

# Plenary Session on Headache

## Craniofacial pain: Brainstem mechanisms

Barry J Sessle BDS MDS BSc PhD

**BJ Sessle.**

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This article reviews recent research advances in animals that have identified critical neural elements in the brainstem receiving and transmitting craniofacial nociceptive inputs, as well as some of the mechanisms involved in the modulation and plasticity of nociceptive transmission. Nociceptive neurons in the trigeminal (V) brainstem sensory nuclear complex can be classified as nociceptive-specific (NS) or wide dynamic range (WDR). Some of these neurons respond exclusively to sensory inputs evoked by stimulation of facial skin or oral mucosa and have features suggesting that they are critical neural elements involved in the ability to localize an acute superficial pain and sense its intensity and duration. Many of the V brainstem nociceptive neurons, however, receive convergent inputs from afferents supplying deep craniofacial tissues (eg, dural vessel, muscle) and skin or mucosa. These neurons are likely involved in deep pain, including headache, because few nociceptive neurons receive inputs exclusively from afferents supplying these tissues. These extensive convergent input patterns also appear to be important factors in pain spread and referral, and in central mechanisms underlying neuroplastic changes in V neuronal properties that may occur with injury and inflammation. For example, application of the small fibre excitant and inflammatory irritant mustard oil into the temporomandibular joint, masseter or tongue musculature induces a prolonged but reversible enhancement of responses to cutaneous and deep afferent inputs of most WDR and NS neurons. These effects may be accompanied by increased electromyographic activity reflexly induced in the masticatory muscles by mustard oil, and involve endogenous N-methyl-D-aspartate and opioid neurochemical mechanisms. Such peripherally induced modulation of brainstem nociceptive neuronal properties reflects the functional plasticity of the central V system, and may be involved in the development of headache and other conditions that manifest craniofacial pain and neuromuscular dysfunction.

**Key Words:** *Brainstem, Craniofacial, Neurons, Neuroplasticity, Pain*

### **Douleur craniofaciale : mécanismes du tronc cérébral**

**RÉSUMÉ :** Le présent article passe en revue les dernières avancées de la recherche sur les animaux qui ont permis d'identifier des éléments neuraux cruciaux localisés dans le tronc cérébral qui reçoivent et transmettent des signaux nociceptifs craniofaciaux, et quelques-uns des mécanismes impliqués dans la modulation et la plasticité de la transmission nociceptive. Les neurones nociceptifs dans le complexe des noyaux sensoriels du nerf trijumeau (V) situé dans le tronc cérébral peuvent être classifiés comme neurones nociceptifs spécifiques et neurones nociceptifs non spécifiques. Certains de ces neurones répondent exclusivement à des signaux sensoriels suscités par une stimulation de la peau du visage ou de la muqueuse buccale, et sont dotés de caractéristiques laissant croire que ce sont des éléments neuraux cruciaux impliqués dans la capacité de localiser une douleur superficielle aiguë et d'en sentir l'intensité et la durée. Cependant, de nombreux neurones nociceptifs du nerf trijumeau situé dans le tronc cérébral reçoivent des signaux convergents de fibres afférentes innervant les tissus craniofaciaux profonds (par exemple, les vaisseaux durs, les muscles) ainsi que la peau et la muqueuse. Ces neurones sont vraisemblablement impliqués dans la douleur profonde, y compris les céphalées, parce que peu de neurones nociceptifs reçoivent des signaux provenant exclusivement de fibres afférentes innervant ces tissus. Ces réseaux étendus de signaux convergents semblent aussi jouer un rôle important dans la propagation de la douleur et dans la douleur référée, et dans des mécanismes centraux sous-jacents aux changements neuroplastiques des propriétés neuronales du trijumeau qui peuvent se produire lors d'une blessure ou d'une inflammation. Par exemple, l'application d'huile de moutarde, stimulant des fibres de petit calibre par irritation et inflammation, dans l'articulation temporomandibulaire, le muscle masseter ou le muscle de la langue, induit une amplification prolongée mais réversible des réponses aux signaux des afférents profonds et cutanés de la plupart des neurones nociceptifs spécifiques et non spécifiques. Ces effets peuvent s'accompagner d'une augmentation réflexe de l'activité électromyographique induite dans les masticateurs par l'huile de moutarde, et impliquent le N-méthyl-D-aspartate endogène ainsi que des mécanismes neurochimiques opioïdes. Ce type d'induction périphérique de la modulation des propriétés neuronales nociceptives du tronc cérébral reflète la plasticité fonctionnelle du noyau trigéminé, et pourrait être impliqué dans le développement des céphalées et d'autres affections où la douleur craniofaciale et la dysfonction neuromusculaire sont présentes.

