Review Article
The Role of the Dorsal Root Ganglion in the Development of Neuropathic Pain

Elliot S. Krames, MD
San Francisco, California, USA

Reprint requests to: Elliot S. Krames, MD, 118A Broderick St., San Francisco, CA 94117, USA.
Tel: 415-515-7246; Fax: 415-864-1730; E-mail: krames118@gmail.com.

Disclosure: The writing and editing of this article was supported by a grant from Spinal Modulation, Inc. of Menlo Park, California, USA.

Abstract
Background. The dorsal root ganglion (DRG), in the not too distant past, had been thought of as a passive organ not involved in the development of abnormal aberrant neuropathic pain (NP), but merely metabolically “supporting” physiologic functions between the peripheral nervous system (PNS) and the central nervous system (CNS). New information regarding metabolic change within the DRG has dispelled this supportive passive role and suggests that the DRG is an active, not a passive, organ, in the process of the development of chronic pain.

Methods. A review of the anatomic and physiologic literature utilizing PubMed and Google Scholar was performed to create a review of the anatomic and physiologic foundations for the development of NP after peripheral afferent fiber injury.

Conclusions. The DRG is as involved in the process of generating NP as is the nociceptor and the dorsal horn of the spinal cord.

Key Words. Dorsal Root Ganglion; Pathophysiology; Peripheral Afferent Fiber; Inflammation; Neuropathic Pain; Injury

Introduction
Because it is anatomically and physically accessible [1–3] to clinical interventions for the control of peripheral acute and chronic pain, and, as we shall see in this review, the dorsal root ganglia (DRG) has an integral and important role in the modulation of peripheral and central sensory processing that includes inflammation, somatic pain, and the development of aberrant, neuropathic pain (NP), the DRG is an excellent clinical target for pain control, both from outside of the neural foramina into the epidural space and from the epidural space to the outside through the neural foramina. The DRG, in fact, is a known clinical target for the delivery of anti-inflammatory steroids [4,5], for surgery (ganglionectomy) [6], for radio-frequency ablation [7–9], for pulsed-radio frequency [10], and for electrical neurmodulation therapies. In fact, recent literature supports the notion that electrical stimulation of the DRG reduces pain states [11–13].

We shall see in this review article of what is known regarding processes that occur in the DRG after peripheral afferent fiber (PAF) injury that a cascade of events within the DRG and upstream within the dorsal horn (DH) of the spinal cord leads to constitutive release of cytokines, production of abnormal ion channels, abnormal ion currents, early and late gene changes, and the development of chronic NP. With this new knowledge regarding the role of DRG neurons and nonneuronal cells within the DRG in the genesis of NP, new pharmacologic agents such as tctrotoxin [14] and non-pharmacologic treatments for NP including electrical stimulation (neurmodulation) therapies targeting the DRG [11–13] have been or are being developed. It is intended by this review of the role of the DRG in the development of NP after PAF to foster a greater understanding on why the DRG is a good target for therapies directed at NP.

Anatomy of the DRG
In humans, there are 31 right and left paired “mixed” spinal nerves carrying autonomic, motor, and sensory information between the spinal cord and the periphery, 8 cervical spinal nerve pairs, 12 thoracic pairs, 5 lumbar pairs, 5 sacral pairs, and 1 coccygeal pair. These spinal nerves, formed from afferent sensory dorsal axons (the dorsal root) and motor ventral efferent axons (the ventral root), emerge from the intervertebral neural foramina between adjacent vertebral segments [2,3,15]. As the dorsal sensory root exits the neural foramina, it forms the DRG, a collection of bipolar cell bodies of neurons surrounded by glial cells and the axons of the DRG sensory cells that form...
the primary afferent sensory nerve. Because DRG neurons have two branches that act as a single axon, a distal process and a proximal process, connected by a cell body as an offshoot, they are called pseudounipolar neurons to differentiate them from bipolar cells, where the body is interspersed between two axons. See Figure 1. As most studies of the DRG, as reported in this article, are performed in rats, it is important to know that the rat has 8 paired cervical spinal nerves, 13 paired thoracic spinal nerves, 6 paired lumbar spinal nerves, and 4 paired sacral nerves [16].

