Convergence of Cervical and Trigeminal Sensory Afferents

Elcio J. Piovesan, MD, Pedro A. Kowacs, MD, and Michael L. Oshinsky, PhD*

Address
*Jorge Manços do Nascimento Teixeira 868, São José dos Pinhais, 83005-500 Brazil.
E-mail: piovesan1@hotmail.com or piovesan@avalon.sul.com.br

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Cranial nociceptive perception shows a distinct topographic distribution, with the trigeminal nerve receiving sensory information from the anterior portions of the head, the greater occipital nerve, and branches of the upper cervical roots in the posterior regions. However, this distribution is not respected during headache attacks, even if the etiology of the headache is specific for only one nerve. Nociceptive information from the trigeminal and cervical territories activates the neurons in the trigeminal nucleus caudalis that extend to the C2 spinal segment and lateral cervical nucleus in the dorsolateral cervical area. These neurons are classified as multimodal because they receive sensory information from more than one afferent type. Clinically, trigeminal activation produces symptoms in the trigeminal and cervical territory and cervical activation produces symptoms in the cervical and trigeminal territory. The overlap between the trigeminal nerve and cervical is known as a convergence mechanism. For some time, convergence mechanisms were thought to be secondary to clinical observations. However, animal studies and clinical evidence have expanded our knowledge of convergence mechanisms. In this paper, the role of convergence mechanisms in nociceptive physiology, physiopathology of the headaches, clinical diagnosis, and therapeutic conduct are reviewed.

Introduction

The transmission and modulation of pain in the nervous system is complex and involves different pathways and levels of modulation. The activation of nociceptors from the dura mater and cranial vessels is considered to be the substrate of pain in primary headaches, such as migraine and cluster headache [1]. In these headaches, the pain frequently exceeds trigeminal innervations to the back of the head, which is territory innervated by the greater occipital nerve (GON), a branch of the C2 [2]. For example, stimulation of the upper cervical roots by posterior fossa tumors [3], direct cervical roots [3], infratentorial dura mater [4], and subcutaneous tissue innervated by the GON [5••] produces frontal head pain. These clinical features suggested an overlap between trigeminal and cervical sensory afferents projections in the central nervous system (CNS), probably in the upper cervical segments such as the trigeminal nucleus caudalis (TNC).

The meninges and cranial vessels are richly innervated by nociceptors (C-fibers and α-δ fibers) from the first division of the trigeminal nerve. Stimulating these fibers induces the release of neuropeptides, such as substance P (SP) [6], calcitonin gene-related peptide (CGRP) [7], and neurokinin A. These neuropeptides induce cell activation within the medullary dorsal horn of the TNC [8–11] that extends to the C2 spinal segment [9,10] and within the dorsolateral area (DLA), which contains the lateral cervical nucleus (LCN) [12,13]. This activation occurs within the superficial lamina (I and II) of the TNC, where many of the afferents synapse on projection neurons to other brain stem sites or the thalamus [14]. Upper cervical root stimulation (*ie,* GON manipulation) produces changes in the TNC [15,16] and LCN [17] neurons. Moreover, the LCN also receives input from other receptive fields, which included some parts of the arm and trunk [18]. This is the reason why some headaches are associated with limb pain [18]. The authors have described a patient with migraine who showed recurrent extratrigeminal stabbing and burning sensation with allodynia on different parts of the body [19]. These features support the view that the perception of cranial pain is caused by a functional continuum between trigeminal and cervical fibers that converge on neurons in the TNC and upper cervical segments [15]. The TNC also receives afferents from the autonomic nervous system (vagus nerve) [20,21] and the hypoglossal nerve [22].

To review this convergence mechanism, the authors of this paper used published reports of referred pain, trigeminocervical convergence in clinical studies, animal research that used headache and other pain models, and therapeutic responses to blocking the trigeminal afferents or the GON.

Basic Science Evidence

The evidence for convergence between trigeminal and cervical nociception in the TNC is from electrophysiologic studies and other methods of detecting neuronal

activation. These include the measurement of c-fos with immunohistochemistry, metabolic activity with 2-deoxyglucose, and single-cell electrophysiologic techniques. The studies are based on animal headache models, which provide anatomic and physiologic knowledge of cranial nociceptive pathways.

