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The role of chemical transmitters in neuron-glia interaction and pain in sensory ganglion

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ABSTRACT

Neuropathic pain (NP) develops because of damage to the peripheral or central nervous system. It results in the hyperalgesia and allodynia. In the recent years, various researchers have studied the involvement of neuro-immune system in causing persistence of pain. The absence of synaptic contacts in the sensory ganglion makes them distinctive in terms of pain related signalling. In sensory ganglia, the neurotransmitters or the other modulators such as inflammatory substances produced by the ganglion cells, because of an injury, are responsible for the cross-excitation between neurons and neuron-glial interaction, thus affecting chemical transmission. This chemical transmission is considered mainly responsible for the chronicity and the persistent nature of neuropathic pain. This review examines the pain signalling due to neurotransmitter or cytokine release within the sensory ganglia. The specific areas focused on include: 1) the role of neurotransmitters released from the somata of sensory neurons in pain, 2) neuron-glia interaction and 3) role of cytokines in neuromodulation and pain.

1. Introduction

Injured peripheral nerves induce neuropathic pain (NP) and neuronal excitability within the sensory ganglia (Ma et al., 2003). Although there are no synaptic contacts in the peripheral sensory ganglia (Bird and Lieberman, 1976; Bunge et al., 1979), sensory neuron somata can exhibit cross-excitation from neighboring neurons in the peripheral ganglia (Amir and Devor, 1999). A small proportion of primary afferent neurons in intact dorsal root ganglia (DRGs) fire spontaneously where peripheral afferent axons were intact. A gentle or firm rubbing of the foot was shown to be capable of evoking cross-excitation of sensory neurons (Devor and Wall, 1990). However, the percentage of neurons undergoing cross-excitation is increased after axotomy and may be related to NP (Devor and Wall, 1990). Cross-excitation has been reported to be chemically mediated (Amir and Devor, 1996), although the specific chemical mediator remains unknown. Both our own and other previous studies, involving *in vivo* and *in vitro* settings, have reported that neurotransmitters such as substance P (SP), calcitonin gene-related peptide (CGRP) or adenosine 5′-triphosphate (ATP) are released from the somata of neurons within the sensory ganglia due to inflammatory and NP condition (Huang and Neher, 1996; Neubert et al., 2000; Matsuka et al., 2001; Ulrich-Lai et al., 2001; Matsuka et al., 2007; Matsuka et al., 2008) (Fig. 1).

The cross-excitation occurring within the sensory ganglion following activation of neurons in one-region results in neurons and glial cell activation throughout the ganglion (Thalakoti et al., 2007; Dublin and Hanani, 2007). Activated glial cells release various pro and anti-inflammatory substances, which regulate the neuronal microenvironment and the neuronal excitability, therefore suggesting a relationship between glial activation and neurogenic stimulation (Dublin and Hanani, 2007). Furthermore, CGRP enhances purinergic neuron/glia communication (Ceruti et al., 2011). Through the use of pain models, results have shown that there is an increased activity of the satelite glia cells (SGCs) and an increase in the cytokine level during pain condition (Thalakoti et al., 2007; Üçeyler et al., 2007).

This review examines the relationship between pain generation and neurotransmitter or cytokine released within the sensory ganglia during NP conditions, and examines the future direction of the research into pathological pain mechanisms.

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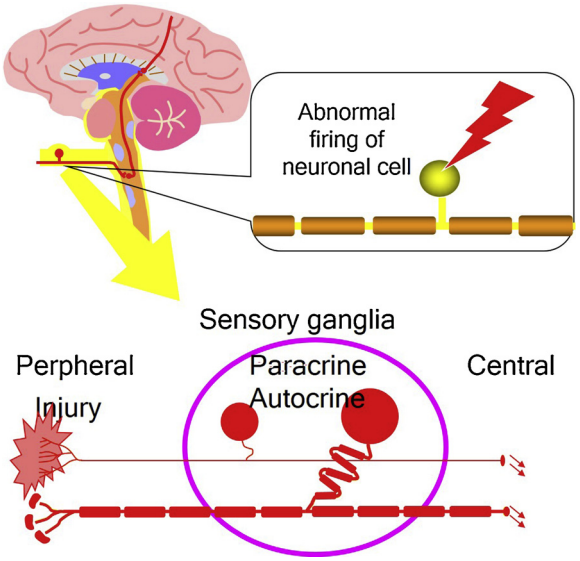

Fig. 1. Mechanisms of chronic pain in sensory ganglion. Pictorial depiction of the hypotheses for the chemical mode of neurotransmission in the sensory ganglion, which may be paracrine or autocrine. This mechanism is responsible for the abnormal firing of sensory neurons in the ganglion and is responsible for the maintenance of chronic pain.

