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Review

Migraine pathophysiology: Anatomy of the trigeminovascular pathway and associated neurological symptoms, cortical spreading depression, sensitization, and modulation of pain

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ABSTRACT

Scientific evidence supports the notion that migraine pathophysiology involves inherited alteration of brain excitability, intracranial arterial dilatation, recurrent activation, and sensitization of the trigeminovascular pathway, and consequential structural and functional changes in genetically susceptible individuals. Evidence of altered brain excitability emerged from clinical and preclinical investigation of sensory auras, ictal and interictal hypersensitivity to visual, auditory, and olfactory stimulation, and reduced activation of descending inhibitory pain pathways. Data supporting the activation and sensitization of the trigeminovascular system include the progressive development of cephalic and whole-body cutaneous allodynia during a migraine attack. In addition, structural and functional alterations include the presence of subcortical white mater lesions, thickening of cortical areas involved in processing sensory information, and cortical neuroplastic changes induced by cortical spreading depression. Here, we review recent anatomical data on the trigeminovascular pathway and its activation by cortical spreading depression, a novel understanding of the neural substrate of migraine-type photophobia, and modulation of the trigeminovascular pathway by the brainstem, hypothalamus and cortex.

1. Introduction

Migraine is a disabling neurovascular disorder characterized by mostly unilateral throbbing head pain and a host of neurological symptoms including hypersensitivity to light, sound, and smell; nausea; and a variety of autonomic, cognitive, emotional, and motor disturbances [73,94]. Although the initiation of a migraine attack is frequently associated with a wide variety of internal and external triggers such as stress, hormonal fluctuations, sleep disturbances, meal skipping, or sensory overload [54,70], the neural and vascular mechanisms underlying the development of this primary condition remain to be elucidated. Because of the complexity of this disorder, which is not limited to its multifactorial origin but also includes remarkable premonitory symptomatology, it is thought that migraine headache is a manifestation of a brain state of altered excitability capable of activating the trigeminovascular system in genetically susceptible individuals [24,101,119].

An estimated 16% of the worldwide population suffer from migraine headache, and about one-third of those migraines are preceded by neurological symptoms associated with a transient cortical malfunction, collectively known as aura [66,124]. Such cortical disturbances arise from the phenomenon of cortical spreading depression (CSD), which occurs spontaneously in the human cortex before the onset of the headache [18,43]. The susceptibility for its occurrence likely depends on genetic factors that render the cerebral cortex hyperexcitable through abnormal excitatory/inhibitory balance [128]. Although there is a large body of evidence that supports the role of CSD as a key event for the activation of the trigeminovascular system [16,86,136,137], scientific evidence of asymptomatic CSD-like events in migraine without aura remain to be provided. This review will focus on relevant preclinical and clinical data that improve our understanding of the pathophysiology of migraine and its associated symptoms.

2. Anatomical substrate of the trigeminovascular pain pathways

2.1. Peripheral innervation of the trigeminovascular system

The headache phase of a migraine attack is thought to originate in activation of nociceptors innervating pial, arachnoid, and dural

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blood vessels, as well as large cerebral arteries and sinuses [95,99,105]. Activation of these structures by mechanical, electrical, or chemical (proinflammatory molecules, blood, or infection) stimulation, give rise to headaches that are remarkably similar to the pain of migraine and its most common associated symptoms: nausea, throbbing pain, photophobia, and phonophobia. The nociceptive innervation of intracranial vasculature and the meninges consists of nonmyelinated (C-fibers) and thinly myelinated (Aδ fibers) axons containing vasoactive neuropeptides such as substance P (SP) and calcitonin gene–related peptide (CGRP). They originate in the trigeminal ganglion [53,69,126] and reach the dura mainly through the ophthalmic branch of the trigeminal nerve (V1) and, to a lesser extent, through the maxillary (V2) and mandibular (V3) divisions. Additional innervation of the dura is provided by neurons in the upper cervical dorsal root ganglia [80].

Whether the vascular origin of the headache during migraine is or is not a viable theory has been debated for decades. In a recent study using magnetic resonance angiography in patients undergoing triggered attacks, Asghar et al. [4] described the reversal of unilateral intracranial dilatation of the medial meningeal artery by sumatriptan (5HT-1B/1D receptor agonist), along with the amelioration of same-sided headaches. In a follow-up study, however, Amin et al. [2] found evidence for slight intracranial vasodilatation that was not affected by sumatriptan, and no evidence for extracranial vasodilatation in patients undergoing spontaneous attacks, suggesting that vascular changes might not have a primary role in migraine.

2.2. Central projections of meningeal primary afferents

Central processes of meningeal sensory afferents enter the brainstem via the trigeminal tract and pass caudally while giving off collaterals that terminate in the spinal trigeminal nucleus (SpVC) and upper cervical spinal cord (C1–3). Anatomical and electrophysiological studies have shown that the vast majority of Aδ and C nociceptive primary afferents terminate in the superficial layers (laminae I and II), and that some Aδ fibers terminate in lamina V of the SpVC [11,22,72]. These meningeal nociceptors converge on trigeminovascular SpVC neurons that receive additional input from the adjacent skin and muscles [22]. The resultant convergence of intracranial (visceral) and extracranial (somatic) primary afferents onto SpVC neurons likely contributes to the referred pain perception in the periorbital and occipital regions.

2.3. Ascending projections of SpVC trigeminovascular neurons

A wide variety of symptoms that are associated with migraine headache, such as irritability, fatigue, sleepiness, exaggerated emotional responses, nausea, and loss of appetite, may appear before or after the onset of the headache. Most likely, the symptoms that appear before the onset of migraine (i.e., prodromes) are related to abnormal neuronal activity in cortical, diencephalic, and/or brainstem structures. In contrast, the most likely explanation for symptoms that appear after the onset of migraine (more common and more consistent) is the bombardment of supramedullary brain structures involved in sensory, affective, endocrine, and autonomic functions by intracranial pain signals originating in the meninges. Such nociceptive information is transmitted to second-order trigeminovascular neurons in the SpVC. Available data describe projections of functionally identified trigeminovascular neurons from SpVC to the parabrachial area (PB), anterior hypothalamic (AH), lateral hypothalamic (LH), and perifornical (PeF) hypothalamic areas, lateral preoptic nucleus (LPO), zona incerta, and ventral osteromedial (VPM), posterior (Po), and parafascicular (Pf) thalamic nuclei [22]. In addition, the ventrolateral area of the upper cervical and medullary dorsal horn, an area containing the majority of second-order trigeminovascular neurons [22,120,121], projects to the ventrolateral periaqueductal gray matter (vlPAG), rostral trigeminal spinal nuclei, nucleus of the solitary tract, brainstem reticular areas, superior salivatory nuclei, and cuneiform nuclei [22,39,92].

2.4. Projections from thalamic trigeminovascular neurons to the cerebral cortex

In agreement with human functional imaging studies that show activation of posterior/dorsal thalamic areas in spontaneous migraine [1,21], animal studies have identified trigeminovascular neurons in the posterior (Po), lateral posterior/dorsal (LP/LD), and ventral posteromedial (VPM) thalamic nuclei [3,21,25,91,115,135]. A recent neuroanatomical study showed that the axonal trajectories and cortical projections of such neurons are defined by their thalamic nucleus of origin. For example, VPM dura-sensitive neurons

