Chapter 1
Anatomy of Headache

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1.1 Introduction

Clinical and experimental observations provide evidence for an essential contribution of peripheral, intracranial, as well as extracranial nociceptive processes in the generation of headaches [1]. A large body of evidence supports the hypothesis that most types of headaches, including migraine, are of trigeminovascular origin, caused or influenced by nociceptive afferents innervating the cranial meninges, particularly the dura mater encephali and large intracerebral blood vessels [2]. The primary role of the meningeal sensory innervation in generating headaches fits well to the intraoperative studies of Ray and Wolff and other investigators [3, 4], who demonstrated that headache-like pain, but not other sensations, can be evoked by electrical, mechanical, thermal, or chemical stimulation of dural blood vessels and sinuses or large intracerebral arteries. Importantly, the painful sensations were referred to the trigeminal dermatomes where typically headaches are localized [5]. These early studies formed the basis of many anatomical and physiological examinations in animals regarding the pathophysiology of headaches. Recordings of

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action potentials from trigeminal nerves [6] and the trigeminal ganglion [7] as well as higher neurons in the spinal trigeminal nucleus [8, 9] and in the thalamus [10, 11] provided further evidence for an important role of the trigeminovascular system in meningeal nociception.

1.2 Peripheral Structures Involved in Headache States

### 1.2.1 Trigeminal and Other Cranial Nerves Associated with Headache

1.2.1.1 Organization of the Trigeminal Ganglion and Meningeal Representation

Due to the limited experimental access to intracerebral arteries, most of the morphological and nearly all functional studies have focused on the innervation of the cranial dura mater and the dural venous sinuses. Using neuronal tracing, afferents around the middle meningeal artery have been found predominantly originating in the ophthalmic division (V1) of the ipsilateral trigeminal ganglion but to a minor extent also in the maxillary (V2) and mandibular (V3) divisions [12, 13]. The basal dura mater in the middle cranial fossa was represented mainly in V3. New retrograde tracings in the rat confirmed that meningeal nerves innervating the territorium of the middle cranial fossa, which is mainly supplied by the middle meningeal artery, origin predominantly in V3 and to a lesser extent in V2 [14]. The finding that all three divisions of the trigeminal nerve, though not equally, contribute to the innervation of the meninges is in accordance with old anatomic observations in primates [15]. Moreover, retrograde labeling of nerve fibers around basal intracranial arteries and the superior sagittal sinus, from which in humans headache can be provoked [3], appeared not only in the rat trigeminal ganglia but also in the first and second spinal ganglia [16] projecting to the cervical dorsal horn.

1.2.1.2 Afferent Innervation of the Meninges and Intracerebral Arteries

The innervation of the human cranial dura mater, which has firstly been described centuries ago by the anatomists Arnold [17] and Luschka [18], is regarded as pivotal for the generation or aggravation of headaches. Neuroanatomical studies demonstrated the close relationship between meningeal blood vessels and nerve fibers of different origin (Fig. 1.1a). Besides the trigeminal fibers originating in the ipsilateral trigeminal ganglion [19, 20], a network of sympathetic fibers mainly from the superior cervical ganglion [21, 22] and a comparatively sparse innervation by parasympathetic fibers originating in the sphenopalatine and otic ganglia has been described [23, 24]. The innervation of intracerebral (pial) blood vessels is similarly organized [25] but with a higher proportion of parasympathetic fibers coming mainly from the internal carotid and sphenopalatine ganglia [26].

Fig. 1.1 Histochemical demonstration of afferent and efferent innervation of the rat dura mater and markers of trigeminal ganglion neurons. (**a**) Confocal image of putative sympathetic and afferent nerve fibers in the rat dura mater labeled by tyrosine hydroxylase (*TH, green*) and calcitonin gene-related peptide (*CGRP, red*) immunofluorescence. Both TH- and CGRP-immunoreactive fibers form a dense network around the middle meningeal artery (MMA). Scale bar 200 μm. (**b**) Confocal image of trigeminal ganglion neurons labeled by retrograde tracing with Texas red from the temporal muscle (see red nerve fiber, *arrowhead*) and with Rhodamine green from the parietal dura mater. The yellow neuron with *mixed red* and *green* innervates both temporalis muscle and dura mater by afferent collaterals. Scale bar 50 μm. (**c**) Confocal image of a trigeminal ganglion section immunohistochemically stained for puringeric (*P2X_3*) receptor channels and nuclei (*DAPI*). The majority of neuronal cell bodies, mostly small ones, are $P2X_3$ immunopositive. Scale bar 50 μm (Courtesy of S. Vilotti, SISSA Trieste)
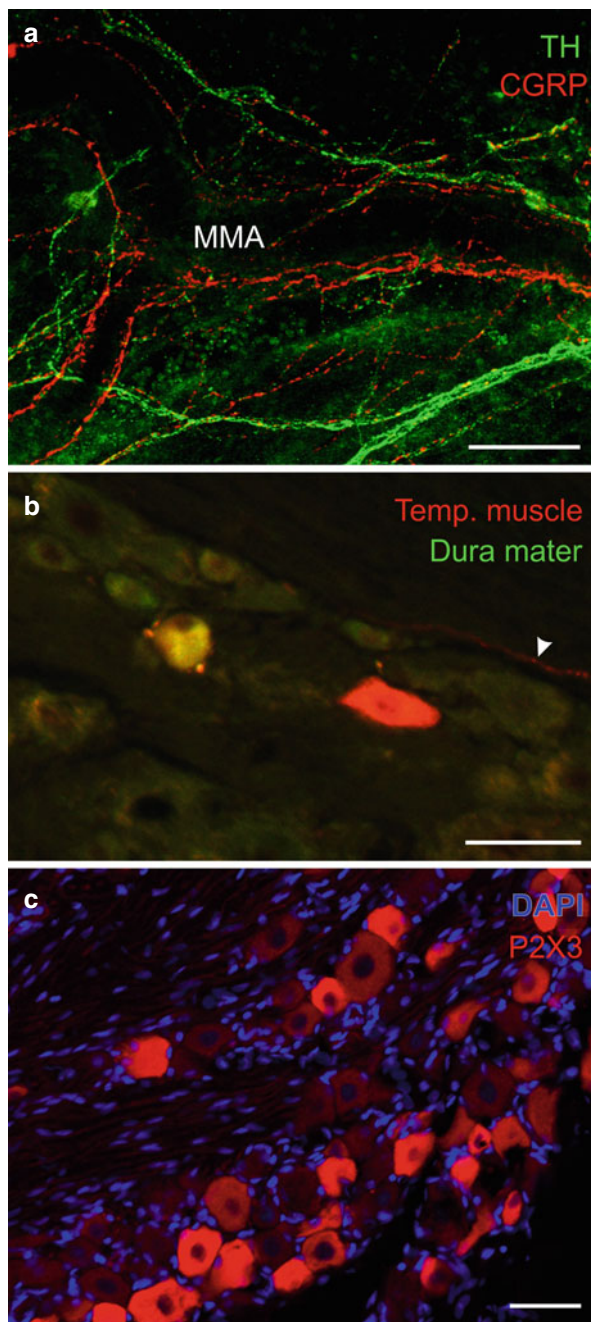
Several immunohistochemical studies described neuropeptide-immunoreactive nerve fibers in the dura mater [27–29] and around cerebral (pial) blood vessels in different species including humans [30, 31]. Meningeal nerve fibers immunoreactive for substance P (SP), neurokinin A (NKA), and calcitonin gene-related peptide

