Headache
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Neuromodulation in Headache and Facial Pain Management

Principles, Rationale and Clinical Data

Springer

Headache

Series Editor

Paolo Martelletti
Roma, Italy

The purpose of this Series, endorsed by the European Headache Federation (EHF), is to describe in detail all aspects of headache disorders that are of importance in primary care and the hospital setting, including pathophysiology, diagnosis, management, comorbidities, and issues in particular patient groups. A key feature of the Series is its multidisciplinary approach, and it will have wide appeal to internists, rheumatologists, neurologists, pain doctors, general practitioners, primary care givers, and pediatricians. Readers will find that the Series assists not only in understanding, recognizing, and treating the primary headache disorders, but also in identifying the potentially dangerous underlying causes of secondary headache disorders and avoiding mismanagement and overuse of medications for acute headache, which are major risk factors for disease aggravation. Each volume is designed to meet the needs of both more experienced professionals and medical students, residents, and trainees.

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Neuromodulation in Headache and Facial Pain Management

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Part I
Principles of Neuromodulation in Headache Field and Facial Pain Field

Chapter 1
Trigeminal Mechanisms of Nociception

Anna P. Andreou and Lars Edvinsson

1.1 Introduction

The trigeminal nerve (Vn) is the largest cranial nerve and it supplies sensory fibres to all craniofacial structures. Sensory innervation of the craniofacial region is important in functional, psychological and emotional aspects, given the significance of the head as an organ in whole, of facial communication and of all specialised sense organs of the head such as the retina, olfactory epithelium, taste papillae, tooth pulp and cochlea, which are highly innervated by trigeminal fibres [1]. Trigeminal fibres are organised to warn the organism against changing environmental conditions, ranging from changes in environmental chemicals, temperature, injury or other external stimuli. The craniofacial region has a rich innervation and an extensive somatosensory representation in the CNS. These aspects make the Vn the most complex of the 12 cranial nerves. Mechanisms of nociception along the trigeminal nerve are of particular interest in headache conditions and orofacial pain [2].

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1.2 The Trigeminal Nerve

The trigeminal ganglion (TG) is the sensory ganglion of the trigeminal nerve and occupies the Meckel's cavity (cavum Meckelii) in the dura mater covering the trigeminal impression near the apex of the petrous part of the temporal bone [3]. The TG consists of pseudounipolar primary sensory neurons (the dendrite of these neurons are located in the trigeminal nerve, the cell bodies are located in the trigeminal ganglion and the axons protrude through the sensory root and into the ventrolateral midpons) and is analogous to the dorsal root ganglia (DRG) of the spinal cord, which contain the cell bodies of incoming sensory fibres from the rest of the body [2, 4]. TG neurons have no synaptic interconnections with one another and they are surrounded by satellite glial cells (SGCs). However, the SGCs are connected with the TG neurons with gap junctions that intimately communicate between them [5].

The TG gives rise to the trigeminal nerve (Vth cranial nerve), which is the largest of the cranial nerves. The trigeminal nerve trifurcates into ophthalmic (V1), maxillary (V2) and mandibular nerves (V3) distally from the trigeminal ganglion. The divisions of the trigeminal nerve exit the skull base through the superior orbital fissure for V1, through the foramen rotundum for V2, and through the foramen ovale for V3 [6]. The ophthalmic and maxillary nerves are purely sensory, whereas the mandibular nerve has both sensory and motor functions. These three branches converge on the TG from which a single large sensory root enters the brainstem at the level of the pons. Immediately adjacent to the sensory root, a smaller motor root emerges from the pons at the same level, and thus the trigeminal nerve is a mixed nerve containing both motor and sensory components [1, 3]. Motor fibres are distributed together with sensory fibres in branches of the mandibular nerve and supply the muscles of mastication and the tensor tympani and tensor veli palatine muscles.

