Abstract: Nociceptive stimuli to the orofacial region are typically received by the peripheral terminal of trigeminal ganglion (TG) neurons, and previous orofacial information is subsequently conveyed to the trigeminal spinal subnucleus caudalis and the upper cervical spinal cord (C1-C2). This information is further transmitted to the cortical somatosensory regions and limbic system via the thalamus, which then leads to the perception of pain. It is a well-established fact that the presence of abnormal pain in the orofacial region is etiologically associated with neuromodulatory changes that may occur at any point in the pain transmission pathway from the peripheral to the central nervous system (CNS). Recently, several studies have reported that functional plastic changes in a large number of cells, including TG neurons, glial cells (satellite cells, microglia, and astrocytes), and immune cells (macrophages and neutrophils), contribute to the sensitization and disinhibition of neurons in the peripheral and CNS, which results in orofacial pain hypersensitivity.

Keywords: orofacial pain, spinal trigeminal nucleus, trigeminal ganglion, upper cervical spinal cord

Introduction

Physiological pain induced by noxious stimuli plays an important role in the body’s defense mechanism and is essential for supporting several life processes. Alternatively, chronic pathological pain is induced by non-noxious stimuli or persistent spontaneous pain hypersensitivity, leading to the impairment of processes involved in the body’s defense mechanism. Pathological orofacial pain conditions, such as trigeminal neuralgia, burning mouth syndrome, myofacial pain syndrome, and temporomandibular joint dysfunction, are considered variations of chronic pain, and they can be addressed by therapeutic intervention. Nevertheless, several aspects regarding the pathogenetic mechanisms of these variations remain unclear, and, consequently, a number of clinicians struggle to control abnormal pain hypersensitivity.

Orofacial inflammation, trigeminal nerve disturbances, and oral cancer are known to underlie nociceptive trigeminal neuronal hyperexcitability, leading to orofacial pain hypersensitivity, which is induced by various molecular signaling mechanisms that are closely associated with several mediators released from immune or glial cells [1,2]. Furthermore, the trigeminal sensory nucleus complex consists of the main trigeminal sensory nucleus and trigeminal spinal nuclei. The main sensory nucleus receives information regarding touch, pressure, and vibration from the craniofacial region. The trigeminal spinal nucleus is located caudally to the main trigeminal sensory nucleus and receives sensory information from the face and oral cavity. The ophthalmic, maxillary, and mandibular trigeminal nerves terminate the trigeminal spinal nucleus, which is essentially divided into three subnuclei: oralis, interpolaris, and caudalis (Vc). The mandibular, ophthalmic, and maxillary projections are predominantly located in the dorsal, ventral, and medial regions of the body, respectively. Nociceptive input from the orofacial region terminates in the Vc as well as the upper cervical spinal cord (C1-C2) [3]. Since the cellular organization of the Vc is similar to that of the spinal dorsal horn, the Vc is also referred to as the medullary dorsal horn. Pathological plastic changes in the trigeminal neuronal circuitries lead to orofacial pain hypersensitivity.

Recent studies have demonstrated that neuronal hyperexcitability in the orofacial pain transmission pathway contributes to persistent orofacial pain mechanisms following orofacial pathogenesis [4-6]. This pathway extends from the orofacial region to the pain information-processing region in the cerebrum and is associated with the pathological plastic changes in satellite glial cells in the trigeminal ganglion (TG), secondary neurons, microglia, and astrocytes in the Vc and C1-C2. This review utilizes the latest available studies to outline the mechanisms behind pain abnormalities that occur in the orofacial region.

Local pathological changes contribute to nociceptive neuronal hyperexcitability

Dental pulpitis, periodontitis, and pericoronitis lead to the infiltration of inflammatory cells along with the release and promotion of several inflammatory mediators, such as nerve growth factor (NGF) and tumor necrosis factor-alpha (TNFα), in inflammatory sites [7,8]. TNFα signaling via TNF receptor-1 (TNFR-1) and TNF receptor-2 (TNFR-2), which are expressed in nociceptive endings, sensitize voltage-gated sodium channel 1.8 (Nav 1.8) by activating the protein kinase C, which results in the predisposition to generate action potentials [9,10]. The transient receptor potential (TRP) channel superfamily plays an important role in functions associated with sensing pain [11]. Furthermore, TRP vanilloid 1 (TRPV1) is activated in the presence of high-temperature conditions (>42°C), low pH, capsaicin, and vanilloid, while TRPA1 is activated by low temperatures (<15°C) and in the presence of numerous chemical irritants [12]. Facial inflammation subsequently reduces the acidity in the inflamed site, which increases TRPV1 expression in nociceptors. TRPV1 activation facilitates the intracellular influx of Ca2+, which sensitizes TRPA1, leading to orofacial cold hypersensitivity [13].

