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Review Article

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

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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 aberrent 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 Afferant 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 neuromodulation 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 tedtrodotoxin [14] and non-pharmacologic treatments for NP including electrical stimulation (neuromodulation) 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

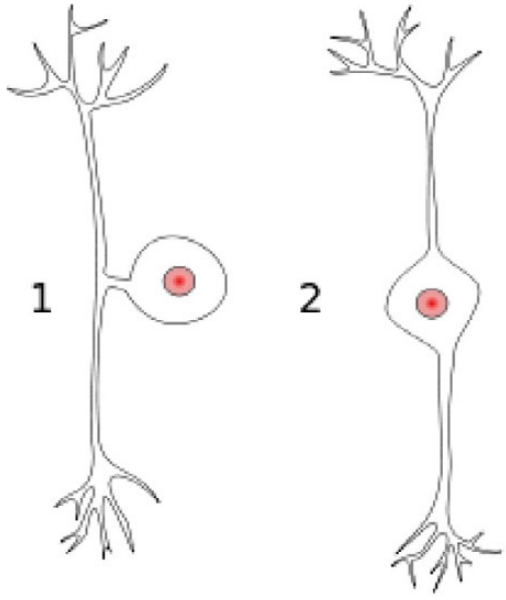

Figure 1 (1) A pseuodunipolar sensory neuron. A pseudounipolar neuron has one axon that is divided into two separate branches, one from the periphery to the body and one from the body to the spinal cord. There are no dendrites. Unipolar cells are not to be confused with bipolar cells (2) where the body lies within the path of the axon. Unipolar cells have a T-stem axon that is away from the main axon. Taken with permission from the Internet: http://en.wikipedia.org/wiki/Pseudounipolar_neuron.

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 intersperced 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].

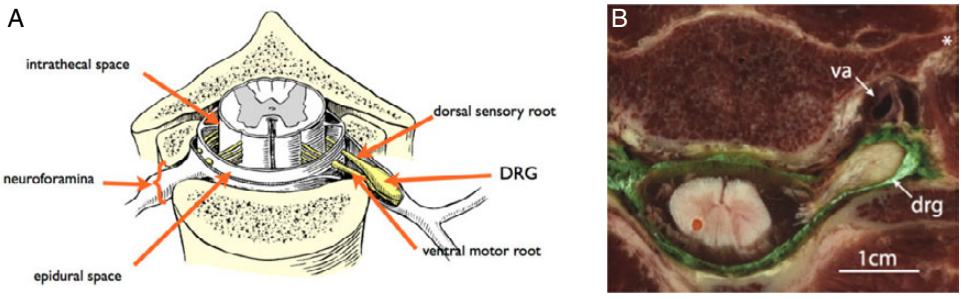

Figure 2 (A) A cartoon of a section through the cervical intravertebral foramen showing the position of the DRG outside of the intervertebral neural foramen and its relationship to the IT space, the neuroforamina, the epidural space and dorsal and ventral roots. Taken from the Internet with permission: http://www.csus.edu/indiv/m/mckeoughd/AanatomyRev/CNS/scXsect/scXsect.htm. (B) Used with permission from Hogan [21]. "An axial cryomicrotome section throught the C5–6 interverteral foramen in a human specimen injected with green ink by an epidural approach before freezing the section. As we see the DRG lies outside the neural foramen, posterior to the vertebral artery (va)".

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

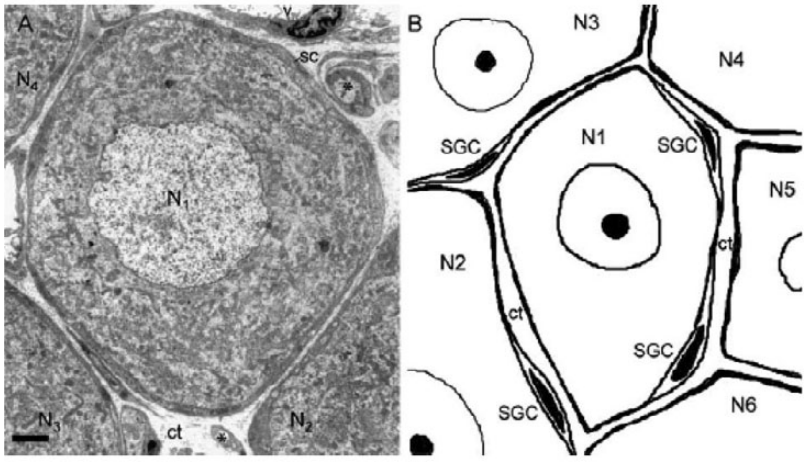

Figure 3 "The sensory neuron-SGC unit. (A) A low power electron micrograph of mouse dorsal root ganglion, showing the arrangement of SGCs around the neurons (N1–4). The neurons with their associated SGCs are separated by a connective tissue space. Note that the outer contour of the glial sheath is smooth. The asterisks indicate non-myelinated axons that are surrounded by Schwann cells. Two SCG cell bodies are indicated with arrows. (B) Schematic diagram describing the anatomic relations between neurons (N1–N6) and SGCs in sensory ganglia." Taken directly from Hanani with permission [26].

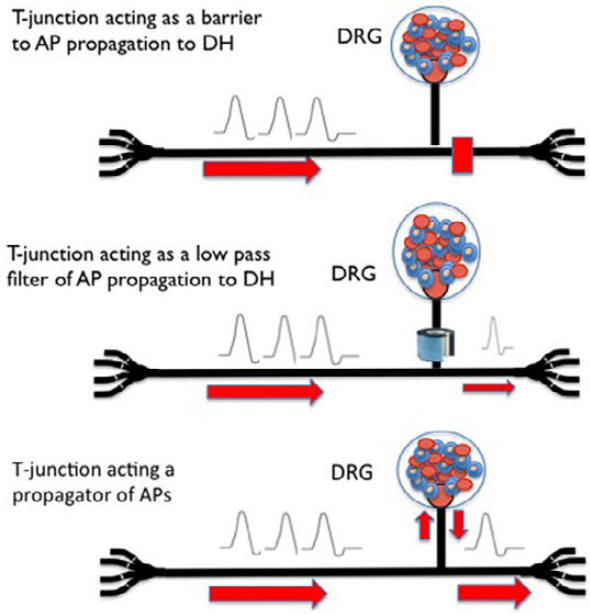

Figure 4 The t-junction acts either as 1) a barrier to the propagation of action potentials (APs) to the dorsal horn (DH) of the spinal cord; 2) a low pass filter to the propagation of APs to the DH of the spinal cord; or 3) an active participant in the propagation of APs to the DH of the spinal cord.

