Review

Multi-dimensional role of the parabrachial nucleus in regulating pain-related affective disturbances in trigeminal neuropathic pain

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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-glia interactions in the trigeminal ganglion. Increased nociceptive inputs from C- and Aδ-fiber and innocuous 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 trigeminal nerve branches. Rat models of inferior alveolar nerve transection [5] show hyperalgesia in the mental skin during the nerve regeneration [6,7] and secondary hyperalgesia outside the injured zone [5,8]. Additionally, rat models of lingual nerve crush [9] and infraorbital nerve-chronic constriction injury [10,11] show mechanical allodynia and heat hypersensitivity in regions that are innervated by the respective nerves. These animal models exhibit behavioral changes that mimic the pain symptoms in patients with neuropathic pain due to trigeminal nerve injuries [12]. Thus, this article reviews the recent findings on the role of ascending nociceptive pathways in the development of neuropathic pain and pain-related affective disturbances. The first part of the review consists of an overview of the ascending nociceptive pathways and followed by recent findings about the peripheral mechanisms that alter the excitability of the trigeminal ganglion neurons via neuron-glia interaction. Subsequently, the activity of the ascending nociceptive pathways from the trigeminal spinal subnucleus caudalis (Vc) to the thalamus and parabrachial nucleus (PBN) in response to noxious stimuli under trigeminal neuropathic pain will be examined. Finally, the potential role of the ascending nociceptive pathways through the PBN in the development of pain-related affective disturbances is proposed.

Ascending nociceptive pathway

Nociceptive inputs from the primary afferent fibers to the trigeminal spinal subnucleus caudalis

The cell bodies of nociceptive neurons are located in the trigeminal ganglion with the peripheral axonal fibers innervating the target tissues. Large-, medium-, and small-sized trigeminal ganglion neurons are composed of myelinated Aβ-, myelinated thin Aδ-, and unmyelinated C-fibers, respectively [13,14]. C- and Aδ-fibers mainly transmit noxious thermal, mechanical, or chemical information, while Aβ-fibers transmit innocuous tactile information under normal conditions [15]. Primary afferent fibers convey noxious and innocuous sensory information to neurons in different laminae of the caudal portion of the Vc [16-18]. The superficial laminae (laminae I and II) of the Vc predominantly receive sensory inputs from the nociceptive afferents, C- and Aδ-fibers, while the deep laminae of the Vc receive innocuous information from the Aδ- and Aβ-fibers (Fig. 1A) [16-18].

The trigeminal spinal nucleus is rostrocaudally subdivided into oralis, interpolaris, and caudalis (Vc) [19], with the Vc being the largest subdivision. The rostral part of the Vc is medi ally adjacent to the caudal end of the interpolaris and forms a distinct transition zone [20]. This trigeminal spinal interpolaris/caudalis transition zone does not exhibit a laminar structure. Neurons in the trigeminal spinal interpolaris/caudalis transition zone play an important role in relaying nociceptive inputs from the deep orofacial tissues, including the temporomandibular joint and masseter muscles, and play a minor role in discriminative pain [21]. The caudal portion of the Vc has a laminar structure that is considerably similar to the spinal dorsal horn. The Vc elongates to the cervical dorsal horn without a clear boundary. The initial processing of trigeminal nociceptive inputs is relayed within the laminated Vc [22]. This suggests that Vc neurons in trigeminal spinal interpolaris/caudalis transition zone and more caudal portion of the Vc serve different functions in trigeminal nociception [21,23].

