Received: September 25, 2012 Revised: November 8, 2013 Accepted: February 4, 2014

(onlinelibrary.wiley.com) DOI: 10.1111/ner.12247

The Dorsal Root Ganglion in Chronic Pain and as a Target for Neuromodulation: A Review

Elliot S. Krames, MD*

Background: In the not-too-distant past, the dorsal root ganglion (DRG) was portrayed as a passive neural structure without involvement in the development or maintenance of chronic neuropathic pain (NP). The DRG was thought of as a structure that merely "supported" physiologic communication between the peripheral nervous system (PNS) and the central nervous system (CNS). Newer scientific information regarding the anatomic and physiologic changes that occur within the DRG as a result of environmental pressures has dispelled this concept and suggests that the DRG is an active participant in the development of NP. This new information, along with new clinical data showing that stimulation of the DRG reduces intensity of pain, suggests that the DRG can be a robust target for neuromodulation therapies.

Methods: A review of the anatomical and physiological literature regarding the role of the DRG in the development of NP was performed utilizing SciBase, PubMed, and Google Scholar. The information gathered was used to lay an anatomic and physiologic foundation for establishing the DRG as a relevant target for neuromodulation therapies and to formulate a hypothesis as to how electrical stimulation of the DRG might reverse the process and perception of NP.

Conclusions: The DRG is an active participant in the development of NP. DRG stimulation has multiple effects on the abnormal changes that occur within the DRG as a result of peripheral afferent fiber injury. The sum total of these stimulation effects is to stabilize and decrease hyperexcitability of DRG neurons and thereby decrease NP.

Keywords: Dorsal root ganglion, electrical stimulation, mechanisms of action, neuropathic pain, pathophysiology

Conflict of Interest: Dr. Krames is a paid consultant for Spinal Modulation, Inc.

INTRODUCTION

There are numerous targets for neuromodulation therapies used today, including the brain, the spinal cord, the cardiovascular system, the peripheral neuromuscular system, the peripheral nervous system (PNS), the gastroesophageal system, and the sacral nerves. Various intraspinal structures are often targeted in both specific and non-specific ways by the application of electrical fields to modulate their function as a greater part of what is referred to as spinal cord stimulation. This review focuses on the dorsal root ganglion (DRG) and the extent to which this structure is involved in the development of chronic neuropathic pain (NP). Furthermore, the DRG is highly accessible to clinical interventions for the control of pain (1–3) and is a robust target for neuromodulation therapy (i.e., electrical stimulation) for the relief of NP (4–6).

ANATOMY

Structure and Function

The DRG contains the cell bodies of the primary sensory neurons responsible for transducing and modulating sensory information and transmitting it to the spinal cord. There are several types of DRG neurons, classified by the size of the cell bodies and their function. Type A DRG neurons are large and are responsible for touch, vibration, and proprioception; type B neurons are small in size and are responsible for nociception. Histological studies estimate that the number of small neurons (type B) exceeds that of large neurons (type A) at a ratio of 71:29 (7).

The cell bodies, previously thought to be only metabolic storage "helpers" to peripheral processes, are now known to participate in the signaling process by sensing certain molecules and manufacturing other molecules that modulate these processes (8). Because of its important roles in the modulation of sensory processing, including nociceptive pain, and the development of NP, along with its anatomic accessibility to clinical intervention (2,3), the DRG is an excellent clinical target for pain control. The DRG can be accessed both from outside the neural foramen into the epidural space and from the epidural space to the outside through the neural foramen (Fig. 1). The DRG is a known clinical target for the delivery of anti-inflammatory steroids (10,11), for surgical ablation (ganglionectomy) (12), for radio-frequency ablation (13–15), for pulsed-radio frequency therapy (16), and also for neuromodulation therapy (4–6).

Pseudo-Unipolar Neurons and Axons

In humans, there are 31 right-and-left pairs of "mixed" spinal nerves carrying autonomic and sensorimotor information between

Address correspondence to: Elliot S. Krames, MD, 118 Broderick Street, San Francisco, CA 94117, USA. Email: krames118@gmail.com

* Pacific Pain Treatment Centers, San Francisco, California, USA

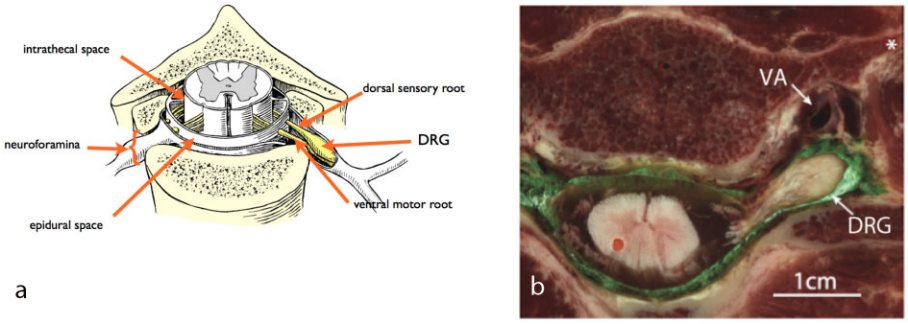

Figure 1. Anatomic relationships of the dorsal root ganglion (DRG) within the spinal canal. a. A cartoon of a section through the cervical intravertebral foramen showing the position of the DRG outside of the intervertebral neural foramen and its relationship to the intrathecal space, the neuroforamina, the epidural space, and the dorsal and ventral roots. Taken from the Internet with permission (http://www.csus.edu/indiv/m/mckeoughd/AanatomyRev/CNS/scXsect/scXsect.htm). b. Axial cryomicrotome section through the C5–6 intervertebral foramen in a human specimen; injected with green ink by an epidural approach before freezing. Notice that the dorsal root ganglion (DRG) lies outside the neural foramen, posterior to the vertebral artery (VA). Reprinted from Hogan (9), with permission from Lippincott Williams & Wilkins.

the spinal cord and the periphery. These spinal nerves, formed from dorsal afferent sensory axons that became the dorsal rootlets and ventral efferent motor axons that became the ventral rootlets, emerge from the intervertebral neural foramina between adjacent vertebral segments and between the superior and inferior pedicles. As the dorsal sensory root fibers travel laterally, their processes connect via a T-junction with their cell bodies, which make up the DRG. The DRG lies between the medial and lateral aspects of the pedicle within the neural foramen. This collection of pseudo-unipolar cell bodies is surrounded by complexes of satellite glial cells (SGCs). The distal axons of the dorsal sensory root form the primary sensory nerve. As most studies of the DRG are performed in rats, it should be stated that the rat and the human differ with respect to the number of spinal segments and thus primary sensory nerves (17).

The primary sensory neuron starts in the neuron's peripheral receptive field, a region of the body in which a stimulus—as in injury or inflammation—alters the firing of the neuron, and ends within the central nervous system (CNS) (18). These neurons are the largest neurons in the body, up to 1.5 m in length (9), and send collaterals to the prevertebral sympathetic ganglia (19). Pseudo-unipolar neurons within the DRG are endowed with receptors for numerous neurotransmitters.

