

## A review of dorsal root ganglia and primary sensory neuron plasticity mediating inflammatory and chronic neuropathic pain

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### ABSTRACT

Pain is a sensory state resulting from complex integration of peripheral nociceptive inputs and central processing. Pain consists of adaptive pain that is acute and beneficial for healing and maladaptive pain that is often persistent and pathological. Pain is indeed heterogeneous, and can be expressed as nociceptive, inflammatory, or neuropathic in nature. Neuropathic pain is an example of maladaptive pain that occurs after spinal cord injury (SCI), which triggers a wide range of neural plasticity. The nociceptive processing that underlies pain hypersensitivity is well-studied in the spinal cord. However, recent investigations show maladaptive plasticity that leads to pain, including neuropathic pain after SCI, also exists at peripheral sites, such as the dorsal root ganglia (DRG), which contains the cell bodies of sensory neurons. This review discusses the important role DRGs play in nociceptive processing that underlies inflammatory and neuropathic pain. Specifically, it highlights nociceptor hyperexcitability as critical to increased pain states. Furthermore, it reviews prior literature on glutamate and glutamate receptors, voltage-gated sodium channels (VGSC), and brain-derived neurotrophic factor (BDNF) signaling in the DRG as important contributors to inflammatory and neuropathic pain. We previously reviewed BDNF's role as a bidirectional neuromodulator of spinal plasticity. Here, we shift focus to the periphery and discuss BDNF-TrkB expression on nociceptors, non-nociceptor sensory neurons, and non-neuronal cells in the periphery as a potential contributor to induction and persistence of pain after SCI. Overall, this review presents a comprehensive evaluation of large bodies of work that individually focus on pain, DRG, BDNF, and SCI, to understand their interaction in nociceptive processing.

### 1. Introduction

Pain is a physiological response to injury that has been defined by the IASP as 'an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage' (Pain, 2017). Pain can be categorized as adaptive or maladaptive. Adaptive pain includes inflammatory pain, which is an increase in sensitivity due to an inflammatory response resulting from tissue damage, and nociceptive pain which is caused by the activation of primary nociceptors located in the peripheral nervous system in somatic (skin, muscle, or bone) or visceral (body organs) tissue. Maladaptive pain typically involves abnormal functioning of the nervous system and is neither protective nor informative. Neuropathic pain, which results from injury to the somatosensory nervous system, is an example of maladaptive pain. Nociceptive processing underlying adaptive and maladaptive pain involves both peripheral and central mechanisms. In the periphery, post-translational modification results in peripheral

sensitization, a process where there is an increased sensitivity of the peripheral terminals of primary nociceptors (Lewin et al., 1993; Lewin et al., 1994). Meanwhile, central mechanisms involve central sensitization (Woolf, 1983), which is an increased excitability of spinal neurons triggered by peripheral noxious input thereby creating a state where the response to normal input is greatly enhanced.

The dorsal root ganglion (DRG) houses the cell bodies of primary sensory neurons and projects axons to both the peripheral site of injury and the dorsal horn of the spinal cord. Hence, it is conceivable that the DRG is a major site of nociceptive processing in both adaptive and maladaptive pain states. Various membrane proteins implicated in the pain pathways are found in DRGs and expressed in nociceptors, including voltage gated ion channels, glutamate receptors and transporters, and G-coupled receptors. DRG neurons also express numerous cytokines and chemokines and their receptors, highlighting the important role DRGs play in nociception after tissue injury. While much focus has been given to the spinal cord dorsal horn (SCDH), an important

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central site for the integration of incoming sensory and descending input, less attention has been given to the DRG and peripheral processes that lead to pain hypersensitivity, particularly neuropathic pain.

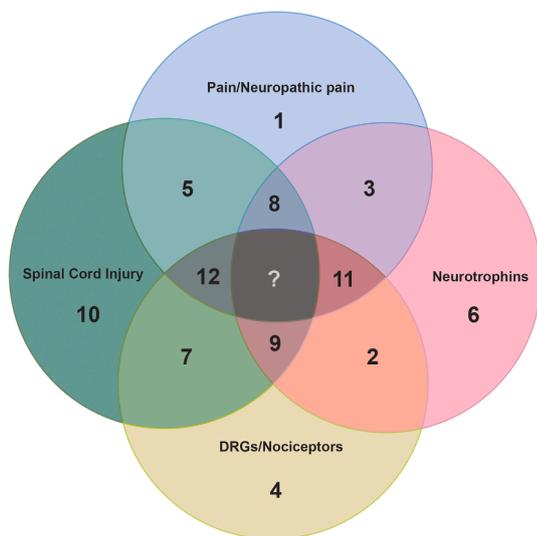
Spinal cord injury (SCI) leads to significant sensorimotor dysfunction, including chronic neuropathic pain. A wealth of studies has focused on changes in the spinal cord that potentially contribute to development and maintenance of neuropathic pain. One of the most promising targets for adaptive plasticity and functional recovery after SCI is brain-derived neurotrophic factor (BDNF) because of its role in neuronal growth and development (Barde et al., 1982; Park & Poo, 2013). BDNF acting through its high affinity receptor, tropomyosin receptor kinase (Trk) B, has been shown to promote adaptive plasticity in both uninjured and injured spinal cord. However, BDNF has also been implicated in pain modulation (Merighi et al., 2008; Pezet, Malcangio, & McMahon, 2002) and in central sensitization (Alles et al., 2021; Biggs et al., 2010; Sikandar et al., 2018). While the expression of BDNF in nociceptors has long been recognized, more recent studies have shown that BDNF is expressed in non-nociceptors in the DRG (Rutlin et al., 2014) as well as non-neuronal cells in the periphery (Hahn et al., 2006; Hahn et al., 2005; Wang et al., 2015). Therefore, any exploration into the peripheral processes mediating neuropathic pain and the role of the DRG must also include BDNF signaling, as BDNF is very likely modulating the activity and function of ion channels, glutamate receptors, and cytokines in the DRG.

Given the limited number of studies that have methodically examined DRG plasticity and peripheral BDNF signaling in the development of neuropathic pain after SCI, we take this opportunity to write a review evaluating what is currently known. We recognize a need to bring together the large bodies of work that independently focus on pain, nociceptors and DRG, BDNF, and SCI, and to understand how all the substrates implicated in the individual components work together (Fig. 1, Table 1). Although similar acknowledgments can be made of

**Table 1**

Examples of 12 representative review literatures on pain, SCI, neurotrophins, and/or nociceptors through the past 30 years. Each article can be located as a corresponding number (designated by # column) in Fig. 1.

| # | Reference                 | Conclusions/summary  | Topic   |
|---|---------------------------|--|---|
| 1 | Millan (1999)             | The induction of pain: an integrative review   | Pain  |
| 2 | Mendell (2003)            | Peripheral neurotrophic factors and pain   | Neurotrophic factors<br>Periphery/nociceptors |
| 3 | Pezet and McMahon (2006)  | Neurotrophins: mediators and modulators of pain  | Neurotrophic factors<br>Pain                  |
| 4 | Woolf and Ma (2007)       | Nociceptors: noxious stimulus detectors  | Nociceptors                                   |
| 5 | Yeziarski (2009)          | SCI pain: Spinal and supraspinal mechanisms  | Pain<br>SCI                                   |
| 6 | Numakawa et al. (2010)    | BDNF function and intracellular signaling in neurons   | Neurotrophins                                 |
| 7 | Walters (2012)            | Nociceptors as chronic drivers of pain and hyperreflexia after SCI: an adaptive-maladaptive hyperfunctional state hypothesis | Nociceptors<br>SCI                            |
| 8 | Garraway and Huie. (2016) | Spinal Plasticity and Behavior: BDNF-Induced Neuromodulation in Uninjured and  | SCI<br>Pain<br>Neurotrophins                  |



**Fig. 1.** Examples of some review literature on pain, SCI, neurotrophins, and nociceptors through the past 30 years. This figure shows 12 recent review articles related to the field. Each number in the diagram can be linked to an article listed in Table 1. Although not demonstrative of the full scope of each topic, these reviews i) show most recent developments in the field or ii) are highly cited in other work, which implies their impact on driving the direction of other research. It should be noted that while several articles focus on 2 (article #2, 3, 5 and 7) or 3 (article # 8, 9, 11 and 12) topics, none of the articles examines all 4 topics (center space designated by '?'). This demonstrates a lack of reviews that discuss all the topics together to shed light on central as well as peripheral mechanisms including DRG and nociceptor plasticity in pain hypersensitivity, including neuropathic pain after SCI. The gap in perspective shows potential future research opportunities and development of new research questions for the field.

(continued on next page)

Table 1 (continued)

| #  | Reference              |  | Conclusions/<br>summary  | Topic  |
|----|------------------------|--|--|--|
| 9  | Keefe et al. (2017)    | Injured Spinal Cord<br><br>Targeting Neurotrophins to Specific Populations of Neurons: NGF, BDNF, and NT-3 and Their Relevance for Treatment of Spinal Cord Injury | BDNF-induced nociceptive plasticity in naïve and SCI conditions<br><br>Review of neurotrophins NGF, BDNF, and NT-3 and their effects on specific populations of neurons, including nociceptors, after SCI  | SCI<br>Neurotrophins<br>Nociceptors              |
| 10 | Alizadeh et al. (2019) | Traumatic SCI: An overview of pathophysiology, models, and acute injury mechanism  | Comprehensive overview of pathophysiology of SCI, neurological outcomes of human SCI, and available experimental model systems that have been used to identify SCI mechanisms                              | SCI  |
| 11 | Cao et al. (2020)      | Function and Mechanisms of truncated BDNF receptor TrkB.T1 in Neuropathic pain   | Review of studies on truncated TrkB.T1 isoform, and its potential contribution to hyperpathic pain through interaction with neurotrophins and change in intracellular calcium levels.                      | Neuropathic pain<br>Neurotrophins<br>Nociceptors |
| 12 | Garraway (2023)        | BDNF-Induced plasticity of spinal circuits underlying pain and learning  | Review of literature on various types of plasticity that occur in the spinal cord and discussion of BDNF contribution in mediating cellular plasticity that underlies pain processing and spinal learning. | Pain<br>SCI<br>Neurotrophins                     |

other ganglia systems such as the trigeminal, this review focuses on the critical role of the DRG to the development and expression of chronic pain. The present review begins with a brief overview of adaptive and maladaptive pain. Next, we discuss the DRG as an important peripheral site for nociceptor hyperexcitability and nociceptive processing that leads to pain, including neuropathic pain after SCI. BDNF-TrkB signaling in pain after SCI is also reviewed; however, because detailed reviews of BDNF-TrkB signaling in pain and plasticity after SCI were recently published by our laboratory (Garraway, 2023; Garraway & Huie, 2016), the present review focuses on cellular and molecular changes in the DRGs and the primary afferent sensory neurons after peripheral inflammatory insults and SCI to explore how the altered mechanisms may underlie development and maintenance of neuropathic pain.