(CGRP) are thought to belong to the afferent (trigeminal and spinal sensory) system, while nerve fibers immunopositive for neuropeptide Y (NPY) are most likely of sympathetic and those immunoreactive for vasoactive intestinal polypeptide (VIP) of parasympathetic origin [21, 19]. The peptidergic nerve fibers form a dense network around blood vessels but can also be found in nonvascular regions [29, 20]. On the light microscopic level, sympathetic nerve fibers can be labeled by tyrosine hydroxylase (TH) immunoreactivity and thereby discriminated from peptidergic afferents (Fig. 1.1a). It is important to note, however, that a major proportion of trigeminal afferents does not express neuropeptides [32]. For differentiation of sensory fibers, other markers have been used such as neurofilament 200, which is present in myelinated fibers, and isolectin B4, which characterizes mostly unmyelinated, non-peptidergic fibers [33].

Electron microscopic examinations revealed myelinated (Aδ possibly Aβ) and unmyelinated (C) nerve fibers in the cranial dura mater [29, 34, 35]. An attempt was made to classify the C fibers according to their three-dimensional structure and their content of different kinds of vesicles into afferent and autonomic fibers [36]. The majority of meningeal C and Aδ fibers terminate as free nerve endings, but encapsulated Ruffini-like receptors and lamellated nerve terminals have additionally been described in higher vertebrates including man, particularly at sites where cerebral veins enter the sagittal sinus [34]. Myelinated and unmyelinated axons terminate also within the arachnoid granulations at different tissue structures suggesting that they have different mechano- and chemoreceptive functions [37].

1.2.1.3   Extracranial Collaterals of Meningeal Afferent Innervation

Long ago anatomical studies by Luschka [18] on the primate and human meningeal innervation reported on nerves that penetrate the skull, believed to innervate extracranial tissues. Recently a role for pericranial afferents in headache generation is again a matter of discussion [1]. Histological examinations in the mouse have revealed peripherin- and CGRP-immunopositive nerve fibers traversing the bones of the calvaria between the galea aponeurotica and the meninges [38]. The historical intraoperative data from Wolff's group, who observed that noxious stimulation not only of dural but also extracranial structures like pericranial muscles and arteries can cause headache, support this concept [3]. Likewise, further experimental and clinical observations indicated that noxious activation of afferents in pericranial tissues, particularly in the temporal and occipital–cervical regions, can contribute to headache generation [39, 40] and peripheral sensitization in migraine pain [41].

A couple of new studies have been made using in vitro and in vivo neuronal tracing and electron microscopy in rodents and human skulls to investigate extracranial projections from meningeal nerves and their origin in the trigeminal ganglion [14]. In particular, anterograde and retrograde neuronal in vitro tracing with DiI revealed nerve fiber bundles leaving the skull through emissary canals and fissures to innervate the pericranial temporal, parietal, and occipital periosteum as well as deep layers of the temporal and upper neck muscles. A variety of functional measurements

in rats confirmed the afferent nature of extracranial afferent collaterals and the impact of their activation on the intracranial secretion of neuropeptides and their vasodilatory function [42]. Following in vivo tracing with different dextran amines applied to the dura mater and the pericranial muscles, some neurons were detected in the trigeminal ganglion containing tracer from both structures (Fig. 1.1b). These data affirmed functional afferent connections between intra- and pericranial tissues and provide a new view on the influence of extracranial meningeal afferent projections on meningeal nociception and headache generation.

1.2.2 Molecular Signature of Trigeminal Afferents and Neurogenic Inflammation of the Dura Mater

Meningeal afferents convey the nociceptive information to the central nervous system, but through the antidromic release of vasoactive peptides from their perivascular peripheral terminals, they also promote a sterile "neurogenic inflammation" in the meningeal tissue characterized by vasodilatation and increased permeability of blood vessels [43, 44]. Neurogenic inflammation is considered to contribute to the peripheral mechanisms in the pathophysiology of headaches.

1.2.2.1 Receptors, Transduction, and Conduction Channels

Although headache-like pain is the only sensation induced by activation of intracranial afferents, regardless of the mode of their stimulation [5, 4], the nerve fibers innervating meningeal tissues consist of a heterogenous population based on their morphological and immunohistochemical properties (Fig. 1.2).

TRP Channels

Chemosensitive meningeal afferents likely contribute to sensitization of the nociceptive pathway [45]. Successful prevention of cluster headache and migraine attacks with the topical, desensitizing application of capsaicin to the patients' nasal mucosa has focused attention to the significant role of capsaicin-/chemosensitive population of trigeminal afferents [46, 47]. Chemosensitive meningeal afferents express different members of the transient receptor potential (TRP) channel family. Sixteen percent of the neurons in the trigeminal ganglion of humans and 21–31 % of dural afferent neurons in rodents have been found to express the transient receptor potential vanilloid 1 (TRPV1) channel [48, 32]. The TRPV1 receptor is a nonspecific cation channel, which can be activated by noxious heat, acidic pH (pH < 5.3), and different compounds like some endogenous membrane lipid metabolites (anandamide, *N*-arachidonoyl dopamine) and exogenous capsaicin or resiniferatoxin.
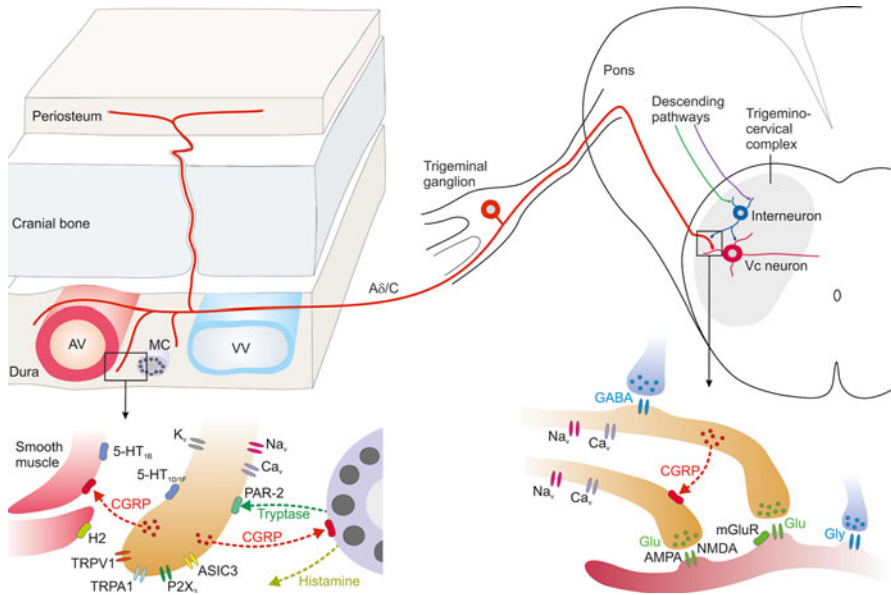
Fig. 1.2 Schematic representation of the trigeminovascular system of the cranial dura mater with arterial vessel (*AV*), venous vessel (*VV*), central canal (*circle*) and mast cell (*MC*) and the afferent projection to the trigeminocervical complex with a second-order neuron in the subnucleus caudalis (*Vc*) and an inhibitory interneuron. One and the same single (Aδ or C) fiber may innervate the dura mater and, with collaterals projecting through the skull, the periosteum. Afferent fibers may contain and release CGRP in the periphery and the CNS. The *left inset* shows some important transduction channels (TRPV1, TRPA1, P2X₃, ASIC3), receptors (5-HT₁, PAR-2), and voltage-gated conduction channels (Ca$_v$, Na$_v$, K$_v$) and the proposed signaling between the afferent ending, AV and MC. The *right inset* shows the proposed nociceptive transmission in superficial laminae of the trigeminocervical complex to Vc neurons expressing glutamate (*Glu*) receptor channels (NMDA, AMPA) and metabotropic glutamate receptors (*mGluR*). CGRP signaling is probably between terminals of primary afferents facilitating neurotransmitter release. Inhibitory neurons act pre- and postsynaptically on GABA and glycine (*Gly*) receptors, targeted by descending serotonergic and noradrenergic inhibitory pathways and segmental connections