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.

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 nociciptors (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

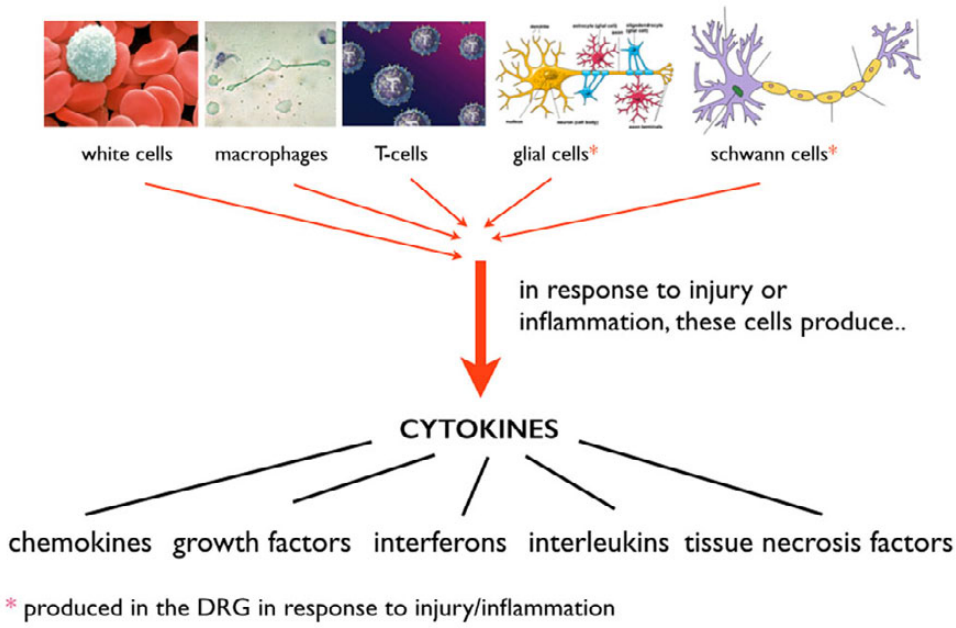

Figure 5 In response to injury or inflammation, white blood cells, T-cells, macrophages and glial cells, and Schwann cells in the nervous system produce cytokines locally which regulate the function of neighboring cells.

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 minocyline 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 interkeukin-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 allodynia 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

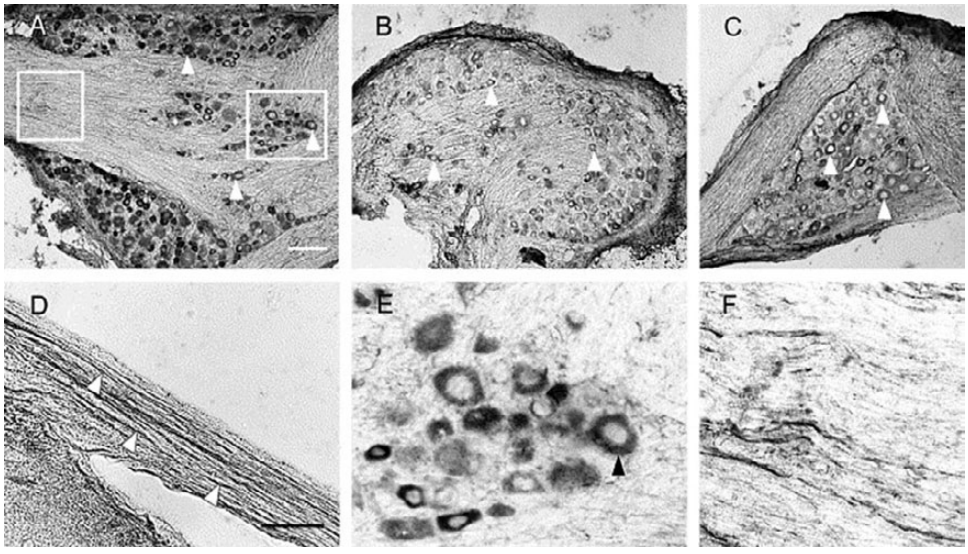

Figure 6 "Constitutive expression of TNFR1-ir in fibers of passage and cell bodies of the dorsal root ganglia. Cell bodies immunoreactive for TNFR1 (white arrows) were observed in cervical (A), thoracic (B), and lumbar (C) dorsal root ganglia. Fibers traversing through the ganglia were also observed to be immunoreactive for TNFR1, though TNFR1-ir appeared to be confined to small bundles of fibers, rather than a uniform distribution throughout the nerve (D, arrowheads). Higher power (40×) magnification of insets from (A) show detail of TNFR1-ir labeling in cell bodies (E, black arrowhead is reference point from inset) and fiber bundles (F). Scale bar = 100 μm (A–C); 40 μm (D–F) [82]." Used with permission from Holmes et al. [82].

