Migraine and the Neck: New Insights from Basic Data

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The clinical presentation of pain in patients with migraine showing spread and referral of pain throughout the trigeminal and cervical innervation territories accompanied by hyperalgesia and allodynia indicates a dynamic trigemino-cervical interaction. The physiologic mechanisms may be convergence of trigemino-cervical afferents and central sensitization of trigemino-cervical neurons leading to dynamic neuroplastic changes during migraine. This review highlights the clinical phenotype and mechanisms of how nociceptive input from neck structures of the upper cervical spine are integrated into the trigemino-cervical system. The nociceptive input into the spinal cord also is subject to a modulation by segmental mechanisms in the spinal cord and by inhibitory projections from brain stem structures such as the periaqueductal gray. The functional relevance of these basic mechanisms is discussed with reference to recent studies using neurostimulation of afferent nerves aiming at pain modulation in patients with migraine.

Introduction

Patients with migraine mostly report pain that involves the front of the head in the cutaneous distribution of the first (ophthalmic) division of the trigeminal nerve. However, the pain in due course frequently exceeds the trigeminal territory as pain from the back of the head, innervated by the greater occipital nerve (GON), which is a branch of the C_2 spinal root, also is described, or it can represent the sole manifestation of pain and is accompanied by muscle hypersensitivity and hypertenderness, restrictions of movements, and hyperalgesia [1–3]. The pain often has a dull, burning quality that often hampers an exact topographic classification.

Earlier clinical observations showed that stimulation of structures in the neck, which are innervated by the upper cervical roots, elicit occipital pain sensations, but also may be perceived in trigeminally innervated dermatomes. Posterior fossa tumors [4], stimulation of infratentorial dura mater [5], direct stimulation of cervical roots [4], vertebral artery dissection [6], and stimulation of subcutaneous tissue innervated by the GON [7] may be perceived as cervical pain, but may spread to other cervical or trigeminal dermatomes.

Similarly, direct stimulation of the supratentorial dura mater leads to pain mostly referred to the first (ophthalmic) division of the trigeminal nerve [5], but also may be referred to dermatomes supplied by the upper cervical roots [8].

A mechanism that could explain these clinical and experimental findings is the trigemino-cervical interaction in terms of a convergence of trigeminal and cervical afferents on to neurones in the trigemino-cervical complex of the brain stem. These second-order neurons can be sensitized showing an increased excitability in due course, leading to clinical correlates such as hypersensitivity and allodynia. These mechanisms may play a role in the clinical phenomena of spread and referred pain whereby pain originating from an affected tissue is perceived as originating from a distant receptive field [9]. These mechanisms also could participate in the transition and maintenance from acute to chronic migraine pain states.

This review highlights basic neurophysiologic mechanisms of trigemino-cervical interaction and pain processing in the brain stem in the context of recent experimental findings using neurostimulation that may modulate pain processing and thus pain sensation.

Anatomic and Physiologic Mechanisms

Neurosurgical observations in patients showed that stimulation of trigeminally innervated intracranial structures, such as the supratentorial dura mater and large cranial vessels, evokes painful sensations regardless of the stimuli applied [10]. The dura mater is densely innervated by small-diameter A- and C-fiber afferents in the ophthalmic division of the trigeminal nerve and from afferents supplied by the upper cervical roots. This implies that the innervation of the dura mater and the afferent input from dural structures can be considered the neural substrate of head pain, particularly migraine pain.

The nociceptive inflow from the dura mater to the second-order neurone in the brain stem is transmitted through small-diameter A- and C-fiber afferents in the ophthalmic division of the trigeminal nerve through the

trigeminal ganglion to nociceptive second-order neurons in the superficial and deep layers of the medullary dorsal horn of the trigemino-cervical complex [11]. The trigemino-cervical complex extends from the trigeminal nucleus caudalis to the segments of C_2 to C_3 [12]. Ascending nociceptive pathways project in the spino-thalamic tract to supraspinal relay sites such as the thalamus and higher cortices [13].

The upper cervical spinal roots represent the sensory innervation of cranial and cervical structures, which can be sources of neck and head pain [1,14,15]. The major afferent contribution to the trigemino-cervical complex is mediated by the C_2 spinal root, which is peripherally represented by the GON [16]. Similarly, the nociceptive inflow from structures of the neck, such as vessels and dura mater of the posterior fossa, deep paraspinal neck muscles (zygapophyseal) joints, ligaments, and spinal discs are transmitted in spinal nerves of the upper cervical spinal cord to the dorsal horn and the trigemino-cervical complex [17].

