Abstract: Neuropathic pain is characterized by sensory abnormalities, such as mechanical allodynia and heat hyperalgesia, associated with alteration in the peripheral and central nervous systems. After trigeminal nerve injury, phenotypic changes that involve the expression of calcitonin gene-related peptide occur in large- and medium-sized myelinated neurons; primary afferent neurons exhibit hyperexcitability because of neuron-glial interactions in the trigeminal ganglion. Increased nociceptive inputs from C- and Aδ-fiber and innocent inputs from Aβ-fiber into the trigeminal spinal subnucleus caudalis (Vc) contribute to the phenotypic changes; further, they potentiate noxious information transmission in the ascending nociceptive pathways to the thalamus and parabrachial nucleus (PBN). It is noteworthy that C-fiber mediated nociceptive inputs can activate both the Vc-ventral posteromedial thalamic nucleus and Vc-PBN pathways, while mechanoreceptive fiber inputs specifically activate the Vc-PBN pathway. The Vc-PBN pathways project to the central nucleus of the amygdala (CeA) where affective behaviors are modulated. In addition, the PBN interacts with wakefulness-regulating neurons and hunger-sensitive neurons in the hypothalamus, suggesting that the Vc-PBN pathway can modulate sleep and appetite. Therefore, phenotypic changes in primary neurons and stimulus modality-specific activation of ascending nociceptive pathways to the PBN may exacerbate affective aspects of trigeminal neuropathic pain, including behavioral problems, such as sleep disturbance and anorexia, via the PBN-CeA-hypothalamus circuits.

Keywords: neuronal phenotypic change, pain-related behavioral symptoms, parabrachial nucleus, trigeminal ganglion, trigeminal neuropathic pain, trigeminal subnucleus caudalis

Introduction

The definition of neuropathic pain is “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system” [1]. Neuropathic pain is characterized by sensory abnormalities, such as unpleasant abnormal sensations (dysesthesia), increased responses to painful stimuli (hyperalgesia), and pain in response to an innocuous stimulus that does not normally provoke pain (allodynia). Patients with neuropathic pain experience prolonged stress due to chronic pain that may lead to feelings of helplessness; these patients generally develop depression, anxiety disorders, and sleep disorders [2].

The prevalence of neuropathic pain in the orofacial region is not much lower than that in the other body parts [3]. Orofacial structures, such as the face, tongue, intraoral mucosa, and teeth, are predominantly innervated by the branches of the trigeminal nerve. The branching pattern of the trigeminal nerves is unique because there is limited overlap among the trigeminal dermatomes innervated by the inferior alveolar nerve, lingual nerve, infraorbital nerve, and other nerve branches [4]. Therefore, in order to investigate the neural mechanisms of orofacial neuropathic pain, animal pain models have been developed to assess the anatomical variation of tri-
Aspects of trigeminal neuropathic pain.\[34\] Projections from the PBN to RVM in the rostral ventrolateral medulla (RVM) [25], which plays a significant role in pain processing, these neurons receive capsaicin responsive nociceptive inputs and project to the PBN rather than the thalamus [27]. The rostrocaudal distribution of these NK1 receptor-positive neurons that project to the thalamus in the Vc-parabrachial nucleus (PBN) pathways; mechanoreceptive myelinated fiber inputs specifically activate the Vc-parabrachial nucleus (PBN) pathways.

Two major ascending nociceptive pathways in the orofacial region originate from laminae I to III, mainly from lamina I of the Vc, and project to the thalamus and PBN (Fig. 1A) [24-27]. A recent study has shown that NK1 receptor-positive neurons in the superficial lamina of the Vc are involved in pain processing, these neurons receive capsaicin responsive nociceptive inputs and project to the PBN rather than the thalamus [27].

Fig. 1. Schematic diagram of activated ascending nociceptive pathways under trigeminal neuropathic pain. (A) Normal condition: Large, medium, and small trigeminal ganglion neurons are composed of myelinated Aβ-, myelinated thin Aδ-, and unmyelinated C-fibers, respectively. Calcitonin gene-related peptide (CGRP) is synthesized and released from small-sized trigeminal ganglion neurons along with C-fibers. CGRP receptors and peripheral nerve injury induce CGRP release, extracellular signal-regulated kinase (ERK) phosphorylation, and purinergic receptors, facilitate neuron-glial interaction. Increase in the nociceptive input to the neurons of the trigeminal subnucleus caudalis (Vc) and PBN are not comprised of distinct neurons in the Vc. Approximately 20% of projection neurons in the lamina I of Vc have axon collaterals that innervate both the VPM and PBN [26]. Most of them are glutamatergic, predominantly expressing vesicular-glutamate transporter 2 (VGLUT2), and NK1 receptor-positive [33]. Thus, these projection neurons may be involved in both sensory-discriminative and affective aspects of orofacial pain.

Activation of satellite glial cells and facilitation of neuron-glial interaction in response to the trigeminal nerve injury, satellite glial cells encircling the trigeminal ganglion neurons are activates; it is noteworthy that the activation of satellite glial cells is more remarkable around large-sized trigeminal ganglion neurons than small-sized neurons [9]. The activation of satellite glial cells induced by activation of trigeminal ganglion neurons in response to peripheral nerve injury further increases the excitability of trigeminal ganglion neurons. This circular interaction is called the neuron-glial interaction and plays a significant role in the development and maintenance of neuropathic pain [37,41]. Neuron-glial interaction causes hyper-activation of nociceptive sensory transmission in the primary afferents. Hyper-activation of primary afferent neurons has also been reported in electrophysiological studies; trigeminal ganglion neurons generate a considerable action potential following nerve injury [8].