## 2. Overview of pain

Pain is a complex sensory state that integrates a variety of external pain-causing, or noxious, inputs through peripheral and central nervous system (CNS) processing. Pain can be broadly defined as adaptive or maladaptive and is composed of a perceptive, reflexive component as well as an affective and emotional component (Melzack & Casey, 1968; Raja et al., 2020). Normal pain is acute and occurs to minimize contact

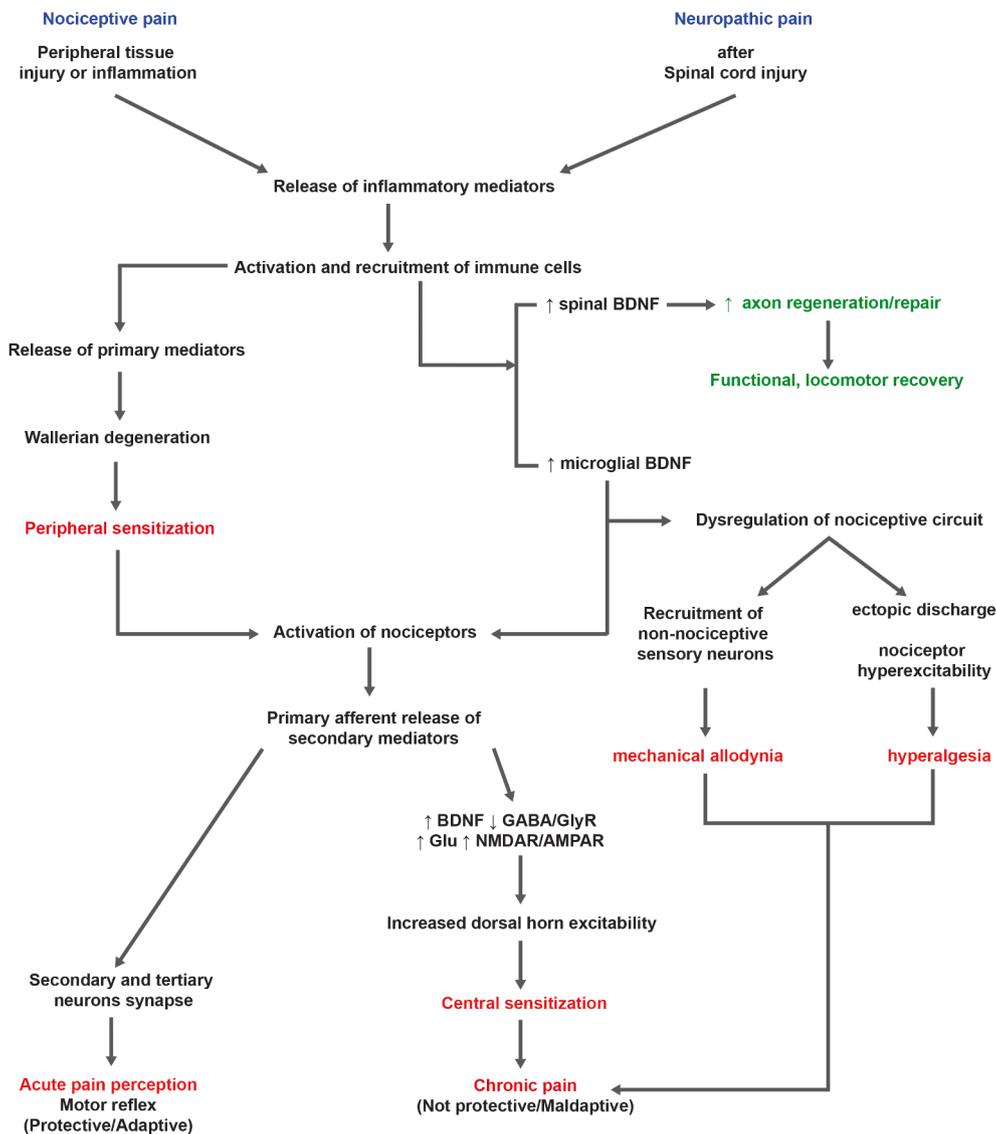
with the noxious mechanical, thermal, or chemical stimuli that is high-threshold and intense (Basbaum et al., 2009), demanding immediate attention and activating a motor withdrawal reflex to prevent further damage (Millan, 1999). In response to injury or tissue damage, specialized peripheral sensory neurons called nociceptors detect nociceptive stimuli and transmit pain information to the initial pain processing site of the CNS, SCDH. Nociceptors release neuropeptides and other substances to trigger an immune response that promotes wound healing and protection against potential infections (Millan, 1999). Activation of the immune system serves to lower the pain-sensing threshold, so that the nociceptors can now detect stimuli with a wider range of intensities, which prevents further damage. The decreased activation threshold results in a phenomenon known as pain hypersensitivity (Woolf, 2010).

Some pain outlasts the initial inflammatory, tissue or nerve injury and is not elicited by a particular external stimulus. This maladaptive pain becomes chronic and debilitating and can be expressed as hyperalgesia (i.e., painful stimulus is perceived as more painful) and allodynia (i.e., non-painful stimulus now perceived as painful). Maladaptive pain is neither protective nor adaptive and can occur spontaneously. Moreover, it can result in potential cognitive effects that are comparable to depressive-like states (Millan, 1999; Peirs & Seal, 2016). Neuropathic pain, which is pain caused by injury to the nervous system (Costigan et al., 2009; Woolf & Mannion, 1999) is an example of maladaptive pain. Fig. 2 illustrates the fundamental difference between nociceptive and neuropathic pain.

### 2.1. Neuropathic pain after SCI

SCI is a mechanical damage to the spinal cord that leads to motor deficits below the site of the lesion, autonomic dysfunction, and chronic pain. In the U.S., there are approximately 302,000 individuals living with SCI, with an estimated 18,000 new cases occurring each year (NSCISC, 2023). After SCI, spontaneous functional recovery can take place to regenerate and restore the connectivity of the damaged axons. Studies have shown that while neuroplasticity is necessary for recovery, the same mechanisms may also be maladaptive. Nociceptive pain is a very common effect of SCI that occurs shortly after the primary injury, typically due to inflammation of the lesion area (Finnerup, 2013). However, within months after the injury, a more clinically relevant neuropathic pain develops in 40–50 % of individuals, often described as burning, stabbing, and/or shock-like (Finnerup et al., 2001; Siddall et al., 2003). Although its underlying neural mechanisms are not fully elucidated, neuropathic pain after SCI involves central and peripheral mechanisms (Bedi et al., 2010; Carlton et al., 2009; Christensen & Hulsebosch, 1997; Crown et al., 2006; Garraway et al., 2014; Hulsebosch et al., 2009; Yeziarski et al., 2004), with many neural substrates implicated in these processes. Because the mechanisms of neuropathic pain are complex, therapeutic interventions aimed at the alleviation of neuropathic pain are often limited. For instance, despite development of diverse treatment strategies, from neurosurgery (Jug et al., 2015; Rath & Balain, 2017) to behavioral (Ilha et al., 2019; Sandrow-Feinberg & Houle, 2015) and pharmacological (Baroncini et al., 2021; Bracken et al., 1997) therapies, chronic neuropathic pain remains refractory (Baastrup & Finnerup, 2008), an effect that is directly linked to the diverse neural processes and substrates that are implicated and the heterogeneity of SCI and chronic pain etiologies.

Neuropathic pain after SCI can be localized or widespread in that the symptoms can occur at the level of the injury (“at-level”) or below the injury site (“below-level”) throughout the entire body. A variety of factors change after SCI that can ultimately contribute to neuropathic pain, which makes studying the underlying mechanism particularly difficult (Finnerup, 2013). One major cellular change is central sensitization, which is a potentiation of pain by CNS mechanisms. Central sensitization occurs because neurons in the nociceptive pathway exhibit increased membrane excitability and synaptic efficacy (Woolf, 1983),



**Fig. 2.** Comparison of nociceptive and neuropathic pain. Diagram illustrates an overview of critical mechanisms that lead to development of nociceptive and neuropathic pain after peripheral or central (e.g., SCI) injuries. Some mechanisms overlap, but distinct pathways and modulators involved are noted. Highlighted text indicates negative (red) or positive (green) outcomes of neural plasticity. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

although it is now thought to involve spinal mechanisms that are independent of primary afferent input (Harte et al., 2018). Nonetheless, the onset of central sensitization drives nociceptive neurons to become hyperexcitable and consequently leads to pain (Brown & Weaver, 2012).

### 3. Overview of the dorsal root ganglia (DRG)

Pain is transmitted by primary afferent sensory fibers known as nociceptors. The cell bodies of nociceptors, along with other primary sensory neurons, are in the DRG. DRGs are highly complex structures situated on either side of the spinal cord, spanning the length of the spinal column. Each DRG rises from the SCDH as an enlargement of the dorsal root (Krames, 2014). The structure and function of the DRGs have been studied primarily in rodents (Abraira & Ginty, 2013; Koltzenburg et al., 1997; Li et al., 2016; Lynn & Carpenter, 1982; Reinhold et al., 2015; Usoskin et al., 2015), providing insight into signaling pathways, network connectivity, and molecular and functional involvement in transduction of pain (Mogil, 2009). Rodent models have been useful as DRGs are almost impossible to access in living humans and even very difficult to obtain postmortem (Rostock et al., 2018). Recent

advancements have been made in investigation of human DRGs using human-derived DRGs (Davidson et al., 2014; Rostock et al., 2018) or human embryonic stem cells that can be differentiated into human sensory neuron-like cells (Blanchard et al., 2015; Chambers et al., 2012). With genetic tools, such as RNA sequencing (RNA-seq) and proteomics, human DRGs have been better characterized and compared to previously established features of rodent DRGs, which is important for development of targeted treatments in the clinic. Ray et al. (2018) found that human DRG transcriptome highly corresponds to that of mouse DRGs, and that the majority of DRG-related genes found in the commonly used C57BL/6 mouse strain are strongly associated with human DRGs, suggesting that the mouse is indeed a valid translational model for studies of sensory neurons and pain research. Furthermore, proteomic studies comparing human and mouse DRGs have also found a large overlap. Schwaid et al. (2018) found shared proteins for extracellular trafficking and myelin sheath, which are both integral for signal transmission, as well as ion channels (such as voltage-gated sodium channel, Nav 1.7) that are important for nociception. However, while the general proteomic and transcriptome profiles of human and mouse DRGs are similar, specific expression levels and functions can be distinct.