Immunohistochemical detection of the protein product fos of the c-fos immediate-early gene

Electrical stimulation of the superior sagittal sinus (SSS) in cats and rats has provided a useful means to study trigeminal vascular pain mechanisms. SSS stimulation produces neuronal chances within the TNC and medullary dorsal horn, which increases c-fos immediate-early gene expression. Electrical stimulation over the SSS induces fos-positive cells in lamina I and II of the medullary dorsal horn of the upper cervical spinal cord [10]. In model experiments using macaca nemestrina, electrical stimulation over the SSS produced expression of fos-positive cells in the caudal superficial lamina of the trigeminal nucleus and in the superficial lamina of the dorsal horn at the C1 level of the upper cervical spinal cord [23]. Because of the close anatomy of cranial structures of monkeys to humans, it is likely that the cells described in this study represent (for primates) the nucleus that mediates the pain of migraine, suggesting a convergence process [23]. Mechanical stimulation of the transverse sinus and SSS produced a predominantly ipsilateral increase in the number of fos-positive neurons in the TNC (lamina I) and upper cervical dorsal horn [24]. Other studies using mechanical and electrical stimulation of the SSS also evoked significant increases in fos-positive cells in the lamina I and II of the superficial dorsal horn of C1–C3 cervical spinal cord and TNC [25].

Using chemical stimuli (injection of autologous blood or carrageenin subdurally into the cisterna magna), Nozaki *et al.* [26] introduced fos-like positive cells in the superficial lamina of the medullary dorsal horn. Electrical stimulation of the middle meningeal artery also produces fos-positive cells in the dorsal horn of the caudal medulla (TNC) and the upper two divisions of the cervical spinal cord on the ipsilateral and contralateral sides [27].

Although the c-fos method is a good way to identify cell activation after sensory stimulation, it does not allow for the differentiation of the origin of activation of the secondary sensory neurons. Because there is an increase in c-fos positive neurons in both of these nuclei after SSS stimulation or GON stimulation, we are not able to predict the source of the sensory activation based on pattern of c-fos expression. Therefore, c-fos studies are an indirect method for identifying convergence mechanisms.

Metabolic mapping approach and other studies

Electrical stimulation over the SSS induces neuronal activation within the TNC and LCN followed by vascular changes. Blood flow and metabolic activity increases in the TNC and LCN after electrical stimulation over the SSS in cats [28]. Stimulation of a purely cervical input, such as the GON, also increases metabolic activity in both typically cervical regions of the spinal cord and in the TNC [29]. The exact nature of this activation cannot be detected using 2-deoxyglucose methods. One shortcoming of this method is that increased activity can be excitatory or inhibitory.

After stimulation, trigeminal nociceptors produce neuropeptides (*ie*, CGRP, SP, and neurokinin A) [6,7]. SP is a neurotransmitter released in the lamina I and II of the TNC and spinal cord neurons, which then can diffuse to laminas III to V depending on the intensity of the stimuli [30]. Teeth extraction of the incisor and molar induces SP release in bilateral and unilateral neurons, respectively, of the TNC and cervical spinal cord [31]. The authors of this study propose that bilateral activation occurs because the incisor tooth receives bilateral trigeminal afferents. Other studies show that bilateral activation of the TNC and LCN was not caused by multiple afferents, but by the same afferent sending bilateral projections to the TNC and LCN [27].

Electrophysiologic studies

Electrophysiologic studies are versatile methods of assessing nociceptive responses and studying the overlap between trigeminal and cervical nociception. These studies measure the progression of nociceptive responses over time in one experiment. They produce important information concerning convergent mechanisms. Time course for inducing convergence mechanisms, intensity of the stimuli, sensitization of neurons involved in sensory processing, and therapeutic actions have been studied using these methods.

The trigeminocervical reflex in humans is used to measure convergent mechanisms between trigeminal and cervical nociceptors. This method consists of electrical stimulation over the supra-orbital nerve, which produces a sternocleidomastoid muscle contraction (cervical inputs). The reflex occurs with motoneuron participation (interneurons) within the TNC [32]. This test has been used for patients with headache to assess nociceptive processing of the TNC [33].