A direct coupling between meningeal afferents and cervical afferents in the spinal dorsal horn recently has been described. A population of neurons in the C_2 dorsal horn was characterized as receiving convergent input from the supratentorial dura mater and the GON [11,18••].

This anatomic arrangement of trigeminal and cervical afferents from the periphery throughout the trigemino-cervical complex suggests that the afferent organization of the cranial innervation can be seen as a functional continuum. Does this arrangement also have functional implications?

Nociceptive spinal cord neurons can be sensitized due to a strong afferent stimulation by small-fiber afferents. This hyperexcitability is reflected in a reduction of the activation threshold, an increased responsiveness to afferent stimulation, an enlargement of receptive fields or the emergence of new receptive fields, and the recruitment of silent nociceptive afferents. The clinical correlates of this central hypersensitivity in patients with migraine include the development of spontaneous pain, hyperalgesia, and allodynia [19]. The hypersensitivity of the afferent synaptic input in the spinal cord is thought to be due to the stimulation-induced release of various neuropeptides, such as calcitonin gene-related peptide, or to glutamate release and action at the *N*-methyl-D-aspartate receptor, but also may be due to a decrease of local segmental spinal inhibition in response to the afferent stimulation [20].

These stimulation-induced neuroplastic changes also could be found in the neural population of the trigemino-cervical complex, which receives convergent synaptic input from the dura mater and the GON [18••]. Noxious stimulation of the dura mater was eliciting facilitated responses in the GON and vice versa. These findings highlight the potential of dura-GON-sensitive neurons in the trigemino-cervical complex to undergo a central sensitization with an increased excitability to converging synaptic inputs. This shows that dural afferents and GON afferents do not just represent an anatomic connection, but that these connections are functionally relevant in terms of mutual changes of excitability.

The mechanisms of convergence and central sensitization described previously are important to understanding the clinical phenomena of spread and referral of pain by which pain originating from an affected tissue is perceived as originating from a distant receptive field that does not necessarily involve a peripheral pathology in the cervical innervation territory [9,21•].

Beyond Pure Sensory Mechanisms: Sensomotoric Integration

It is very well known that patients with migraine often experience pain that is accompanied by suboccipital muscle stiffness and hyperalgesia. This is most likely a reflection of the central sensitization involving the efferent output to neck muscles with regard to connections between afferent neurons and motoneurons in the spinal cord. Positive feedback mechanisms of muscle efferents, such as α- and γ-motoneurons with secondary activation of Ia and II muscle spindle afferents, may be incorporated in spinal reflex mechanisms, resulting in a further increase of cervical muscle tone [22]. Activation of dural nociceptors also evokes responses in spinal motoneurons with an increase in electromyography activity in suboccipital paraspinal muscles [23]. This is in accordance with clinical and experimental data showing changes in the electromyography of neck muscles or muscle hypersensitivity in headache patients and supports our observation of an increased central excitability [2,5,24].

Central pain modulation and headache

Experimental evidence suggests that the nociceptive inflow to second-order neurons in the spinal cord and the trigemino-cervical complex is subject to a modulation by descending inhibitory projections from brain stem structures such as the periaqueductal gray (PAG), nucleus raphe magnus, and the rostroventral medulla, as stimulation of these regions produces profound antinociception [25]. Recent findings emphasize the role of the ventrolateral division of the PAG (vlPAG) in trigeminal nociception as stimulation of the vlPAG modulates dural nociception and selectively receives input from trigeminovascular afferents [26–28].

Indeed, recent functional imaging studies in patients with spontaneous attacks of right-sided migraine without aura point to a specific role of the PAG in migraine pathophysiology [29,30] (Fig. 1).

Pain Modulation: Clinical Application

The findings of the anatomic arrangement and functional interaction between trigeminal and cervical neurons on various levels of the trigemino-cervical complex are closely coupled with the therapeutic interest in modulating these