2. Neurotransmitter release from the somata of sensory ganglia

Various chemical mediators are expressed from the somata of sensory neurons and are involved in chemical transmission. These substances include the classical transmitters glutamine, gamma-amino butyric acid (GABA) (Lazarov, 2002), ATP (Matsuka et al., 2008), neuropeptides (SP, CGRP, neuropeptide Y), galanin (GAL) (Lazarov, 2002), gaseous neuro-messengers (nitric oxide (NO)), (Stoyanova and Lazarov, 2005; Kolesár et al., 2006; Fan et al., 2008) and other neuroactive molecules (nerve growth factor, brain-derived neurotrophic factor) (Lazarov, 2002; Buldyrev et al., 2006; Tarsa et al., 2011; Kurata et al., 2013). It has also been reported that after nerve injury, there is a change in the expression (up or down-regulation) of these chemical mediators that may be responsible for neural plasticity (Lazarov, 2002). An exocytotic vesicular release of ATP occurs from the somata of the sensory neurons (Burnstock et al., 2007). The ATP released from the somata of DRG neurons is vesicular following action potential stimulation, which is distinctly different from synaptic release (Zhang et al., 2007). Non vesicular release of ATP was also suggested based on the evidence from an experimental set up where a specific test has shown that ATP was released after treatment with botulinum toxin (BoNT) which prevents vesicle fusion with the plasma membrane by cleaving SNAP-25 (25-kD synaptosome-associated protein). ATP was still released from neurons by action potential firing induced by electrical stimulation (Fields and Yingchun, 2010; Fields, 2011). ATP is stored in lysosomes via a vesicular nucleotide transporter (VNUT) and released into the intercellular space through exocytosis. Thus, indicating the role of VNUT in ATP accumulation in DRG neurons, especially in small- and medium-sized, and ATP-mediated nociceptive signaling in DRGs (Nishida et al., 2014). Conduction of pain due to ATP activated receptors P2X 3, P2X2 and P2X2/3 as well as P2Y1, P2Y2, P2Y4, P2Y6 and related purines P1 receptors on the neuronal cells of the trigeminal ganglion (TG) and DRG is well documented in the literature (Staikopoulos et al., 2007; Ruan and Burnstock, 2003; Shinoda et al., 2007). The P2X3R is present in small-diameter sensory neurons and mediates nociceptive responses (Dunn et al., 2001; North, 2002; Xiang et al., 1998). It has been demonstrated by our research that calcium ion-dependent ATP release takes place from the TG in vivo as well as from isolated somata of TG sensory neurons (Matsuka et al., 2001, 2007). The sciatic nerve entrapment (SNE) injury models resulted in significantly high basal ATP on the ipsilateral side as compared to both contralateral side and naïve rat DRG (Matsuka et al., 2008). To test the hypotheses that the blockade of the evoked release of ATP after SNE results from the conversion of extracellular ATP to adenosine and subsequent activation of A1 receptor (A1R) on DRG neurons, A1R blocker was used. A robust release of ATP in DRG ipsilateral to SNE in the presence of A1R antagonist (Matsuka et al., 2008) was noted. This hypothesis was also supported by other research where A1R agonist was effectively used in inhibiting trigeminal nociception in animal models as well as human subjects (Goadsby, 2005; Giffin et al., 2003; Goadsby et al., 2002).