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*Faculty of Dentistry, University of Toronto, Toronto, Ontario*

*Correspondence: Dr BJ Sessle, Faculty of Dentistry, University of Toronto, 124 Edward Street, Toronto, Ontario M5G 1G6. Telephone 416-979-4921, fax 416-979-4937*

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Many of the difficulties associated with the diagnosis and management of acute and chronic pain conditions stem from uncertainties of the etiology or pathogenesis of the conditions. This report reviews recent research advances in animals that have identified critical brainstem neural elements receiving and transmitting craniofacial nociceptive inputs, as well as some of the mechanisms involved in the modulation and neuroplasticity of brainstem nociceptive transmission. Such peripherally induced modulation of brainstem neuronal properties reflects the functional plasticity of the central trigeminal (V) system, and may be involved in the development of headache and other conditions that manifest craniofacial pain and neuromuscular dysfunction.

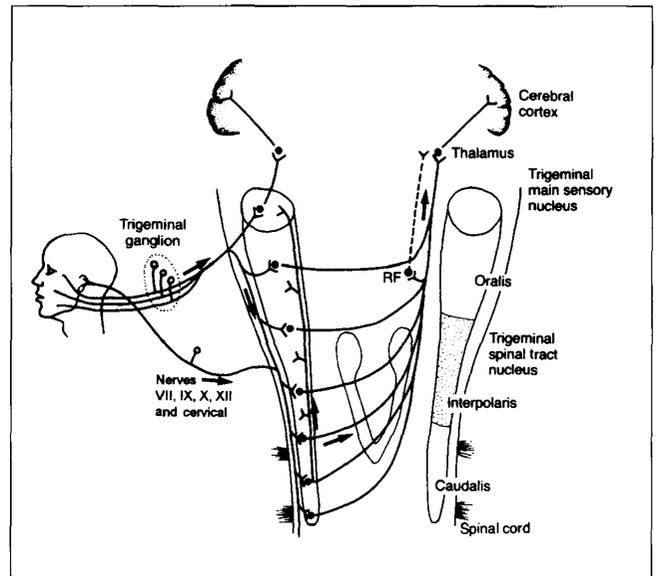
### BRAINSTEM RELAY MECHANISMS

It is well established that neural information from the craniofacial tissues innervated by the V nerve is carried through the semilunar or gasserian ganglion, where the V primary afferent cell bodies are located, and then into the brainstem. Here the primary afferent nerve fibres may ascend or descend in the V spinal tract before entering the V brainstem sensory nuclear complex and activating second-order neurones within this brainstem complex (Figure 1). Note that the V brainstem sensory complex (especially its subnucleus caudalis) may also receive afferent inputs from other cranial nerves (eg, VII, IX, X, XII) and from upper cervical nerves which, in addition, contribute afferent inputs to the upper cervical dorsal horn (1-4).

The V brainstem sensory complex can be subdivided into the principal or main sensory nucleus and the spinal tract nucleus, which comprises three subnuclei (oralis, interpolaris, caudalis). Subnucleus caudalis is the most caudal of these and is a laminated structure that extends into the cervical spinal cord and merges with the spinal dorsal horn (Figure 1); indeed, it is sometimes referred to as the 'medullary dorsal horn'. The low threshold mechanosensitive primary afferents, which carry tactile information into the central nervous system (CNS), primarily terminate in the more rostral components of the V brainstem complex and in laminae III to VI of subnucleus caudalis. Some nociceptive cutaneous and dental pulp afferents also terminate in some of these rostral components and in subnucleus caudalis (5-9).

Neurones in some of these components project to areas such as the ventrobasal thalamus, pontine parabrachial area, periaqueductal grey (PAG) and brainstem reticular formation; these neurones thus contribute to ascending nociceptive pathways involved in pain sensation or modulation. Other neurones, however, project to brainstem reflex centres or to other components of the V brainstem complex (10-15), and thereby contribute to processes associated with muscle reflexes and autonomic responses, and to more complex operant conditioning and avoidance behaviour that can be evoked by noxious craniofacial stimuli (11,13,16). Changes in cardiac, adrenal or respiratory function, for example, can be evoked by these stimuli, and appear to involve the caudal part of the V brainstem complex in particular (17).

