Neurobiological Mechanisms of Chronic Orofacial Pain

3

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Abstract

This chapter reviews the several mechanisms in orofacial tissues and trigeminal nociceptive pathways in the brain that may account for chronic orofacial pain. Peripheral sensitization and central sensitization are particularly emphasized since they have characteristics that can explain the spontaneous nature, hyperalgesia, allodynia, and spread and referral of pain resulting from injury or inflammation of orofacial tissues and nerves. The chapter also notes several neural and non-neural modulatory factors influencing these mechanisms and their clinical implications.

3.1 Introduction

Pain is a multidimensional experience encompassing sensory-discriminative, cognitive, affective, and motivational dimensions, the expression of which can vary from one individual to another [1, 2]. The face, mouth, and jaws represent some of the most common areas of pain in the body, and epidemiological studies have documented the high prevalence of several acute or chronic orofacial pain conditions [3–5]. These chronic pain conditions in particular can present diagnostic and management challenges to the clinician. This is because of (i) the complex, even bizarre, nature of some of these pains; (ii) the multidimensional experience of pain itself that reflects a host of biopsychosocial influences; (iii) the special biological, emotional, and psychological meaning that the face and mouth have to humans; and (iv) the limited knowledge of the etiology, pathogenesis, and mechanisms underlying the initiation and progression of these pain conditions. This chapter reviews recent advances in our understanding of the mechanisms underlying orofacial pain, and chronic orofacial pain in particular, in order to assist clinicians in their management of the various chronic orofacial pain conditions. It first outlines relevant orofacial pathways and mechanisms and then focusses on processes involved in chronic orofacial pain.

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3.2 Overview of Orofacial Nociceptive Pathways and Mechanisms

3.2.1 Peripheral Processes

The fifth cranial nerve, the trigeminal nerve, provides the major sensory innervation of the face, mouth, and jaws. These tissues are densely innervated by trigeminal primary afferent (i.e., sensory) nerve fibers, each of which terminates peripherally as nerve endings termed receptors that "sense" stimuli applied to the face, mouth, and jaws. As a result of these stimuli, action potentials may be generated by these receptors in their associated afferent fibers, which conduct the action potentials into the brainstem. The orofacial receptors can be broadly categorized into two types: specialized or corpuscular receptors, of which several anatomically distinct types exist, and free nerve endings.

Many of the receptors associated primarily with large-diameter, fast-conducting myelinated primary afferent fibers (A-β afferents, some A-δ afferents) function as low-threshold mechanoreceptors since they respond to innocuous mechanical stimuli applied to the localized orofacial area supplied by the afferent (i.e., the receptive field of the afferent). There are mechanoreceptors in the facial skin, oral mucosa, periodontal tissues, periosteum, jaw muscles, and temporomandibular joint (TMJ), and their mechanoreceptive primary afferents provide sensory inputs into the central nervous system (CNS) that reflect detailed information of the quality, location, intensity, duration, and rate of movement of an orofacial mechanical stimulus [6, 7]. Mechanoreceptors located in the periodontal tissues, TMJ, and jaw muscles also account for our ability to detect and discriminate the size of small objects placed between the teeth, their hardness and texture, and bite force. Receptors in the TMJ and jaw muscles also underlie our conscious perception of jaw position (mandibular kinesthesia). The orofacial region also has thermoreceptors that are specifically activated by a small thermal change in either a cooling (cold receptors) or warming (warm receptors) direction. They are associated with some of the small-diameter, slow-conducting primary afferent fibers that are either myelinated (e.g., A-δ afferents) or unmyelinated (C-fiber afferents), and these thermoreceptive primary afferents provide the CNS with accurate information on the location, magnitude, and rate of the temperature change. There are of course also chemoreceptors in the oral cavity and nose that through other cranial nerves provide the CNS with information related to taste and smell.

Many of the free nerve endings in the orofacial tissues function as receptors (nociceptors) that sense the occurrence of a noxious stimulus [6–8]. They are the endings of primary afferents that are small diameter and slowly conducting (Aδ and C fibers). Several chemical mediators and cellular changes occur following the noxious stimulus, resulting in the activation of the nociceptive endings and their associated nociceptive afferents, which conduct the nociceptive signals into the CNS and thus may lead to the experience of pain. A prolonged increase in their excitability (so-called nociceptor or peripheral sensitization) may also occur, to such an extent that they become more responsive to subsequent noxious stimuli or even start responding to stimuli that normally are innocuous; they may also develop spontaneous (background) activity. In addition, some mechanically or thermally insensitive endings ("silent nociceptors") may be activated or sensitized by noxious chemical stimuli and then become responsive to noxious stimuli.