Because DRG neurons have axons that divide into two separate branches, connected by a T-junction that goes from the branching axon to the cell body, they are called pseudo-unipolar neurons to distinguish them from unipolar neurons, which have axons that leave both "poles" of the cell body toward their respective synapses (Fig. 2).

One branch of the axon of the pseudo-unipolar neuron extends from the T-junction to the periphery, and one branch extends from the T-junction toward the spinal cord. The T-junction of the DRG neuron can act as an impediment to electrical impulses traveling from the peripheral nociceptor to the dorsal root entry zone of the spinal cord, participate in the propagation of the electrical pulse, or act as a low-pass filter to electrical information from the periphery (20) (Fig. 3).

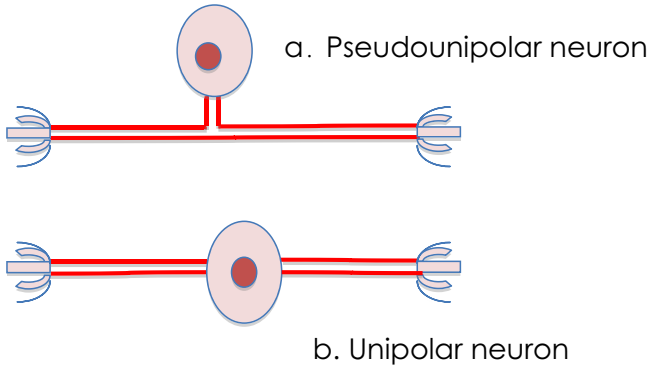

Figure 2. Pseudounipolar neurons. a. A pseudo-unipolar sensory neuron. A pseudopolar neuron has one axon that is divided into two separate branches, one from the periphery to the body and one from the body to the spinal cord, connected to the soma by a T-stem axon. There are no dendrites. Unipolar cells are not to be confused with bipolar cells (b), where the body lies within the path of the axon.

Satellite Glial Cells

The cell bodies of the DRG neurons are separated from each other by an envelope of SGCs that do not interact with one another, but do respond to peripheral and central processes, including nociception, peripheral afferent fiber (PAF) injury, and inflammation. SGCs form units of function that surround the peripheral sensory neuron within the DRG and play important roles, both in health and in disease. SGCs carry receptors for numerous neuroactive agents (cytokines, ATP, bradykinins, etc.), receive signals from other cells, respond to changes in their environment, and influence other neighboring cells, including DRG neurons (21). Therefore, it is likely that SGCs participate in signal processing and transmission within the DRG. Damage to the axons of sensory neurons (PAF injury) is known to contribute to neuropathic pain by affecting SGCs, and it may be that these cells have a role in pathological changes within the ganglia (21) (Fig. 4).

Glial cells are active participants in most processes of the CNS (22–25) and have been shown to undergo both morphological and biochemical changes after nerve damage (26–28). Glial cells have important roles in pathological states such as pain and inflammation (29–31), are involved in the regulation of transmission between synapses (22,32), form Ca^{++} waves that transmit signals over long distances (33), and contain numerous receptors to neurotransmitters and other bioactive molecules (23).

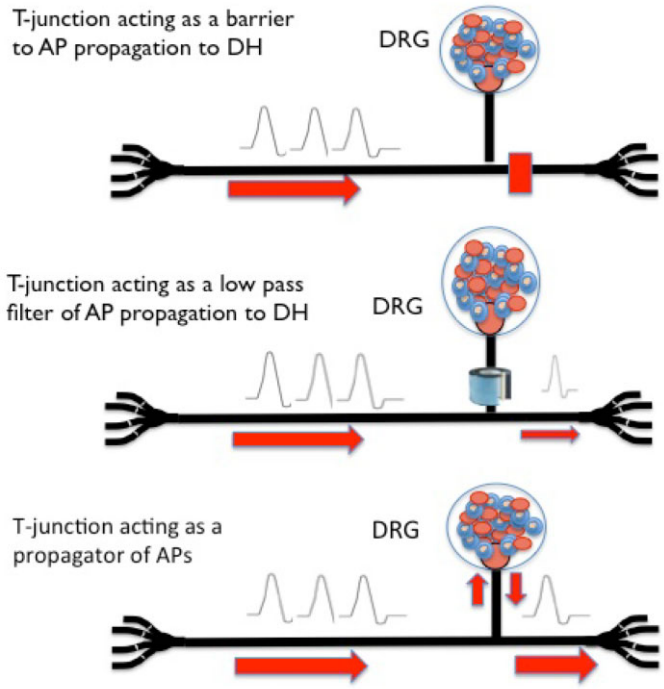

Figure 3. The T-junction acts either as 1) a barrier to the propagation of action potentials (APs) to the dorsal horn (DH) of the spinal cord, 2) a low-pass filter to the propagation of APs to the DH, or 3) an active participant in the propagation of APs to the DH of the spinal cord.

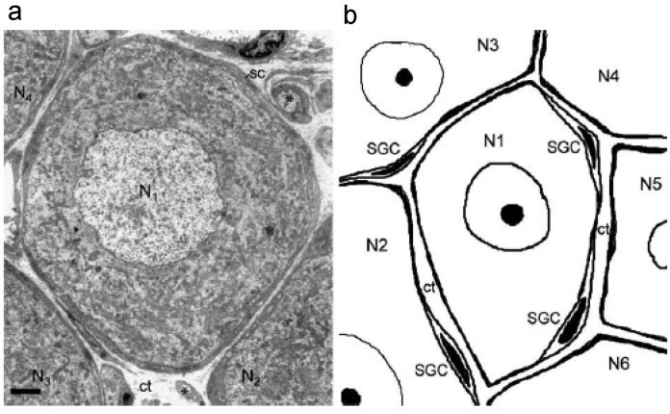

Figure 4. a. A low-power electron micrograph of mouse dorsal root ganglion, showing the arrangement of satellite glial cells (SGCs) around the neurons (N1–4). The neurons with their associated SGCs are separated by a connective tissue (ct) space. Note that the outer contour of the glial sheath is smooth. The asterisks indicate nonmyelinated axons that are surrounded by Schwann cells (SC). Two SGC cell bodies are indicated with arrows. b. Schematic diagram describing the anatomic relations between neurons (N1–N6) and SGCs in sensory ganglia. Reprinted from Hanani (21) with permission from Elsevier.

ROLE AFTER PERIPHERAL AFFERENT FIBER INJURY

Development of Neuropathic Pain

Injury to a PAF results in hyperexcitability only in axotomized DRG neurons, sparing nonaxotomized neurons (34). Injured DRG neurons become more excitable; their SGC sheaths increase their number of cells (35,36), and they exhibit ectopic firing (37,38). Wall and Devor showed that electrical impulses in PAF injury may originate not only from the damaged PAF, but from within the DRG itself (38), and that systemic application of lidocaine suppressed ectopic impulse discharges generated both at sites of experimental nerve injury and within axotomized DRG cells (39). These studies suggest that these electrical impulses, originating in the DRG, are due in part to activation of normal or abnormal sodium (Na^+) channels, which play a very important role in the development of hyperexcitability and NP.