Based on anatomical, clinical and electrophysiological observations, subnucleus caudalis is usually viewed as the principal brainstem relay site of V nociceptive information. Anatomical



**Figure 1** Major pathway for transmission of sensory information from the mouth and face. Trigeminal primary afferents project via the trigeminal ganglion to second-order neurones in the trigeminal brainstem sensory complex. These neurones then may project to neurones at higher levels of the central nervous system (for example, in the thalamus) or in brainstem regions such as the reticular formation (RF) or cranial nerve motor nuclei. Some afferents from cranial nerves VII, IX, X and XII and cervical nerve afferents may also synapse in the trigeminal complex as shown, although many VII, IX and X afferents also relay (not shown) in the solitary tract nucleus (the horseshoe-shaped structure in the middle of the diagram). Modified from reference 89

studies (4,5,18) have revealed that the small diameter afferents carrying nociceptive information from the various craniofacial tissues predominantly terminate in caudalis laminae I, II, and V and VI. Moreover, recent immunocytochemical studies of the expression of proto-oncogenes such as *c-fos* have revealed that increased *c-fos* expression occurs in caudalis neurones following noxious stimulation of craniofacial tissues including skin, temporomandibular joint (TMJ), cornea and cranial vessels (19-25). Analogous features characterize the spinal dorsal horn, which is also a laminated structure and which represents the integral component of spinal nociceptive mechanisms (18,26). Other anatomical and immunohistochemical findings that further emphasize the parallels between caudalis and spinal dorsal horn (7,26-30) include, for example, evidence that caudalis neurones projecting out of the V brainstem complex are found mainly in caudalis laminae I and III to VI and that some of these express glutamate receptor subtypes, whereas, in lamina II, the so-called substantia gelatinosa (SG), the axons of most SG neurones arborize locally within the V brainstem complex. The SG is also notable in that it represents an important interneuronal system contributing to the powerful segmental and descending modulation of somatosensory transmission that occurs in subnucleus caudalis and more rostral components of the V complex. Several morphologically distinct cell types have been described in SG. Neurones in SG contain neuromodulatory substances such as enkephalin or GABA and receive a mix of low and high threshold peripheral afferent inputs, as well as inputs from higher brain centres involved in somatosensory modulation (26-28,30-34).

Clinical and related experimental observations in animals of the effects of V tractotomy (a neurosurgical procedure used to relieve V neuralgia in humans) also point to the involvement of subnucleus caudalis in craniofacial pain mechanisms. A transection near the obex has been reported to produce a profound craniofacial analgesia (and thermanesthesia) and only a limited loss of tactile sensibility (35,36), although some more recent reports dispute the general applicability of these effects.

Electrophysiological data also support the view that subnucleus caudalis may be the essential V brainstem relay for craniofacial pain. Caudalis neurones responding to cutaneous noxious stimuli have been found in anesthetized, decerebrate or unanesthetized experimental animals (10,13,16,37). Their electrophysiological properties are noteworthy because on the basis of their cutaneous (or mucosal) mechanoreceptive field (RF) properties they can be classified into two main groups: nociceptive-specific (NS) neurones, which respond only to noxious stimuli such as pinch or heat applied to a localized craniofacial RF; and wide dynamic range (WDR) or convergent neurones, which are excited by non-noxious (eg, tactile) stimuli and noxious stimuli. The responsiveness of the NS neurones reflects a primary afferent input derived only from the small diameter, slower conducting nociceptive afferents (A delta and/or C fibres). In contrast, the sensitivity of the WDR neurones to tactile and noxious stimuli results from their input from both large diameter, rapidly conducting A fibre mechanosensitive afferents and the smaller diameter afferents. The NS and WDR neurones are concentrated in the superficial (I/II) and deep (V/VI) laminae of caudalis, and it has been documented that they project to areas (eg, pontine parabrachial area, reticular formation, ventrobasal thalamus) implicated in nociceptive transmission or control. The neurones have a graded response as the intensity of the noxious stimulus is progressively increased or as more of the RF is stimulated. This characteristic plus other spatial and temporal coding features (11) point to their role as critical neural elements involved in the ability to localize an acute pain to craniofacial skin or oral mucosa and to sense its intensity and duration. Comparable neurones occur in the spinal dorsal horn, and this close functional similarity between V subnucleus caudalis and the spinal dorsal horn, along with the morphological similarities mentioned above, have led to the designation of subnucleus caudalis as the medullary dorsal horn.