It has become apparent over the past two decades that the mechanisms involved in the activation or peripheral sensitization of orofacial nociceptive endings are very complex [7, 9, 10]. Ion channels or membrane receptors occur on the nociceptive afferent endings and include serotonergic, cholinergic, opioid, purinergic, bradykinin, histamine, prostaglandin, anandamide, excitatory amino acid and acid-sensitive receptors, adrenoreceptors, and vanilloid receptors [11–13]. Some of these ion channels and membrane receptors are activated, or their afferent endings are sensitized relatively directly by several types of noxious mechanical, chemical, and thermal stimuli (e.g., some vanilloid receptors [TRPVI] respond to protons (H^+), heat, and alge-

sic chemicals such as capsaicin), whereas others are acted upon by intermediary chemical mediators that are released in the peripheral tissues as a result of the noxious stimulus causing injury to the tissues. In addition, noxious stimuli producing tissue damage may cause the release of neurochemicals that are synthesized in the trigeminal ganglion cell bodies of the primary afferents themselves and released from their afferent endings; these include substance P, calcitonin gene-related peptide (CGRP), somatostatin, glutamate, and nerve growth factors. Some of these neurochemicals act on platelets, macrophages, mast cells, and other cells of the immune system to cause them to release inflammatory mediators such as serotonin (5-HT), histamine, bradykinins, and cytokines. The resulting redness, edema, and local temperature increases reflect what has been termed neurogenic inflammation since the inflammation may be initiated from these chemical mediators released from the nerve fibers themselves. Many of the chemical mediators also spread through the tissues and act on the ion channels and membrane receptors of adjacent nociceptive afferent endings and contribute to their peripheral sensitization. Glutamate, for example, is synthesized in the primary afferent cell bodies in the trigeminal ganglion and is released from not only the central endings of the primary afferents in the CNS (i.e., brainstem) but also from their endings in the orofacial tissues. Some afferent endings in peripheral tissues have glutamatergic receptors (N-methyl-D-aspartate [NMDA] and non-NMDA receptors) by which glutamate may excite or sensitize the nociceptive afferents. Some other chemical mediators (e.g., opioids and δ-amino butyric acid [GABA]) in contrast may decrease afferent excitability by acting on GABA and opiate receptors on the afferent endings. Interestingly, there is a sex difference in the peripheral action of glutamate and the opiate-related drug morphine; e.g., jaw or TMJ muscle nociceptive afferents show a greater sensitivity in females than in males to the application of glutamate, but females are less sensitive than males to the peripheral application of morphine [7, 8]. There is also increasing evidence that orofacial tissue inflammation or injury, especially of nerve fibers, can also cause changes in the properties of trigeminal ganglion cell bodies that may contribute to an abnormal sensory input into the brainstem (see Sect. 3.3).

There are several clinically relevant aspects of these peripheral processes. Peripheral sensitization of the nociceptive afferents is an important process contributing to the increased sensitivity that is usually a feature of a peripheral injury or inflammation site, e.g., as in the pain of a sunburn, arthritis, myositis, and pulpitis. The increased sensitivity may be reflected as an exaggerated perceptual response to a noxious stimulus ("hyperalgesia) or as a pain response to a stimulus (e.g., tactile) that is normally innocuous ("allodynia") or as an ongoing spontaneous pain; the sensitization of adjacent afferent endings beyond the initial injury site is a peripheral process contributing to the spread of pain in these tissues. Furthermore, the identification of substances released in painful tissues (e.g., glutamate, 5-HT, etc.) suggests that they may prove useful as biomarkers for certain types of pain states [13, 14], and other chapters in this book discuss this further (Chaps. 6, 7, 8, and 9). Also, the physiologically based sex differences noted above in the sensitivity of jaw muscle and TMJ nociceptive afferents to glutamate and opiate-related substances (i.e., morphine) may also contribute, along with the sex differences documented in environmental and psychosocial influences and the sex differences in CNS nociceptive mechanisms [4], to the sex differences in many orofacial pain conditions involving these tissues.