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 (predominantly CD4 T cell lymphocytes), monocytes, 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-1α and IL-1β are pro-inflammatory cytokines that influence genesis and are involved in both acute and chronic inflammation and autoimmune disorders. Increase in IL-1β 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-1β 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-1β, which contributes to allodynia and hyperalgesia [95]. IL-1β 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]. $P2X_3$ 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 [123,127]. This analgesic effect of GDNF is due to the blockade of TTX-R Na^+ channel subtype, $Na_V1.3$ 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, nociciptive 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 include increases 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 Ca^{++} 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 ion 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 Ca^{++} 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 differentiated 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, leads 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 $[Na^+]_o$ 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 excitable DRG neurons depend on the voltage-gated channels $Na_v1.1$–1.9 [147]. $Na_v1.3$, $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ are essential for transmission along pain pathways. $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ are preferentially expressed in DRG neurons, and $Na_v1.3$ 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 activated TTX-R, Na^+ channels via the p38MAPK system [89]. GDNF blocks the expression of the voltage-gated, TTX-R, Na^+channel subtype, $Na_V1.3$, 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 hyperexcitibility within the DRG, making it amenable to pharmocotherapies 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 *Ca^{++}/K^+ channel*, which opens in the presence of Ca^{++} 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 α_2-adrenoceptors, opioid receptors, $GABA_B$ receptors, muscarinic M_2 receptors, adenosine A_1 receptors, serotonin 5-HT_{1A} 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.

Ca^{++} Channels. Ca^{++} 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 Ca^{++} 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 Ca^{++} 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 Ca^{++} currents contribute to inflammation-induced increases in afferent signaling because 1) increases in low-threshold, or T-type voltage-activated (LVA) Ca^{++} 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 α-subunit protein thought to be foundational to P/Q-type, high-threshold voltage-activated (HVA) Ca^{++} currents [169]; 3) persistent inflammation increases Ca^{++} 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 transmiting 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 ω-conotoxins MVIIA and GVIA, blocking polypeptides derived from the venom of marine cone snails, have been used to investigate the physiologic role of $Ca_v2.2$ channels [179]. Opening of presynaptic $Ca_v2.2$ 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 $Ca_v2.2$ channels that suggests that these channels have an enhanced role in the development of NP [181]. Some strains of $Ca_v2.2$ gene knockout mice have reduced sensitivity to noxious stimuli that causes pain in normal mice [182] and the IT injection of $Ca_v2.2$ 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], radio-frequency 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

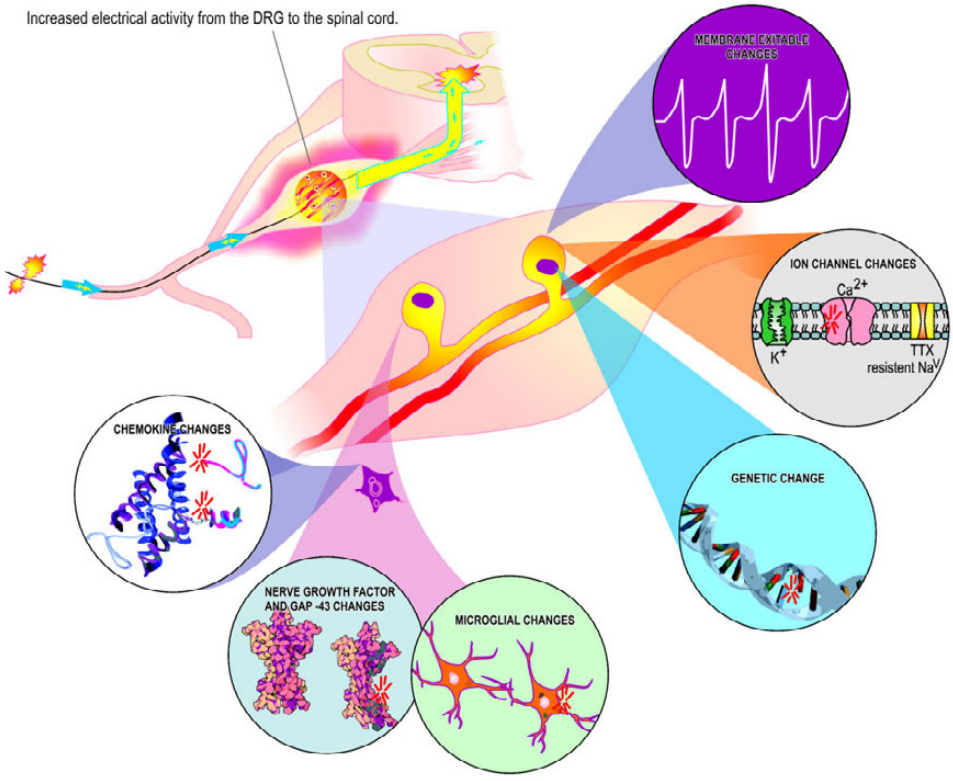

Figure 7 In response to tissue inflammation or injury of a peripheral afferent fiber, the DRG produces changes in glial cells, chemokines, nerve growth factors, produce genetic change and change to ion channels including Na^+ channels, K^+ channels and Ca^{++} channels.

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

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(1):46–56.

2 Hasegawa T, An HS, Haughton VM. Imaging anatomy of the lateral lumbar spinal canal. Semin Ultrasound CT MR 1993;14(6):404–13.

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(9):1005–9.

4 Manchikanti L. Transforaminal lumbar epidural steroid injections. Pain Physician 2000;3(4):374–98.

5 Vad VB, Bhat AL, Lutz GE, Cammisa F. Transforaminal epidural steroid injections in lumbosacral radiculopathy: A prospective randomized study. Spine 2002;27(1):11–5.

6 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(2):106–12.

7 Nash TP. Percutaneous radiofrequency lesioning of dorsal root ganglia for intractable pain. Pain 1986;24(1):67–73.

8 Lord SM, Barnsley L, Wallis BJ, et al. Percutaneous radio-frequency neurotomy for chronic cervical zygapophyseal joint pain. N Engl J Med 1996;335:1721–6.

9 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(2):169–74.

10 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(1–2):173–82.

11 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(1):67–72.

12 Liem L, Russo M, Huygen FJPM, 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(5):471–82.

13 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(10):1477–96.

14 Nieto FR, Cobos EJ, Tejada MA, et al. Tetrodotoxin (TTX) as a therapeutic agent for pain. Mar Drugs 2012;10(2):281–305.

15 Sheng SR, Wang XY, Xu HZ, et al. Anatomy of large animal spines and its comparison to the human spine: A systematic review. Eur Spine J 2010;19(1):46–56.

