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Are glia targets for neuropathic orofacial pain therapy?

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Abstract

Post traumatic trigeminal neuropathy, presenting frequently as a complication of dental procedures, is often detrimental to the patient, with psychological and socioeconomic ramifications. Following a neuronal injury, numerous changes occur in both the peripheral (PNS) and central nervous systems (CNS) contributing to neuronal plasticity. Over the years, many studies have documented neuronal mechanisms involved in neuropathic pain, whereas non neuronal mechanisms, such as those based on glia have gained increased focus only recently. While the question of whether chronic neuropathic pain is a gliopathy remains enigmatic, activation and proliferation of glial cells and their interaction with neurons are believed to be key mechanisms underlying chronic neuropathic pain following a traumatic trigeminal nerve injury. Glial cells such as microglia, astrocytes and satellite glial cells have been extensively studied based on spinal neuropathic pain models, but the available literature on trigeminal pain models is very limited. In this review we aim to discuss i) available evidence on the role of central and peripheral glial cells in trigeminal neuropathic pain (TNP); and ii) gaps in knowledge between spinal and trigeminal pain models with regards to glial plasticity

Keywords

post traumatic trigeminal neuropathy; trigeminal ganglia; glial cells; astrocytes; microglia; satellite glial cells; GFAP; rodents

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Author contributions

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Introduction

Post traumatic trigeminal neuropathy occurs as a consequence of an injury to the peripheral branches of the trigeminal nerve. Examples include neuronal trauma during placement of dental implants, endodontia and extractions. Dental procedures such as these, with the potential to cause trauma to the trigeminal system, resulting in anesthesia and neuropathic pain are performed throughout the world on a daily basis [1]. The prevalence of neuropathic pain following dental procedures for example, post endodontic pain lasting more than six months is reported in 3.4 % of patients [2], while estimates of post dental implant neuropathy range from 1-8% of patients with alteration of sensation and the estimates of chronic pain are 20% [3]. To better understand the pathophysiology of TNP, animal models are needed. In rodents, the unilateral infraorbital chronic constriction injury (IoN-CCI) model is widely used to study trigeminal neuropathic pain (TNP). The IoN-CCI model induces neuropathic pain following loosely tied ligatures around the surgically exposed infraorbital nerve [4]. Following a CCI, allodynia and hyperalgesia in the injured nerve dermatome are associated with development of neuropathic pain and measured by behavioral assessment. Although the exact mechanisms involved in TNP are unknown, neuronal hyperexcitability/central sensitization is believed to be a key mechanism in its development. Although well documented neuronal mechanisms led to drug therapies targeting ion channels/receptors, such therapies require long term management and might be ineffective over time [5]. For this reason, studying neuronal mechanisms alone are insufficient and there is a greater need to study non neuronal mechanisms such as glial mechanisms, glial-glial interactions and neuron – glial interactions to attain a broader understanding of the pathophysiology of TNP.

Gliopathy, defined as dysregulation of glial cell function is a newly emerging research area in our understanding of TNP. TNP, triggered by a nerve injury, which in turn leads to the activation of glial cells, implicates lasting changes in intracellular and extracellular signaling and communication. Adding to the complexity of TNP pathophysiology, glial interactions with neurons drive the inflammatory as well as neuropathic pain processes by altering neuronal excitability and also by exerting effects at the synaptic level. Most of the available literature on glial interactions in peripheral nerve injury induced neuropathic pain are focused on spinal cord injury or sciatic nerve injury models but are very limited in TNP models. Here we discuss 5 types of glia and their putative role in TNP. The glial cells in the CNS are microglia, astrocytes and oligodendrocytes. PNS glia are comprised of satellite glial cells and Schwann cells.

1. CNS glia:

1.1. Microglia

Microglia supports the immune defense system of the CNS and are heterogeneously distributed throughout the brain and spinal cord. Although initially microglia were believed to be inactive or quiescent in a healthy brain, studies have shown that resting microglia are actively surveilling the cellular environment with their ramified or branchlike processes [6, 7]. In addition, microglia interact with surrounding astrocytes in the healthy as well as injured brain. During postnatal brain development, microglia are involved in engulfing

synapses and synaptic pruning leading to activation of the complement system, suggesting that deficits in microglial function during development may lead to synaptic abnormalities that are evident in neurodevelopmental diseases such as autism [8-11].