For example, human DRGs express Na<sub>v</sub> 1.7 in higher subtype proportions and lower Na<sub>v</sub> 1.8 expression, while the mouse DRGs show the opposite (Chang et al., 2018).

Because most previous molecular and functional analyses of nociceptive neurons have used rodent models, especially for studies of peripheral nerve injury (Dowdall et al., 2005), SCI, and inflammatory and neuropathic pain (Jang et al., 2017; Nirogi et al., 2012), the current review will discuss rodent DRGs unless specified (see (Haberberger et al., 2019)) for a thorough review of human DRGs).

DRGs are typically circular to oval (Esposito et al., 2019; Lee et al., 1986). They are pseudounipolar neurons with an offshoot cell body connected by a single axon that branches into two different directions. The DRG cell bodies do not synapse onto each other (Krames, 2014) as they are separated by layers of intermittent satellite glial cells (SGCs) (Pannese, 2010) and Schwann cells. The sheaths allow penetration of neurotransmitters and other molecules into the neuron, rendering the DRG somas susceptible to inflammatory mediators and drugs in the system (Crawford & Caterina, 2020; Esposito et al., 2019). DRG cell bodies can also filter information received from the peripheral branch at the T-junction (Du et al., 2017; Hao et al., 2023).

### 3.1. DRG modulation of sensory information

DRGs have a critical role in the modulation of peripheral and central sensory processing, such as inflammation and development of neuropathic pain. The offshoot cell body allows continuity of information transmission between the peripheral (somatosensory) end organ (e.g., skin, viscera) and the CNS (spinal cord) through two axons, which display distinct electrophysiological, structural, and molecular properties. The peripheral process behaves similarly to a dendrite. It generates the action potential at the terminal that propagates towards the stem and the T-junction. The central process receives the signal from the bifurcation and sends it to the CNS. Some factors that may contribute to pain have been observed in the peripheral axon after inflammation or injury. These include extracellular-signal-regulated kinase (ERK), a kinase that is usually found downstream of many receptors' activation (Perlson et al., 2005), and Transient receptor potential vanilloid (TRPV) –1, a membrane ion channel that is linked to noxious heat stimuli in pain-sensing neurons. TRPV1 was one of the first receptors associated with sensory transduction (Caterina et al., 1997) and is expressed in peripheral and central terminals, and at the cell bodies of sensory neurons (Clark et al., 2018). TRPV1 was shown to be selectively transported to the peripheral axonal branch after inflammation (Ji et al., 2002), which implicates its role in the development of pain. The central branch of the DRG enters the spinal cord and terminates in the SCDH (Basbaum et al., 2009; Millan, 1999).

### 3.2. Sensory neurons – nociceptors

Primary sensory neurons are known as the first-order neurons because they receive external sensory stimuli and initiate the transmission process. Upon activation, the first-order neurons conduct action potentials to the SCDH, where information can be carried via second-order neurons through the dorsal column (e.g., mechanosensory, proprioception) or the spinothalamic pathway (e.g., temperature, pain) (Purves D, 2001). DRGs contain the largest proportion of sensory neurons, but other ganglia, such as trigeminal (Bhuiyan et al., 2023; Edvinsson et al., 2022; Goto et al., 2016; Lopes et al., 2017) and vagal (Herrity et al., 2015; Ichikawa et al., 2007; Lázár et al., 2018) ganglia are also enriched with sensory neurons, though outside of the scope of the current review. Traditionally, sensory neurons are morphologically and functionally classified as A $\beta$ -, A $\delta$ -, or C-fibers, based on the degree of myelination, sensory modality, and action potential conduction velocity (Gardner, 2010; Horch et al., 1977). Recent single-cell RNA-seq (Li et al., 2016; Usoskin et al., 2015; Wang et al., 2021) and spatial transcriptomic studies (Jung et al., 2023; Tavares-Ferreira et al., 2022) have found

more diversity in subclasses of DRGs and describe a more complex and nuanced understanding of the molecular heterogeneity within the DRG neurons. High-coverage single-cell RNA-seq was performed to find 10 types and 14 subtypes of DRG neurons with distinct marker genes, such as galanin, natriuretic peptide B, tyrosine hydroxylase (TH), and MAS-related GPR family member D (Li et al., 2016). Electrophysiological analysis and deep sequencing have identified specific ion channels mediate subtype-specific stimulus modalities (Zheng et al., 2019) that correspond to the subtypes established by transcriptome profiles. Though not fully demonstrative of the heterogeneity of the sensory neurons, this review uses the traditional, albeit simpler, morphology- and function-based classification system, as it appropriately demonstrates the diversity of morphologies and molecular properties among the sensory neurons, especially in the context of how different sensory neurons can selectively fire action potentials with stimulus intensities that reach distinct thresholds (Basbaum et al., 2009). The sensory neurons process a variety of sensory modalities such as temperature (thermoreceptors), pain (nociceptors), pressure (mechanoreceptors), and orientation (proprioceptors). The nociceptors are the smallest of the primary afferents innervating the skin and deep visceral tissues, and are activated by high threshold, intense stimuli. They can detect thermal, mechanical, and combination of different sensory stimuli (Basbaum et al., 2009; Dubin & Patapoutian, 2010; Mendell et al., 1999). Nociceptors are broadly classified into two types: A $\delta$ -fibers and C-fibers. A $\delta$ -fibers are small-diameter, thinly myelinated neurons that produce fast onset pain (Djouhri & Lawson, 2004) described as sharp and pricking (Hladnik et al., 2015). A $\delta$ -fibers can be type I, which is activated by mechanical stimuli and high threshold heat (>50 °C), or type II, which has a high mechanical threshold but lower temperature threshold and is responsible for the initial acute pain response (Hladnik et al., 2015). Most nociceptors are small-diameter unmyelinated C-fiber neurons (Lumpkin & Caterina, 2007), which are polymodal and can detect mechanical, thermal, and chemical stimuli. The activation of C-fibers produces diffused dull, burning pain that is poorly tolerated (Hladnik et al., 2015).

Nociceptors are composed of four functional components: i) peripheral terminal transduces the stimuli and initiates action potentials if the stimuli cross the threshold, ii) the axon propagates the action potentials towards the central terminal and becomes the presynaptic terminal of the first synapse in the CNS sensory pathway (Woolf & Ma, 2007), iii) the cell body responds to changes in the environment by altering transcription of neuropeptides, growth factors, and expression of ion channels and receptors, and iv) the central terminal. Noxious stimuli are received through the free unencapsulated nerve endings innervating the wall of arterioles, connective tissue, and skin (Zylka et al., 2005). Under normal, physiological circumstances, nociceptors respond exclusively to painful or potentially painful stimuli but are otherwise electrically silent (Dubin & Patapoutian, 2010; Woolf & Ma, 2007), requiring stimuli to cross the threshold at sufficient amplitude and duration to depolarize peripheral terminals. The nociceptors transduce the high intensity stimuli, conduct action potentials, and transmit signals to CNS neurons through activation of different receptors and channels on the membrane (Snider & McMahon, 1998). Some of the ion channels, receptors, and intracellular signaling proteins include voltage-gated sodium channels (VGSCs), specifically, Nav 1.7, 1.8 and 1.9 (Bennett et al., 2019; Wang et al., 2011), TRP receptors (Caterina et al., 1999), neurofilament peripherin (Bae et al., 2015), and isolectin B4 (IB4; Bogen et al., 2005). The depolarizing currents generated by the receptors, if sufficient, turn into action potentials, which are propagated to the CNS. VGSCs and potassium channels determine neuronal excitability by transferring the electrical input from the peripheral nerve terminals to the central neurons in the spinal cord (Woolf & Costigan, 1999).

The action potential that is generated in the first order neuron is conducted to specific laminae in the SCDH where nociceptor terminals are topographically organized. The distinct organization allows

activation of second order projection neurons that underlie acute pain and emotional, affective, and reflexive responses (Woolf & Costigan, 1999). When nociceptors synapse with dorsal horn neurons, they release glutamate and peptides, such as substance P (SP), calcitonin gene-related peptide (CGRP), and somatostatin, to alter synaptic and efferent signaling (Dubin & Patapoutian, 2010). Glutamate acts primarily on the ionotropic glutamatergic receptors,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) (Yoshimura & Jessell, 1990) and N-methyl-D-aspartate (NMDA) (King et al., 1988; Woolf & Salter, 2000), to mediate fast excitatory postsynaptic potentials (EPSPs) produced by the AMPARs, followed by NMDAR-mediated slow EPSPs. Glutamate, along with the neuromodulators, act on metabotropic receptors that can induce the activation of several second messenger systems and downstream protein kinases. The growth factor, BDNF is also released from nociceptors and shown to mediate actions akin to central sensitization (Thompson et al., 1999). A more detailed description of the role of VGSCs, glutamate, and BDNF in pain sensation is provided in the following sections.

### 3.3. VGSCs in DRG and sensory neuron are critical in pain

While there is a large body of work evaluating other channels, this review focuses on VGSCs because sodium channels are critical to the action potential initiation and can be regulated by various receptors, including receptor tyrosine kinases (D'Arcangelo et al., 1993; Hilborn et al., 1998), such as TrkB. In fact, some subtypes of VGSCs that are exclusively expressed on sensory neurons have been reported to be in association with TrkB for normal function (Blum et al., 2002) and also contribute to neuropathic pain (Sun et al., 2022).