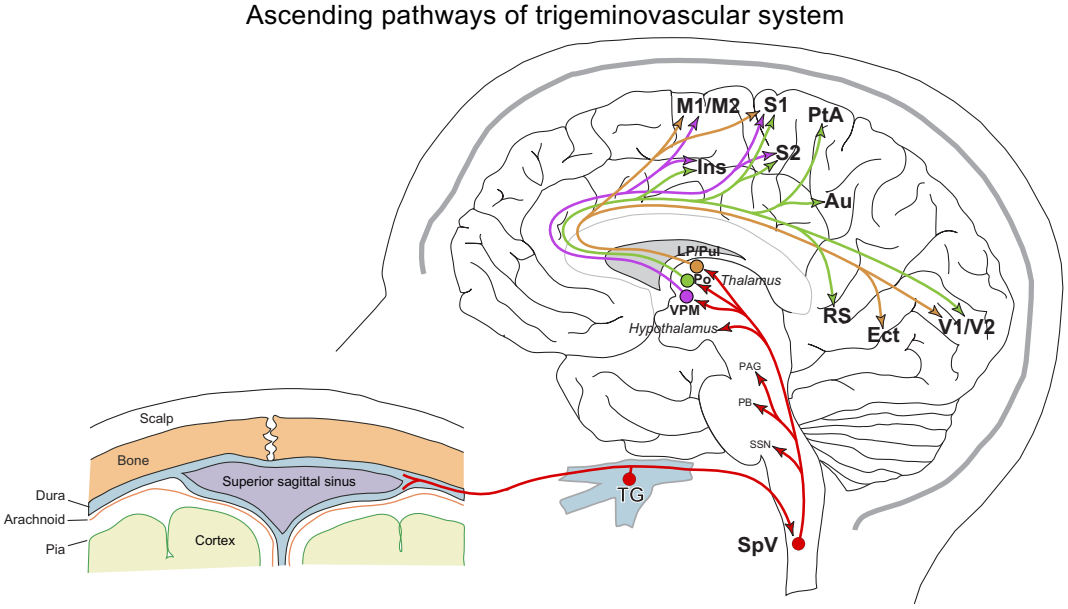

Fig. 1. Schematic representation of ascending neuronal pathways of the trigeminovascular system that are involved in the different aspects of migraine.

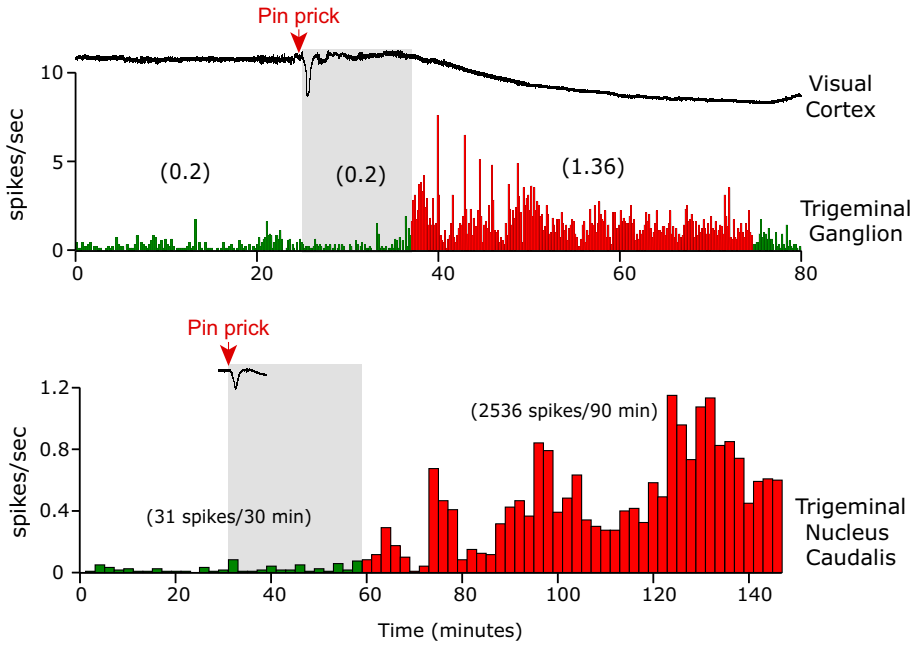

Fig. 2. Electrophysiological recordings showing delayed activation of meningeal nociceptors (top) and spinal trigeminal nucleus (SpVC) trigeminovascular neurons (bottom) by cortical spreading depression. (Adapted from Zhang et al. [136] and Zhang et al. [136].)

in VPM project to trigeminal areas of the primary and secondary somatosensory (S1/S2) cortices, as well as the insula, suggesting a role in sensory-discriminative components of migraine such as location, intensity, and quality of pain . On the contrary, dura-sensitive neurons in Po, LP, and LD project to multiple cortical areas such as motor, parietal association, retrosplenial, somatosensory, auditory, visual and olfactory cortices, suggesting a role in motor clumsiness, difficulty focusing, transient amnesia, allodynia, phonophobia, photophobia and osmophobia [90,91] (Fig. 1).

3. Activation and sensitization of the trigeminovascular pathway: Animal studies and clinical correlation

3.1. Cortical spreading depression and the activation of peripheral and central trigeminovascular neurons

About one-third of migraines are preceded by visual, motor, or somatosensory symptoms known as aura. The most frequent type of aura is characterized by a visual perception of light flashes moving across the visual field, and has been associated with a reversible, transient cortical event termed cortical spreading depression (CSD) [65,66]. CSD is a slowly propagating wave (2–6 mm/min) of neuronal and glial depolarization followed by a prolonged inhibition (15–30 minutes) of cortical activity [116,117]. First identified by Leão [67] in the rabbit, this distinctive electrophysiological phenomenon has been correlated with the visual aura that precedes the onset of headache in migraine [18,43,49,65,96]. At the cellular and molecular level, CSD has been shown to involve the local release of ATP, glutamate, potassium, and hydrogen ions by neurons, glia or vascular cells, and CGRP and nitric oxide by activated perivascular nerves [23,106,109,130]. These molecules are thought to diffuse toward the surface of the cortex, where they come into contact and activate pial nociceptors, triggering a consequential neurogenic inflammation (vasodilatation, plasma protein extravasation, and mast cell degranulation) and persistent activation of dural nociceptors [7,85]. Until recently, the notion that CSD activates the trigeminovascular system was supported only by indirect evidence showing that CSD induces an increase of c-fos expression in SpVC [16,86]. In support of this notion, direct electrophysiological confirmation of meningeal nociceptors activation by CSD, as well as the subsequent activation of central trigeminovascular neurons in SpVC, has emerged [136,137] (Fig. 2). In addition, a potential mechanistic explanation for how meningeal nociceptors activation begins after CSD has been recently proposed [51]. In that study, various experimental approaches were performed in mice to demonstrate that CSD causes the opening of neuronal Panx1 megachannels, resulting in a downstream cascade of events that leads to the release of pro-inflammatory molecules in the meninges. Novel anatomical evidence of dural nociceptors that issue collateral branches that cross the arachnoid and terminate in the pia provide a neural substrate for this possibility [59].

Although it is not clear how CSD begins in the human brain, genetic factors are likely to play a role in individual CSD susceptibility [7,100]. The current understanding of the genetic factors underlying migraine and CSD comes from studies of rare monogenic mutations in patients diagnosed with the common form of familial hemiplegic migraine (FHM) [26,27,31,98]. In agreement with the human data, mice carrying FHM mutations have shown increased susceptibility to CSD and altered synaptic transmission [36,68,125,127]. That cortical excitability is also altered in common migraine is evident in psychophysical and neurophysiological studies that demonstrate abnormal processing of sensory information even between attacks [6,24,64,119,133]. Such altered excitability may also contribute to typical migraine with aura, as suggested by a genetic mutation in a two-pore domain potassium channels that regulate neuronal resting potential and excitability [61]. Together, these findings support the notion that neuronal excitability plays a pivotal role in the predisposition to develop the different forms of migraine.

3.2. Peripheral and central sensitization

A large number of endogenous inflammatory mediators believed to be released during migraine are capable of activating and sensitizing peripheral and central trigeminovascular neurons.

Peripheral sensitization mediates the throbbing perception of the headache [122] (Fig. 3), whereas sensitization of second-order neurons in the SpVC mediates cephalic allodynia as well as muscle tenderness [19,21] (Fig. 4). Until recently, no neural substrate had been proposed for the extracephalic allodynia during migraine. A recent study showed (1) that innocuous brush and heat stimuli induce larger oxygen-level–dependent (BOLD) signal in the pulvinar thalamic nucleus of patients exhibiting signs of whole-body allodynia (cannot wear tight clothing, cannot use heavy blanket, cannot take a shower) during migraine, as compared to pain-free state; and (2) that topical application of inflammatory molecules on the rat meninges sensitized thalamic trigeminovascular neurons located in VPM, Po, and LP (Fig. 5). Collectively, these data suggest that the whole-body allodynia is mediated, at least in part, by the rostral subdivision of the pulvinar in the posterior thalamus of human beings and by the most dorsal and posterior part of the thalamus (i.e., Po) in animals [21].