Neurons in sensory ganglion show immune-reactivity towards GABA (Nakagawa et al., 2003; Hayasaki et al., 2006). GABA is synthesized within the cell bodies of rat TG neurons and GABA-A receptors are present on neuronal cell bodies of rat TG (Hayasaki et al., 2006). Under physiological conditions, peripheral GABA limits transient receptor potential vanilloid 1 (TRPV1) mediated hyperalgesia. GABA-B's analgesic property can result by inhibiting TRPV1 activity. TRPV1 and GABA-B1 complex are shown to be present on intact sensory neurons. GABA derived from human blister fluid inhibited the TRPV1 sensitisation in cultured DRG neurons in GABA-B1-dependent manner (Hanack et al., 2015). GABA-B receptors activation inhibits the excitability of rat small diameter TG neurons, which are potential targets for the analgesic action of baclofen (Takeda et al., 2004). A negative cross-talk between ionotropic receptors activated by ATP or GABA on DRG neurons is reported. The GABAergic mediated reduction in the excitatory action of ATP may be considered to be involved in sensory information processing (Sokolova et al., 2001, 2003). Co-expression of P2X3 and GABA-B receptor has been shown to be present mainly on small diameter TG neurons. GABA-B receptor activation could inhibit the ATP induced excitability of small diameter TG neurons through P2X3 receptors (Takeda et al., 2013). The GABA-B receptor immune-reactivity is shown to be present on the SGC also (Takeda et al., 2015). So, the pain generation may be modified by modulating GABA and ATP secretion and expression of GABA and purinergic receptors in sensory ganglions.

Modulation of pain signals due to CGRP and SP are well documented in the literature (Benemei et al., 2009; Russell et al., 2014). SP and CGRP, which have excitatory effects and depolarize the sensory neurons (Spigelman and Puil, 1988), have been reported to play a significant role as co-transmitters that cause pain in humans (Edvinsson and Uddman, 2005). In one study axotomy of the inferior alveolar nerve lead to a marked reduction in the total SP and CGRP expression in TG neurons in the ferret (Elcock et al., 2001). In TG, CGRP is primarily found in the small- and medium-diameter neurons, and the CGRP receptors, are found on large diameter TG neurons and satellite glial cells (Eftekhari and Edvinsson, 2010; Eftekhari et al., 2010). CGRP is expressed in approximately 45 % of small diameter unmyelinated C-type DRG neurons (Averill et al., 1995; Ruscheweyh et al., 2007). These peptidergic nociceptors, which also coexpress SP, represent approximately one-half of C-type nociceptors. CGRP is also expressed in small-to-medium–diameter Aδ -type neurons, approximately 70 % of which are nociceptors, and in some large-diameter Aβ sensory fibers. (Averill et al., 1995; Ruscheweyh et al., 2007; Lazarov, 2002; Lin et al., 2015).

CGRP expression in axons regenerating from the sites of selective sural nerve crush injury, in ipsilateral lumbar ganglion perikarya and their central projections suggested complex forms of neuropeptide-mediated plasticity with selective expression in sprouts and down-regulation in perikarya. An apparent induction of intense expression of CGRP in a small uninjured population of neurons in dorsal root ganglion has also been noticed in the same study suggesting cross-excitation of nociceptors, thus enhancing the nociceptive signals in sensory ganglion (Li et al., 2004). CGRP can cause activation of cultured trigeminal ganglia glial cells leading to an increased inducible nitric oxide synthases activity and NO release (Li et al., 2008). NO increases the excitability of neurons and diffuses into the adjacent neurons (Amir and

Devor, 1996; Stoyanova and Lazarov, 2005). Whereas, conditioned medium from SGC activated by IL-1β and NO augments the release of CGRP from TG neurons (Capuano et al., 2009).