16 Gelderd JB, Chopin SF. The vertebral level of origin of spinal nerves in the rat. Anat Rec 1976;188:45–8.

17 Devor M. Unexplained peculiarities of the dorsal root ganglion. Pain Suppl 1999;6:S27–35.

18 Ballabh P, Braun A, Nedergaard M. The blood–brain barrier: An overview: Structure, regulation, and clinical implications. Neurobiol Dis 2004;16(1):1–13.

19 Shimizu F, Sano Y, Abe MA, et al. Peripheral nerve pericytes modify the blood–nerve barrier function and tight junctional molecules through the secretion of various soluble factors. J Cell Physiol 2011;226(1):255–66.

20 Hu P, McLachlan EM. Macrophage and lymphocyte invasion of dorsal root ganglia after peripheral nerve lesions in the rat. Neuroscience 2002;112:23–38.

21 Hogan QH. Labat lecture: The primary sensory neuron: Where it is, what it does, and why it matters. Reg Anesth Pain Med 2010;35:306–11.

22 Moon HS, Kim YD, Song BH, et al. Position of dorsal root ganglia in the lumbosacral region in patients with radiculopathy. Korean J Anesthesiol 2010;59(6): 398–402.

23 Nedergaard M, Ransom B, Goldman SA. New roles for astrocytes: Redefining the functional architecture of the brain. Trends Neurosci 2003;26:523–30.

24 Rozanski GM, Li Q, Stanley EF. Transglial transmission at the dorsal root ganglion sandwich synapse: Glial cell to postsynaptic neuron communication. Eur J Neurosci 2013;37(8):1221–8.

25 Cherkes PS, Hueng TY, Pannicke MT, et al. The effects of axotomy on neurons and satellite cells in mouse trigeminal ganglion. Pain 2003;110:290–8.

26 Hanani M. Satellite glial cells in sensory ganglia: From form to function. Brain Res Rev 2005;48(3):457–76.

27 Aldskogius H, Kozlova EN. Central neuron-glial and glial-glial interactions following axon injury. Prog Neurobiol 1998;55:1–26.

28 Rambourg A, Clermont Y, Beaudet A. Ultrastructural features of 6 types of neurons in rat dorsal root ganglia. J Neurocytol 1983;12:47–66.

29 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;49:2763–74.

30 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 USA 1986;83(7):2248–52.

31 Hjerling-Leffleler J, AlQatari M, Ernfors P, Koltzen-burg M. Emergence of functional sensory subtypes as defined by transient receptor potential channel expression. J Neurosci 2000;27:2435–43.

32 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; 243:335–46.

33 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;329:269–76.

34 Khan AA, Naushad M, Dilkash A. Morphological heterogeneity in the cervical dorsal root ganglion neurons of mice. Curr Neurobiol 2011;2(2):125–8.

35 Stephenson JL, Byers MR. GFAP immunoreactivity in trigeminal ganglion satellite cells after tooth injury in rats. Exp Neurol 1995;131:11–22.

36 Watkins LR, Maier SF. Beyond neurons: Evidence that immune and glial cells contribute to pathological pain states. Physiol Rev 2002;82:981–1011.

37 Hansson E, Ronnback L. Glial neuronal signaling in the central nervous system. FASEB J 2003; 17:341–8.

38 Haydon PG. Glia: Listening and talking to the synapse. Nat Rev Neurosci 2001;2:185–93.

39 Newman EA. New roles for astrocytes: Regulation of synaptic transmission. Trends Neurosci 2003;26: 452–536.

40 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 wheat germ agglutinin-horseradish peroxidase conjugate. J Auton Nerv Syst 1986;15:179–90.

41 Matthews MR, Cuello A, Substance P. immunoreactive peripheral branches of sensory neurons innervate guinea pig sympathetic neurons. Proc Natl Acad Sci USA 1982;79:1668–72.

42 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(4): 1111–31.

43 Lawson SN. Morphological and biochemical cell types of sensoryneurons. In: Scott AS, ed. Sensory Neurons, Diversity, Development and Plasticity. New York: Oxford University Press; 1992:27–59.

44 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(4):321–39.

45 Devor M, Wall PD, Catala N. Systemic lidocaine silences ectopic neuroma and DRG discharge without blocking nerve conduction. Pain 1992;48(2): 261–8.

46 Watkins LR, Milligan ED, Maier SF. Glial activation: A driving force for pathological pain. Trends Neurosci 2001;24(8):450–5.

47 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(2):135–43.

48 Scholz J, Woolf CJ. The neuropathic pain triad: Neurons, immune cells and glia. Nat Neurosci 2007;10(11):1361–8.

49 Chessell IP, Hatcher JP, Bountra C, et al. Disruption of the P2X7 purinoceptor gene abolishes chronic inflammatory and neuropathicpain. Pain 2005; 114(3):386–96.

50 Sweitzer S, Martin D, DeLeo JA. Intrathecal interleukin-1 receptor antagonist in combination with soluble tumor necrosis factor receptor exhibits an anti-allodynic action in a rat model of neuropathic pain. Neuroscience 2001;103(2):529–39.

51 Zalenka M, Schafers M, Sommer C. Intraneural injection of interleukin-1beta and tumor necrosis factor-alpha into rat sciatic nerve at physiological doses induces signs of neuropathic pain. Pain 2005; 116(3):257–63.

52 Wagner R, Myers RR. Endoneurial injection of TNF-alpha produces neuropathic pain behaviors. Neuroreport 1996;7(18):2897–901.

53 Ignatowski TA, Covey WC, Knight PR, et al. Brain-derived TNF "Nature neuroscience". Brain Res 1999;841(1–2):70–7.

54 Geis C, Grauliche M, Wissmanj A, et al. Evoked pain behavior and spinal glia activation is dependent on tumor necrosis factor receptor 1 and 2 in a mouse model of bone cancer pain. Pain 2010;169(1):463–74.