4. Neural substrate of migraine-type photophobia

There are a few definitions of photophobia in the literature that refer to several light-induced neurological symptoms including exacerbation of headache, hypersensitivity to light, and ocular discomfort/pain. These symptoms are not manifested as a fear of light, as the term "phobia" suggests. They have been associated with intracranial pathologies such as migraine, meningitis, subdural hemorrhage, and intracranial tumors, as well as disorders of the anterior segment of the eye such as uveitis, cyclitis, iritis, and blepharitis [5,32,52,63,132]. In the last few years, new insights into the neurobiological mechanisms of light-induced neurological symptoms have emerged (Fig. 6).

4.1. Central mechanisms involved in exacerbation of headache by light, hypersensitivity to light, and ocular discomfort/pain

The perception of migraine headache is uniquely intensified during exposure to ambient light [52,73]. This migraine-type photophobia, commonly described as exacerbation of the headache by light, is experienced by nearly 90% of migraineurs with normal eyesight [33,73,84,113]. Clinical observations in blind migraineurs suggest that the exacerbation of headache by light depends on photic signals from the eye that converge on trigeminovascular neurons somewhere along its path.

The critical contribution of the optic nerve to migraine-type photophobia is best illustrated in migraine patients lacking any kind of visual perception because of complete damage of the optic nerve. Such patients testify that light does not hurt them during migraine, that their sleep cycle is irregular, and that light does not induce pupillary response. Conversely, exacerbation of headache by light is preserved in blind migraineurs with intact optic nerve, partial light perception, but no sight because of severe degeneration of rod and cone photoreceptors [91]. Retinal projections to the brain constitute 2 functionally different pathways. The first pathway allows the formation of images by photoactivation of rods and cones, and the second allows regulation of biological functions such as circadian photoentrainment, pupillary reflex, and melatonin release by activation of intrinsically photosensitive retinal ganglion cells containing melanopsin photoreceptors [38,56,75]. The activation of these cells is achieved not only by virtue of their unique photopigment melanopsin [15,103], but also extrinsically by rods and cones [42]. It is thus likely that all retinal photoreceptors contribute to migraine-type photophobia in migraineurs with normal eyesight.

Integrating the existing knowledge of the neurobiology of the trigeminovascular system and the anatomy of visual pathways, the following information is available: (1) light enhances the activity of thalamic trigeminovascular neurons; (2) a subgroup of light/dura-sensitive neurons located mainly in the LP/Po area of the posterior thalamus receive direct input from RGCs; and (3) the axons of these neurons project to cortical areas involved in the processing of pain and visual perception. Such convergence of photic signals from the retina onto the trigeminovascular thalamo-cortical pathway has been proposed as a neural mechanism for the exacerbation of migraine headache by light [91]. Further evidence

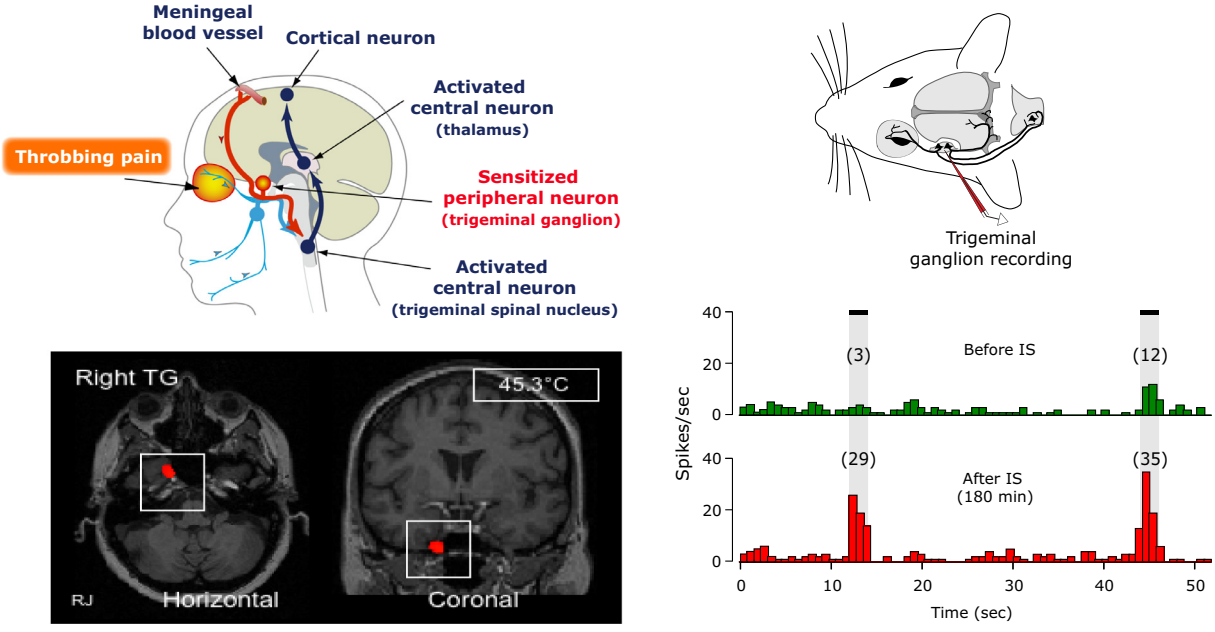

Fig. 3. Sensitization of meningeal nociceptors believed to mediate the throbbing nature of migraine pain. (Left) Schematic representation of peripheral sensitization and periorbital throbbing pain in human beings. Functional magnetic resonance imaging evidence showing activation of the trigeminal ganglion during migraine. (Right) Electrophysiological recording of a neuron in the rat trigeminal ganglion showing increased responsiveness to mechanical stimulation of the dura after topical application of inflammatory mediators (IS).

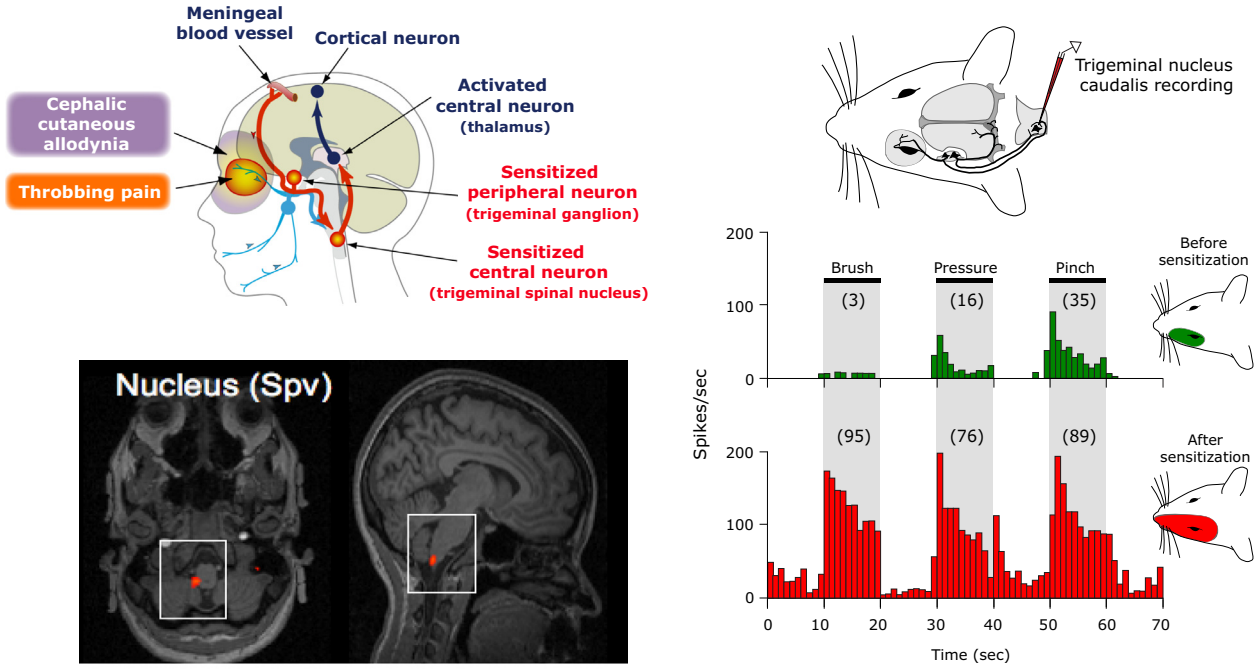

Fig. 4. Sensitization of central trigeminovascular neurons in the trigeminal nucleus caudalis believed to mediate cephalic cutaneous allodynia during migraine. (Left) Schematic representation of central sensitization of spinal trigeminal nucleus (SpVC) trigeminovascular neurons and cephalic cutaneous allodynia in human beings. Functional magnetic resonance imaging evidence showing activation of the spinal trigeminal nucleus during migraine. (Right) Electrophysiological recording of a neuron in the rat SpVC showing increased responsiveness to innocuous and noxious stimulation of the skin and the corresponding receptive field after induction of central sensitization.