In addition to these cutaneous nociceptive neurones, subnucleus caudalis also contains low threshold mechanoreceptive (LTM) neurones, especially in its laminae III/IV where many of the low threshold mechanosensitive primary afferents terminate. These LTM neurones are activated by light tactile stimuli applied to their localized RF, and they have properties comparable with the predominant neurone type found more rostrally in the V brainstem complex. The rostral and caudal LTM neurones do not respond to noxious cutaneous stimuli and are considered the essential brainstem elements involved in the perception of craniofacial touch.

Despite the obvious role of subnucleus caudalis in craniofacial pain mechanisms, the rostral components (subnuclei interpolaris and oralis) of the V spinal tract nucleus have also been recently implicated in these mechanisms (12,13,38). These ros-

tral components project to some of the same areas that represent the projection sites of caudalis neurones and that are implicated in nociceptive transmission or its modulation. It has also been shown that stimulation of these modulatory sites can suppress rostral V neurone activity (39) and, consistent with evidence of opioid-containing terminals and opiate receptors in these rostral components, that injection of analgesic chemicals such as morphine into the rostral components can suppress nociceptive behaviour (40). Moreover, tooth pulp as well as cutaneous nociceptive afferents may terminate in the rostral components (5-9), and nociceptive neurones with an RF usually localized to intraoral or perioral regions have been documented in subnuclei interpolaris and oralis (38,41-43). In addition, caudalis lesions may not completely eliminate all reflex or behavioural responses to noxious orofacial stimuli, whereas rostral lesions may interfere with pain behaviour evoked by noxious stimuli applied to intraoral or perioral tissues (44-46). These findings strongly suggest that the rostral components of the V spinal tract nucleus are involved in craniofacial pain processes, especially those related to intraoral and perioral nociceptive mechanisms. In addition, the distinctive response of oralis nociceptive neurones to algescic chemicals such as formalin have led to the suggestion that subnucleus oralis may be more involved in processing nociceptive signals of short duration whereas subnucleus caudalis may be involved in processing more tonic nociceptive information (38).

#### CONVERGENCE OF AFFERENT INPUTS

Almost 50% of the WDR and NS neurones in subnucleus caudalis of cats and rats receive exclusively craniofacial cutaneous (or mucosal) afferent inputs, and these cutaneous nociceptive neurones are considered to be essential elements in the ability to localize and discriminate superficial pain in the craniofacial region (47-49). However, most of the caudalis neurones responding to cutaneous noxious stimulation can also be excited by electrical or natural stimulation of afferents supplying the dental pulp, cranial vessels, jaw and tongue muscles, or the TMJ; in contrast, LTM neurones typically respond only to cutaneous stimuli (47-54).

Several lines of evidence suggest that TMJ or muscle afferent-evoked responses in caudalis nociceptive neurones reflect predominantly nociceptive afferent inputs (55). In addition, *c-fos* expression in neurones of lamina I and V of subnucleus caudalis and C1 to C2 dorsal horn can be induced by injection of the small fibre excitant and irritant chemical mustard oil into deep craniofacial tissues (24). Because very few caudalis neurones respond only to stimulation of TMJ or muscle afferents, the extensive convergent inputs from TMJ and muscle afferents to cutaneous nociceptive neurones in subnucleus caudalis may explain the poor localization, spread and referral of pain that are typical of pain conditions involving deep tissues such as the TMJ and associated musculature (56-58). This extensive convergence is also consistent with analogous findings in the spinal somatosensory system and the convergence theory of referred pain.

The poor localization of pain in most toothaches and headaches and the frequent occurrence of pain referral in these conditions may also be explained by analogous convergence patterns from tooth pulp and cranial vessel afferents. For example, most

of the neurones in the V brainstem complex that can be excited by stimulation of cranial vessel afferents are WDR or NS neurones with a cutaneous RF involving the ophthalmic division (52,53); the predominant periorbital RF of these neurones is consistent with the common referral patterns of vascular cephalic pain to this region of the head. There is also extensive convergence in subnucleus caudalis from non-V afferents, eg, around 50% of the cutaneous nociceptive neurones can be excited by several other cranial nerve afferents and by upper cervical nerve afferents (47,55). Thus, a physiological basis exists to explain the referral of pain between sites innervated by the V nerve and these non-V innervated sites.