The DRG contains the greatest proportion of the body’s sensory neurons, cells that are primarily responsible for the transduction of sensory information from the periphery and transmitting the information to the central nervous system (CNS). The cell bodies, previously thought to be only metabolic storage “helpers” to processes that occur in the periphery that include nociception, as we shall see, are now known to actually participate in the signaling process by sensing certain molecules and manufacturing other molecules that modulate the process [17]. The cell bodies of DRG neurons do not interact with one another and are separated from each other and surrounded by layers of satellite glial cells (SGCs).

The entire CNS and peripheral nervous system (PNS) are designed to protect and isolate its neurons from certain plasma molecules. The blood-brain barrier protects the CNS [18] and the blood–nerve barrier protects and isolates the PNS [19]. Because the DRG is not protected by a blood nerve barrier, small and large molecules and even macrophages can cross the SGC wrap of the DRG neuron [20].

Because of its important role in the modulation of peripheral and central sensory processing that includes nociceptive pain, and, as we shall see, the development of NP, and because of its clinical accessibility by bridging the neuroforamina between adjacent pedicles [1–3], the DRG is an excellent clinical target for pain control from both the outside into the epidural space through the neural foramen and from the epidural space to the outside (see Figure 2). The DRG is a known clinical target for the delivery of anti-inflammatory steroids [4,5], for surgery (ganglionectomy) [6], for radio-frequency ablation [7–9], for pulsed-radio frequency [10], and for electrical stimulation (neuromodulation) [11–13]. It is also known that, although the DRG is highly accessible, there is some variability of the location of the DRG within the spinal canal and the neural foramina. Moon et al. [22] studied the location of the DRG at different levels within the lumbar spinal canal and found that at the 4th lumbar spine the DRG was 48% intraforaminal (IF), 41% within the spinal canal or intraspinal (IS), and 6% was extraforaminal (EF). In the 5th lumbar spine, the DRG positions were 75% IF, 10% IS, and 6% EF. In the first sacral spine, DRG locations were 8% IF and 83% IS (Figure 2).

The cell bodies of DRG neurons are separated from each other by a wrap of SGCs and do not interact with one another. They do, however, respond to peripheral and central processes including nociception, PAF injury and inflammation. SGCs form a functional unit of the sensory neuron within the DRG and are important to both health and disease. “Glial cells tell the nervous system what to do” [23]. Rozanski et al. [24] reported that stimulation of one DRG neuron triggers a delayed and long-lasting response by a pathway between glia that is termed the “sandwich synapse” (SS). DRG neurons that are solely separated by the thin SGC membrane form a “trimer” of cells. The identification of the glial-to-DRG neuron transmission provides support for a DRG/SS molecular transmission pathway [25].

SGCs carry receptors for many agents involved in neuroactive processing that include chemokines, cytokines, adenosine-5′-triphosphate (ATP), bradykinins, and others. SGCs receive signals from other cells, influence DRG neurons, and respond to signals within their immediate environment [26]. Therefore, it is likely that SGCs participate in the process of transmission within the DRG. PAF injury is known to contribute to NP by affecting SGCs within the DRG (see Figure 3) [21].
Glial cells are active participants in most processes of the CNS and PNS [27–31] and change both morphologically and biochemically after PAF injury [32–34]. They have important roles in pathological states such as pain and inflammation [25,27,35,36], they control the environmental surroundings of the brain [37], are involved in the regulation of transmission between synapses [38], form Ca^{++} waves that signal transmission over long distances [39], and contain numerous receptors to neurotransmitters and other bioactive molecules [27].

The Primary Sensory Neuron (PSN) and the Role of the DRG

The primary sensory neuron with its cell body in the DRG starts in the peripheral receptive field of the neuron, a region of the body in which a stimulus alters the firing of the neuron and ends within the CNS starting with the DH of the spinal cord and ending in the relevant portions of the thalamus and brain [40]. Pseudopolar neurons of the DRG are the largest neurons in the body with lengths that can...
reach 1.5 meters in length [20] and send collaterals to the prevertebral sympathetic ganglia [41]. The neurons, which lie within the DRG but outside of the axonal path at the end of a “t-branch” of the axon, have axons that are split peripherally and centrally. The T-junction of the DRG neuron can either act as an impediment to electrical impulse from the nociceptor to the dorsal root entry zone, can participate in the propagation of the electrical pulse, or act as a low pass filter to electrical information from the periphery [42] (see Figure 4).