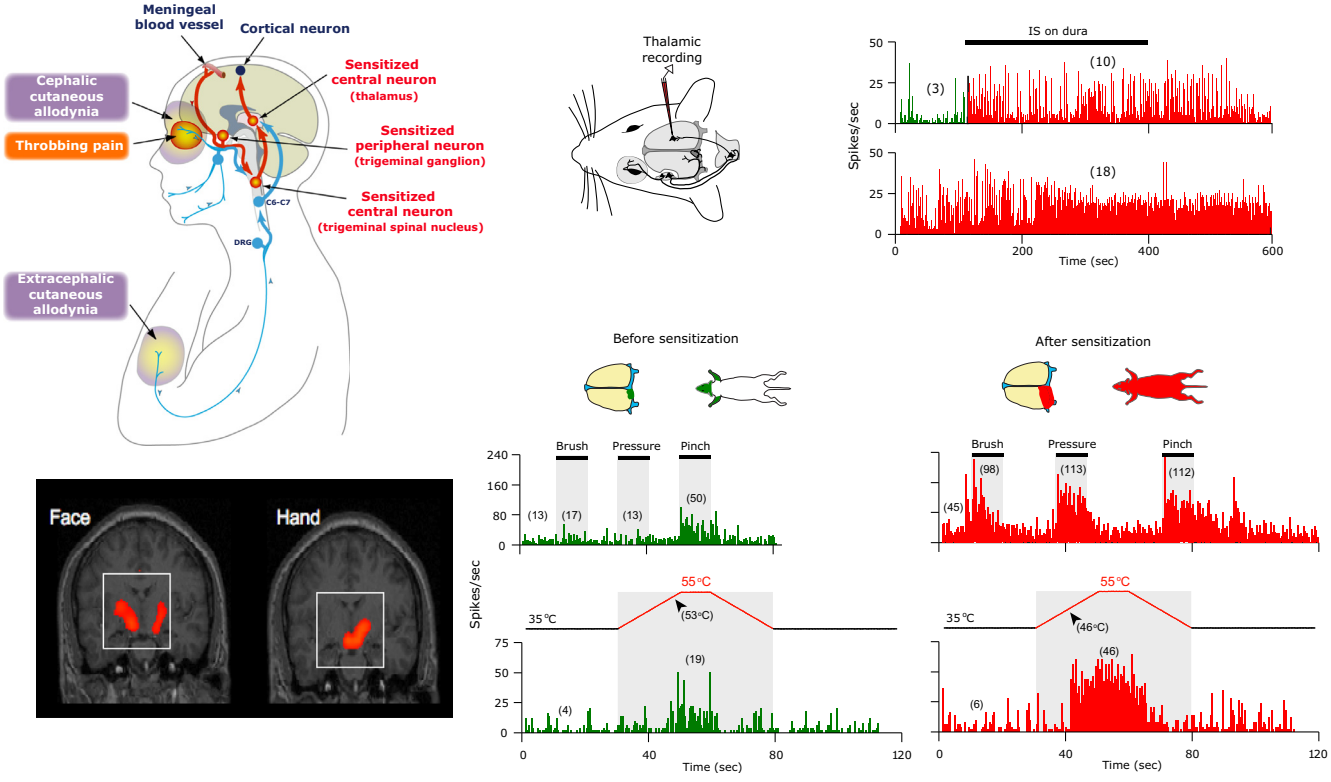

Fig. 5. Sensitization of central trigeminovascular neurons in the thalamus believed to mediate the extracephalic (whole-body) cutaneous allodynia during migraine. (Left) Schematic representation of central sensitization of thalamic trigeminovascular neurons and extracephalic cutaneous allodynia in human beings. Functional magnetic resonance imaging evidence showing activation of the thalamus during migraine. (Right) Electrophysiological recording of a neuron in the rat posterior thalamus showing increased responsiveness to mechanical and thermal stimulation of the skin and the corresponding dural and cutaneous receptive fields after induction of central sensitization by inflammatory mediators (IS) on the dura.

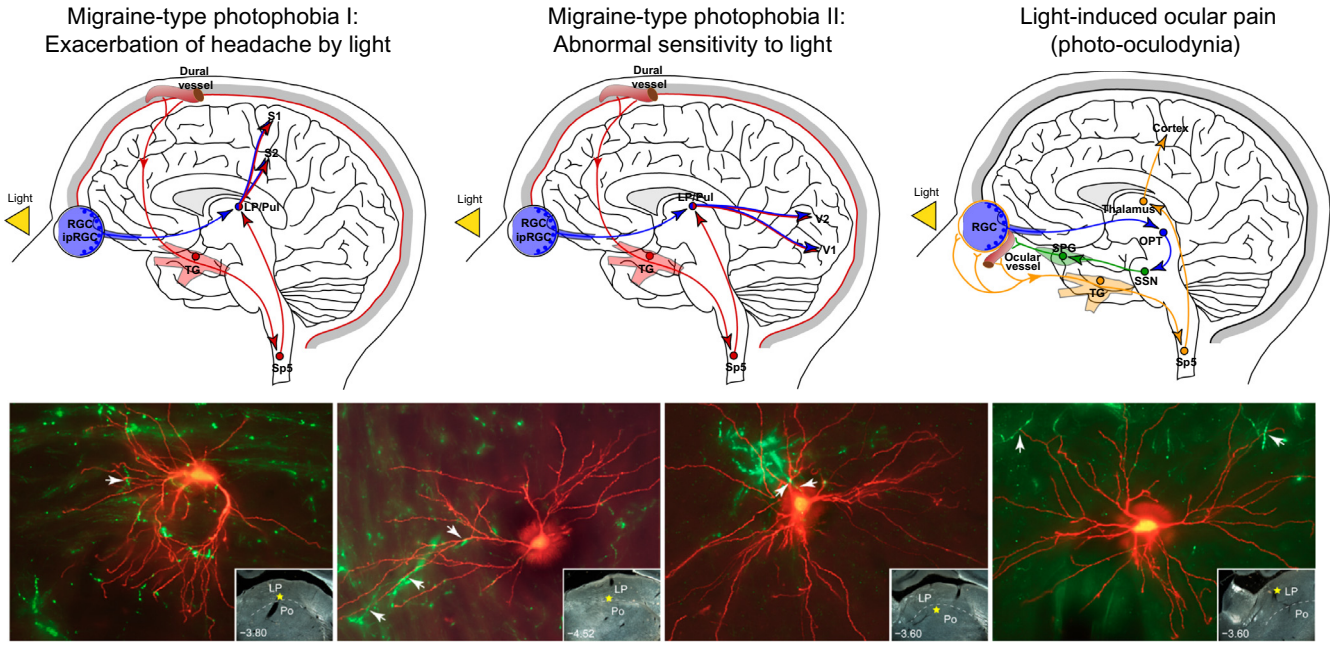

Fig. 6. Mechanisms of photophobia. (Top) Proposed mechanism for exacerbation of headache by light, hypersensitivity to light in migraine patients and ocular pain induced by light (Adapted from Noseda and Burstein [88]). (Bottom) Dura/light-sensitive neurons (red) closely apposed to retinal afferents (green) in the posterior thalamus (Adapted from Noseda et al. [91].)

supporting the existence of such pathway in human beings comes from imaging studies and probabilistic tractography that show BOLD responses in the pulvinar (LP/Po area in the rat) of patients undergoing a migraine attack with extracephalic allodynia [21], and direct pathways from the optic nerve to the pulvinar [76].