Some of the convergent afferent inputs, a proportion of which may be 'relatively ineffective' because they can be documented only by electrical stimulation of peripheral sites, may also become 'unmasked' or 'strengthened' due to injury or inflammation (26,59-61) and may be involved in the V brainstem neuroplastic changes that can be induced by these pathophysiological conditions. These changes will be outlined in the final section.

#### **MODULATION OF BRAINSTEM NOCICEPTIVE TRANSMISSION: NEUROCHEMICAL MECHANISMS**

The intricate organization of each component of the V brainstem complex, plus the variety of inputs and interconnections of each, provide the basis for numerous interactions between the various inputs derived from peripheral or intrinsic brain regions. Examples include the interneuronal system within the SG of subnucleus caudalis, the ascending modulatory influence of caudalis on more rostral neurones within the V brainstem complex (14,62), and the descending inputs to rostral and caudal components of the V brainstem complex from the cerebral cortex, PAG, nucleus raphe magnus and other brain centres. These modulatory processes use a variety of endogenous neurochemical substances (13,26,32,34,63), some of which underlie the facilitatory influences on nociceptive transmission (eg, substance P, N-methyl-D-aspartate [NMDA]), whereas others primarily exert inhibitory influences (eg, enkephalin, GABA, galanin, serotonin) that may involve presynaptic or postsynaptic regulatory mechanisms.

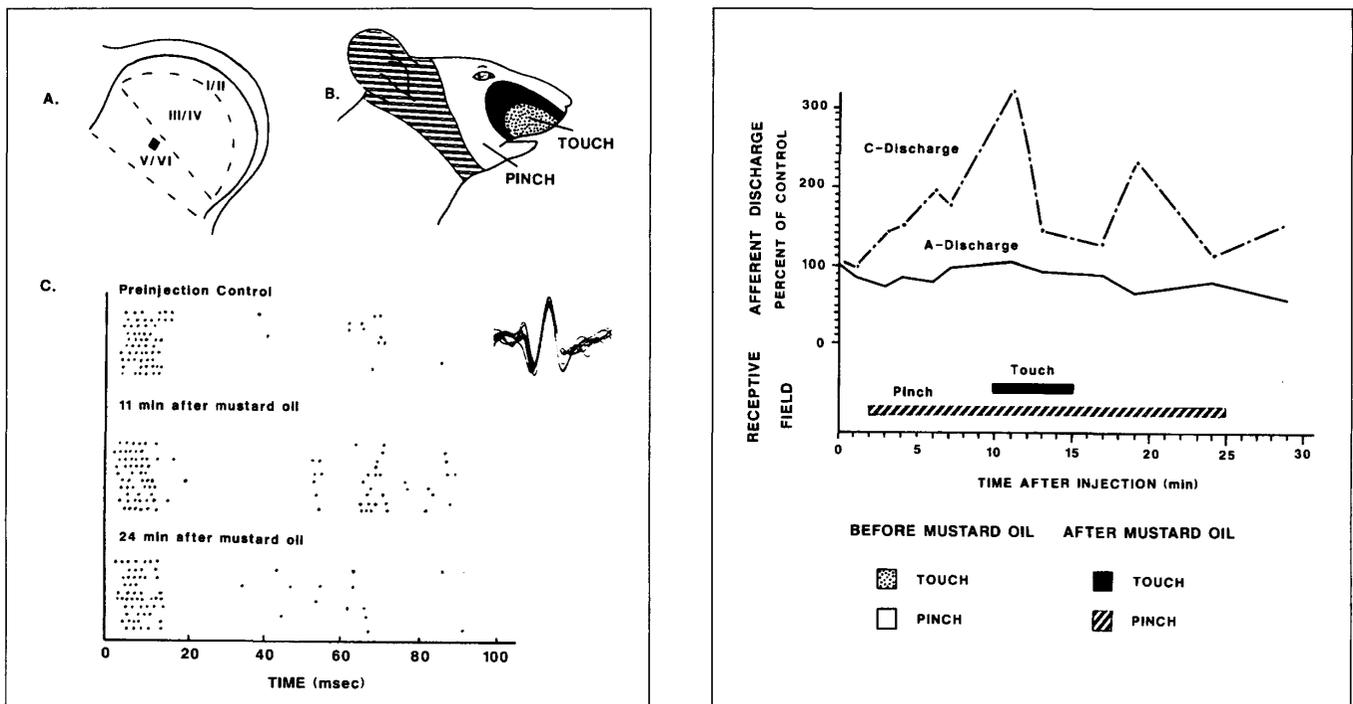
The central endings of small diameter, presumed nociceptive, primary afferents within caudalis contain certain neuropeptides and amino acids which may be involved in transmitting the nociceptive signals from the primary afferents to second-order V nociceptive neurones. An important role for the neuropeptide substance P has been suggested from immunocytochemical, iontophoretic and electrophysiological studies (7,26,31,64,65). Substance P is found in small diameter afferents (the spectrum of afferents carrying nociceptive information) supplying cutaneous and deep tissues and in their ganglion cell bodies, and has been implicated in processes related to peripheral injury and inflammation (66,67). However, it also plays a role in nociceptive transmission within the CNS. Substance P is concentrated in afferent endings in the superficial and deep laminae of subnucleus caudalis (and the spinal dorsal horn) where the nociceptive neurones predominate. Noxious craniofacial stimulation is reported to result in the release of substance P within caudalis, presumably from the nociceptive afferent terminals within the subnucleus, and substance P is especially effective in producing

