Translational Perioperative and Pain Medicine
ISSN: 2330-4871 (Open Access)
Review

Neuron-glia interactions in pain

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Abstract

Glia contributes to pain by interacting with neighboring neurons in the spinal cord or sensory ganglion. There are two types of glia in the spinal cord: microglia and astrocyte, which are different from the satellite in sensory ganglion including dorsal root ganglion and trigeminal ganglion. Signals that mediate the two-way communication between glia cells and their adjacent neurons may include abnormal neuronal activity, calcium waves, cytokines, nitric oxide, and growth factors. These highly localized paracrine signals may account for the observation that both injured and non-injured neurons in the same ganglion play important roles in pain behaviors in partial nerve injury models of chronic pain. In this review, we will describe roles of spinal glia and satellite glia in pain resulting from peripheral nerve injury or local inflammation followed by discussion of the mechanisms of neuron-glia communications in pain. Relatively more attention is focused on the neuron-glia interactions in the sensory ganglion.

Keywords: Neuron, Glia, Pain, Mechanism

Spinal glial cells play key roles in pathological pain

Recent studies indicate that activated glial cells in spinal cord and dorsal root ganglion (DRG) play key roles in chronic pain conditions (1-5). There are two main types of glial cells in the central nervous system (CNS), microglia and astrocytes. Long viewed as a mere matrix for neurons, they have recently been found to play complex and important roles in regulation of the local neuronal environment and the synapse. In response to neuronal damage or inflammatory stimulation, the glial cells become activated, undergo gliosis, and release a number of signals. This communication between spinal/sensory neurons and glia, which may be highly localized or paracrine, can occur through a number of messengers. These include excitatory amino acid transmitters (6), substance P (SP) (7), prostaglandins (8), adenosine triphosphate (ATP) (9), nitric oxide (NO) (10), and fractalkine (11,12). Activated glia are known to release a number of key pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin (IL)-1β, and IL-6 (13-16).

It has been well documented that glial activation in the spinal cord is critical for the initiation and persistence of neuropathic pain (17-24). Spinal administration of fractalkine produces cutaneous mechanical hyperalgesia, whereas blocking spinal fractalkine receptor using selective antagonist alleviates neuropathic pain (25). Furthermore, neurogenic pain induced by topical application of zymosan can be blocked by a glial inhibitor fluorocitrate (18,26-28). Similarly, administration of another glial inhibitor, minocycline (29-31), also blocks neuropathic pain (32,33).

Following peripheral nerve injury, the two types of glial cells in the spinal cord also undergo morphological changes. Microglial cells proliferate, while astrocytes change in shape and manifest increased expression of GFAP (25,34). Blocking neuronal activity originating from the injured DRG neurons suppressed microglia activation in the spinal cord (35). It suggests that peripheral activity may contribute to the activation of spinal glia.

Roles of satellite glia in the DRG in pathological pain

The satellite glial cells (SGC) in the sensory ganglia are different from those in the central nervous system (CNS). Though they share many characteristics, these SGC do not fit neatly into the astrocyte/microglia classification scheme, showing some ultrastructural

characteristics of both. DRG neurons lack dendrites, and each neuron is wrapped with its own sheath of SGC and connective tissue, a structure unique to the DRG (36,37).

Changes in SGC in pathological pain models have been well-described, though not as extensively as in the CNS (38). Following peripheral nerve injury, the SGC that surround the soma of the axotomized sensory neurons proliferate (39-41), elaborate processes (42), and become immunoreactive (IR) for GFAP (43). The expression of GFAP is different between glia in DRG and CNS; in the CNS, some GFAP expression is observed even under normal conditions, while in DRG, the expression of GFAP is not detected until some form of nerve injury occurs (Figure 1). SGC activation is also observed in DRGs with localized inflammation without peripheral nerve injury (44) and in DRGs with chronic compression (45).

Satellite glial activation in paravertebral sympathetic ganglia

While much works on glia have been focused on the spinal cord and the DRG, there has been little attention about glial activation in the sympathetic ganglia. Since post-sympathetic efferents travel with peripheral nerves, it is anticipated that injury to the peripheral nerve also damages axons of the sympathetic nerves in addition to the sensory and motor fibers. One early study compared the effects of sciatic nerve transection on neuroinflammatory responses in DRG as compared to lumbar sympathetic ganglia. They report that GFAP level, macrophage immunoreactivity, and T cell responses were even stronger in the sympathetic ganglia than in the DRGs (46).

