NASCIC
SCI RESEARCH
ADVOCACY COURSE

Module 9 – Neuroplasticity

Harnessing Neuroplasticity for Functional Recovery

Neuroplasticity is the key to functional recovery and in the future will be essential when regeneration promoting treatments are available.

It is noteworthy that most treatments originally explored for promoting regeneration of injured spinal cord neurons also promote neuroplasticity, and many beneficial effects that were reported are likely due to plasticity, rather than axon regeneration.

Research strategies that leverage plasticity for functional gain after SCI have included but are not limited to: 1) rehabilitative training, 2) delivery of growth factors, and 3) neutralizing the growth the inhibitory environment of the CNS including myelin associated growth inhibitors, the scar formed at the injury site, and the perineuronal net.

1) Rehabilitative training and physical therapy are essential to improve outcomes after SCI. Intensive training in the months after a SCI drives plasticity in an activity dependent manner that can lead to lasting improvements in functional abilities. The extent that functional abilities can be improved with rehabilitation is dependent on the amount of tissue spared from injury. Training specific activity of injured and spared neurons plays an important role in rewiring the nervous system in a functionally meaningful way to enable motor recovery.

An example of how important plasticity within the spinal cord can be to functional recovery comes from historic experiments that used cats with completely transected spinal cords. The spinal cords of cats were cut completely and then the cats performed intensive forced locomotor training on a treadmill. This training induced plasticity within the spinal cord that enabled the animals to perform weight supported stepping on a treadmill, despite lacking communication with the brain. The locomotor abilities were driven entirely by circuitry within the spinal cord that coordinate rhythmic walking behaviors of the legs called central pattern generators.

Central pattern generators are a grouping of neurons that serve a specialized purpose to coordinate rhythmic locomotor movements of the legs. Much of the ability to coordinate walking behaviors occurs automatically within the spinal cord. Plasticity within central pattern generators within the spinal cord can be strengthened to better coordinate walking behaviors independent of the brain. In the previous example, the cats were unable to voluntarily control

their legs because no signal was coming to and from the brain. These experiments demonstrate that circuitry within the spinal cord can be trained and learn through neuroplasticity.

The most common method to facilitate adaption in the nervous system is physical therapy and activity-based therapy. Activity-based therapy (or ABT) consists of movements that occur in your daily life using large groups of muscles working together throughout the body. ABT includes load-bearing exercises and task-specific movements that are performed at a high intensity with high repetitions and frequency. Re-enforcing neural circuits through repetitive activity can strengthen the connectivity between neurons and result in improvements in functions through the trained task.

2) The delivery of growth-promoting agents such as growth factors aim to induce plasticity with a goal of improving function. Historic experiments delivered neurotrophic factors which can induce neuronal sprouting and axon growth of spared axons as well as in injured neurons. Axon growth caused by the delivery of neurotrophic factors was reported to improve motor abilities in animal models, however, concern for off-target effects of axon growth have emerged. A big challenge has also been where the factors should be delivered and when. For example some growth factors attract axons down a concentration gradient towards the highest concentration where the proteins are being released.

Further, delivery of neurotrophic factors causes neuronal hyperexcitability and growth of pain fibers that may form aberrant connections with neurons they should not be connected to. While the role of neurotrophic factors on inducing pain is still being investigated, the threat of exacerbating neuropathic pain has forced the re-consideration for using neurotrophic factors as clinically viable treatments for SCI.

It is likely that many approaches that aim to induce axon growth and plasticity in an unspecific manner may induce similar growth effects on axons involved in pain or other maladaptive plasticity occurring after SCI. Decoupling the unwanted from desirable effects caused from promoting unspecific plasticity remains a challenge. Driving meaningful and task-specific plasticity may require coupling growth-related strategies with intensive rehabilitative training to direct aberrant plasticity into meaningful connections.

3) Finally, neurons in the brain and spinal cord face a growth inhibitory environment unlike in the peripheral nerves where regeneration is possible. Growth inhibition is created by many inhibitory molecules that affect regeneration and plasticity. Notably, myelin associated inhibitors found on the cells that wrap around and insulate axons (i.e., oligodendrocytes), chondroitin sulfate proteoglycans (CSPGs) found in the scar around the lesion, and the perineural net which is a matrix surrounding neurons, have been identified as potent growth inhibitors that limit plasticity and regeneration. Early after an SCI the perineural net weakens and allows for a critical window whereby structural plasticity in the gray matter can readily occur. The perineural net reforms in the months after an SCI which can interfere with driving structural plasticity.

Digesting CSPGs has been found to weaken the peri-neural net and re-open a window for driving enhanced structural plasticity. Interfering with the inhibitory nature of the perineural net remains a focus of ongoing research strategies. Similarly, neutralizing the effect of myelin associated inhibitors has been reported to result in axonal sprouting and recovery, which has given rise to various clinical trials.