55 Choi JI, Svensson CI, Koehrn FJ, Bhuskute A, Sorkin LS. Peripheral inflammation induces tumor necrosis factor dependent AMPA receptor trafficking and Akt phosphorylation in spinal cord in addition to pain behavior. Pain 2010;149(2):243–53.

56 Segond von Blanchet G, Boettger MK, Fischer N, et al. Experimental arthritis causes tumor necrosis factor-α-dependent infiltration of macrophages into rat dorsal root ganglia which correlates with pain-related behavior. Pain 2009;145(1–2):151–9.

57 Nakamae T, Mitsu O, Olmarker K. Pharmacological inhibition of tumor necrosis factor may reduce pain behavior changes induced by experimental disc puncture in the rat: An experimental study in rats. Spine 2011;36(4):E232–6.

58 Renno T, Krakowski M, Piccirillo C, Lin JY, Owens T. TNF-alpha expression by experimental allergic encephalomyelitis. Regulation by Th1cytokines. J Immunol 1995;154(2):944–53.

59 Reyes-Gibby CC, Spitz MR, Yennurajalingam SY, et al. Role of inflammation gene polymorphisms on pain severity in lung cancer patients. Cancer Epidemiol Biomarkers Prev 2009;18(10):2636–42.

60 Brack A, Rittner HL, Machelska H, et al. Mobilization of opioid-containing polymorphonuclear cells by hematopoietic growth factors and influence on inflammatory pain. Anesthesiology 2004;100(1):149–57.

61 Woolf CJ, Mannion RJ. Neuropathic pain: Aetiology, symptoms, mechanisms, and management. Lancet 1999;353(9168):1959–64.

62 White FA, Jung H, Miller RJ. Chemokines and the pathophysiology of neuropathic pain. PNAS 2007; 104(51):20151–8.

63 Baggioline M. Chemokines and leukocyte traffic. Nature 1998;392(6676):565–8.

64 Zlotnick A, Yoshei O. Chemokines: A new classification review system and their role in immunity. Immunity 2000;12(2):121–7.

65 Whie FA, Bhangoo SK, Miller RJ. Chemokines: Integrators of pain and inflammation. Nat Rev Drug Discov 2005;4:834–44.

66 Gao YJ, Ji RR. Chemokines, neuronal–glial interactions, and central processing of neuropathic pain. Pharmacol Ther 2010;126:56–68.

67 Watkins LR, Maier SF, Goehler LE. Immune activation: The role of pro-inflammatory cytokines in inflammation, illness responses and pathological pain states. Pain 1995;63(3):289–302.

68 Kiguchi N, Kobayashi Y, Kishioka S. Chemokines and cytokines in neuroinflammation leading to neuropathic pain. Curr Opin Pharmacol 2012;12(1):55–61.

69 Kung LH, Gong K, Adedoyin M, et al. Evidence for glutamate as a neuroglial transmitter within sensory ganglia. PLoS ONE 2013;8(7):e68312.

70 Turnbull AV, Rivier CL. Regulation of the hypothalamic-pituitary-adrenal axis by cytokines: Actions and mechanisms of action. Physiol Rev 1999;79(1):1–71.

71 DeLeo JA, Tanga FY, Tawfik VL. Neuroimmune activation and neuroinflammation in chronic pain and opioid tolerance/hyperalgesia. Neuroscientist 2004; 10(1):40–52.

72 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(2):289–304.

73 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(2):624–30.

74 Sommer C, Kress M. Recent findings on how pro-inflammatory cytokines cause pain: Peripheral mechanisms in inflammatory and neuropathic hyperalgesia. Neurosci Lett 2004;361:184–7.

75 Okamoto K, Martin DP, Schmelzer JD, Mitsui Y, Low PA. Pro- and anti-inflammatory cytokine gene expression in rat sciatic nerve chronic constriction injury model of neuropathic pain. Exp Neurol 2001; 169:386–91.

76 Schafers M, Geis C, Svensson CL, Luo ZD, Sommer C. Selective increase of TNF-α in injured and spared myelinated primary afferents after chronic constrictive injury of rat sciatic nerve. Eur J Neurosci 2003;17:791–804.

77 Shubeyev VI, Myers RR. Anterograde transport from rat dorsal root ganglion to spinal cord and injured sciatic nerve. Neurosci Lett 2002;320:99–101.

78 Hua XY, Svensson CI, Matsuie T, et al. Intrathecal minocycline attenuates peripheral inflammation-induced hyperalgesia by inhibiting p38 MAPK in spinal microglia. Eur J Neurosci 2005;22(10):2431–40.

79 Tsuda M, Mizokoshi A, Shigemoto-Mogami Y, Koizumi S, Inoue K. Activation of p38 mitogen activated protein kinase in spinal hyperactive microglia contributes to pain hypersensitivity following peripheral nerve injury. Glia 2004;45(1):89–95.

80 Kim JY, Moon SM, Ryu HJ, et al. Identification of regulatory polymorphisms in the TNF–TNF receptor superfamily. Immunogenetics 2005;57(5):297–303.

81 Lee YB, Schrader JW, Kim SU. P38 map kinase regulates tnf-fication of regulator astrocytes and microglia by multiple mechanisms. Cytokine 2000;12(7):874–80.

82 Holmes GM, Hebert SL, Rogers RC, Hermann GE. Immunocytochemical localization of TNF type-1 and type-2 receptors in the rat spinal cord. Brain Res 2004;1025(1–2):210–9.

83 Bennett GJ, Xie YK. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. Pain 1998;33(1):87–107.

84 George A, Schmidt C, Weishaupt A, Toyka KV, Sommer C. Serial determination of tumor necrosis factor-alpha content in rat sciatic nerve after chronic constriction injury. Exp Neurol 1999;160(1):124–32.

85 Schafers M, Lee DH, Brors D, Yaksh TL, Sorkin LS. Increased sensitivity of injured and adjacent uninjured rat primary sensory neruons to exogenous tumor necrosis factor-alpha after spinal nerve ligation. J Neurosci 2003;23:3028–38.

86 Sekiguchi M, Sekiguchi Y, Konno S, et al. Comparison of neuropathic pain and neuronal apoptosis following nerve root or spinal nerve compression. Eur Spine J 2009;18:1978–85.