Some migraineurs describe photophobia as abnormal intolerance to light. Such description of photo-hypersensitivity suggests that the flow of nociceptive signals along the trigeminovascular pathway converges on the visual cortex and alters its responsiveness to visual stimuli. Indeed, the visual cortex appears to be hyperexcitable in migraineurs and may be the neural substrate of abnormal processing of light sensitivity [28]. Support for how meningeal pain could induce increased perception of light intensity refers to light/dura-sensitive thalamic neurons located outside the VPM nucleus that project directly to the primary and secondary visual cortices [88,91]. In addition, a transgenic mouse model of migraine to study light aversion or increased sensitivity to light has been recently developed. This genetically engineered model presents increased sensitivity to CGRP due to overexpression of the human receptor activity–modifying protein 1 (hRAMP1), and provides strong behavioral evidence of aversion to light after intracerebroventricular administration of CGRP [107,108].

Another clinical entity falling into the definition of photophobia is ocular discomfort or pain induced in the eye by exposure to bright light [88]. More appropriately termed photo-oculodynia, this type of photophobia is thought to originate from indirect activation of intraocular trigeminal nociceptors. As proposed by Okamoto et al. [93], bright light causes pain in the eye through activation of a complex neuronal pathway involving the olivary pretectal nucleus, the superior salivatory nuclei, and the sphenopalatine ganglion, which drives parasympathetically controlled vasodilatation and mechanical deformation of ocular blood vessels, which, in turn, activates trigeminal nociceptors and second-order nociceptive neurons in the SpVC. Lack of evidence for induction of vasodilatation by light in the human retina throws this scenario into question.

5. Brain regions associated with modulation of migraine pain

5.1. Cerebral cortex as a major source of trigeminovascular modulation

Endogenous modulation of trigeminal nociception certainly originates from the cortex, as most nociceptive relays within the central nervous system are under corticofugal control. A large and growing body of clinical and preclinical evidence points to an alteration in cortical excitability (dysexcitability) as a determinant factor for the susceptibility to migraine [6,8,24,64,119,128,133]. The mechanisms by which cortical dysexcitability contributes to migraine pathophysiology are largely unknown; however, it is possible that different cortical areas and their degree of excitability might be involved in the modulation of migraine pain through cortico-trigeminal pathways. In this respect, several anatomical studies have described direct, descending projections from the cerebral cortex to the SpVC in rats [30,48,89] and in human beings [60] (Fig. 7). Such cortico-trigeminal projections originate mainly from the contralateral primary somatosensory and insular cortices, and innervate both deep and superficial layers of the SpVC, respectively. These precisely organized cortico-trigeminal networks are anatomically positioned to influence meningeal nociception as shown by S1-mediated inhibition and insula-mediated facilitation of the excitability of SpVC dura-sensitive neurons [89,114].

5.2. Hypothalamic modulation of the trigeminovascular system

Although most of the functional imaging studies showing increased hypothalamic activity have been obtained from trigeminal autonomic cephalalgias (TACs) [82,83], there is 1 study implicating the hypothalamus in migraine [29]. The hypothalamus plays a critical role in autonomic and endocrine regulation [112], and has been implicated in the premonitory symptoms frequently experienced by migraineurs such as sleep–wake cycle disturbances, changes in mood, appetite, thirst, and urination [40]. The reciprocal anatomical connections between the hypothalamus and SpVC

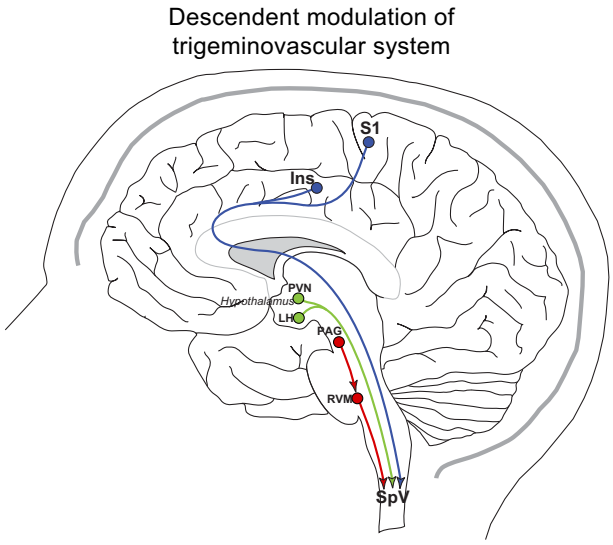

Fig. 7. Schematic representation of descending neuronal pathways that modulate trigeminovascular nociceptive transmission in the spinal trigeminal nucleus (SpVC).

[39,44,77,79,110,123] (Figs. 1 and 7) and the presence of neurons expressing c-fos in several hypothalamic nuclei after dural stimulation [14,78] support the role of the hypothalamus in different aspects of migraine [20]. For example, noxious stimulation of the dura activates parabrachial and ventromedial hypothalamic nucleus (VMH) neurons that expresses the receptor of the anorectic peptide cholecystokinin, creating a trigemino-parabrachial-hypothalamic circuit that can potentially mediate the loss of appetite during migraine [78]. Evidence showing that hypothalamic regions become activated during migraine [29] is also consistent with a role in pain modulation and therefore may contribute to the development of central sensitization of trigeminovascular neurons. In this regard, a recent study has provided experimental support for this scenario by showing in rodents that paraventricular hypothalamic nucleus (PVN) directly control both spontaneous and evoked activities of SpVC [110]. These findings suggest that PVN neurons could act either as modulators or triggers of migraine and/or TACs through the integration of nociceptive, autonomic, and stress responses. Such hypothalamic modulation of pain could be exerted through direct and indirect projections to the spinal and medullary dorsal horn by release of several neuropeptides such as orexin, somatostatin, dopamine, and oxytocin [45,50,74,111,134]. Furthermore, the hypothalamus also sends dense projections to the superior salivatory nuclei in the brainstem [47,118], suggesting that this circuit is contributing to the parasympathetic autonomic symptoms observed in migraine and cluster headache [41,62].

5.3. Brainstem nuclei as unspecific migraine modulator

Since the first published report describing delayed migraine-like pain in patients undergoing electrode implantation near the periaqueductal gray matter [104], and the first imaging study that followed it showing activation of the brainstem in spontaneous migraine [131], the notion of PAG as a "migraine generator" has been adopted. However, evidence supporting the role of PAG as a headache generator are lacking (see references in Borsook and Burstein [17]).

In theory, dysfunctional brainstem areas including the PAG could either enhance activity of neurons that facilitate trigeminovascular pain transmission or suppress activity of neurons that inhibit trigeminovascular pain transmission in the spinal and medullary dorsal horn [102] to generate migraine-like pain. Functionally, the activation of lateral and ventrolateral PAG neurons by direct ascending lamina I projections, produces nonselective, nonspecific pain relief, cardiovascular reactions (decrease in blood pressure), homeostatic reactions (temperature changes) and defensive reactions (immobility, arousal, avoidance behavior, and vocalization), as well as a more general emotional state of fear and anxiety [10,97]. Because the PAG projects minimally to the spinal and medullary dorsal horn but densely to the rostral ventromedial medulla (RVM), RVM neurons constitute a direct link for descending modulation through bilateral projections to all levels of spinal and medullary dorsal horns [12,37,46,81] (Fig. 7). These functional and anatomical studies are consistent with a broader modulatory role of the PAG–RVM circuit and suggest an absence of specificity for headache. Accordingly, descending modulatory "on" and "off" cells in the RVM are thought of as modulators because they can inhibit or facilitate the responses of ascending nociceptive neurons to noxious stimulation of their corresponding receptive fields. In this regard, facilitatory influences mediated by RVM neurons have been recently reported in an animal model of migraine pain through the assessment of cutaneous allodynia as a manifestation of central sensitization [35]. Furthermore, it has been shown that evoked neuronal activity in SpVC was inhibited by stimulation of the PAG [58] and that blocking the P/Q-type calcium channels in the PAG facilitates the activity of SpVC nociceptive neurons [57]. These studies support the role of descendent modulation and the inability of PAG-RVM to induce de novo activity in previously quiescent nociceptive neurons.