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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]. The rostrocaudal distribution of these NK1 receptor-positive neurons that project to the thalamus and PBN in the Vc are different [27]. The Vc neurons, which are the secondary neurons, project to the lateral thalamus [e.g., ventral posteromedial thalamic nucleus (VPM)], posterior thalamic nuclear group, and posterior triangular area] [24,28], forming the ascending projection to the primary and secondary somatosensory cortex. Therefore, the Vc-thalamus pathway mediates the sensory-discriminative pain inputs, such as pain quality, intensity, modality, and location (Fig. 1A). In another ascending pathway from the Vc to the PBN, nociceptive neurons were primarily identified in the lateral parabrachial complex nucleus [29] and have multiple projection targets, such as the central nucleus of the amygdala (CeA) and the hypothalamus [25]. This contributes to the affective aspects of pain as well as control of autonomic functions (Fig. 1A) [30,31]. A more recent study has demonstrated that lateral PBN receives monosynaptic projections from trigeminal ganglion neurons, suggesting that primary afferents directly transmit nociceptive information to third order neurons in the lateral PBN; further, these direct connections contribute to heightening of orofacial affective pain [32]. A few studies have shown that the two ascending pathways from the Vc to the VPM or 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 were 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 aspect of the orofacial pain. In another pathway, the PBN neurons also send axons directly to the rostral ventrolateral medulla (RVM) [25], which plays a significant role in the descending pain modulation [34]. Projections from the PBN to RVM suggest that the Vc-PBN pathway is a part of a recurrent pain-modulatory network parallel to the ascending nociceptive transmission. In sum, the above findings of nociceptive transmission from the Vc to the thalamus and PBN underlie the neurophysiological mechanism involved in multiple aspects of trigeminal neuropathic pain.
Modulation of projection neurons in the trigeminal spinal subnuclei underlying persistent orofacial neuropathic pain

Hyperexcitability of neurons in the superficial lamina of the Vc

Previous studies have demonstrated that nociceptive neurons located in the superficial laminae of the Vc become hyperexcitable after trigeminal nerve injury (Fig. 1B) [5,6,49]. ERK phosphorylation is also significantly enhanced in neurons at the superficial lamina of the Vc [11,49]. Enhanced phosphorylation of ERK in the Vc can be attributed to increased nociceptive inputs to the superficial lamina of the Vc after nerve injury [5,6,49]. It is important to note that some studies have suggested distinct role of primary afferents in the development of mechanical allodynia and thermal hypersensitivity [5,9,10]. Capsaicin, an agonist of transient receptor potential vanilloid type 1 (TRPV1), selectively activates small myelinated and unmyelinated sensory nerve fibers [50]. Capsaicin stimulation activates mechanically insensitive C-fibers [51] and heat-insensitive Aδ-fibers [52]. C-fibers have limited effects on mechanical allodynia [53], while Aδ-fibers transmit innocuous mechanical and thermal information [54]. Aδ-fibers that express TRPV1 are also involved in mechanical allodynia [55]. Aδ-fibers from low threshold mechanoreceptors terminate in the deeper laminae of the Vc [17] and may mediate tactile allodynia after nerve injury, resulting in innocuous mechanical stimuli being perceived as painful [15].

As discussed earlier, following nerve injury, trigeminal ganglion neurons exhibit phenotypic changes wherein large-sized neurons with primary afferents, such as Aβ-fibers, are involved in nociceptive information transmission (Fig. 1B) [37]. Touch-related information from the Aβ-fibers is also relayed to nociceptive circuits in the superficial laminae [56,57] where they have polysynaptic connections including interneurons [58-60]. Therefore, projection neurons in the superficial lamina of the Vc, expressing neuropekinin-1 receptors, can receive increased excitatory inputs from Aβ-fibers when the trigeminal nerves are injured [58-60], resulting in the generation of touch-evoked pain [56,57].

The Vc-PBN pathway receiving noxious input from Aβ-fiber

The noxious information from the superficial laminae of the Vc is sent directly to the PBN rather than to thalamus [27]. A recent study has suggested that ascending nociceptive neurons in the Vc which project to the VPM or PBN are activated differently in a nociceptive stimulus modality-specific manner in the presence of trigeminal neuropathic pain (Fig. 1B) [11]. Both Vc-VPM and Vc-PBN nociceptive pathways were potentiated by capsaicin stimulation, including the activation of principally C-fibers, while only Vc-PBN, not the Vc-VPM, nociceptive pathway was potentiated by noxious mechanical stimulation following trigeminal nerve injury [11]. These results agree with a previous study where neurons in lamina I of the spinal dorsal horn responding to low threshold mechanical stimuli and projecting to PBN were activated after a nerve injury [61]. The two principal manifestations of neuropathic pain, hyperalgesia and mechanial allodynia, are mediated through separate mechanisms and neuronal pathways [62]. Behaviorally relevant pain modalities can be selectively regulated by targeting distinct subsets of primary afferent fibers, such as opioid receptors, peptidergic/non-peptidergic, and unmyelinated/myelinated fibers [63]. Changes in the GABA/glycine inhibitory systems are also associated with mechanical allodynia, but not thermal hyperalgesia [64,65]. Together with these findings, activation of the Vc-PBN nociceptive pathway can play a significant role in the development of tactile allodynia in trigeminal neuropathic pain.

