Reversing a block on nerve growth

Spinal cord injury (SCI) can damage the axons of spinal nerve cells, preventing communication and resulting in paralysis that can affect movement as well as bodily functions such as urination. After SCI, axon regeneration is inhibited, hindering recovery. Research has shown that this inhibition is mediated by compounds called chondroitin sulphate proteoglycans (CSPGs), which block axon growth by interacting with a receptor called protein tyrosine phosphatase sigma (PTP σ). Under the direction of Jerry Silver (Case Western Reserve University School of Medicine, Cleveland, OH), scientists have been working to understand this block in hopes of learning how to circumvent it in order to rescue axon growth and improve functional recovery after SCI. In a paper published recently in *Nature*, they reported success in removing the CSPG–PTP σ block, restoring locomotor and bladder function in rats that had suffered contusive SCI (doi:10.1038/nature13974; published online 3 December). The key is a drug called intracellular sigma peptide (ISP), which

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binds PTP σ and relieves CSPG-mediated inhibition of neuronal axon extension.

Rats with SCI were given subcutaneous injections of ISP or of a placebo daily for 7 weeks beginning the day after injury. Several weeks later, rats treated with ISP showed significant improvements in bladder function or in movement. Untreated rats with SCI had less frequent bladder voiding and greater void volume than uninjured rats, but treatment with ISP increased bladder voiding frequency and decreased void volume. Bladder function was more closely analyzed in 15 rats treated with ISP, 10 of which showed evidence of reconnection of

bladder functional circuitry. Thirty percent of rats with SCI treated with ISP showed improvements in locomotion, suggestive of recovery of sensorimotor coordination and balance. In total, 21 of 26 rats treated with ISP recovered at least some locomotor or bladder function.

Further analysis showed that the improvements were related to increases in serotonin levels. Serotonin is a neurotransmitter that enables communication among nerve cells. Axon growth induced by ISP flooded the surrounding tissue with serotonin, which amplified the signals being carried by intact nerves in the area. “If you have lots of extra serotonin in the spinal cord, those few nerve connections that are just a whisper will become a roar,” Silver told NPR’s Jon Hamilton, “and you can get function back really nicely.”

Modulation of PTP σ may offer a new therapeutic strategy for enhancing functional recovery in humans with SCI and other disorders involving CSPG-mediated inhibition of axon regeneration.

Monica Harrington

PINPOINTING THE NEURONS THAT SIGNAL HUNGER IN MICE

Organisms must feed in order to meet their nutritional requirements. In humans, dysfunctional feeding behavior can take the form of destructive eating disorders including anorexia, bulimia, overeating and addiction. Feeding behavior comprises discrete elements that include motivation (or hunger) and consumption. Understanding the neurological pathways that underlie these elements could provide mechanistic insight into the causes of eating disorders, but identifying the neural processes associated with hunger and consumption has proven challenging. As global research initiatives have encouraged the development of new technologies to study the brain, advanced biological imaging techniques have become more widely available. Scientists led by Garret Stuber (University of North Carolina at Chapel Hill) recently applied innovative bioimaging technology to identify specific neurons that are activated in the brains of mice in conjunction with hunger and with consumption. The discovery adds to our knowledge about the brain’s involvement in feeding behavior and might lead to more effective treatment strategies for eating disorders. The findings were presented at Neuroscience 2014, the annual meeting of the Society for Neuroscience (15–19 November 2014; Washington, DC).

“The area of the brain we focused on—the lateral hypothalamus—is known to be involved in elements of eating, including hunger and consumption. Until now, however, we didn’t know which particular cells within that area of the brain contribute to each of those behaviors,” said Stuber in a press release.

To identify the neurons associated with hunger and consumption, Stuber and his colleagues used tiny visual probes called microendoscopes implanted directly into the lateral hypothalamus in mice. The microendoscopes were coupled with miniature, very-high-resolution fluorescence microscopes, enabling the researchers to observe individual neurons labeled with fluorescent proteins. The mice were given several behavioral tests in which they had to expend effort to obtain food, and their neural activity patterns were recorded. The researchers then looked for changes in neural activity patterns that correlated with behavioral demands.

Stuber’s group discovered that specific groups of neurons in the lateral hypothalamus became activated when the mice were working to gain access to food (reflecting the motivation or hunger element of feeding behavior). Different neurons were activated during food consumption. The findings suggest that dysfunction or alteration of specific neurons in the lateral hypothalamus might contribute to the development of eating disorders and that regulating the activity of those neurons might form the basis for new ways of treating them.

Monica Harrington