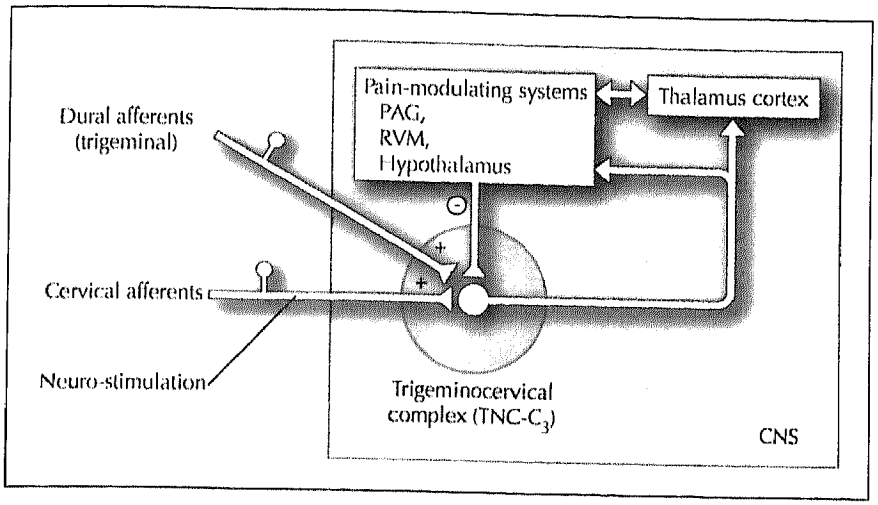

Figure 1. Schematic drawing illustrating the convergence of trigeminal and cervical afferents on to the same nociceptive second-order neuron in the trigemino-cervical complex. The convergent neuron in the trigemino-cervical complex may be sensitized as a result of an increased afferent inflow into the spinal cord by strong noxious stimuli. The nociceptive input is transmitted to supraspinal relay sites (*eg*, thalamus and cortex) and is subject to inhibitory antinociceptive projections by pain modulatory circuits in the brain stem. Pain processing on different levels also may be modulated by neurostimulation of peripheral nerves. CNS—central nervous system; PAG—periaqueductal gray; RVM—rostralventral medulla.

mechanisms. In this context, two procedures and clinical effects using blockade and stimulation of peripheral nerves are summarized.

Cervical and occipital nerve blockades

Many headache forms benefit from a blockade of the GON, including migraine [31–33]. The GON (C_2) or facet joints on various spinal levels (C_2-C_7) are the most common sites of injection [34•]. However, despite the clinical effects, it is still unclear which mechanisms determine the effect of the blockade. In certain headache syndromes, such as cervicogenic headache or headache of cervical origin, the source of pain is thought to be in structures of the upper cervical cord. A blockade of the cervical spinal nerves therefore would act as a peripheral conduction block leading to a reduction of the afferent nociceptive inflow and subsequent decrease of the central sensitization [35].

However, this does not explain how a cutaneous or subcutaneous anesthetic block in migraine patients may influence the meningeal or deep somatic muscle input, assuming that there is no peripheral pathology present that could be blocked [34•]. Thus, it may be reasonable to assume that the effect of the peripheral blockade is due to influencing central pain-processing mechanisms with regard to modulating convergent synaptic input. This arrangement in combination with the mechanisms outlined previously may explain why a suboccipital injection alleviates frontal headaches. However, more human data are needed to further corroborate this thesis [34•]. The lack of a pathophysiologic model may partly explain why various procedures using different applications (local anesthetics, steroids), doses, and sites of injection have been described. Differences in study design and patient selection may further contribute to the heterogeneous success rates in the different headache syndromes studied [34•].

Spinal cord and peripheral nerve stimulation

It is very well known that a non-painful stimulation of peripheral nerves can elicit analgesic effects [36]. This phenomenon has been used in certain pain syndromes using transcutaneous electrical stimulation, spinal cord stimulation, dorsal column stimulation, or subcutaneous stimulation [37].

In a recent publication using functional imaging (PET), eight patients with chronic migraine (more than 15 attacks/month) with a history of cervical headache were observed. They responded to non-painful, high-frequency stimulation (50–120 Hz) of afferents in the GON using bilaterally implanted neurostimulators. The neurostimulators were implanted subcutaneously adjacent to the GON. The patients were analyzed in different states: during stimulation when the patient was pain-free, during non-stimulation with pain and autonomic features, and during partial activation of the stimulator with different levels of paraesthesia [38••]. The stimulation decreased the pain ratings of the patients by 75% within the first 30 minutes or even to complete pain abolition. Pain consistently occurred after turning off the device. The stimulation elicited a sensation of paraesthesia within the dermatome of the GON, which was used as a monitor of a valid stimulation. The pain state elicited changes in cerebral blood flow in the dorsal rostral pons, anterior cingulate cortex, and cuneus, which are sites that are known to be activated during migraine [29,30]. The activation pattern in the dorsal rostral pons is highly suggestive of a role for this structure in the pathophysiology of chronic migraine and it may be a locus of neuromodulation by suboccipital stimulation. In the paraesthesia state during neurostimulation, anterior cingulate cortex and left pulvinar activation was observed, indicating that suboccipital neurostimulation can modulate activity in the left pulvinar (Fig. 2A–2C).

The suboccipital stimulation in this study is similar to the stimulation of the spinal cord and dorsal column stimulation [37,39] during which segmental circuits or ascending tracts of the spinal cord are stimulated. The therapeutic effect is restricted mostly to the spinal cord segment of the stimulated afferents [39,40].