It is well known that NP induces hyperexcitation of injured neurons and cross-excitation of the neighboring neurons in primary sensory ganglia (Gold, 2000; Devor, 2006; Dray, 2017). We reported the co-release of ATP and SP within the TG in vivo by using a micro dialysis probe (Matsuka et al., 2001). In this experiment, significant reversible increase in ATP and SP was observed after neuronal stimulation. In our experiment, we monitored this by using (N-(3-triethylammonium-propyl)-4-(6-(4- (diethylamino)phenyl)hexatrienyl)pyridinium dibromide (FM4-64) in acutely dissociated TG neurons (Matsuka et al., 2007). The secretory activity of acutely dissociated TG neurons from naïve and infraorbital nerve constriction (IoNC) rats can be evaluated by measuring the fluorescence intensity of the membrane-uptake marker FM4-64 (Kitamura et al., 2009). FM4-64 dyes reveal membrane turnover of neurons following stimulation, thus showing the vesicular release of neurotransmitters. These vesicles release neurotransmitters when they fuse with the plasma membrane (exocytosis), and they become ready for another cycle of release after being regenerated from the plasma membrane (endocytosis) and reloaded with neurotransmitters. Thus, the changes in FM fluorescence intensity are indicators of vesicle exo- and endocytosis (Iwabuchi et al., 2014). We observed two different vesicular release pattern suggesting secretion of different compounds from different neuron subgroups (Matsuka et al., 2007). BoNT has been reported to block vesicular neurotransmitter release by disabling the soluble N-ethylmaleimide sensitive factor attachment protein receptor complex proteins that mediate the vesicular transmitter release (Niemann et al., 1994; Schiavo et al., 2000). We observed that there was a significantly reduced rate of FM4-64 dye release in BoNT pretreated acutely dissociated TG neurons from naïve rats. In addition, the TG neurons with IoNC exhibited a faster onset of FM4-64 release compared to the contralateral side of IoNC (Kitamura et al., 2009). Peripheral intradermal injections of BoNT in the facial area of rats decreased the IoNC-induced pain behavior and reduced the exaggerated FM4-64 release from the TG neurons (Kumada et al., 2012). Thus, the results of these experiments showed that evoked vesicular release of neurotransmitters was inhibited by BoNT. In another experimental set-up, direct application of BoNT to the ipsilateral L4 DRG led to a reversal of the sciatic nerve entrapment (SNE)-induced pain behavior within 2 days. Histologically BoNT was localized in the cell bodies of the DRG thus strengthening the evidence that neurotransmitter release is responsible for causing pain and its blockade may relief the pain symptoms (Omoto et al., 2015). Additional studies have reported on various other neurotransmitters involved in pain initiation and maintenance in the sensory ganglion, such as somatostatin (Takeda et al., 2007; Takahashi et al., 2014), galanin, (Shi et al., 2006) or nociceptin (Hou et al., 2003).

3. Glial cell involvement in pain - neuron-glia interaction in sensory ganglia

Activation of the sensory neurons leads to changes in the adjacent glia (Fig. 2), which involves communication through gap junctions and paracrine signaling. A retrograde tracer True Blue dye was detected in both the neuronal cell bodies and the adjacent glia in the TG following capsaicin stimulation of peripheral facial site (Thalakoti et al., 2007). The involvement of the glial cells in the initiation and maintenance of the neuronal changes that underlie the NP has been referred to as “gliopathic pain” (Ohara et al., 2009). Activation of glial cells in the peripheral nervous system leads to an increased in the level of glial fibrillary acidic protein (GFAP), a definitive marker for glial cell activation, in the DRG and trigeminal nerve injury model (Vit et al., 2006; Xie et al., 2009; Katagiri et al., 2012; Donegan et al., 2013; Matsuura et al., 2013; Souza et al., 2013; Hanani et al., 2014; Gong et al., 2015). These activated SGCs release substances that may contribute to the sustainment of the pain state. ATP is reported to be the main mediator of the interaction between the neuron and the glia (Gu et al., 2010; Suadicani et al., 2010). The SGC express P2Y1, P2Y2, P2Y4, P2Y6, P2Y12 and P2Y13 receptors (Katagiri et al., 2012; Weick et al., 2003; Ceruti et al., 2008; Magni et al., 2015) and exhibit an inflammation-induced change in the sensitivity of SGCs to ATP involving P2X receptors (Zhang et al., 2007; Kushnir et al., 2011; Nowodworska et al., 2017). The exclusive expression of P2X3R in neurons and P2X7R in SGCs facilitates the communication between neuronal somata and SGCs (Chen et al., 2008; Kobayashi et al. 2005; Zhang et al., 2005; Dunn et al., 2001; Nakatsuka and Gu, 2006). Neuron-glia interaction is accomplished by ATP released from the neuronal soma and activation of P2X7Rs in SGCs (Gu et al., 2010; Zhang et al., 2007). Neuron-glia signaling due to CGRP released from the neuronal soma occurs due to activation of CGRP receptors (calcitonin receptor like receptor (CRLR) and receptor activity modifying protein 1 (RAMP1)) present on satellite glial cells and neurons (Eftekhari and Edvinsson, 2010; Eftekhari et al., 2010). Moreover, CGRP also potentiates the purinergic P2Y receptors on the SGCs (Ceruti et al., 2011). Presence of the N-methyl-D-aspartate receptor (NMDAr) on SGCs and on the neurons may also contribute to neuron-glia interactions due to glutamatergic transmission contributing to pain initiation and maintenance after nerve injury (Castillo et al., 2013; Marvizón et al., 2002; Kung et al., 2013). Under the normal resting condition, GABA is synthesized in the neuronal cell body, released at the interface and taken up and stored by SGC and can be released on subsequent neuron-glial activation (Nakagawa et al., 2003; Hayasaki et al., 2006). Nucleotides secreted by TG neurons increase the calcium concentration inside the SGC, which may be responsible for cross-excitation and pain generation (Costa and Neto, 2015).