The development of NP involves not only neuronal pathways, but also Schwann cells, SGCs, components of the peripheral immune system, and activated spinal microglia (40). Broadly speaking, PAF injury, as in axotomy, results in neuroimmune activation that involves activation of cells that interface with the PNS, including DRG neurons and glial cells (41). Cutting spinal nerves just distal to the DRG triggers massive spontaneous ectopic discharge in axotomized afferent A neurons within the DRG. Observations by Sukhotinsky et al. (42) support the hypothesis that ectopic firing in DRG A neurons induces central sensitization and clinical allodynia.

Activation of glia by PAF injury leads to the release of an immune cascade of inflammatory mediators, which sensitizes and lowers the threshold for neuronal firing, leading to peripheral and central sensitization and chronic, aberrant NP (43–45) (Fig. 5).

Changes in Gene Expression

Changes in gene expression within primary sensory neurons also represent an important mechanism underlying NP. Studying molecular alterations within the DRG 14 days after peripheral axotomy, Xiao et al. (46) found up-regulation of multiple neuropeptides, receptors, ion channels, signal transduction molecules, synaptic vesicle proteins, and other factors involved in the development of NP. Herdege et al. (47) studied the effect of changes in gene expression after transection of the sciatic nerve in adult rats and found increases in c-Jun and Jun-D within the DRG. Many of these changes in gene transcription manifest themselves by altering function at the level of the cell body. Although further work on translational and post-translational response mechanisms is needed, the resultant focus on changes at the level of the perikaryal membrane is a key element to neuromodulation of these cells.

Ion Channel and Ion Current Changes

Much is known regarding the role of Na^+, K^+, and Ca^{++} ion current changes and up- and down-regulation of ion channels as a result of PAF injury in the development of NP. DRG neurons coexpress several types of Na^+ channels (48), and it is hypothesized that various subtypes of these channels are associated with NP (49–52). Na^+ channels within the DRG after PAF injury can change expression levels and gating properties and can give rise to spontaneous action potential activity or pathological burst firing, which is the electrophysiological signature of NP (53,54).

DRG neurons also show pharmacological differences, including varying degrees of sensitivity to the Na^+ channel blocking drug tetrodotoxin (TTX) (55–58). Tumor necrosis factor alpha enhances the up-regulation of tetrodotoxin-resistant (TTX-R) Na^+ channels in nociceptive DRG neurons (59–61) and, as such, could be an underlying cause of hyperexcitability and NP. The neurotrophin, glial cell line-derived neurotrophic factor, is known to be necessary for the survival of DRG cells that bind the LB4 ion (62), and its analgesic effects are attributed to a blockade of the expression of TTX-R Na^+ channels in the injured DRG (63). Given the putative importance of

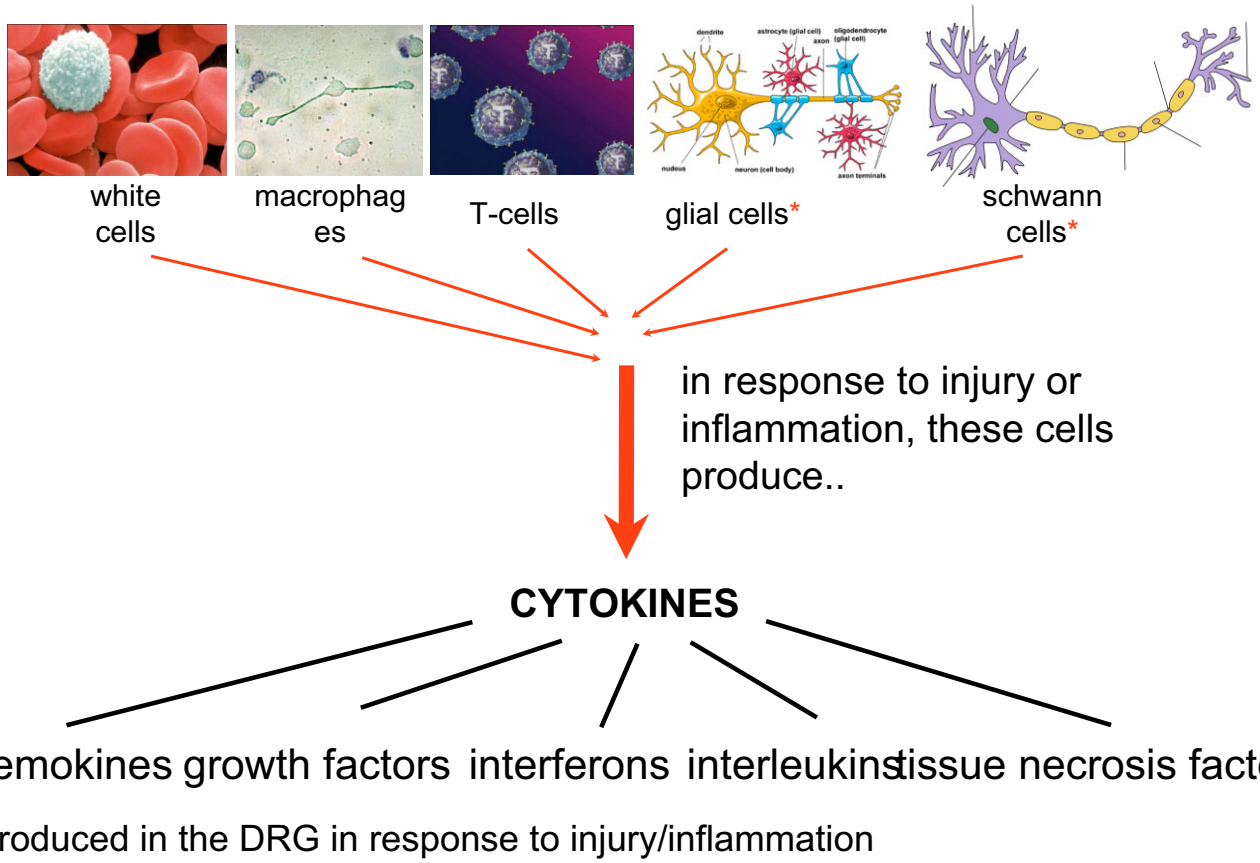

Figure 5. Immune cascade as a result of peripheral afferent fiber (PAF) injury. In response to injury or inflammation, white blood cells, T-cells, macrophages, glial cells, and Schwann cells in the nervous system produce cytokines locally which regulate the function of neighboring cells. *Produced in the dorsal root ganglion in response to injury/inflammation.

these channels in NP, they are potential therapeutic targets. TTX-R Na^+ channels are amenable to pharmacotherapies (59) that block, stabilize, or phenotypically alter these channels. Electrical stimulation is also known to modulate Na^+ channels *in vitro* (60) and in muscle cells (61). Klein et al. (62) wrote that "a change in neuronal activity (electrical stimulation) can alter the expression of sodium channel genes in a subtype-specific manner." Thus, one could envision electrical stimulation inducing changes in sodium channel expression and function, thereby changing the effective membrane physiology to the extent that pathology is partly reversed, stabilizing function to more "normal" or healthy levels.