Following an insult to the brain such as a nerve injury, microglia not only undergo morphological changes, but also various functional changes. Such changes include, alteration of the shape of microglia from ramified to ameboid shape and upregulation of microglial markers such as C-chemokine receptor 3 (CCR3), cluster of differentiation molecule 11b (CD11b), major histocompatibility complex-II (MHC II), and ionized calcium binding adaptor protein- 1 (IBA1) [6, 12].

The critical role of microglia in the development and maintenance of neuropathic pain is well documented in both spinal and trigeminal neuropathic pain models [13-15]. Microgliosis in the medullary dorsal horn, associated with trigeminal nerve transectional injury, was shown to be initiated at day 1, reached maximal levels at day 3, and was maintained at high levels until day 14 [16]. In a chronic infraorbital nerve constriction injury model (IoN- CCI), hyperactivation of microglia was shown in rostral ventral medulla (RVM), a major component of the pain modulatory circuit. Injection of a microglial inhibitor, minocycline, reversed nerve injury-induced allodynia and hyperalgesia in rats [15]. Similarly, microglial activation was also shown in the terminal relay center for pain processing, i.e. the somatosensory cortex. Following trigeminal nerve injury, injection of a microglial inhibitor into the cortex attenuated pain like behaviors [17]. Because activation and inactivation of microglia alone in critical areas of pain processing such as RVM and somatosensory cortex have an effect on pain outcomes, it is questionable whether microglia are exhibiting such outcomes by affecting signal transmission via interaction with neurons or whether those outcomes are neuron independent. On that note, Wang et al demonstrated a parallel increase in microglia and glutamatergic neuronal activity in the somatosensory cortex following trigeminal nerve injury [17]. This increase in glutamatergic neuronal activity was successfully reversed by microglial inactivation alone in the cortex along with pain reversal [17] implying that the effect of microglial cells is possibly mediated through neuronal activity. In addition, microglial mediators such as cytokines, chemokines and ATP released from activated microglia were shown to modulate spinal and supraspinal neuronal activity [18]. The signaling changes that are involved for effective microglial-neuron interactions are vast and beyond the scope of this review. However, a few important examples of microglial-neuron interactions are discussed below.

1.2. Astrocytes

Astrocytes are abundant in the CNS and their dysfunction is implicated in neurological conditions such as epilepsy, stroke and ischemia. Astrocytes are the only glial cells in the CNS that form gap junctions. Gap junctions are intercellular channels that allow the transfer of small molecules and ions between cells. Each astrocyte enwraps more than 100,000 synapses, multiple neuronal cell bodies and 600 dendrites in the rodent brain allowing astrocytes to not only to nourish the neurons but also to control the external environment during synaptic transmission [19]. Following an insult to a nerve, increased release of ATP, glutamate, and chemokines from neurons is considered essential for

the activation of astrocytes [20]. Because astrocytes form a tripartite synapse with pre and post synaptic neurons, they are ideally positioned to modulate and respond to such neurotransmitter release from neurons through an increase in intracellular Ca2+ [21]. This increase in intracellular Ca2+ triggers the release of gliotransmitters from the astrocytes leading to activation of pre and post synaptic glutamatergic and purinergic receptors [22, 23]. Astrocytes are also shown to modulate neuronal activity by regulating glutamate, ATP/adenosine, K+ and D-serine. [23-25]