Stimulation of nociceptive afferents from the trigeminal [8] and cervical [34] territories can produce changes that are reflected in an increase in excitability of CNS neurons. Chemical and electrical stimulation over upper cervical roots (GON) produces an increase in the excitability of the meningeal neurons, which coincides with a central trigeminal sensitization [35•]. In this study, convergent neurons were found in deep layers of the dorsal horn (lamina V–VI) that correspond with the C2 neurons (superficial layers [lamina I–II] from cervical neurons) [35•]. These data provide clear evidence of functional coupling between nociceptive meningeal afferents and cervical afferents, with central trigeminal sensitization secondary to GON stimulation.

The time course and intensity of changes in excitability in neurons that receive convergent inputs was determined by recent studies. Stimulation of the upper cervical roots (GON) produces an initial decreased excitability of the trigeminal neurons and then a subsequent increased excitability [35•]. These results are consistent with results in our laboratory in experiments using chemical stimulation of the dura (unpublished results).

Secondary sensory neurons in the TNC can receive ipsilateral and contralateral inputs from the GON or trigeminal afferents [10,35•,38]. Severe injury of trigeminal nociceptive afferents, such as extraction of the incisor tooth, produces activation in bilateral neurons of the TNC and spinal cord [31]. The bilateral activation after unilateral stimulation may correspond to the sensation of a dull and poorly localized quality of pain spread from deep somatic afferents in the trigeminocervical regions (c-fibers) [37].

Clinical Evidence

Several clinical studies have demonstrated an overlap in nociceptive processing between the trigeminal and cervical systems [3,4,38]. The authors have studied (three cases) the clinical behavior of convergence in these systems [5••]. Patients were administered upper cervical stimulation with intradermal sterile water over the GON. The intensity of the pain was mapped and measured using a visual analogue scale (VAS) during stimulation and 10, 30, and 120 seconds after stimulation: at 10 seconds after GON stimulation, all of the patients developed severe pain at the site of the injection; in two patients (case 1 and 3), the pain spread from the right GON territories to the areas innervated by the first branch of the trigeminal nerve (V1) on the ipsilateral to the intradermal injection; after 30 seconds, the pain increased and spread to the periorbital region head innervated by the trigeminal nerve (case 1). In cases 2 and 3, the intensity of the pain increased, but did not spread. These patients developed ipsilateral facial flushing and conjunctival injection and tearing, which subsided after 60 seconds; at 2 minutes after the stimulation, the intensity of the pain decreased in the ipsilateral trigeminal region and kept the same intensity in the cervical territories (case 1 and 2); in the third patient, the pain maintained the same intensity in both territories. The pain was described as lancinating with intermingled paroxysms that lasted for approximately 2 to 3 seconds. For all of the patients, the occipital pain was perceived to be more intense than the trigeminal pain. Ipsilateral occipital pain lasted an average of 4 hours and was the only pain that the second patient experienced. The time course of spread of the pain from the occipital to the trigeminal region is very fast, which is shown in the study by the authors. This process cannot be explained by central sensitization, which generally begins at least 45 minutes after the stimuli.

Using pressure algometry, the authors studied the influence of light stimulation on pain perception in the cervical and trigeminal territories in migraineurs and control subjects. Migraineurs presented a significant and persistent drop in pain thresholds in the trigeminal and cervical region after light stimulation. These results indicate that light may have a relevant role in modulating trigeminal and cervical pain perception [39].

Another headache type that displays convergence of trigeminal and cervical areas is cervicogenic headache. Cervicogenic headache is a final common pathway for several neck disorders [40]. Pain stemming from the neck usually spreads to the oculofrontal area (trigeminal region). The most characteristic features are symptoms and signs of neck involvement (such as mechanical precipitation of attack). Blocking the GON can improve these symptoms. The distribution of these symptoms over the trigeminal territory and the response after a GON block can be explained by the convergence of trigeminal and cervical afferents in the TNC or LCN.

