Chapter 1
The Neurobiology of Orofacial Pain

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Introduction

Pain is a health issue that affects many Americans. It is estimated that $6 billion is spent annually in the treatment of pain in the USA [1]. Pain disorders cause severe psychological, emotional, and social stresses and may interfere with activities of daily living and sleep, thereby perpetuating a vicious cycle of pain and social dysfunction.

The orofacial area holds special significance in daily actions such as eating, drinking, speech, and sexual behavior, and pain in that region is especially debilitating. The area is also richly innervated, and the influx of such sensations may be the reason why so many people find going to the dentist unpleasant [2]. There have been numerous recent advances in the understanding of the unique pathophysiology of orofacial pain, and this chapter details both neurologic pathways in which the pain is generated as well as the biochemical modalities by which the pain is modulated.

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Finally, the neurobiology and key aspects of neuropathic orofacial pain and pain due to temporomandibular dysfunction, two of the most perplexing orofacial syndromes, are also discussed.

Primary Afferent Nociceptor

There are three different types of primary peripheral afferents. Aβ fibers are myelinated and thick, allowing the Aβ fibers to be the fastest conducting fibers. Aδ fibers have thinner, myelinated axons and are slower than Aβ fibers. Finally, C fibers are the thinnest and unmyelinated, making C fibers the slowest fibers for conductance [3].

The orofacial region is mainly innervated by the trigeminal nerve, whose primary afferent cell bodies rest within the trigeminal ganglion. These neurons generally possess type Aδ or C fibers [4]. While the fast type Aβ fibers are activated via light touch and pressure, the slower Aδ and C fibers of the trigeminal region, collectively termed nociceptors, respond to pain. The activation of these two types of nociceptors is associated with substantial release of substance P, which modulates pain sensitivity by the activation of neurokinin-1 receptors [5].

These nociceptors can be further subdivided into mechanonociceptors (sensitive to mechanical stimuli), thermo-nociceptors (sensitive to heat or cold), and chemo-nociceptors (sensitive to chemicals). The thermo-nociceptors are found to possess vanilloid receptor 1-like receptors that contribute to the pain caused by extreme temperatures [6]. Similarly, the mechanoreceptors found in the root pulp are lined with epithelial Na^+ channels that are responsible for sharp pain induced by liquid motion in the dentinal tubules [7].

Modulation to these nociceptors can also be mechanical or chemical in nature. Canine studies have demonstrated that the threshold for mechanonociception can be lower with periodontal inflammation and can thus increase sensitization [8]. This may be due to the hydrodynamic mechanism of inflammation in the noncompliant environment of the dentine-encased pulp, which increases the pressure on the pulp and thereby activates the nociceptors [9]. Furthermore, there is considerable peripheral and central modulation due to the many types of neuropeptides released during tissue damage and localized within the trigeminal ganglia. These peptides, such as substance P and calcitonin-related peptide, play a vital role in sensitizing the nociceptors leading to allodynia (pain to innocuous stimuli) and hyperalgesia (increased response to painful stimuli) [10].

Finally, unlike the spinal system, where damage of a peripheral nerve causes hypersensitivity to noxious stimuli of nearby skin, nerve damage and territorial hypersensitivity of the trigeminal spinal nucleus are much less predictable [11]. Transection of the inferior alveolar nerve induces hypersensitivity of the trigeminal neurons in the upper lip, outside the territory of the inferior alveolar nerve [12]. A possible explanation of this phenomenon may have to do with the uniquely different central relay of the trigeminal system.

Central Relay

In the brainstem, the primary afferent neurons terminate at the trigeminal spinal tract nucleus. This nucleus consists of three subnuclei: subnucleus oralis, subnucleus interpolaris, and subnucleus caudalis. The subnucleus caudalis serves as the main brainstem relay for nociception and is so structurally similar to the spinal dorsal horn, an important structure in spinal nociception, that it is often referred to as the trigeminal dorsal horn [13]. The subnucleus caudalis or the trigeminal dorsal horn is an important central structure for the modulation of nociception. Rat studies have suggested that disinhibition of the trigeminal subnucleus caudalis plays a major role in the appearance of allodynia after nerve damage [14]. Inflammation or trauma induces a central sensitization of the subnucleus caudalis through its afferent nociceptors via various physiologic and biochemical mechanisms such as ion channels, neurokinins, and *N*-methyl-D-aspartate (NMDA). This increases the excitability of the subnucleus and leads to allodynia, hyperalgesia, or even spontaneous pain. Conversely, descending inhibitory modulation, found mainly in the dorsomedial fields, occurs via behavioral or environmental triggers and can be a contributing mechanism in the efficacy of certain analgesics such as morphine and tricyclic antidepressants [15].