Astrocyte reactivity is characterized by hyperplasia, hypertrophy and altered metabolism for example, activation of astrocytes leads to increase in adenosine metabolizing enzyme, adenosine kinase (ADK) with subsequent reduction in adenosine, which is a known endogenous pain regulator. In trigeminal pain models, such as trigeminal CCI and trigeminal transection injury, astrocyte reactivity was demonstrated by glial fibrillary acidic protein (GFAP) upregulation in the medullary dorsal horn, another key feature of astrocyte reactivity [26] [27]. Furthermore, astrocytic activation was associated with increased release of chemokine C-C motif ligand 2 (CCL-2) from the astrocytes which is demonstrated in both sciatic nerve (spinal dorsal horn) and trigeminal nerve (medullary dorsal horn) constriction injuries [28, 29]. Similarly, following trigeminal nerve injury, increase in D-serine, was also shown in the medullary dorsal horn [24]. D-serine is an endogenous NMDA receptor co-agonist and may facilitate pain transmission via increased NMDA receptor activity, which is thought to play a role in the transition from acute to chronic pain. Essentially, blockade of D-serine by an intracisternal injection of its degrading enzyme D-amino-acid-oxidase (DAAO) and blockade of CCL-2 with its receptor (CCR-2) antagonist (intracisternal injection) alleviated TNP mediated allodynia and hyperalgesia in rodents [24, 28], suggesting a potential role of astrocytes in regulating neuronal mechanisms implicated in central pain development/perception. In addition, the proliferation of astrocytes may play a role in central pain pathophysiology. Thus, astrocyte proliferation was demonstrated in a spinal nerve ligation (SNL) neuropathic pain model and the inhibition of astrocyte proliferation alleviated neuropathic pain states [30].

Studies supporting the presence of astrogliosis (increased number of astrocytes) in neuropathic pain models are few, when compared to other neurological conditions such as epilepsy. Astrogliosis is a common pathological hallmark of epilepsy and neurodegenerative conditions, and it is believed that astrogliosis, by reducing the availability of adenosine, an endogenous neuroprotectant and seizure terminator, plays a key role in the pathogenic processes that turn a healthy brain into an epileptic brain [31, 32]. These findings are especially important for the pain field because it is believed that epilepsy, neuropathic pain and other neurological diseases share similar pathophysiology. Remarkably, antiseizure drugs such as gabapentin and pregabalin are clinically useful for the treatment of neuropathic pain [33]. Future studies investigating how astrogliosis and adenosine metabolism effects of neuronal activity in trigeminal neuropathic pain may be enlightening.

1.3. Oligodendrocytes

Oligodendrocytes are the only myelinating glia in the CNS. The abundantly present oligodendrocyte precursor cells (OPC) effectively proliferate to form oligodendrocytes and promote tissue repair after CNS insults [34]. Studies have shown cross talk between astrocytes and oligodendrocytes and that astrocytes promote OPC maturation following a white matter injury, whereas the absence of astrocytes reduces remyelination mediated by oligodendrocytes [35]. The role of oligodendrocytes in neuropathic pain is not well established, however, some studies explored oligodendrocytes in rodent models of trigeminal neuralgia. In a microvascular chronic compression injury model it was shown that the balance between CNS and PNS myelination in the CNS/PNS transition zone at the trigeminal root entry zone (TREZ) could play a major role in the development of trigeminal neuralgia [36]. Such balance between CNS and PNS myelinating glia, i.e. oligodendrocytes and Schwann cells respectively, is believed to be achieved by STAT3 (signal transducer and activator of transcription 3) mediated astrocytic activation demonstrated by Stat3 knockout mouse where an imbalance between central (reduced) and peripheral (increased) myelination were noticed when compared to control mice [37]. These findings unfold novel therapeutic targets based on glial – glial interactions and might be implicated in trigeminal neuralgia and other demyelinating diseases such as multiple sclerosis.