Many small, unmyelinated, nociceptive c-fiber cells within the DRG are involved with thermo-mechanical reception and contain substance P or calcitonin gene-related peptide (CGRP). The terminals of the larger, myelinated A-fiber neurons are low-threshold mechanoreceptors [43]. DRG neurons are not merely passive and “helper” neurons, but they respond to changes in the periphery and changes within the CNS by producing molecules that react to environmental change around them, either modulating the changes or participating in the changes. In their study utilizing fine filament dissection, Wall and Devor [44] showed that electrical impulses may originate from within the DRG and concluded that “the DRG, with its ongoing activity and mechanical sensitivity, could be a source of pain producing impulses and could particularly contribute to pain in those conditions of peripheral nerve damage where pain persists after peripheral anaesthesia or where vertebral manipulation is painful.” Following this trend of thought, Devor et al. found that “systemic application of lidocaine in rats suppressed ectopic impulse discharge generated both at sites of experimental nerve injury and in axotomized DRG cells,” [45] suggesting, as we shall later see, that these electrical impulses originating in the DRG might be due to activation of normal or abnormal sodium (Na+) channels. We shall also see in this review that PAF injury not only leads to activation of abnormal Na+ channels, but also leads to activation of SGCs within the DRG to release a cascade of pro-inflammatory cytokines, abnormal flux of Ca++ and K+ ions, changes in the immune system, changes to early and late genes, and changes in neural growth factors, the end result being hyperexcitability of DRG neurons and NP.

Figure 4 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 of the spinal cord; or 3) an active participant in the propagation of APs to the DH of the spinal cord.

Neuropathic Pain and the Role of the DRG

Nociceptive pain results from signaling of noxious stimuli by nociceptors and transmission of action potentials (APs) and warning signals to the spinal cord and brain. In contrast, NP, as chronic pain after PAF injury, is characterized by hypersensitivity resulting from decreased threshold to AP firing of nociceptors. With NP, this decreased firing threshold of nociceptors (hyperalgesia) occurs even from normal non-noxious stimuli (allodynia). This peripheral hyperexcitability is called peripheral sensitization. NP from peripheral sensitization is abnormal, aberrant, and chronic.

The development of NP is complex and involves the peripheral immune system, many different cell types that include DRG cell bodies, SGCs, glial cells, astrocytes and Schwann cells and neuronal pathways [46]. A massive spontaneous discharge within large, axotomized A-neurons within the DRG occurs after cutting spinal nerves distal to the DRG. This and observations by Sukhotinsky et al. support the hypothesis that “ectopic firing in DRG A-neurons induces central sensitization” [47] and clinical allodynia.

Scholz and Wolfe state that “NP has many of the features of a neuro-immune disorder” [48]. After injury to primary sensory neurons leading to NP, a host of pro-inflammatory mediators [49] produced by Schwann cells and SGCs within the DRG are released and include eicosanoids, bradykinins, serotonin, neurotrophins, cytokines such as the interleukins [50,51], TNF-α [52–58], interferons [59], growth factors [60,61], and chemokines [62–66], ATP and reactive oxygen species [67,68]. It is now conventional wisdom that pharmacologic immunosuppression that blocks transmission between DRG neurons and SGCs offers new opportunities for disease and pain management [69].

Cytokines are glycoproteins that are mainly secreted by anti-inflammatory cells that include neutrophils, t-cells, and macrophages; however, they are also secreted by glial cells and Schwann cells within the DRG. These proteins are similar to prostanoids in that they have a relatively short half-life, are locally secreted in response to tissue...
damage (constitutive) and inflammation, and act to regulate the function of neighboring cells in response to tissue damage or inflammation [70]. After tissue damage, glial cells and Schwann cells are activated and release a cascade of cytokines and other constitutive pro-inflammatory proteins that lead to inflammation and pain. The activation of these cells also leads to the production of pain mediators that sensitize and lower the threshold of glial cells to AP firing, leading to peripheral and central sensitization and chronic NP [71–75] (see Figure 5).

