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SPINAL CORD INJURY

Clamping down on calpains to treat injury-induced spasticity

Following spinal cord injury (SCI), spasticity resulting from hyperexcitability of motor neurons is common. A recent study has shown that calpain-mediated cleavage of sodium channels in motor neurons contributes to this complication of SCI and provides evidence that pharmacological inhibition of a calpain could be a useful therapeutic strategy for such spasticity.

Upregulation of the persistent sodium current (I_{NaP}) underlies much of the increased excitability of motor neurons after SCI. To investigate the mechanisms that link SCI with I_{NaP}, the authors of the current study performed spinal cord lesion in rodents followed by immunohistochemistry of spinal cord samples. Compared with sham-operated rodents, SCI was associated with upregulation of the voltage-gated sodium channel $Na_v1.6$ in motor neurons.

Next, the authors carried out further analysis of $Na_v1.6$ expression using western blotting on the membrane fractions of rodent motor neurons. A Na_v-specific antibody revealed an ~250 kDa band consistent with full-length Na_v. Notably, although the intensity of the ~250 kDa band was unchanged by SCI, an ~120 kDa cleavage product was strongly upregulated.

In adult rat spinal cord homogenates, addition of calcium generated a similar ~120 kDa band, suggesting the involvement of a calcium-dependent protease, which the investigators posited could be a calpain. To test this hypothesis, they pretreated the spinal cord homogenates with MDL28170, a calpain inhibitor, and indeed saw no formation of an ~120 kDa band in response to calcium. Together, these findings suggest that calpains mediate the cleavage of $Na_v1.6$ following SCI.

To investigate how this mechanism might contribute to upregulation of I_{NaP}, the team performed patch clamp and voltage clamp recordings in neonatal rat motor neurons after SCI. Compared with vehicle treatment, intraperitoneal injections of MDL28170 for 8 days following SCI significantly reduced the formation of the ~120 kDa band on western blots and reduced the amplitude and the density of I_{NaP}. Moreover, calpains similarly increased I_{NaP} in HEK293 cells expressing $Na_v1.6$.

Finally, in adult rats with SCI, injection of MDL28170 daily for 10 days, beginning 30–60 days after injury, suppressed the cleavage of Na_v and significantly reduced muscle spasms relative to vehicle-treated SCI rats. Importantly, the beneficial effects of MDL28170 were maintained at 3 weeks after discontinuation of treatment.

The authors noted some residual upregulation of I_{NaP} after calpain inhibition with MDL28170, and they suggest that this could be due to mechanisms involving 5-HT receptors, which are known to be upregulated after SCI and to stimulate I_{NaP}.

This study suggests inhibition of calpains, even long after SCI, could have beneficial effects on subsequent spasticity.

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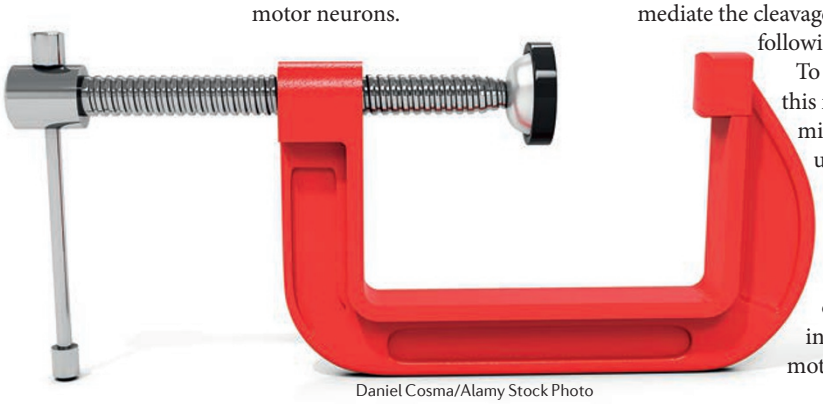

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