a sustained and long excitation of caudalis nociceptive neurones when applied microiontophoretically.

The excitatory processes underlying nociceptive transmission appear to involve several other endogenous neurochemicals, such as amino acids and somatostatin (7,26,31,64,65). Anatomical and immunohistochemical evidence, for example, points to a role for glutamate in V and spinal nociceptive mechanisms: first, there are high concentrations of glutamate binding sites in the V subnucleus caudalis and spinal cord dorsal horn (27,32); second, nociceptive neurones, including V brainstem neurones receiving pulp afferent inputs, can be activated by glutamate (31,64); and third, glutamate has been localized in rat pulp afferents peripherally and in the central endings of afferents in the V brainstem complex (68,69). Mechanisms involving the NMDA receptor, an ionotropic receptor subtype of the excitatory amino acid receptor family, and non-NMDA receptor mechanisms have been specifically implicated in nociceptive transmission and, as noted below, central sensitization (26,31,32,70-72).

Space limitations do not permit an extensive outline of the many other endogenous neurochemicals that can modulate nociceptive transmission, but opioids must be mentioned because they have been the most extensively studied in relation to the V brainstem complex. Systemically administered opiate-related drugs produce analgesia mainly through an action in the CNS (although a peripheral action now also appears likely [73]). Mu, delta and kappa opiate receptors and receptor-selective opioid peptides, although widely distributed in the CNS, are concentrated in several sites, including the PAG, amygdala, anterior cingulate cortex, and spinal dorsal horn and V subnucleus caudalis (33,34,63). All three opiate receptors have been implicated in the modulation of nociceptive processes, some exerting facilitatory effects, others inhibitory influences. In the latter case, for example, the analgesia produced by the microinjection of certain opioids at these intracerebral sites appears to involve activation of descending antinociceptive pathways that originate in these sites, and these descending inputs can inhibit nociceptive transmission at the level of the spinal cord and V brainstem nuclei (13,34,63,74). Analgesia and suppression of nociceptive transmission can also be induced by applying opioids directly to the spinal cord or V brainstem complex, presumably by acting on opiate receptors related to these descending or other inputs or to endings of opioid-containing neurones intrinsic to the spinal dorsal horn or V subnucleus caudalis (eg, in SG).