It is known that cutaneous afferent DRG neurons express K^+ currents (63). Nerve injury leads to striking reductions in voltage-gated K^+ channel subunit expression in DRG neurons, suggesting that besides up-regulation of TTX-R Na^+ channels, K^+ channels play an important role in the development of hyperexcitability of injured nerves (64–68). Again, modulating the expression and/or function of these channels can help normalize membrane function and provide potential mechanisms by which electrical fields can chronically modulate these cells.

There are many reasons to suggest that an increase in voltage-activated Ca^{++} currents may contribute to inflammation-induced increase in afferent nerve input associated with NP: 1) an increase in low-threshold, or T-type, voltage-activated (LVA) Ca^{++} currents in peripheral afferent terminals is associated with a decrease in nociceptive threshold (68); 2) inflammatory injuries are associated with an increase in the α-subunit protein thought to underlie P- and Q-type high-threshold voltage-activated (HVA) Ca^{++} currents (69); 3) persistent inflammation results in an increase in Ca^{++}-dependent transmitter release from primary afferents (70); 4) inflammation and nerve injury appear to have opposite effects on the expression of several ion channels (71), and nerve injury results in a decrease in both HVA (72) and LVA Ca^{++} currents in primary afferents (73); and 5) persistent inflammation alters the density and distribution of voltage-activated Ca^{++} channels in subpopulations of rat cutaneous DRG neurons (74).

After chronic constriction injury of the peripheral axon, LVA Ca^{++} currents are significantly reduced, contributing to increased excitability after injury to sensory neurons. Through decreased Ca^{++} influx, the cell becomes less stable and more likely to initiate or transmit bursts of action potentials. Loss of inward Ca^{++} current in A-type neurons within the DRG after peripheral nerve injury contributes to increased sensory neuron excitability (75), and restoring the inward Ca^{++} current leads to decreased neuronal excitability (76). For a review of the role of decreased DRG neuron membrane Ca^{++} currents in the genesis of neuropathic pain, see Hogan (77).

Lee showed that external electrical stimulation of the DRG modifies both bursting and tonic activity of pseudounipolar neurons within the DRG (78). Koopmeiners et al. (79) showed that electrical field stimulation of the DRG increases Ca^{++} influx into DRG neurons, decreases the frequency of multiple action potentials within DRG neurons, and significantly reduces conduction velocity when compared with baseline before stimulation. These authors concluded that direct excitation of the DRG by electrical

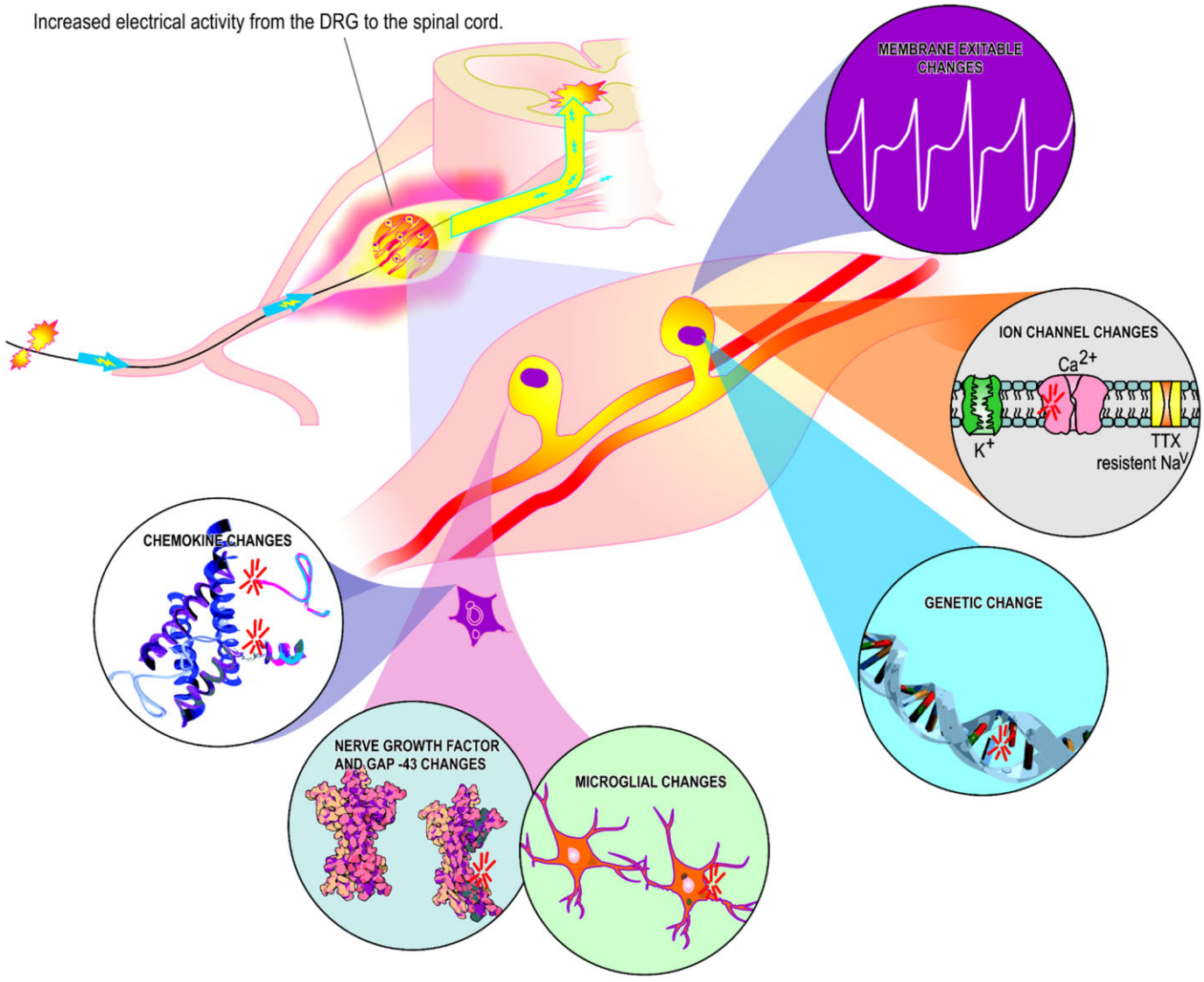

Figure 6. Release of various factors after injury or inflammation to a peripheral afferent fiber. In response to tissue inflammation or injury of a peripheral afferent fiber, the dorsal root ganglion (DRG) produces changes in glial cells, chemokines, nerve growth factors, gene expression, and ion channels including Na^+ channels, K^+ channels, and Ca^{++} channels.

fields reduces neuronal excitability and may provide a new analgesic approach. Consequently, modulation of Ca^{++} currents by electrical stimulation of the DRG may be a potential method of therapeutic intervention for NP.

