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Central Mechanisms of Orofacial Pain

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A review of the literature for temporomandibular disorders (TMD) has shown little appreciation for basic pain science, but with the expansion of the perspective into the broader context of orofacial pain, there is a developing interest in understanding the pathophysiology of pain as it relates to TMD and orofacial pain. The possibility of TMD being associated with neuropathic pain has received little attention.

The International Association for the Study of Pain has defined pain as "an unpleasant, sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." This definition includes not only the sensory aspect of pain but also the emotional and interpretive or cognitive aspects of pain. The emotional factors are more significant in chronic than in acute pain and assert a significant influence that usually has to be recognized and addressed to effectively treat the patient who has chronic pain. Often, chronic pain treatment failures can be traced to ignoring the psychologic issues that are affecting the patient's pain condition.

The understanding of chronic pain has advanced significantly in the last 10 years. This understanding has led to improved diagnosis and treatment strategies for pain. Until recently, patients who had facial pain that did not fit the existing understanding and taxonomy were given the diagnosis of "atypical facial pain." The recent IHS Classification of Headache provides a comprehensive classification system for head and neck pain and has removed the "atypical facial pain" diagnosis in favor of "persistent idiopathic facial pain." This is an important step in disengaging the less understood facial pain condition from a co-psychosomatic diagnosis that was implied in atypical facial pain [23].

To be able to diagnose and treat orofacial pain, one must understand basic neurophysiology of pain from the periphery to the central nervous

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system (CNS). This article describes the basis of central sensitization as it relates to orofacial pain.

Pain transmission from periphery to central nervous system

Afferent sensory system: C-polymodal nociceptors and A-δ and A-β fibers

A basic understanding of the peripheral and CNS is necessary to understand pain mechanisms and to understand how central sensitization develops. Most text books on pain discuss dorsal horn mechanisms when referring to the CNS. For orofacial pain, the trigeminal correlate of the dorsal horn is the trigeminal nucleus within the pontine brain stem. Peripherally, the trigeminal nerve provides sensory input from the anterior part of the head, including the intraoral structures. Because the nociceptive endings of pain fibers lack specialized receptors, they are named from their afferent fiber and the stimulus that activates them. The sensory fibers are divided into A-β mechanoreceptors and three types of nociceptors: A-δ fibers, C–polymodal nociceptors (C-PMNs), and silent or sleeping nociceptors, which are unmyelinated or thinly myelinated. The A-β fibers that respond to light-touch mechanostimulation are large diameter, fast conducting, and myelinated. No matter what the frequency or intensity of the stimulus, these fibers normally encode only low-frequency, non-noxious stimuli that are interpreted as light touch [36]. After trauma, the A-β fibers may begin to signal pain. The A-δ fibers respond to painful mechanical stimuli with an output in the high-frequency range. This is perceived as sharp or stabbing pain. Because the A-δ fibers are myelinated, the convey impulses more rapidly than the C-PMNs (Fig. 1) [7–9]. The silent nociceptors are normally mechanically insensitive. They become active when tissue is injured. These fibers add to the nociceptive input to the CNS [18,26,27]. The afferent impulses from all the sensory fibers travel from the periphery through the trigeminal ganglion and trigeminal root, enter the pons, and descend in the trigeminal tract to enter the trigeminal nucleus. Once the fibers have entered the pons, they are in the CNS.

The trigeminal nerve innervates the anterior of the head. These fibers travel to the trigeminal ganglion and to the trigeminal nucleus in the pons. The trigeminal nucleus is subdivided into three parts: the uppermost subnucleus oralis, the middle subnucleus interpolaris, and the subnucleus caudalis (Fig. 2) [24]. Most of the pain fibers synapse in the subnucleus caudalis. For pain, the wide dynamic range neurons (WDRs) are the most important second-order neurons in the subnucleus caudalis. They receive convergent sensory input from primary afferent nociceptors and low-threshold mechanoreceptors.