87 Jin X, Gereau RW. Acute p38-mediated modulation of tetrodotoxin resistant Na+ channels in mouse sensory neurons by tumor necrosis factor-alpha. J Neurosci 2006;26:246–55.

88 Czeschik JC, Hagenacker T, Shcafers M, Busselberf D. TNF-alpha differentially modulates ion channels of nociceptive neurons. Neurosci Lett 2008;434(3): 293–8.

89 Özaktay AC, Kallakuri S, Takebayashi T, et al. Effects of interleukin-1 beta, interleukin-6, and tumor necrosis factor on sensitivity of dorsal root ganglion and peripheral receptive fields in rats. Eur Spine J 2006;15(10):1529–37.

90 Brocker C, Thompson D, Matsumoto A, Nebert DW, Vasiliou V. Evolutionary divergence and functions of the human interleukin (IL) gene family. Hum Genomics 2010;5(1):30–55.

91 Mizel SB. The interleukins. FASEB J 1989;3(12): 2379–88.

92 Dinarello CA. Biologic basis for interleukin-1 in disease. Blood 1996;87(6):2095–147.

93 Braddock M, Quinn A. Targeting IL-1 in inflammatory disease: New opportunities for therapeutic intervention. Nat Rev Drug Discov 2004;3(4):1–10.

94 Sweitzer SM, Colburn RW, Rutkowski M, DeLeo JA. Acute peripheral inflammation induces moderate glial activation and spinal IL-1β expression that correlates with pain behavior in the rat. Brain Res 1999;829(1–2):209–21.

95 Samad TA, Moore KA, Sapirstein A, et al. Interleukin-1beta-mediated induction of Cox-2 in the CNS contributes to inflammatory pain hypersensitivity. Nature 2001;410:471–5.

96 Safieh-Garabedian B, Poole S, Allchrone A, Winter J, Woolf CJ. Contribution of interleukin-1 beta to the inflammation-induced increase in nerve growth factor levels and inflammatory hyperalgesia. Br J Pharmacol 1995;115(7):1265–75.

97 Alstergren P, Ernberg M, Kvarnström M, Kopp S. Interleukin-1beta in synovial fluid from the arthritic temporomandibular joint and its relation to pain, mobility, and anterior open bite. J Oral Maxillofac Surg 1998;56(9):1059–65.

98 Portanova JP, Zhang Y, Anderson GD, et al. Selective neutralization of prostaglandin E2 blocks inflammation, hyperalgesia, and interleukin 6 production in rats. J Exp Med 1996;184(3):883–91.

99 Huygen FJPM, De Bruijn AGJ, De Bruin MT, et al. Evidence for local inflammation in complex regional pain syndrome type 1. Mediators Inflamm 2002; 11(1):47–51.

100 Dubový P, Klusáková I, Svíženská I, Brázda V. Satellite glial cells express IL-6 and corresponding signal-transducing receptors in the dorsal root ganglia of rat neuropathic pain model. Neuron Glia Biol 2010;6(01):73–83.

101 Deleo J, Colburn RW, Nichols M, Malhotra A. Interleukin-6-mediated hyperalgesia/allodynia and increased spinal il-6 expression in a rat mononeuropathy model. J Interferon Cytokine Res 1996;16(9):695–700.

102 Knowles JR. Enzyme-catalyzed phosphoryl transfer reactions. Annu Rev Biochem 1980;49:877–919.

103 Saks VA, Rosenshtraukh LV, Smirnov VN, Chazov EI. Role of creatine phosphokinase in cellular function and metabolism. Can J Physiol Pharmacol 1978; 56(5):691–706.

104 Chen CC, Akopian AN, Sivilottit L, et al. A P2X purinoceptor expressed by a subset of sensory neurons. Nature 1995;377(6548):428–31.

105 Lewis C, Neidhart S, Holy C, et al. Coexpression of P2X2 and P2X3 receptor subunits can account for ATP-gated currents in sensory neurons. Nature 1995;377:432–5.

106 Vulchanova L, Arvidsson U, Riedl M, Wang J, Buell G. Differential distribution of two ATP-gated ion channels (P2X receptors) determined by immunocytochemistry. Proc Natl Acad Sci USA 1996;93: 8063–7.

107 Hamilton SG. ATP and pain. Pain Pract 2002;2(4): 289–94.

108 Hayashida M, Fukuda KI, Fukunaga A. Clinical application of adenosine and ATP for pain control. J Anesth 2005;19(3):225–35.

109 Collo G, North RA, Kawashima E, et al. Cloning of P2X5 and P2X6 receptors and the distribution and properties of an extended family of ATP-gated ion channels. J Neurosci 1996;16:2495–507.

110 Bradbury EJ, Burnstock G, McMahon SB. The expression of P2X3 purinoreceptors in sensory neurones: Effects of axotomy and glial-derived neurotrophic factor. Mol Cell Neurosci 1998;12:256–68.

111 Vulchanova L, Riedl MS, Shuster SJ, et al. P2X3 is expressed by DRG neurones that terminate in inner lamina II. Eur J Neurosci 1998;10:3470–8.

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.

113 Gu JG, MacDermott AB. Activation of ATP P2X receptors elicits glutamate release from sensory neuron synapses. Nature 1997;389:749–53.

114 Bodin P, Burnstock G. Synergistic effect of acute hypoxia on flow-induced release of ATP from cultured endothelial cells. Experientia 1995;51:256–9.

115 Hamilton SG, Barburton J, Bhattachariee A, Ward J, McMahon SB. ATP in human skin elicits a dose-related pain response, which is potentiated under conditions of hyperalgesia. Brain 2000;123(6):1238–46.

116 Sah DYW, Porreca F, Ossipov MH. Modulation of neurotrophic growth factors as a therapeutic strategy for neuropathic pain. Drug development research modulation of neurotrophic growth factors as a therapeutic strategy for neuropathic pain. Drug Dev Res 2006;67(4):389–403.