The transient receptor potential ankyrin 1 (TRPA1) ion channel, another member of the TRP receptor superfamily, has recently emerged as another important receptor activated by noxious chemical agents [49]. TRPA1 receptors can be activated by noxious cold, different environmental irritants like acrolein, and also by pungent ingredients of plant origin, like cinnamaldehyde and umbellulone that is the major volatile constituent of the "headache tree" *Umbellularia californica* [50, 51]. Endogenous activators of the receptor recently defined are some prostaglandin metabolites, hydrogen peroxide and nitroxyl (HNO), the one-electron-reduced sibling of nitric oxide (NO) [52]. Both endogenous and exogenous activators of the TRPA1 modify cysteine residues of the receptor (e.g., by forming disulfide bonds). Similar to TRPV1, activation of trigeminal afferents through TRPA1 receptors induces nociceptive responses and release of CGRP (Fig. 1.2). Histological and functional observations have revealed colocalization of TRPV1 and TRPA1 in trigeminal ganglion neurons [50, 53].

In humans, inhaled irritants may stimulate TRPA1 receptors of extracranial trigeminal afferents that innervate the nasal mucosa and may project collaterals to meningeal blood vessels. Nociceptive stimulation of extracranial tissues may activate intracranial collaterals by an axon reflex mechanism, releases vasoactive neuropeptides in meningeal tissue, and increases intracranial blood flow [42].

ASIC Channels

Some dural afferents express acid-sensing ion channels (ASICs), predominantly the ASIC3 subtype responding to low meningeal pH [54]. ASICs belong to the ENaC/DEG (epithelial amiloride-sensitive Na^+ channel and degenerin) family of ion channels [55]. Relative small changes in the meningeal proton concentration activate the ASIC3 channel initiating an afferent signal in the trigeminal nociceptive pathway. The reason for an acidification of the local meningeal pH can be ischemia of the dura mater possibly developing as a consequence of cortical spreading depression that has been linked to the aura phase of migraine attacks [56, 57]. Degranulation of dural mast cells as a result of neurogenic inflammation of the dura mater can be an additional source of acidic metabolites leading to the activation of sensory nerve endings.

Purinergic Receptors

Purinergic ($P2X_2$ and $P2X_3$) receptor channels that may contribute to the transduction of nociceptive signals have been localized to trigeminal ganglion neurons innervating the dura mater (Fig. 1.1c). Purine receptor immunoreactivity is present predominantly in medium- and small-sized neurons that are mainly non-peptidergic and unmyelinated [33]. An important pathophysiological function of purinergic receptors may be peripheral sensitization of the trigeminal nociceptive pathway through the communication between different clusters of neurons within the trigeminal ganglion. In vitro studies have provided evidence that CGRP release from neurons stimulates the ERK1/2 MAP kinase signaling pathway in surrounding satellite glial cells and increases P2Y1,2 receptor-mediated intracellular calcium responses, which leads to the release of inflammatory cytokines from the activated satellite cells. Increased levels of cytokines have been shown to result in local inflammatory reactions and modulation of the neuronal function [58, 59]. By this way, CGRP may function as a paracrine factor to stimulate adjacent glial cells within a cluster and to cause excitation of more distant neurons and glial cells located in other clusters, thereby propagating an inflammatory signal across the entire ganglion [33, 60].

5-HT Receptors

One of the most effective classes of drugs for the treatment of migraine pain is the triptans, serotonin 1B/1D/1F ($5\text{-}HT_{1B/1D/1F}$) receptor agonists. While the $5\text{-}HT_{1B}$ receptors appear to be located primarily on vascular smooth muscle

mediating vasoconstriction, the 5-HT$_{1D/1F}$ receptors are located on the peripheral and central terminals of meningeal afferents [61, 62] (Fig. 1.2). Activation of these G protein-coupled receptors inhibits the release of transmitters from the trigeminal afferents leading to the attenuation of the central transmission of nociceptive signals.

The presence of 5-HT$_7$ receptors on trigeminal nerve endings and middle meningeal arteries has been demonstrated recently. Vasodilatation induced by the activation of trigeminal 5-HT$_7$ receptors seems to be the result of CGRP release from the nerve terminals [63].

Calcium Channels

Activation of voltage-gated P/Q-type and N-type calcium channels has a key role in the regulation of synaptic function. Clinical and experimental data provide evidence that changes in the channel structure influence the release of neurotransmitters in the nociceptive transmission (Fig. 1.2). A rare hereditary form of migraine with aura and hemiparesis is the familial hemiplegic migraine type 1 (FHM-1). The FHM-1 gene encodes the pore-forming Ca$_V$2.1 subunit of P/Q-type Ca^{2+} channels. The mutation of the channel structure results in a gain of P/Q-type channel activity in trigeminal neurons and a selective increase in low-voltage-activated T-type currents in the small (IB4$^-$) neuron population. This condition may lead to hyperexcitability of small, probably peptidergic, trigeminal neurons [64, 65].