Certain features of pain have long puzzled clinicians and researchers. The stimulation of pain from a normally nonpainful stimulus has defied explanation. Conversely, Beecher [1] puzzled over a battlefield phenomenon he

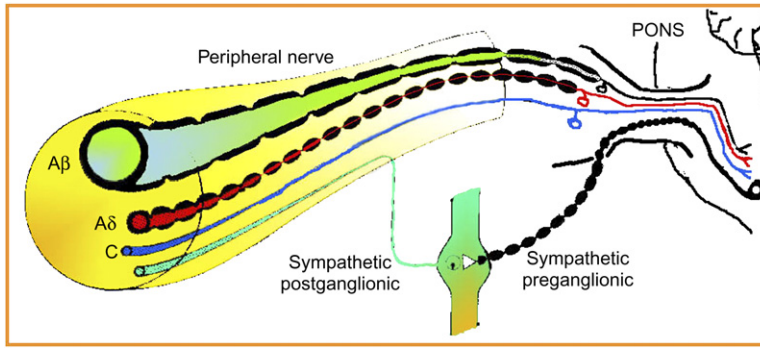

Fig. 1. Afferent and efferent fibers. This figure shows diagrammatically the make up of a typical bundle of afferent sensory nerves going from periphery to the central nervous system. The efferent sympathetic nerves follow a separate route from the central nervous system but eventually innervate the peripheral area in close proximity to the afferent sensory fibers. The large-diameter Aβ fibers are mechanoreceptors that respond only to non-noxious mechanostimulation. The Aδ and C fibers carry noxious stimulation. Figure suggested by Fields [7] and altered for the trigeminal system. (*Adapted from* Fields HL. Pain. New York: McGraw-Hill Book Company; 1987. p. 14.)

noted during the Second World War on Enzio Beach in Italy. Beecher attracted attention to the role of cognitive appraisal with his observations that soldiers wounded during battle complain far less than civilians comparably injured during accidents, presumably because the soldiers were

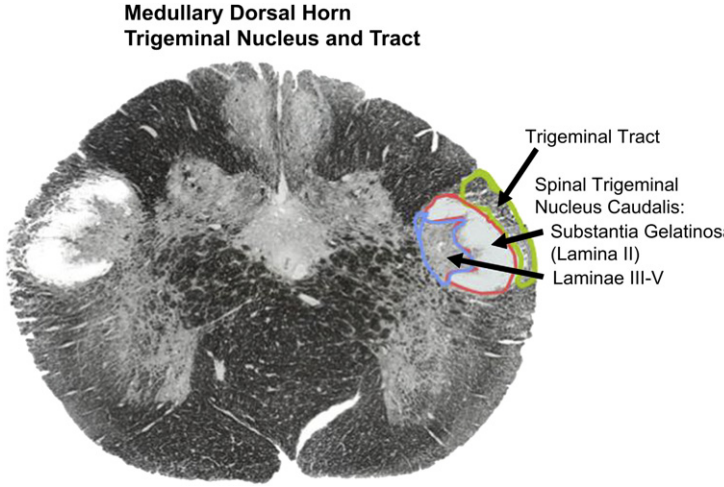

Fig. 2. The trigeminal nucleus caudalis has been outlined in the medullary dorsal horn. Note the lateral position of the nucleus and the somatotopic arrangement, which is similar to the spinal cord dorsal horn Rexed laminar arrangement. Nociceptor axons descend in the trigeminal tract and cross into lamina I/II or substantia gelatinosa at the level of the subnucleus caudalis. The A-β fibers synapse in lamina IV and V.

relieved that they had escaped from the battlefield and expected to return home, whereas the civilians evaluated the injury as a threat to comfortable, established lives. Contrasting findings have shown that people who "catastrophize" or self-alarm by focusing negatively upon their distress suffer higher levels of anxiety and are the most disabled and benefit the least from conventional medical care [14,21]. Patients who have chronic low back pain and are depressed have also been found to misinterpret or distort the nature and significance of their pain. These observations highlight the presence of pain-modulating systems in the body that can turn down or turn up the volume control for pain. This had been implied by Melzack and Wall [20] but was poorly understood when they proposed the Gate Control Theory in 1965.

