

Neuropathic Pain in SCI Patients Attributable to the Persistent Hyperexcitability of Human Primary Sensory Neurons

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Introduction:

Neuropathic pain (NP) develops in approximately 40% of patients following SCI. The pain can be localized above, at the level, or below the level of the SCI. Unfortunately, NP in SCI patients is largely refractory to the current standard medical therapies. Such drugs include antiepileptics, antidepressants and opioids. The failure of these treatments to adequately control the pain while causing continuing suffering in SCI patients, points to an alternative mechanism and contributor of NP in SCI patients. Recent studies using animal models in SCI have revealed that primary sensory neuronal hyperexcitability may be an important contributor. Whether this pathophysiology occurs in human primary sensory neurons after SCI has yet to be established using human models or samples. In this study, human dorsal root ganglia (DRG) or primary sensory neurons were obtained from several patients with and without SCI undergoing oncological spine surgery that necessitated sacrifice of spinal nerve roots as part of standard of care. By confirming if the sensory neurons are the main contributors of neuropathic pain in SCI patients, a more precise and evidence-based treatment approach can be established that targets the DRG to provide patients pain relief.

Methods:

The human DRG (sensory neurons) were extracted from patients undergoing oncological spine surgery who required their spinal nerve roots to be sacrificed as part of standard of care. The clinical data was obtained through retrospective design or collected at time of study enrollment.

Dissected neurons from surrounding neural tissue were maintained in cell-culture for 24 to 72 hours and then examined using whole-cell patch clamp technique (figure 1.)

Electrophysiological measures of excitability of the primary sensory neurons were quantified and compared between surgical patients with and without prior SCI.

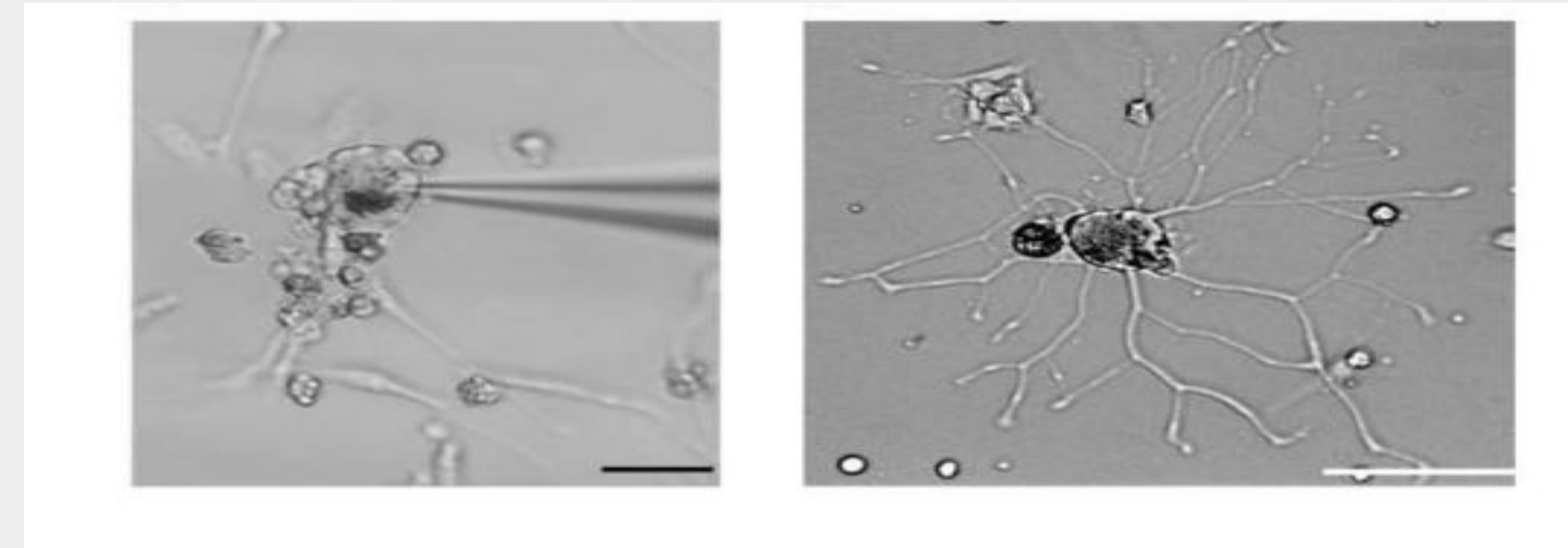


Figure 1- Whole-cell patch clamp technique with presence of human DRG neuron and satellite glial cells².