The sensory fibres of the ophthalmic, maxillary and mandibular nerves have a diversity of arrangement of trigeminal endings in craniofacial tissues, supplying the cutaneous exteroceptors of the face, the retina, cochlea, the mucous membranes of the nasal and oral cavities, and a large portion of the intracranial dura mater and vessels [2, 7]. Early anatomical studies provided evidence for the meningeal representation in the trigeminal ganglion by using horseradish peroxidase histochemistry [7, 8] and more specifically using retrograde tracing with True Blue [9–11]. Most of the nociceptors around meningeal vessels were found to project mainly to the ophthalmic division of the ipsilateral trigeminal ganglion and to a minor degree to the maxillary and mandibular divisions [12, 13]. In addition the True Blue tracing revealed that the distribution was no strictly unilateral because some overlap existed for autonomic as well as sensory innervation [9, 14, 15]. The dermatomes of the three branches of the trigeminal nerve have relatively little overlap, unlike dermatomes in the rest of the body, which show considerable overlap. More specifically the three branches of the trigeminal nerve cover the following sensory areas [16]:

– The ophthalmic nerve carries sensory information from the skin of the forehead, the upper eyelids and the nose ridge and the mucosa of the nasal septum and some paranasal sinuses.

– The maxillary nerve innervates the skin of the middle facial area, the side of the nose and the lower eyelids, the maxillary dentition, the mucosa of the upper lip, the palate, the nasal conchae and the maxillary sinus.
– The mandibular nerve innervates the skin of the lower facial area, the mandibular dentition, the mucosa of the lower lip, cheeks and floor of the mouth, part of the tongue and part of the external ear.

Within the TG the somata of neurons giving rise to the three branches of the trigeminal nerve are somatotopically organised. Somatotopic organisation is not only found within the ganglion but also in the brainstem distribution in the trigeminocervical complex. The cell bodies of the ophthalmic nerve are found medially in the ganglion, those of the mandibular nerve are grouped laterally, while in the middle of these two groups, the cell bodies of the maxillary nerve are grouped [17–19]. The proprioceptive fibres in the motor root of the trigeminal nerve have their cell bodies in the mesencephalic nucleus of the pons. The axons of these motor neurons run pass the trigeminal ganglion as an independent bundle without synapsing within it. The motor trigeminal nucleus is directly stimulated via the corticobulbar tract, originating from the contralateral cerebral cortex. Within the motor nucleus, there is also a large amount of somatotopy. Via efferent fibres the motor trigeminal nucleus receives proprioceptive information from the masticatory muscles, temporomandibular joint and periodontium.

1.3 The Primary Trigeminal Sensory Fibres

The trigeminal sensory fibres convey information regarding pain, temperature, touch and proprioception. The nociceptors are the sensory fibres that convey nociceptive information. The nociceptors run largely adjacent to the blood vessels and transmit nociceptive information mainly through Aδ- (thinly myelinated) and C- (unmyelinated) fibre types [20–22] although other types of primary afferents transmitting somatic sensations have also been characterised [23]. Recent work has shown that the C-fibres store CGRP while the Aδ-fibres contain CGRP receptor elements [24]. Similarly to somatic pain, the pain associated with trigeminal Aδ-fibres activation is characterised by an initial extremely sharp pain and is referred to as the “first” pain. The “second” pain is referred to the more prolonged and delayed feeling of dull ache or burning pain as a result of C-fibre activation. What makes trigeminal nerve unique is that it has ~100 times more dense C-fibres than any other nerve (Fig. 1.1).

