Review Article

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Role of neuron and non-neuronal cell communication in persistent orofacial pain

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It is well known that trigeminal nerve injury causes hyperexcitability in trigeminal ganglion neurons, which become sensitized. Long after trigeminal nerve damage, trigeminal spinal subnucleus caudalis and upper cervical spinal cord (C1/C2) nociceptive neurons become hyperactive and are sensitized, resulting in persistent orofacial pain. Communication between neurons and non-neuronal cells is believed to be involved in these mechanisms. In this article, the authors highlight several lines of evidence that neuron-glial cell and neuron macrophage communication have essential roles in persistent orofacial pain mechanisms associated with trigeminal nerve injury and/or orofacial inflammation.

Keywords: Cell Communication; Orofacial Persistent Pain; Spinal Trigeminal Nucleus; Trigeminal Ganglion.

INTRODUCTION

The oral and craniofacial regions consist of unique structures, including the tongue, teeth, and oral mucosa, which are highly organized for various orofacial functions such as mastication, taste and/or speech. The trigeminal nerve innervates the orofacial structures, and conveys a variety of orofacial sensory information to the central nervous system. In particular, the lingual nerve fibers innervating taste buds in the tongue contribute to taste sensation as well as somatic sensation. The trigeminal nerve consists of 3 branches innervating the orofacial regions somatotopically. Each branch has a different function in orofacial sensation, and their cell soma are located in close proximity to one another. Orofacial noxious, as well as non-noxious, sensory information is sent to the trigeminal spinal subnucleus caudalis (Vc) and upper cervical spinal cord (C1/C2) via the trigeminal ganglion (TG) [1]. The Vc has a laminated structure similar to that of the spinal dorsal horn, known as the medullary dorsal horn [2]. Orofacial noxious sensory information is sent to the superficial laminae of the Vc and C1/C2. Recent studies have reported that nociceptive neurons in the Vc and C1/C2 regions are involved in different functions for processing orofacial nociception [3]. A large number of non-neuronal glial cells, such as satellite glia, microglia, astroglia and oligodendroglia, are distributed throughout the brain. These non-neuronal glial cells are believed to be involved in the nutrition and structural maintenance of neuronal networks in the micro-environment of the peripheral and central nervous system [4]. Conversely, non-neuronal glial cells and macrophages have been reported to have essential roles in the modulation of neuronal excitability, in addition to structural and maintenance functions [5]. After nerve injury or

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chronic inflammation in the peripheral structures, non-neuronal glial cells and macrophages are activated and are believed to be involved in the modulation of neuronal excitability [5].

After trigeminal nerve injury, a barrage of action potentials is generated in TG neurons and sent to the Vc and C1/C2 regions [6]. After the hyperactivation of TG neurons, non-neuronal glial cells and macrophages are activated. Activated glial cells and macrophages produce a variety of cytokines that are involved in the modulation of neuronal excitability [7]. It is essential to understand the mechanisms underlying the functional interaction between non-neuronal cells and neurons in the orofacial pathological pain state to develop appropriate treatment strategies for patients with persistent orofacial pain.

SATELLITE GLIA AND NEURON INTERACTION IN THE TG

It is well known that the soma of a primary afferent neuron is tightly surrounded by satellite glial cells in the TG and dorsal root ganglion (DRG). The gap between the soma of a primary neuron and satellite glial cells is only 20 nm, and is where these cells communicate with one another by releasing chemical messengers knowns as neurotransmitters. Recent studies have indicated that peripheral nerve injury induces morphological changes in satellite glial cells (hypertrophy and enhanced expression glial fibrillary acidic protein) and functional hyperactivity [8,9]. In fact, peripheral nerve injury with the blockade of primary neural conduction under local anesthesia does not induce morphological and functional changes in satellite glial cells and attenuates neuropathic pain intensity [10,11]. Consequently, although it is certain that the enhancement of primary afferent neuronal activity following peripheral nerve injury or inflammation is involved in morphological and functional changes of satellite glial cells, detailed mechanisms have not been entirely elucidated.

The P2X7 receptor is a purinergic ionotropic receptor channel expressed in satellite glial cells in the TG [12]. A clinical study reported increased P2X7 receptor expression in satellite glial cells in the DRG following peripheral nerve injury [13]. Moreover, earlier studies have indicated that nociceptive stimuli elicited adenosine triphosphate (ATP) release from the soma of primary neurons to peripheral tissues, and the sensitivity of satellite glial cells in the TG to ATP was markedly enhanced following orofacial inflammation [12,14]. Enhanced P2X7 signaling in satellite glial cells augments P2X3 receptor expression in primary TG neurons, which may be a possible mechanism of orofacial mechanical allodynia following peripheral nerve injury [15].

P2X7 signaling in satellite glial cells in the TG also increases intracellular calcium concentration [16]. The increment in intracellular calcium concentration induces the synthesis and release of cytokines such as tumor necrosis factor-alpha (TNFα) or interleukin (IL) 1-beta (IL-1β) from satellite glial cells in a sciatic or trigeminal nerve injury model [17,18]. IL-1β binds to the IL-1 receptor in small-diameter TG neurons, and IL-1β signaling reduces the outward potassium current responsible for repolarization of the membrane, which enhances TG nociceptive neuronal excitability [19]. Additionally, TNF-α signaling in DRG neurons increases transient receptor potential vanilloid 1 (TRPV1) expression via extracellular signal-regulated kinase (ERK), which enhances TRPV1-dependent inward current [20]. TNF-α signaling also regulates voltage-gated sodium channel (Nav) excitability by the activation of tetrodotoxin (TTX)-sensitive and TTX-resistant Nav 1.3 and Nav 1.8 in DRG neurons via p38 mitogen-activated protein kinase (MAPK) signaling following peripheral nerve injury [21-23]. It is assumed that these mechanisms are also involved in the sensitization of primary nociceptive neurons, which are responsible for orofacial mechanical allodynia following peripheral nerve injury.