Clinical and experimental observations provide evidence for N-type voltage-gated calcium channels (Ca$_V$2.2) as therapeutic targets for chronic pain conditions. N-type calcium channels are present in the presynaptic terminals of primary afferent sensory neurons, especially in Aδ and C fibers [66]. Blocking the channel function has a significant antinociceptive effect. In an experimental migraine model, inhibition of the channel function reduced neurotransmitter release from the primary sensory neurons and decreased the excitability of second-order neurons in the trigeminal brainstem [67].

Sodium Channels

The voltage-gated sodium channels with the pore-forming alpha-subunits Na$_V$1.7 and Na$_V$1.8 have emerged as molecules involved in peripheral pain processing and in the development of an increased pain sensitivity associated with inflammation [68]. In experimental models of meningeal nociception, amitriptyline, a tricyclic antidepressant, which is used to prevent migraine attacks, blocked the Na$_V$1.8 currents in trigeminal ganglion neurons and alleviated nociceptive behavior induced by electrical stimulation of the superior sagittal sinus. These results strongly support the contribution of Na$_V$1.8 channels to the pathophysiology of migraine and provide a novel guideline to migraine prophylaxis [69].

Potassium Channels

A subtype of voltage-gated K^+ channels, K_V7 expressed in nociceptors, is recognized to be one of the most important regulators of resting membrane potential and action potential firing threshold. Expression of this K^+ channel contributes strongly to the excitability of the nociceptors. The analgesic drug flupirtine opens K_V7 channels and by this way exerts an analgesic effect in migraine, chronic musculoskeletal pain, and neuralgia [70, 71]. Some of the nonsteroidal anti-inflammatory drugs such as diclofenac used in migraine therapy have also strong K_V7 channel opener activity, which may at least partly be responsible for their analgesic effect [72]. Recent observations indicate an NO-mediated K_V7 channel inhibition in trigeminal ganglion neurons that correlate with increased excitability and release of CGRP in nociceptors. It was suggested to contribute to excitatory effects of NO in headaches [73].

1.2.2.2 Mast Cells and Immunocytes in the Dura Mater

Activated meningeal nociceptors releasing the neuropeptides CGRP and SP, which induce direct vascular effects, can also activate and degranulate dural mast cells [74]. The local release of inflammatory mediators such as histamine from activated mast cells is believed to further stimulate meningeal nociceptors possibly promoting headache (Fig. 1.2). Clinical observations have shown that infusion of histamine induces headaches preferentially in migraineurs [75, 76].

The cranial dura mater is rich in connective tissue-type mast cells in both humans [77] and rodents [78] that are in close apposition to meningeal nociceptive nerve fibers and blood vessels [78]. This anatomical situation allows a multidirectional communication between blood vessels, nociceptors, and mast cells leading to the sensitization or activation of the trigeminal nociceptive pathway and changes in meningeal blood flow [79]. Direct vascular effects of histamine released by activated mast cells are mediated by multiple receptors localized on different histological components of the arterial vessel wall (Fig. 1.2). Relaxation of dural arteries is mediated by H2 receptors of vascular smooth muscle cells and by endothelial H1 receptors. In addition, H1 receptors on smooth muscle cells may mediate vasoconstriction [80].

Additional molecules known to be released from activated mast cells such as prostaglandins, leukotrienes, cytokines, and tryptase may also take part in the sensitization or activation of meningeal nociceptors [81]. The serine protease tryptase released from mast cells upon stimulation cleaves and activates the proteinase-activated receptor 2 (PAR-2) of meningeal nociceptors amplifying the initial vasodilation caused by sensory neuropeptides and possibly also the central transmission of nociceptive signals [82] (Fig. 1.2).

Resident macrophages of the dura mater expressing the inducible nitric oxide synthase (iNOS) are considered to play a significant role in delayed headache induced by infusion of the so-called NO-donor nitroglycerin. Following administration of nitroglycerin, a strong activation of iNOS was observed in the macrophages

along the branches of the middle meningeal artery together with an upregulation of pro-inflammatory cytokines. Cytokines and NO synthesized by macrophages can sensitize small unmyelinated trigeminal afferents and generate headache. Activation of trigeminal afferents, in turn, promotes neuropeptide release and local blood flow changes in the meninges [83]. Nuclear factor kappa B (NF-κB) seems to mediate the transcriptional signal to iNOS and inflammatory cytokines. Since NF-κB can be activated by diverse pathological and inflammatory stimuli such as oxidative stress and bacterial and viral metabolites, its activation may provide the substrate within meningeal macrophages that contributes to headaches in response to different exogenous agents in susceptible individuals [84].

1.3 Central Structures Involved in Headache States

1.3.1 Subcortical Structures Implicated in Headaches

1.3.1.1 Morphofunctional Organization of the Trigeminocervical Complex and Meningeal Representation

The central processes of trigeminal ganglion neurons forming the trigeminal nerve enter the brainstem at the pontine level and terminate in the trigeminocervical complex, which consists of the pontine principal sensory nucleus (Vp) and the spinal trigeminal nucleus (Vsp) (Fig. 1.2). Basically, the thick myelinated mechanoreceptive trigeminal afferents terminate in the Vp, whereas both large-diameter and small-diameter fibers descend in the spinal trigeminal tract (SVT) projecting to the Vsp, which is subdivided into three subnuclei [85]: a rostral subnucleus oralis (Vo), a middle subnucleus interpolaris (Vi), and a caudal subnucleus caudalis (Vc). The Vc is often referred to as the medullary dorsal horn (MDH) because of the smooth transition to the anatomically and functionally similar spinal dorsal horn. Olszewski [85] identified three histologically different regions in the MDH: an outer marginal region, the substantia gelatinosa, and a deep magnocellular region. Later Gobel et al. [86] proposed a laminar subdivision of the MDH similar to Rexed's nomenclature of the spinal dorsal horn [87] in which lamina I corresponds to the marginal layer, lamina II to the substantia gelatinosa, and laminae III and IV to the magnocellular region. The most ventral lamina V merges with the medullary reticular formation [88] without clear boundary. Groups of neurons intermingled in the spinal trigeminal tract down to the transition of Vi and Vc are referred to as the interstitial islands of Cajal or as the paratrigeminal or interstitial nucleus [89]. The neurons of these islands are regarded as nociceptive, similar to the neurons in laminae I and II of the Vc [10, 90].

Anatomical and electrophysiological studies [91, 92] revealed that the TBNC is topographically organized in ventrodorsal and in rostrocaudal direction. Mandibular afferents terminate preferentially in the dorsal region of each trigeminal subnucleus (dorsomedial in the MDH), ophthalmic afferents terminate ventrally (ventrolateral

in MDH), and maxillary terminals are interposed. The rostrocaudal organization of the trigeminocervical complex is less clear, but within the Vc the rostrocaudal axis of the face is represented from rostral to caudal [93]. Early anatomical [94] and neurophysiological [95] studies suggest that each subnucleus receives information from all parts of the head. Jacquin et al. found mandibular nerves in the rat projecting to all trigeminal subnuclei, although the anterior oral afferents tended to terminate most heavily in the rostral trigeminocervical complex, whereas the posterior perioral–auricular afferents terminated preferentially in the caudal aspect of the complex [96]. Tracing from the superficial temporal artery revealed afferent terminals mainly in the rostral cervical spinal dorsal horn and sparsely in the Vi and Vc of the spinal trigeminal nucleus [97]. Because of a lack of tracing studies, it is not clear if a similar somatotopic distribution in ventrodorsal and rostrocaudal directions exists for intracranial trigeminal structures.