The peripheral terminal of the nociceptor is where noxious stimuli are detected and transduced into inward currents that, if sufficiently large, begin to drive action potentials along the axon to the CNS and set a train of events that ultimately lead to a conscious awareness of the noxious stimulus [25]. The sensory specificity of the nociceptor is established by expression of ion channels which respond with a high threshold only to particular features of the mechanical, thermal and chemical environment [25, 26]. The high threshold of these transducers differentiates nociceptors from sensory neurons that respond to innocuous stimuli by expressing transducers with low thresholds [25]. Such transducer channels are TRPV1-4, TRPM8, TRPA1,

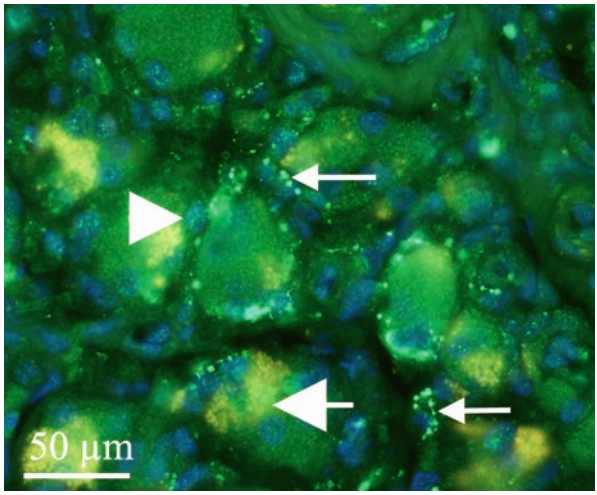

Fig. 1.1 In *human TG*, CGRP positive pearl-like fibres were observed (thin arrows). Thick arrow points at autofluorescent lipofuscin and arrowhead at a satellite glial cell

ASICs, P2X3, TREK, kainate receptors and 5-$HT_{1B/1D}$ receptors [27–36]. A number of studies have involved these channels in trigeminal nociception. Potentially, blockade of these transducers could act as an emerging treatment for trigeminal related disorders. 5-$HT_{1B/1D}$ receptors are the target of triptans, the migraine specific medications [37]. Single nucleotide polymorphisms in the TRPM8 gene have been repeatedly found to be significant in migraine genome-wide association studies [38–42].

Transmission of nociception occurs in response to calcium influx at the central terminal and releasing glutamate, as well as multiple neuropeptides and other signalling molecules that act as synaptic modulators which will activate post-synaptic receptors on second order neurons [23]. In response to inflammatory or noxious stimuli, trigeminal ganglia neurons release neuropeptides and other molecules that initiate and maintain neurogenic inflammation in the peripheral tissue that facilitate peripheral sensitisation of trigeminal nociceptors [43].

1.3.1 Neuropeptides of the Trigeminal Ganglion

Neurons of the TG express at different percentages several different neuropeptides, including calcitonin gene-related peptide (CGRP), substance P (SP), pituitary adenylate-cyclase-activating polypeptide (PACAP), neuropeptide Y (NPY), somatostatin, dynorphin, galanin, orexin, nociception, neurokinin A and neurokinin B, as well as nitric oxide synthase, inter alia [44]. Peripherally, upon their release, the majority of these neuropeptides are vasodilators, while centrally they are involved in signal transmission by acting as neuromodulators. TG neurons and their terminals also express many of the receptors for these neuropeptides. The actions of these neuropeptides have been extensively reviewed by Lazarov [44] and Goto and colleagues [45].

The expression of different neuropeptides in the TG, as well as the expression of their receptors, is altered following inflammation or injury, potentially to induce an autocrine-like reaction. For example, the expression of SP and its receptor neurokinin 1-receptor (NK_1-R) increases following maxillary molar extraction [46], while CGRP is increased following induction of periodontium inflammation [47]. It has been suggested that the build-up of these vasodilatory neuropeptides at injury site may be related to the development of neurogenic inflammation, ectopic neural activity and to contribute to the development of neuropathic pain. Interestingly though, such upregulation is often beyond their nerve distribution. As TG neurons are anatomically isolated from one another and not synaptically interconnected, other means of interaction may exist between the three clusters of neurons giving rise to the three branches of the trigeminal nerve, as mentioned above related to the function of the SGCs [5]. One possibility is through SGCs and/or microglia/macrophage-like cells (MLCs), particularly with regard to interactions between the mandibular and maxillary neurons in the TG. SGCs initially become activated by receiving the signal from TG neurons. Following, SGCs activate adjacent SGCs or other TG neurons by release of neurotransmitters. Similar to the dorsal root ganglion, MLCs in the TG are activated by uptake of a transmitter from TG neurons or SGCs. This communication between neurons, SGCs, and MLCs is believed to contribute to the development of ectopic pain, hyperesthesia or peripheral sensitisation [45].

