

Recent Insights into Brainstem Mechanisms Underlying Craniofacial Pain

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Abstract: This article briefly highlights some of the recent advances in knowledge of the neural processes underlying pain in the face and mouth. It particularly focuses on those mechanisms operating in the brainstem that are involved in the transmission and modulation of nociceptive signals and that reveal a remarkable degree of plasticity following injury or inflammation of craniofacial tissues. Insights into these processes hold promise of the development of new or improved therapeutic procedures for the relief of pain.

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Editor's note: This article by Sessle and the one following by Hargreaves and Keiser are presented as companion papers.

Virtually everyone has experienced pain in one form or another. For most of us, this pain takes the form of an acute or brief warning that an injury has occurred to a part of our body. Such acute pain is usually quickly resolvable and readily treated, but sometimes pain can persist and become chronic. There appears to be no biologically useful role for persistent or chronic pain, yet it can be extremely difficult to diagnose and manage effectively. Indeed, rather than simply being seen as a symptom of a disease or disorder, the changes that occur and persist in peripheral tissues or nerves or even within the brain itself have led to an emerging concept that pain is indeed a disease or disorder of the nervous system. And it is a costly one at that, since in the United States, for example, the economic cost of chronic pain alone has been estimated at over US\$65 billion per year. This dollar value of course does not factor in the personal cost or suffering the patient with a chronic pain condition has to endure, as well as the frustration that clinicians and others frequently encounter in trying to manage the pain or help the patient live with his or her condition.¹⁻³

These very same considerations apply to craniofacial pain, since some of the most common acute and chronic pain conditions occur in the face and mouth (for example, toothaches, migraine headaches, temporomandibular disorders [TMD]). Most clini-

cians have not received a good educational grounding in pain mechanisms, diagnosis, and therapy in dental school, despite the existence for many years of appropriate teaching guidelines.^{4,5} Added difficulties for the clinician trying to deal effectively with craniofacial pain stem from the face and mouth having special biological, emotional, and psychological meaning to humans; from pain being a complex, multidimensional experience encompassing a variety of perceptual and behavioral functions; and from the poor understanding that has existed of the mechanisms underlying the initiation and progression of pain disorders. This review provides a brief summary of the recent advances in our understanding of the processes in especially the brainstem that underlie craniofacial pain and its control.¹⁻³ The companion paper by Hargreaves and Keiser focuses on the clinical implications of these brainstem findings as well as complementary data of peripheral pain mechanisms.

A noxious stimulus in the craniofacial region resulting from, for example, injury or inflammation can excite sense organs (nociceptors) in peripheral tissues that sense the occurrence of the noxious stimulus. Several chemical mediators and cellular changes are involved, and as a consequence, the small-diameter A-delta and C-fiber primary afferent nerve fibers with which these nociceptors are associated be-

come activated. In some cases, a prolonged increase in excitability of the nociceptors may occur, to the stage where they become more responsive to noxious stimulation or even start responding to stimuli that normally are innocuous. Thus, this process of “peripheral sensitization” may contribute to the hyperalgesia and allodynia noted by Hargreaves and Keiser in certain pain conditions.

The activation of the primary afferent fibers as a result of the noxious stimulation is reflected in action potentials, which in the case of the fibers of the trigeminal (V) nerve are conducted into the brainstem. These nociceptive signals are transmitted to second-order nociceptive neurons by the release, from the brainstem endings of the primary afferents, of excitatory amino acids (such as glutamate) and other neurochemicals including neuropeptides (such as substance P) that activate the neurons. These neurons are located in the V brainstem sensory nuclear complex.

This structure has several morphologically distinct subdivisions, and has properties commensurate with its strategic role as the major brainstem relay of somatosensory information derived from the face and mouth (Figure 1). It has a crucial role in craniofacial nociceptive transmission, and there is considerable clinical, behavioral, morphological, and electrophysiological evidence of the particular involvement of the most caudal component (subnucleus caudalis) of the V brainstem complex. Many of the caudalis neurons function as nociceptive transmission neurons since they receive and are activated by the nociceptive signals from the primary afferent input to the subnucleus caudalis, and they project to higher brain areas involved in pain perception and behavior. Indeed, subnucleus caudalis has become known as the medullary dorsal horn because of its close structural and functional homology with the dorsal horn of the spinal cord that is critical in the central transmission of nociceptive signals from other parts of the body (such as limbs, trunk, viscera).