Second-order neurons

The first interface between the peripheral nociceptors and the CNS occurs in the spinal cord or trigeminal nucleus, the brainstem extension of the spinal cord dorsal horn (see Fig. 2). There are many types of receptors and ion channels associated with the cell membrane of the WDR that modulate cell activity. Modulatory circuits can suppress WDR activity and decrease pain or facilitate pain transmission.

The Gate Control Theory and pain modulation

Fig. 3 shows the Gate Control of Pain that was proposed by Melzack and Wall in 1962 [20] and republished in 1965. Although there have been some modifications to the original theory, most of the system features have been confirmed by research.

The Melzack and Wall model describes modulation of pain transmission through the interneuron connections in the substantia gelatinosa. Past research had identified a pain-modulating effect of afferent activity from large-diameter A-β fibers. The gate control model identified the spinal cord substantia gelatinosa as one of the areas where pain is modulated. Fig. 3 illustrates the modulating effect of the L (light touch fibers) in reducing the effect of afferent activity from the S (c-nociceptors) fibers. Melzack and Wall [20] also theorized that there were descending inhibitory and facilitatory influences, but little was known of these mechanisms in 1965, and it has only been within the last few years that descending inhibitory and facilitatory systems have been identified.

Central pain processing and central sensitization

The phenomenon of peripheral sensitization develops from an injury-induced inflammatory response. Allodynia and hyperalgesia in this model are due to the inflammatory mediators being released at the site of injury.

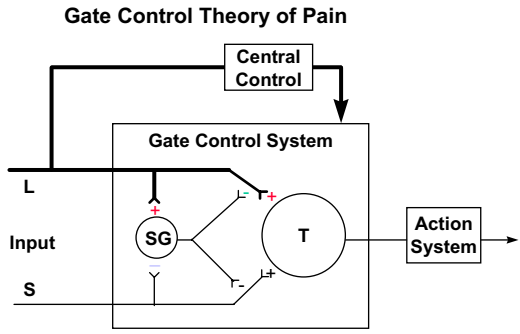

Fig. 3. Melzack and Walls Gate Control of pain proposed that light-touch myelinated mechanoreceptors (L) modulated or decreased the gain of the small-diameter unmyelinated pain fibers (S) in the substantia gelatinosa or dorsal horn lamina II through the intermediary effect of segmental interneurons in that lamina (SG). The action potential synapsed with the second-order wide dynamic range neurons (T) to bring about the response to the signals (Action System). Further modulation was suggested by other poorly understood mechanisms, including descending facilitatory and inhibitory mechanisms (Central Control).

In a tooth extraction site, the inflamed area is marked by increased sensitivity to pressure (static hyperalgesia) that is mediated by sensitized nociceptors. It is expected that this reaction will resolve within a reasonable period of time due to the decreasing activity of the nociceptors and consequent decrease in afferent activity to the dorsal horn. If the inflammatory process and consequent afferent activity is of sufficient intensity and if there has been neuronal damage, a central process is established that increases sensitization, lowers the threshold of response, and causes ectopic discharges (physiologic changes). Additionally, A-β fibers begin signaling pain (dynamic mechanical allodynia), and their inhibitory effect is lost (anatomic changes and disinhibition). There is now an increased central release of excitatory mediators, such as glutamate and nitric oxide production (neurochemical changes). These changes stimulate the MAP kinase cascades, resulting in messenger RNA–mediated changes that alter the phenotype of nociceptors and mechanoreceptors such that normal cell response becomes genetically changed to a pathologic state (Fig. 4).

