(onlinelibrary.wiley.com) DOI: 10.1111/ner.12800

LETTER TO THE EDITOR

Mechanisms of Dorsal Root Ganglion Stimulation in Pain Suppression: Time to Consider Alternative Mechanisms of Action?

To the Editor:

We read with interest the recent study on a computational modeling analysis of dorsal root ganglion stimulation by Kent et al. (1). We applaud the authors for undertaking a challenging study that has provided further insight into the mechanisms that may be responsible for pain relief from dorsal root ganglion (DRG) stimulation therapy. However, we feel certain neurophysiological aspects of DRG stimulation have not been fully addressed in the present effort, and further discussion may be helpful.

The authors followed the conventional paradigm of applying neuromodulation for chronic neuropathic pain by studying a biophysical model of a C-type primary sensory neuron with intrinsic afferent axonal activity or ectopic firing from the soma. Main findings of the study include increased T-junction filtering of afferent signals and a suppression of somatic ectopic firing by hyperporalizing the junction and soma respectively, in response to stimulation. These findings are consistent with the working hypotheses on the mechanisms of DRG stimulation and add important information on the potentially required amplitude, polarity, and location of electrodes required for pain relief from DRG stimulation.

From a larger perspective, we believe the most under-discussed aspect of DRG stimulation is that it actually for the first time enables targeting the route that carries all nociception from the periphery to the ventral and lateral spinothalamic tracts and subsequently to the brain, which is in sharp contrast with conventional dorsal horn spinal cord stimulation, which physiologically allows access to tracts carrying perception of proprioception, vibration, and touch. The therapeutic effect of conventional dorsal horn stimulation has been attributed to neuroplasticity associated with neuropathic pain conditions, as well as to an effect on mechanical hyperalgesia, and as such the focus of dorsal horn spinal cord stimulation has been mainly on chronic neuropathic pain conditions (2). In contrast, the DRG, as a communication station for all nociceptive signaling from the periphery, plays an instrumental role in both neuropathic and nociceptive pain conditions (2). Consistently, it was recently demonstrated in an animal model that depolarization of GABAergic DRG neurons significantly reduced transduction of both chronic neuropathic and nociceptive pain by increased T-junction filtering (3). Along these lines, it would be interesting to study the effects of DRG stimulation in both models of nociceptive and neuropathic pain. Clinical studies highlight the effectiveness of DRG stimulation in pain conditions that are at the least mixed neuropathic/nociceptive in nature (4).

In the study by Du et al. (3). GABA depolarized the majority of DRG sensory neuron somata, which is likely similar to the effects of electrically stimulating the DRG at high amplitudes such as in the study by Kent et al., since the somata of A-neurons have a lower threshold than the somata of C-neurons. Importantly, the ectopic firing within the DRG in axotomized neurons has mostly been described in A-neurons (2), and not in C-neurons. Additionally, Aβ-fibers may possess a significant amount of nociceptive neurons (5), and have been implicated in the development of mechanical allodynia (2). Along these lines, it would be interesting to learn the effects of DRG stimulation on all neurons in the DRG and not just C-neurons. The effects of DRG stimulation on A-neurons may account for the effectiveness of low amplitude DRG stimulation in the clinical setting vs. the high amplitude calculated in the present simulation study.

In conclusion, we feel a more comprehensive experimental and clinical evaluation of the mechanisms of relief from chronic pain in response to DRG stimulation is warranted. The potential inclusion of the lateral and ventral spinothalamic tracts with DRG stimulation constitutes a fundamental difference vs. conventional spinal cord stimulation and calls for research on the effect of DRG stimulation on nociceptive pain. Additionally, the role of A-neurons in pain relief from DRG stimulation requires additional attention, as it may explain the effectiveness of low amplitude DRG-stimulation in the clinical situation. We encourage the authors to follow up with additional studies on the role of other DRG neurons and types of pain to further unravel the mechanisms responsible for the therapeutic clinical effect of DRG stimulation.

Kenneth B. Chapman, MD*[†‡] Noud van Helmond, MD*[§]

**Spine and Pain Institute of New York, New York, NY, USA; [†]Department of Anesthesiology, New York University Langone Medical Center, New York, NY, USA; [‡]Northwell Health, New York, NY; and [§]Department of Anesthesiology, Thomas Jefferson University Hospital, Philadelphia, PA, USA*

Address correspondence to: Kenneth B. Chapman, MD, Spine and Pain Institute of New York, New York, NY, USA. Email: chapmanken@spinepainny.com

For more information on author guidelines, an explanation of our peer review process, and conflict of interest informed consent policies, please go to http://www.wiley.com/WileyCDA/Section/id-301854.html

Source(s) of financial support: The authors have nothing to disclose.

REFERENCES

1. Kent AR, Min X, Hogan QH, Kramer JM. Mechanisms of Dorsal Root Ganglion Stimulation in Pain Suppression: A Computational Modeling Analysis. *Neuromodulation* 2018;21:234–246.
2. Deer TR, Krames E, Mekhail N et al. The appropriate use of neurostimulation: new and evolving neurostimulation therapies and applicable treatment for chronic pain and selected disease states. Neuromodulation Appropriateness Consensus Committee. *Neuromodulation* 2014;17:599–615; discussion 615.
3. Du X, Hao H, Yang Y et al. Local GABAergic signaling within sensory ganglia controls peripheral nociceptive transmission. *J Clin Invest* 2017;127:1741–1756.
4. Liem L, Russo M, Huygen FJ et al. One-year outcomes of spinal cord stimulation of the dorsal root ganglion in the treatment of chronic neuropathic pain. *Neuromodulation* 2015;18:41–48; discussion 48–49.
5. Djouhri L, Lawson SN. Abeta-fiber nociceptive primary afferent neurons: a review of incidence and properties in relation to other afferent A-fiber neurons in mammals. *Brain Res Brain Res Rev* 2004;46:131–145.