Therapeutic Evidence

Laboratory studies

Acute abortive migraine medications used to treat primary headaches, such as sumatriptan and dihydroergotamine (DHE), can inhibit the expression of c-fos positive cells in the TNC and LCN [41,42]. Using electrophysiologic techniques, it has been shown that neurons in the TNC are inhibited by parenteral administration of DHE [43]. The pharmacologic mechanisms of the 5-HT_{1D} receptor agonist (sumatriptan) may be mediated peripherally, whether by inhibition of plasma extravasation or by direct vasoconstriction [42]. In addition, it was shown that triptans act centrally within the trigeminocervical complex. Microiontophoretic injections of ergometrine or sumatriptan into this site produced inhibition of neuronal activation from the SSS nociceptors [43].

These studies suggest that triptans, which are serotonin 5-$HT_{1B/1D}$ receptor agonists, inhibit evoked trigeminovascular nociceptive activity in the trigeminocervical complex. Sumatriptan (after blood-brain barrier disruption), eletriptan, naratriptan, rizatriptan, 4991W93, and zolmitriptan block evoked trigeminal nucleus activity [44]. Opioid receptors also are involved in cardiovascular nociception, specifically within the trigeminocervical complex. Studies using microiontophoresis determined that μ-receptor agonists inhibit neurons in the TNC post-synaptic to trigeminal afferents [45]. Valproic acid, an inhibitor of γ aminobutyric acid (GABA) aminotransferase, when applied to the rat in the trigeminocervical nociceptive models, reduced the expression of c-fos-positive cells in the TNC [46] after trigeminal stimulation. Electrophysiologic studies, combined with microiontophoresis, also suggested that GABA receptors modulate trigeminovascular nociceptive transmission in the trigeminocervical complex [47].

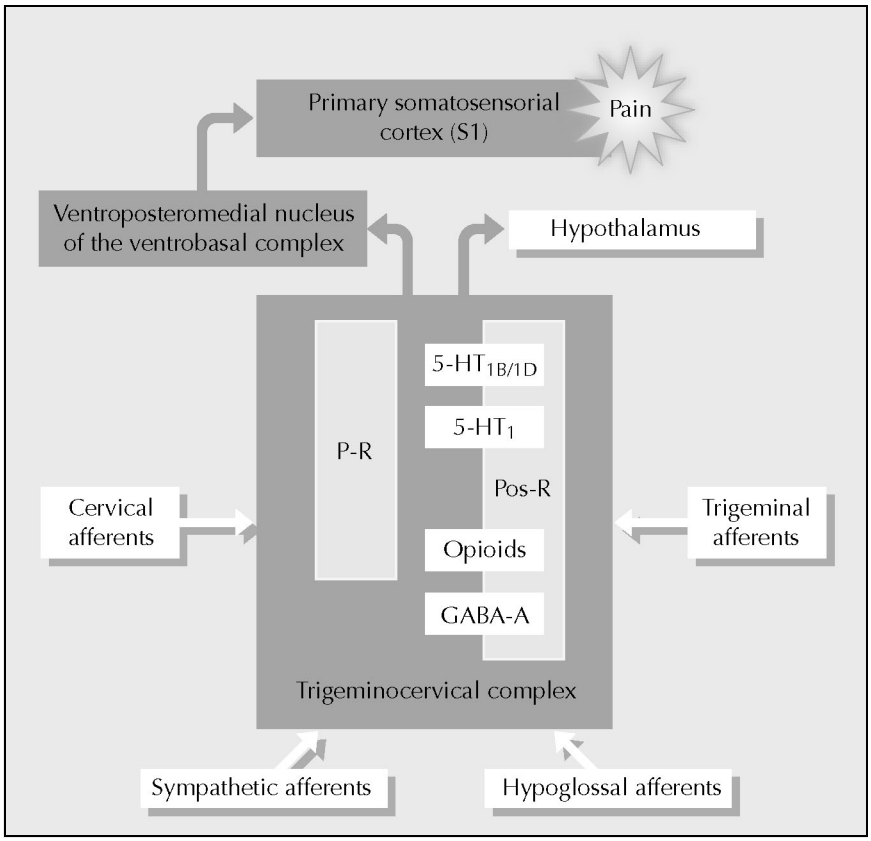

Figure 1. Convergence mechanisms and neurotransmitters involved in pain modulation. PR—prejunctional receptors; pos-R—post-junctional receptors; 5-$HT_{1B/1D}$ receptors for triptans [46]; 5-HT_1 receptors for dihydroergotamine; opioids—receptor [47]; GABA-A—receptors [48,49]; trigeminocervical complex—trigeminal nucleus caudalis and lateral cervical nucleus [10,15–17,23,44,45]; hypoglossal afferents [22]; simpato afferents [20,21].

