SPINAL CORD INJURY

Plasticity provides an opportunity for rehabilitation

Effective treatments for spinal cord injury (SCI) are sorely needed, as prognosis after injury is seldom positive—patients with SCI are usually left with profound disabilities. Regaining lost functions, such as conscious control of body parts, is the holy grail of current SCI research, but progress in this field remains slow. A study on the use of specific rehabilitation in combination with targeted spinal cord plasticity, however, demonstrates that marked improvements in motor function can be achieved.

Research into SCI is still at the experimental stage, which no doubt reflects the fact that SCI is a complex and difficult condition to treat. The endogenous processes that prevent the injured spinal cord from healing are still not fully understood. What is known is that after injury glial scar tissue forms around the injury site in the spinal cord, thereby inhibiting axon regeneration and functional recovery of the 'lost' neuronal connections. Chondroitin sulfate proteoglycans (CSPGs), which are constituents of perineuronal nets and have been shown to turn off plasticity at the end of the developmental critical periods, are also located in the glial scar. At this location CSPGs have been shown to be largely responsible for this inhibitory effect on axon regeneration, and counteraction of this inhibition is currently the focus of a number of research groups.

James Fawcett and colleagues at the University of Cambridge, UK have previously shown, in a rodent model of SCI, that digestion of these CSPGs increases axon regeneration in the glial scar, and that CSPG digestion is linked to a marked improvement in motor behavior. Spinal cord plasticity is believed to be involved in these improvements. The rodent spinal cord, however, is wired differently from that of humans, and it is not immediately obvious from these experiments whether the anti-CSPG treatment would work in humans with spinal cord injury. In an attempt to answer

this question, Fawcett and colleagues have now focussed their research interests on spinal cord regeneration in the corticospinal tract (CST). The CST is a critical spinal pathway in humans, and is essential for controlling fine paw movements in rodents. Severing the CST in rats and treating these animals with chondroitinase ABC (an enzyme that digests CSPGs) evokes 'plasticity' in the form of profuse axon sprouting, but no appreciable recovery of forepaw function. "We reasoned that random CST connections [after injury] probably don't help very much," explains Fawcett. "During development an initial period of exuberant [connectivity] is refined by behaviorally driven activity." By recapitulating this process in the injured spinal cord, Fawcett and colleagues hoped to demonstrate that lost locomotor behavior could be regained.

To achieve this aim, rodents with severed CSTs were given chondroitinase ABC in conjunction with behavior-specific rehabilitation. "The combination of plasticity-inducing chondroitinase with rehabilitation worked really well," notes Fawcett. Training the animals to perform a skilled paw-reaching procedure—picking up seeds—for an hour a day led to a 70% recovery of skilled paw reaching in rats given chondroitinase ABC. By contrast, neither chondroitinase treatment nor rehabilitation worked alone, and animals receiving these therapies separately did not regain skilled paw-reaching abilities.

The authors also assessed whether the improvement in forepaw function was attributable to the specific behavior being performed or to a general increase in activity. Animals with CST lesions that were treated with chondroitinase and had general environment enrichment rehabilitation—climbing and running—had improved general locomotor function. Strikingly, however, recovery of forepaw function was not evident; in fact, as Fawcett notes "...this form of rehabilitation actually made rats worse at skilled reaching".

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These findings have profound implications for how neurorehabilitation is conducted in general. "At present, patients after stroke [or] spinal cord injury ... struggle hard with rehabilitation, often with rather modest results... what we show is that when you reactivate plasticity, even rather locally in the spinal cord as we did, it is much easier for rehabilitation to effect changes in CNS circuitry," explains Fawcett. In the future, Fawcett envisages that plasticity treatments could be used to open up a time window during which rehabilitation could be most effective in providing functional motor recovery. Effective SCI therapies that allow motor function to be regained would be a welcome achievement, given that patients with quadriplegia judge that regaining control over their arms and hands would increase their quality of life the most.

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