In the V system, evidence that endogenous opiate-related mechanisms are involved in modulating nociceptive transmission includes the following: endogenous opioids appear to be involved in reducing the increases in electromyographic (EMG) activity induced by noxious craniofacial stimuli (75,76); some of the suppressive effects of PAG and nucleus raphe magnus stimulation on the jaw-opening reflex and V brainstem nociceptive neurones can be reversed by administering the opiate antagonist naloxone (39,77); noxious craniofacial stimulation can enhance opioid gene expression in V subnucleus caudalis (78) and the nociceptive-related expression of *c-fos* in subnucleus caudalis can be reduced by opioid agonist drugs such as morphine (as well as by other chemical antagonists to excitatory amino acids or substance P) (23,25); morphine microinjected into subnuclei



**Figure 2)** Effects of the application of 5% mustard oil injected into the deep masseter muscle on the cutaneous receptive field properties of a caudalis wide dynamic range neuron. **Left** The neuron was recorded in laminae V/VI of subnucleus caudalis (A). Its mechanoreceptive field and part of its response resulting from C fibre activation are shown (B). A dot raster display (each dot represents one evoked neuronal spike) of its A fibre and C fibre evoked discharges produced by a series of electrical stimuli applied to its mechanoreceptive field before and after the mustard oil application is shown (C). **Right** The time course of this effect is presented. Before application of the mustard oil, the neurone's mechanoreceptive field involved a cutaneous central zone (stippled) on the upper lip from which the neurone could be activated by tactile, pressure and pinch stimuli, and a surrounding zone (black and white) of the ipsilateral facial skin for which pinch was the only effective stimulus (B). Within 3 mins after application of the mustard oil into the masseter, the pinch zone had expanded to involve the striped region in B. This expansion lasted approximately 23 mins; a more transient expansion occurred in the touch zone to involve the region outlined by the black region in B. The time courses of these expansions are also shown on the right. Reproduced with permission from reference 43

caudalis (79) or oralis (40) can reduce responses to noxious facial stimuli; morphine, enkephalin or their agonists/antagonists micro-injected or iontophoretically applied within subnucleus caudalis may modulate the activity of caudalis nociceptive neurones (64, 80,81); enkephalins and opiate receptor sites are, as noted above, concentrated in subnucleus caudalis (26,30,32-34,63); and opioids can modulate the release of substance P from subnucleus caudalis (65,82). These opioid-related effects, as well as other endogenous neurochemical mechanisms, may underlie nociceptive neuromodulatory influences intrinsic to the CNS. In addition, they provide the neurochemical substrate for the analgesic action of several therapeutic procedures that relieve pain, including opiate-related drugs and deep brain stimulation, and therapies involving stimulation of sensory inputs. This sensory stimulation can result in suppression of nociceptive transmission and thus contribute to the analgesic efficacy of procedures such as acupuncture and transcutaneous electrical nerve stimulation (34,83).

#### NEUROPLASTIC EFFECTS OF PERIPHERAL TRAUMA AND INFLAMMATION

While nociceptive transmission in the V brainstem complex and spinal dorsal horn may be suppressed by procedures associated with activation of peripheral afferent inputs, the excitability of V brainstem neurones also may be modulated by alterations to

the peripheral afferent inputs to the V complex that may result from inflammation or trauma. These alterations may represent an enhanced sensory input, as in direct stimulation of peripheral nerves by an injury or inflammation, or a decreased input, as may occur through nerve damage resulting in deafferentation.

In trauma and inflammation, for example, peripheral phenomena related to the release and spread of neurochemical substances have long been considered to underlie the heightened sensitivity and spread of pain from the site of injury and inflammation (66,67). However, if peripheral phenomena are experimentally bypassed so that the peripheral sensitization of nociceptive afferent endings does not occur, injury or inflammation can nonetheless lead to prolonged RF expansions and heightened excitability of central neurones in nociceptive pathways, as well as increased *c-fos* expression and enhanced expression of endogenous opioid genes (26,59-61,70,71). For example, in the rat V system, injection of mustard oil (a small fibre excitant and inflammatory agent) into deep tissues, such as the masticatory muscles or TMJ, can induce *c-fos* expression in subnucleus caudalis (24). It can also induce expansion of the cutaneous RF and enhance responses of caudalis and oralis nociceptive neurones to cutaneous stimuli (Figure 2); these RF and response alterations can be replicated by by-passing peripheral phenomena through the use of high threshold stimulation of hypoglossal nerve afferents

(43,75,76,84). Such changes in the V brainstem complex may occur within minutes and can last several minutes or longer, and may be accompanied by enhanced EMG activity in jaw muscles. Cutaneous application of formalin also can evoke caudalis or oralis activity and overt nociceptive behaviour of the animal (38,40). While this activity may be quite prolonged for some neurones and suggestive of a sustained increased excitability, there is controversy about the extent to which the formalin-induced prolonged activity depends on afferent input (38,85).