However, the traditional view that subnucleus caudalis is the only or essential brainstem element in craniofacial nociceptive transmission has undergone some recent revision since convincing evidence has accumulated that some of the more rostral subdivisions of the V brainstem complex, especially subnuclei interpolaris and oralis, may also play important roles in some of these processes. A particular challenge is the clarification of the relative contributions of the different subdivisions of the V brainstem complex to the perceptual, emotional, and other pain be-

haviors that depend on higher brain center function. An analogous challenge applies to the reflex changes in neuromuscular activity, blood pressure, heart rate, respiration, salivation, and sweating that frequently occur in craniofacial pain conditions since the different parts of the V brainstem complex may also be differentially involved in these nociceptive reflex behaviors.

In the accompanying paper, Hargreaves and Keiser mention the diagnostic and management problems associated with the referral of pain. This is especially so in many cases of dental or musculoskeletal pain. We now know that nociceptive afferent inputs relayed to many neurons in subnucleus caudalis appear to derive exclusively from cutaneous (and oral mucosal) tissues and endow these neurons with coding properties, suggesting that they are critical brainstem neural elements for the detection and discrimination of superficial pain in the face and mouth. However, nociceptive information from other craniofacial tissues (such as tooth pulp, TMJ, muscle) is predominantly processed by other cutaneous nociceptive caudalis neurons that receive extensive convergent afferent inputs from these tissues. These convergence patterns—for example, involving TMJ and muscle afferent inputs as well as cutaneous afferent inputs to the neurons—underlie the brainstem mechanisms contributing to deep pain, and may also explain the poor localization, spread, and referral of pain that are typical of pain conditions involving the TMJ and associated musculature, such as TMD.

These pain referral mechanisms depend not only on the convergent afferent input patterns of nociceptive neurons, but also on the so-called neuroplasticity that may be generated in the neurons by these inputs as a result of injury or inflammation (Figure 2). Some of the afferent inputs appear to be “unmasked” in pathophysiological situations and become more effective in exciting the nociceptive neurons; thus pain is perceived as coming from the tissues supplied by these afferents. In their article Hargreaves and Keiser have highlighted the dynamic state of the nervous system and the clinical implications of this dynamic or plastic state. The plastic state of the nervous system is exemplified in the neuroplasticity that can be manifested in brainstem nociceptive neurons as a result of nociceptive afferent inputs evoked by the injury or inflammation. It involves, in particular, the release of excitatory amino acids that act via NMDA receptor mechanisms to induce a cascade of intracellular events in the neurons. It has far-reaching effects beyond pain referral and