#### 3.3.1. Types of VGSCs

VGSCs are generally expressed throughout the body as Nav 1.1–1.9 (Goldin et al., 2000) and are responsible for generation of the rising phase of the action potential (Hille, 1970, 2022). Thus, they are critical in neuronal excitability (Bennett et al., 2019). VGSCs are classified by their response to the channel blocker tetrodotoxin (TTX), as either TTX-sensitive (TTX-s; Nav 1.1–1.7) or -resistant (TTX-r; Nav 1.8 and 1.9) channels (Bossu & Feltz, 1984; Catterall, 1992; Elliott & Elliott, 1993). TTX-s VGSCs tend to activate more rapidly and display faster kinetics (Blair & Bean, 2002). TTX-r VGSCs recover faster from inactivated state than TTX-s currents almost by tenfold (Cummins & Waxman, 1997; Elliott & Elliott, 1993). At least 5 subtypes of VGSC (Nav 1.1, 1.6, 1.7, 1.8 and 1.9) are highly expressed in DRG neurons, which enable them to produce both fast-inactivating TTX-s and slow-inactivating TTX-r sodium currents (Rush et al., 1998). Specifically, TTX-r VGSCs are preferentially expressed in C and A $\delta$  sensory neurons (Akopian et al., 1996; Djouhri et al., 2003), but other DRG neurons also express a combination of TTX-s and TTX-r channels, which influence their contribution to electrogenic properties under normal or pathological conditions. These subtypes include TTX-s Nav 1.7 (Dib-Hajj et al., 2013), and TTX-r Nav 1.8 (Hameed, 2019; Sangameswaran et al., 1996; Watanabe et al., 2014) and 1.9 (Dib-Hajj et al., 2015; Tate et al., 1998). These three VGSC subtypes are thought to be closely associated with nociceptor function, due to their identification in humans with abnormal sensitivity to pain (Dib-Hajj et al., 2005; Faber et al., 2012; Huang et al., 2015). Nav 1.7 is expressed predominantly in small-diameter DRG neurons (Black et al., 2004) and is also expressed in sympathetic neurons (Black et al., 1996; Toledo-Aral et al., 1997). Nav 1.8 and 1.9 are preferentially expressed in DRG neurons (Djouhri et al., 2003; Fukuoka et al., 2008), but Nav 1.9 is also expressed in myenteric neurons and can also be found in free nerve terminals and central terminals in the spinal cord (Dib-Hajj et al., 1998). Nav 1.9 is only expressed on C fibers, while Nav 1.8 is found in both C and A fibers (Amaya et al., 2000; Decosterd et al., 2002).

Nav 1.7 responds to small depolarizing stimuli close to the neuronal resting membrane potential (Cummins et al., 1998), amplifying accumulated subthreshold signals deployed at nociceptor nerve terminals

(Toledo-Aral et al., 1997). Thus, Nav 1.7 determines the gain of nociceptor activation (Rush et al., 2007). Nav 1.7 also contributes to synaptic transmission by impacting neurotransmitter release (Alexandrou et al., 2016). In addition, Nav 1.7 hyperfunction has been implicated in driving evoked and spontaneous pain symptoms by increasing excitability and spontaneous activity (Dib-Hajj et al., 2005). A large portion of nociceptors are dependent on Nav 1.8 and 1.9 for axonal propagation (Klein et al., 2017). Nav 1.8 channels carry most of the sodium current (Blair & Bean, 2002) and recover more quickly from inactivation (Dib-Hajj et al., 1999), thereby contributing to repetitive firing and regulating neuronal excitability. Nav 1.9 is activated near resting membrane potential and produces a large persistent current due to its slow activation and inactivation kinetics (Cummins et al., 1999). Hence, like Nav 1.7, Nav 1.9 is thought to act as a threshold channel that determines neuronal excitability and prolongs the depolarizing response to stimuli rather than contributing to the amplitude of action potentials (Dib-Hajj et al., 2015; Herzog et al., 2001; Ostman et al., 2008).

#### 3.3.2. VGSCs play a role in mediating injury-induced pain

VGSC expression and the development of neuropathic pain have been linked in other studies (Black et al., 1999; Gold et al., 2003; Lai et al., 2002). Nav 1.7, 1.8 and 1.9 have been targeted to relieve symptoms of neuropathic pain. It was reported that moderate loss of function of Nav 1.8 is associated with reduced pain sensitivity in humans and causes decreased excitability of mouse DRG neurons (Duan et al., 2016). The development of ectopic activity in nociceptors and other sensory neurons (Boucher et al., 2000; Liu et al., 2000; Wall & Gutnick, 1974; Wu et al., 2001) contribute to maintaining peripheral neuropathic pain (Devor, 2006; Haroutounian et al., 2014). Intravenous TTX inhibited ectopic activity in damaged rat DRG and SCDH neurons (Omana-Zapata et al., 1997) and reduced neuropathic pain behaviors (Lyu et al., 2000). After injury or inflammation, primary afferent hyperexcitability has been correlated with upregulation of both TTX-s and TTX-r VGSCs on SCDH neurons (Hains et al., 2003; Hains et al., 2005). Furthermore, studies have shown that the mRNA and/or protein levels of Nav 1.7, 1.8, and 1.9 in DRG neurons are increased after peripheral inflammation (Black et al., 2004; Coggeshall et al., 2004; Okuse et al., 1997; Strickland et al., 2008). Treating DRG neurons with inflammatory mediators increased the number of active Nav 1.9 channels and increased neuronal excitability (Binshtok et al., 2008; Maingret et al., 2008). This finding implicates Nav 1.9 in lowering the threshold and increasing the number of action potentials to drive DRG neuron hyperexcitability associated with inflammatory pain. Nav 1.8 expression was reported to increase in patients with neuropathic pain (Joshi et al., 2006), and Nav 1.9 gain-of-function mutations have also been identified in patients with painful peripheral neuropathy (Huang et al., 2014).

However, specific changes in VGSC expression after peripheral nerve injury or in experimental neuropathic pain models are less clear. For example, in animal models of neuropathic pain, Nav 1.7, 1.8 and 1.9 were reduced in the DRGs (Berta et al., 2008; Cummins & Waxman, 1997; Dib-Hajj et al., 1998; Gold et al., 2003; Kim et al., 2002). Likewise, there was a reduction in Nav 1.8 and Nav 1.9 in the DRGs following peripheral axotomy (Coward et al., 2000) and after lumbar (L) 5 sciatic nerve ligation in the nearby uninjured L4 DRG (Dong et al., 2007). Decosterd et al., 2002 reported near complete depletion of Nav 1.8 and 1.9 in L5 DRG after lesion of the L5 spinal segmental nerve, and the expression in neighboring uninjured DRGs was unchanged. Meanwhile, Nav 1.8 and 1.9 levels in L4 DRG were not changed following a central axonal injury of L4. Contrastingly, increased immunoreactivity for Nav 1.8 was observed in tissue samples from animal pain models (Novakovic et al., 1998), likely in uninjured C-fibers (Gold et al., 2003), and patients of persistent pain conditions (Shembalkar et al., 2001). In rodent neuropathic pain models, Nav 1.8-specific inhibitor reversed mechanical allodynia (Jarvis et al., 2007), but selective deletion of Nav 1.8 (Akopian et al., 1999; Kerr et al., 2001) did not prevent development of neuropathic pain. These different outcomes indicate the tremendous

amount of injury-related plasticity that occurs within the DRG and furthermore show that VGSCs are differentially involved in pain modulation, an effect that might be dependent on both species' differences and the type of injury.

### 3.4. Overview of glutamate and glutamate receptors

Glutamate is one of the most abundant excitatory and nociceptive neurotransmitters in the periphery (Keast & Stephensen, 2000). Glutamate binds to and activates ionotropic AMPA/kainate and NMDA glutamatergic receptors, and several metabotropic receptors. Glutamate receptors, such as NMDARs, are found throughout the nervous system (Monaghan & Cotman, 1985; Monyer et al., 1994) and primary sensory neurons. Receptors that engage with glutamate are synthesized in the DRG cell body and transported to the nerve terminals in the peripheral end organs, such as the skin, muscles, and joints (Carlton et al., 1995; Ma & Hargreaves, 2000). Primary sensory neurons express and release glutamate from central and peripheral terminals (Bae et al., 2000; deGroot et al., 2000) as well as from their cell bodies (Kung et al., 2013). Likewise, glutamatergic receptors and glutamate transporters have been observed in the cell bodies and terminals of the primary sensory neurons.

All four types of AMPAR subunits (GluA1-4) are expressed on sensory ganglia and central terminals. GluA1 is ubiquitously distributed in both myelinated and unmyelinated peptidergic nociceptors (Sato et al., 1993; Tachibana et al., 1994), while the GluA4 subunit is expressed predominantly on non-peptidergic neurons that are strongly associated with neuropathic pain (Willcockson & Valtchanoff, 2008). AMPARs are also expressed on the central terminals of the primary sensory neurons and in the SCDH, generally in laminae I-II, though the expression varies between different subtypes (Larsson & Broman, 2011). AMPARs are located in pre-, post-, and extra-synaptic membranes (Bredt & Nicoll, 2003; Malinow & Malenka, 2002). Synaptic AMPARs have been shown to contribute to nociceptive inputs (Hartmann et al., 2004) and changes to synaptic trafficking and Ca<sup>2+</sup>-permeability have been implicated in excitotoxicity and persistent inflammatory pain (Choi et al., 2010; Ferguson et al., 2008; Hartmann et al., 2004; Tao, 2010). Extrasynaptic AMPARs move rapidly between the membrane and the intracellular compartments (Bredt & Nicoll, 2003; Carroll et al., 1999; Petrini et al., 2009) and have been implicated in the maintenance of persistent inflammatory pain (Kopach et al., 2011) and nerve injury-induced pain (Napier et al., 2012).

The NMDA receptor is a ligand-gated ion channel that mediates a major component of excitatory neurotransmission in the central nervous system. NMDA channel kinetics are much slower than that of AMPARs, due to the requirement for membrane depolarization to release the Mg<sup>2+</sup> block (Paoletti, 2011). NMDARs consist of combinations of GluN1, GluN2, and GluN3 subunits (Paoletti et al., 2013). Functional receptors comprise of two GluN1 subunits, with either 2 GluN2 subunits or a combination of GluN2 and GluN3 subunits. Of the subunits, GluN2 is also expressed as isoforms GluN2A, 2B, 2C, 2D, and the differential composition and expression of these subunits determine NMDAR function (Salter et al., 2009). NMDARs are found on the cell bodies of both small and large diameter sensory neurons (Liu et al., 1994; Marvizón et al., 2002; Sato et al., 1993) and almost half of peripheral axons (Liu et al., 2004). NMDARs and their receptor composition are also differentially distributed in the cell soma and pre-, post-, and extra-synaptic terminals. The differential distribution of NMDAR subunits demonstrates the complexity of NMDAR function and overall contribution in pain. Studies show synaptic inputs into superficial regions of the SCDH, where nociceptive afferents are integrated with interneurons and descending input from the brain (Todd, 2010) are mainly mediated by GluN2A and GluN2B subunits (Bardoni et al., 2004; Shiokawa et al., 2010).

