# The Neural Basis of Temporomandibular Joint and Masticatory Muscle Pain

**Barry J. Sessle, BDS, MDS, BSc, PhD, FRSC**
Dean and Professor
Faculty of Dentistry
University of Toronto
Toronto, Ontario, Canada

**Correspondence to:**
Dr Barry J. Sessle
Faculty of Dentistry
University of Toronto
124 Edward Street
Toronto, Ontario
Canada M5G 1G6
Fax: 416-979-4937
E-mail: barry.sessle@utoronto.ca

Pain from deep structures such as muscular and articular tissues is very common and is a primary symptom of temporomandibular disorders (TMD). This article will review recent advances in our knowledge of the neural processes involved in musculoskeletal pain of the craniofacial region.

## Peripheral Mechanisms

Free nerve endings in peripheral tissues provide the peripheral basis for pain. Many of these free nerve endings act as nociceptors, that is, they are the sense organs that are activated by noxious stimulation of peripheral tissues. Their activation may result in the production of nerve impulses in the small-diameter (A-delta or C) afferent nerve fibers with which they are associated, and this neural information is then conducted along the fibers into the brain, where it is processed so that the location, quality, intensity, and duration of the noxious stimulus can be perceived.

The masticatory muscles and the temporomandibular joint (TMJ) also contain numerous free nerve endings, although the TMJ and several of these muscles do not have an abundance of the more specialized endings (eg, muscle spindles, Golgi tendon organs) that are considered to play a role in perceptual and reflex responses related to low-intensity muscular and articular stimuli (eg, a stretch).[1,2] From the limited number of studies of the physiologic properties of the small-diameter TMJ and masticatory muscle afferents and the more extensive literature on analogous spinal afferents, it is clear that the endings of many of these small-diameter afferents may respond to a wide range of peripheral stimuli that cause pain in humans, eg, heavy pressure, algesic chemicals, and inflammatory agents.[3–5] Ischemia also is an effective stimulus if it is prolonged and associated with muscle contractions. In addition, the sensitivity of the nociceptive afferent endings may increase following mild injury. This increased excitability of the endings, so-called "peripheral sensitization," is reflected in an increased responsiveness, a lowered activation threshold, and often spontaneous activity of deep nociceptive afferents. It is thought to be a major factor in producing hyperalgesia, allodynia, and spontaneous pain. Together with central sensitization (see below), peripheral sensitization can explain why tissues become tender and hurt after injury or disease.[3–5] A number of chemicals

Key words: neurons, pain, craniofacial, neuroplasticity, musculoskeletal

J OROFAC PAIN 1999;13:238–245.

(eg, substance P, prostaglandins, histamine, serotonin, kinins) are released from tissue cells or afferent nerve fiber endings following injury and are involved in the activation of the peripheral endings by noxious stimulation or in their peripheral sensitization.[1,6–8] Antagonism of the synthesis or action of some of these chemical mediators is the basis of several pharmacologic therapies aimed at counteracting pain (eg, nonsteroidal anti-inflammatory drugs, COX-2 inhibitors). Several of these chemicals are also involved in the central processes underlying nociceptive transmission and its modulation (see below).

## Brain Stem and Thalamocortical Mechanisms

The small-diameter primary afferents innervating the TMJ and masticatory muscles project into the brain and terminate centrally in the trigeminal (V) brain stem sensory nuclear complex, where they release excitatory neurochemicals, such as excitatory amino acids (eg, glutamate) and neuropeptides (eg, substance P), that are involved in the activation of second-order neurons in the V brain stem complex. The V brain stem complex can be subdivided into the main or principal sensory nucleus and the spinal tract nucleus, which comprises 3 subnuclei—oralis, interpolaris, and caudalis (Fig 1). Neurons responsive to low-threshold inputs from the TMJ or associated muscles have received little attention, but some do appear to occur at least in the rostral components of the V brain stem complex.[2] In the case of neurons responsive to nociceptive afferent inputs, it should first be noted that subnucleus caudalis is usually considered the principal brain stem relay site of V nociceptive information, and there are several reasons for this.[1,2,9] Anatomically, subnucleus caudalis is a laminated structure resembling the dorsal horn of the spinal cord, which is the integral component of spinal nociceptive processing. Also, by analogy with spinal nociceptive afferents, the small-diameter afferents carrying nociceptive information from the various craniofacial tissues, including the TMJ and masticatory muscles, predominantly terminate in the superficial laminae (I and II) of subnucleus caudalis, as well as in its deeper laminae V and VI. Clinically, a neurosurgical procedure called V tractotomy, which disrupts the rostral part of subnucleus caudalis and can relieve the excruciating pain of trigeminal neuralgia, may also produce a profound loss of pain sensation (and thermanesthesia) to facial noxious stimulation. This analgesic effect is consistent with the reduced nociceptive responses in animals that occur following experimental caudalis lesions. Craniofacial noxious stimulation of deep tissues also evokes reflex autonomic changes (eg, in blood pressure and respiration) as well as reflex increases in muscle activity, and many of these reflex effects also are dependent on a relay in subnucleus caudalis, since they can be markedly reduced by caudalis lesions.[2,9]