1.3.1.1 Calcitonin-Gene-Related Peptide

The α-CGRP isoform is expressed in about 50% of TG neurons and is a key neuropeptide involved in both neural and vascular responses [48–50]. CGRP is present in C-fibre neuronal cells [50–52]. About 30% of CGRP-positive TG neurons also co-express SP [53]. CGRP immunoreactive axons, derived from the ipsilateral ophthalmic division of the trigeminal nerve, are abundant on the walls of the rostral circulation of the major cerebral arteries in the circle of Willis, the rostral cerebral circulation, the dura mater and the eye [54–56]. Sensory terminals expressing CGRP have been also identified in the nasal mucosa, periodontium and gingivae [57–59]. Recent work has described in detail the distribution of CGRP and its receptor in the retina [60]. Some of these CGRP containing fibres originate in the TG, putatively involved in migraine attacks. CGRP acts mainly on the CLR/RAMP1 receptor, which is also found on trigeminal fibres [50] (Fig. 1.2).

CGRP is released from large dense-core vesicles demonstrated in the human temporal artery [61] and the human middle meningeal artery [62]. CGRP is regulated by P/Q-type, N- and L-type voltage-dependent calcium channels, and it is [63] co-released with glutamate contained in separate vesicles [64]. Release from synaptic vehicles involves the SNAP-25 protein of the SNARE complex and hence, like glutamate release, it can be inhibited by botulinum toxin type A [65]. These complexes are found also in the TG [66]. Botox is currently an established preventive

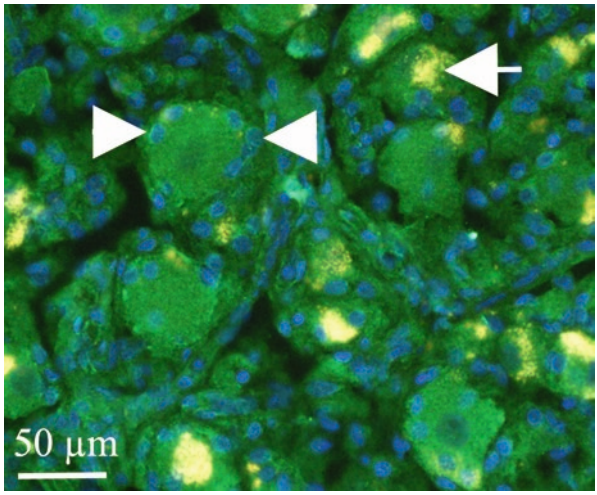

Fig. 1.2 RAMP1 immunoreactivity was exclusively found in satellite glial cells in human TG (arrowheads). Arrow points at lipofuscin

treatment in chronic migraine [67]. Its spontaneous basal release follows a circadian rhythm as it is increased at night [68].

CGRP is the most potent vasodilator when released peripherally, through direct activation of its receptor CLR/RAMP1 on smooth muscle cells [48, 69]. Its release from primary trigeminal afferents innervating blood vessels of the dura mater and the cerebral circulation is one of the main mechanisms of trigeminovascular activation [48], which is believed to be involved in the pathophysiology of primary headaches [70, 71]. CGRP can also induce vasodilation indirectly by activating endothelium CLR/RAMP1, resulting in a rise in cAMP [63, 72] and nitric oxide (NO) production [73]. Diffusion of NO into the smooth muscle cell activates guanylate cyclase inducing relaxation. CGRP as a vasodilator is involved in cardiovascular regulation and may have a protective role against ischaemia. CGRP is spontaneously released during acute blood pressure reflex for cardiovascular regulation, it antagonises sympathetic system-induced vascular resistance and appears to be protective against ischaemia and to reduce brain injury following a stroke [74, 75]. In human aneurysmal subarachnoid haemorrhage (aSAH) has been shown to counterbalance the blood induced vasoconstriction, hence reduced levels are seen in the perivascular nerves with an increase in vascular smooth muscle cells activity [76]. In human aSAH only CGRP was reduced after a fatal stroke [77] and infusion of CGRP could in vivo in patients reduce the vasospasm [78, 79].

