Abstract:

Primary sensory neurons of the dorsal root ganglia (DRG) regenerate their spinal cord axon if the peripheral nerve axon has previously been cut. This conditioning lesion confers axon growth competence to the neurons. However, the signal that is sensed by the cell upon peripheral lesion to initiate the regenerative response remains elusive. We show here that loss of electrical activity following peripheral deafferentiation is an important signal to trigger axon regrowth. We first verified that firing in sensory fibers, as recorded from dorsal roots in vivo, declined after peripheral lesioning but was not altered after central lesioning. We found that electrical activity strongly inhibited axon outgrowth in cultured adult sensory neurons. The inhibitory effect depended on the L-type voltage-gated Ca(2+) channel current and involved transcriptional changes. After a peripheral lesion, the L-type current was consistently diminished and the L-type pore-forming subunit, Ca(v)1.2, was downregulated. Genetic ablation of Ca(v)1.2 in the nervous system caused an increase in axon outgrowth from dissociated DRG neurons and enhanced peripheral nerve regeneration in vivo. Our data indicate that cessation of electrical activity after peripheral lesion contributes to the regenerative response observed upon conditioning and might be necessary to promote...
regeneration after central nervous system injury.