Electrophysiologically, recordings in the superficial and deep laminae of subnucleus caudalis have revealed many neurons that can be activated by cutaneous noxious stimuli; these nociceptive neurons have been categorized as either nociceptive-specific (NS) neurons or wide dynamic range (WDR) neurons. The NS neuron is one that receives small-diameter afferent inputs from A-delta and/or C fibers and responds only to noxious stimuli (eg, pinch, heat) applied to a localized region of the face or mouth, the so-called receptive field (RF) of the neuron. The WDR neuron may, in contrast, receive large-diameter and small-diameter A-fiber inputs as well as C-fiber inputs and can be excited by non-noxious (eg, tactile) stimuli as well as by noxious stimuli. Many NS and WDR neurons in subnucleus caudalis can be excited only by natural stimulation of cutaneous or mucosal tissues and respond with a progressively increasing discharge as the intensity of the peripheral noxious stimulus is gradually increased or as more of the RF is stimulated. These various RF and response properties are consistent with a role for both WDR and NS neurons in the detection, localization, intensity coding, and discrimination of superficial noxious stimuli.[1,2,9,10]

The foregoing clearly implicates a crucial role for caudalis WDR and NS neurons in superficial pain, and because of its structural and functional similarity with the spinal dorsal horn, subnucleus caudalis is now often termed the "medullary dorsal horn."[1,2,9,10] Nonetheless, the majority of cutaneous NS and WDR neurons can also be excited by other types of peripheral afferent inputs that converge onto the neurons, such as those from TMJ or muscle tissues. Indeed, most neurons with a deep nociceptive RF also have a cutaneous nociceptive RF (Fig 2). These neurons can be activated by noxious mechanical stimuli or by algesic chemicals applied to articular and/or muscular tissues, and they are the predominant neurons in the superficial and deep laminae of subnucleus caudalis. They appear to be the brain stem neural elements crucial for the appreciation of deep pain in the craniofacial region.[2,4]