Although the other two subnuclei of the trigeminal spinal tract nucleus, the subnucleus oralis and subnucleus interpolaris, receive input from all three types of fiber, it receives a large proportion of input from fast-conducting Aβ fibers. This makes these subnuclei very versatile. Central neurons within these subnuclei can be further classified into nociceptive specific neurons, which are only Aδ and C fibers responding only to noxious stimuli, or wide dynamic range neurons, consisting of all three fiber types and responding to noxious and innocuous stimuli [16]. Deep pain is attributed to the convergence of different types of receptors into a central nociceptive neuron; the complexity of the convergences leads to misinterpretation of the original sensation, which contributes to hyperalgesia or allodynia [17]. Additional studies also indicate that the transition zone between the subnuclei caudalis and the subnuclei interpolaris also plays a role in the central processing of deep orofacial nociception [18].

Orofacial sensation continues up its path from the brainstem through the thalamus on its way to the cortex. Nociceptive specific neurons and wide dynamic range neurons are found scattered throughout the thalamus including the posterior nucleus, ventrobasal complex or ventral posterior nucleus, and intralaminar nucleus. The posterior nucleus is responsible for classifying a stimulus as pain, the ventrobasal complex or the ventral posterior nucleus localizes the pain to a region, and the intralaminar nucleus provides an affective and motivational dimension to the pain. In other words, the lateral thalamus projects to the somatosensory cerebral cortex to pinpoint the pain, while the medial thalamus projects to other areas such as the cingulate gyrus and hypothalamus to associate the pain with the proper emotions [19].

Biochemical Influences

Biochemical influences play a large role in the transmission and modulation of orofacial pain. Recent studies have focused on various biochemical neuroactive substances and proteins such as nitric oxide (NO), nicotinamide adenine dinucleotide phosphate-diaphorase (NADPH), GABA, glycine, and c-Fos and their roles in orofacial pain modulation.

Neurons within the subnucleus oralis and subnucleus caudalis produce nitric oxide, a substance that increases intracellular cyclic guanosine monophosphate levels to work as both an endothelial relaxing factor as well as a neurotransmitter [20]. Increased levels of nitric oxide have been associated with neuropathic pain associated with NMDA receptor stimulation [21]. Surprisingly, while NO is also associated with the maintenance of chronic pain, it has no association to the initiation of acute pain [22].

NADPH is found within the same neurons that produce NO as well as within neurons that produce GABA and glycine in the spinal dorsal horn. It is also co-localized with calbindin D and calretinin within the subnucleus oralis. These neurons project to the trigeminal motor nucleus and are involved with the modulation of the orofacial sensorimotor reflex. This explains the early appearance of subnucleus oralis NADPH during fetal development. This allows the human fetus to respond to facial stimuli as early as during the 7th week of gestation, long before the cerebral cortex has developed any motion controlling ability [23].

c-Fos is a complex DNA-binding protein that acts at the promoter region of a few neurotransmitter genes including encephalin, dynorphin, and cholecystokinin [24]. Its effect on nociception can vary greatly. Like the associated neurotransmitter dynorphin, the presence of c-Fos can contribute to antinociception through the Kappa-opioid receptor [25]. Conversely, this action is complicated by c-Fos' ability to contribute to the neuro-inflammatory cascade that aids in creating a hyperalgesic state.

Like c-Fos and dynorphins, GABA also has a complicated response to nociception. GABA is an inhibitory neurotransmitter that acts mainly in the central nervous system with two different receptors: GABA(A), which involves Cl channel conductance, and GABA(B), which involves cGMP-coupled regulation of Ca^+ and K^+ conductance.

GABA(A) receptor antagonism increases the sensation of innocuous stimuli within the trigeminal sensory nuclei [26]. This is mainly due to its effects on the segmental sites [27]. In stark contrast, GABAergic disinhibition on the supraspinal sites, such as the nucleus raphe or the periaqueductal grey, decreases the effect of high-intensity noxious stimuli. The systemic effect of the GABA(A) receptors, therefore, is to equilibrate sensation towards a medium.