Glutamate also engages metabotropic receptors, which are family C G-protein-coupled receptors. To date, there are eight subtypes of

metabotropic glutamate receptors (mGluRs; R1–R8), which are classified in three groups based on sequence similarities. Group I, containing mGluR1 and 5 is excitatory, while Groups II and III are inhibitory (Conn & Pin, 1997; Schoepp et al., 1999). All three groups of mGluRs are also expressed in DRGs, mostly mGluR2/3 in 40–52% of small-diameter cells (Carlton & Hargett, 2007; Carlton et al., 2001). These receptors may negatively regulate glutamate release to modulate nociceptive input (Carlton et al., 2001; Palazzo et al., 2014).

#### 3.4.1. Glutamate and glutamate receptors in pain hypersensitivity

While both ionotropic and metabotropic glutamate receptors are implicated in persistent pain states, the role of the ionotropic receptors, primarily the NMDAR, is more thoroughly studied and will be emphasized in this section. NMDARs (Liu et al., 1994; Lu et al., 2003) and AMPARs (Carlton et al., 1995; Coggeshall & Carlton, 1998) are both transported from the cell bodies to the central terminals where they are activated by endogenously released glutamate that ultimately leads to sensitization of spinal cord neurons (Coderre & Melzack, 1992; Dickenson & Sullivan, 1987). Extensive studies have been done on post-synaptic NMDARs in the afferent terminals and their contributions to neuropathic pain, especially in central sensitization (Ji et al., 2003; Woolf & Salter, 2000; Zhang et al., 2016). GluN2B-containing NMDARs have been shown to be involved in neuropathic pain development following injury (Qu et al., 2009; Suzuki et al., 2001). Consistently, the GluN2B subunit is preferentially localized to the unmyelinated axons that synapse in the superficial regions of the SCDH (Temi et al., 2021). The GluN1 subunit is also implicated in pain. Targeted deletion of GluN1 in the SCDH of adult rats and/or mice attenuated both inflammatory (Garraway et al., 2009) and injury-induced pain (South et al., 2003).

In pathological conditions, such as following peripheral nerve injury, glutamate expression is increased in the DRG neurons (Kung et al., 2013), and after injury or inflammation, release of endogenous glutamate activates NMDARs on the primary afferent peripheral terminals, resulting in development of pain behaviors (Omote et al., 1998). Gong et al. (2014) showed that following chronic constriction injury of the sciatic nerve, glutamate-induced inward currents were increased in small diameter neurons, as well as neurons that were responsive to NMDA and AMPA. Also, peripheral inflammation increased the number of peripheral axons that express glutamate receptors (Du et al., 2006; Du et al., 2003). Exogenous administration of glutamate, NMDA, or AMPA caused an induction of mechanical hyperalgesia in the rat hind paws (Ferreira & Lorenzetti, 1994; Parada et al., 2003), and glutamate triggers action potentials in an NMDAR dependent manner (Laursen et al., 2014). On the other hand, blocking NMDA (Christoph et al., 2005) and AMPA/kainate (Lee et al., 2001) receptors resulted in an attenuation of pain behavior and blockade of nociceptor activity in inflammatory and neuropathic models (Jang et al., 2004). Similarly, in rodent neuropathic pain models, NMDAR antagonists, such as memantine, MK801, and ketamine led to a decrease in mechanical hyperalgesia (Burton et al., 1999) by the reduction of spinal cord sensitization.

#### 3.4.2. Presynaptic NMDA receptors contribute to pain

Studies show NMDARs are also found at presynaptic nerve terminals in the SCDH (Bardoni et al., 2004; Krebs et al., 1991; Liu et al., 1994; Lu et al., 2003). About a third of SCDH NMDARs are presynaptic, which are translated in DRG neurons and transported to the synaptic terminal, adjacent to the vesicle release site (Liu et al., 1994). Unlike postsynaptic NMDARs, presynaptic NMDARs can spontaneously release neurotransmitters, such as SP, without neuronal depolarization and removal of the Mg<sup>2+</sup> block (Dore et al., 2017; Kavalali, 2015). A distinct process involving metabotropic signaling through c-Jun N-terminal kinase (JNK) (Abrahamsson et al., 2017) can also trigger neurotransmitter release. Src family kinases, which phosphorylate NMDARs to activation, have also been implicated in primary afferent presynaptic NMDAR regulation (Marvizón et al., 1997) by increasing presynaptic glutamate release (Madara & Levine, 2008), which in turn can promote more

persistent overall increase of glutamate receptor activity. Presynaptic NMDAR activation increases the frequency of miniature excitatory postsynaptic currents (EPSCs) associated with pain hypersensitivity in rodent models of neuropathic pain (S. R. Chen et al., 2014; W. Chen et al., 2014). Xie et al. (2016) found increased mEPSC frequency that was driven by presynaptic NMDARs in rats with paclitaxel-induced neuropathic pain that was through phosphorylation of GluN2A subunits instead of typical GluN2B. These results suggest that presynaptic NMDARs are recruited in conditions of neuropathic pain to facilitate glutamate release that increases SCDH neuronal excitability (Yan et al., 2013).

NMDARs are also found extrasynaptically and can be activated by glutamate in extracellular compartment (Meur et al., 2007), astrocytes (Carmignoto & Fellin, 2006), and glia (Nie et al., 2010), and accordingly, distributed in clusters in very specific cell contact areas to act as a point of contact with these processes (Kharazia & Weinberg, 1999; Papouin & Oliet, 2014; Petralia et al., 2010). Very little is known about the physiological function of extrasynaptic NMDARs, especially in the context of sensory neurons and nociception. Expression of various excitatory and inhibitory glutamate receptors show just a small fraction of variables that could change pain signaling after injury or inflammation. Added to this complex pool of receptors and channels is yet another diverse group of neuromodulators and inflammatory mediators, which we will discuss in more detail below.

#### 4. Brain-derived neurotrophic factor modulates nociceptive and neuropathic pain

During nociceptive signal transduction, one of many different neuromodulators that is released from nociceptor terminals is the neurotrophin, BDNF. BDNF, which was first identified by Barde et al. (1982) has been well studied for its role in neuronal development and plasticity in the CNS (Ferrini & De Koninck, 2013; Merighi et al., 2008; Nijs et al., 2015), as well as in the development of sensory and motor neurons (Jones et al., 1994; Liu et al., 1995). Along with BDNF, other neurotrophins, including nerve growth factor (NGF), neurotrophin (NT) 3, and 4/5, are responsible for the development of the nervous system and are implicated in the survival and differentiation of neurons (Huang & Reichardt, 2001; Mitre et al., 2017; Numakawa et al., 2010). The neurotrophins mediate their actions by cell surface Trk receptors. NGF and NT3 preferentially bind TrkA and TrkC receptors, respectively, while BDNF and NT4/5 activate the TrkB receptor (Kaplan & Miller, 2000). Among the neurotrophins, BDNF is the most abundant and widely distributed in the CNS (Pezet, Malcangio, & McMahon, 2002). It is encoded by the *bdnf* gene (Leibrock et al., 1989; Timmusk et al., 1995; Timmusk et al., 1993) and is synthesized and released by sensory neurons, motor neurons, and peripheral and central immune cells (see reviews by Nijs et al. (2015) and Brigadski and Leßmann (2020)). BDNF exerts most of its cellular actions by engaging its high affinity TrkB receptor and the low affinity non-specific p75 neurotrophin receptor, but this review will focus on its actions through activation of TrkB.

##### 4.1. TrkB receptor

TrkB is a transmembrane receptor with an extracellular ligand binding domain and a catalytically active intracellular domain. BDNF binds to TrkB, leading to the dimerization of the TrkB heteromer and auto-phosphorylation of its tyrosine residues. This activates downstream intracellular transduction pathways such as mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways (Huang & Reichardt, 2001; Numakawa et al., 2010; Pezet, Malcangio, Lever, et al., 2002). BDNF signaling through TrkB is essential for normal function in the brain such as neuronal survival, differentiation, and regulation of neuronal structure and function (Bonhoeffer, 1996; Numakawa et al., 2010). BDNF regulates neuronal excitability and synaptic plasticity in the CNS (Levine et al., 1995) by promoting

neurotransmitter release (Takei et al., 1997), phosphorylating glutamatergic receptors (Levine et al., 1995), and inducing structural and functional changes in neurons (Abidin et al., 2008; Marty et al., 1997). In the CNS, BDNF itself can induce synaptic plasticity and long-term potentiation-like synaptic facilitation similarly to that observed in the hippocampus (Gottschalk et al., 1998; Korte et al., 1998; Novkovic et al., 2015).

##### 4.2. BDNF's expression and function in sensory neurons and spinal cord

BDNF is endogenously and constitutively synthesized in primary sensory neurons in the DRG, based on previous observations of mRNA (Wetmore & Olson, 1995) and protein (Barakat-Walter, 1996; Wetmore & Olson, 1995; Yan et al., 1997) expression. Once synthesized, BDNF is anterogradely transported from the DRG somas to the primary afferent terminals (Michael et al., 1997; Zhou & Rush, 1996) and is released into the SCDH (Lin et al., 2011; Matayoshi et al., 2005). BDNF is also expressed in Schwann cells (Apfel et al., 1996; Cho et al., 1997; Michael et al., 1997) and epithelial cells (Hahn et al., 2006; Hahn et al., 2005; Wang et al., 2015). The subpopulation of DRG neurons that express BDNF are small-to-medium sized peptidergic cells, presumably nociceptors (Luo et al., 2001; Michael et al., 1997). BDNF is stored in large dense core vesicles of these small cells along with SP and CGRP (Michael et al., 1997; Pezet, Malcangio, & McMahon, 2002), which are released in the laminae I and II of the spinal cord in an activity-dependent fashion (Kerr et al., 1999; Lever et al., 2001; Mannion et al., 1999; Qiao et al., 2016; Zhou & Rush, 1996), where SP-containing C-fibers terminate (Michael et al., 1997).

