Abstract

Aims: The paper provided an effective way of analyzing orofacial pain cases based on new findings in the field of central and peripheral sensitizations.

Methods: The non-systematic review was undertaken by searching English literature in the PubMed by pertinent keywords. Case reports and publications with weak levels of evidence were excluded.

Results: Central and peripheral sensitizations affect the pain perception mainly in the way of an imbalance of neurotransmitters, an oversensitivity of neurotransmitter receptors, an initiation of neurogenic inflammation, and a combination of Vitamin B6 or B12 deficiency.

Discussion: Understanding the mechanism will be helpful for clinicians to interpret orofacial pain symptoms at the molecular level. A comprehensive chart was provided.

Keywords: Neurotransmitter; Neurotransmitter Receptor; Neuron; Central Sensitization; Peripheral Sensitization; Orofacial Pain

Abbreviations: SNC: Sensory Nucleus Complex; WDR: Wide Dynamic Range; VPM: Ventral Postero-Medial; CGRP: Calcitonin Gene-Related Protein; GPCRs: G-Protein Coupling Receptors; VGICs: Voltage-Gated Ion Channels; GABA: Gamma-Aminobutyric Acid; RF: Reticular Formation; NE: Nor-Adrenaline; BD: Bradykinin; CCK: Neuropeptide Chole-Cysto-kinin; NO: Nitric Oxide

Introduction

The conception of peripheral and central sensitizations regarding a pain perception was proposed by Schmidt RF in 1991 [1] on the strength of the search result in the PubMed. The article summarized new findings in the field and interpreted orofacial pain symptoms at the molecular level. It will be helpful for clinicians to identify etiologies and set-up treatment plans.

Method

The non-systematic review identified recent original research papers, systematic reviews, meta-analysis articles and narrative reviews from author input supplemented by the PubMed search terms including neurotransmitter, a neurotransmitter receptor, neuron, peripheral sensitization, central sensitization and orofacial pain. An academic book was cited too. Case reports and publications with weak levels of evidence were excluded.

Results

Pain Perception and Pain Inhibitory Pathway

In a normal situation, nociceptive signals are deducted by the pain inhibitory pathway before the pain perception is confirmed in the sensory cortex. The intensity of pain that we can feel is lower than that the initial nociceptive signal has.

The Afferent of Nociceptive Signals [2]: Trigeminal ganglion is the site of the first neuron for processing initial nociceptive signals. Peripheral nerve endings extend to the orofacial region, while the central ending reaches the trigeminal sensory nucleus complex (SNC) in the brain stem that is subnucleus caudalis, oralis and interpolaris. The second nociceptive neurons are within the wide dynamic range (WDR) adjacent to the SNC, while the third nociceptive neurons seat at the ventral posteromedial region (VPM) within the thalamus. Axons of Nociceptive neurons process the signal transduction by the transmembrane influx and efflux of cations including sodium, chloride, potassium, and calcium. How does an axon communicate with the following neuron? The intracellular calcium helps vesicles containing neurotransmitters infuse with the pre-synaptic membrane and then release neurotransmitters into the synapse, which binds to specific receptors in the post-synaptic membrane. Nociceptive signals eventually reach the sensory cortex after passing through three neurons and two synapses.
**Peripheral Sensitization**

Peripheral sensitization is increased responsiveness and a reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields. (Definition from International Association of Study Pain www.iasp-pain.org/taxonomy)

**Increased Responsiveness:** Continuous tissue damage maintains a continuous high concentration of noxious stimuli. Noxious stimuli include prostaglandins (PGs), Bradykinin (BK), neurophin s and cations [2]. Damaged cells release PGs to recruit immune cells. At the same time, PGs bind GPCR alpha s. Irritated vessels trigger BK formation that cleaves from kininogens in plasma. BK links BK1/2 receptors. Broken nerves produce neurotrophins for the reinnervation. Simultaneously neurotrophins attach with transforming tyrosine kinase receptor A (Trk A receptor). GPCR alpha s, BK1/2 receptors, Trk A receptors and NK1 receptors are located at the peripheral endings of nociceptive nerves (C-fiber and A-beta fiber).

Damaged cells release cations counting sodium, potassium, and calcium who bind Voltage-gated ion channels (VGICs) of the terminal ending of C-fiber and A-beta fiber. The peripheral sensitization subsides when PGs, BK, neurotrophins, and cations are diluted; otherwise, patients have a continuous pain. In addition, Mast cells release Substance P that binds NK1 receptors [12]. Substance P and Bradykinin at the peripheral region decrease the threshold of the temperature afferent fiber [2]. Therefore, patients have a burning sensation. On other hands, Vitamin B12 deficiency increases the risk of demyelination. It may increase the responsiveness to nociceptive signals [13].