Summary

The DRG, an anatomically accessible organ for interventional pain management (1–3) and electrical stimulation (4–6), is no longer considered a passive conduit for afferent transmission following PAF injury, inflammation, and the development of NP; rather, it is known to be deeply involved in peripheral processes that lead to NP. As a result of PAF injury or inflammation, a myriad of cellular changes occur within neurons in the DRG, resulting in membrane hyperexcitability. There are several potential ionic changes that contribute to these phenomena, including alterations in Na^+, K^+, and Ca^{++} ion channels and ion current flux. These changes, which occur as a result of injury and inflammation, lead to increased excitability of both peripheral and central neural tissues. Electrical stimulation has effects on the immune system and can restore abnormal Na^+ channels to normal (60) (Fig. 6).

ELECTRICAL STIMULATION OF THE DRG

Recent studies indicate that low-intensity electrical stimulation is functionally equivalent to the administration of various growth factors, enhancing and guiding growth of spinal neurons (80,81), fostering regeneration in bone (82,83) and muscle mass (84), and promoting wound healing (85,86). Because activity of growth factors and of the growth-associated protein GAP-43 within the DRG does play a role in the development of NP, and as it is known that electrical stimulation stimulates the synthesis of growth factors (87), it would not be a gross leap forward to speculate that perturbations of these growth factors within the DRG could be modified by direct

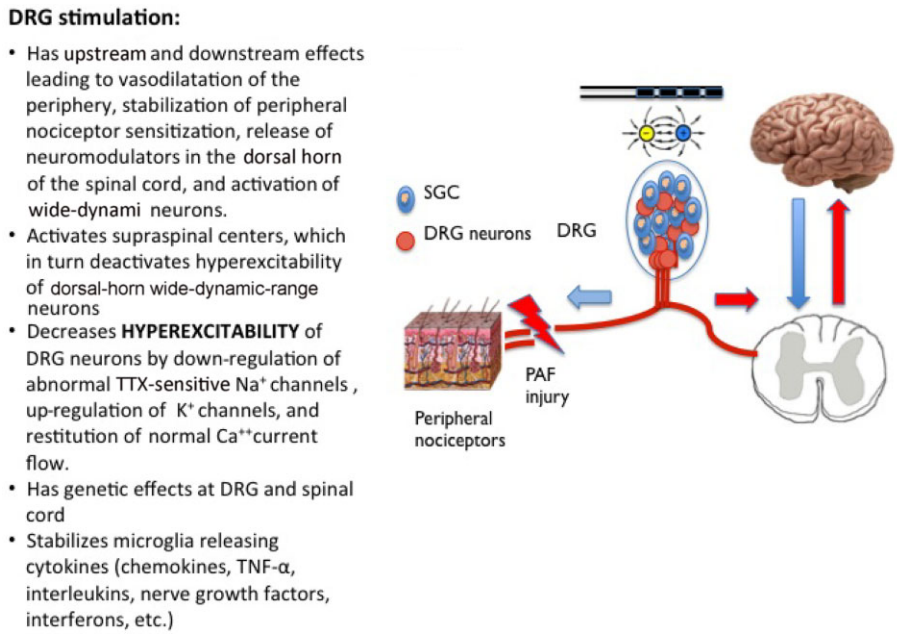

Figure 7. Hypothetical mechanisms of action of electrical neuromodulation of the dorsal root ganglion (DRG). This cartoon representation of the modulating effects of DRG stimulation shows that electrical stimulation of the DRG has both upstream and downstream effects on both DRG pseudo-unipolar neurons and satellite glial cell (SGC) wraps, stabilizing the release of cytokines, the abnormal production of genes for inflammatory proteins, and the production of abnormal Na^+, K^+, and Ca^{++} channels and abnormal ion current flows across membranes resulting from PAF injury. The end result is a decrement of hyperexcitability and decrease in chronic pain.

or indirect electrical stimulation of the DRG, resulting in a decrease in chronic pain. In a similar vein, because the nervous system and the immune system are inexorably integrated, with one system directly affecting the other, and because it is known that stimulation of the nervous system does modify immune responses, it is possible that electrical stimulation of the DRG may decrease chronic pain by impacting the immune response to PAF injury.

Stimulation of the DRG may have both upstream and downstream physiologic effects. We also know that stimulation of the DRG has downstream autonomic effects (88). Also, through normal afferent connective pathways, modulation of neurons within the DRG could provide a substrate for polysynaptic effects on other downstream neurons involved in chronic pain. It is proposed that electrical stimulation of the DRG could result in chronic pain relief and amelioration of secondary symptoms through 1) its upstream vasodilatory effects, 2) its proposed stabilizing effects at the peripheral sensitized nociceptors, 3) its downstream effects of deactivating sensitized wide-dynamic-range neurons within the dorsal horn, and 4) its potential modulation of supraspinal brain regions involved in the development and maintenance of chronic pain.

Amir et al. has shown that PAF injury also leads to abnormal neural patterns of oscillatory and bursting activity within the DRG (59). It is proposed that, like electrical stimulation of deep brain structures (deep brain stimulation, DBS) (89), electrical stimulation of the DRG may alter this abnormal electrical activity of DRG neurons resulting from PAF injury, thereby decreasing chronic pain (89). As previously stated, Lee showed that external electrical stimulation of the DRG modifies both bursting and tonic activity of pseudo-unipolar neurons within the DRG (78), and Koopmeiners et al. (79) showed that electrical field stimulation of the DRG increases Ca^{++} influx into DRG neurons, thereby decreasing the firing of multiple action potentials within DRG neurons and significantly reducing conduction velocity when compared with baseline before stimulation. It is also possible that electrical stimulation of the DRG, like the effect that DBS has on activated astrocytes and glia within the brain (90,91), will reverse changes within DRG microglia resulting from PAF injury that lead to a cytokine cascade. In fact, Zhou et al. (92) have shown that electrical stimulation suppresses the pro-inflammatory effect of microglia in a rat photic model.

Finally, it is proposed that electrical stimulation of the DRG will stabilize the hypersensitivity of DRG neurons that occurs after PAF injury as a result of Na^+, K^+, and Ca^{++} channel changes and ion fluxes. Electrical stimulation is known to modulate Na^+ channels *in vitro* (60) and in muscle cells (61). Klein et al. (62) wrote that "a change in neuronal activity (electrical stimulation) can alter the expression of sodium channel genes in a subtype-specific manner." Koopmeiners et al. (79) showed that electrical field stimulation of the DRG increases Ca^{++} influx into DRG neurons, decreases the frequency of multiple action potentials within DRG neurons, and significantly reduces conduction velocity when compared with baseline before stimulation. Figure 7 and Table 1 summarize this hypothesis of the mechanism of action of electrical stimulation of the DRG for the control of aberrant pain.

CONCLUSION

Electrical stimulation around the DRG may result in the relief of chronic aberrant pain, and direct electrical stimulation of the DRG results in decreased hyperexcitability of the DRG neurons. The DRG is a vibrant and active organ participating in the origination and modulation of electrical activity in response to environmental pressures. In response to injury or inflammation, a whole cascade of events occurs within and around DRG cell bodies, including changes in cytokine and chemokine production, up-regulation of immune factors, changes to glial cells and SGCs, early and late genetic changes, and changes in Na^+, K^+, and Ca^{++} ion channels. With our understanding of the underlying cellular mechanisms of chronic

Table 1. Hypothesized Mechanisms of Action of Dorsal Root Ganglion Stimulation.