Glial cells represent the intrinsic innate immune cells of the central nervous system and peripheral nervous system (Vezzani and Viviani, 2015). The results of various studies have shown that SGCs of sensory ganglion have the properties of tissue-resident antigen presenting cells expressing the common leukocyte marker CD45, the macrophage markers CD14, CD68 and CD11b, the myeloid dendritic cell marker CD11c, the T cell co-stimulatory molecules CD40, CD 54, CD80 and CD86 and major histocompatibility complex class II molecules and toll-like receptors (TLR) especially TLR 2 and 3. Production of pro-inflammatory cytokines IL-6 from glial cells in response to stimulation by TLR 1–5 ligands was also demonstrated (van Velzen et al., 2009; Mitterreiter et al., 2017). Thus, by activating their cognate receptors on neurons these inflammatory substances secreted from the glial cells also contribute to neuron-glia signaling (Takeda et al., 2008). Apart from producing cytokines, SGCs have also been reported to be activated by monocyte chemotactic protein (MCP-1) via CCR-2 receptor, which is similar to that seen in the immune cells (Jeon et al., 2008).

4. Cytokines/chemokines and neuron-glia cross-talk – pain due to sterile inflammation

Release of inflammatory cytokines from the activated glial cells in the absence of infection is also known as sterile inflammation and may be responsible for the persistence of pain. By engaging their respective receptors on neurons, the cytokines released from the glial cells may modulate the excitability of neurons, thus contributing to neuron-glia signaling (Takeda et al., 2008). Hence, the released cytokines/chemokines may be regarded as novel neuromodulators (Vezzani and Viviani, 2015) (Fig. 2).

Evidence recorded from various cell culture studies showed differential responsiveness from neurons of DRG (Binshtok et al., 2008; Chen et al., 2011; Czeschik et al., 2008; He et al., 2010; Jin and Gereau, 2006; Tamura et al., 2014) and TG (Takeda et al., 2008), following exogenous application of cytokines to neurons signifying the neuromodulatory effect of cytokines on pain.The release of various cytokines and increased expression of multiple mitogen-activated protein kinases (MAPK) signalling from glial rich culture of TG after stimulation with