Sensory Inputs

- Facial skin
- Oral mucosa
- Tooth
- Cranial vessels
- Muscle
- TMJ

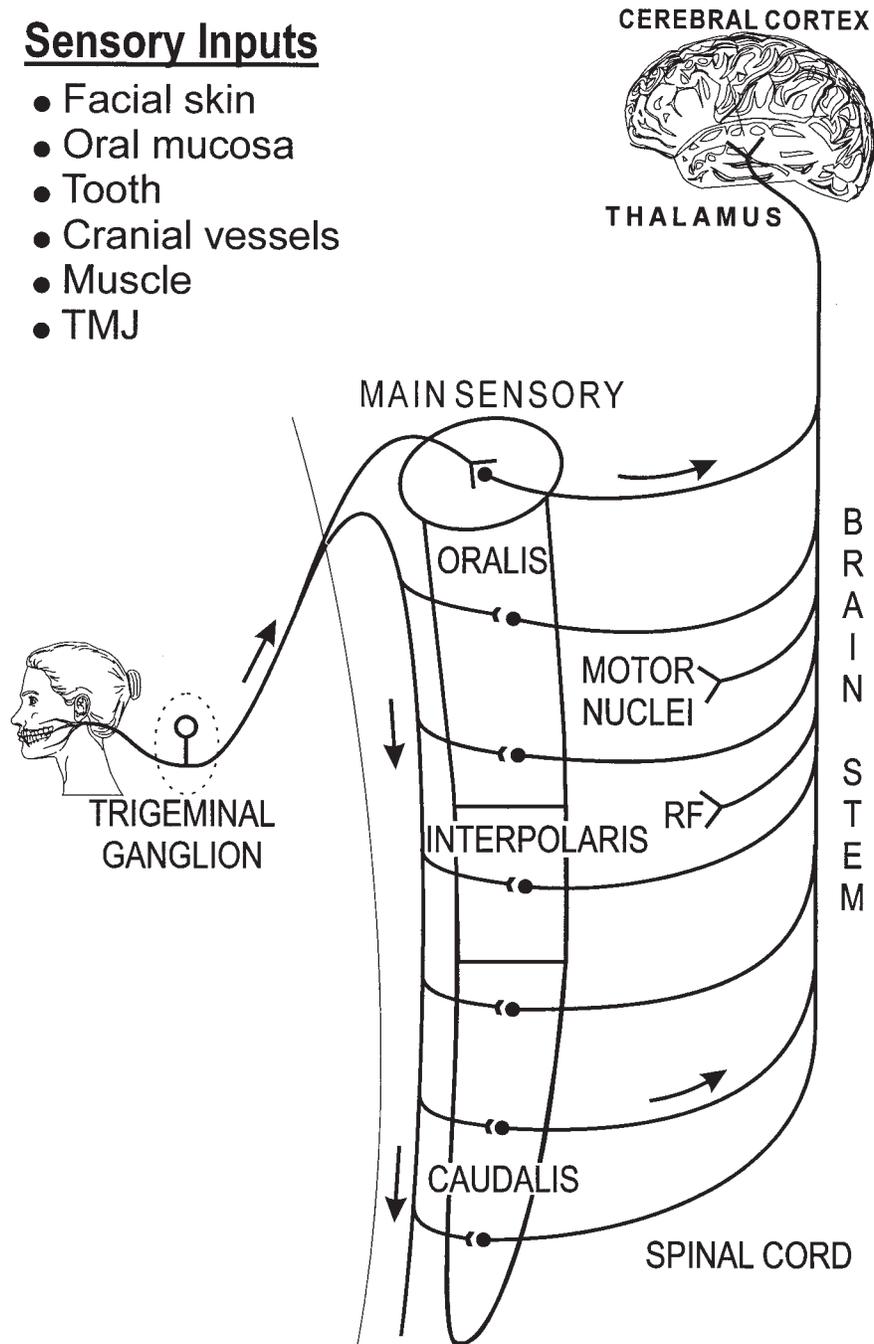


Figure 1. Major somatosensory pathway from the face and mouth. Trigeminal (V) primary afferents have their cell bodies in the trigeminal ganglion and project to second-order neurons in the V brainstem sensory nuclear complex. These neurons may project to neurons in higher levels of the brain (for example, in the thalamus) or in brainstem regions such as cranial nerve motor nuclei or the reticular formation (RF). Not shown are the projections of some cervical nerve and cranial nerve VII, IX, X, and XII afferents to the V brainstem complex and the projection of many V, VII, IX, and X afferents to the solitary tract nucleus. TMJ: temporomandibular joint. (Reprinted with permission from Sessle BJ. Acute and chronic craniofacial pain: brainstem mechanisms of nociceptive transmission and neuroplasticity, and their clinical correlates. *Crit Rev Oral Biol Med* 2000;11:57-91.)