Also based on clinical observations and animal studies, it has been recognized that the Vc is primarily responsible for processing nociceptive and thermoreceptive information from the face and head, whereas the Vp is involved in processing tactile information (Fig. 1.2). Isolated lesions of the Vc caused ipsilaterally complete or partial loss of pain and temperature sensation, whereas tactile sensations remained nearly intact [98]. This clinical experience led Sjoqvist [99] to develop the method of trigeminal tractotomy for the relief of facial pain, in which the spinal trigeminal tract at the level of the obex was transected. The clinical data were supplemented with a large body of neurophysiologic evidence based on trigeminal tractotomy or experimental lesions of different subnuclei demonstrating that the Vc in the perception of pain in trigeminal tissues is essential, whereas for the processing of nociceptive information from intraoral and orofacial tissues, more rostral regions of the trigeminocervical complex are important as well [100, 101].

Transganglionic cholera toxin and HRP tracing of afferents innervating the rat superior sagittal sinus labeled central terminals in the ipsilateral Vc and Vi but also in the ventrolateral area of the C1–C3 spinal dorsal horn on both sides [16]. Labeling was seen in laminae I and II with HRP but in laminae III and IV with cholera toxin [16]. These findings are largely confirmed by electrophysiological recordings from second-order neurons with afferent input from the dura mater in rat [9, 102].

Apart from the abovementioned study [97], the projection of nociceptive afferents to specific laminae of the trigeminocervical complex has again mainly been studied for facial inputs using axonal tracing in cat and rat. Hayashi and Jacquin et al. found high-threshold mechanoreceptive (nociceptive) Aδ afferents forming extensive terminal arbors in the superficial Vi and, most pronounced, in lamina I and, to a lesser extent, outer lamina II of Vc [96, 103]. In the rat, a second termination area was localized in laminae III to V of Vc [96]. Corneal afferents, which are thought to be mainly nociceptive, terminate mainly in the outer laminae of Vc [104]. Corresponding to the distribution of nociceptive afferent terminals in the Vsp, SP- and CGRP-immunoreactive nerve fibers have been demonstrated in different species preferentially around the substantia gelatinosa of Vc and the transition zone between Vi and Vc (Vi/Vc) [105, 106]. Colocalization of immunoreactivity for TRPV1 receptors with SP and CGRP was found in axon collaterals in the dorsal

parts of Vp, Vo, and Vi and in terminals and fibers throughout lamina I and the outer zone of lamina II (IIo) of the Vc [107]. Trigeminal rhizotomy in the cat caused disappearance of most of the CGRP-immunoreactive fibers throughout the trigeminocervical complex, whereas a considerable number of SP-immunoreactive fibers remained intact [108, 109] suggesting that these are of central origin.
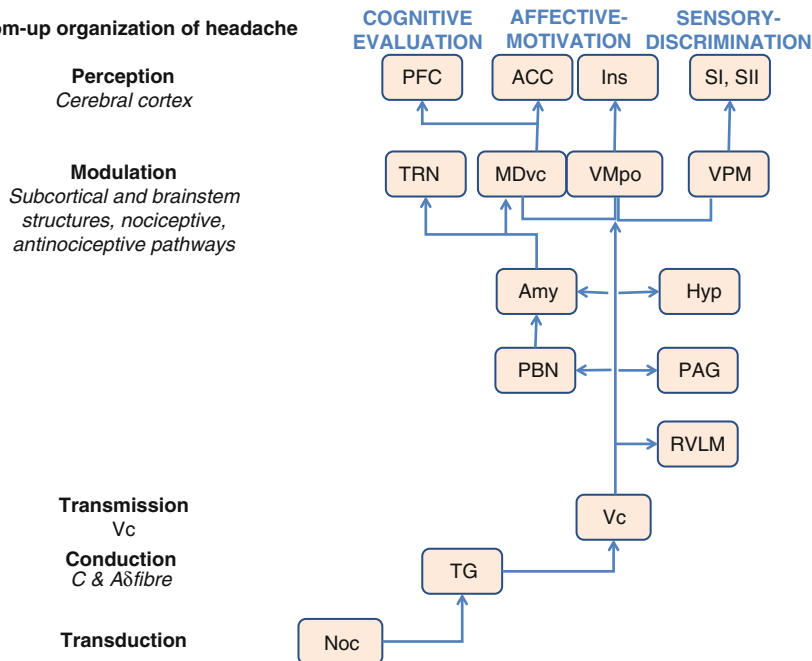
Electron microscopic immunohistochemistry in the cat Vsp revealed CGRP immunoreactivity within the substantia gelatinosa in axon terminals which were presynaptic to dendritic profiles and postsynaptic to other fibers [110]. Likewise, the presence of CGRP receptors in rat and human Vc was found by immunohistochemistry restricted to trigeminal afferent endings in superficial layers (laminae I and II) of the Vc [111, 112]. This implies that CGRP as a central neuromodulator may exert its effects presynaptically to spinothalamic and other second-order neurons (Fig. 1.2).

1.3.1.2   Projections to Thalamic and Other Subcortical Nuclei

Nociceptive information from cranial and upper cervical structures is transmitted via the trigeminal and spinal afferent system to the higher diencephalic and cortical pain-associated areas. According to the well-delineated conventional pathway, the cell bodies of second-order neurons in the trigeminocervical complex mainly project to third-order neurons in the thalamus and then carry information to somatosensory cortical areas. The majority of the caudal part of the trigeminal nucleus (Vc) and the cervical dorsal horn neurons send axons to two contralateral thalamic nuclei that relay ascending somatosensory information to the primary somatic sensory cortex: the ventroposteromedial thalamic nucleus (VPM) and the posterior thalamic nuclear complex (Po) [113–115]. Trigeminal Vc neurons also project to the posterior part of the ventral medial nucleus (VMpo), the ventral caudal part of the medial dorsal nucleus (MDvc), and the nucleus submedius (Sm) of the thalamus [116] (Fig. 1.3). Projections to the thalamus have distinct molecular characteristics as glutamatergic trigeminothalamic projection neurons in the Vc; Vi and Vo mainly express the glutamate transporter VGLUT2. The sensitization of second-order and/ or third-order neurons within the system is an important factor in the development of allodynia during the migraine attack. A recent study revealed that the thalamic reticular nucleus (TRN) was activated following cortical spreading depression (CSD) ipsilaterally in freely moving conscious rodents [117, 118]. Unilateral TRN activation during CSD implicates its potential role in lateralized headache perception and attention, regarding the fact that the parabrachial nuclei (PBN) and amygdala have direct projections on the TRN involved in drawing attention to emotional stimuli [119].