Another clinically significant point is that some drugs that are commonly used to relieve orofacial pain may exert their analgesic action by interfering with some of these peripheral mechanisms. Indeed, many common nonsteroidal anti-inflammatory drugs (NSAIDs) as well as several recently developed analgesics (e.g., cyclooxygenase-2 [COX-2] inhibitors) have their principal analgesic action by their influence on processes that enhance the excitability of nociceptive afferent endings. Furthermore, local anesthetics are effective for nerve blocks in eliminating pain resulting from peripheral tissue injury because they interfere with the ionic channels and currents

involved in the initiation and conduction of action potentials along the nociceptive afferents into the CNS [12, 13].

3.2.2 Central Pathways and Processes

The primary afferent nerve fibers in the trigeminal nerve project via the trigeminal ganglion and the trigeminal sensory nerve root into the trigeminal brainstem sensory nuclear complex, which can be subdivided into a main sensory nucleus and a spinal tract nucleus; the latter is subdivided further into the subnuclei oralis, interpolaris, and caudalis. The neural signals evoked by a light mechanical stimulus (e.g., tactile) of an orofacial tissue are transferred (via synaptic transmission) from the brainstem endings of the mechanoreceptive primary afferents to low-threshold mechanosensitive (LTM) neurons at all levels of the trigeminal brainstem sensory nuclear complex [2, 6, 10]. These second-order neurons conduct the signals onward to local brainstem regions, including those responsible for activating or suppressing muscles, and thereby serve as interneurons involved in reflexes or more complex sensorimotor behaviors. Another major projection from the LTM neurons in the trigeminal spinal tract nucleus and especially the main sensory nucleus is to LTM neurons in the ventroposterior thalamus (termed the ventrobasal thalamus in subprimates), principally on the contralateral side of the brain [2, 15]. Many of these thalamic LTM neurons project to parts of the overlying cerebral cortex, including the so-called somatosensory cortex involved in the perception of an orofacial touch stimulus. It has an extensive and disproportionate representation of the face and mouth relative to other body regions, reflecting the importance of sensory information from orofacial tissues compared to most other body regions. It is also noteworthy that the complex ultrastructure and regulatory processes that exist at each of the brainstem, thalamus, and cortical relay sites underlie the considerable modification of the synaptic transmission of the tactile-related signals that can occur at each of these CNS levels. Such modulatory mechanisms may explain how distraction or focusing one's attention on a particular task at hand can depress our awareness, for example, of the extensive mechanosensory inputs into the CNS from the mechanoreceptors that are being activated by our clothing.

In the case of orofacial thermosensation, the main brainstem relay site of the signals carried in the orofacial thermoreceptive primary afferent fibers is the trigeminal subnucleus caudalis. Some caudalis neurons appear to be exclusively activated by thermal stimulation of localized parts of the face and mouth and relay this thermal-related information to the contralateral thalamus and then to the somatosensory cerebral cortex. Subnucleus caudalis also is the major brainstem relay site of orofacial pain-related information, as noted below.

The vast majority of the nociceptive primary afferent fibers supplying the face and mouth project via the trigeminal ganglion to the trigeminal brainstem sensory nuclear complex, especially to the subnucleus caudalis where they release the chemical mediators that are synthesized in the primary afferent trigeminal ganglion cell bodies (see above). These include glutamate and the neuropeptide substance P which activate neurons in the trigeminal brainstem complex by acting, respectively, on glutamatergic receptors (N-methyl-D-aspartate [NMDA] and non-NMDA receptor subtypes) and neurokin receptors on the neurons. Many caudalis neurons receive the signals from these orofacial nociceptive primary afferents and thus can be excited by noxious stimulation of the face and mouth, TMJ, masticatory muscles, or meninges [6, 10]. These caudalis nociceptive neurons have been categorized as either wide dynamic range (WDR) neurons or nociceptive-specific (NS) neurons, and analogous neurons exist in the spinal dorsal horn of the spinal nociceptive pathways. The WDR neurons are activated by non-noxious (e.g., tactile) stimuli as well as by noxious stimuli applied to an orofacial receptive field and receive large-diameter (A-β) and small-diameter (A-δ and C fiber) afferent inputs. In contrast, NS neurons normally respond only to noxious stimuli (e.g., pinch, heat) and receive small-diameter afferent

inputs from A-δ and/or C fibers. Both types of neurons relay nociceptive information to other brainstem regions and also to the contralateral thalamus from where it is then relayed from analogous WDR or NS neurons to the overlying cerebral cortex or other thalamic regions [2, 6, 10, 15] where the information is processed and expressed as one or more of the many dimensions of the pain experience (see Sect. 3.1).