Recent studies have suggested that CGRP and purinergic signaling in the trigeminal ganglion have pivotal roles in the facilitation of neuron-satellite glial cell interaction after a trigeminal nerve injury. CGRP receptors are expressed in the satellite glial cells in the trigeminal ganglion [42]. In addition, the activation of satellite glial cells after peripheral nerve injury is associated with phosphorylation of extracellular signal-regulated kinase (ERK), one of the mitogen-activated protein kinases (MAPKs) (Fig. 1B)
Pathways that mediate pain sensations are composed of discrete neuronal circuits. For instance, the trigeminal spinal trigeminal tract (NST), a major pathway in the trigeminal nociceptive system, consists of small- and medium-sized Aδ-fibers and C-fibers that convey nociceptive information from the periphery to the brainstem. These fibers are part of the trigeminal nociceptive pathway, which is activated by noxious stimuli from the head, mouth, and face. The pathway consists of several neuronal relay stations, including the trigeminal ganglion, spinal trigeminal tract, trigeminothalamic tract, and thalamus, before reaching the somatosensory cortex, where pain perception is processed. The pathway is modulated by various neurotransmitters and neurohormones, including substance P, galanin, and vasoactive intestinal peptide (VIP). These molecules play a crucial role in modulating nociceptive information at different levels of the pain processing hierarchy.

Intracellular signaling pathways activated by noxious stimuli contribute to the generation of pain-related behaviors. For example, the activation of transient receptor potential (TRP) channels, such as TRPV1 and TRPA1, in nociceptors is crucial for the generation of noxious pain. These channels are activated by noxious stimuli, such as heat, cold, or chemical irritants, and their activation leads to the generation of depolarizing currents that trigger action potentials. The influx of calcium ions through these channels activates downstream signaling pathways, such as the mitogen-activated protein kinase (MAPK) and the extracellular signal-regulated kinase (ERK) pathways. These pathways are activated by various upstream stimuli, such as neurotransmitters, neuropeptides, and cytokines, and they play a crucial role in the modulation of pain-related behaviors.

The role of the trigeminal nociceptive pathway in the development of persistent pain is highlighted in several studies. For example, the activation of the Vc-PBN nociceptive pathway plays a significant role in the development of mechanical allodynia after trigeminal nerve injury. The Vc-PBN nociceptive pathway is activated by noxious mechanical stimuli, which trigger the release of neurotransmitters, such as glutamate and substance P, that activate nociceptive neurons in the Vc. These neurons then project to the PBN, which is a major relay station in the trigeminal nociceptive pathway. The activation of the Vc-PBN nociceptive pathway results in the generation of neural activity that is perceived as pain.

The role of the PBN in the development of persistent pain is also highlighted in several studies. The PBN is a major relay station in the trigeminal nociceptive pathway and is involved in the modulation of pain-related behaviors. For example, the activation of the Vc-PBN nociceptive pathway results in the generation of neural activity that is perceived as pain. The PBN is also involved in the modulation of pain-related behaviors through the activation of the CeA, a major brainstem area involved in the modulation of pain-related behaviors. The CeA is a major relay station in the trigeminal nociceptive pathway and is involved in the modulation of pain-related behaviors. The activation of the Vc-PBN nociceptive pathway results in the generation of neural activity that is perceived as pain. The PBN is also involved in the modulation of pain-related behaviors through the activation of the CeA, a major brainstem area involved in the modulation of pain-related behaviors.

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minute at the caudal NTS where visceral afferent information is integrated [90,91]. According to a recent study, trigeminal nerve injury causes ERK phosphorylation in caudal NTS neurons projecting to the PBN [92], suggesting that trigeminal nerve injury can potentiate activity of the lateral PBN through the caudal NTS. Visceral signals from the gut activate NTS neurons via the vagus nerve in response to eating; moreover, these neurons excite CGRP-positive neurons in the lateral PBN [69]. The activation of CGRP-positive neurons in the lateral PBN produces anoxia and loss of body weight by facilitating the affective functions of CeA, while their inhibition increases hunger [68,69]. These CGRP-positive neurons in the lateral PBN are believed to be suppressed by orexigenic hunger-sensitive agouti-related protein (AgRP) neurons located in the lateral hypothalamus [68]. In contrast, a recent study has revealed that AgRP neurons may form a pain modulation pathway to the lateral PBN; AgRP neurons suppress neurons to the Vc in the lateral PBN, and consequently, persistent pain is attenuated during hunger [93]. Therefore, pain inhibits the feeding behavior in association with decreased activity of AgRP neurons [93].

Together with this data, it can be considered that the PBN-CeA pathway, modulated by AgRP through neuropeptide Y signaling, may integrate nociception and anoxia in the presence of pain.

In conclusion, studies using animal models of trigeminal neuropathic pain have revealed that trigeminal nerve injury induces phenotypic changes and hyperexcitability though neuron-glial interactions in the trigeminal ganglion neurons. These changes in the primary afferent neurons lead to modulatory effects on ascending nociceptive information processing, resulting in a more pronounced effect on the ascending pathway from the Vc to the thalamus. The PBN has complex neural networks with the CeA and hypothalamus that regulates affective behavior; therefore, modulation of the Vc-PBN ascending nociceptive pathways in trigeminal neuropathic pain can underlie persistent orofacial neuropathic pain and pain-related behavioral disturbances, such as sleep problems and anoxia.

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Conflict of Interest
The authors declare no conflict of interest with this article.

References