Previous studies have implicated both spinal and peripheral BDNF in pro-nociceptive actions (Ferrini & De Koninck, 2013; Nijs et al., 2015) that can potentially contribute to the development of central sensitization leading to pain (see reviews by Thompson et al., 1999, Garraway and Huie (2016), and Cappoli et al. (2020)). Short bursts of high frequency electrical stimulation of C-fibers and/or NGF treatment (i.e., inflammatory condition) (Lever et al., 2001) or sciatic nerve transection (Lever et al., 2001; Walker et al., 2001) induced the release of BDNF in the dorsal horn. Further, BDNF facilitated C-fiber evoked synaptic responses lamina II of the spinal cord, which required post-synaptic NMDARs (Garraway et al., 2003). BDNF is also linked to dysregulation of inhibitory neurotransmission, where reduction of BDNF release after spinal nerve ligation resulted in decreased levels of GABA to impair the GABAergic signaling in the SCDH contributing to hyperexcitability and central sensitization (Lever et al., 2003). Together, these observations show the importance of BDNF released from sensory neurons in synaptic and nociceptive plasticity in the spinal cord.

##### 4.3. BDNF's contribution to injury-induced pain

BDNF is also implicated in injury-induced pathophysiology, including neuropathic pain. Peripherally, Schwann cell-derived BDNF is increased after peripheral nerve axotomy (Michael et al., 1997; Pezet, Malcangio, & McMahon, 2002). BDNF synthesis and anterograde transport from the DRG somas to the terminals is enhanced by peripheral injury (Mannion et al., 1999; Qiao et al., 2016; Zhou & Rush, 1996), and increase in BDNF in the DRGs correlated with development of allodynia in rats with spinal nerve injury (Zhou et al., 2000). Injury can also cause a phenotypic switch in BDNF expressing neurons in the DRG. After spinal nerve ligation, de novo synthesis and expression of BDNF is increased in the uninjured small neurons (Mannion et al., 1999) and in injured medium and large neurons, which was also observed after axotomy or peripheral nerve injury (Michael et al., 1999; Zhou et al., 1999). Similarly, after sciatic nerve crush, not only is the intensity of BDNF immunoreactivity increased in the small-diameter DRG neurons, but the number of medium- and large-diameter DRG neurons that express BDNF are also increased (Cho et al., 1998). Antisense and antibody against TrkB decreased mechanical hypersensitivity from repeated

tactile stimulation (Mannion et al., 1999), acute heat pain, and thermal hyperalgesia (Groth & Aanonsen, 2002). Beyond the sensory neurons, microglial BDNF has been shown to downregulate the expression of the chloride transporter,  $K^+$ - $Cl^-$  cotransporter (KCC2), to disrupt GABAergic-glycinergic-mediated inhibition and produce an overall increase in excitation. Altogether, these studies indicate the involvement of BDNF-TrkB signaling in the DRG and sensory neurons, in inflammatory and injury-induced neuropathic pain.

#### 4.4. Peripheral BDNF-TrkB signaling in mechanotransduction and pain

The aforementioned studies support the pro-nociceptive role of BDNF-TrkB signaling in the nociceptive pathways after peripheral and central injury. Because BDNF's functions in the CNS are well established, it is conceivable that BDNF will also mediate adaptive or maladaptive plasticity at peripheral sites. BDNF may regulate pro-nociceptive effects through regulation of synaptic transmission, afferent plasticity, and long-term modification in pain pathways to alter nociceptive processing both peripherally and centrally. For example, it was recently shown that BDNF in sensory neurons is necessary for the transition from acute to chronic inflammatory pain and some neuropathic states (Sikandar et al., 2018).

Previous studies have shown TrkB expression in different subpopulations of sensory neurons (Ernfors et al., 1993; Foster et al., 1994; Kashiba et al., 1995; Wright & Snider, 1995) and sensory nerve endings innervated by or connected to primary afferent sensory neurons (García-Piqueras et al., 2019; Montaña et al., 2010; Zimmerman et al., 2014). Importantly, BDNF and/or TrkB signaling has been shown to be required for normal mechanosensation (Carroll et al., 1998; Li et al., 2011; Rutlin et al., 2014). Specifically, BDNF-TrkB expression and signaling in hairy skin is required for development and normal functioning of a subpopulation of cutaneous afferents known as the A $\delta$ -Low-Threshold Mechanoreceptors (LTMRs) (Li et al., 2011; Rutlin et al., 2014), previously classified as D hair cells (Abraira & Ginty, 2013; Koltzenburg et al., 1997). The thinly myelinated A $\delta$ -LTMRs express TrkB and transduce directional touch in a BDNF dependent manner. BDNF is also expressed in a population of myelinated primary afferents, although according to Dembo et al. (2018), its expression in these primary afferents makes limited contributions to pain or itch. BDNF can be released in the periphery from non-neuronal cells, including Merkel cells (Reed-Geaghan et al., 2016) epithelial cells of the skin (Cefis et al., 2020; Rutlin et al., 2014), and peripheral immune cells (see references in Brigadski and Leßmann (2020)). Clearly, the widespread nature of BDNF's expression suggests it can also modify nociceptor and sensory neuron function by actions in the periphery.

### 5. Other events that contribute to inflammatory or injury-induced plasticity of DRG

Inflammation and tissue or neural injury can lead to functional, chemical, or structural modification of all the components of the nociceptive pathway. When injury or inflammation takes place, primary nociceptors, mainly C- and A $\delta$ -fibers, display lowered firing thresholds (hypersensitivity) and increased spontaneous firing (hyperexcitability), a phenomenon known as peripheral sensitization. During peripheral sensitization, neuropeptides are released from the peripheral branch of the nociceptor at the injured site or inflamed environment to attract leukocytes and activate receptors that are expressed on the terminals and/or cell bodies of nociceptors (Basbaum et al., 2009; Gold & Gebhart, 2010). Leukocytes, once recruited, are activated to macrophages for removal and regeneration of degenerating axons (Beuche & Friede, 1984; Brown et al., 1991; Hu & McLachlan, 2002; Perry & Brown, 1992). Extending to the CNS, glial activation, characterized by upregulated microglial (e.g., IBA1) and astroglial (e.g., GFAP; glial fibrillary acid protein) markers, and morphological changes can also occur that have been implicated in pathogenesis of chronic pain.

#### 5.1. Effect of peripheral inflammation on DRG plasticity

Inflammatory responses, such as microglial proliferation and macrophage recruitment, have been observed in DRGs with peripheral nerve injury (Eckert et al., 1999; Hu & McLachlan, 2002; Lu & Richardson, 1993) or DRG compression (Zhang et al., 1999). SGCs around the DRG soma proliferate (Barron et al., 1990; Gehrmann et al., 1991; Lu & Richardson, 1991) and contribute to generation of ectopic discharges and oscillatory activity (Devor, 2006). Somal ectopic firing is pathological and produces sensory signals even in the absence of pain stimuli (Woolf & Ma, 2007). SGCs also release cytokines that contribute to development and persistence of nerve injury-induced mechanical hypersensitivity (Ji & Strichartz, 2004; Schafers et al., 2003; Svensson et al., 2005; Zelenka et al., 2005). Localized immune activation has been shown to induce prolonged inflammatory responses and elevated cytokine production, including interleukins (IL)  $-1\beta$ ,  $-6$ ,  $-18$ , monocyte chemoattractant protein (MCP)-1, and growth-related oncogene CXCL1 by 17 folds (Xie et al., 2006). Upregulation of the prototypical cytokines IL- $1\beta$  and tumor necrosis factor (TNF)  $-\alpha$  is one of the earliest indications of sensory inflammation and increased nociception (Miller et al., 2009). The release of cytokines from immune and other non-neuronal cells (e.g. keratinocytes) can directly interact with the sensory neurons or affect further downstream mediators, including other cytokines, chemokines, prostanooids, neurotrophins, and ATP (Binshtok et al., 2008; Chiu et al., 2012; Gold & Gebhart, 2010; Julius & Basbaum, 2001; Levin et al., 2008; Liu & Ji, 2013; Pezet & McMahon, 2006; White et al., 2005). Several cytokines such as IL- $1\beta$ , IL-6 and TNF- $\alpha$  have been linked to DRG neuron excitability (Gadient & Otten, 1996; Gardiner et al., 2002; Inoue et al., 1999; Lee et al., 2004; Li et al., 2005; Nilsson et al., 2005) by sensitizing the TRP channels, which stimulate CGRP release (Obreja et al., 2005; Obreja et al., 2002; Oprea & Kress, 2000), or by enhancing TTX-r Na $^+$  currents (Jin & Gereau, 2006). Consistent with this observation, TNF- $\alpha$  antibodies attenuate the development of thermal hyperalgesia and mechanical allodynia in models of neuropathic pain (Cunha et al., 2007; Sasaki et al., 2007; Zanella et al., 2008). Increased TRPV1 activation produces increasing inward current with repeated exposure to heat through peripherally released NGF (Zhang et al., 2005), which maintains peripheral sensitization. These changes lead to an increase in substrate for other receptors and amplify and prolong peripheral sensitization, leading to an increase in nociceptor activity.

#### 5.2. Effect of SCI on pain and DRG plasticity

Immediately after the initial damage caused by SCI, the local area undergoes ischemia due to damaged blood vessels and cellular membranes, and inflammation. The insult leads to calcium and glutamate excitotoxicity, ionic imbalance, reactive oxygen species (ROS) production, and further inflammation and apoptosis, which progressively damage the surrounding spinal cord tissue. Microglia are activated to release cytokines and recruit more inflammatory cells like macrophages, which infiltrate the damaged spinal cord and remain activated for several weeks (Popovich et al., 1997; Sroga et al., 2003). The primary injury triggers systemic, cellular, and molecular changes that spread the damage to adjacent white and gray matter (secondary injury). Glutamate levels also increase that drive NMDA and AMPA receptors to be hyperactive. Hence, glutamate-induced excitotoxicity becomes a leading cause of several secondary mechanisms that further the damage. Amplification of pain responses and spread of pain sensitivity to uninjured regions results in secondary hyperalgesia (Ji et al., 2003).

Nociceptor-specific changes after SCI have yet to be investigated fully, but a few studies have shown that SCI can alter nociceptor activity typically by causing increased activity. Due to the injury, sensory signals are strengthened to transform nociceptors to be activated with just low-threshold, usually innocuous stimuli, which leads to neuronal hyperactivity and hyperexcitability. If C-fiber activity that does not cross the normal threshold is induced for prolonged periods, the heightened

synaptic transmission results in persistent sensitization (Ji et al., 2003). CGRP-expressing peptidergic nociceptors (Ackery et al., 2007; Christensen & Hulsebosch, 1997; Helgren & Goldberger, 1993) and small- and medium-sized dissociated DRG neurons (Bedi et al., 2012) sprout new branches after SCI, indicating aberrant axonal growth and increased activity. Non-peptidergic C-fibers also undergo aberrant sprouting in the SCDH after SCI, consistent with injury-induced allodynia (Detloff et al., 2014). SCI can recruit typically non-nociceptive primary afferent neurons to the pain pathway (Torebjork et al., 1992), causing phenotypic changes in myelinated fibers, like A $\beta$ -fibers (Woolf & Salter, 2000), which do not normally drive nociceptive output (Latremoliere & Woolf, 2009). Such functional changes in the primary afferent sensory neurons appear as allodynia.