117 Donnerer J, Schuligoi R, Stein C. Increased content and transport of substance P and calcitonin gene-related peptide in sensory nerves innervating inflamed tissue: Evidence for a regulatory function of nerve growth factor in vivo. Neuroscience 1992; 49(3):693–8.

118 Woolf CJ, Safieh-Garabedian B, Ma QP, Crilly P, Winter J. Nerve growth factor contributes to the generation of inflammatory sensory hypersensitivity. Neuroscience 1994;62(2):327–31.

119 Sevcik MA, Ghilardi JR, Peters CM, et al. Anti-NGF therapy profoundly reduces bone cancer pain and the accompanying increase in markers of peripheral and central sensitization. Pain 2005;115(1):128–41.

120 Hefti FF, Rosenthal A, Walicke PA, et al. Novel class of pain drugs based on antagonism of NGF. Trends Pharmacol Sci 2006;27(2):85–91.

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

regional pain syndrome type I. Pain 2008;138(1):47–60.

122 Wang R, Guo W, Ossipov MH, et al. Glial cell line-derived neurotrophic factor normalizes neurochemical changes in injured dorsal root ganglion neurons and prevents the expression of experimental neuropathic pain. Neuroscience 2003;121(3):815–24.

123 Munson JB, BcMahon SB. Effects of GDNF on axotomized sensory and motor neurons in adult rats. Eur J Neurosci 1997;9(6):1126–9.

124 Ramer MS, Kawaja MD, Henderson JT, Roder JC, Bisby MA. Glial overexpression of NGF enhances neuropathic pain and adrenergic sprouting into DRG following chronic sciatic constriction in mice. Neurosci Lett 1998;251(1):53–6.

125 Herzberg U, Eliav E, Dorsey JM, Gracely RH, Kopin IJ. NGF involvement in pain induced by chronic constriction injury of the rat sciatic nerve. Neuroreport 1997;8(7):1613–8.

126 Bennett DLH, Michael GJ, Ramachandran N, et al. A distinct subgroup of small DRG cells express GDNF receptor components and GDNF is protective for these neurons after nerve injury. J Neurosci 1998;18(8):3059–72.

127 Boucher TJ, Okuse K, Bennett DLH, et al. Potent analgesic effects of GDNF in neuropathic pain states. J Neurosci 1998;18(8):3059–72.

128 Black JA, Liu S, Tanaka M, Cummins TR, Waxman SG. Changes in the expression of tetrodotoxin-sensitive sodium channels with the dorsal root ganglia neurons in inflammatory pain. Pain 2004; 108:237–47.

129 Coull C, Boudreau JA, Bachand D, et al. Trans-synaptic shift in anion gradient in spinal lamina I neurons as a mechanism of neuropathic pain. Nature 2003;424:938–42.

130 Ha SO, Kim JK, Hong HS, et al. Expression of brain-derived neurotrophic factor in rat dorsal root ganglia, spinal cord and gracile nuclei in experimental models of neuropathic pain. Neuroscience 2001;107(2): 301–9.

131 Sebert ME, Shooter EM. Expression of mRNA for neurotrophic factors and their receptors in the rat dorsal root ganglion and sciatic nerve following nerve injury. J Neurosci Res 1993;36(4):357–67.

132 Obata K, Tsujino H, Yamanaka H, et al. Expression of neurotrophic factors in the dorsal root ganglion in a rat model of lumbar disc herniation. Pain 2002;99(1–2):121–32.

133 Woolf CJ, Reynolds ML, Molander C, et al. The growth-associated protein gap-43 appears in dorsal root ganglion cells and in the dorsal horn of the rat spinal cord following peripheral nerve injury. Neuroscience 1990;34(2):465–78.

134 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. PNAS 2002;99(12):8360–5.

135 Herdege T, Fiallos-Estrade CE, Schmid W, et al. 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(3): 155–65.

136 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(1):55–62.

137 Pannese E. The satellite cells of sensory ganglia. Adv Anat Embryol Cell Biol 1981;65:1–111.

138 Devor M. Ectopic discharge in Aof sensory ganglia. Adv Anat Embryol Cell Biol 1981;65:1–111.

139 Wu G, Ringkamp M, Hartke TV, et al. Early onset of spontaneous activity in uninjured C-fiber nociceptors after injury to neighboring nerve fibers. J Neurosci 2001;21(8):RC140.

140 Reichling DB, Levine JD. Critical role of nociceptor plasticity in chronic pain. Trends Neurosci 2009; 32(12):611–8.

141 Catterall WA. Mechanisms: The structure and function of voltage-gated sodium channels. Neuron 2000;26:13–25.

142 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: 283–97.

143 Waxman SG, Cummins TR, Sulayman DH, Fjell J, Blak JA. Sodium channels, excitability of primary sensory neurons and the molecular basis of pain. Muscle Nerve 1999;22:1177–87.

144 Honmou O, Utzschneider DA, Rizzo MA, et al. Delayed depolarization and slow sodium currents in cutaneous afferents. J Neurophysiol 1994;71:1627–41.

145 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(19):8589–96.

146 Kostyuk PG, Veselovsky NS, Tsyandryenko AY. Ionic currents in the somataic membrane of rat dorsal root ganglion neurons. I. Sodium currents. Neuroscience 1981;6:2423–30.

147 McCormack K, Santos S, Chapman ML, et al. Voltage sensor interaction site for selective small molecule inhibitors of voltage-gated sodium channels. PNAS 2013;110(29):E2724–32.

148 Dib-Hajj SD, Cummins TR, Black JA, Waxman SG. Sodium channels in normal and pathological pain. Annu Rev Neurosci 2010;33:325–47.

149 Hains BC, Klein JP, Saab CY, et al. Upregulation of sodium channel Nav1.3 and functional involvement in neuronal hyperexcitability associated with central neuropathic pain after spinal cord injury. J Neurosci 2003;23(26):8881–92.

150 Roza C, Laird JMA, Souslova V, Wood JN, Cervero F. The tetrodotoxin-resistant sodium channel Nav1.8 is essential for the expression of spontaneous activity in damaged sensory axons of mice. J Physiol 2003;550:921–6.