Tracing studies revealed that the Vc also projects to other brainstem and diencephalic structures such as the brainstem reticular formation, nucleus of the solitary tract, superior salivatory nucleus, A5 cell group region, lateral periaqueductal gray matter, inferior colliculus, parabrachial nuclei, hypothalamus, and cerebellum [114, 120]. Trigeminal neurons send axons to the ipsilateral cerebellum, and trigeminocerebellar projection neurons predominantly express the glutamate transporter

Bottom-up organization of headache

| COGNITIVE EVALUATION | AFFECTIVE-MOTIVATION | SENSORY-DISCRIMINATION |

Perception
Cerebral cortex

PFC | ACC | Ins | SI, SII

Modulation
Subcortical and brainstem structures, nociceptive, antinociceptive pathways

TRN | MDvc | VMpo | VPM

Amy ← → Hyp

PBN ← → PAG

RVLM

Transmission
Vc

Vc

Conduction
C & Aδ fibre

TG

Transduction

Noc

Fig. 1.3 Schematic representation of ascending nociceptive pathways in perception of headache. Bipolar neurons in the trigeminal ganglion (*TG*) conduct noxious signals from peripheral nociceptors of perivascular trigeminal afferents to nociceptive laminae in the spinal trigeminal nucleus (*Vc*) through Aδ and C fibers. Transmission of nociceptive impulses to second-order neurons in the dorsal Vc is a critical step in pain transmission. Trigeminal projections from the Vc to third-order neurons in the thalamic ventroposteromedial (*VPM*) nuclei are relayed to the primary and secondary somatosensory cortex. The latter pathway is also known as a lateral pain system and related to the sensory discriminative aspects of headache perception. The Vc also projects to a large number of the brainstem and diencephalic structures including the rostral ventrolateral medulla (*RVLM*), parabrachial nucleus (*PBN*), periaqueductal gray matter (*PAG*), amygdala, and hypothalamus. The pathway from Vc-PBN-amygdala-medial thalamus to the anterior cingulate cortex (*ACC*) and insula is known as medial pain pathway and is involved in affective aspects of headache. The prefrontal cortex plays a role in cognitive evaluation of headache perception. The thalamic reticular nucleus (*TRN*) seems to be involved in attention and emotional components of pain perception. Reciprocal connections between subcortical structures and cerebral cortex are not shown for clarity. *ACC* anterior cingulate cortex, *Amyg* amygdala, *Ins* insular cortex, *Noc* nociceptor, *MDvc* thalamic mediodorsal ventrocaudal nucleus, *PAG* periaquaductal gray matter, *PBN* parabrachial nucleus, *PFC* prefrontal cortex, *Po* posterior group, *RVLM* rostroventrolateral medulla, *SI and SII* primary and secondary somatosensory cortices, *Vc* caudal trigeminal brainstem nucleus, *VMpo* thalamic ventromedial posterior nucleus, *VPM* ventroposteromedial thalamic nucleus, *TG* trigeminal ganglia, *TRN* thalamic reticular nucleus

VGLUT1 [121]. Trigeminal projections also target the lateral reticular formation, mainly the rostral ventrolateral medullary reticular formation (RVLM), which participates in viscero-sympathetic reflexes. It was shown that trigemino-RVLM axons can be CGRP immunopositive [122].

The parabrachial nuclei (PBN), particularly their lateral parts, are an important projection site for trigeminal nociceptive information. The majority of nociceptive neurons in lamina I mainly in the Vc and Vi send axons to the PBN where many neurons respond preferably to noxious stimuli [90, 123, 124]. When retrograde tracer was injected into the PBN, projection neurons were detected ipsilaterally in lamina I of the Vc [125] though bilateral projection from the Vc to parabrachial nuclei has been identified [124]. Many of the neurons in the lateral parabrachial area project to the ventromedial hypothalamus and central nuclei of amygdala. Parabrachial-projecting neurons in the Vc have a topographic distribution [126]. Corneal afferents rather synapse with parabrachial-projecting neurons in the trigeminal nucleus and barely target neurons projecting to the thalamus. The trigeminal projections to the PBN are related with autonomic emotional responses to pain [127–129]. It is noteworthy that the PBN has reciprocal connections with forebrain areas and the insular cortex [130] and receives input from the amygdala [131]. The PBN was activated during CSD in rodents [132].

The amygdala, as a part of the trigemino–parabrachio–amygdaloid pathway, is another important subcortical nociceptive relay station. The central nucleus of the amygdala receives noxious information indirectly from the superficial lamina of the Vc through the lateral parabrachial area [133]. The amygdala, particularly the basolateral amygdaloid (BLA) nucleus, projects to the perirhinal area, the agranular insular area, and the mediodorsal thalamic nucleus. A direct amygdalofugal pathway to the trigeminal nuclear complex also exists in rodents. Particularly, the central amygdaloid nucleus sends extensive unilateral projections to all the trigeminal sensory nuclei, in addition to relatively light projections to the contralateral Vc [134]. Activation of amygdaloid nuclei along with the ipsilateral Vc was identified following CSD in awake freely moving rodents [135].

The perception of trigeminal pain is significantly modulated by the hypothalamus in the diencephalon. A considerable number of Vc neurons directly send their axons to hypothalamic regions [102]. Vc neurons projecting to the hypothalamus respond exclusively to noxious stimulation of the dura mater. In turn, the paraventricular nucleus, the lateral hypothalamic area, the perifornical hypothalamic area, the A11 nucleus, and the retrochiasmatic area send projections to the Vc. Hypothalamic projections are preferentially involved in the processing of meningeal and cutaneous inputs from the ophthalmic branch of the trigeminal nerve [136]. The latter finding indicates a somatotopic modulation of the Vc neurons by the hypothalamus. Descending hypothalamic projections to the Vc are bilateral, except those from the paraventricular nucleus that exhibit an ipsilateral predominance.