Role of Vc-PBN pathway in the behavioral symptoms related to trigeminal neuropathic pain

The PBN neurons show hyper-activation in the presence of trigeminal neuropathic pain [66]. Recently, the PBN has been recognized as a major area for relay of nociceptive information to pain-modulating circuits for the development of pain-related behavioral symptoms. The PBN consists of complex nuclei that contain subpopulations of neurons that regulate wake-sleep behavior [67] and anorexia [68,69], in addition to pain [11,25,27].

Enhanced affective aspects of pain underlying neuropathic pain

The Vc-PBN nociceptive pathway is a major neuronal circuit that relays noxious information from the orofacial region to the higher brain regions, processing affective aspects of pain because PBN neurons project directly to the CeA [18]. A recent study has demonstrated that optically stimulated non-nociceptive primary afferent Aδ-fibers activate the spinal dorsal horn-PBN-CeA pain pathway after nerve injury [70]. The CeA play an essential role in the expression of aversive signal-induced emotional behaviors, such as fear-conditioned responses [71]. The projections from the PBN to the CeA are involved in the regulation of pain-related negative emotions, including anxiety, depression, aversion [72], as well as nociceptive transmission [73]. This is because of the stimulation of the PBN neurons that contain CGRP and projections to the CeA that induce defensive responses and a threat memory [74]. Research has demonstrated that C-fiber afferents do not participate in the development of neuropathic pain; however, they play an essential role in the establishment of nerve injury-evoked synaptic potentiation of the PBN-CeA transmission [75]. Recently, it has been observed that CeA neurons that receive monosynaptic excitatory inputs from the PBN were modified based on the molecular identity and topographical location within the CeA after nerve injury [76], suggesting neuronal changes in the PBN-CeA pathway. Therefore, enhanced activity of Vc-PBN-CeA pathway undoubtedly contributes not only to the development of hyperalgesia and mechanical allodynia, but also to affective aspects of persistent orofacial pain after trigeminal nerve injury.

Sleep problems and pain associated with orexinergic neurons

A recent study has suggested that neurons in the lateral PBN may play a role in the ascending arousal system [77]; the activation of PBN potently drives arousal-related circuits and suppresses sleep-related circuits [67]. Glutamatergic neurons, VGLUT2 positive fibers in the lateral PBN project to the lateral hypothalamus [78], where the neuropeptide orexin is specifically synthesized [79]. Orexinergic neurons in the lateral hypothalamic pathway to the brainstem arousal-promoting areas and activation of these neurons promotes wakefulness [67,80,81]. Therefore, increased activity in the Vc-PBN nociceptive pathway can play an arousal-promoting role in trigeminal neuropathic pain. However, trigeminal nociceptive transmission from the Vc during the sleep states remains to be fully defined [82-84]. In contrast, hypothalamic orexinergic neurons were found to project to the Vc [85]. A recent study has demonstrated that activity of orexinergic receptors can modulate nociceptive information processing in the superficial layer of the Vc [86]. The above findings about the reciprocal connections between the PBN and lateral hypothalamus suggest that orexinergic neurons that receive excitatory inputs from the lateral PBN might exacerbate the vicious interactions between sleep disturbance and nociceptive sensitivity in trigeminal neuropathic pain [87]. In fact, sleep complaints are commonly reported by patients with trigeminal neuropathic pain [88].

Anorexia and pain associated with agouti-related protein/neuropeptide Y circuit

The lateral PBN receives visceral sensory inputs from the caudal part of the nucleus tractus solitarii (NTS) [89]. A previous study has demonstrated that trigeminal primary afferents, such as trigeminal ganglion neurons, ter-
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; AGPR neurons suppress neuronal firing in the lateral PBN, and consequently, periodontal 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 PBN that 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.

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