These studies suggest that the trigeminal nociceptive system in the trigeminocervical complex is modulated by several neurotransmitter systems, such as 5-HT, GABA, opioid, and others (Fig. 1).

Clinical studies

Some headaches, in which the etiology is trigeminal activation, benefit from anesthetic blockage of the upper cervical roots (GON) [2,48–50]. This therapeutic response can be explained only by a convergence mechanism between trigeminal and cervical roots. However, other studies showed that blocking the GON did not influence migraine attacks [52] or other primary headaches [51]. Electrical stimulation of the GON or the suboccipital regions produces improvement in chronic headaches, such as cluster (unpublished data) and chronic migraine [53].

The authors' experience with GON blockage with bupivacaine 0.5% for migraine prophylaxis showed increased headache intensity for the first 30 days [54]. The migraine attacks improved after this time and this improvement was maintained for more than 60 days. Studies that used prilocaine hydrochloride 2% over the GON [55] and bupivacaine 0.5% over the GON and supraorbital nerve [56] showed reduced intensity during attacks. In an isolated study with a limited number of patients, GON blockage did not reduce the intensity of acute migraine attacks [52].

Greater occipital nerve manipulation is a good therapeutic option for some chronic headaches. Cluster headache attacks were improved after blocking the GON [49]. Patients with chronic migraine who received subcutaneous suboccipital neurostimulation showed headache improvement after activation of this device [53]. Less effective responses occurred for chronic paroxysmal hemicrania and hemicrania continua, in which GON block did not reduce the pain [51].

Those headaches that we know have an etiology restricted to the trigeminal afferents show a good response after the upper cervical roots (GON) are blocked. There is good evidence that trigeminocervical convergence mechanisms exist. GON block produced improvement of the frontal pain that occurs in some headaches with a cervical etiology. Perhaps the best example for this is that the diagnostic criteria for cervicogenic headache include significant headache improvement after GON block [40]. In a study by Piovesan *et al.* [57], patients suffering from cervicogenic headaches with chronic presentation showed a positive response after GON block.

Other Connections with Trigeminocervical Complex

Autonomic-trigeminocervical connections

The TNC is a nociceptive structure that exerts fundamental control over inputs from cervical and trigeminal nociceptors. However, it also receives other inputs that participate in head pain control. The parasympathetic system (vagus nerve), together with the TNC and LCN (trigeminocervical