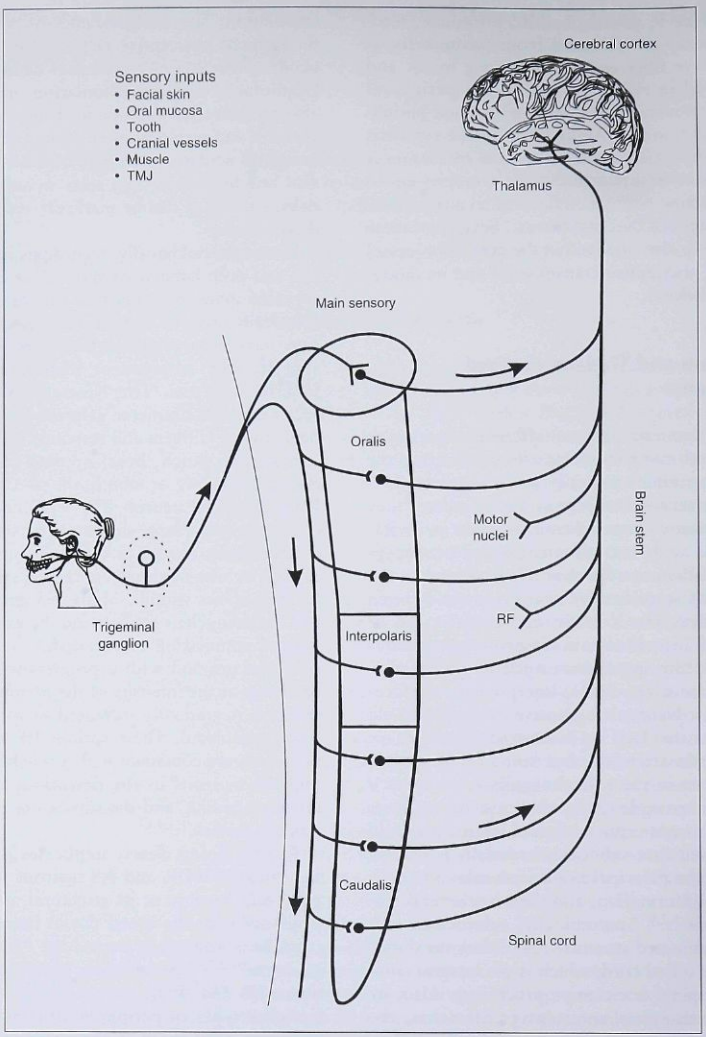


**Fig 1** Major somatosensory pathways from the face and mouth. Note that trigeminal primary afferents project via the trigeminal (V) ganglion to second-order neurons in the V brain stem complex. These neurons may project to neurons in brain stem regions such as cranial nerve motor nuclei or the reticular formation (RF) or in higher levels of the brain (for example, in the thalamus). Not shown are the projections of some cervical nerve afferents and cranial nerve VII, IX, X, and XII afferents to the V complex and the projection of many VII, IX, and X afferents to the solitary tract nucleus (from Sessle[9]; reprinted with permission).

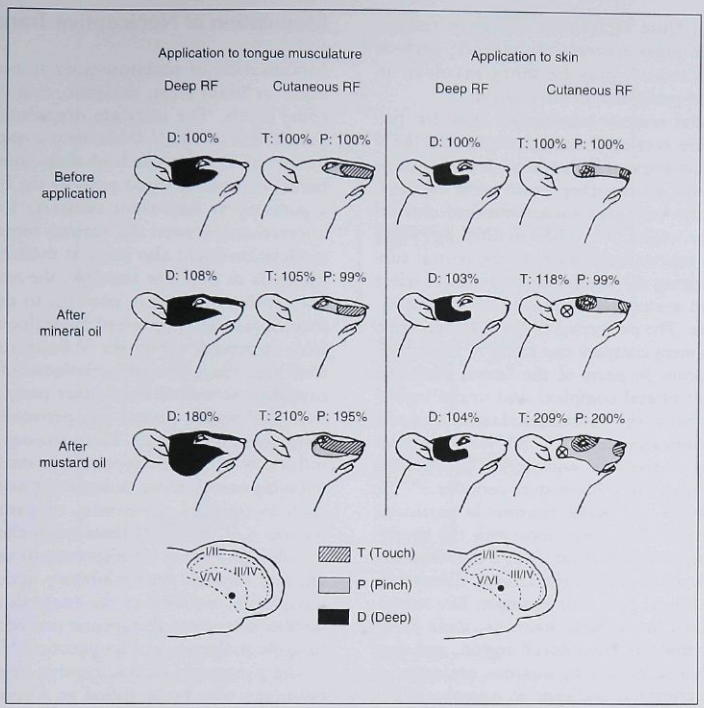


**Fig 2** Two examples of caudalis nociceptive neurons exhibiting receptive field (RF) expansion after application of mustard oil to the tongue musculature or skin. The deep RFs (blackened areas) of the 2 wide dynamic range neurons are shown separately on the left of each group, and on the right are shown their cutaneous RFs; each neuron could be activated by both pinch and tactile stimulation of the touch (T) component of the cutaneous RF, and by pinch only from the pinch (P) component. In each group, the 2 drawings in the top row show the RFs of the neuron before application of mineral oil (the vehicle for mustard oil); the areas of the deep, touch, and pinch RF components of each neuron in the group on the right were expressed as 100%, and the changes in area after mineral oil or mustard oil application are expressed relative to this control value. The drawings in the middle row show the peak RF expansion after mineral oil application, and the drawings in the bottom row show the peak RF expansion after mustard oil application. ⊗ indicates the site of cutaneous application of either mineral oil or mustard oil. The drawings at the bottom of the figure indicate the neuron's location (dot) within the V subnucleus caudalis (from Yu et al[21]; reprinted with permission).

