

Public Abstract

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Title:Neuronal Changes Underlying Altered Biophysical Properties of Reticulospinal Neurons Following Spinal Cord Injury in the Lamprey

Following a severe spinal cord injury (SCI), the descending axons of reticulospinal (RS) neurons are damaged, resulting in paralysis below the site of the injury. For higher vertebrates, including humans, RS neurons are unable to regenerate their axons through the spinal lesion, resulting in permanent loss of voluntary motor control below the site of the injury.

Conversely, some lower vertebrates, such as the lamprey, possess the remarkable ability to restore locomotor behavior below the site of the injury within weeks. This is possible because the central nervous system of the lamprey is a permissive environment for regeneration, and the injured RS neurons undergo dramatic changes that are collectively referred to as the "injury phenotype"

The present study investigated several mechanisms that might contribute to the injury phenotype. First, for injured lamprey RS neurons, a delayed membrane repolarization was activated at depolarizing potentials just below as well as above threshold, while for uninjured RS neurons the repolarization was mostly absent below threshold. Current and voltage clamp experiments were performed to characterize the current mediating the delayed repolarization, as well as to estimate the effective activation voltage of these channels for injured and uninjured RS neurons. Additionally, pharmacology experiments indicated that the delayed membrane repolarization was significantly reduced in the presence of voltage-gated potassium channel blockers, and thus following SCI, there might be an up-regulation of outward rectifying potassium channels for injured lamprey RS neurons to reduce excitability.

Second, for injured RS neurons, it appears that voltage-gated sodium channels are also up-regulated, but to a lesser degree than the voltage-gated potassium channels. This was tested by applying low doses of TTX to uninjured RS neurons to partially block voltage-gated sodium channels to experimentally simulate a differential increase in conductance for voltage-gated potassium channels. Applying low doses of TTX converted uninjured RS neurons from displaying normal biophysical properties, to displaying aspects of the "injury phenotype" such as altered firing properties and membrane resonance.

Together, these possible neuronal changes account for many components of the "injury phenotype" seen in individual action potentials, as well as in repetitive firing. Understanding the neuronal changes that mediate the injury phenotype is critical, because these changes presumably create a cellular environment supportive for robust axonal regeneration. This and other knowledge will be critical for developing therapies to promote axonal regeneration and treat SCI in higher vertebrates, including hopefully one day, humans.