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Review

Basic research and clinical investigations of the neural basis of orofacial pain

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A B S T R A C T

Background: Trigeminal nerve injury or orofacial inflammation causes severe pain in the orofacial regions innervated by uninjured nerves or uninflamed tissues as well as injured or inflamed tissues. Pathological orofacial pain associated with trigeminal nerve injury or inflammation is difficult to diagnose and treat.
Highlight: To develop appropriate treatments for patients with orofacial pathological pain, various animal models of trigeminal nerve injury or orofacial inflammation have been developed. Further, the possible mechanisms involving the trigeminal ganglion (TG), trigeminal spinal subnucleus caudalis (Vc), and upper cervical spinal cord (C1–C2) have been studied.
Conclusion: (1) Neurotransmitters released from the somata of TG neurons are involved in peripheral sensitization. (2) Neurotransmitter release from TG neurons is decreased by botulinum toxin-type A administration, suggesting that this toxin suppressed neurotransmitter release and alleviated the neuropathic pain-related behavior. (3) Altered states of glial cells and nociceptive neurons, in the Vc and C1–C2 are involved in pathological orofacial pain associated with trigeminal nerve injury or orofacial inflammation. (4) The trigeminal sensory nuclear complex, especially the trigeminal spinal subnucleus oralis, is involved in normal and pathological orofacial pain conditions after peripheral nerve injury. (5) Neuroimaging analyses have suggested functional changes in the central and peripheral nervous systems in neuropathic pain conditions.
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Abbreviations: ACSF, artificial cerebrospinal fluid; ATP, adenosine-5′-triphosphate; BoNT/A, botulinum toxin-type A; Cm, membrane capacitance; DRG, dorsal root ganglia; ES, electrical stimulation; FM4-64, N-(3-triethylammoniumpropyl)-4-(6-(4-(diethylamino)phenyl)) exatrienyl pyridinium dibromide; Fos-LI, c-Fos protein-like immunoreactivity; FA, fractional anisotropy; HRP, horseradish peroxidase; IAN, inferior alveolar nerve; IANX, inferior alveolar nerve transection; IB4, isolectin B4; ION-CCI, chronic constriction injury of the infraorbital nerve; L/L, luciferin–luciferase; LN, lingual nerve; MAPKs, mitogen-activated protein kinases; NGF, nerve growth factor; NS, noxious specific; PrV, rostral-most trigeminal principal sensory nucleus; SNE, sciatic nerve entrapment; SP, substance P; TG, trigeminal ganglion; TMD, temporomandibular disorder; TSNC, trigeminal sensory nuclear complex; Vc, trigeminal spinal subnucleus caudalis; Vi, trigeminal spinal subnucleus interpolaris; Vo, trigeminal spinal subnucleus oralis; WDR, wide dynamic range

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1. Introduction

Research on pain has been avoided in the past because of the technical difficulties in objectively analyzing data on the subjective sensation of pain. However, control of pain in is one of the most important issues in the field of medicine that emphasizes on the patients quality of life. Only the pulp contains sensory receptors for pain. Thus, researchers have been actively targeting nociceptors. Here we discuss how the management of orofacial pain can be improved in the future. We describe the basic orofacial pain mechanisms and clinical approaches for such patients.

Allodynia and/or hyperalgesia frequently occur in the orofacial region following trigeminal nerve injury or orofacial inflammation [1,2]. Pathological pain associated with such injury/inflammation is severe and difficult to treat and occurs in wide areas innervated by injured as well as uninjured nerve fibers. Similar symptoms have been observed in the uninflamed as well as inflamed areas [3]. The extraterritorial orofacial pain that occurs in areas innervated by uninjured nerves or in uninflamed areas sometimes leads to misdiagnosis or inappropriate treatment [1,2]. It is very important to understand the mechanisms underlying extraterritorial orofacial pain associated with trigeminal nerve injury or orofacial inflammation in order to develop appropriate measures for treatment of patients with extraterritorial orofacial pain.

This review describes recent findings in animal models and the future directions of investigations of pathological pain mechanisms.

2. Mechanisms of orofacial pain transmission in the trigeminal ganglia (TG) and development of new treatment procedures: neurotransmitter release from the somata of sensory ganglia

Many patients with trigeminal neuropathy suffer from severe pain. Anticonvulsants or antidepressants prescribed for pain management induce adverse effects in the central nervous system, such as dizziness and drowsiness. Understanding the mechanisms that lead to trigeminal neuropathic pain is essential for development of new treatment modalities without adverse side effects. Animal models of peripheral nerve injuries have been used to mimic human neuropathic pain symptoms (e.g., tactile allodynia or thermal hyperalgesia) [4–8]. Neuropathic pain states are known to induce hyperexcitability in injured or neighboring primary sensory neurons in sensory ganglia [9–11]. Our research aimed at determining whether neuronal excitability induces neurotransmitter release from the somata of sensory ganglia and whether neurotransmitter release is related to the pain symptoms.