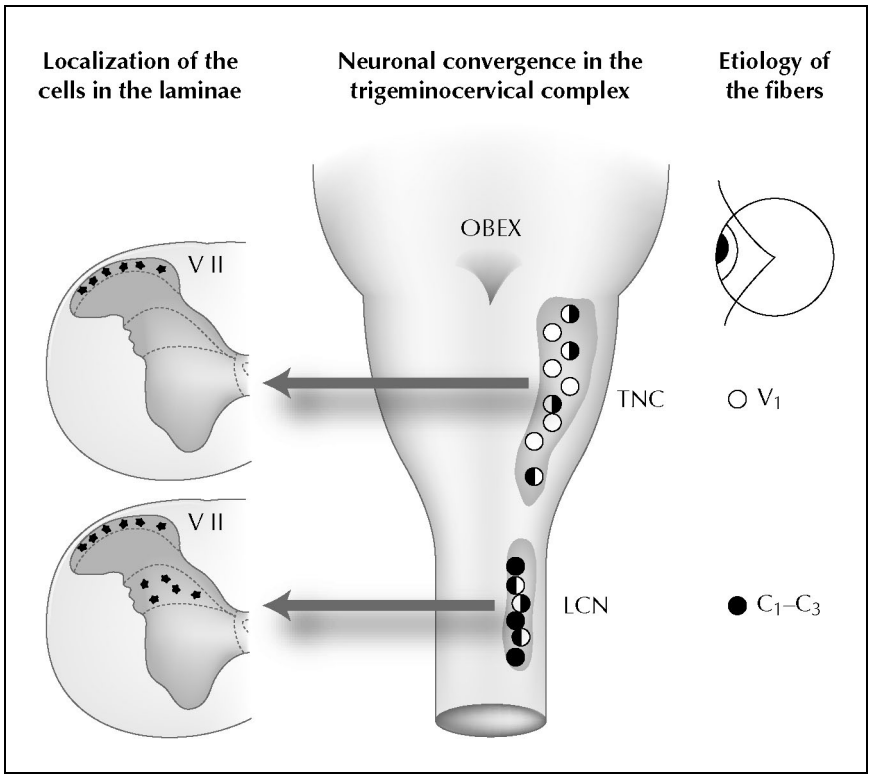

Figure 2. Anatomic and physiologic distribution of elements involved in the convergence mechanisms. TNC—trigeminal nucleus caudalis; LCN—lateral cervical nucleus; trigeminocervical complex—TNC and LCN; V_1—branch from the trigeminal first division; C_1–C_3—branch from the upper cervical roots; empty circle—secondary nociceptive neurons that receive input from the trigeminal territory; colored circle—secondary neurons that receive input from the cervical territory; partially colored circle—secondary neurons that receive inputs from the trigeminal and cervical territory (multimodal cells).

structures), could increase or decrease the pain signals. Vagus nerve stimulation produces inhibitions in the trigeminothalamic projection neurons from the TNC [58] and in tooth pulp-responsive units (trigeminal) in ventroposteromedial nucleus of the thalamus [59,60]. Low-intensity stimulations of cervical vagal afferents facilitate nociceptive reflexes such as the jaw-opening reflex [61] or the tail-flick reflex [62].

Continuous vagal nerve stimulation (VNS) for 24 hours in awake rats produced significant antinociceptive effects in a model of trigeminal pain [64]. This showed that VNS stimulation significantly inhibits activation of second-order nociceptors in the TNC and pain-related behavior on the side of the facial nociceptive stimulus during the early and late phase. Vagal afferent stimulation predominantly inhibits sensory processing in the TNC [58,65] and in the ventral posteromedial thalamic nucleus [59] (Fig. 2).

Hypoglossal-trigeminocervical

Chemical and electrical stimulation of the distal hypoglossal (12th) nerve trunk produced a significant increase in fos-positive neurons in the dorsal paratrigeminal nucleus and laminae I and II of the TNC and upper cervical dorsal horn in rats [22].

Projections from the trigeminocervical nociceptive complex

The TNC sends nociceptive information to the ventroposteromedial (nucleus of the ventrobasal complex) of the thalamus and to other medial nuclei [66]. It also relays information from the hypothalamus in the trigeminohypothalamic pathway [67], which may explain some of the premonitory symptoms that are associated with primary headaches disorders. Some studies speculate that there may be convergence of trigeminal sensory information and sensory information from other areas in the thalamus.

Conclusions

The first step of complex central modulation of cranial pain syndromes starts in the TNC and upper cervical horn. The TNC and LCN are the main nuclei that receive nociceptive information and together they form the trigeminocervical complex. These nuclei are anatomically separated, but functionally connected between the convergent mechanisms. Recent clinical and laboratory evidence suggests that this complex is involved in nociceptive modulation during migraine, cluster, and other headache attacks. Cells inside these nuclei are considered to be multimodal neurons. One multimodal cell can receive two or more inputs from distinct origins (*ie*, from the trigeminal nerve, cervical roots, parasympathetic nerve, or other nociceptive areas). These physiologic properties produce divergent symptoms, which are manifested by diffuse pain without regard to topographic anatomic nerve distribution. Some of the neurotransmitters that regulate these mechanisms include 5-HT, GABA, opioid, norepinephrine, and other substances. Understanding the anatomy, physiology, and pharmacology of convergence mechanisms may help understand the

clinical features and future treatments for headache and other facial pain.

This review shows that convergence of trigeminal and cervical afferents, which are located within the trigeminocervical complex, produce diffuse painful symptoms and are responsible for the first step in nociceptive modulation in patients with primary headaches.

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