Baclofen is an antispasmodic that works as a GABA(B) receptor agonist. As stated above, GABA(B) receptors, located in the Aδ and C fibers, decrease excitatory transmission via decreased Ca^+ influx and increased K^+ currents. Baclofen, via its agonism of the GABA(B) receptors, has been found to aid in decreasing nociceptive response in both the trigeminal as well as the spinal systems [28].

There are a plethora of biochemical influences that moderate the trigeminal sensory system. They combine to moderate nociception, but a dysfunction or a misbalance of these substances can lead to pathologic orofacial pain processes as seen in neuropathic pain or temporomandibular disorders (TMD).

Neuropathic Orofacial Pain

The trigeminal system is relatively insulated from neuropathic pain. Compared with the spinal system, there is a lower disposition to and quicker recovery from neuropathic pain [29]. This, however, does not make it immune to neurologic pain states. Three orofacial pain conditions that must be considered are trigeminal neuropathic pain, atypical facial pain, and progression into chronic pain.

Neuropathic orofacial pain can be classified into four types: pain associated with nerve damage, insidious pain generally from an organic source such as a neoplasm, vascular pain associated with migraines, and burning, constant pain without any inciting event [30]. Trigeminal neuropathic pain is an example of the first type as there is often evidence of a trigeminal nerve lesion, although there may also be a vascular etiology to this condition [31]. Centrally, this condition may also be by multiple sclerosis. Neuropathic orofacial pain usually presents with sensory symptoms such as burning pain, allodynia, and hyperalgesia that are well localized with defined trigger zones.

In contrast to trigeminal neuropathic pain, atypical facial pain really lacks a significant cause and generally presents with constant, burning, deep, and poorly localized pain. In fact, the International Headache Society classifies atypical facial pain as "Facial Pain Not Fulfilling Other Criteria." While it is suggested that atypical facial pain may be caused by hyperactive central neuronal activity due to damage to the primary afferent neurons, it is likely that atypical facial pain is also a combination of different clinical entities as a result of biological and psychological contributions [32]. In addition, phantom tooth pain, a type of atypical facial pain, has been associated with a neurovascular etiology [33]. There is a high correlation of atypical facial pain with psychological disorders, but there is often a question of whether the pain is the cause or rather the effect of these disorders. Studies have found that a large percentage of patients also suffer from clinical depression and had histories of abuse. This suggests that the pain may in fact be an effect of the prior psychological insults [34].

Neuropathic orofacial pain may eventually persist into a chronic pain state following neuronal injury. This is because certain initially insensitive mechanonociceptors may become sensitized following injury leading to hyperalgesia and allodynia. Central sensitization also plays a vital role. This concept suggests that an increased sensitivity of central pain signaling causes an elevated responsiveness to and reception of the initial sensation. This can help explain phantom limb syndromes as well as hyperalgesia and allodynia associated with neuronal and tissue damage [35].

Temporomandibular Joint Disorders

Another prominent orofacial pain pathology is classified as TMD. These are pain conditions related to the jaw muscles and the temporomandibular joint (TMJ) and are major cause of non-dental orofacial pain [36]. The symptoms include deep and diffuse pain associated with jaw motion, ear pain, TMJ clicking, and limited jaw opening.

Although the pathophysiology of TMD pain is unclear, it is associated with psychologic factors [37]. Interestingly, TMD also seems to be associated with irritable bowel syndrome, another pain syndrome with a very different anatomic location. These associations suggest that chronic pain conditions such as TMD are related via a central mechanism, regardless of the site of pain [38]. Recent studies have also suggested that there are genetic risk factors associated with TMD symptomatology, especially those related to estrogen [39]. Estrogen status and chronic inflammation, through a common mitogen-activated protein kinase/extracellular regulated kinase, enhance central nociception in TMD [40].

Conclusion

From the primary afferent nociceptors to the somatosensory cerebral cortex, the neurobiology of orofacial pain is a complex and dynamic process, with ongoing biochemical modulation of orofacial pain and TMD. There are often genetic, psychological, and social components to the development of orofacial pain, and its neurobiology is best examined with a multidisciplinary approach.

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Conflict of Interest None declared.

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