Modification of growth factor release	Release of abnormal growth factors and inhibition of normally produced growth factors within the DRG resulting from PAF injury may be modified by direct or indirect electrical stimulation of the DRG, resulting in a decrease in chronic pain.
Reversal of cytokine release	We have seen that PAF fiber injury leads to activation of microglia within the DRG, which, in turn, leads to a cytokine cascade. This cytokine cascade leads to inflammation and neuropathic pain. Electrical stimulation of the DRG reverses activation of microglia within the DRG, thereby reversing the abnormal cytokine cascade that leads to the development of neuropathic pain.
Downstream and upstream effects	It is proposed that electrical stimulation of the DRG results in chronic pain relief through its downstream effects of vasodilation and stabilizing the sensitized peripheral nociceptors and its upstream effects of deactivating sensitized wide-dynamic-range neurons within the spinal cord and turning off brain centers that are turned on by PAF injury and inflammation.
Rectification of electrical activity patterns	It is proposed that electrical stimulation of the DRG may alter abnormal patterns of electrical activity of DRG neurons resulting from PAF injury, thereby decreasing chronic pain.
Reversal of genetic changes	It is proposed that electrical stimulation of the DRG reverses nonphysiological early and late genetic changes that result from PAF injury.
Down-regulation of abnormal ion channels and restitution of normal ion flux	We have also seen that there are changes to Na^+, K^+, and Ca^{++} ion channels and ion current flux resulting from injury and inflammation that lead to increased excitability of the periphery, the DRG, and the spinal cord. We have also seen that electrical stimulation has effects on the immune system, Ca^{++} currents, and Na^+ channels. Therefore, it is proposed that electrical stimulation of the DRG reverses the production of abnormal Na^+, K^+, and Ca^{++} channels and reverses abnormal flux of Ca^{++} ions.
Filtering of electrical impulses	The T-junction of the DRG neuron can either act as an impediment to electrical impulses from the nociceptor to the dorsal root entry zone, participate in the propagation of the electrical pulse, or act as a low-pass filter to electrical information from the periphery.

DRG, dorsal root ganglion; PAF, peripheral afferent fiber.

pain comes our ability to potentially understand the impact of electrical neuromodulation on the DRG and its subsequent impact on chronic pan. Moreover, by understanding the basic neuroscience and the contributions that specific neural tissues and cells make in the development and maintenance of chronic pain, we can better develop targeted therapies to treat this condition.

Authorship Statement

Dr. Krames is the sole author of this manuscript.

How to Cite this Article:

Krames E.S. 2014. The Dorsal Root Ganglion in Chronic Pain and as a Target for Neuromodulation: A Review. Neuromodulation 2014; E-pub ahead of print. DOI: 10.1111/ner.12247

REFERENCES

1. Sheng SR, Wang XY, Xu HZ, Zhu GQ, Zhou YF. Anatomy of large animal spines and its comparison to the human spine: a systematic review. *Eur Spine J* 2010;19:46–56.
2. Hasegawa T, An HS, Haughton VM. Imaging anatomy of the lateral lumbar spinal canal. *Semin Ultrasound CT MR* 1993;14:404–413.
3. Hasegawa T, Mikawa Y, Watanabe R, An HS. Morphometric analysis of the lumbosacral nerve roots and dorsal root ganglia by magnetic resonance imaging. *Spine* 1996;21:1005–1009.
4. Deer TR, Grigsby E, Weiner RL, Wilcosky B, Kramer JM. A prospective study of dorsal root ganglion stimulation for the relief of chronic pain. *Neuromodulation* 2013;16:67–72.
5. Liem L, Russo M, Huygen FJ et al. A multicenter, prospective trial to assess the safety and performance of the spinal modulation dorsal root ganglion neurostimulator system in the treatment of chronic pain. *Neuromodulation* 2013;16:471–482.
6. Pope JE, Deer TR, Kramer J. A systematic review: current and future directions of dorsal root ganglion therapeutics to treat chronic pain. *Pain Med* 2013;14:1477–1496.
7. Kishi M, Tanabe J, Schmelzer JD, Low PA. Morphometry of dorsal root ganglion in chronic experimental diabetic neuropathy. *Diabetes* 2002;51:819–824.
8. Devor M. Unexplained peculiarities of the dorsal root ganglion. *Pain* 1999;6 (Suppl. 1):S27–S35.
9. Hogan Q. Labat Lecture: the primary sensory neuron: where it is, what it does and why it matters. *Reg Anesth Pain Med* 2010;35:306–311.
10. Manchikanti L. Transforaminal lumbar epidural steroid injections. *Pain Physician* 2000;3:374–398.
11. Vad VB, Bhat AL, Lutz GE, Cammisa F. Transforaminal epidural steroid injections in lumbosacral radiculopathy: a prospective randomized study. *Spine* 2002;27:11–15.
12. Acar F, Miller J, Golshani KJ et al. Pain relief after cervical ganglionectomy (C2 and C3) for the treatment of medically intractable occipital neuralgia. *Stereotact Funct Neurosurg* 2008;86:106–112.
13. Nash TP. Percutaneous radiofrequency lesioning of dorsal root ganglia for intractable pain. *Pain* 1986;24:67–73.
14. Lord SM, Barnsley L, Wallis BJ et al. Percutaneous radio-frequency neurotomy for chronic cervical zygapophyseal joint pain. *N Engl J Med* 1996;335:1721–1726.
15. DeLouw AJA, Vles HSH, Freling G et al. The morphological effects of a radio frequency lesion adjacent to the dorsal root ganglion (RF-DRG): an experimental study in the goat. *Eur J Pain* 2001;5:169–174.
16. Van Zundert J, Patijn J, Kessels A et al. Pulsed radiofrequency adjacent to the cervical dorsal root ganglion in chronic cervical radicular pain: a double blind sham controlled randomized clinical trial. *Pain* 2007;127:173–182.
17. Gelderd JB, Chopin SF. The vertebral level of origin of spinal nerves in the rat. *Anat Rec* 1976;188:45–48.
18. Aldskogius H, Elfvin LG, Forsman CA. Primary sensory afferents in the inferior mesenteric ganglion and related nerves of the guinea pig. An experimental study with anterogradely transported wheatgerm agglutinin-horseradish peroxidase conjugate. *J Auton Nerv Syst* 1986;15:179–190.
19. Matthews MR, Cuello A. Substance P-immunoreactive peripheral branches of sensory neurons innervate guinea pig sympathetic neurons. *Proc Natl Acad Sci U S A* 1982;79:1668–1672.
20. Gemes G, Koopmeiners A, Rigaud M et al. Failure of action potential propagation in sensory neurons: mechanisms and loss of afferent filtering in c-type units after painful nerve injury. *J Physiol* 2012;591:1111–1131.
21. Hanani M. Satellite glial cells in sensory ganglia: from form to function. *Brain Res Brain Res Rev* 2005;48:457–476.
22. Rambourg A, Clermont Y, Beaudet A. Ultrastructural features of 6 types of neurons in rat dorsal root ganglia. *J Neurocytol* 1983;12:47–66.
23. Kamiya H, Zhang W, Sima A. Degeneration of the Golgi and neuronal loss in dorsal root ganglia in diabetic Bio Breeding/Worcester rats. *Diabetologia* 2006;49:2763–2774.
24. Regan LJ, Dodd J, Barondes SH, Jessell TM. Selective expression of endogenous lactose-binding lectins and lactoseries glycoconjugates in subsets of rat sensory neurons. *Proc Natl Acad Sci U S A* 1986;83:2248–2252.
25. Hjerling-Leffler J, Al Qatari M, Ernfors P, Koltzenburg M. Emergence of functional sensory subtypes as defined by transient receptor potential channel expression. *J Neurosci* 2007;27:2435–2443.
26. Lee KH, Chung K, Chung JM, Coggeshall RE. Correlation of cell body size, axon size, and signal conduction velocity for individually labeled dorsal root ganglion cells in the cat. *J Comp Neurol* 1986;243:335–346.