1.3.1.3 Descending Antinociceptive Systems

The transmission of nociceptive information to second-order trigeminal neuron is controlled by the inhibitory pathway descending from the periaqueductal gray matter (PAG) and from the rostral ventromedial medulla (RVM) (Figs. 1.3 and 1.4). The PAG located in the mesencephalon around the Sylvius aqueduct is the key structure

Top-down modulation of headache perception
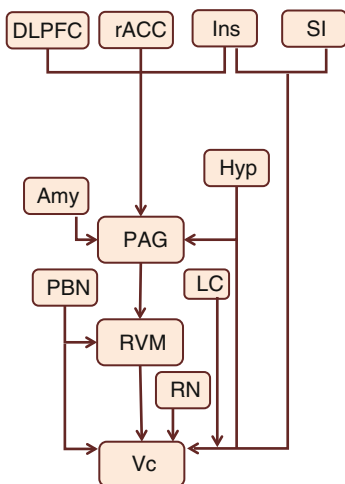
Fig. 1.4 Schematic representation of top-down, descending modulation of headache. The transmission of nociceptive information to second-order trigeminal neurons is controlled by inhibitory pathways descending from the periaqueductal gray (*PAG*) and from the rostral ventromedial medulla (*RVM*). Cortical inputs from pain-processing cortical areas such as the somatosensory areas, the insular cortex, the prefrontal cortex, and the anterior cingulate cortex project to the PAG. The hypothalamus, amygdala, PBN, locus coeruleus, and Raphé nuclei send projections to the descending pain inhibitory system. The dorsolateral prefrontal cortex (*DLPFC*) is related to attentional modulation of pain, the rostral anterior cingulate cortex (*rACC*) is implicated in placebo response, and morphine, noradrenaline, and serotonin are essential players in that system. *rACC* rostral anterior cingulate cortex, *Amy* amygdala, *Ins* insular cortex, *LC* locus coeruleus, *PAG* periaquadctal gray matter, *PBN* parabrachial nucleus, *DLPFC* dorsolateral prefrontal cortex, *RN* Raphé nucleus, *RVM* rostroventromedial medulla, *SI* primary somatosensory cortex, *Vc* caudal trigeminal brainstem nucleus

in descending pain modulation with its powerful inhibitory properties on pain perception. Higher cerebral cortical structures, such as the hypothalamus and amygdala, have been also implicated in the descending modulation of nociceptive activity [137–139]. Cortical inputs from pain-processing cortical areas such as the somatosensory areas, the insular cortex, the prefrontal cortex, and the anterior cingulate cortex to the PAG were demonstrated in several species [140, 141]. It is suggested that the RVM is the final relay station for descending antinociceptive information from the forebrain [142], as inputs from higher brain centers converge on the PAG and the RVM to exert pain-suppressive effects. Stimulation of the RVM as well as PAG stimulation has been shown to suppress nociceptive responses [143].

There are distinct neuronal subpopulations within the RVM that project caudally. Depending on the features of nociceptive stimuli (such as strength and duration), RVM neurons could yield either excitatory (on cells) or inhibitory (off cells) response to a noxious stimulus. Both neuronal subtypes are activated by electrical stimulation of the PAG. Morphine applied into the PAG or given systemically

suppresses on-cell activity and increases off-cell activity [144]. Supraspinal opioid receptors play a key role in descending inhibitory controls relaying through the PAG and RVM.

In addition, there are serotonergic RVM cells projecting to the spinal cord [145] which contribute to descending antinociceptive inhibition by stimulation of the RVM or PAG [138, 146]. Descending projections from the noradrenergic neuronal cell groups in the locus coeruleus, subcoeruleus, A5, and A7 have a significant antinociceptive influence through spinal α2-adrenoceptors [146, 147]. It is notable that the locus coeruleus has direct inputs from the central nucleus of the amygdala, preoptic area, and paraventricular nucleus of the hypothalamus. GABAergic and glycinergic interneurons within the nociceptive laminae of the Vc mediate inhibitory effect on the transduction of nociceptive impulses to second-order neurons [148].

The amygdala plays a key role in emotional behavior, as inputs from the tri-gemino–parabrachio–amygdaloid pathway contribute to pain-induced changes in affective behavior and direct amygdalofugal projections to the PAG–RVM system provide feedback modulation of emotions on pain [137]. Through the latter pathway, application of opioids into the amygdala has been shown to induce antinociceptive effects [137] (Fig. 1.4). The parabrachial nuclei have direct projections to the trigeminocervical complex [149], and their electrical stimulation also exerted inhibitory effects on the activity of nociceptive neurons in the Vc.

Neurons of the paraventricular nucleus of the hypothalamus (PVN) send descending projections to laminae I and II of the Vc as well as the superior salivatory nucleus (Fig. 1.4). The latter nucleus gives rise to parasympathetic outflow to the cephalic vasculature, particularly in response to trigeminal activation, and could modulate neurogenic inflammation in the meninges [56, 150, 151]. Stimulation of the hypothalamic A11 nucleus has been shown to decrease the dural stimulation-evoked responses of Vc neurons. As a whole, those findings support the top-down modulation of the hypothalamus on Vc activities particularly driven by meningeal nociceptors.

The hypothalamic nuclei, particularly the paraventricular nucleus and/or arcuate nucleus, are involved in stress-induced analgesia [152]. Electrical stimulation of the hypothalamus results in antinociception. The hypothalamic PVN, PAG, and central nuclei of the amygdala take part in the stress-induced analgesic system [153]. It is notable that the rostral ACC, which is rich in opiate receptors, also participates in the endogenous analgesia [154]. During the analgesia induced by opioids or placebo, functional connectivity between the rACC and PAG has been found [155].

1.3.2   Cortical Areas Associated with Discriminative and Affective Aspects of Nociception

Perception of headache is a complex function of the cerebral cortex and involves distinct parts of the brain, which processes sensory discriminative, affective–emotional, and metacognitive aspects of nociception. Pain studies demonstrated that the

activation of a cortical network of brain structures involving the somatosensory cortices SI and SII, the insular cortex, the anterior cingulate cortex (ACC), and the frontal cortex (DLPFC, orbitofrontal) is associated with nociceptive experience.

1.3.2.1 Cortical Structures of Discriminative Head Pain

The sensory discriminative and affective–motivational aspects of pain are transmitted through different systems and encoded in distinct cortical regions. The bottom-up organization of pain perception occurs through at least two major ascending pathways, the lateral and medial nociceptive systems [156]. The lateral nociceptive system comprises lamina I neurons projecting to the primary and secondary somatosensory cortex via the lateral thalamus and is involved in sensory discrimination of nociception [157, 158] (Fig. 1.3). Accordingly, it was demonstrated that manipulation of pain intensity was associated with changes mainly in the SI cortex, while the subjective ratings of pain unpleasantness were correlated with activity in the ACC [159].

Nociceptive stimulation of the ophthalmic branch of the trigeminal nerve, which preferably provides nociceptive information mediating headache, also activates similar cerebral cortical regions such as the somatosensory cortex, the insula, and the anterior cingulate cortex [160]. Descending cortical projections from the cerebral cortex to the trigeminal nucleus caudalis (Vc) have been demonstrated. Cortical projections originate contralaterally from insular (Ins) and primary somatosensory (SI) cortices. Projections from the primary sensory cortex terminate in deeper lamina, while projections from the insular cortex target solely superficial nociceptive laminae (laminae I and II) [161, 162] and inhibit trigeminal nociception, and meningeal-driven nociceptive inputs onto Vc were shown to be facilitated and inhibited by projections from the insula and SI, respectively [162].