It is noteworthy that different parts of caudalis per se may conceivably have different functional roles. There is, for example, recent evidence that the rostral and caudal portions of subnucleus caudalis have some different neuronal RF and response properties, and they appear to be differentially involved in the autonomic and muscle reflex responses to noxious stimulation of some craniofacial tissues.[9,11] Recent studies have also implicated more rostral components of the V brain stem complex (eg, subnuclei interpolaris and oralis) in V nociceptive processes; they suggest that the role of subnucleus caudalis in pain may be primarily related to processing of nociceptive

information from facial skin and deep tissues, whereas the more rostral components, such as subnucleus oralis, may be more involved in intraoral and perioral pain mechanisms.[9]

Craniofacial sensory information from the primary afferents is relayed through neurons in the V brain stem complex to higher brain levels, such as the thalamus, or to other brain stem regions, including the reticular formation and cranial nerve motor nuclei.[1,2,12] The circuitry involving the latter 2 regions contributes to the central substrate underlying the autonomic and muscle reflex responses to craniofacial stimuli that were mentioned above. The projection to the thalamus from the V brain stem complex can result in the activation of neurons in parts of the lateral thalamus (eg, the ventrobasal complex) and in the medial thalamus. Both the lateral thalamus and the medial thalamus contain NS and WDR neurons that receive craniofacial nociceptive information relayed through the V brain stem complex.[2,4] The ventrobasal NS and WDR neurons in particular have properties and connections with the overlying somatosensory cerebral cortex that indicate their role is principally in the sensory-discriminative dimension of pain. For example, like subnucleus caudalis nociceptive neurons, their RF is localized within the craniofacial region, and they show graded responses to noxious craniofacial stimuli. In contrast, nociceptive neurons in the medial thalamus (eg, intralaminar nuclei, parafascicular nucleus) generally have properties (eg, extensive RF) and connections (eg, with anterior cingulate cortex; see below) suggestive of a role more in the affective or motivational dimensions of pain. Neurons also occur in the somatosensory cortex with properties similar to those of caudalis or ventrobasal NS or WDR neurons, indicating that they play a role in pain localization and intensity coding. Nociceptive neurons also occur in other cortical regions, such as the anterior cingulate cortex, which has been implicated in the affective dimension of pain. The significance of these mechanisms in human pain processes is underscored by recent brain imaging findings that noxious stimulation in humans can activate several cortical regions, including the somatosensory cortex and anterior cingulate cortex.[13] There is, however, no detailed information available about how nociceptive information from the TMJ and masticatory muscles is processed in the thalamus or cortex.[2,4]

## Modulation of Nociceptive Transmission

Modification of somatosensory transmission can occur at brain stem, thalamic, and cortical neuronal levels. The intricate organization of each subdivision of the V brain stem complex and the variety of inputs to each of them from peripheral tissues or from different parts of the brain provide a particularly important substrate for numerous interactions between the various inputs, although modulation might also occur at thalamic and cortical levels as well. For example, the responses of V nociceptive brain stem neurons to deep noxious stimuli can be suppressed by influences derived from structures within the V brain stem complex itself (eg, the substantia gelatinosa of subnucleus caudalis), as well as from other parts of the brain stem and higher centers (eg, periaqueductal gray, somatosensory cortex). These various modulatory influences on V nociceptive transmission act by releasing one or more endogenous neurochemicals such as opioids, serotonin, or gamma aminobutyric acid. Many of these neurochemicals have an inhibitory effect on responses to noxious stimuli, and through such inhibitory actions they are thought to contribute to the analgesic efficacy of a number of current therapeutic procedures, such as narcotic analgesics and acupuncture.[9,11,14]

The properties of nociceptive neurons in the brain can also be modified as a consequence of peripheral nerve injuries, as well as by peripheral tissue trauma and inflammatory conditions. The afferent inputs to the brain evoked by these peripheral events indeed induce modifications by utilizing some of the modulatory substrates noted above. For example, the injection of the small-fiber irritant mustard oil or other inflammatory agents, particularly into such deep tissues as the TMJ or masticatory muscles, can lead to a cascade of events that results in expansion of the cutaneous and/or deep RF, lowering of activation threshold, and enhancement of the responses of NS and WDR caudalis and oralis neurons to craniofacial stimuli (eg, Fig 2).[5,9,11,15] These and other neuronal changes reflect an increased excitatory state of the neurons and are thought to result in part from a disinhibition and an unmasking and increased efficacy of the extensive convergent afferent inputs to these neurons (see above). In experimental animals they may be accompanied by reflexly induced increased activity in both jaw-opening and jaw-closing muscles,[5,9,16,17] and neuromuscular changes can also occur in humans following the experimental induction of muscle pain.[5,18,19] Depending on the stimulus or form of injury or inflammation,