To the contrary, heat hypersensitivity following a facial skin incision is induced by the sensitization of TRPV1 through protein kinase A signaling and is facilitated by activating TRPA1 in the TG neurons that innervate the facial skin surrounding the incision [14]. Alternatively, there is a notable upregulation of artemin (ATN) mRNA expression, a member of the glial cell line-derived neurotrophic factor family, in the epithelial cells of tongue mucosa sampled from patients with burning mouth syndrome [5]. ATN signal upregulation, facilitated by the phosphorylation of p38 mitogen-activated protein kinase (MAPK) in the tongue mucosa, produces heat hypersensitivity in the tongue due to the hyperexpression of TRPV1 in nociceptors that innervate the tongue [5,15]. The p75 neurotrophin receptor (p75NTR) and tyrosine kinase receptor A (TrkA) act as NGF receptors in the primary nociceptive neurons [16]. NGF signaling via p75NTR and TrkA, which are expressed in nociceptive endings, has been reported to enhance the tetrodotoxin-resistant sodium current density and decrease the threshold potential of Nav 1.8, which is etiologically associated with inflammatory neuronal alldynia [17,18].

Furthermore, the NGF/TrkA complex is formed after NGF successfully binds to TrkA at the nociceptor endings and is internalized in the endings to be retrogradely transported to the soma of the primary neuron [19]. Neuronal firing induces NGF secretion into the extracellular space in vitro, which increases the concentration of NGF in the culture medium [20,21]. Following local orofacial inflammation, NGF secreted from the TG neurons innervating the inflamed site binds to NGF receptors expressed in other TG neurons. This subsequently leads to an increased expression of TRPV1 within the intact TG neurons innervating the intact sites, which

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Color figures can be viewed in the online issue at J-STAGE. doi.org/10.2334/josnusd.19-0373
DN/JST/JSTAGE/journal/19-0373
in turn contributes to ectopic orofacial pain [22]. Local orofacial inflammation also increases the activity of the P2X₃ receptors, which are one of the adenosine triphosphate (ATP) receptors in TG neurons innervating the intact site. Increased P2X₃ receptor activity is typically noted after the sensitization of primary afferent neurons, followed by ectopic orofacial mechanical allodynia [23].

Neuronal communication among TG
TG neurons innervating the injured inferior alveolar nerve release humoral factors, including cytokines and neuroepitopes, along with nitric oxide (NO); this free-radical gas is an important neurotransmitter with several widespread effects. It is synthesized in the somata of primary neurons via NO synthase (NOS) signaling and is subsequently released to the extracellular space [24,25]. Synthesis using the NOS signaling pathway and the release of NO from these particular TG neurons are responsible for an increase in NO levels in the TG, which is associated with chronic orofacial ectopic mechanical allodynia [26]. Heat shock protein (Hsp70) that is produced in the pulpal tissues following tooth pulpitis is transported to the somata of the TG neurons, which innervate the inflamed pulp, and are released into the TG. The Hsp70 signaling via toll-like receptor (TLR) 4 in TG neurons innervates the tongue and thus enhances its neuronal excitability and leads to a condition known as tongue pain hypersensitivity [27]. However, these reports concurrently indicate that communication among TG neurons via various signaling pathways mediated by neurotransmitters contributes to orofacial pain hypersensitivity.

Neuron and non-neuronal cell communication in TG
Some of the primary afferents, satellite glial cells, macrophages, and lymphocytes are typically present in the TG. The soma is surrounded by satellite glial cells; the gap between the soma and satellite glial cells is approximately 20 nm, and these cells communicate with each other using neurotransmitters [28]. Recent studies have revealed that morphological changes in satellite glial cells (soma and processes swelling) strongly correlate with their function [29]. Although the primary neuronal hyperactivity caused by peripheral inflammation or nerve injury plays an essential role in the morphology and function of satellite glial cells, the precise mechanism underlying this phenomenon currently remains unclear. It was observed that lingual nerve injury triggers a release of ATP molecules from NO synthase (NOS) signaling and is subsequently released to the extracellular space [24,25]. Synthesis using the NOS signaling pathway and the release of NO from these particular TG neurons are responsible for an increase in NO levels in the TG, which is associated with chronic orofacial ectopic mechanical allodynia [26]. Heat shock protein (Hsp70) that is produced in the pulpal tissues following tooth pulpitis is transported to the somata of the TG neurons, which innervate the inflamed pulp, and are released into the TG. The Hsp70 signaling via toll-like receptor (TLR) 4 in TG neurons innervates the tongue and thus enhances its neuronal excitability and leads to a condition known as tongue pain hypersensitivity [27]. However, these reports concurrently indicate that communication among TG neurons via various signaling pathways mediated by neurotransmitters contributes to orofacial pain hypersensitivity.