Conversely, several neuroimaging studies reporting brainstem activation in migraine patients do not include the PAG as an activated region during spontaneous or induced attacks. They do, however, show activation in nearby nuclei in the dorsolateral pons (DLP), which includes the mesencephalic trigeminal nucleus, principal sensory trigeminal nucleus, PB, vestibular nucleus, inferior colliculus, LC, and cuneiform nucleus [1,9,87,119,131]. This complex pattern of activation appears as not specific to migraine [13,34,55,71,129] and reflects a potential role in facial and muscle tenderness, abnormal tactile sensation, motion sickness, nausea, altered auditory perception, and, more importantly, modulation of pain.

5.4. Conclusion

The last 30 years of basic and clinical research in the field of headaches have greatly improved our understanding of migraine pathophysiology and therapy. Most likely, migraine headache depends both on activation of the trigeminovascular pathway by pain signals that originate in peripheral intracranial nociceptors, and on dysfunction of CNS structures involved in the modulation of neuronal excitability and pain. Because there is no evidence to date of paroxysmal conditions causing pain without peripheral afferent input, efforts to study this complex disorder must continue, to incorporate additional elements and to open the framework within which we conceptualize migraine pathophysiology.

Conflict of interest statement

The authors declare no conflict of interest.

References

[1] Afridi SK, Giffin NJ, Kaube H, Friston KJ, Ward NS, Frackowiak RS, Goadsby PJ. A positron emission tomographic study in spontaneous migraine. Arch Neurol 2005;62:1270–5.

[2] Amin FM, Asghar MS, Hougaard A, Hansen AE, Larsen VA, de Koning PJ, Larsson HB, Olesen J, Ashina M. Magnetic resonance angiography of intracranial and extracranial arteries in patients with spontaneous migraine without aura: a cross–sectional study. Lancet Neurol 2013;12:454–61.

[3] Angus-Leppan H, Olausson B, Boers P, Lambert GA. Convergence of afferents from superior sagittal sinus and tooth pulp on cells in the thalamus of the cat. Cephalalgia 1995;15:191–9.
[4] Asghar M, Hansen A, Amin F, van der Geast R, de Koning P, Larsson HB, Olesen J, Ashina M. Evidence for vascular factor in migraine. Ann Neurol 2011;69(4):635–45.
[5] Aurora SK, Cao Y, Bowyer SM, Welch KM. The occipital cortex is hyperexcitable in migraine: experimental evidence. Headache 1999;39:469–76.
[6] Aurora SK, Wilkinson F. The brain is hyperexcitable in migraine. Cephalalgia 2007;27:1442–53.
[7] Ayata C. Cortical spreading depression triggers migraine attack: pro. Headache 2010;50:725–30.
[8] Ayata C, Jin H, Kudo C, Dalkara T, Moskowitz MA. Suppression of cortical spreading depression in migraine prophylaxis. Ann Neurol 2006;59(4):652–61.
[9] Bahra A, Matharu MS, Buchel C, Frackowiak RS, Goadsby PJ. Brainstem activation specific to migraine headache. Lancet 2001;357:1016–7.
[10] Bandler R, Carrive P, Zhang SP. Integration of somatic and autonomic reactions within the midbrain periaqueductal grey: viscerotopic, somatotopic and functional organization. Prog Brain Res 1991;87:269–305.
[11] Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. Cell 2009;139:267–84.
[12] Basbaum AI, Fields HL. Endogenous pain control mechanisms: review and hypothesis. Ann Neurol 1978;4:451–62.
[13] Becerra L, Morris S, Bazes S, Gostic R, Sherman S, Gostic J, Pendse G, Moulton E, Scrivani S, Keith D, Chizh B, Borsook D. Trigeminal neuropathic pain alters responses in CNS circuits to mechanical (brush) and thermal (cold and heat) stimuli. J Neurosci 2006;26:10646–57.
[14] Benjamin L, Levy MJ, Lasalandra MP, Knight YE, Akerman S, Classey JD, Goadsby PJ. Hypothalamic activation after stimulation of the superior sagittal sinus in the cat: a Fos study. Neurobiol Dis 2004;16:500–5.
[15] Berson DM, Dunn FA, Takao M. Phototransduction by retinal ganglion cells that set the circadian clock. Science 2002;295:1070–3.
[16] Bolay H, Reuter U, Dunn AK, Huang Z, Boas DA, Moskowitz MA. Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. Nat Med 2002;8:136–42.
[17] Borsook D, Burstein R. The enigma of the dorsolateral pons as a migraine generator. Cephalalgia 2012;32:803–12.
[18] Bowyer SM, Aurora KS, Moran JE, Tepley N, Welch KM. Magnetoencephalographic fields from patients with spontaneous and induced migraine aura. Ann Neurol 2001;50:582–7.
[19] Burstein R, Cutrer FM, Yarnitsky D. The development of cutaneous allodynia during a migraine attack: clinical evidence for the sequential recruitment of spinal and supraspinal nociceptive neurons in migraine. Brain 2000;123:1703–9.
[20] Burstein R, Jakubowski M. Unitary hypothesis for multiple triggers of the pain and strain of migraine. J Comp Neurol 2005;493:9–14.
[21] Burstein R, Jakubowski M, Garcia-Nicas E, Kainz V, Bajwa Z, Hargreaves R, Becerra L, Borsook D. Thalamic sensitization transforms localized pain into widespread allodynia. Ann Neurol 2010;68:81–91.
[22] Burstein R, Yamamura H, Malick A, Strassman AM. Chemical stimulation of the intracranial dura induces enhanced responses to facial stimulation in brain stem trigeminal neurons. J Neurophysiol 1998;79:964–82.
[23] Charles A, Brennan K. Cortical spreading depression—new insights and persistent questions. Cephalalgia 2009;29:1115–24.
[24] Coppola G, Pierelli F, Schoenen J. Is the cerebral cortex hyperexcitable or hyperresponsive in migraine? Cephalalgia 2007;27:1427–39.
[25] Davis KD, Dostrovsky JO. Properties of feline thalamic neurons activated by stimulation of the middle meningeal artery and sagittal sinus. Brain Res 1988;454:89–100.
[26] De Fusco M, Marconi R, Silvestri L, Atorino L, Rampoldi L, Morgante L, Ballabio A, Aridon P, Casari G. Haploinsufficiency of ATP1A2 encoding the Na+/K+ pump alpha2 subunit associated with familial hemiplegic migraine type 2. Nat Genet 2003;33:192–6.
[27] de Vries B, Frants RR, Ferrari MD, van den Maagdenberg AM. Molecular genetics of migraine. Hum Genet 2009;126:115–32.
[28] Denuelle M, Boulloche N, Payoux P, Fabre N, Trotter Y, Geraud G. A PET study of photophobia during spontaneous migraine attacks. Neurology 2011;76:213–8.
[29] Denuelle M, Fabre N, Payoux P, Chollet F, Geraud G. Hypothalamic activation in spontaneous migraine attacks. Headache 2007;47:1418–26.