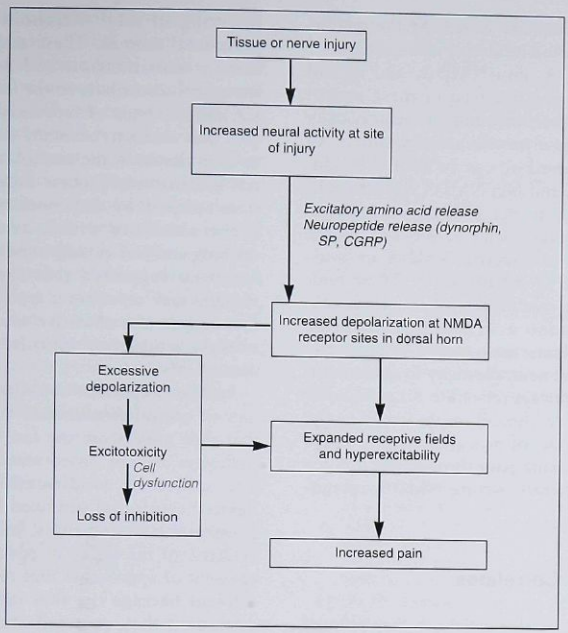


Fig 3 Outline of the sequence of events that may occur following peripheral tissue injury and inflammation or peripheral nerve injury. SP = substance P; CGRP = calcitonin gene-related peptide; dynorphin is an endogenous opioid (from Dubner[22]; reprinted with permission).

these central neuronal changes can last for hours or days, even weeks, and are associated with behavioral changes in pain sensitivity. They represent a prolonged increased excitability of central nociceptive neuronal circuits and thereby reflect a "functional plasticity" or "central sensitization" of nociceptive neurons (Fig 3).

Recently, there has been a focus on the neurochemical processes that underlie this neuroplasticity of central nociceptive pathways. Several neuropeptide (eg, substance P, neurokinin A, calcitonin gene-related peptide) and excitatory amino acid (eg, glutamate, aspartate) receptor mechanisms appear to be crucial (eg, Fig 3). For example, both N-methyl-D-aspartate (NMDA) and non-NMDA (eg, AMPA) receptor subtypes underlie the involvement of excitatory amino acids in nociceptive processing. Centrally acting NMDA antagonists are particularly effective in preventing the increased jaw muscle activity and the RF expansion and related hyperexcitability of V brain stem–nociceptive neurons induced by the peripheral inflammatory conditions of the TMJ or masticatory muscle tissues that were mentioned above.[9,11]

Several other potential centrally acting neurochemicals may contribute to these central modulatory effects but are too numerous to detail here.[9,14] Just one example is the endogenous opioids. It has been documented in animals that opioid antagonists delivered into the brain can "rekindle" the increased jaw muscle activity and brain stem neuronal excitability induced by the inflammatory irritant mustard oil.[9] This suggests that a peripheral injury or inflammation can evoke a nociceptive afferent barrage that enters the brain and triggers increased nociceptive neuronal excitability and associated neuromuscular changes, but these

neuroplastic alterations are limited by the recruitment of a central opioid inhibitory mechanism.

Peripheral NMDA, non-NMDA, and opioid processes may also be involved in these neurochemical processes that contribute to neuroplasticity. For example, jaw muscle activity similar to that evoked by mustard oil can be elicited by glutamate and NMDA and non-NMDA receptor subtypes applied locally to the TMJ region, and the increased muscle activity can be blocked by the local application of specific NMDA or non-NMDA antagonists or morphine.[18,19] These findings clearly indicate that *peripheral* as well as *central* excitatory amino acid and neuropeptide receptor mechanisms may play a role in the expression of central neuroplasticity in somatosensory and motor pathways related to deep craniofacial pain. They have clinical implications in the potential development of new peripherally based approaches for blocking pain through the use, for example, of peripherally acting NMDA antagonists or opiates.