The mechanisms of these analgesic effects within the trigemino-cervical complex and supraspinal structures are unclear. The projection fibers within the spinal ascending

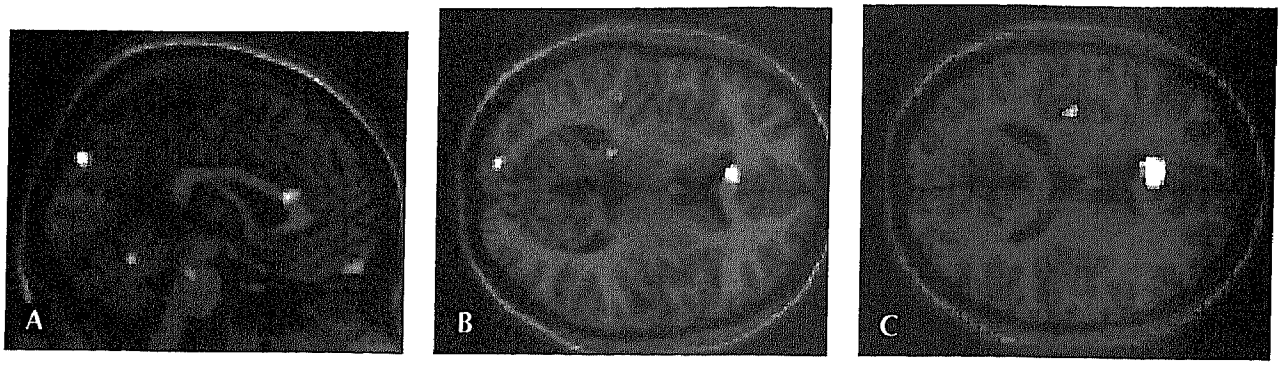

Figure 2. Statistical parametric maps of functional imaging data (positron-emission tomography) illustrating changes in cerebral blood flow (rCBF) during different states of peripheral (suboccipital) neuromodulation. **A**, During the pain state, changes in rCBF can be observed in the dorsal rostral pons, anterior cingulate cortex, and cuneus. **B**, Suboccipital neurostimulation with concomitant paraesthesia elicits changes in rCBF in anterior cingulate cortex and **C**, the pulvinar nucleus of the thalamus. *Data adapted from* Matharu *et al.* [38••].

tracts represent only a minority, whereas propriospinal neurons and interneurons of the spinal dorsal horn outnumber projection neurons [41]; thus, the segmental neural network may represent the site of this neuromodulatory effect [42]. It has been suggested that the somatosensory neurostimulation of afferent A-β fibers blocks the nociceptive transmission on a segmental level [40–44].

There is recent experimental evidence indicating that supraspinal structures (*eg*, the PAG) also are involved in mediating the antinociceptive effects of peripheral neurostimulation [45,46]. A microdialysis study on transmitter release in the PAG of rats receiving spinal cord stimulation demonstrated that neurostimulation caused a decrease of γ-aminobutyric acid (GABA) levels, but not of serotonin or substance P. Because GABA neurons in the PAG exert a tonic inhibitory effect on the activity in descending pain inhibitory pathways, including trigeminovascular inputs [49], it is suggested that a decreased GABA level in this region after repeated spinal cord stimulation may lead to activation of descending antinociceptive projections with subsequent pain reduction [50–52]. Furthermore, a PET study investigating the effect of spinal cord stimulation in pain-free angina pectoris patients demonstrated increased blood flow in the ventrolateral PAG during neurostimulation [53]. However, further effects also were observed at the thalamic level [47,48].

Conclusions

In this review, we described the anatomic and physiologic substrate of migraine pain processing with a focus on the integration of input from neck structures and the role of suboccipital neurostimulation in the modulation of migraine pain.

The studies reviewed provide clear evidence of anatomic and functional coupling between nociceptive dural afferents and cervical afferents in the GON on to neurons in the trigemino-cervical complex. These convergent neurons may be sensitized during a headache and may be involved in the clinical phenomenon of hypersensitivity, spread, and referred pain to trigeminal and cervical dermatomes.

Recent studies indicate that stimulation of peripheral neural structures (*eg*, the GON) can elicit a pain modulatory effect on migraine pain. Pain-modulating circuits in the spinal cord may contribute to this modulatory effect; however, recent findings also point to the role of the PAG and the thalamus.

An understanding of the physiological mechanisms of the pain transmission and the trigemino-cervical coupling has fundamental implications for the understanding of very common clinical phenomena and may provide a basis for therapeutic modulation of pain processing.

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