Our lab recently investigated changes in T cells, macrophage responses and GFAP expression in lumbar sympathetic ganglia in the SNL model (47). In this model, the injured L5 spinal nerve contains post-sympathetic axons. To examine inflammatory responses in the sympathetic ganglia with remote inflammation without nerve injury, we also compared the effects of spinal nerve ligation (SNL) on these neuroinflammatory markers to the effects observed in the radicular pain model after local inflammation of the L5 DRG. Neuroinflammation in the inflamed DRG is strongly mitigated by cutting the gray rami, the source of sympathetic fibers in the spinal nerve and nearby DRG (48). It was found that compared to local DRG inflammation, SNL induced greater activation of satellite glial cells in sympathetic ganglia that innervate the L5

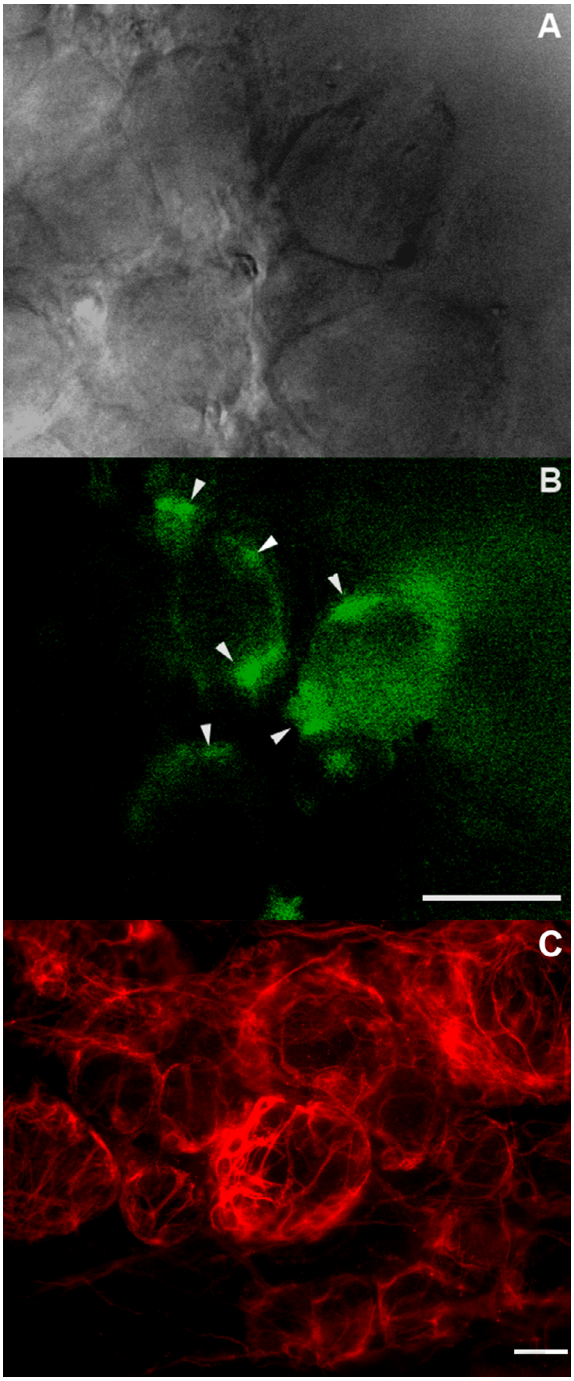

Figure 1. Activated satellite glia in axotomized DRGs. A & B: Visualizing reactive satellite glial cells surrounding live DRG neurons in an *in vitro* nerve-DRG preparation in mouse. Satellite glia are activated by sciatic nerve section 2 weeks prior. **A**: The surface of a DRG visualized under an up-right light microscope. **B**: Same DRG visualized under a fluorescent microscope. Scale bar=50 µm. Arrows indicate activated SGC. **C:** GFAP immunoreactivity in a rat DRG section showing GFAP-positive SGCs surrounding nerve-injured DRG neurons. Scale bar=20 µm.

DRG.

The roles of satellite glia activation in the parasympathetic ganglia are not clear. It is also unknown whether neuron and glia interact in a similar way as they do in the sensory ganglion. It is anticipated that satellite glial activation may contribute to enhanced excitability of the sympathetic neurons after sensory nerve injury or localized DRG inflammation as recently demonstrated by our group (48). Since sympathetic activity is reported to regulate immune homeostasis under physiological conditions (49), altered sympathetic neuron properties may, in turn, contribute to inflammatory responses in the sensory ganglion after peripheral nerve injury or local DRG inflammation.