The Role of Microglia

Colburn et al. studied the importance of the site of nerve injury vs the type of nerve injury in eliciting spinal glial responses and mechanical allodynia in rats [76]. These authors found that spinal nerve lesion, freeze injury, and tight ligation produce mechanical allodynia and intense glial response. These glial responses are dependent upon DRG-mediated signals and occur when the lesion was made peripheral to the cell body within the DRG. Activation of astrocytes was always observed following injury to axons and was reliably associated with allodynia and hyperalgesia in the rats. The injection of minocycline, a broad spectrum tetracycline antibiotic and microglial activation inhibitor, attenuates the development of and existing mechanical allodynia and hyperalgesia in an L5 spinal nerve transection model of NP [77] and correlates with inhibition of microglial activation and suppression of pro-inflammatory cytokines. It is also known that the intrathecal (IT) injection of minocycline attenuates inflammation-induced hyperalgesia by inhibiting the p38MAPK (mitogen activated protein kinases) system in spinal microglia [78]. p38MAPK “are a class of protein kinases that are responsive to stress stimuli, such as cytokines, ultraviolet irradiation, heat shock, and osmotic shock, and are involved in cell differentiation” [79] and apoptosis.

Tissue Necrosis Factor-α (TNF-α) Release

TNF-α, a cytokine involved in systemic inflammation, belongs to a family of receptor proteins called the tnf-tnf-receptor-superfamily proteins [80]. The primary role of TNF is the regulation of immune cells but is also involved in the development of NP [63–68]. Microglia responding to PAF injury change and transform into macrophage-like cells, which secrete pro-inflammatory cytokines that include interleukin-6 (IL-6), TNF-α, and others, which mediate their effects via the p38MAPK system [81]. This constitutive upregulation of TNF within the DRG can be seen in Figure 6.

TNF-α up-regulation is found at various sites of local tissue injury including the chronic constriction injury (CCI) model [83] of the sciatic nerve [84] and within the DRG itself [76]. Exogenous TNF-α, when injected into the DRG of nerve roots injured using the chronic CCI model is transported to the injury site and into the DH of the spinal cord [77], precipitating alldynia in the receptive fields of the ligated and non-ligated nerves [85]. A study that compared crush injury of L5 spinal nerves distal to the DRG with crush injury proximal to the DRG in rats found that the distal crush injury resulted in greater neuronal cell death (apoptosis) and increased TNF-α expression that

Figure 5 In response to injury or inflammation, white blood cells, T-cells, macrophages and glial cells, and Schwann cells in the nervous system produce cytokines locally which regulate the function of neighboring cells.
correlated with higher incidence of NP [86], supporting the hypothesis that NP can derive from TNF-α/apoptosis signaling. In addition to enhancing tetrodotoxin resistant (TTX-R) Na\(^+\) channels in DRG neurons [87], which, as we shall see later, is a cause of NP, TNF-α also increases membrane potassium (K\(^+\)) ion conductance leading to neuronal hyperexcitability and NP [88]. A p38MAPK inhibitor blocks TNF-α increased TTX-R Na\(^+\) currents in cultured DRG wild type cells but not TNFR1 knockout mice implying that TNF-α enhances TTX-R Na\(^+\) channels via TNFR1 and the p38MAPK system [89].

The Interleukins

Interleukins are classes of cytokines produced by leukocytes and other immune cells for regulating immune responses. “The term interleukin derives from (inter) as a means of communication, and (-leukin) deriving from the fact that many of these proteins are produced by leukocytes, macrophages and endothelial cells and act on leukocytes” [90]. The interleukins are involved in the development and differentiation of T-cells, B-cells, and hematopoietic cells. There are 35 known human interleukins (IL-1–35) [91].

IL-1\(\alpha\) and IL-1\(\beta\) are pro-inflammatory cytokines that influence genesis and are involved in both acute and chronic inflammation and autoimmune disorders. Increase in IL-1\(\beta\) is involved in the pathogenesis of different diseases such as NP, rheumatoid arthritis, osteoarthritis, vascular disorders, inflammatory bowel disease, multiple sclerosis, and Alzheimer’s disease [92,93]. Acute inflammation activates glial cells and spinal IL-1\(\beta\) expression that correlates with pain behaviors in the rat [94]. In the CNS, cox-2 is induced by nociception and by release of cytokines such as IL-1\(\beta\), which contributes to allodynia and hyperalgesia [95]. IL-1\(\beta\) also contributes to increased nerve growth factor (NGF) levels and inflammatory hyperalgesia [96] and is strongly associated with resting pain and hyperalgesia over the temperomandibular joint [97].