[30] Desbois C, Le Bars D, Villanueva L. Organization of cortical projections to the medullary subnucleus reticularis dorsalis: a retrograde and anterograde tracing study in the rat. J Comp Neurol 1999;410:178–96.
[31] Dichgans M, Freilinger T, Eckstein G, Babini E, Lorenz-Depiereux B, Biskup S, Ferrari MD, Herzog J, van den Maagdenberg AM, Pusch M, Strom TM. Mutation in the neuronal voltage-gated sodium channel SCN1A in familial hemiplegic migraine. Lancet 2005;366:371–7.
[32] Digre KB, Brennan KC. Shedding light on photophobia. J Neuroophthalmol 2012;32:68–81.
[33] Drummond PD. A quantitative assessment of photophobia in migraine and tension headache. Headache 1986;26:465–9.
[34] Dunckley P, Wise RG, Fairhurst M, Hobden P, Aziz Q, Chang L, Tracey I. A comparison of visceral and somatic pain processing in the human brainstem using functional magnetic resonance imaging. J Neurosci 2005;25:7333–41.
[35] Edelmayer RM, Vanderah TW, Majuta L, Zhang ET, Fioravanti B, De Felice M, Chichorro JG, Ossipov MH, King T, Lai J, Kori SH, Nelsen AC, Cannon KE, Heinricher MM, Porreca F. Medullary pain facilitating neurons mediate allodynia in headache-related pain. Ann Neurol 2009;65:184–93.
[36] Eikermann-Haerter K, Dilekoz E, Kudo C, Savitz SI, Waeber C, Baum MJ, Ferrari MD, van den Maagdenberg AM, Moskowitz MA, Ayata C. Genetic and hormonal factors modulate spreading depression and transient hemiparesis in mouse models of familial hemiplegic migraine type 1. J Clin Invest 2009;119:99–109.
[37] Fields HL, Malick A, Burstein R. Dorsal horn projection targets of ON and OFF cells in the rostral ventromedial medulla. J Neurophysiol 1995;74:1742–59.
[38] Freedman MS, Lucas RJ, Soni B, von Schantz M, Munoz M, David-Gray Z, Foster R. Regulation of mammalian circadian behavior by non-rod, non-cone, ocular photoreceptors. Science 1999;284:502–4.
[39] Gauriau C, Bernard JF. A comparative reappraisal of projections from the superficial laminae of the dorsal horn in the rat: The forebrain. J Comp Neurol 2004;468:24–56.
[40] Giffin NJ, Ruggiero L, Lipton RB, Silberstein SD, Tvedskov JF, Olesen J, Altman J, Goadsby PJ, Macrae A. Premonitory symptoms in migraine: an electronic diary study. Neurology 2003;60:935–40.
[41] Goadsby PJ. Pathophysiology of cluster headache: a trigeminal autonomic cephalgia [Review]. Lancet Neurol 2002;1(4):251–7.
[42] Guler AD, Ecker JL, Lall GS, Haq S, Altimus CM, Liao HW, Barnard AR, Cahill H, Badea TC, Zhao H, Hankins MW, Berson DM, Lucas RJ, Yau KW, Hattar S. Melanopsin cells are the principal conduits for rod-cone input to non-image-forming vision. Nature 2008;453:102–5.
[43] Hadjikhani N, Sanchez Del Rio M, Wu O, Schwartz D, Bakker D, Fischl B, Kwong KK, Cutrer FM, Rosen BR, Tootell RB, Sorensen AG, Moskowitz MA. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. Proc Natl Acad Sci USA 2001;98:4687–92.
[44] Hancock MB. Cells of origin of hypothalamo-spinal projections in the rat. Neurosci Lett 1976;3:179–84.
[45] Holland PR. Modulation of trigeminovascular processing: novel insights into primary headache disorders. Cephalalgia 2009;29:1–6.
[46] Holstege G, Kuypers HG. The anatomy of brain stem pathways to the spinal cord in cat. A labeled amino acid tracing study. Prog Brain Res 1982;57:145–75.
[47] Hosoya Y, Matsushita M, Sugiura Y. A direct hypothalamic projection to the superior salivatory nucleus neurons in the rat. A study using anterograde autoradiographic and retrograde HRP methods. Brain Res 1983;266:329–33.
[48] Jacquin MF, Wiegand MR, Renehan WE. Structure-function relationships in rat brain stem subnucleus interpolaris. VIII. Cortical inputs. J Neurophysiol 1990;64:3–27.
[49] James MF, Smith JM, Boniface SJ, Huang CL, Leslie RA. Cortical spreading depression and migraine: new insights from imaging? Trends Neurosci 2001;24:266–71.
[50] Jones SL, Gebhart GF. Inhibition of spinal nociceptive transmission from the midbrain, pons and medulla in the rat: activation of descending inhibition by morphine, glutamate and electrical stimulation. Brain Res 1988;460:281–96.
[51] Karatas H, Erdener SE, Gursoy-Ozdemir Y, Lule S, Eren-Kocak E, Sen ZD, Dalkara T. Spreading depression triggers headache by activating neuronal Panx1 channels. Science 2013;339:1092–5.
[52] Kawasaki A, Purvin VA. Photophobia as the presenting visual symptom of chiasmal compression. J Neuroophthalmol 2002;22:3–8.
[53] Keller JT, Marfurt CF. Peptidergic and serotoninergic innervation of the rat dura mater. J Comp Neurol 1991;309:515–34.
[54] Kelman L. The triggers or precipitants of the acute migraine attack. Cephalalgia 2007;27:394–402.
[55] Keltner JR, Furst A, Fan C, Redfern R, Inglis B, Fields HL. Isolating the modulatory effect of expectation on pain transmission: a functional magnetic resonance imaging study. J Neurosci 2006;26:4437–43.
[56] Klein DC, Weller JL. Rapid light-induced decrease in pineal serotonin N-acetyltransferase activity. Science 1972;177:532–3.
[57] Knight YE, Bartsch T, Kaube H, Goadsby PJ. P/Q-type calcium-channel blockade in the periaqueductal gray facilitates trigeminal nociception: A functional genetic link for migraine? J Neurosci 2002;22(5):RC213.
[58] Knight YE, Goadsby PJ. The periaqueductal grey matter modulates trigeminovascular input: a role in migraine? Neuroscience 2001;106:793–800.
[59] Kosaras B, Jakubowski M, Kainz V, Burstein R. Sensory innervation of the calvarial bones of the mouse. J Comp Neurol 2009;515:331–48.
[60] Kuypers HG. Corticobular connexions to the pons and lower brain-stem in man: an anatomical study. Brain 1958;81:364–88.
[61] Lafreniere RG, Cader MZ, Poulin JF, Andres-Enguix I, Simoneau M, Gupta N, Boisvert K, Lafreniere F, McLaughlan S, Dube MP, Marcinkiewicz MM, Ramagopalan S, Ansorge O, Brais B, Sequeiros J, Pereira-Monteiro JM, Griffiths LR, Tucker SJ, Ebers G, Rouleau GA. A dominant-negative mutation in the TRESK potassium channel is linked to familial migraine with aura. Nat Med 2010;16:1157–60.
[62] Lai TH, Fuh JL, Wang SJ. Cranial autonomic symptoms in migraine: Characteristics and comparison with cluster headache. J Neurol Neurosurg Psychiatry 2009;80:1116–9.
[63] Lamonte M, Silberstein SD, Marcelis JF. Headache associated with aseptic meningitis. Headache 1995;35:520–6.
[64] Lang E, Kaltenhauser M, Neundorfer B, Seidler S. Hyperexcitability of the primary somatosensory cortex in migraine—a magnetoencephalographic study. Brain 2004;127(pt 11):2459–69.