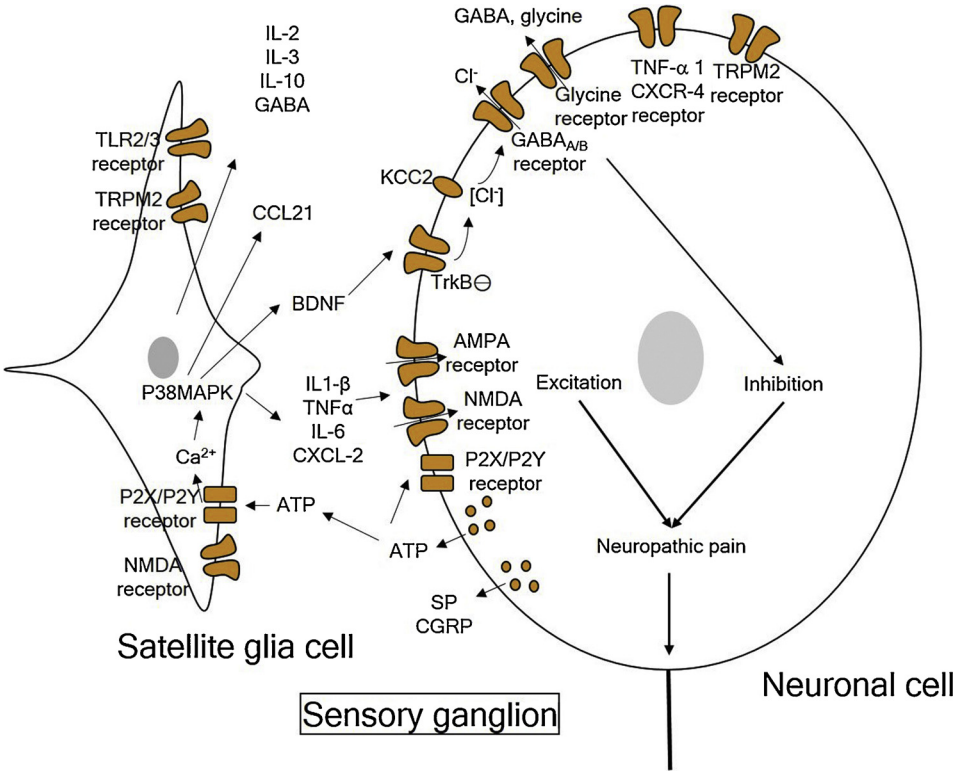

Fig. 2. The interaction between the sensory neurons and the glial cells. Hypothetical interpretation of the interaction between the neuron and glial cells in the sensory ganglion due to chemical transmission.

CGRP has been demonstrated (Afroz et al., 2019; Ceruti et al., 2011; Thalakoti et al., 2007; Vause and Durham, 2012, 2010). Lipopolysaccharide (LPS) primed schwann cells from mouse DRG were shown to synthesize large amounts of IL-1β (Colomar et al., 2003). When the SGC from TG were exposed to IL-1β or NO donor namely diethylenetriamine/nitric oxide, an increased prostaglandin E2 (PGE2) release was observed from SGCs. Subsequently, conditioned medium harvested from activated SGC was used to test possible modulatory effects of glial factors on trigeminal neuronal activity, which resulted in an evoked release of CGRP by trigeminal neurons (Capuano et al., 2009). In-vitro incubation of SGC with fractalkine induced the production and release of Tumor necrosis factor-α (TNFα), IL-1β and PGE_2 (Souza et al., 2013). Activation of transient receptor potential melastatin (TRPM2) under oxidative stress lead to increased expression of IL-6 and CXCL2 in dissociated TG. TRPM2 was found to be expressed on both neurons and SGC, and the treatment of SGC with H2O2 significantly up-regulated IL-6 and CXCL2 gene expression (Chung et al., 2015).