1.3.2.2 Cortical Structures of Affective Pain Modulation

The medial nociceptive system that is directed toward the anterior cingulate cortex (ACC) through the parabrachial nucleus (PBN), parafascicular nucleus, and amygdala is involved in the affective–emotional aspects of nociception [157, 163, 164] (Fig. 1.3). Furthermore nociceptive information may be transmitted to the forebrain from the PBN and amygdala. The prefrontal cortex and the orbitofrontal cortex are implicated in the evaluation of affective experiences [165]. These pathways may contribute to the emotional aspects of pain and to the interactions between hedonic and cognitive processes of pain.

The majority of trigeminal ganglion neurons project multisynaptically to the anterior cingulate cortex (ACC). Iwata et al. [164] demonstrated by employing extracellular unit recordings that the ascending somatosensory pathways to the ACC from the trigeminal primary afferents arise mainly from Aδ and Aβ fibers but not from C fibers. The ACC predominantly receives projections from the lateral parabrachial nucleus. The parabrachial nuclei convey incoming nociceptive

information from the Vc to the basolateral amygdaloid BLA nucleus [133]. The anatomical connections from Vc-parabrachial-BLA-ACC are thought to be involved in emotional and autonomic functions during trigeminal nociception.

The insula and amygdala, as components of the medial nociceptive pathway, have been implicated in evaluative and affective processes. The insular cortex sends projections to trigeminal nucleus caudalis. Tracing studies identified that many neurons in the granular and dysgranular insular cortex project to the laminae I/II of Vc bilaterally with a contralateral predominance. It is important to note that the direct projections from the insula only target to laminae I/II while sparing the lamina V of Vc [166]. Strong projections from the insular cortex to the bilateral rostral ventromedial medulla (RVM) and the nucleus of the solitary tract were detected. Bilateral insular projections with an ipsilateral predominance to the parabrachial nucleus were shown [161]. The insula is one of the important cortical pain-associated centers, and nociceptive processing of Vc neurons may be directly modulated through the insula or indirectly through brainstem nuclei such as PAG, PBN, and RVM. The insular cortex is pivotal in interoception and homeostatic functions [167]. Lesions of the insula are often associated with increased tolerance of pain.

Pain perception was also modulated by expectations and attention, and studies implicated the role of the dorsolateral prefrontal cortex (DLPFC) and the orbitofrontal cortex (OFC) during distraction and anticipation. The DLPFC may have a "top-down" mode of inhibition on the ascending nociceptive systems and is related with attentional modulation of pain (Figs. 1.3 and 1.4). In support of the pain modulatory function of the DLPFC, the anatomical connections between prefrontal cortices and the midbrain structure periaqueductal gray (PAG) were demonstrated by using diffuse tensor imaging [168]. Increased DLPFC activity was correlated with reduction in the affective component of nociceptive pain [169] and increased activity in the anterior cingulate cortex (ACC) along with increased activity in the PAG. Since the DLPFC activation was associated with decrease of nociception, repetitive transcranial magnetic stimulation (TMS) application to DLPFC was used for chronic migraine and fibromyalgia management [169, 170].

1.3.2.3 Functional Connectivity and Cortical Networks

Acute pain is a complex experience that is associated with activation of many structures in the brain that is often called pain matrix. The main components of the pain network are cortical structures of SI, SII, IC, ACC and PFC and the thalamus, which is the gate to sensorial input to the cerebral cortex and pacemaker for thalamocortical oscillations. The functional connectivity of such a network is important, and recent imaging studies have been focused on the alterations of functional connectivity during resting state (default mode network) or task performance. Chronic headache disorders have often been reported to be associated with changes in the brain networks during resting state and/or in response to stimuli.

Resting-state abnormalities were found in brain regions associated with pain processing and cognition in migraine patients [171–173]. Functional connectivity

studies in patients suffering from temporomandibular disorders (TMD) revealed an increased connectivity of the anterior insula and anterior cingulate cortex. The latter finding was suggested to indicate an adaptation of the pain modulatory system early in the chronification process [174].

The resting-state functional connectivity of the hypothalamus was increased with parts of the frontal, parietal, and temporal cortex interictally in cluster headache patients [175]. However, the increased resting-state functional connectivity of the hypothalamus with the ACC and the posterior cingulate cortex (PCC) was detected during acute spontaneous cluster headache attacks. Functional MR studies revealed a diffuse abnormality of brain functional connectivity in cluster headache patients, which extends beyond the pain matrix primarily to cerebellar, frontal, and occipital areas [176, 177]. A recent case study demonstrated that cerebral activation of the ipsilateral trigeminal root entry zone, ventral pons, red nucleus, basal ganglia, cerebellum, prefrontal cortex, insula, and cingulate cortex was associated with ipsilateral hypothalamic activation during the cluster headache attack [178].

Structural MR studies in medication overuse headache (MOH) patients demonstrated increased gray matter thickness in the midbrain including periaqueductal gray matter and nucleus cuneiformis, which was partially reversed by the treatment in parallel to clinical improvement. It was proposed that the decreased gray matter in the orbitofrontal cortex could be predictive of poor response to treatment in MOH [179].

1.4 Gender Differences in Headache Anatomy

Gender differences in the epidemiology of headache disorders are well known; however, experimental headache studies conducted on females are significantly scarce [180, 181]. After reviewing the literature on headache and gender differences, it can be concluded that the medial pain pathway related to the affective–motivational aspects of headache seems to be more involved in women, which is briefly presented in the following section: (a) Capsaicin-induced trigeminal sensitization as detected by the visual flair and allodynic areas was greater in women particularly during menstruation phase compared to men [182]. (b) In women the resting cerebral metabolic glucose utilization in the orbitofrontal area was greater than in men [183]. (c) During negative affects such as anxiety and anger, the cerebellum, midbrain, thalamus, and ACC were more activated in women [184]. (d) In default mode network, there is a difference in insular processing between men and women's brain [185]. (e) In migraineurs, the posterior insular and precuneus cortices are thicker in women [186]. (f) Heat pain induced greater activation in the PFC, ACC, insula, and thalamus in women [187–189].

Experimental animal studies are in line with human data: (a) In female mice, the functional connectivity between nodes of descending antinociception and affective system was stronger compared to male mice [63]. (b) Female rats exhibited significant sex differences in activation pattern of temporomandibular joint-responding neurons in the trigeminal brainstem and their projections on subcortical structures

[190]. (c) In female rats, the density of dural mast cells is higher than in males, and estradiol promotes an increase in mast cell numbers along with a change in the phenotype [191]. (d) There are estrogen receptors and terminals in PBN subregions that are related to pain modulation [192]. (e) Estrogens modify nitroglycerin-induced c-fos expression in PVH, SON, SPVC, and CGRP expression in female rat brain [193]. (f) Cortical spreading depression susceptibility of FHM-1 knock-in mice was increased in female sex which was influenced by gonadal hormones [194, 180].

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