Process and non-neuronal cell communication in TG
Satellite glial cells, which play a key role in peripheral nerve injury, are responsible for the anti-inflammatory response and tissue repair. A number of macrophages that infiltrate the TG due to peripheral nerve injury, indicated by the enhancement of CCL2 signaling via TLR2, facilitate the infiltration of activated macrophages into the TG [53]. The intracellular signaling cascades, such as extracellular signal-regulated kinase (ERK) and p38 MAPK, regulate the inflammatory effectors, including the synthesis of substance P (SP), which is secreted into the sensory ganglion [57]. The secreted SP signaling promotes the release of TNFα via the ERK 1/2 and p38 MAPK signaling from the activated macrophages in the TG [58-60]. To summarize, TNFα or SP is released from activated macrophages after peripheral nerve injury [59-60]. To summarize, TNFα or SP is released from activated macrophages after peripheral nerve injury in the orofacial region, consequently resulting in the release of TNFα or SP signaling, which is responsible for TNFα-mediated orofacial hypersensitivity followed by orofacial pain hypersensitivity (Fig. 1) [61].

Neuronal circuits in the trigeminal sensory nucleus complex
Sensory information is integrated into the Vc, which consists of local circuit interneurons and projection neurons. A majority of the interneurons in the Vc are inhibitory gamma-aminobutyric acid (GABA)ergic and glycinegic neurons that suppress neuronal activity through the influx of Cl⁻ through GABAₐ and glycine receptors. These neurons serve as the gate control of nociception. The balance between excitatory and inhibitory input into the neurons that transmit information to the CNS can be used to determine nociceptive information [62]. Local ablation of spinal glycinegic neurons using an intraspinal injection of AAV-FLEX diphtheria toxin A in glycine transporter 2-Cre mice shows a significant reduction in the mechanical threshold [63]. Additionally, prostaglandin E2, an inflammatory factor, downregulates the glycine receptor α3 subunit in the spinal dorsal horn, resulting in hyperalgesia [64]. Gate control in the Vc is regulated by GAB-Aergic neurons, and their reduction is observed seven days after inferior alveolar nerve transection [65]. Recently, an experiment that supports gate control theory was conducted using conditional ablation of somatostatin (SOM)-immunopositive neurons in lamina II of the spinal cord. SOM-immunopositive neurons receive both Aβ/C fiber-mediated noxious mechanical inputs and Aβ fiber-mediated noxious mechanical inputs, which are relayed via dynorphin-immunopositive neurons [66]. The loss
of Aβ fiber-mediated inputs onto SOM-immunopositive neurons caused mechanical allodynia by enhancing noxious mechanical inputs [66]. These data indicate that the transmission of noxious information from the spinal cord to higher brain regions is regulated by non-noxious information onto SOM-immunopositive neurons. Local circuit interneurons play an important role in pain sensation.

Sensory information that is integrated into a local, inter-neuronal circuit in the Vc is conveyed to the ventral postero medial thalamic nucleus (VPM) and the parabuccal nucleus (PBN) by projection neurons [67]. The projection patterns are dependent on modality. In the case of a chronic constriction injury of the infraorbital nerve, C fiber-mediated responses are carried into both VPM and PBN. In contrast, mechanosensitive afferents preferentially terminate in the VPM and PBN. After binding to their respective receptors (i.e., TNFR, IL-1RI, and TrkB), they prominently express on secondary neuronal terminals and drive the intracellular signaling systems that are associated with chronic and ectopic pain. Glutamine synthetase activation in activated astrocytes increases the amount of glutamate released. Glutamate is transported into primary afferent terminals to accelerate the release of glutamate into the synaptic cleft, which results in hyperexcitation of the second-order neurons.

Abnormal pain
Glia cells play a crucial role in addressing chronic pain, which is typically resistant to therapeutics, including nonsteroidal anti-inflammatory drugs and opioids. After cellular activation, microglia retrace their elaborated processes and enlarge their somata. The factors that induce microglial activation are primary afferent-derived chemokine (C-C motif) ligand 21, colony-stimulating factor 1 [69,70], de novo synthesis of lysophosphatidic acid, and ATP from spinal neurons [71,72]. Activated microglia release several proinflammatory cytokines, such as IL-1β, IL-6, and TNFα, and a brain-derived neurotrophic factor (BDNF) [73]. Among the proinflammatory cytokines, IL-1β potentiates glutamatergic neurotransmission and inhibits both GABAergic and glycinergic neurotransmission [74], resulting by genetic tools [68]. Distinct input patterns from the TG and Vc into the PBN might be instrumental in determining the severity of pain.
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