Although some differences between the two structures do exist, there is a close structural and functional homology between subnucleus caudalis and the spinal dorsal horn, and so subnucleus caudalis has become known also as the medullary dorsal horn [6, 16]. Nonetheless, subnucleus caudalis is not the only or essential brainstem element in orofacial nociceptive transmission since there is evidence that some of the more rostral subdivisions of the trigeminal brainstem complex, especially subnuclei interpolaris and oralis, may also play an important role [2, 17]. For example, afferent fibers from the tooth pulp, generally assumed to represent a nociceptive input, synapse with neurons present not only in subnucleus caudalis but also in the more rostral components of the complex, and the transitional zone between subnuclei caudalis and interpolaris has recently been shown to be important in muscle, autonomic, and endocrine responses to noxious orofacial stimuli and in intrinsic CNS modulatory influences on orofacial nociceptive transmission.

3.2.2.1 Modulatory Processes and Influences

At each relay in the trigeminal somatosensory pathways, the transmission process may vary depending on such diverse factors as maturational stage, age and sex, and behavioral state of the individual, plus genetic, nutritional, and immunological influences [2, 10, 18]. The intricate organization of the trigeminal brainstem complex, especially subnucleus caudalis, as well as the numerous afferent inputs to the trigeminal brainstem complex from peripheral tissues and from several CNS regions, provides the neural circuitry for the several interactions between these many inputs that influence somatosensory transmission. Some of these processes are involved in modifying touch, as noted above, but modulation of nociceptive transmission in the trigeminal system can also occur. For example, the responses of caudalis nociceptive neurons to small-fiber nociceptive afferent inputs can be markedly suppressed by large-fiber afferent inputs to caudalis that are activated by tactile stimulation of orofacial tissues (so-called sensory interaction); in some situations, even small-fiber nociceptive afferent inputs from other parts of the body may also suppress their activity. Their activity can also be suppressed by intrinsic inputs to caudalis from the spinal cord, brainstem, and higher CNS centers, such as the reticular formation, the periaqueductal gray, rostroventral medial medulla, and sensorimotor cortex. These modulatory influences result from endogenous neurochemicals, such as opioids, 5-HT, norepinephrine, and GABA, being released from these inputs and acting on the caudalis nociceptive neurons. Modulatory influences on trigeminal nociceptive transmission may also occur at thalamic and cortical levels [2, 10, 18].

There are several clinically relevant points about these modulatory influences. The influences on the nociceptive neurons of state of alertness, sleep, distraction and attention, and cognitive behavioral therapy are examples of behavioral factors whereby descending influences emanating from CNS regions involved in these behavioral functions and operating at the trigeminal brainstem complex and at higher brain levels may affect orofacial pain [2, 10, 19]. Placebo analgesia, which contributes to the effect of most pain-relieving procedures, also involves some of these systems [10, 20, 21]. Descending influences also have been implicated as intrinsic mechanisms contributing to the analgesic effects of several other procedures used to control pain. Morphine, for example, suppresses the activity of the nociceptive neurons by mimicking the action of the endogenous opioid chemical enkephalin which is a peptide that is pharmacologically similar to the opiate drugs such as morphine and which acts on opiate receptors existing on the nociceptive neurons and on neurons in some of the intrinsic modulatory pathways. Other pain-relieving drugs act

on other receptor processes to suppress the neurons, for example, amitriptyline on 5-HT receptor processes and pregabalin on voltage-gated calcium channels [22, 23]. The analgesic effects of some physical procedures (such as acupuncture or transcutaneous electrical nerve stimulation) appear also to involve some of these endogenous neurochemical processes and intrinsic pain-modulatory circuits [2, 10].