In response to PAF injury, microglia secretes a host of cytokines including IL-6. Neutralization of prostaglandin E2 blocks IL-6 production in rats, reduces inflammation, and significantly reduces clinical hyperalgesia [98]. Huygen et al. studied the role of IL-6 and other pro-inflammatory cytokines in patients with complex regional pain syndrome-1 and found significant elevations of IL-6 and TNF-α in the involved extremity when compared with the uninvolved extremity [99]. The interleukins also are expressed within the DRG to increase hyperexcitability of pseudopolar neurons [89,100,101].

ATP, Inflammation, and Pain

ATP is a nucleoside triphosphate, is an end product of photophosphorelation and cellular respiration, and is the
main unit of energy transfer within cells [102,103]. ATP is also used by proteins and enzymes in a host of biosynthetic reactions, cell division, and motility. ATP is a ligand for the recently discovered new family of ion channels, the P2X family of ligand-gated ion channels, which are expressed by DRG nociceptive neurons [104–106]. The discovery of the P2X family of ligand-gated ion channels has led to an increased interest in the pathophysiologic actions of ATP as a causative agent for chronic NP [107,108]. Sensory neurons have been shown to express mRNA for six out of the seven members of the P2X ion family [109]. P2X3 mRNA is highly distributed within small c-fiber sensory nociceptors and their sensory neurons [110–112]. APs produced by painful stimuli to the skin propagate to neurons within the DRG and then to the DH of the spinal cord. These APs within the DH evoke release of glutamate onto postsynaptic DH neurons. P2X receptors have been identified in the superficial laminae of the DH associated with nociceptive DRG central terminals [113].

ATP is present in all cells of the body and therefore there is unlimited circumstances where ATP might be released as a mediator of inflammation apoptosis and injury. The release of ATP activates P2Y receptors on endothelial cells, but it also may act on P2X receptors in adventitia [114]. ATP, when iontophoretically placed on human skin, produces a modest burning pain [115]. Metabotropic, ATP receptors potentiate capsaicin receptor activity. ATP reduces the temperature threshold for the vanilloid capsaicin receptor (VR-I receptor) so that non-painful thermal stimuli activates the VR-I receptor [112].

**The Role of Neurotrophic Growth Factors, Pain, and the DRG**

The nervous system’s growth, maintenance, and survival is supported by neurotrophic growth factors such as NGF, brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), glial cell line-derived neurotrophic factor (GDNF), insulin-like growth factor-I, and ciliary neurotrophic factor. Some of these neurotrophic growth factors also play key roles in the development of disease and injury or the amelioration of disease or injury as seen in animal models [116].

The antagonism of NGF and the addition of the GDNF-family growth factor are promising strategies for the control of and treatment of NP [117–123]. NGF sensitizes peripheral nociceptors. Glial release of NGF within the DRG increases NP and adrenergic sprouting into DRG following CCI in mice [124,125]. The very survival of DRG neurons that bind lectin 1B4 depends on GDNF [126]. The behavioral responses to NP arising from PAF injury in rats is reversed by the IT infusion of GDNF [127,128]. This analgesic effect of GDNF is due to the blockade of TTX-R Na⁺ channel subtype, Na⁺,1.3 expression in the injured DRG [128].

BDNF is also involved in the development of NP. Microglial stimulation by ATP results in the P2RX-mediated release of BDNF, which in lamina-1, nociceptive neurons of the DH of the spinal cord produces an inversion of inhibitory GABA currents, leading to the development of allodynia [129]. Ha et al. [130] showed that the CCI in rats results in increases in the numbers of small, medium, and large BDNF-immunoreactive neurons in the L4 and L5 DRG ipsilateral to the injury site. M-RNA for NGF and BDNF is produced by the DRG of adult rats in response to injury and many DRG neurons respond to these factors [131], a model consistent with the regeneration of sensory neurons supported by these growth factors synthesized within the DRG itself. Lumbar disk herniation in a rat model results in changes in NGF and BDNF expression, suggesting a role of these neurotrophic growth factors in the development of NP as a result of disk herniation [132].