Previous studies in DRG neurons have demonstrated that nociceptors become chronically hyperexcitable and display increased spontaneous activity (Bedi et al., 2010; Yang et al., 2014), which is neuronal firing not driven by any sensory input. While spontaneous activity occurring under physiological conditions aids in development of and rehabilitation of the spinal cord (e.g., motor neuron pathfinding, maturation of synapses, axon regrowth), increase in the incidence of spontaneous activity in the pain-transducing neurons after injury could lead to hyperalgesic priming (Reichling & Levine, 2009), so that the nociceptors are now more predisposed to enter a stable hypersensitive state (Walters, 2012). Because primary afferent somas are located distantly from their receptive fields, somal hyperexcitability may emerge to compensate for damage or loss of peripheral sensory branches after injury (Walters, 2012). Nociceptors also display increased afterdischarge (Eller et al., 2022). These aforementioned changes are consistent with the fact that sensory neurons can exhibit lowered thresholds to thermal and mechanical stimuli (Bishop et al., 2010) that indicate their involvement in the generation of pain.

Transcriptional changes occur in the DRG after SCI that are critically associated with the generation of pain (Costigan et al., 2002; Cuevas-Diaz Duran et al., 2023; Perkins et al., 2014; Wang et al., 2002). For example, changes have been reported in synaptogenesis signaling pathways and networks responsible for inflammatory signaling mechanisms (Yasko et al., 2019). Along these lines, we recently showed that pERK levels are robustly elevated in the adjacent trunk skin after SCI in adult mice that exhibited mechanical pain (Martin et al., 2022). While increased pERK levels might indicate plasticity of sensory neurons, we did not characterize the specific cell types that express pERK. However, a previous study by Dai et al. (2002) showed pERK is elevated in peripheral nerve terminals following noxious stimulation.

### 5.3. Peripheral changes after SCI that contribute to pain

While the neural mechanisms that underlie the emergence of nociceptive and neuropathic pain after SCI have been studied extensively in the spinal cord, the functional, morphological, and molecular changes in the periphery still need investigation. Studies suggest peripheral changes play a role in the induction and maintenance of pain, specifically after SCI. Also, sympathetic, and sensory neurons show increased interaction after injury through increased sympathetic fiber density and sprouting into the DRGs (García-Poblete et al., 2003; Kinnman & Levine, 1995b; Shinder et al., 1999; Xie et al., 2007). Many neurotransmitters and neuromodulators such as SP and BDNF are synthesized, stored, and released from the central terminals of the sensory neurons in the SCDH, in response to the injury. Previous studies also showed that intense activation of nociceptors shortly after SCI worsens hind paw mechanical hypersensitivity (Garraway et al., 2014; Martin et al., 2019), suggesting that peripheral nociceptor hyperexcitability can exacerbate pain responses after SCI. Although less understood, recent evidence suggests that peripheral TrkB signaling may also underlie pain after SCI. Specifically, we found that pharmacogenetic inhibition of TrkB systemically delayed the onset of mechanical allodynia after SCI for up to 4 weeks, and reversibly attenuated established pain (Martin et al., 2022). This

observation is supported by a previous study that reported maladaptive TrkB signaling contributes to neuropathic pain after SCI (Wu et al., 2002). Altogether, these observations indicate that peripheral processes, including nociceptor hyperactivity, critically underlie pain after SCI.

### 5.4. Other SCI-induced changes: non-nociceptors such as C-LTMRs contribute to pain

Even though nociceptors are essential drivers of pain, non-nociceptors can also undergo plasticity that contributes to pain hypersensitivity. C-low threshold mechanoreceptors (C-LTMRs) are small diameter, unmyelinated afferents that innervate the trunk hairy skin and terminate in lamina II of the dorsal horn (Li et al., 2011). In the spinal cord, C-LTMRs form a synaptic glomeruli, demonstrating C-LTMR signals are integrated at the first synapse like other primary afferents (Larsson & Nagi, 2022). They are identified by TH expression (Li et al., 2011; Lou et al., 2013) and vesicular glutamate transporter (VGLUT) 3 expression (Gras et al., 2002; Seal et al., 2009). C-LTMRs normally encode gentle, pleasant touch contributing to social interactions (Bessou et al., 1971; Iggo, 1960; Li et al., 2011; Liljencrantz & Olausson, 2014; Löken et al., 2009; Morrison et al., 2010; Olausson et al., 2002; Zimmermann et al., 2014) and modulation of heat pain (Habig et al., 2017). However, C-LTMRs represent a sub-population of cutaneous afferents that may indeed convey pain under pathological conditions (Mahns & Nagi, 2013; Seal et al., 2009), including SCI. VGLUT3-knockout mice showed impaired acute mechanical allodynia in inflammatory and neuropathic pain models (Seal et al., 2009), demonstrating for the first time, that C-LTMRs are involved not only in low-threshold mechanosensation but may also be required for generation of pain response to innocuous mechanical stimuli. Similarly, ablation of Nav 1.8-expressing nociceptors (Abrahamsen et al., 2008) or knocking out T-type calcium channels (Cav3.2) in nociceptors and C-LTMRs also resulted in attenuation of mechanical allodynia (François et al., 2015), suggesting a possible mechanistic overlap between C-LTMRs and nociceptors. Previous studies undertaken in human subjects found that individuals with SCI respond with hyperesthesia and allodynia to activation of C-tactile fibers (i.e., human equivalent of C-LTMRs (Löken et al., 2009)) with a gentle brush stroke (Finnerup et al., 2003). Recently, we reported further evidence that C-LTMR afferent plasticity produces pain after SCI. Using a conditioned place-aversion paradigm, which investigates the affective component of pain, we showed that adult mice with SCI avoided the chamber associated with C-LTMR stimulation (i.e., mechanical, and optical stimulation) (Noble et al., 2022). Importantly, these changes took place in parallel to the establishment of hind paw mechanical hypersensitivity, suggesting that C-LTMR afferent plasticity promotes at-level affective pain following SCI, concurrent with below level pain. We also observed that stimulation of C-LTMRs increased pERK levels in TH+ DRG neurons (presumed C-LTMRs) only after SCI (Noble et al., 2022). C-LTMRs may excite nociceptive lamina I projection neurons through PKC $\gamma$ -expressing neurons (Artola et al., 2020), which are also required for injury-associated mechanical hypersensitivity (Malmberg et al., 1997). Electrophysiological studies have shown sympathetic neurons directly excite C-LTMRs and increase their sensitivity to mechanical stimuli (Barasi & Lynn, 1986; Roberts & Elardo, 1985; Roberts & Levitt, 1982), and increased sympathetic activity is associated with injury-induced pain (Jänig et al., 1996; Kinnman & Levine, 1995a, 1995b; Ramer et al., 1999). Hence, it can be suggested that C-LTMR interaction with sympathetic neurons may take place after injury that consequently produces maladaptive changes. Despite these observations implicating C-LTMRs in pain, further investigation focusing on the neural mechanisms that enable the functional switch from touch-to-pain encoding is needed.

### 5.5. Sympathetic efferents and sensory neurons interact to produce pain

The organization of the sympathetic nervous system enables it to

transmit information from the CNS to target tissue/organ. Sympathetic efferent fibers leave the spinal cord in the ventral roots to make their first synaptic connections with neurons in prevertebral sympathetic ganglia located in the abdomen. Apart from the C-LTMRs-sympathetic interaction mentioned in the preceding section, it has long been shown that the sympathetic nervous system contributes to pain in both animal models of neuropathic pain (Kim & Chung, 1991; Levine et al., 1986) and in human studies (McDonnell et al., 2011). Minett et al. (2012) showed that ablation of Nav 1.7 in sensory and sympathetic neurons abolished pain sensation following a nerve ligation model of neuropathic pain in mouse, thereby supporting sympathetic and sensory neurons interaction in distinct types of pain sensation. Specifically, the exact mechanism underlying the interaction remains unclear, but previous studies have investigated interactions at nerve terminals, cell bodies, and central terminals (Jänig & Häbler, 2000). Importantly, a prior study by Ren et al. (2005), showed that sympathetic efferent is necessary for C- and A $\delta$ -pain fiber sensitization by capsaicin, also demonstrating that pain afferents are directly modulated by sympathetic activity (also see Lin et al. (2003)). Sensory neurons and sympathetic nerves are normally only associated with blood vessels, but several pain models have shown increased sympathetic fiber density and sprouting of sympathetic nerves into the DRGs as “basket” structures known as Dogiel’s arborizations (McLachlan et al., 1993). Dogiel’s arborizations were observed by Ramón y Cajal (García-Poblete et al., 2003), in human neuropathic pain patients (Shinder et al., 1999), axotomized cells (Ma & Bisby, 1999), and locally inflamed (Xie et al., 2006) or compressed (Chien et al., 2005) DRGs though in small numbers. The link between basket cells and behavioral studies have been conflicting (Xie et al., 2010), but electrophysiological data demonstrate basket cells to be the main source of spontaneous activity (Xie et al., 2011). Basket cells also showed increased nociceptive markers, such as TrkA, CGRP and SP, demonstrating that sprouting sympathetic fibers are probably closely apposed to nociceptive cells.

Sympathetic activity can indirectly interact with sensory pain systems through the neuro-endocrine and immune systems. Notably, sympathetic activity can impact immune functions by producing inflammation, which can then modify sensory systems such as nociceptor activity (see review by Jänig (2014)). Similarly, spontaneously active DRG cells can cause sympathetic sprouting, presumably by the release of neurotrophic factors or cytokines from SGC or glial cells (Xie et al., 2007; Zhang & Strong, 2008). Receptors for norepinephrine and ATP are also expressed on SGCs, which may be activated to release inflammatory neuromodulators after injury or inflammation that recruit sympathetic fibers (Hanani, 2005; Maruo et al., 2006; Tan et al., 2011). Here, we provide a brief overview of C-LTMRs and sympathetic contribution to pain, although noting that these interactions are quite complex and beyond the scope of this review.