## Further Clinical Correlates

In the first section of this article, it was pointed out that acute injury or inflammation of TMJ or muscular tissues may be associated with a peripheral sensitization process. This increased excitability of peripheral nociceptive afferents could thus account for the pain and tenderness of deep tissues when they are injured or inflamed. But central neural changes may also contribute. As noted above, the deep nociceptive afferent inputs into the V brain stem complex activate caudalis NS and WDR neurons; few such neurons are activated exclusively by deep noxious stimuli, and the vast majority of the caudalis neurons transmitting deep nociceptive information receive additional inputs from afferents supplying other tissues, including skin. The presence of a cutaneous RF and a deep RF in most of these neurons, as well as the efficacy of deep nociceptive afferent inputs (eg, activated by mustard oil) in inducing an expansion of both cutaneous and deep RFs (see above), represents neuronal properties that may explain the poor localization, spread, and referral of pain that are typical of deep pain conditions involving the TMJ and associated musculature.[4,5,9,11] The neuronal RF expansion induced by deep nociceptive afferent inputs is one feature of so-called central sensitization or neuroplasticity. In addition, these RF changes may be accompanied by an increased responsiveness of the nociceptive neurons and a lowering of their threshold for activation by peripheral stimuli. These additional features of central sensitization and neuroplasticity are thought to contribute to the tenderness, hyperalgesia, and allodynia of superficial as well as deep tissues that characterize many cases involving injury to deep tissues in the craniofacial region. The central sensitization process induced in the V brain stem complex by deep nociceptive afferent inputs is also associated with increased activity in jaw-opening and jaw-closing muscles in animals, and it has been suggested that these neuromuscular changes may represent a type of "splinting" effect that counteracts excessive movement and so protects the articular or muscular tissues from further damage.[2,9]

Another important consideration of these findings of central sensitization and neuroplasticity is that they underscore the fact that the nociceptive pathways are not "hard-wired" but are "plastic" and subject to modification by peripherally induced events and sustained by central as well as peripheral neural changes. Indeed, there is recent evidence of the utility in postoperative pain management of approaches that reduce the nociceptive afferent barrage (ie, that induced by a surgical operation) that, as noted above, can trigger and perhaps maintain central sensitization.[9,11,20] The clinical potential of peripherally acting NMDA antagonists or opioids also has been pointed out (see above). In addition, the emerging knowledge of the central as well as peripheral neurochemical mechanisms contributing to the neuroplastic changes and to the modulation of nociceptive transmission offer promise of further new or improved pharmacologic approaches to the management of deep craniofacial pain. N-methyl-D-aspartate receptor mechanisms in particular appear to be very important in the central sensitization process, to the extent that centrally acting NMDA antagonists may be useful as analgesics, especially in the treatment of persistent pain.[11,20]

## Conclusions

In reviewing the neural pathways and mechanisms involved in craniofacial musculoskeletal pain, this article first has emphasized the importance of peripheral processes, in particular peripheral sensitization, that contribute to the pain, and especially the hyperalgesia, allodynia, and spontaneous pain, that may characterize many pain conditions affecting the TMJ or masticatory musculature. The article next has outlined some of the central neural

mechanisms that primarily involve nociceptive neurons receiving convergent afferent inputs from deep tissues as well as other craniofacial tissues. These nociceptive neurons may occur at thalamic and cortical levels, but their RF and response properties and associated neurochemical processes have been better defined in the V brain stem complex. Their afferent inputs and central circuitry are not "hard-wired" but are plastic, and nociceptive afferent barrages may indeed induce neuroplastic changes in their properties that reflect a central sensitization that may, along with peripheral sensitization, contribute to the clinical features of TMJ or masticatory muscle pain. Further definition of these sensitization phenomena, including their underlying neurochemical basis, holds promise of new or more effective therapeutic approaches to the management of craniofacial musculoskeletal pain.

## Acknowledgments

The secretarial assistance of Fong Yuen is gratefully acknowledged. The cited studies by the author were supported by Canadian MRC Grant MT-4918 and NIH Grant DE04786.