27. Tandrup TA. Method for unbiased and efficient estimation of number and mean volume of specified neuron subtypes in rat dorsal root ganglion. *J Comp Neurol* 1993;329:269–276.
28. Khan AA, Naushad M, Dilkash A. Morphological heterogeneity in the cervical dorsal root ganglion neurons of mice. *Curr Neurobiol* 2011;2:125–128.
29. Cherkes P, Hueng T, Pannicke T et al. The effects of axotomy on neurons and satellite glial cells in mouse trigeminal ganglion. *Pain* 2003;110:290–298.
30. Aldskogius H, Kozlova EN. Central neuron–glial and glial–glial interactions following axon injury. *Prog Neurobiol* 1998;55:1–26.
31. Watkins LR, Maier SF. Beyond neurons: evidence that immune and glial cells contribute to pathological pain states. *Physiol Rev* 2002;82:981–1011.
32. Haydon PG. Glia: listening and talking to the synapse. *Nat Rev Neurosci* 2001;2:185–193.
33. Newman EA. New roles for astrocytes: regulation of synaptic transmission. *Trends Neurosci* 2003;26:452–536.
34. Sapunar D, Ljubkovicm M, Lirk P, McCallum JB, Hogan QH. Distinct membrane effects of spinal nerve ligation on injured and adjacent dorsal root ganglion neurons in rats. *Anesthesiology* 2005;103:360–363.
35. Ledda M, De Palo S, Pannese E. Ratios between number of neuroglial cells and number and volume of nerve cells in the spinal ganglia of two species of reptiles and three species of mammals. *Tissue Cell* 2004;36:55–62.
36. Pannese E. The satellite cells of sensory ganglia. *Adv Anat Embryol Cell Biol* 1981;65:1–111.
37. Devor M. Ectopic discharge in Aβ afferents as a source of neuropathic pain. *Exp Brain Res* 2009;196:115–128.
38. Wu G, Ringkamp M, Murinson BB et al. Degeneration of myelinated efferent fibers induces spontaneous activity in uninjured C-fiber afferents. *J Neurosci* 2002;22:7746–7753.
39. Wall PD, Devor M. Sensory afferent impulses originate from dorsal root ganglia as well as from the periphery in normal and nerve injured rats. *Pain* 1983;17:321–339.
40. Devor M, Wall PD, Catala N. Systemic lidocaine silences ectopic neuroma and DRG discharge without blocking nerve conduction. *Pain* 1992;48:261–268.
41. Watkins LR, Milligan ED, Maier SF. Glial activation: a driving force for pathological pain. *Trends Neurosci* 2001;24:450–455.
42. Sukhotinsky I, Ben-Dor E, Raber P, Devor M. Key role of the dorsal root ganglion in neuropathic tactile hypersensibility. *Eur J Pain* 2004;8:135–143.
43. DeLeo JA, Tanga FY, Tawfik VL. Neuroimmune activation and neuroinflammation in chronic pain and opioid tolerance/hyperalgesia. *Neuroscientist* 2004;10:40–52.
44. Colburn RW, Rickman AJ, DeLeo JA. The effect of site and type of nerve injury on spinal glial activation and neuropathic pain behavior. *Exp Neurol* 1999;157:289–304.
45. Raghavendra V, Tanga F, DeLeo JA. Inhibition of microglial activation attenuates the development but not existing hypersensitivity in a rat model of neuropathy. *J Pharmacol Exp Ther* 2003;306:624–630.
46. Xiao HS, Huang QH, Zhang FX et al. Identification of gene expression profile of dorsal root ganglion in the rat peripheral axotomy model of neuropathic pain. *Proc Natl Acad Sci U S A* 2002;99:8360–8365.
47. Herdege T, Fiallos-Estrade CE, Schmid W, Bravo R, Zimmermann M. The transcription factors c-JUN, JUN-D and CREB, but not FOS and KROX-24, are differentially regulated in axotomized neurons following transection of rat sciatic nerve. *Brain Res Mol Brain Res* 1992;14:155–165.
48. Honmou O, Utzschneider DA, Rizzo MA, Bowe CM, Waxman SG, Kocsis JD. Delayed depolarization and slow sodium currents in cutaneous afferents. *J Neurophysiol* 1994;71:1627–1641.
49. Dong XW, Goregoaker S, Engler H et al. Small interfering RNA-mediated selective knockdown of $Na_V1.8$ tetrodotoxin-resistant sodium channel reverses mechanical allodynia in neuropathic rats. *Neuroscience* 2007;146:812–821.
50. Ekberg J, Jayamanne A, Vaughan CW et al. muO-conotoxin, MrVIB, selectively blocks $Na_v1.8$ sensory neuron specific sodium channels and chronic pain behavior without motor deficits. *Proc Natl Acad Sci U S A* 2006;103:17030–17035.
51. Gold MS, Weinreich D, Kim CS et al. Redistribution of $Na_V1.8$ in uninjured axons enables neuropathic pain. *J Neurosci* 2003;23:158–166.
52. Joshi SK, Mikusa JP, Hernandez G et al. Involvement of the TTX-resistant sodium channel Na_v 1.8 in inflammatory and neuropathic, but not post-operative, pain states. *Pain* 2006;123:75–82.
53. Waxman SG, Cummins TR, Dib-Haj S, Fjell J, Black JA. Sodium channels, excitability of primary sensory neurons, and the molecular basis of pain. *Muscle Nerve* 1999;22:1177–1187.
54. Devor M, Govrin-Lippmann R, Angelides K. Na^+ channel immunolocalization in peripheral mammalian axons and changes following nerve injury and neuroma formation. *J Neurosci* 1993;13:1976–1992.
55. Caffrey JM, Eng DL, Black JA, Waxman SG, Kocsis JD. Three types of sodium channels in adult rat dorsal root ganglion neurons. *Brain Res* 1992;592:283–297.
56. Elliott AA, Elliott JR. Characterization of TTX-sensitive and TTX-resistant sodium currents in small cells from adult rat dorsal root ganglia. *J Physiol* 1993;463:39–56.
57. Kostyuk PG, Veselovsky NS, Tsyandryenko AY. Ionic currents in the somatic membrane of rat dorsal root ganglion neurons. I. Sodium currents. *Neuroscience* 1981;6:2423–2430.
58. Roy ML, Narahashi T. Differential properties of tetrodotoxin sensitive and tetrodotoxin-resistant sodium channels in rat dorsal root ganglion neurons. *J Neurosci* 1992;12:2104–2111.
59. Amir R, Michaelis M, Devor M. Membrane potential oscillations in dorsal root ganglion neurons: role in normal electrogenesis and neuropathic pain. *J Neurosci* 1999;19:8589–8596.