GAP-43 is a membrane, growth-associated phosphoprotein that is involved with neuronal development and plasticity. When adult DRG cells are dissociated from peripheral and central connections and maintained in vitro there are increases GAP-43 that are transported to both the peripheral and the central terminals of the afferent neurons. Sensory disorders that follow PAF injury may result from elevated GAP-43 associated inappropriate synaptic reorganization in afferent terminals [133].

**Gene Changes Within the DRG in Response to PAF Injury**

Gene changes within DRG neurons is an important cause of NP or results from PAF injury and inflammation. After PAF injury in rats there is modification of genes for neuropeptides, receptors, ion channels, signal transduction molecules, synaptic vesicle proteins, and others in DRG neurons that suggest that there are dynamic and complex changes in molecular diversity among DRG neurons after PAF injury [134]. After transection of the left sciatic nerve in adult rats, there are early genetic changes within L4 and L5 DRG neurons and the spinal cord that increase in c-JUN and JUN D and late changes that remain in c-JUN only [135].

**Ion and Ion Channels and Pain: Na⁺, K⁺, and Ca²⁺ Channels and Neuropathic Pain**

DRG neurons express differing kinds of ion channels/receptors that have three main functions that include transduction, transmission, and modulation of sensory information. It is also important to note that, after PAF injury, DRG neurons become hyperexcitable, their SGC sheaths expand by numbers of cells [136,137] and they exhibit ectopic firing [138,139]. The Na⁺,K⁺, and Ca²⁺ channels and receptors at the peripheral terminals of DRG neurons involved in transduction of noxious information to electrical signals include transient receptor potential channels, Na⁺ channels, acid-sensing ion channels, and ATP-sensitive receptors [140]. Channels produced that involve conduction through propagation of APs include Na⁺ and K⁺ channels. Modulation of synaptic transmission through regulation of the release of neurotransmitters is performed by voltage-gated Ca²⁺ channels and glutamate receptors,
which are expressed on presynaptic membranes at the terminals of the primary afferents of the DH.

**Na⁺ Channels.** Na⁺ channels, formed by integral membrane proteins that conduct Na⁺ ions through a cell’s plasma membrane, produce APs that signal messages within DRG primary sensory neurons [141]. DRG neurons also exhibit multiple and different Na⁺ currents that can be differentia ted on the basis of kinetics and their voltage dependence differences, as ascertained by patch-clamp techniques [142]. This differentiation of Na⁺ currents implies that DRG neurons can co-express several types of Na⁺ channels [143,144].

Some Na⁺ channels, after PAF injury or inflammation within the DRG, become hyperexcitable, leading to spontaneous electrical activity or pathological electrical activity, which, in turn, lead to NP. After excising the rat DRG, some cells produce subthreshold, voltage-sensitive oscillations in their membrane potential [145], which, upon reaching threshold, give rise to APs and are necessary for sustained spiking. Prior nerve injury increases the numbers of neurons that have subthreshold oscillations and induced spike discharge. These oscillations and therefore abnormal spike discharge are eliminated by [Na⁺]; substitution or bath application of lidocaine or TTX, implying that TTX-S, Na⁺ conductance contributes to the oscillations [146].

The production and conduction of APs in excitatory DRG neurons depend on the voltage-gated channels Na⁺1.1–1.9 [147]. Na⁺1.3, Na⁺1.7, Na⁺1.8, and Na⁺1.9 are essential for transmission along pain pathways. Na⁺1.7, Na⁺1.8, and Na⁺1.9 are preferentially expressed in DRG neurons, and Na⁺1.3 is upregulated after PAF injury [148,149]. The Nav1.8 Na⁺ channel is responsible for spontaneous AP activity in damaged sensory axons, and contributes to the development of ectopic mechanosensitivity and NP [150–154]. Decreasing the expression of TTX-R, Na⁺ channel Nav1.8 inhibits the development of NP [155]. To date, Nav1.3, Nav1.7, Nav1.8, and Nav1.9 have been identified as possible targets for analgesic medication development [156].