On the other hand, some modulatory CNS pathways have the opposite effect, i.e., facilitation of the nociceptive neurons, and contribute to the enhancement of pain, as might occur, for example, in the development and persistence of a chronic pain state or in the enhanced pain levels associated with fear, anxiety, and catastrophizing (Chap. 2). Facilitatory interactions also occur between various convergent afferent inputs to trigeminal nociceptive neurons in the CNS and contribute to the so-called referral of pain that may sometimes occur following tissue injury or inflammation (see Sect. 3.3.2 below). An especially noteworthy facilitatory effect may be initiated by injury or inflammation of peripheral tissues and can result in a prolonged increase in excitability of nociceptive neurons in the CNS. This so-called central sensitization is thought to be an important process contributing to the hyperalgesia, allodynia, and pain referral that characterize pain resulting from an orofacial injury or inflammation [2, 10, 24]. Furthermore, the development and maintenance of a central sensitization state appears to underlie most chronic pain conditions. Central sensitization reflects a neuroplasticity of the nociceptive pathways in the CNS and emphasizes that the nociceptive system is not hard wired but is dynamic and plastic, such that its excitability can change from one moment to another depending on the signals that its constituent WDR and NS neurons receive from peripheral tissues and on the CNS state of the individual. Central sensitization is manifested as an increase in excitability (e.g., spontaneous activity, increased receptive field size and responses to noxious stimuli, decreased activation threshold) of WDR and NS neurons.

In the trigeminal nociceptive system, central sensitization has been most studied in subnucleus caudalis and especially involves the release from the caudalis endings of trigeminal nociceptive afferents of excitatory amino acids (e.g., glutamate) that act via NMDA receptor mechanisms to induce a cascade of intracellular events in caudalis nociceptive neurons [2, 10, 24, 25]. A number of other brain chemicals such as those operating through neurokinin, opioid, GABA, and 5-HT receptor mechanisms contribute to or modulate these central neuroplastic changes induced by peripheral injury or inflammation. Other factors that influence these changes include genetic and environmental factors as well as non-neural (e.g., glial) cells, as noted below.

3.3 Chronic Orofacial Pain Mechanisms

With this background in processes underlying orofacial nociceptive transmission and its modulation, we can now focus on the peripheral and CNS mechanisms contributing to chronic orofacial pain states.

As Chap. 2 notes, chronic orofacial pain may accompany several types of painful and non-painful comorbidities. Chronic orofacial pain also can arise following injury or inflammation of orofacial tissues, including that associated with dental treatments (e.g., following endodontic treatment, dental implant placement, orthognathic surgery, tooth extraction), emphasizing the importance of trying to provide appropriate and timely management of acute pain so as to reduce the likelihood that it will transition into a chronic pain state (see Chap. 2). But for several chronic orofacial pain conditions (e.g., temporomandibular disorders [TMD], burning mouth syndrome, trigeminal neuralgia, so-called atypical odontalgia or persistent idiopathic facial pain), the etiology and pathogenesis are still unclear. The following sections on peripheral processes and central processes outline what is known of the peripheral and CNS processes that are associated with chronic inflammatory or neuropathic pain states and how they may explain chronic orofacial pain conditions. It is noteworthy that while many of these conditions may involve processes similar

to those in the spinal nociceptive system, there are some differences between trigeminal and spinal systems [6, 16]. For example, recovery from injury or inflammation may be faster in the trigeminal system, autonomic responses differ (e.g., no sprouting of sympathetic terminals on trigeminal ganglion cells following peripheral nerve injury), and the specific patterns of up- and downregulation of some ion channels and neurochemicals in primary afferents appear to be different between the two systems following chronic inflammation or injury. Thus, it cannot be assumed that processes involved in chronic inflammatory or neuropathic pain states in the spinal system can be automatically applied to the trigeminal system.

3.3.1 Peripheral Processes

It was noted earlier in the peripheral processes section that peripheral sensitization is reflected in enhanced spontaneous firing, an increase in responsiveness to noxious stimuli, and a decrease in activation threshold of nociceptive primary afferents, features that may contribute to the spontaneous pain, hyperalgesia, and allodynia that characterize many pain states, such as the increased sensitivity of the temporomandibular tissues in TMD, and the thermal sensitivity and spontaneous pain of an inflamed tooth [7, 9, 10, 13]. In addition, the spread of pain that occurs following tissue injury or inflammation may be explained by the chemical mediators released as part of the peripheral sensitization process that may spread through the tissues to act upon adjacent nociceptive afferent endings. Peripheral sensitization is normally reversible and gradually dissipates as the injured or inflamed tissue heals. But persistence of a peripheral inflammatory state and the continual sensitizing effect of chemical mediators on nociceptive afferent endings (e.g., as in an arthritic joint) can lead to accompanying CNS changes (see below) and thereby to a chronic pain state. Likewise, nerve injury may affect the nociceptive endings by producing prolonged changes in the expression and activity of voltage-gated calcium, sodium, or potassium ion channels on the endings and contribute, for example, to spontaneous or ectopic discharges that are conducted along the afferents into the brainstem; such changes have been implicated in the development of many types of neuropathic pain including those manifested in the orofacial region [9, 24, 26]. On the other hand, if the nerve injury transects afferent nerve fibers, there may be loss of sensation in the peripheral area supplied by the transected afferents, but the neuropathology may still produce a neuropathic pain state because of the central consequences of the nerve injury (see below). Nociceptive afferents may also become sensitive to sympathetic modulation following nerve injury, and this is thought to contribute to some pain conditions, e.g., some types of complex regional pain syndrome [9, 27].

