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EDITORIAL COMMENT

Neuromodulation of Dorsal Root Ganglia

Chronic Pain Mitigation and Autonomic Implications*

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Bioelectric modulation of specific peripheral nerves or sites of the central nervous system is an emerging and targeted therapeutic approach that is being applied across a wide range of pathologies ranging from cardiac disease, chronic pain, and gastrointestinal disorders to epilepsy (1). In contrast to ablations, bioelectric interventions are scalable, reversible, and available on demand. The efficacy of bioelectric interventions is critically dependent on understanding the underlying pathology, identifying the nexus point within the neural network to which stimulation is delivered, form/fit for the neural interface, and optimizing the stimulus protocol, among other factors. Failure to consider each of the parameters is the reason why promising preclinical studies have failed to translate into the clinical arena.

In this issue of *JACC: Basic to Translational Science*, Sverrisdottir et al. (2) present intriguing data with respect to short- and long-term autonomic effects of lumbar dorsal root ganglia (DRG) stimulation, a therapy delivered chronically to patients with severe focal, refractory neuropathic pain. Although neuromodulation for visceral pain is a well-recognized therapy (3), the associated cardiovascular effects remain poorly understood. Data presented by Sverrisdottir el al. (2) show a short-term decrease in muscle sympathetic nerve activity during the on-phase stimulation of DRG, with minimal change in hemodynamics, and a sustained reduction in blood pressure during the 2-year follow-up, albeit with efficacy restricted to left-sided DRG in the 14-patient cohort. No sex differences were noted in efficacy. Only 1 frequency was evaluated—20 Hz—and critical aspects of pulse width and stimulus intensity were restricted to those determined by pain management. Nevertheless, an initial proof of concept is provided for DRG stimulation to treat autonomic disorders.

Autonomic control of cardiovascular function is dependent on the dynamic interplay between the peripheral and central neural networks (4). These neural networks are capable of independent and interdependent reflex control of organ function within the heart and viscera in addition to modulation of peripheral blood flow distribution (4,5). Disruptions in organ function often lead to adverse effects in sensory transduction, and that alteration in afferent transduction is a primary driving force for adverse remodeling of cardiovascular control, including those leading to sympathoexcitation (4). Selective targeting of the aberrant sensory transduction, without producing masking of that pain, is the rationale for a therapeutic strategy to counteract both pain perception and the resulting alterations in autonomic reflex control.

Electrical stimulation, delivered to the immediate vicinity of DRG, modulates neural activity within adjacent axonal projections. The stimulation protocol used here will not penetrate to the ventral roots or elements of the spinal cord, including the dorsal horn and sympathetic pre-ganglionic soma contained within the intermediolateral cell column. However, such electrical stimulation will alter neural activity projecting in both directions. DRG-mediated alterations in orthodromic afferent activity will affect spinal neural networks, likely with a resulting stabilization/mitigation of intrasegmental and

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intersegmental sympathoexcitation, analogous to what has been shown with dorsal horn stimulation (4). DRG stimulation likewise evokes antidromic activity that has the potential to alter reflex processing within intrathoracic ganglia, including extracardiac and intrinsic cardiac ganglia (4), mediated in part by fibers of passage and via direct connections on peripheral soma of the autonomic ganglia. It should also be considered that DRG-mediated alterations in efferent and afferent projections to target organs can potentially alter the metabolic substrate of those tissues and thereby alter the primary sensory neurite transduction process (4). Future studies should consider each of these factors, both in terms of the short-term effects of DRG stimulation and the impact on neural network remodeling to the chronic stressor of pain or other disease processes that evoke chronic sympathoexcitation.

The stimulus protocol is a critical determinant of therapeutic efficacy. It should be appreciated that when a stimulus is delivered, the endogenous neural networks that receive inputs from that stimulus site will often respond to oppose that change. This concept can be viewed as "push-push back." Stimulation protocols that operate around the neural fulcrum—that point where afferent and efferent evoked effects are balanced—allow floating point control neural networks to move to new states where homeostatic control is maintained (5). The stimulation protocol used in the paper by Sverrisdottir et al. (2) was 20 Hz, with a pulse width from 190 to 400 ms depending on the patient. Future studies should consider changes in the lower frequency ranges (e.g., 10 to 50 Hz) and explore the potential for much higher frequencies (e.g., kilohertz frequency alternating current [KFAC]) (6) and hybrid waveforms that combine KHFAC with direct current for control of onset response. Although continuous DRG stimulation was used in the treatment phase for this study, intermittent DRG stimulation may also prove effective and help to extend battery life. Such duty cycle stimulation takes advantage of the memory function associated with the neuromodulation of autonomic neural circuits (4).

In summary, chronic pain is a debilitating condition that affects multiple indices of morbidity, including adverse cardiovascular events. DRG stimulation provides a promising new therapeutic approach to concurrently deal with pain while, at the same time, counteracting the adverse consequence of such pain, including but not limited to chronic sympathoexcitation. As compared to transcutaneous stimulation or dorsal column stimulation, neuromodulation energy can be focused to the primary area of insult. DRG stimulation may likewise find utility in other diseases with underlying sympathoexcitation such as hypertension, ischemic heart disease, and heart failure (4).

AUTHOR RELATIONSHIP WITH INDUSTRY

Dr. Ardell has reported that he has no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Horn CC, Ardell JL, Fisher LE. Electroceutical targeting of the autonomic nervous system. Physiology 2019;34:150–62.

2. Sverrisdottir YB, Martin SC, Hadjipavlou G, et al. Human dorsal root ganglion stimulation reduces sympathetic outflow and long-term blood pressure. J Am Coll Cardiol Basic Trans Science 2020;5:973–85.

3. Foreman RD, Garrett KM, Blair RW. Mechanisms of cardiac pain. Compr Physiol 2015;5:929–60.

4. Ardell JL, Andresen MC, Armour JA, et al. Translational neurocardiology: preclinical models and cardioneural integrative aspects. J Physiol 2016;594:3877–909.

5. Kember G, Ardell JL, Shivkumar K, Armour JA. Recurrent myocardial infarction: mechanisms of free-floating adaptation and autonomic derangement in networked cardiac neural control. PLoS One 2017;12:e0180194.

6. Kilgore KL, Bhadra N. Reversible nerve conduction block using kilohertz frequency alternating current. Neuromodulation 2014;17:242–54.

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