**Reduced Threshold:** A-beta fiber has a lower threshold of depolarization than C-fiber, while C-fiber relatively is very easy to be damaged [14]. In condition of a persistent and severe tissue injury, A-beta fiber replaces C-fiber to transmit nociceptive signals [15]. The lower threshold in A-beta fiber renders nociceptive signals set off action potentials easily. A-beta is a mechanoreceptive fiber too. Accordingly, patients present with allodynia, a light touch triggering pain. When A-beta fiber begins to transmit nociceptive inputs the peripheral inhibitory mechanism will stop to work because A-beta fiber doesn’t have mu opioid receptors, which are only present in C-fiber [2]. On that account, a chronic pain doesn’t respond to opioid drugs.

**Neurogenic Inflammation:**

Continuously activated 1st neurons produce neuropeptides peripherally as an axon reflex that is substance P, neuropokin, calcitonin gene-related protein (CGRP) and Glutamate [2,3]. The involving field of neuropeptides is beyond the tissue injury area because of the distribution of the nerve branches. Therefore, patients have a radiating pain. Neuropeptides have an independent function of vasodilation and permeability. In addition, substance P stimulates mast cell degranulation by binding substance P receptors [12,16]. Granules and secretions from mast cells coordinate with the preceding inflammation. The consequence is the surrounding field adjacent to the tissue injury area has an inflammation too. It also magnifies the original inflammation. Clinically patients have hyperalgesia, an over-response to pain stimuli. Substance P also stimulates platelets producing 5-HT and mast cells producing histamine. The symptom will be burning sensation with a reddish and edematous appearance.

**Central Sensitization**

Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input. (Definition from International Association of Study Pain www.iasp-pain.org/taxonomy)

**Increased Responsiveness to the Normal Afferent Input:**

Reportedly anxiety [17,18] or a higher level of dopamine [19,20] accompanies with a lower level of GABA and Glycine. Neuropeptide cholecystokinin (CCK), an antagonist of endogenous opioids, will be produced in the situation of chronic pain [2]. The level of 5-HT and NE is lower in the situation of depression. The activated Histamine Receptor 3 is related to interneurons in the WDR spontaneously firing [21]. On other hands, Vitamin B6 is the cofactor of an enzyme of Glutamate decarboxylase, which is the way of the GABA synthesis. Deficiency of Vitamin B6 relatively reduces the amount of GABA [22].

**Increased Responsiveness to the Sub threshold Afferent Input:**

In the scenario of hypoxia, ischemia or other CNS injury WDR Glenn Gba including microglia and astrocytes produces prostaglandins (PGs), nitric oxide (NO) and cytokines exciting 2nd neurons by intracellular calcium accumulation that wipes off the magnesium blockage to NMDA receptor [2]. The consequence is 2nd neurons expressing more NMDA receptors, which are more sensitive to Glutamate than AMPA receptors.
Discussion

The orofacial pain includes toothache, myalgia, arthralgia, and neuralgia. Sometimes it is difficult to find the initial injury area because of complicated anatomy structures. It could be the best way beyond the anatomy restriction to analyze orofacial pain symptoms at the molecular level (Table 1). The interpretation could be beneficial for clinicians to identify etiologies and set up an appropriate treatment plan.

Table 1: Symptoms, molecular mechanisms and underlying causes of the Orofacial Pain

<table>
<thead>
<tr>
<th>Orofacial pain symptoms</th>
<th>Potential mechanisms</th>
<th>Underlying causes</th>
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<tbody>
<tr>
<td>Continuous pain</td>
<td>Persistent tissue injury or inflammation</td>
<td>Anxiety or depression</td>
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<tr>
<td>Burning sensation</td>
<td>High level of substance P or bradykinin</td>
<td>A higher level of dopamine</td>
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<tr>
<td>Radiating pain</td>
<td>The first neuron is activated.</td>
<td>Active histamine receptor 3</td>
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<tr>
<td>Allodynia</td>
<td>C-fibre is replaced by A-beta fibre.</td>
<td>Vitamin B6 or B12 deficiency</td>
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<td>Hyperalgesia</td>
<td>Mast cell degranulation</td>
<td>Headache caused by hypoxia</td>
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References