Central sensitization is a form of neuroplasticity in which nociceptor activity triggers a prolonged increase in the excitability of dorsal horn neurons. It is initiated by a brief burst of C-fiber activity. The peripheral manifestation of this central process is dynamic hyperalgesia. Torebjork [36] has provided evidence showing that once central sensitization has occurred, Aβ fiber afferents begin to evoke painful response (allodynia) [36]. C-nociceptors have been identified as the primary nociceptor involved in the initiation of central sensitization due to the slow synaptic currents they generate and the low-stimuli repetition rates that cause an increased rate of depolarization in the dorsal horn [35]. This occurs as a result of the activation of ligand-gated ion channels, initially the alpha-amino-3-hydroxy-5-methyl-4-isoxazole

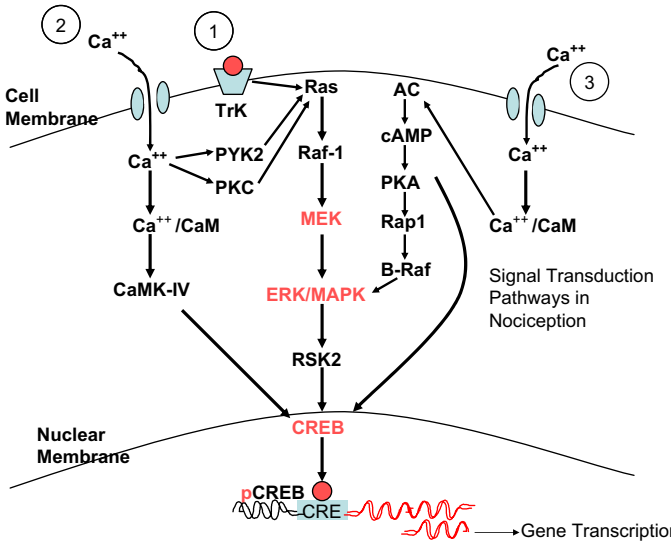

Fig. 4. The MAP kinase cascades. This diagram illustrates the intracellular responses to nociceptor depolarization. There are three main pathways of the MAP kinase cascades that result in the stimulation of cAMP response element binding protein and in the transcription of genes that produce target proteins altering the phenotypic expression of the nociceptors and postsynaptic neurons in the nociceptive chain. The gene transcription causes long-term potentiation and cell memory for pain. *Abbreviations:* CamK, calmodulin kinase; CRE, cAMP response element; CREB, cAMP response element binding protein; ERK, extracellular signal-regulated protein kinase; MAPK, mitogen-activated protein kinase; MEK, MAPK/ERK kinase; Ras/Raf-1, proteins that are molecular switches in the MAPK pathway; TRK, tyrosine kinase

proprionate (AMPA) receptor allowing calcium to enter the cell through the calcium channels. In addition, activation of the metabotropic glutamate and neurokinin receptors by glutamate and substance P causes a G-protein–coupled transduction signal that releases calcium from intracellular stores, further increasing the intracellular calcium levels. This calcium activates a calcium-dependent enzyme system, including protein kinases that phosphorylate the N-methyl-D-aspartate (NMDA) receptor. The NMDA receptor at normal resting membrane potentials has a magnesium ion block in the channel, but when the receptor is phosphorylated, the ion is released. Before phosphorylation, the NMDA receptor generates little inward current when glutamate is bound, but after phosphorylation and release of the ion channel block, the NMDA receptor generates inward synaptic currents at normal resting membrane potentials [39]. This process causes increased glutamate sensitivity and is the underlying mechanism that is represented by the expansion of receptive fields and a decrease in the threshold of the dorsal horn neurons.

Aβ fiber–mediated dynamic hyperalgesia may also be the result of central reorganization of neuronal connections in the dorsal horn. Woolf and others [4,39] have found that A-β fibers sprout into dorsal horn lamina I

and II after peripheral injury, forming new connections in areas normally occupied only by c-fiber nociceptors. These new connections can apparently signal pain. Additionally, it has been reported that with the neuronal organization and transcriptional changes induced by the sensitization, Aβ fibers begin expressing substance P, previously thought to be associated only with c-fibers [22]. μ−Opioid receptors are found presynaptically on c-fibers but not on A-β fibers. Part of the descending inhibitory system uses endogenous opioid action on presynaptic μ-opioid receptor. Because these receptors are not found on A-β fibers, this may account for the relative lack of response to opioid agonists in neuropathic pain.