151 Dong XW, Goregoaker S, Engler H, et al. Small interfering RNA-mediated selective knockdown of Na(V)1.8 tetrodotoxin-resistant sodium channel reverses mechanical allodynia in neuropathic rats. Neuroscience 2007;146(2):812–21.

152 Ekberg J, Jayamanne A, Vaughan CW, et al. muO-conotoxin MrVIB selectively blocks Nav1.8 sensory neuron specific sodium channels and chronic pain behavior without motor deficits. Proc Natl Acad Sci USA 2006;103(45):17030–5.

153 Gold MS, Weinreich D, Kim CS, et al. Redistribution of Na(V)1.8 in uninjured axons enables neuropathic pain. J Neurosci 2003;23(1):158–66.

154 Joshi SK, Mikusa JP, Hernandez G, et al. Involvement of the TTX-resistant sodium channel Nav 1.8 in inflammatory and neuropathic, but not post-operative, pain states. Pain 2006;123(1–2):75–82. [Epub 2006 Mar 20].

155 Lai J, Gold MS, Kim CS, et al. Inhibition of neuropathic pain by decreased expression of the tetrodotoxin-resistant sodium channel, NaV1.8. Pain 2002;95(1):143–52.

156 Theile JW, Cummins TR. Recent developments regarding voltage-gated sodium channel blockers for the treatment of inherited and acquired neuropathic pain syndromes. Front Pharmacol 2011;2:2104–11.

157 Elliott AA, Elliott JR. Characterization of TTX-sensitive and TTX-resistant sodium currents in small cells from adult rat dorsal root ganglia. J Physiol (Lond) 1993;463:39–56.

158 Roy ML, Narahashi T. Differential properties of tetrodotoxin sensitive and tetrodotoxin-resistant sodium channels in rat dorsal root ganglion neurons. J Neurosci 1992;12(6):2104–11.

159 Hille B. Chapter 5: Potassium channels and chloride channels. In: Hille B, ed. Ion Channels of Excitable Membranes. Sunderland, Mass: Sinauer.; 2001:131–68.

160 Jessell TM, Kandel ER, Schwartz JR. Chapter 6: Ion channels. In: Kandel E, Schwartz JH, Jessell TM, eds. Principles of Neural Science, 4th edition. New York: McGraw-Hill; 2000:105–24.

161 Rang HP, Dale MM, Ritter JM, Moore PK. Pharmacology. New York: Churchill Livingstone; 2003: 60.

162 Ocana M, Cendan CM, Cobos EJ, Entrena JM, Baeyens JM. Potassium channels and pain: Present realities and future opportunities. Eur J Pharmacol 2004;500(1–3):203–19.

163 Kim SH, Chung JM. An experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat. Pain 1992;50:355–63.

164 Rasband MN, Park EW, Vanderah TW, et al. Distinct potassium channels on pain-sensing neurons. PNAS 2001;98(23):13373–8.

165 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(4):502–50.

166 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(2): 225–8.

167 Catterall WA, Perez-Reyes E, Snutch TP, Striessnig J. International Union of Pharmacology. XLVIII. Nomenclature and structure-function relationships of voltage-gated calcium channels. Pharmacol Rev 2005;57(4):411–25.

168 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(6):527–31.

169 Westenbroek RE, Byers MR. Upregulation of class A Ca2+ channels in trigeminal ganglion after pulp exposure. Neuroreport 1999;10(2):381–5.

170 Neubert JK, Maidment NT, Matsuka Y, et al. Inflammation-induced changes in primary afferent-evoked release of substance P within trigeminal ganglia in vivo. Brain Res 2000;871(2):181–91.

171 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):S1–29.

172 McCallum JB, Kwok WM, Sapunar D, et al. Painful peripheral nerve injury decreases calcium current in axotomized sensory neurons. Anesthesiology 2006; 105(1):160–8.

173 McCallum JB, Kwok WM, Mynlieff M, et al. Loss of T-type calcium current in sensory neurons of rats with neuropathic pain. Anesthesiology 2003;98:209–16.

174 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(3):633–43.

175 Lirk P, Poroli M, Rigaud M, et al. Modulators of calcium influx regulate membrane excitability in rat dorsal root ganglion neurons. Anesth Analg 2008;107(2):673–85.

176 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(3):1045–51.

177 Hogan QH. Role of decreased sensory neuron membrane calcium currents in the genesis of neuropathic pain. Croat Med J 2007;48(1):9–21.

178 Dubel SJ, Starr TV, Hell J, et al. Molecular cloning of the alpha-1 subunit of an omega-conotoxin-sensitive calcium channel. Proc Natl Acad Sci USA 1992; 89(11):5058–62.

179 Olivera BM, Miljanich GP, Ramachandran J, Adams ME. Calcium channel diversity and neurotransmitter release: The omega-conotoxins and omega-agatoxins. Annu Rev Biochem 1994;63:823–67.

180 Evans AR, Nichol GD, Vasko MR. Differential regulation of evoked peptide release by voltage-sensitive calcium channels in rat sensory neurons. Brain Res 1996;712(2):265–73.

181 Cizkova D, Marsala J, Lukacova N, et al. Localization of N-type Ca2+ channels in the rat spinal cord following chronic constrictive nerve injury. Exp Brain Res 2002;147(4):456–63.

182 Cao YQ. Voltage-gated calcium channels and pain. Pain 2006;126(1):5–9.

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.

184 Voscopoulos C, Lema M. When does acute pain become chronic? Br J Anaesth 2010;105(S1): i69–85.

185 Gold M, Gebhart G. Peripheral pain mechanisms and nociceptor sensitization. In: Fishman S, Ballantyne JC, Rathmell JP, eds. Bonica's Pain Management, 4th edition. Philadelphia, PA: Lippincott Williams & Wilkins (LWW); 2010:25–34.

186 D'Mello R, Dickenson AH. Spinal cord mechanisms of pain. Br J Anaesth 2008;101:8–16.