### 5.6. Central sensitization

While this review aims to shed much needed light on the role DRG and sensory neuronal plasticity play in pain, it is important to briefly discuss cellular plasticity that occurs centrally, particularly the SCDH where nociceptors terminate. At the central axon terminal of the DRG, the release of neurotransmitters and neuromodulators triggers activation of postsynaptic glutamatergic receptors (i.e., NMDARs, AMPARs), which initiate recruitment of subthreshold synaptic inputs to nociceptive neurons to generate a state of potentiation known as the central sensitization (Woolf, 1983). Central sensitization is a C-fiber-mediated enhancement of synaptic efficacy in the spinal dorsal horn neurons following peripheral noxious stimuli, tissue injury, or nerve damage (Ji et al., 2003). Increased synaptic transmission decreases pain threshold, increases membrane excitability, and spreads pain sensitivity to non-injured areas by decreasing overall inhibitory tone (Ji et al., 2003). After the onset of central sensitization, sensory neurons respond to normally subthreshold innocuous stimuli. This response of the sensory

neuron can occur independently of intense, noxious stimuli. For example, SCI can cause neuroinflammation and central sensitization that leads to chronic pain without peripheral insult (Hains & Waxman, 2006), by potentially inducing hyperexcitability of primary sensory neurons (Yang et al., 2014), or triggering the release of inflammatory mediators that can regulate DRG gene expression. Similarly, pain after SCI is worsened by intense activation of nociceptors, requiring mechanisms that overlap with central sensitization (Ferguson et al., 2006; Garraway et al., 2014; Grau, 2017). Thus, central and peripheral sensitization may be involved in bi-directional interactions (Ji et al., 2018) to mediate pain after inflammation or tissue injury.

## 6. Conclusion

Significant advances have been made in our understanding of the neurobiology of pain. Adaptive pain, such as nociceptive pain, is understood to involve peripheral and central mechanisms. Though more complex and less understood, neuropathic pain may also require plasticity at central and peripheral sites. Similarly, our understanding of functional plasticity after SCI has greatly improved with clinical and experimental evidence. Initially focused on neuronal survival, regeneration, and functional recovery of the damaged spinal cord, more recent investigations demonstrate that both adaptive and maladaptive plasticity can extend beyond the spinal cord to peripheral sites.

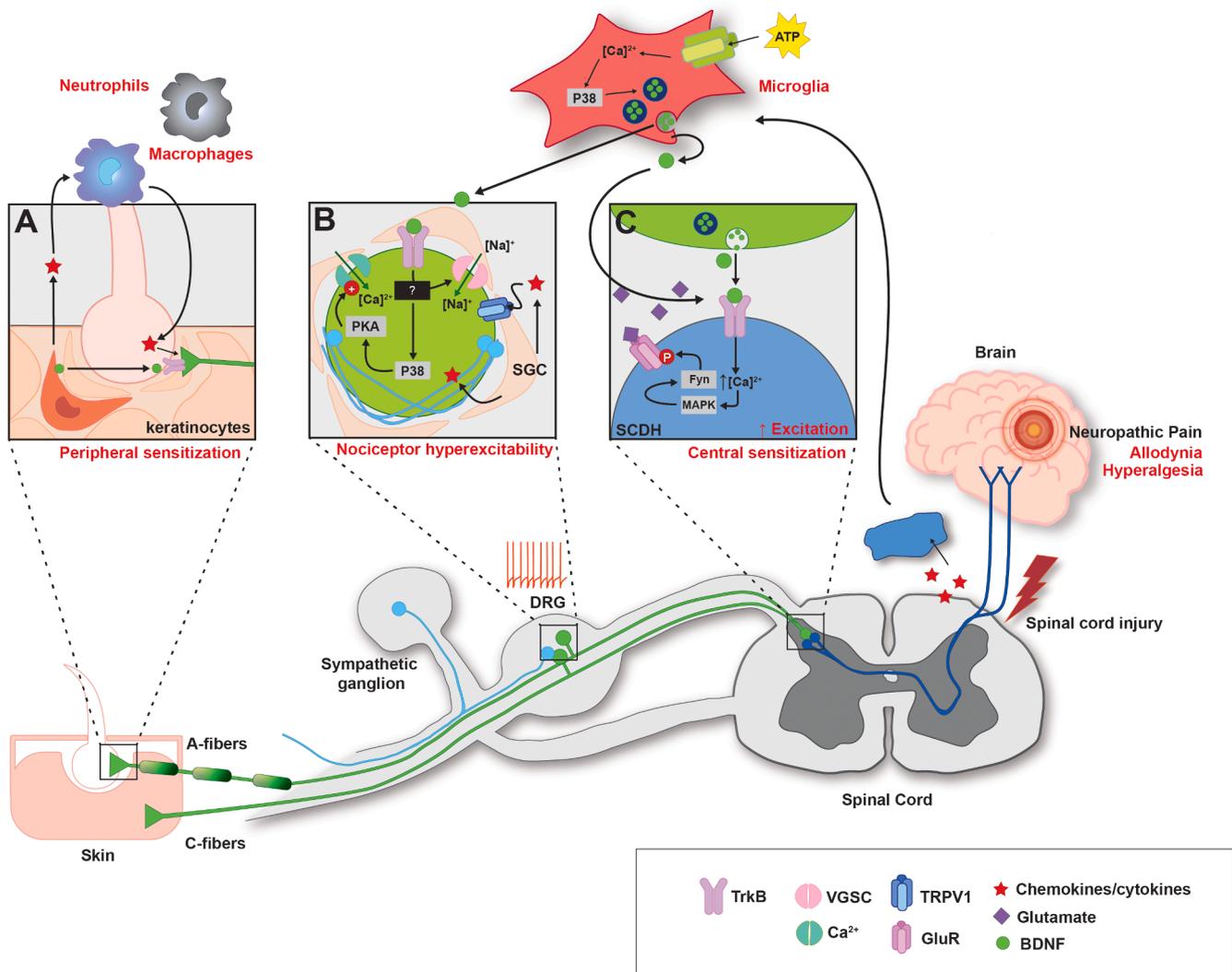
The DRGs are uniquely positioned at the intersection of the periphery and SCDH and are anatomically accessible, making them important targets for treatment and therapies of neuropathic pain. Additionally, the DRGs house the cell bodies of nociceptors, which are the drivers of pain under normal and pathological conditions. Thus, in this review, we highlighted critical features of the DRG, commonly expressed pain substrates, and DRG plasticity in inflammatory pain, as well as neuropathic pain after SCI.

Also, despite the remarkable progress made in identifying the neuroanatomy and molecular mechanisms of peripheral pain transduction and diversity of sensory neurons involved, understanding individual components of the nociceptive circuits and how they interact to contribute to pain under pathological conditions remains to be studied. For example, while sensory neuron hyperexcitability is thought to underlie chronic pain after SCI, the exact mechanisms that lead to neuronal hyperexcitability is unknown. In examining the wealth of changes that occur after SCI, specifically those that may contribute to pain, our laboratory has focused on BDNF and recently reviewed BDNF as a bidirectional neuromodulator of spinal plasticity (Garraway & Huie, 2016), resulting in multifaceted effects on the spinal cord after SCI, and the role of BDNF-induced plasticity in spinal learning circuits (Garraway, 2023; Garraway & Huie, 2016). In the current review, we examine the role DRGs play in inflammatory and neuropathic pain states by focusing on the changes in nociceptor cell soma, terminals, and adjacent non-neuronal cells, such as microglia or skin cells (see Fig. 3 for summary of the peripheral processes potentially involved in injury-induced pain). We also discuss peripherally expressed BDNF and TrkB as an example of many potential contributors to induction and persistence of pain after SCI.

The present review brings together many studies and reviews on mechanisms of pain, SCI, neurotrophins, and nociceptors, and their interactions, while highlighting the contribution of the DRGs underlying the individual components. Whereas significant progress has been made in our understanding of nociceptive processing in the SCDH, the initial CNS processing site, there remains a need for continued research emphasizing the critical roles peripheral plasticity and DRGs play in nociception.

### CRedit authorship contribution statement

**Kyeongran Jang:** Investigation, Writing – original draft, Writing – review & editing. **Sandra M. Garraway:** .



**Fig. 3.** Summary of various components in the periphery implicated for dysregulation of nociceptive circuit after SCI with BDNF-TrkB system as an example. A) Keratinocytes release growth factors (including BDNF) and cytokines to recruit macrophages and neutrophils, which further amplify inflammatory response by secreting more pro-inflammatory cytokines and chemokines (e.g., IL-1 $\beta$ , TNF- $\alpha$ ). TrkB receptors are expressed on non-nociceptor sensory neurons (e.g., A $\delta$ -LTMRs). During pathological conditions, BDNF derived from immune, epithelial, and Schwann cell can presumably interact with peripherally situated TrkB receptors to functionally alter the nociceptive circuit. B) BDNF acting through TrkB may participate in nociceptor hyperactivity by subsequent activation of downstream signaling cascades, such as PI3K and MAPK (p38). Studies implicate p38-dependent PKA signaling that stimulates T-type calcium Cav3.2 to regulate T-currents that may contribute to nociceptor hyperfunction. Certain subtype of VGSCs (TTX-R Nav 1.9) have been observed to underlie BDNF-TrkB-evoked excitation. Interaction between TrkB and VGSCs has not been clarified, but it may alter influx of sodium to change nociceptor excitability. DRGs also express TRPV1, which is sensitized by cytokines such as TNF- $\alpha$ . Proliferating SGCs surrounding DRGs release cytokines to further activate immune cells and trigger release of microglial BDNF. Sympathetic neurons sprout into the DRGs to form Dogiel's arborization, which has been observed in spontaneously firing DRG neurons. Complex interactions between these components lead to changes in nociceptor threshold and behavior, leading to hyperexcitability. C) Synaptic interactions between primary afferent terminals and dorsal horn neurons lead to central sensitization. Primary afferent terminals release neurotransmitters and modulators (e.g., glutamate and BDNF) that activate respective receptors on SCDH neurons. Sensitized C-fibers release glutamate and BDNF. BDNF binds to TrkB receptors, which engage downstream intracellular signaling cascades including PLC, PKC, and Fyn to increase intracellular Ca<sup>2+</sup>. Consequently, increased Ca<sup>2+</sup> increases phosphorylation of GluN2B subunit of NMDAR to facilitate glutamatergic currents. Released glutamate activates NMDA/AMPA receptors to activate post-synaptic interneurons.

**Declaration of competing interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Data availability**

No data was used for the research described in the article.

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