It is important to note that changes are not limited to the peripheral endings of the primary afferents. Injury or inflammation of orofacial tissues, including primary afferent nerve fibers, can also be associated with persistent physiological and neurochemical changes in the neuronal cell bodies of the primary afferents in the trigeminal ganglion and involve modulatory influences on the ganglion neuronal cell bodies from non-neural (satellite glial cells) that are closely associated with the cell bodies [24, 28]. The injury or inflammation can send signals via the involved afferent nerve fibers to the trigeminal ganglion and produce alterations in gene expression, intracellular signaling (e.g., ERK, p38MAPK, phosphatases), and excitability of the ganglion neurons. The satellite glial cells may also show intracellular changes and themselves can be acted upon by chemical mediators (e.g., substance P, CGRP, ATP) released from the affected neurons. The existence of gap junctions between these cells, and between them and the neurons, provides an additional process by which the satellite glial cells and neurons may communicate and contribute to the spread of excitation in the trigeminal ganglion. These forms of communication between them may explain recent findings that injury to sensory nerves or inflammation of one trigeminal division (e.g., V3) can lead to excitability changes in trigeminal ganglion neurons subserving another division (e.g., V2) [24, 25]. It is however not yet

clear if the neurons involved in these changes are nociceptive and/or non-nociceptive neurons. Nonetheless, these cellular events in the trigeminal ganglion likely are important processes involved in the generation of increased or abnormal trigeminal afferent inputs to the brainstem that can influence neuronal and glial cell functions in the central trigeminal nociceptive processes underlying orofacial chronic pain mechanisms.

The clinical implications of these events in peripheral orofacial tissues and trigeminal ganglion are several. As noted above, the alterations in the properties of trigeminal nociceptive afferents as part of the peripheral sensitization process may contribute to spontaneous pain, hyperalgesia, allodynia, and pain spread in chronic pain states. In addition, it was noted earlier (Sect. 3.3.1) that the several chemical mediators and cellular processes involved in the activation or sensitization of the nociceptive afferents represent potential or realized targets of peripherally acting analgesic (e.g., COX-2 inhibitors, local anesthetics). Nonetheless, the multiplicity of processes, often acting in parallel, implies that targeting only one or a few of them is unlikely to have a significant analgesic impact [12]. The recent findings of spread of excitation to other trigeminal division(s) within the ganglion following inflammation or injury within another trigeminal division also have clinical relevance since such a process could conceivably be important in the extraterritorial sensory changes reported in some clinical cases of chronic pain [29–34]; as noted below, central processes may also contribute to such extraterritorial spread. Also of clinical relevance are recent findings in animal models mimicking the compression of the trigeminal ganglion or trigeminal sensory root that has been reported to occur in many trigeminal neuralgia patients and to be of etiological significance. Such compression produces nociceptive behavior in the animals and trigeminal brainstem cellular changes apparently reflecting the consequences of the abnormal afferent inputs to the brainstem produced by the compression [35]. These findings further emphasize the importance of trigeminal ganglion changes and the generation of abnormal afferent inputs in the production of an altered CNS state that, as the following section indicates, underpins the development and maintenance of a chronic orofacial pain condition.

3.3.2 Central Processes

As noted above, a number of alterations can occur in the CNS in association with tissue injury or inflammation and contribute to the development and maintenance of a chronic orofacial pain condition. Central sensitization appears to be the dominant central neural change associated with these pain states.