MACROPHAGE ACTIVATION IN TG

Previous studies have indicated that peripheral nerve

injury induces the increase in the number of resident and proliferating macrophages in the DRG [24-26]. In the TG, trigeminal nerve injury induces extensive macrophage infiltration; these infiltrating macrophages exhibit larger cell bodies and thicker ramifications, which indicate activation [27]. In the DRG, the chemokine C-C motif ligand 2 (CCL2), released from injured neurons, binds to the C-C chemokine receptor type 2 (CCR2) in macrophages, which activates macrophage proliferation in peripheral nerve injury [28,29]. Furthermore, deficiencies in toll-like receptor 2 (TLR2) depresses the enhancement of CCL2 expression in sensory neurons and macrophage infiltration in the sensory ganglion following peripheral nerve injury [30], indicating that the abundant infiltration of activated macrophages in the TG is induced by CCL2 released from injured neurons via TLR2 signaling following trigeminal nerve injury.

Macrophages are also a source of TNF-α in DRG, and TNF-α is released via intracellular signaling cascades including p38 MAPK and extracellular signal-regulated kinase (ERK) cascades [31-33]. Substance P (SP) expression is enhanced in DRG neurons, and SP release into the DRG after peripheral nerve injury [34]. These reports indicate that SP released from TG neurons binds to the neurokinin 1 receptor, which is expressed in macrophages, resulting in TNF-α release from activated macrophages via the ERK 1/2 and p38 MAPK signaling cascades [35-37]. Based on these reports, TNF-α or SP released from proliferating macrophages, and these signaling pathways may contribute to the enhancement of TG neuronal excitability, resulting in orofacial mechanical allodynia following trigeminal nerve injury [7].

NEURON-GLIAL INTERACTION IN THE Vc AND C1/C2

Orofacial noxious information is sent to the Vc and C1/C2 regions, and nociceptive neurons in these nuclei are somatotopically organized [38]. After trigeminal nerve injury or orofacial inflammation, a barrage of action potentials is generated in TG neurons, which become sensitized [39]. The release of various excitatory neurotransmitters from sensitized primary afferent terminals, such as glutamate, is enhanced, and synaptic transmission is further accelerated in Vc and C1/C2 and, subsequently, Vc and C1/C2 nociceptive neurons are sensitized.

ERK is phosphorylated in Vc and C1/C2 nociceptive neurons approximately 5 min after noxious stimulation of the orofacial regions [40]. This molecule is known as a useful marker of excitability in nociceptive neurons in the Vc and C1/C2 activated by various noxious stimuli to the orofacial regions [38]. ERK phosphorylation is significantly enhanced following trigeminal nerve injury or orofacial inflammation, and this molecule is believed to be involved in the sensitization of Vc and C1/C2 nociceptive neurons [41]. It has also been reported that microglia and astroglia are activated in the Vc and C1/C2 after trigeminal nerve injury [42,43].

Activated microglial and astroglial cells alter their morphological features and release various molecules that are involved in the modulation of Vc and C1/C2 nociceptive neuronal activity. The glutamate-glutamine shuttle is one of the possible mechanisms underlying neuron-astroglial cell interaction, which is involved in the enhancement of neuronal activity in Vc and C1/C2 neurons following trigeminal nerve injury [44]. After trigeminal nerve injury, astroglial cells are activated and release glutamine. The glutamine is then removed from the primary afferent terminals of the trigeminal nerve, and glutamate release from the terminals is strongly enhanced, resulting in further enhancement of Vc and C1/C2 nociceptive neuronal activity [42].

Microglial cells are also activated after trigeminal nerve injury [43]. ATP is released from the primary afferent terminals and bind to the P2X4 receptor in microglial cells, which are then activated. Activated microglial cells are known to release brain-derived neurotrophic factor (BDNF), which binds TrkB in the Vc and C1/C2 nociceptive neurons, resulting in hyperexcitation. KCC2 down-regulation associated with BDNF binding with TrkB is also known to be involved in the enhancement of the Vc and C1/C2 nociceptive neuronal activity [45].

Recently, it has been reported that microglial cells and astroglial cells closely communicate with one another, and that microglial cells regulate the activation of astroglial cells [46].

After trigeminal nerve injury, a barrage of action potentials is generated and conveyed to TG neurons. Within the TG, various molecules are produced in satellite glial cells and macrophages are activated, and various molecules are generated in these cells and released from these cells, which in turn further enhance TG neuronal activity. According to similar mechanisms, Vc and C1/C2 nociceptive neurons are also strongly activated via astrocyte and microglial cell activation. Activated astroglial and microglial cells release various molecules that are involved in the enhancement of Vc and C1/C2 neuronal activity. Although these mechanisms are involved in hyperactivation of nociceptive neurons in the Vc and C1/C2 regions, resulting in the orofacial persistent pain associated with trigeminal nerve injury.

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