CGRP and co-stored with SP are in the periphery involved in mediating axon-reflex mechanisms and an inflammation response [80–82]. CGRP application on the dura mater does not activate or sensitise the ascending trigeminal pathway [83, 84]. Application of CGRP in the temporomandibular joint (TMJ) in rats has been shown to increase expression of mitogen-activated protein kinases (MAPK) in trigeminal ganglia and of c-Fos neurons in the spinal trigeminal nucleus, as well as expression of glial fibrillary acidic protein (GFAP) in astrocytes and OX-42 in microglia [43]. Centrally, CGRP on its own has either no effect on spontaneous neuronal firing or a

slow excitatory effect on non-nociceptive neurons [85, 86]. However it can facilitate SP- evoked firing [86, 87]. Intracerebral CGRP may locally induce increase in local cerebral blood flow (Edvinsson, unpublished).

A number of studies have also investigated the actions of CGRP on glutamate excitation given their co-release following stimulation of sensory fibres. It has been shown that CGRP can facilitate, inhibit or cause no changes to glutamate-evoked firing [86–89]. Interestingly, CGRP was shown to facilitate nociceptive-evoked firing on second order neurons and CGRP antagonists to inhibit nociceptive activity [86–89].

CGRP has been implicated in migraine pathophysiology as its levels were found to be elevated during a migraine attack in plasma, saliva and CSF samples from patients [70, 90–92]. Intravenous infusion of CGRP has been shown to trigger a migraine-like attack without aura in a proportion of sufferers [92], while CGRP antagonists had been used in clinical trials for the treatment of migraine [93–96]. CGRP antibodies and CGRP receptor antibodies have now been studied in clinical trials for the preventive treatment of frequent episodic and chronic migraine with promising results [97, 98]. These monoclonal antibodies are now approved by the FDA and the EMA. Triptans, 5-$HT_{1B/D}$ receptor agonists and migraine specific treatments, have been also shown to reduce CGRP plasma levels in migraine patients [99] and in cluster headache [100], but not in healthy subjects [101, 102].

Evidence for the importance of CGRP in migraine also comes from experimental animal models. Stimulation of the cat superior sagittal sinus led to increased release of CGRP and VIP levels while there was no change in SP or NPY [103]. When the dura mater was electrically stimulated in rats, it caused dilation of dural blood vessels [104], due to CGRP release from trigeminal sensory nerves that innervate the cranial blood vessels [48] since this effect was abolished by the rat CGRP receptor antagonist $CGRP_{8–37}$ [104]. Significant attenuation of the neurogenic meningeal vasodilator response is similarly seen with triptans, such as sumatriptan [105]. Intravenous administration of CGRP also causes extracranial dural blood vessel dilation that is similarly abolished by $CGRP_{8–37}$. CGRP-induced dilation however is not abolished by sumatriptan, indicating that it is likely the triptans act prejunctionally to prevent CGRP release [106], rather than on the smooth muscles of the blood vessels [105]. In the TCC, CGRP receptor antagonists inhibited trigeminovascular neurons activated by L-glutamate, demonstrating a possible central site of action for CGRP receptor antagonists [88].

1.3.1.2 Substance P

Substance P (SP) is present in about 10–30% of TG neurons with nearly all fibres that store SP being unmyelinated, arising from small to medium-sized neurons [107–109]. All SP-containing TG cells are also immunopositive for CGRP [110, 111], and coexist with the excitatory neurotransmitter glutamate in primary afferents that respond to painful stimulation. SP-positive fibres innervate same structures