We investigated adenosine 5′-triphosphate (ATP) release from the rat dorsal root ganglia (DRG) after inducing peripheral neuropathic pain by unilateral sciatic nerve entrapment (SNE) [12]. Ipsilateral hind paw withdrawal threshold in response to mechanical or thermal stimulation was decreased in rats that underwent SNE [8]. The DRG was perfused with normal artificial cerebrospinal fluid (ACSF) in a sample collection chamber, and the perfusate was analyzed for ATP contents with the firefly luciferin–luciferase (L/L) assay. The ipsilateral L4–L5 DRG showed significantly more basal extracellular ATP release after SNE than the control DRG. Because extracellular ATP is degraded to adenosine, we applied a selective adenosine 1 receptor (A1R) agonist, 2-chloro-N6-cyclopentyladenosine, and found a significant decrease in basal and evoked ATP release. This indicated that functional A1R activation reduced ATP release. Conversely, a selective A1R antagonist, 8-cyclopentyl-1,3-dipropylxanthine, increased basal ATP release and attenuated the blockade of KCl-evoked ATP release, suggesting that increased A1R activation reduced evoked ATP release in neurons ipsilateral to the SNE. In addition, we examined whether altered ATP release was related to DRG metabolism and measured O_2 consumption in control and neuropathic DRG. The neuropathic DRG consumed more O_2 than the control or contralateral DRG; suggesting that neuropathic pain states increase DRG metabolism and ATP release, which is modulated by increased A1R activation.

In addition, co-release of ATP and substance P (SP) was found within the TG [13]. The TG of anesthetized guinea pigs was perfused with ACSF using microdialysis probes. The perfusate was analyzed for ATP and SP contents with a L/L assay and radioimmunoassay, respectively. Significant reversible increases in ATP and SP were observed after neuronal stimulation with KCl or capsaicin (Fig. 1) [13]. Ca^{2+}-free ACSF induced an eight-fold increase in ATP release, suggesting a reduction in the activity of Ca^{2+}-dependent ectonucleotidases that degrade ATP. In contrast, KCl-induced ATP release under normal Ca^{2+} conditions was blocked by Cd^{2+}, a voltage-gated Ca^{2+} channel blocker, indicating that ATP release was Ca^{2+} dependent. We tested ATP release from acutely dissociated TG neuron somata. Neuron-enriched dissociated TG cells were plated onto glass plates. The measured ATP release increased after the application of capsaicin, suggesting that ATP was concomitantly released with SP from the somata of TG.

Next, we investigated whether neurotransmitters were released directly from the somata of TG and if there were differences in neurotransmitter release between cells that did and did not contain neuropeptides. Neurotransmitter release from the dissociated neurons of rat TG was monitored using cell membrane capacitance (Cm) measurements and the fluorescent membrane-uptake marker N-(3-triethylammoniumpropyl)-4-(6-(4-(diethylamino)phenyl) hexatrienyl) pyridinium dibromide (FM4-64). Cm measurements were performed during whole-cell patch clamping with neurons depolarized from 75 mV to 10 mV to induce neurotransmitter release. TG cells were classified into two categories based on the binding of the plant isolectin B4 (IB4). Most of the nerve growth factor-responsive IB4-negative [IB4(−)] nociceptors contain neuropeptides such as SP and calcitonin gene-related peptide, whereas the glial-derived neurotrophic factor-responsive IB4-positive [IB4(+)] neurons lack such neuropeptides [14,15]. TG neurons show calcium-dependent increases in Cm, indicating neurotransmitter release upon electrical stimulation. Moreover, the peak Cm of IB4(+) neurons decays faster toward baseline than that of the IB4(−) neurons. While IB4(+) neurons have stable Cm responses to repeated stimuli, IB4(−) neurons show reduced responses. These data suggest that the IB4(+) neurons show a faster rate of endocytosis and vesicle replenishment than to IB4(−) neurons. To test this, we measured vesicle trafficking with the fluorescent membrane dye FM4-64. Staining revealed that IB4(−) neurons contained a larger pool of endocytosed vesicles compared to IB4(+) neurons because the peak fluorescence increases in IB4(−) neurons were larger but slower compared to IB4(+) neurons. The recycled vesicles were released faster in IB4(+) than IB4(−) neurons.

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