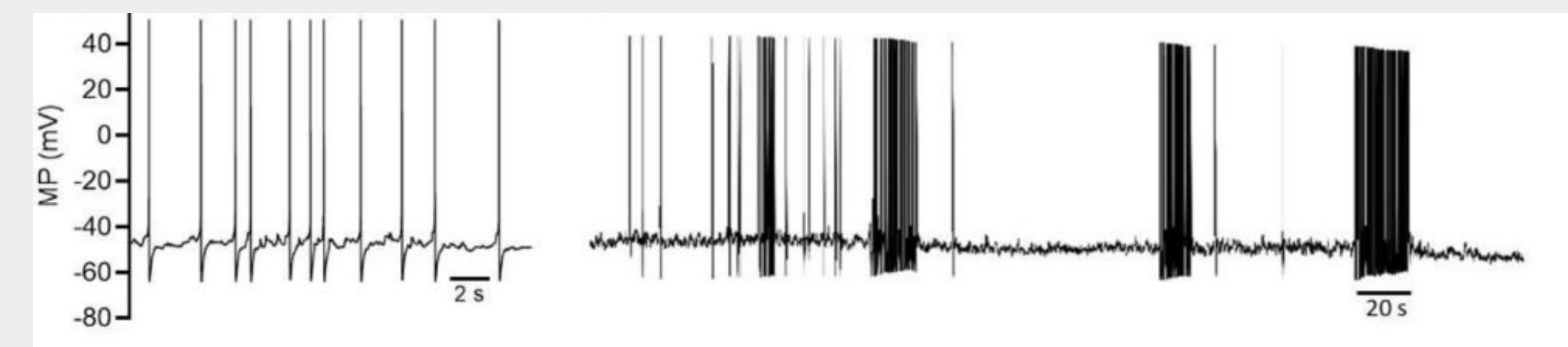


Figure 2 - Spontaneous activity (SA) recorded from dissociated human DRG neuron with left graph showing the low-frequency with irregular discharge pattern. The recording on the right shows a sampled neuron demonstrating bursting pattern during SA.²

Results:

Electrophysiological recordings from 26 dissociated human sensory neurons (DRG) were obtained from 5 patients. 8 sensory neurons were studied from a single patient with a prior T10 ASIA D spinal cord injury that occurred greater than 6 months prior. 18 sensory neurons were extracted from the other 4 patients without any prior history of SCI.

Compared to the data collected from the patients without SCI, human sensory neurons from the patient with the SCI were significantly more excitable (Step rheobase: 0.250 ± 50 vs 1140 ± 200 nA $p < 0.001$, Threshold potential: -15.5 ± 2.5 vs 4.7 ± 3.4 mV $p < 0.05$).

Discussion:

We provide the first evidence of persistent hyperexcitability in human primary sensory neurons (DRG) after spinal cord injury. Compared to the data collected from the patients without SCI, human sensory neurons from the patient with the SCI were significantly more excitable. These findings support the hypothesis that the peripheral nervous system, in addition to the central nervous system, may be responsible for the development of SCI-related NP. It has been shown in literature that the DRG or primary sensory neurons maintain a hyperexcitable state with spontaneous activity (SA), contributing to NP in SCI. However, this has only been proven using animal models. According to a recently published report, by scrutinizing the critical electrophysiological alterations underlying SA, the importance of this step was established as unexpected differences in pain-related features of human and rodent DRG neurons were seen. For instance, inactivation of tetrodotoxin-resistant currents is almost absent in human DRG neurons, leading to their potential sustained hyperexcitability. This divergence across mammalian species may explain the failure to translate preclinical treatments to clinical application, as most information about neuropathic pain has come from rodents.²

It is important to note that using a human model for the first time to understand the important contributing pathophysiology of NP may provide the opportunity to help create the most evidence-based treatment. In this case, confirming the DRG involvement via human tissue sampling may support the use of targeted interventional treatments such as a DRG stimulator at the localized level of NP. The use of a DRG stimulator could be one of the first promising treatment options utilized based on a human evidenced model of NP. Such an unparalleled finding of hyperexcitability in human primary sensory neurons can help to better translate preclinical treatments into clinical application as data related to NP isn't extracted from rodents this time.

References:

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2. . North RY, Odem MA, Yan Li, Claudio E Tatsui, R. Cassidy, P. Dougherty, E. Walters. Electrophysiological Alterations Driving Pain-Associated Spontaneous Activity in Human Sensory Neuron Somata Parallel Alterations Described in Spontaneously Active Rodent Nociceptors. The Journal of Pain 23(8):1343-1357, 2022. PMID: 35292377.