2. PNS glia:

2.1. Satellite glial cells

Satellite glial cells (SGCs) in the PNS are characterized by a thin cellular sheath. SGCs are present in autonomic and sensory ganglia such as the trigeminal ganglia (TG) and dorsal root ganglia (DRG). Although SGCs are fewer in number than astrocytes, because of their location in sensory ganglia, it is believed that they can effectively influence pain behavior. Each SGC surrounds only one neuron unlike astrocytes, with a 20 nm space between the neuronal plasma membrane and the SGC sheath, allowing for effective signaling between the neuron and its associated SGC. Activation and increase in the number of SGCs after injury is well documented not only in spinal and TNP models but also in a dental pulp inflammation model, where ipsilateral SGC activation in the trigeminal ganglion was triggered by complete Freund’s adjuvant (CFA) induced dental pulp inflammation [38]. Interestingly, SGC activation occurred prior to the activation of central glia in an SNL model. In this study, the proliferation of SGCs in the DRG was initiated 4 hours after the injury and was significantly higher when compared to control animals, at day 3 and 7 and maintained at high levels until day 56 [39]. These findings raise several questions such as: i) is activation of SGCs in the PNS, an initial step in driving the neuropathic pain process? ii) will targeting SGCs in the initial stages of neuropathic pain prevent central glial activation, thereby preventing central sensitization? iii) Because the SGCs activation is maintained at high levels until day 56, unlike any other glia which are reduced overtime, is long term activation of PNS glia essential for maintenance of central glial activation and neuropathic pain?

SGCs are similar to astrocytes as both express the same glial markers GFAP and glutamine synthetase and both form gap junction following an insult to a nerve. In a trigeminal

nerve injury model, SGCs underwent phenotypical changes demonstrating an increase in gap junctions and reducing the expression of gap junction protein using genetic approaches altered the pain behavior [40]. Such an increase in gap junctions in SGCs allows for increased glutamate recycling (glutamate-glutamine cycle) contributing to the maintenance of neuropathic pain [41]. The neuronal glutamate uptake by glial cells is the initial step in glutamate recycling and is carried out by transporters such as glutamate aspartate transporter (GLAST), blocking the expression of GLAST in SGCs in the trigeminal ganglion was shown to produce mechanical hypersensitivity even without an injury [42], probably by increasing extracellular glutamate and subsequent neuronal hyperexcitability. From these findings, it can be assumed that SGCs in the trigeminal ganglion are scavenging extracellular glutamate, similar to astrocytes in the CNS. Also, Connexin 43 (Cx43), a major gap junction structural component, expressed in SGCs and in only injured neurons in the TG, were shown to upregulate following trigeminal nerve injury [41]. This upregulation of Cx43 in the trigeminal ganglion is believed to play a key role in ectopic mechanical hypersensitivity following an injury to the inferior alveolar branch of the trigeminal nerve (IAN) [43]. The available data suggests, there is a relation between Cx43 gap junction protein and GFAP expression in the SGCs of trigeminal ganglion and that Cx43 drives the activation of SGCs. Inhibiting the gap junction function by carbenoxolone (CBX) was shown to reduce neuropathic pain by reducing Cx43 and GFAP expression in the SGCs of TG [44, 45]. A similar relationship is seen between GFAP and Cx43 expression in the astrocytes in different neuropathic pain models [46]. Furthermore, involvement of the purinergic system in the SGCs is also well documented. Increased ATP release from the neurons after a nerve injury is shown to activate P2X7 receptors on SGCs, leading to release of cytokines [47] driving the peripheral sensitization process seen in post-traumatic neuropathic pain patients.

2.2. Schwann cells

Schwann cells are abundant in the PNS and are known for supporting long axons and for releasing growth factors such as NGF, GDNF, BDNF required to nourish and myelinate the large axons. In a mature neuron, the myelinating SC surrounds larger diameter axons at a one to one ratio and produces a myelin sheath. The non-myelinating SC embed small diameter axons and form remak bundles. Following a peripheral nerve injury, myelinating Schwann cells undergo plastic changes to induce PNS myelination, whereas non-myelinating SCs differentiate and drive the regeneration process [48]. In a CCI sciatic nerve injury model, dramatic changes in SCs were observed including proliferation and release of growth factors which promotes nerve regeneration overtime [49]. Through a protective process called autophagy SC were shown to undergo axonal degradation and recycling of cellular components in a SNI model. Studies have shown that deficiency in SC autophagic activity is an early indication of neuropathic pain and modulation of this autophagic activity was shown to have an effect in the chronification of neuropathic pain [50]. Most studies used SNI model to study modulation of SCs in neuropathic pain and little is known about how SCs modulate trigeminal neuropathic pain.