DRG neurons also show varying degrees of sensitivity to the Na⁺ channel-blocking drug, TTX [146,157,158]. We have already seen that TNF-α released by activated DRG SGCs enhances the production of TTX-R, Na⁺ channels and the upregulation of K⁺ ion conductance in a non-voltage, gated fashion leads to neuronal hyperexcitability and NP [99]. Also, as we have seen, TNF acts via TNFR1 and activates TTX-R, Na⁺ channels via the p38MAPK system [89], GDNF blocks the expression of the voltage-gated, TTX-R, Na⁺ channel subtype, Na⁺1.3, in the injured DRG and prevents and reverses NP arising from PAF injury [139].

Upregulation of certain Na⁺ channels, particularly upregulation of TTX-S Na⁺ channels leads to the development of hyperexcitability within the DRG, making it amenable to pharmacotherapies that either block, stabilize, or phenotypically alter these channels. For a more exhaustive reviews of the role of Na⁺ channels in chronic pain see Theile and Cummins [156] and Catterall [141].

**K⁺ Channels.** K⁺ channels are the most numerous of ion channels in the body, they form K⁺-selective pores that cross cell membranes and are found in all living organisms [159,160]. There are four major classes of K⁺ channels, which include the Ca²⁺/K⁺ channel, which opens in the presence of Ca²⁺ ions and other signaling molecules; the inwardly rectifying K⁺ channel, which passes positive charge current into the cell; the tandem pore K⁺ channel including the resting K⁺ channel or leak channel, which sets the resting membrane potential for neurons; and the voltage-gated K⁺ channel, which responds to changes in the transmembrane voltage by opening and closing [161].

The antinociception induced by agonists of many G-protein-coupled receptors that include α₂-adrenoceptors, opioid receptors, GABAA receptors, muscarinic M3 receptors, adenosine A1 receptors, serotonin 5-HT₃A receptors, and cannabinoid receptors is fostered by opening of K⁺ channels [162]. We have already seen that TNF-α increases membrane K⁺ ion conductance leading to neuronal hyperexcitability and NP [89].

Downregulation of the K⁺ channel is involved in the development of NP. Nerve injury induced by the Kim and Chung model [163] of NP or axotomy leads to reduction of voltage-gated K⁺ channels in DRG neurons that suggests a potential molecular mechanism for hyperexcitability of injured nerves besides upregulation of TTX-R Na⁺ channels [164,165]. Furthermore, Kajander et al. [166] found that, in response to injury to the sciatic nerve in rats, the spontaneous discharge and the sensitivity to K⁺ channel blockade seen in Aβ and Aδ primary afferents at the time of the onset of the NP syndrome appeared to originate in the DRG.

**Ca²⁺ Channels.** Ca²⁺ channels are sometimes synonymously termed voltage-dependent C⁺⁺ channels although there are ligand-gated calcium channels as well [167]. There are five different voltage-gated Ca²⁺ channels, which include the L-type, the P-type/Qtype, the N-type, the R-type, and the T-type. The P-type/Q-type and N-type Ca²⁺ channels are highly voltage-gated and are involved in neurotransmitter release, while the T-type is involved in cardiac rhythm and the L-type is involved in muscle function including cardiac smooth muscle function.

An increase in voltage-gated Ca²⁺ currents contribute to inflammation-induced increases inafferent signaling because 1) increases in low-threshold, or T-type voltage-activated (LVA) Ca²⁺ currents in sensory terminals is associated with reduced thresholds to nociception (hyperalgesia) [168]; 2) PAF injury and resultant inflammation results in an increase in the α₁-subunit protein thought to be foundational to P/Q-type, high-threshold voltage-activated (HVA) Ca²⁺ currents [169]; 3) persistent inflammation increases Ca²⁺ dependent transmitter release such as glutamate from primary afferents [170]; and 4)
inflammation and PAF injury have opposite effects on the expression of ion channels [171]. Nerve injury results in a decrease in both HVA-Ca$^{++}$ and LVA-Ca$^{++}$ currents in primary afferents [172,173].