The influx of calcium through voltage-gated ion channels also occurs on the inhibitory interneurons in lamina II. Calcium may induce excitotoxic cell death, resulting in a loss of inhibitory connections [33,38]. Mao and colleagues [17] showed that pretreatment with NMDA receptor antagonists seemed to protect the dorsal horn from changes that produced prolonged sensory hypersensitivity. Nitric oxide, arachidonic acid, superoxide, and intracellular calcium overload are the ultimate mediators of neuronal death.

Pain-modulating circuits

Pain is strongly affected by emotions. In the presence of anger, fear, or elation, major injury may be essentially painless. Conversely, in situations associated with dysphoria or when pain is anticipated, subjects often report the occurrence or worsening of pain without additional noxious stimulation. Psychologic factors influence the firing of dorsal horn pain transmission neurons.

It has been observed that stimulation of the periaquaductal gray area in the midbrain increased tail-flick latency in rats that were given a painful stimulus. The periaquaductal gray area was demonstrated to be heavily innervated with serotonergic neurons. Subsequently it has been demonstrated that there are connections to the nucleus raphe magnus of the rostral ventral medulla and thence to the nucleus caudalis of the trigeminal nucleus or the dorsal horn of the spinal cord. This system is part of the descending inhibitory system mediated by serotonin. Additionally, a descending system modulated by norepinephrine travels from cortical stimulatory centers to the periaquaductal gray and on to the dorsolateral pontine tegmentum area of the medulla, also connecting to the relay neurons (wide dynamic range) in the nucleus caudalis or dorsal horn. The dorsolateral pontine tegmentum is directly linked to the periaquaductal gray and rostral ventral medulla and projects directly to the spinal cord dorsal horn and the nucleus caudalis. Pain modulation requires action from both circuits acting in tandem (Fig. 5).

Many of the centrally acting medications used to modulate pain act within these two systems to bring about a reduction of pain that does not involve the opioid system and consequently does not build tolerance to

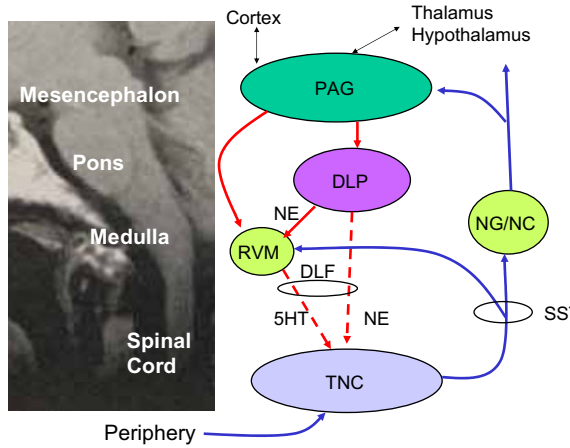

Fig. 5. Pain-modulating circuitry in the dorsal horn. Action potentials from trigeminal nociceptors enter the trigeminal nucleus caudalis (TNC), where they synapse with second-order neurons. In the TNC, the relayed signals "ascend" in the spinothalamic tract (SST), going to the rostroventromedial medulla (RVM) and through the nucleus gracilis (NG) from the lower body or the nucleus cuneatus (NC) from the upper body to the periaquaductal gray (PAG), the hypothalamus and thalamus where tertiary synapses occur. One of the major descending inhibitory systems in the pathways is the linkage with the serotonergic cells of the PAG and RVM. An additional inhibitory pathway involves a descending connection from the PAG to the dorsolateral pontine tegmentum (DLP), which is modulated by norepinephrine. The inhibitory signals from the RVM and the DLP descend in the dorsolateral faniculus (DLF) to the TNC, mediating TNC nociceptive activity. The information is transmitted to the cortex and can be modulated (inhibited or disinhibited) through cortical influence.

the effects of the medications. One of the most widely used classes of medications for chronic pain is the tricyclic antidepressants. Medications such as amitriptyline and nortriptyline are commonly used for central pain conditions such as postherpetic neuralgia and diabetic neuropathy and work within the serotonin system. Another tricyclic antidepressant, desipramine, works primarily through the norepinephrine system. Their pain inhibitory effects are not linked to the antidepressant effects.