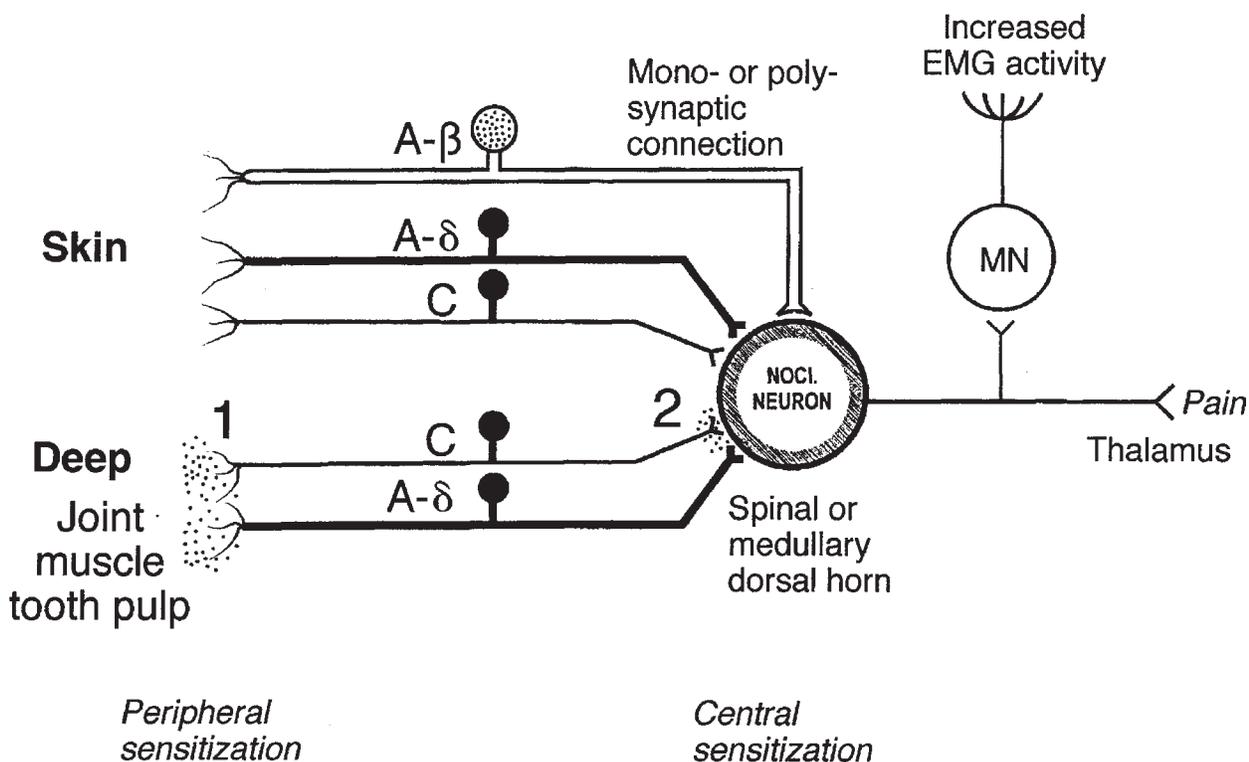


Figure 2. Convergence of primary afferent inputs from cutaneous and deep tissues to a nociceptive neuron in trigeminal subnucleus caudalis (medullary dorsal horn) or spinal dorsal horn. Injury or inflammation of deep tissues, for example, (1) can lead to an increased excitability of the peripheral endings of A-delta and C-fiber primary afferent endings in the tissues (“peripheral sensitization”). It can also produce a nociceptive afferent input into the dorsal horn that produces (2) an increased excitability of the nociceptive neuron (“central sensitization”). This central sensitization results in changes in the neuron’s properties, such as enlargement of its receptive field, reduction of its activation threshold, and increase of its response magnitude and spontaneous activity. Since such neurons project to higher brain centers (for example, thalamus) involved in the processing of pain as well as to local reflex centers, this sensitization process may lead to increased pain (for example, hyperalgesia, allodynia) and a number of other changes, such as increased excitation of motoneurons (MN) that results in an increase in muscle (EMG) activity. (Modified with permission from Hu JW. Neurophysiological mechanisms of head, face and neck pain. In: Vernon H, ed. The cranio-cervical syndrome: mechanisms, assessment and treatment. Oxford: Butterworth-Heinemann, 2000:31-48.)

spread since neuroplasticity is manifested as an increase in neuronal excitability and reflects what has been termed a “central sensitization” of the nociceptive neurons.

The neuroplastic alterations in the nociceptive neuronal properties, and in the reflex neuromuscular changes and other behavioral activities that may be induced by injury or inflammation, represent mechanisms that along with peripheral sensitization (see above) can explain the allodynia and hyperalgesia as well as pain spread and referral that characterize several craniofacial pain conditions. This is consistent with the clinical examples given by

Hargreaves and Keiser. Another example is TMD, since these neuroplastic changes can also explain the increased pain sensitivity (that is, hyperalgesia) and lowered threshold for evoking pain (that is, allodynia) as well as the diffuse, often referred, character of TMD pain. The painful limitation of mandibular movement that is so characteristic of TMD may also be explained by the reflex neuromuscular changes accompanying the nociceptive neuronal neuroplasticity.

The activity of the V brainstem nociceptive neurons can be modulated by afferent inputs and by descending influences from other brainstem and

higher brain centers. Several neurochemicals, most notably gamma-amino butyric acid (GABA), serotonin (5-HT), and opioids (such as enkephalins), provide a neurochemical substrate by which many of the afferent and descending inputs can exert their inhibitory actions. The modulatory influences on the nociceptive neurons of behavioral factors, including state of alertness, attention, and distraction, are just some examples whereby descending influences operating at the V brainstem level may affect craniofacial pain. In addition, descending inhibitory influences on nociceptive neurons have been implicated as intrinsic mechanisms contributing to the analgesic effects of several procedures used to control pain, including deep brain stimulation, acupuncture, and opiate-related (such as morphine) and 5-HT agonist (such as amitriptylene) drugs. Such insights not only help explain how a number of approaches currently in use to manage pain may operate, but also hold out the promise of the development of new therapeutic approaches targeting these brain areas and mechanisms.

These various findings provide new insights into pain mechanisms, including features such as hyperalgesia and pain referral that are common in craniofacial pain conditions. This article and the accompanying one have also emphasized that the data on neuroplastic and modulatory mechanisms and their neurochemical basis are particularly relevant to many approaches currently in use for the management of pain. They are also relevant to the development of

new or improved diagnostic and therapeutic procedures aimed at manipulating peripheral afferent inputs and central processes underlying nociceptive transmission and its control within the V brainstem complex.

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