Central sensitization reflected in a hyperexcitability of brainstem nociceptive neurons in trigeminal subnucleus caudalis has been well documented in several chronic as well as acute inflammatory or neuropathic pain models [10, 24, 25]. Central sensitization also occurs in other components of the trigeminal brainstem complex (e.g., subnucleus oralis and the interpolaris/caudalis transitional zone) as well as at higher levels of the trigeminal nociceptive system (e.g., thalamus) although it appears to depend on the functional integrity of subnucleus caudalis for its expression since it can be abolished in these CNS sites by experimentally blocking the synaptic function of subnucleus caudalis [36]. It is also noteworthy that excitability changes following trigeminal nerve injury are not limited to the trigeminal somatosensory system but may also occur in CNS regions involved in the psychosocial functioning of the individual or in motor functions such as motor cortex pathways projecting to trigeminal motoneurons [37–39] and thus contribute to comorbid psychosocial and motor disruptions that are frequently associated with chronic pain states.

Like peripheral sensitization (see above), central sensitization appears to be normal physiological reaction to sustained noxious stimulation, and in most situations it is reversible and the pain state resolves. However, if central sensitization becomes maintained, chronic or persistent pain may develop [2, 10, 24, 25]. Unfortunately, the factors that predispose to the prolongation of

these reactions to tissue injury or inflammation are not yet well understood, but there is emerging evidence that they include genetic as well as environmental, immunological, and psychophysiological factors [10, 40]. For example, different rodent strains may express different levels of trigeminal central sensitization and nociceptive orofacial behavior, and environmental influences related to stress may also modify the behavior [41, 42]. Recent findings also point to changes in the inhibitory or facilitatory intrinsic modulatory processes that were noted earlier to influence trigeminal nociceptive processing in the CNS. An increase in descending facilitatory influences or a decrease in inhibitory influences can enhance trigeminal neuronal excitability. Another related mechanism is that in some circumstances, the normal inhibitory action of the neurotransmitter GABA is switched in chronic pain models to an action that facilitates neuronal excitability leading to a centrally sensitized state [43].

Recent findings also point to another factor important in the development and maintenance of a centrally sensitized state. Like the involvement of non-neural cells in peripheral tissues and the trigeminal ganglion in chronic inflammatory and neuropathic pain states (see above), central sensitization in subnucleus caudalis nociceptive neurons also involves non-neural cells. Indeed it is dependent on the functional integrity of glial cells in the brainstem. There are two types of CNS glial cells that are particularly involved, namely, astrocytes and microglia. Glial cells are even more numerous than neurons in most CNS areas, and they normally serve to nurture neurons, maintaining the chemical environment around them and protecting and assisting in their repair and regeneration following injury, infection, or inflammation. In the brainstem and spinal cord, they are in close proximity to neurons and the afferent inputs to the neurons and so are uniquely placed to interact with them. Indeed, following injury or inflammation of orofacial tissues, those in subnucleus caudalis and adjacent regions become "activated" and release inflammatory cytokines and other substances that can influence the excitability of the nociceptive neurons. Recent electrophysiological, immunocytochemical, and behavioral studies in animal models of chronic orofacial inflammatory or neuropathic pain have documented a role for both astrocytes and microglia in trigeminal central sensitization. For example, interfering with glial cell function in the medulla can prevent the development of trigeminal central sensitization in caudalis nociceptive neurons and the associated nociceptive behavior of the animal and can also reverse the sustained central sensitization and nociceptive behavior that are a feature of chronic orofacial pain models [10, 24, 25, 28]. The normal or baseline nociceptive processing, in caudalis neurons, for example, is not affected by blockade of glial cells; only the hyperexcitable state of the sensitized nociceptive neurons is affected.

These recent findings are of clinical importance from several perspectives. The documentation of the critical role in trigeminal central sensitization of glial cells offers the possibility of new therapeutic targets for pain control, which pharmacologically in the past has been dominated by drugs targeting neuronal mechanisms. In addition, central sensitization reflects a neuroplasticity of the trigeminal nociceptive system, and more and more evidence is emerging from brain imaging and other approaches in humans that such neuroplasticity in certain CNS regions is associated with a chronic pain state such as TMD, trigeminal neuralgia, or other neuropathic pain conditions [44] and may prove useful as a pain biomarker.

The recent findings in chronic pain states of changes in excitability occurring in orofacial motor pathways (e.g., motor cortex) and the changes that may occur in CNS regions involved in psychosocial functions are also clinically relevant. Such alterations may contribute to the motor limitations and psychosocial problems that are often seen in chronic orofacial pain conditions.