These neuronal alterations in RF and response properties induced by nociceptive inputs have been considered to reflect a 'functional plasticity' or 'central sensitization', and have been explained (26,59-61) in terms of an 'unmasking' or 'strengthening' centrally of convergent afferent inputs to the neurones. It has also been recently proposed that enhanced nociceptive input from the injury site may result in excessive depolarization of the central neurones that promote excitotoxicity and loss of inhibitory mechanisms (26,86). These neuroplastic changes are viewed as important processes underlying the development and maintenance of chronic pain as well as acute pain associated with injury and inflammation. Both neuropeptide (eg, substance P) and excitatory amino acid receptor mechanisms appear to be involved in these processes. For example, both NMDA and non-NMDA receptor mechanisms underlie the involvement of excitatory amino acids in nociceptive processing (31,32,72). Findings that NMDA receptor mechanisms in particular appear to be very important in the central sensitization process have led to suggestions that NMDA antagonists may be useful as analgesics and in the treatment of persistent injury and pain (26,70,87). NMDA antagonists have been shown to be especially effective in preventing RF expansion and hyperexcitability of nociceptive neurones in the spinal dorsal horn and subnucleus caudalis induced by inflammatory conditions or by C fibre strength electrical stimulation of afferent nerves (26,59,75,76). These antagonists also reduce the flexion reflex produced by application of the small fibre excitant and inflammatory irritant mustard oil to skin (70) and the mustard oil-induced enhancement of jaw muscle EMG activity (75,76). In addition to the NMDA and non-NMDA receptor subtypes, several second messenger systems, such as nitric oxide and protein kinase C, may also be involved in this central sensitization process (31,72).

In the V system, application of mustard oil to the rat TMJ can evoke increases in EMG activity of both the jaw-opening (eg, digastric) and jaw-closing (eg, masseter) muscles (75,76), reflexes that have been shown to depend on a relay through subnucleus caudalis (88). Indeed, mustard oil can induce neuro-

plastic changes in the RF and response properties of caudalis neurones with a time course comparable with that of induced EMG changes (75). Moreover, a central opioid depressive effect may be 'triggered' by mustard oil injection because the intrathecal or systemic administration of the opiate antagonist naloxone can 're-ignite' the EMG activity and neuronal RF changes in caudalis, but only if the naloxone is administered in conjunction with mustard oil (75,76, unpublished data). These findings suggest that a nociceptive afferent input, triggered in this case by the inflammatory irritant mustard oil, evokes neuronal activity in subnucleus caudalis and associated neuromuscular changes, but that these neural changes are limited by the recruitment of a central opioid inhibitory mechanism. The findings receive support from reports of the up-regulation of opioid expression in subnucleus caudalis and spinal dorsal horn following noxious stimulation (34,71,78).

The neuroplastic changes outlined above are not restricted to alterations in the cutaneous RF properties but are also reflected in changes in the deep RF properties of V nociceptive brainstem neurones. If mustard oil is injected into deep craniofacial tissues such as the masticatory musculature, the threshold for activation of neurones by peripheral afferent inputs is lowered, and an expansion of **both** the deep and the cutaneous components of the RF of caudalis nociceptive neurones receiving superficial and deep orofacial and/or cervical nociceptive inputs occurs (43,75, 76,84). In contrast, mustard oil applied to facial skin may be effective in inducing analogous changes only in the cutaneous RF of the neurones.

These neuroplastic alterations in nociceptive neuronal properties and in associated neuromuscular and behavioural activity may explain many features that characterize several craniofacial pain conditions. For example, the allodynia, hyperalgesia, paraesthesia or dysesthesia that can occur after inflammation, trauma or neural injury in the craniofacial region may involve such neuroplastic changes (26,60,61,70,75,86). Hyperalgesia is also a characteristic of temporomandibular disorders, and in these conditions may be accompanied by diffuse pain that is often referred and by painful limitation of mandibular movement (56-58). These features can be explained by peripheral sensitization and thereby the lowered threshold of peripheral nociceptors that may occur from peripheral damage to deep tissues, and by the central sensitization of convergent afferent inputs to nociceptive V brainstem neurones. In addition, changes in EMG activity reflexly induced in both jaw-opening and jaw-closing muscles as a consequence of painful craniofacial stimulation may also contribute to the limitation of movement.

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