Various animal pain models are used to study the cytokine/chemokine related neuron-glia interaction in sensory ganglion. The expression of various cytokines and proteins from TG ganglion and spinal trigeminal nuclei are increased as demonstrated by protein array analysis after capsaicin injection in the ophthalmic division of trigeminal nerve region (Vause and Durham, 2012). Similarly, in an animal model of prolonged jaw opening simulating TMD following lengthy dental appointments, differential cytokine expression was detected in the TG and upper cervical spinal cord. This increase in cytokine expression was consistent with the nocifensive head withdrawal to mechanical stimuli in the masseter muscle region (Hawkins and Durham, 2016). Dysregulation of numerous serum cytokines and microglial activation, in the spinal trigeminal nucleus in the TNFR1/2 knock out mouse, with trigeminal inflammatory compression model, was identified. P38, MAPK inhibitor and minocycline a glial inhibitor reduced mechanical hypersensitization thus produced (Ma et al., 2015). Use of a restraint stress animal model had shown to activate the SGCs, which led to a release of IL-1β in the TG, thereby causing masseter muscle allodynia (Zhao et al., 2015). This study additionally showed that injection of L-α aminoadipate (an SGC inhibitor) in the TG ganglion significantly attenuated the masseter allodynia. In orofacial NP model created by IoNC, the effect of Pregabalin (PG) and Diclofenac on the pain behavior and pro-inflammatory cytokines showed that pain induced by the nerve injury and IL-1β was significantly reduced by PG, and this effect was dose-dependent (Khan et al., 2018). In another study, IoNC was accompanied with pain behaviour and glial activation. Pro-inflammatory cytokine CXCL2 levels were increased during the early phase of neuropathic pain induction and decreased gradually, while anti-inflammatory cytokine IL-10 levels showed the opposite trend. Recombinant IL-10 or anti-CXCL2 injection into trigeminal ganglia in an IoNC model decreased pain behaviour (Iwasa et al., 2019). Intraganglionar (IG) injection of CGRP in TG resulted in increased sensitivity to heat, neuronal and glial activation, and a time related differential regulation of cytokines (increase in mRNA expression of IL-1β and IL-1RA) in the TG. All these effects were reversed when minocycline was administered before CGPR IG (Afroz et al., 2019). Chronic constriction injury (CCI) of the sciatic nerve showed an increased mRNA expression of the pro-inflammatory cytokines TNF-α, IL-1β and the anti-inflammatory cytokines IL-4, IL-10 in DRG (Üçeyler et al., 2007). Increased expressions of TNF-α and the TNF-α1 receptor on the neurons and the associated SGCs have been reported in an animal pain model (Ohtori et al., 2004; Dubový et al., 2006). Furthermore, TNF-α activates SGCs, which leads to increased phosphorylation of the protein kinase regulated extracellular signals (ERK) in the DRG (Takahashi et al., 2006). The increased activation of this protein in SGCs after a nerve injury in the DRG has been shown to be associated with chronic pain (Doya et al., 2005). Intradermal injection of capsaicin in hind paw induced hyper-excitability of DRG neurons and glia activation. Pretreatment with minocycline inhibited glial activation and neuronal excitability. This effect was mainly mediated by inhibiting the syntheses of TNF-α in SGC and blocking the up-regulation of TNFR1s in

neurons with more potent effect observed on SGC (Gong et al., 2015). IG fractalkine injection (DRG) induced mechanical hypernociception was attenuated by treatment with neutralizing antibody against CX3CR1 and fractalkine, and pretreatment with fluorocitrate (IG), a glial inhibitor, showing possible SGCs involvement. IG injection of thalidomide and infliximab (anti-TNF-α therapies), IL-1 receptor antagonist and indomethacin (cyclooxygenase inhibitor) reduced the carrageenan and IG fractalkine induced mechanical hypernociception, suggesting the involvement of TNF-α, IL-1β, and prostaglandins (Souza et al., 2013). In an NP model of rat DRG, IL-6 and the corresponding signal transducing receptor were expressed in the SGCs (Dubovy et al., 2010). Bilateral increase in IL-6 protein and mRNA in unilateral CCI of sciatic nerve in lumbar and cervical DRG was also reported (Dubový et al., 2013). The results of some studies show that CXCL-12/CXCR4 signalling is found to be enhanced in DRG after chronic compression of DRG. In this study, CXCR4 was detected in DRG neurons, but not in SGC. The mechanical and thermal hypernociception was alleviated by administration of CXCR4 antagonist AMD3100 (Yu et al., 2017). However, one study reported the increased expression of CXCL-12 and its cognate receptor CXCR4 in DRG neurons as well as SGCs after spared nerve injury (SNI). SNI also increased the sustained expression of TNF-α in DRG and spinal cord. Intraperitoneal administration of the TNF-α synthesis inhibitor thalidomide reduced the SNI-induced mechanical hypersensitivity and inhibited the expression of CXCL-12 in the DRG and spinal cord. Thus, indirectly indicating the effect of TNF-α upregulation on CXCL-12 expression. (Bai et al., 2016).

5. Conclusion

Various studies provide the necessary evidence to support the role of chemical messengers, secreted by neurons and SGC, in genesis and maintenance of pain in sensory ganglion. These chemical messengers are involved in modulating the microenvironment in sensory ganglion leading to the neuron-glia interaction. This provides the evidence of availability of various targets and probability of exploring more such targets, which can be manipulated by various drugs to control the pain signals in the sensory ganglion.

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

Ethical approvals are not required for this review.

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