Also of clinical relevance are the features of central sensitization of nociceptive neurons in trigeminal nociceptive pathways in chronic orofacial pain models, namely, spontaneous activity, hyperexcitable responses to noxious stimuli, and decreased activation threshold, which also reflect

features that, along with peripheral sensitization (see above), can explain the spontaneous pain, hyperalgesia, and allodynia that characterize several orofacial chronic pain conditions and may through quantitative sensory testing (QST) reflect biomarkers for some of these conditions (see Chap. 5). An example is the pain of a chronic arthritic condition, which may involve central sensitization of nociceptive neurons as well as peripheral sensitization of the afferents in the inflamed region. Another example is TMD, since these central and peripheral processes can explain the ongoing pain, increased pain sensitivity (i.e., hyperalgesia), and the lowered threshold for evoking pain (i.e., allodynia). The diffuse character of TMD pain can also be explained by involvement of adjacent afferents as part of the peripheral sensitization process, but also by central sensitization since neuronal receptive field expansion is a major feature of trigeminal central sensitization in chronic as well as acute orofacial pain models. As a consequence of the expansion of its receptive field, the centrally sensitized nociceptive neuron starts sending signals to higher brain centers from more widespread parts of the orofacial region and thereby contributes to the perception of a diffuse pain. On a related point, central sensitization also appears to be important in the referral of pain, which is a common feature of TMD and some other types of chronic orofacial pain states (e.g., headaches). Trigeminal nociceptive afferent inputs relayed to many caudalis nociceptive neurons appear to derive exclusively from cutaneous (and oral mucosal) tissues and endow these neurons with coding properties important for the detection and discrimination of superficial orofacial pain, which is usually well localized. In contrast, nociceptive information from deeper tissues (e.g., tooth pulp, TMJ, muscle, meninges) is predominantly processed by other subsets of caudalis nociceptive neurons (both NS and WDR) receiving extensive convergent afferent inputs from these tissues as well as cutaneous afferent inputs [2, 25]. These convergence patterns are also a feature of analogous nociceptive neurons in the thalamus and cortex and reflect processes contributing to deep pain and also to the poor localization, extraterritorial spread, and referral of pain from these deep tissues. Nonetheless, the pain referral mechanisms may depend not only on the convergent afferent input patterns to the nociceptive neurons but also on the neuroplastic changes expressed as central sensitization generated in the neurons by these inputs as a result of injury or inflammation. There is evidence suggesting that some of the widespread afferent inputs to the nociceptive neurons are normally "weak" and held in check by inhibitory processes but become "unmasked" in pathophysiological situations and are more effective in exciting the nociceptive neurons that have become hyperexcitable through the central sensitization process and a decrease of the inhibitory processes.

Also clinically relevant is evidence that central sensitization depends on nociceptive afferent inputs for its initiation and perhaps also for its maintenance. This underpins the now standard incorporation into dental restorative and surgical procedures of approaches such as local anesthesia and pre- and postoperative analgesic drugs that reduce nociceptive afferent inputs into the CNS and thus reduce the risk for the development of central sensitization and a persistent pain state. It also emphasizes again the point made above of the importance of timely and appropriate treatment of an acute pain state to reduce the possibility that it could lead to persistent sensitization processes and a chronic pain condition. Moreover, caudalis central sensitization and the accompanying nociceptive behavior that occur in animal models of orofacial inflammatory or neuropathic pain can be prevented from developing, or attenuated once developed, by analgesic drugs (e.g., morphine, pregabalin) used clinically in chronic orofacial pain patients [2, 13, 45, 46]. These findings emphasize the crucial role that central sensitization plays in the development and maintenance of chronic orofacial pain states.

Summary

Several mechanisms accounting for chronic orofacial pain have been identified in orofacial tissues and trigeminal nociceptive pathways in the CNS. These include peripheral sensitization and

central sensitization that have characteristics that can explain the spontaneous nature, hyperalgesia, allodynia, and spread and referral of pain resulting from injury or inflammation of orofacial tissues and nerves. A number of neural and non-neural modulatory factors influencing these mechanisms have been documented. Further elucidation of these mechanisms holds out promise for the development of new or improved diagnostic and management approaches for orofacial pain states.

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