Glial influences on pain

Glial cells (microglia and astrocytes) have been viewed classically as support cells in the CNS and were not seen to have an active role in pain transmission because they did not possess axons. This view has changed with recent research, and there is evidence that glia have an important role in the development of central sensitization. This role is being defined as research explores the interactions from dorsal horn neurons to the glia and the glia to the dorsal horn neurons. Consequently, glia are no longer viewed as only passive support cells but as active participants in modulating pain transmission and other types of neuronal activity in the CNS.

Synapses in the CNS are surrounded by glial cells, and neurotransmitter receptors have been identified on these glia. The implication is that the glia can respond to central neurotransmitter release from presynaptic nociceptor endings [13,25]. Furthermore, transport mechanisms have been identified in glia that oversee the uptake and release of neurotransmitters from the glia [28,15]. More recently, glial cells have been shown to be involved in the development of hyperalgesia due to nerve trauma and other conditions that can lead to central sensitization [5,34].

Because glia possess receptors and transport mechanisms for neurotransmitters, one might assume that they release neurotransmitters in the synaptic cleft that would have a presynaptic and postsynaptic effect on pain modulation. Watkins [37] demonstrated that glia were involved in central sensitization from nerve injury when hyperalgesia was reduce by disrupting glial activation [37]. It has also been observed that glia are normally involved only in pathologic pain processes [19].

The classical model of central sensitization did not include glial influence, but current evidence has shown that glial activation is intimately involved in the central sensitization process.

Part of the mechanism responsible for enhancing glial-mediated central sensitization is the release of the neurotransmitter nitric oxide, prostaglandins, and excitatory amino acids such as glutamate that have been linked to the development of central sensitization in the classic model [37]. A central synaptic feedback loop has been described that involves the second-order neurons and the central terminals of the nociceptors. Now, a similar feedback loop is described between the glia and the central synaptic neurons that would further affect central sensitization.

Impact of central sensitization on orofacial pain and temporomandibular disorders

Myofascial pain

Myofascial pain probably represents a neurosensory disorder involving peripheral and centrally sensitized muscle nociceptors. There are many characteristics of the disorder that are best accounted for by equating the pain phenomena with a neurosensory pathophysiology. For example, the primary indication of myofascial pain is the characteristic radiation of the pain from the primary site of palpation to unrelated sites that can be in different dermatomes. This most likely occurs secondarily to central phenomena, including convergence and activation of adjacent second-order neurons, which would explain the expansion of the receptive field, the lowering of the threshold to stimulation, and the allodynia associated with active trigger points.

Simons proposed a central mechanism for the development of the disorder [12,29–31]. He postulated that the muscle nociceptors, when activated by

peripheral injury, released substance P, which would diffuse and spread between segments of the spinal cord to activate other adjacent nociceptors and second-order neurons. As we now understand central sensitization, there are many neurotransmitters and ion channels that become involved in the central sensitization process in addition to glial activation (Fig. 6). The ultimate result is activation of the NMDA receptors on the second-order neurons. When the NMDA receptor is activated, the pain becomes modulated primarily in the CNS and is only partially affected by peripheral mechanisms. In neuropathic pain conditions, NMDA activation connotes a more protracted change in pain. In neuropathic pain, these changes seem to be permanently persistent or at least of long duration. Central sensitization has also been associated with migraine. This situation does not typically have an enduring impact on migraine because the headache tends to resolve within hours. Timely treatment of the migraine can stop the sensitization, and the headache will resolve, or if left untreated, will resolve by itself. Therefore, the sensitization that occurs is of shorter duration. This may be the case with myofascial pain.