60. Bradford HF. Metabolic response of synaptosomes to electrical stimulation: release of amino acids. *Brain Res* 1970;19:239–247.
61. Offord J, Catterall WA. Electrical activity, cAMP, and cytosolic calcium regulate RNA encoding sodium channel-α subunits in rat muscle cells. *Neuron* 1989;2:1447–1452.
62. Klein JP, Tendi EA, Dib-Hajj SD, Fields RD. Patterned electrical activity modulates sodium channel expression in sensory neurons. *J Neurosci Res* 2003;74:192–198.
63. Everill B, Rizzo MA, Kocsis JD. Morphologically identified cutaneous afferent dorsal root ganglion neurons express three different potassium currents in varying proportions. *J Neurophysiol* 1998;79:1814–1824.
64. Ishikawa K, Tanaka M, Black JA, Waxman SG. Changes in expression of voltage-gated potassium channels in dorsal root ganglion neurons following axotomy. *Muscle Nerve* 1999;22:502–507.
65. Rasband MN, Park EW, Vanderah TW, Lai J, Porreca F, Trimmer JS. Distinct potassium channels on pain-sensing neurons. *Proc Natl Acad Sci U S A* 2001;98:13373–13378.
66. Kajander KC, Wakisaka S, Bennett GJ. Spontaneous discharge originates in the dorsal root ganglion at the onset of a painful peripheral neuropathy in the rat. *Neurosci Lett* 1992;138:225–228.
67. Kawano T, Zoga V, McCallum JB et al. ATP-sensitive potassium currents in rat primary afferent neurons: biophysical, pharmacological properties, and alterations by painful nerve injury. *Neuroscience* 2009;162:431–443.
68. Bilici D, Akpinar E, Gürsan N et al. Protective effect of T-type calcium channel blocker in histamine-induced paw inflammation in rat. *Pharmacol Res* 2001;44:527–531.
69. Westenbroek RE, Byers BM. Upregulation of class A Ca^{2+} channels in trigeminal ganglion after pulp exposure. *Neuroreport* 1999;10:381–385.
70. Neubert JK, Maidment NT, Matsuka Y, Adelson DW, Kruger L, Spigelman I. Inflammation-induced changes in primary afferent-evoked release of substance P within trigeminal ganglia *in vivo*. *Brain Res* 2000;871:181–191.
71. Amir R, Argoff CE, Bennett GJ et al. The role of sodium channels in chronic inflammatory and neuropathic pain. *J Pain* 2006;7 (5 Suppl. 3):S1–S29.
72. McCallum JB, Kwok WM, Sapunar D, Fuchs A, Hogan QH. Painful peripheral nerve injury decreases calcium current in axotomized sensory neurons. *Anesthesiology* 2006;105:160–168.
73. McCallum JB, Kwok WM, Mynlieff M, Bosnijak ZJ, Hogan QH. Loss of T-type calcium current in sensory neurons of rats with neuropathic pain. *Anesthesiology* 2003;98:209–216.
74. Lu SG, Zhang XL, Luo ZD, Gold MS. Persistent inflammation alters the density and distribution of voltage-activated calcium channels in subpopulations of rat cutaneous DRG neurons. *Pain* 2010;151:633–643.
75. Lirk P, Poroli M, Rigaud M et al. Modulators of calcium influx regulate membrane excitability in rat dorsal root ganglion neurons. *Anesth Anal* 2008;107:673–685.
76. Hogan Q, Lirk P, Poroli M et al. Restoration of calcium influx corrects membrane hyperexcitability in injured rat dorsal root ganglion neurons. *Anesth Analg* 2008;107:1045–1051.
77. Hogan QH. Role of decreased sensory neuron membrane calcium currents in the genesis of neuropathic pain. *Croat Med J* 2007;48:9–21.
78. Lee DC. Modulation of bipolar neuron activity by extracellular electric field. Presented at Neuroscience 2011, Washington, DC, November 2011.
79. Koopmeiners AS, Mueller S, Kramer J, Hogan Q. Effect of electrical field stimulation on dorsal root ganglion neuronal function. *Neuromodulation* 2013;16:304–311.
80. Ming GL, Henley J, Tessier-Lavigne M, Song H, Poo M. Electrical activity modulates growth cone guidance by diffusible factors. *Neuron* 2001;29:441–452.
81. Sisken BF, Walker J, Orgel M. Prospects on clinical applications of electrical stimulation for nerve regeneration. *J Cell Biochem* 1993;51:404–409.
82. Kane WJ. Direct current electrical bone growth stimulation for spinal fusion. *Spine* 1988;13:363–365.
83. Steinberg ME, Brighton CT, Steinberg DR, Tooze SE, Hayken GD. Treatment of avascular necrosis of the femoral head by a combination of bone grafting, decompression, and electrical stimulation. *Clin Orthop Relat Res* 1984;186:137–153.
84. Goldspink G. Changes in muscle mass and phenotype and the expression of autocrine and systemic growth factors by muscle in response to stretch and overload. *J Anat* 1999;194:323–334.
85. Kloth LC. Electrical stimulation for wound healing: a review of evidence from *in vitro* studies, animal experiments, and clinical trials. *Int J Low Extrem Wounds* 2005;4:23–44.
86. Messerli MA, Graham DM. Extracellular electrical fields direct wound healing and regeneration. *Biol Bull* 2011;221:79–92.
87. Aaron RK, Boyan BD, Ciombor DM, Schwartz Z, Simon BJ. Stimulation of growth factor synthesis by electric and electromagnetic fields. *Clin Orthop Relat Res* 2004;429:30–37.
88. Croom JE, Foreman RD, Chandler MJ, Barron KW. Cutaneous vasodilation during dorsal column stimulation is mediated by dorsal roots and CGRP. *Am J Physiol* 1997;272 (Pt 2):H950–H957.
89. McIntyre C, Savasta M, Kerkerian-LeGoff L, Vitek JL. Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. *Clin Neurophysiol* 2004;115:1239–1248.

90. Malatesta P, Hartfuss E, Gotz M. Isolation of radial glial cells by fluorescent-activated cell sorting reveals a neuronal lineage. *Development* 2000;127:5253–5263.
91. Vedam-Mai V, van Battum EY, Kamphuis W et al. Deep brain stimulation and the role of astrocytes. *Mol Psychiatry* 2012;17:124–131.
92. Zhou WT, Ni YQ, Jin ZB et al. Electrical stimulation ameliorates light-induced photoreceptor degeneration *in vitro* via suppressing the proinflammatory effect of microglia and enhancing the neurotrophic potential of Müller cells. *Exp Neurol* 2012;238:192–208.