3. Neuronal-glial crosstalk

Physiological glial-neuronal networks play a critical role in achieving homeostatic function of the nervous system. Glial plasticity leads to many alterations such as, increased release of proinflammatory cytokines and chemokines, ATP, glutamate, over expression of receptor and ion channels, which in turn activates a feedforward cycle between neurons and glia contributing to neuronal hyperexcitability [51, 52]. The same was shown in electrophysiological studies showing that activated glia contribute to sensory neuronal hyperexcitability [53]. The signaling cascades between neuron vs SGCs at a peripheral level and neuron Vs astrocyte at central levels, appear to have similarities in many aspects. Of note, ATP and glutamate recycling in SGCs and astrocytes play a major role in peripheral as well as central sensitization processes [54]. In order to show a bidirectional link between neuron and glia, central sensitization associated with interleukin 1-beta treatment in the dorsal horn neurons was successfully attenuated by glial inhibitor, propentofylline (PPF), which acts by blocking adenosine and inhibition of phosphodiesterase production [55]. Similarly, glial inhibition by intrathecal PPF treatment, desensitized wide dynamic range (WDR) neurons in the dorsal horn of spinal cord injury rodents [56]. In a sciatic nerve injury model, peripheral nerve activity was shown crucial for activation of spinal microglia demonstrated by the expression of p38 MAPK, blocking the peripheral nerve activity with bupivacaine (sodium channel blocker), prevented P38 activation. Conversely, blockade of P38 activation with a p38 inhibitor reduced the activity in the peripheral nerve followed by reversal of pain behavior's [57]. P38 MAPK acts as key signaling molecule in the microglia, and are activated by ATP, IL1b, TNF alpha [58, 59]. After injury, activation of p38 leads to BDNF release via P2X4 activation and help maintain pain hypersensitivity [60]. Furthermore, early peripheral nerve activity is shown to drive extracellular signal-regulated kinase (ERK) phosphorylation and subsequent astrocyte activation, contributing to pain hypersensitivity [61]. In many trigeminal pain models including the dental pulpal inflammation models, persistent bilateral activation of P38 in microglia and P-ERK in astrocytes in the CNS are shown to contribute to the chronification and maintenance of trigeminal neuropathic pain [62].

4. Glia as targets for pain

Although a significant number of rodent models have demonstrated glial plasticity and therapeutic effects of its inhibition in neuropathic pain, the same findings in clinical studies are under debate. Currently available glial modulators are minocycline, a tetracycline derivative; PPF and ibidilast (phosphodiesterase inhibitors). In a spinal cord injury phase 2 randomized controlled trial, IV minocycline for 7 days showed no statistical significance between treatment and placebo groups, however, clinical improvement was noted in patients that received minocycline and the drug was shown as safe and feasible [63]. On the other hand, human microglia are shown as less responsive to PPF and PPF failed to modulate pain outcomes [64]. Although not much is known regarding human glia as compared to rodent glia, some known differences exist, such as astrocytes being 2 fold larger in diameter in human cortex compared to rodents and can contact up to approximately 2 million synapses in humans as opposed to 60,000 in rodents [65]. Future research should focus

on developing techniques to study real time glial activation in patients in order to develop alternate strategies for targeting glial metabolism and interactions.

5. Conclusion

Post traumatic trigeminal neuropathy, although affecting only a percentage of patients, can result in devastating pain and loss of quality of life. While injury to a peripheral branch of the trigeminal nerve results in pain at the site of injury, clinicians must recognize the phenotypical presentation of a patient undergoing chronification of acute pain and the associated changes in the CNS and PNS in order to provide appropriate treatment. A better understanding of pain mechanisms based on glial cells involved in the evolution of chronic trigeminal nerve pain can lead to novel therapies targeting glia and improvement of patient's complaints. This article focused strictly on glial dysfunction secondary to nerve injury in order to discuss the complexity of chronic pain on a molecular and physiological basis. Armed with this knowledge, we can develop a greater understanding of molecular mechanisms and conduct research for the discovery of novel treatments.

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