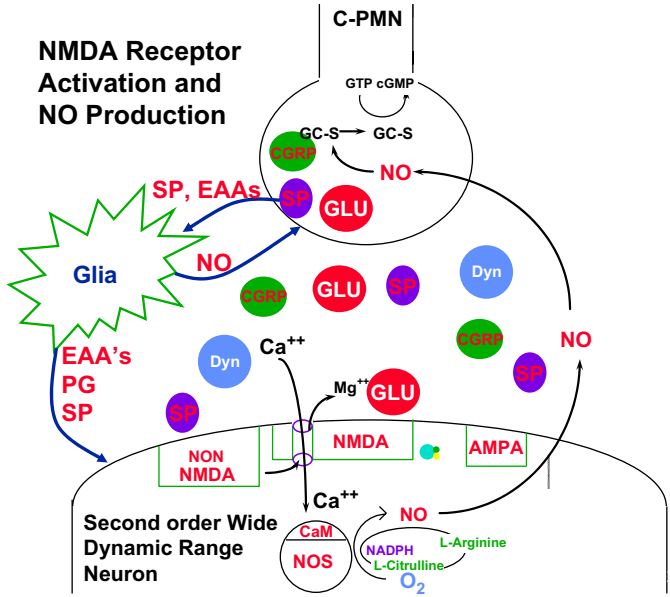

Fig. 6. Glial activation and central sensitization. Classic description of central sensitization involved central release neurotransmitters from nociceptors (C-PMN) that caused a cascade of events in the second-order neuron, including activation of the NMDA receptor and opening of its ion channel, allowing calcium to flow into the wide dynamic range neurons. The calcium interacts with the calmodulin protein complex, nitric oxide synthetase, and L-arginine to form nitric oxide (NO). NO diffuses out of the postsynaptic neuron and stimulates further release of excitatory amino acids (EAAs) and neurokinins from the presynaptic buton to continue the process. This process is understood to be enhanced by a similar response in the glial cells (glial activation).

Although the focus of this article is on central sensitization, peripheral sensitization needs to be considered as a component leading to central changes. If myofascial pain is a disorder with characteristics of peripheral and central sensitization, the other phenomena of myofascial pain become more understandable. For example, the trigger point may represent peripheral sensitization of muscle nociceptors. A component of peripheral sensitization is the activation of nociceptors that release neurotransmitters such as substance P, calcitonin gene related peptide (CGRP), and prostaglandins. These neurotransmitters cause a localized inflammatory reaction by acting on neurokinin and prostaglandin receptors on the nociceptors and on the blood vessels resulting in the expansion of the blood vessels and plasma extravasation (swelling = taut bands), increased pain with palpation (local allodynia and twitch response) at the site neurotransmitter release, and expansion of the pain into the area immediately around the site (static mechanical allodynia = decreased threshold to palpation resulting in twitch response). The dorsal horn reflex causes muscle tightening when the nociceptors relay pain to the dorsal horn. These mechanisms are consistent with mechanism of peripheral sensitization in neuropathic pain. The action of trigger point injections also would be consistent with peripheral neurosensory mechanisms when myofascial pain is viewed as a neurosensory disorder. Injecting a local anesthetic would block sodium channels in the pain fibers, stopping the release of neurotransmitters peripherally and centrally. The net effect of this would be to decrease the local neurogenic inflammatory response. Heating the area, stretching the muscle fibers, and the irritation by dry needling would increase the blood flow to the area, diluting or washing out the neurotransmitters and eventually decreasing the neurogenic inflammation. Centrally, these effects decrease the release of neurotransmitters that are responsible for the central sensitization that is characterized by expansion of the peripheral receptive field and autonomic activation through parasympathetic fiber release of norepinephrine.