Roles of satellite glia in communication between injured and non-injured neurons in partial nerve injury

The sciatic nerve, which arises from neurons primarily in the L4/L5 DRG, is commonly used for partial nerve injury models such as the Seltzer (50) and CCI (51) models. These partial peripheral nerve injury models were developed in order to model certain clinical situations more closely than nerve transection models. Studies using these models have shown the importance of uninjured neurons for maintained pathological pain behaviors (52), and have shown that uninjured neurons as well as injured neurons undergo changes in electrical properties and gene or protein expression (52-55). This raises the question of how information about the injury is "transmitted" to the uninjured cells. Some possible mechanisms include electrical cross-excitation between neurons (56) and exposure of intact axons to Wallerian degeneration in adjacent injured axons (for review (57)). However, it has been proposed that some of the SGC mechanisms may also provide a pathway for injured neurons to communicate with and alter the properties of uninjured neurons (43,58,59). For example, in the trigeminal ganglion, where sensory neurons have a more somatotopic organization than in the DRG, it was observed that injury to a particular tooth caused glia activation not only around the damaged neurons innervating that tooth (as demonstrated by both anatomical location and retrograde tracers), but also around some adjacent uninjured neurons (59).

Possible mechanisms of neuron-glia communications

Evidence from single recordings of the SGC and neurons suggests that neuronal activity and glial cell activation are intricately linked (60-62). A number of plausible mechanisms underlying neuron-glia communications has been suggested. First, K^+ accumulation in the extracellular space between neurons and the sheath formed by surrounding SGC (5). In cultured spinal astrocytes, elevation of $[K^+]$ results in altered GFAP expression (63). Depolarization or hyperpolarization of glial cell membranes has been observed in response to changes in adjacent neurons (64). On the other hand, satellite glial cells may affect neuronal excitability/activity through similar mechanisms (65,66). These membrane responses in glial cells may be associated with the concentration of ions in the glia. Second, spontaneously active neurons may also influence adjacent SGC by local release of SP, ATP, or other messengers (67-72). Third, in response to glutamate application or electrical stimulation, glia respond with slow alternating flows of calcium ions into and out of the cells, which has been described as "calcium waves" (73,74). Thus, calcium wave is believed to be another method for glial cells to communicate with nearby neurons. Lastly, abnormal spontaneous activity of the injured or inflamed sensory neurons may affects surrounding SGC by regulating the synthesis/release of neurotrophins.

As discussed above, abnormal electrical activity may be a key way for injured neurons to communicate with their surrounding glia. In commonly used animal models of neuropathic pain, abnormal spontaneous activity of neurons and pain behaviors both appear within the first 12 hours to 2 days post injury (50,51,75). Most other pathological changes described above, including glial activation, begin later than this. Spontaneous afferent activity is therefore a likely candidate for initiating chronic pain. A key observation is that temporarily blocking spontaneous activity beginning at the time of injury reduces or eliminates spontaneous pain, hyperalgesia, and allodynia. This has been demonstrated in several different pain models, using methods to suppress spontaneous activity that vary widely in their specific targets (76-80). Data from our own group showed that, in two different partial nerve injury models, early temporary blockade of spontaneous activity was sufficient to permanently prevent

development of pain behaviors (81). In another study (35), we tested effects of suppressing DRG neuron activity with sodium channel blockers on SGC activation in the rat SNL model, and found that local perfusion of the axotomized DRG with tetrodotoxin significantly reduced this activation as evidenced by decreased GFAP immunoreactivity (Figure 2). Similar findings

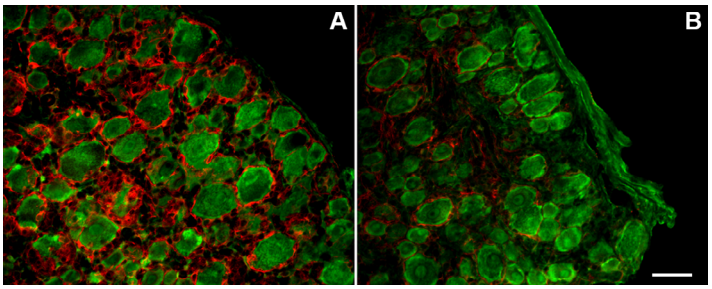

Figure 2. Neuronal blockade with TTX reduced satellite glia activation after spinal nerve ligation. Sections of DRG stained for GFAP (red) and Neu-N (Green). A: GRAP-immunoreactive satellite glia activation following SNL on POD3; B: Applying TTX locally to the axotomized DRG starting at the time of nerve injury reduced the nerve injury-induced GFAP expression. Scale bar = 50 μm. Modified from Xie et al., Neuroscience 2009 (35).

