 days before receiving a thoracic dorsal hemisection. Analysis 5 weeks after the injury revealed that EE enhanced regeneration of sensory axons in the dorsal columns, confirming the effects of EE *in vivo*.

To identify the mechanisms involved in EE-dependent regeneration, RNA-seq was performed on DRG neurons isolated from EE and SH mice. Gene expression analysis revealed that EE modulates the expression of genes associated with ion channels, neuronal activity, Ca^{2+} signalling, energy metabolism, and neuronal projection. A chemogenetics approach was then used to inhibit or enhance neuronal activity of DRG neurons in mice exposed to a sciatic nerve crush after housing in SH or EE. Neuronal activation through Ca^{2+} release from intracellular stores enhanced axon regeneration in SH mice whereas neuronal inactivation attenuated axon regeneration of EE mice, highlighting the role of neuronal activity and Ca^{2+} signalling in mediating the effect of EE on DRG neurons.

Reasoning that epigenetic modifications could explain the enduring effects of EE on transcriptional and neuronal

activity, the investigators compared histone modifications in DRG neurons from mice housed in EE and SH. They found that EE exposure increased histone acetylation of H3K27 and H4K8 and identified CREB-binding protein (Cbp), a lysine acetyltransferase that has been previously involved in activity-dependent neuroplasticity, as the mediator of this EE-induced epigenetic reprogramming. Pharmacological activation of Cbp with CSP-TTK21 increased H4K8 acetylation and regeneration in DRG neurons *in vitro*, therefore recapitulating the effects observed with EE.

To test the effects of CSP-TTK21 *in vivo*, two rodent models of SCI were used: in mice with midthoracic dorsal hemisection, CSP-TTK21 increased sensory axon regeneration and the recovery of sensorimotor functions compared with control treatment and in adult rats with midthoracic spinal cord contusion—a more clinically relevant model—CSP-TTK21 significantly improved locomotor performance.

“In summary, we found a drug that mimics the regenerative effect of increased activity by environmental enrichment, opening a realistic pathway for clinical evaluations,” says Di Giovanni. The team is planning to investigate whether adding the drug to neurorehabilitation and/or electrical stimulation approaches increases plasticity and functional recovery after SCI compared with rehabilitation alone. These studies will be attempted in rat models of SCI, and the team is also considering using non-human primates.

The study also supports that the lifestyle of the patient might influence recovery after injury. “If humans lead active lifestyles, this might prime them for better recovery after injury, regardless of the drug or treatment they undergo after SCI,” says Di Giovanni, adding that it could be also interesting to test whether exposing injured patients to a variety of environmental stimuli and enriched sensory and social settings promotes plasticity and neurological recovery. “Being in a lonely hospital room resting the whole day is probably not a good thing,” he concludes.

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