Temporomandibular joint pain

Pain of the temporomandibular joint (TMJ) joint is commonly associated with redness and swelling and allodynia of the skin over the joint. These reactions are modulated by release of peripheral neurotransmitters in the joint space, causing peripheral sensitization. Occasionally, an inflamed joint continues to be painful despite appropriate treatment aimed at decreasing joint inflammation and pain. In some patients, attempting to quell the joint inflammation with intracapsular injections can be met with a significant increase rather than a decrease in pain. This reaction may be seen in patients who have had long-standing TMJ inflammation subsequent to trauma or surgery. This reaction is difficult to manage with traditional conservative TMJ therapy. The clinician may begin to suspect that a centralized neuropathy has developed in the joint. These joints may not respond to local

anesthetic injections, and, if epinephrine is injected with the local anesthetic, the pain can become significantly worse, suggesting that sympathetically mediated pain has developed. Often, these patients are recommended to have another surgery to try to correct what is thought to be a musculoskeletal problem but which is a peripheral or central neuropathy. Temporomandibular joints can develop peripheral and centralized neuropathy, and once this occurs, the treatment needs to focus on the types of treatment used in neuropathic pain, such as antiseizure medications, tricyclic antidepressants, narcotics, and sympathetic ganglion blocks to evaluate for sympathetically mediated pain.

Neurovascular disorders

Neurovascular disorders relate primarily to headaches. Until recently, the "science" of headache disorders did not try to equate them with known mechanisms of central neurophysiology. Burstein [2,3,16,32] published several articles in the late 1990s that showed that migraine and other headache disorders were affected by the same central pathophysiology as neuropathic pain. The mechanisms of central sensitization made some of the characteristics of migraine more understandable, such as the lack of response to analgesics and triptans, if they are taken too late in the development of the headache attack. Additionally, the development of central sensitization causes static and dynamic mechanical allodynia of the head and neck, including the masticatory and cervical muscles. It is not uncommon for a patient to report to an OFP clinician that they get moderate to severe jaw and neck pain with a headache. When a patient is seen during one of these attacks, administration of a triptan or DHE-45 can stop the attack and relieve the jaw and neck pain within minutes. The clinician needs to differentiate between jaw and neck pain due to secondary or central sensitization associated with headache and headache due to painful TMJ and muscle inputs into the CNS that result in headache. In the first case, treating the headache relieves the muscle pain; in the last case, treating the muscle pain can relieve the headache.

Neuropathic pain

Neuropathic pain is commonly seen in the orofacial region. It may develop as a consequence of trauma, simple dental treatment, extractions, endodontic treatment, oral surgery, implants, or orthognathic surgery. The development of a neuropathy does not imply improper or poor treatment. It is not understood why some dental patients develop neuropathies when most do not, even in the face of fairly severe neurotrauma that can occur in everyday general dentistry. Researchers are beginning to suspect that there is a genetic diathesis due to variables such as receptor polymorphism that may predispose someone to develop a neuropathy [6].

Neuropathic pain in the oral environment due to central sensitization is characterized by chronic aching and burning pain that is persistent over a 24-hour period but which may fluctuate in intensity during this time. The distinguishing characteristic of centralized neuropathic pain is the lack of response to a topical, local, or regional anesthetic. Neurosensory testing may find that the painful area has pin-prick hyperalgesia and dynamic mechanical allodynia. These neurosensory responses are mediated by central sensitization and A-β fiber stimulation. The classical dental term for this oral neuropathy is "atypical odontalgia" [10,11]. Marbach, in the 1990s, suggested that they were phantom tooth pains [40]. Neither of these terms indicates a mechanism behind the pain. In reviewing the characteristics of these two conditions, it becomes apparent that both are describing peripheral and central neuropathies. A more useful title should reference the likely mechanism underpinning the condition. If the tooth pain is blockable and is characterized by static mechanical allodynia, it is a chronic peripheral neuropathy. If the tooth pain is not blockable and is characterized by dynamic mechanical allodynia or pinprick hyperalgesia, it is a chronic centralized neuropathy [9]. Treatment of these conditions differs, and it is important to distinguish whether the pain is due to peripheral sensitization or central sensitization.

Summary

The orofacial pain clinician must understand the difference between peripheral and central mechanisms of pain. Particularly, one has to understand the process of central sensitization as it relates to the various orofacial pain conditions to understand orofacial pain. Understanding leads to more effective treatment.

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