were made with a more distal nerve injury (the spared nerve injury or SNI model), using a local anesthetic (the depot form of bupivacaine) at the nerve injury site. Local perfusion of the DRG in the SNL model also significantly reduced microglia (OX-42 immunoreactivity) and astrocytic (GFAP immunoreactivity) activations in the adjacent spinal cord. Results from these experiments indicate that early abnormal spontaneous activity from injured sensory neurons may play important roles in glial activation as well as pathological pain.

Messengers for neuron-glia communication

A number of different messengers may serve for the communication between sensory neurons and surrounding/adjacent glia. These include:

Cytokines/chemokines: At the level of the DRG, a number of different cytokines and their receptors have been shown to be increased in response to various experimental pathologic conditions (82-85). In a few cases, the SGC have been shown to be the source of particular cytokines or receptors (e.g., TNF-α (36)), but in most cases the cell of origin is not well defined. Fractalkine also known as chemokine (C-X3-C motif) ligand 1 is a protein that in humans is encoded by the CX3CL1 gene. Unlike the spinal cord, in the DRG, fractalkine is constitutively expressed by the primary nociceptive neurons. Increased SGC activation as indicated by increased GRAP mRNA expression following carrageenan injection in the hind paw was inhibited by anti-fractalkine antibody administered into the DRG (86). These findings suggest that fractalkine released by nociceptive neurons contributes to the genesis of inflammatory pain through the activation of the SGCs. SGC are also responsive to other inflammatory mediators such as bradykinin and ATP. Both SGC and DRG neurons can synthesize and respond to prostaglandins, another inflammatory mediator, though much of the evidence is from cultured neurons and SGC (36).

NO/cGMP: The nitric oxide signaling system is one of the best defined in DRG. Some neurons express NO synthase, and many SGC contain cGMP cyclase, the enzyme activated by NO. NO is released in a non-vesicular fashion and can diffuse short distances between cells. The SGC also accumulate NO precursors (87), and this system has been proposed as a likely candidate for neuron-SGC signaling. Components of the system are upregulated after neuronal injury, and some but not all investigators report reduction of pain behaviors by NO inhibitors (for review see (36)).

Neurotrophins: Neurotrophins such as nerve growth factor (NGF), neurotrophin (NT)-3, and brain-derived neurotrophic factor (BDNF) may play roles in chronic pain states in addition to their roles in neuronal development and survival. SGC express NGF receptors and may express NGF and NT-3, especially after injury. These have been proposed to play a role in injury-induced sympathetic sprouting in the DRG (88-90). Hence these molecules represent another possible communication route between neurons and SGC.

Glial coupling

Several studies have demonstrated that nerve injury leads to increased coupling (indicated by diffusion of injected dye) among SGC around an individual neuron, and among SGC surrounding neighboring neurons (91,92). The functional significance of this coupling, and its relationship to glial activation, are not yet clear. However, these observations may reflect another mechanism by which glia mediate abnormal communication between neurons following nerve

injury and may contribute to cross-talk among DRG neurons after nerve injury (93).

Summary

Glial cells in the spinal cord and sensory ganglion react to peripheral nerve injury or inflammation, and contribute to pain by interacting with neighboring neurons. Preclinical studies have demonstrated robust effects of inhibiting glial activation in alleviating pain. However, clinical trials using glial inhibitors for managing neuropathic pain have been generally disappointing. Much more works remain to be done to further understand neuro-glia interactions in pain and to translate preclinical studies to clinical pain management.

Acknowledgements

None

Disclosure of Funding: Supported in part by National Institutes of Health grants AR0068989, NS045594 and NS055860.

Conflict Interests Disclosure: The authors have no conflicting interests to disclose.

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Additional publication details

Journal short name: Transl Perioper & Pain Med
Received Date: June 1, 2017
Accepted Date: June 13, 2017
Published Date: June 17, 2017
Transl Perioper & Pain Med 2017; 2 (3):14-22

Citation and Copyright

Citation:Zhang JM. Neuron-glia interactions in pain. Transl Perioper & Pain Med 2017; 2(3): 14-22

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