## References

1. Dubner R, Sessle BJ, Storey AT (eds). The Neural Basis of Oral and Facial Function. New York: Plenum Press, 1978:483.
2. Hannam AG, Sessle BJ. Temporomandibular neurosensory and neuromuscular physiology. In: Zarb GA, Carlsson GE, Sessle BJ, Mohl ND (eds). Temporomandibular Joint and Masticatory Muscle Disorders. Copenhagen: Munksgaard, 1994:67–100.
3. Hargreaves KM, Roszkowski MT, Jackson DL, Bowles W, Richardson JD, Swift JQ. Neuroendocrine and immune response to injury, degeneration, and repair. In: Sessle BJ, Bryant PS, Dionne RA (eds). Temporomandibular Disorders and Related Pain Conditions. Progress in Pain Research and Management, Vol. 4. Seattle: IASP Press, 1995:273–292.
4. Sessle BJ, Hu JW. Mechanisms of pain arising from articular tissues. Can J Physiol Pharmacol 1991;69:617–626.
5. Lund JP, Sessle BJ. Neurophysiological mechanisms related to chronic pain disorders of the temporomandibular joint and masticatory muscles. In: Zarb GA, Carlsson GE, Sessle BJ, Mohl ND (eds). Temporomandibular Joint and Masticatory Muscle Disorders. Copenhagen: Munksgaard, 1994:188–207.
6. Alstergren P, Ernberg M, Kopp S, Lundeberg T, Theodorsson E. TMJ pain in relation to circulating neuropeptide Y, serotonin, and interleukin-1ß in rheumatoid arthritis. J Orofac Pain 1999;13:49–55.
7. Ernberg M, Hedenberg-Magnusson B, Alstergren P, Lundeberg T, Kopp S. Pain, allodynia, and serum serotonin level in orofacial pain of muscular origin. J Orofac Pain 1999;13:56–62.
8. Kopp S. Rheumatoid arthritis. In: Zarb GA, Carlsson GE, Sessle BJ, Mohl ND (eds). Temporomandibular Joint and Masticatory Muscle Disorders. Copenhagen: Munksgaard, 1994:346–366.
9. Sessle BJ. Neural mechanisms in craniofacial pain. Crit Rev Oral Biol Med (in press).
10. Dubner R. Recent advances in our understanding of pain. In: Klineberg I, Sessle B (eds). Oro-facial Pain and Neuromuscular Dysfunction: Mechanisms and Clinical Correlates. Oxford: Pergamon Press, 1985:3–19.
11. Ren K, Dubner R. Focus article: Central nervous system plasticity and persistent pain. J Orofac Pain 1999; 13:155–163.
12. Craig AD, Dostrovsky JO. Processing of nociceptive information at supraspinal levels. In: Yaksh TL, Lynch C III, Zapol WM, Maze M, Biebuyck JF, Saidman LJ (eds). Anesthesia: Biologic Foundations. Philadelphia: Lippincott-Raven, 1997:625–642.
13. Casey KL, Minoshima S. Can pain be imaged? In: Gebhart GF, Hammond DL, Jensen TS (eds). Proceedings of the 7th World Congress on Pain. Progress in Pain Research and Management, Vol 2. Seattle: IASP Press, 1994:855–866.
14. Yaksh TL, Malmberg AB. Central pharmacology of nociceptive transmission. In: Wall PD, Melzack R (eds). Textbook of Pain, ed 3. London: Churchill Livingstone, 1994:165–200.
15. Hu JW. Critical commentary 2: Central nervous system plasticity and persistent pain. J Orofac Pain 1999; 13:166–167.
16. Bakke M, Hu JW, Sessle BJ. Morphine application to peripheral tissues modulates nociceptive jaw reflex. Neuroreport 1998;9:3315–3319.
17. Cairns BE, Sessle BJ, Hu JW. Evidence that excitatory amino acid receptors within the temporomandibular joint region are involved in the reflex activation of the jaw muscles. J Neurosci 1998;18:8056–8064.
18. Stohler CS. Clinical perspectives on masticatory and related muscle disorders. In: Sessle BJ, Bryant PS, Dionne RA (eds). Temporomandibular Disorders and Related Pain Conditions. Progress in Pain Research and Management, Vol. 4. Seattle: IASP Press, 1995:3–29.
19. Svensson P, Arendt-Nielsen L, Houe L. Muscle pain modulates mastication: An experimental study in humans. J Orofac Pain 1998;12:7–16.
20. Dionne R. Critical commentary 1: Central nervous system plasticity and persistent pain. J Orofac Pain 1999; 13:164–165.
21. Yu X-M, Sessle BJ, Hu JW. Differential effects of cutaneous and deep application of inflammatory irritant on mechanoreceptive field properties of trigeminal brain stem nociceptive neurons. J Neurophysiol 1993;70:1704–1707.
22. Dubner R. Spinal cord neuronal plasticity: Mechanisms of persistent pain following tissue damage and nerve injury. In: Vecchiet L, Albe-Fessard D, Lindblom U (eds). New Trends in Referred Pain and Hyperalgesia. Pain Research and Clinical Management, Vol. 7. Amsterdam: Elsevier, 1993:109–117.