Ca$^{++}$ currents within the DRG participate in the development of NP. Persistent inflammation alters the density and distribution of voltage-activated Ca$^{++}$ channels populations of rat DRG neurons, whose receptive field lie in the skin [174]. After CCI of peripheral axons in rats, LVA-Ca$^{++}$ currents are reduced significantly contributing to hyperexcitability of sensory neurons. Because of this decrease in Ca$^{++}$ influx, the cell becomes less stable initiating and/or transmitting bursts of APs. Loss of inward Ca$^{++}$ current in A-type neurons within the DRG after PAF injury contributes sensory neuron hyperexcitability [175] and restoring the inward Ca$^{2+}$ current leads to decreased hyperexcitability [176]. For a more thorough review of the role of decreased Ca$^{++}$ currents within the DRG neuron membrane in the genesis of NP, see Hogan [177].

N-type Ca$^{++}$ channels are largely restricted to the CNS and PNS [178]. The $\omega$-conotoxins MVIIA and GVIA, blocking polypeptides derived from the venom of marine cone snails, have been used to investigate the physiologic role of Ca,2.2 channels [179]. Opening of presynaptic Ca,2.2 channels the terminals of primary afferent nerves induces an influx of extracellular Ca$^{2+}$ ions resulting in the release of glutamate, substance P, and CGRP into the neuronal synapse, directly modulating nociceptive signaling [180]. In some pain states, there is an increased expression of Ca,2.2 channels that suggests that these channels have an enhanced role in the development of NP [181]. Some strains of Ca,2.2 gene knockout mice have reduced sensitivity to noxious stimuli that causes pain in normal mice [182] and the IT injection of Ca,2.2 blocking conopeptides attenuates hyperalgesia and allodynia resulting from PAF fiber injury or inflammation behavioral models of chronic NP [183].

In Summary

In this review of the DRG and its role in the development of NP, we have seen that the DRG, an anatomically accessible organ [1–3] for therapies including injections of anti-inflammatory medications [4,5], ganglionectomy [6], radiofrequency ablation [7–9], for pulsed radio-frequency [10], and neuromodulation therapies (DRG stimulation) [11,12] is no longer considered a passive organ to peripheral processes such as PAF injury, inflammation, and the development of NP, but is an organ deeply involved in peripheral processes that lead to NP (see Figure 7). We

**Figure 7** In response to tissue inflammation or injury of a peripheral afferent fiber, the DRG produces changes in glial cells, chemokines, nerve growth factors, produce genetic change and change to ion channels including Na$^+$ channels, K$^+$ channels and Ca$^{++}$ channels.
have learned that, as a result of PAF injury or inflammation, there are changes within the DRG that includes release of cytokines including chemokines, growth factors, interleukins, interferons, TNF-α, early and late genetic changes and change within the ATP and p38-mapk systems from activated microglia. We have also seen that there are changes to Na+, K+, and Ca++ ion channels and ion current flux as a result of injury and inflammation that leads to hyperexcitability of DRG neurons.

In this context of the DRG’s involvement in the development of NP, we should also state that the DRG is involved in the process of chronicity, from acute to chronic pain. According to Voscopoulos and Lema, “the transition from acute to chronic pain appears to occur in discrete pathophysiological and histopathological steps” [184]. It is the release of algogenic substances in the periphery from nociception (surgery, trauma, inflammation) that, if ongoing, can lead to activation and sensitization of nociceptors [185] in the periphery. Nociceptor sensitization, in turn, leads to activation of SGCs in the DRG to release pro-inflammatory chemokines and cytokines and alteration of ion channels and dysregulation of ion flux within the DRG that leads to upstream effects at the 2nd order neuron within the DH of the spinal cord, which, in turn, leads to central sensitization [186] and the transition from acute to chronic pain.

References


72 Colburn RW, Rickman AJ, DeLeo JA. The effect of site and type of nerve injury on spinal glial activation


Krames


112 Tominaga M, Wada M, Masu M. Potentiation of capsaicin receptor activity by metabotropic ATP receptors as a possible mechanism for ATP evoked pain and hyperalgesia. PNAS 2001;98(12):6951–6.


121 Sabsovich I, Wei T, Guo TZ, et al. Effect of anti-NGF antibodies in a rat tibia fracture model of complex


145 Amir R, Michaelis M, Devor M. Membrane potential oscillations in dorsal root ganglion neurons: Role


183 Malmberg AB, Yaksh TL. Effect of continuous intrathecal infusion of omega-conopeptides, N-type calcium-channel blockers, on behavior and antinociception in the formalin and hot-plate tests in rats. Pain 1995;60(1):83–90.