[65] Lashley KS. Patterns of cerebral integration indicated by the scotomas of migraine. Arch Neurol Psychiatry 1941;46:259–64.
[66] Lauritzen M. Pathophysiology of the migraine aura. The spreading depression theory. Brain 1994;117:199–210.
[67] Leao A. Spreading depression of activity in cerebral cortex. J Neurophysiol 1944;7:359–90.
[68] Leo L, Gherardini L, Barone V, De Fusco M, Pietrobon D, Pizzorusso T, Casari G. Increased susceptibility to cortical spreading depression in the mouse model of familial hemiplegic migraine type 2. PLoS Genet 2011;7:e1002129.
[69] Levy D, Strassman AM. Mechanical response properties of A and C primary afferent neurons innervating the rat intracranial dura. J Neurophysiol 2002;88:3021–31.
[70] Levy D, Strassman AM, Burstein R. A critical view on the role of migraine triggers in the genesis of migraine pain. Headache 2009;49:953–7.
[71] Linnman C, Moulton EA, Barmettler G, Becerra L, Borsook D. Neuroimaging of the periaqueductal gray: state of the field. NeuroImage 2012;60:505–22.
[72] Liu Y, Broman J, Edvinsson L. Central projections of the sensory innervation of the rat middle meningeal artery. Brain Res 2008;1208:103–10.
[73] Liveing E. On megrim, sick headache. Nijmegen: Arts & Boeve Publishers; 1873.
[74] Lovick TA. Integrated activity of cardiovascular and pain regulatory systems: role in adaptive behavioural responses. Prog Neurobiol 1993;40:631–44.
[75] Lucas RJ, Douglas RH, Foster RG. Characterization of an ocular photopigment capable of driving pupillary constriction in mice. Nat Neurosci 2001;4:621–6.
[76] Maleki N, Becerra L, Upadhyay J, Burstein R, Borsook D. Direct optic nerve pulvinar connections defined by diffusion MR tractography in humans: implications for photophobia. Hum Brain Mapp 2012;33:75–88.
[77] Malick A, Burstein R. Cells of origin of the trigeminohypothalamic tract in the rat. J Comp Neurol 1998;400:125–44.
[78] Malick A, Jakubowski M, Elmquist JK, Saper CB, Burstein R. A neurohistochemical blueprint for pain-induced loss of appetite. Proc Natl Acad Sci USA 2001;98:9930–5.
[79] Malick A, Strassman RM, Burstein R. Trigeminohypothalamic and reticulohypothalamic tract neurons in the upper cervical spinal cord and caudal medulla of the rat. J Neurophysiol 2000;84:2078–112.
[80] Marfurt CF. The central projection of trigeminal primary afferent neurons in the cat as determined by the transganglionic transport of horseradish peroxidase. J Comp Neurol 1981;203:785–98.
[81] Mason P. Deconstructing endogenous pain modulations. J Neurophysiol 2005;94:1659–63.
[82] Matharu MS, Cohen AS, McGonigle DJ, Ward N, Frackowiak RS, Goadsby PJ. Posterior hypothalamic and brainstem activation in hemicrania continua. Headache 2004;44:747–61.
[83] May A, Bahra A, Buchel C, Frackowiak RS, Goadsby PJ. Hypothalamic activation in cluster headache attacks. Lancet 1998;352:275–8.
[84] Miller NR. Photophobia. In: Miller NR, editor. Walsh and Hoyt's clinical neuro-ophthlmology, vol. 2. Baltimore: Williams & Wilkins; 1985. p. 1099–106.
[85] Moskowitz MA, Macfarlane R. Neurovascular and molecular mechanisms in migraine headaches. Cerebrovasc Brain Metab Rev 1993;5:159–77.
[86] Moskowitz MA, Nozaki K, Kraig RP. Neocortical spreading depression provokes the expression of c-fos protein-like immunoreactivity within trigeminal nucleus caudalis via trigeminovascular mechanisms. J Neurosci 1993;13:1167–77.
[87] Moulton EA, Burstein R, Tully S, Hargreaves R, Becerra L, Borsook D. Interictal dysfunction of a brainstem descending modulatory center in migraine patients. PLoS One 2008;3:e3799.
[88] Noseda R, Burstein R. Advances in understanding the mechanisms of migraine-type photophobia. Curr Opin Neurol 2011;24:197–202.
[89] Noseda R, Constandil L, Bourgeais L, Chalus M, Villanueva L. Changes of meningeal excitability mediated by corticotrigeminal networks: a link for the endogenous modulation of migraine pain. J Neurosci 2010;30:14420–9.
[90] Noseda R, Jakubowski M, Kainz V, Borsook D, Burstein R. Cortical projections of functionally identified thalamic trigeminovascular neurons: implications for migraine headache and its associated symptoms. J Neurosci 2011;31:14204–17.
[91] Noseda R, Kainz V, Jakubowski M, Gooley JJ, Saper CB, Digre K, Burstein R. A neural mechanism for exacerbation of headache by light. Nat Neurosci 2010;13:239–45.
[92] Noseda R, Monconduit L, Constandil L, Chalus M, Villanueva L. Central nervous system networks involved in the processing of meningeal and cutaneous inputs from the ophthalmic branch of the trigeminal nerve in the rat. Cephalalgia 2008;28:813–24.
[93] Okamoto K, Tashiro A, Chang Z, Bereiter DA. Bright light activates a trigeminal nociceptive pathway. PAIN® 2010;149:235–42.
[94] Olesen J. The international classification of headache disorders. Headache 2008;48:691–3.
[95] Olesen J, Burstein R, Ashina M, Tfelt-Hansen P. Origin of pain in migraine: evidence for peripheral sensitisation. Lancet Neurol 2009;8:679–90.
[96] Olesen J, Larsen B, Lauritzen M. Focal hyperemia followed by spreading oligemia and impaired activation of rCBF in classic migraine. Ann Neurol 1981;9:344–52.
[97] Oliveras JL, Besson JM. Stimulation-produced analgesia in animals: behavioural investigations. Prog Brain Res 1988;77:141–57.
[98] Ophoff RA, Terwindt GM, Vergouwe MN, van Eijk R, Oefner PJ, Hoffman SM, Lamerdin JE, Mohrenweiser HW, Bulman DE, Ferrari M, Haan J, Lindhout D, van Ommen GJ, Hofker MH, Ferrari MD, Frants RR. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene CACNL1A4. Cell 1996;87:543–52.
[99] Penfield W. A contribution to the mechanism of intracranial pain. Assoc Res Nerv Dis Proc 1935;15:399–416.
[100] Pietrobon D. Familial hemiplegic migraine. Neurotherapeutics 2007;4:274–84.
[101] Pietrobon D, Moskowitz MA. Pathophysiology of migraine. Annu Rev Physiol 2013;75:365–91.
[102] Porreca F, Ossipov MH, Gebhart GF. Chronic pain and medullary descending facilitation. Trends Neurosci 2002;25:319–25.
[103] Provencio I, Jiang G, De Grip WJ, Hayes WP, Rollag MD. Melanopsin: an opsin in melanophores, brain, and eye. Proc Natl Acad Sci USA 1998;95:340–5.
[104] Raskin NH, Hosobuchi Y, Lamb S. Headache may arise from perturbation of brain. Headache 1987;27:416–20.
[105] Ray BS, Wolff HG. Experimental studies on headache. Pain-sensitive structures of the head and their significance in headache. Arch Surg 1940;41:813–56.
[106] Read SJ, Smith MI, Hunter AJ, Parsons AA. Enhanced nitric oxide release during cortical spreading depression following infusion of glyceryl trinitrate in the anaesthetized cat. Cephalalgia 1997;17:159–65.
[107] Recober A, Kaiser EA, Kuburas A, Russo AF. Induction of multiple photophobic behaviors in a transgenic mouse sensitized to CGRP. Neuropharmacology 2010;58:156–65.
[108] Recober A, Kuburas A, Zhang Z, Wemmie JA, Anderson MG, Russo AF. Role of calcitonin gene-related peptide in light-aversive behavior: implications for migraine. J Neurosci 2009;29:8798–804.
[109] Reuter U, Weber JR, Gold L, Arnold G, Wolf T, Dreier J, Lindauer U, Dirnagl U. Perivascular nerves contribute to cortical spreading depression-associated hyperemia in rats. Am J Physiol 1998;274:H1979–87.
[110] Robert C, Bourgeais L, Arreto CD, Condes-Lara M, Noseda R, Jay T, Villanueva L. Paraventricular hypothalamic regulation of trigeminovascular mechanisms involved in headaches. J Neurosci 2013;33:8827–40.
[111] Rojas-Piloni G, Lopez-Hidalgo M, Martinez-Lorenzana G, Rodriguez-Jimenez J, Condes-Lara M. GABA-mediated oxytocinergic inhibition in dorsal horn neurons by hypothalamic paraventricular nucleus stimulation. Brain Res 2007;1137:69–77.
[112] Saper CB. The central autonomic nervous system: conscious visceral perception and autonomic pattern generation. Annu Rev Neurosci 2002;25:433–69.
[113] Selby G, Lance JW. Observations on 500 cases of migraine and allied vascular headache. J Neurol Neurosurg Psychiatry 1960;23(1):23–32.
[114] Sessle BJ, Hu JW, Dubner R, Lucier GE. Functional properties of neurons in cat trigeminal subnucleus caudalis (medullary dorsal horn). II. Modulation of responses to noxious and nonnoxious stimuli by periaqueductal gray, nucleus raphe magnus, cerebral cortex, and afferent influences, and effect of naloxone. J Neurophysiol 1981;45:193–207.
[115] Shields KG, Goadsby PJ. Propranolol modulates trigeminovascular responses in thalamic ventroposteromedial nucleus: a role in migraine? Brain 2005;128:86–97.
[116] Smith JM, Bradley DP, James MF, Huang CL. Physiological studies of cortical spreading. Depression. 2006;81(4):457–81.
[117] Somjen GG. Mechanisms of spreading depression and hypoxic spreading depression-like depolarization. Physiol Rev 2001;81:1065–96.
[118] Spencer SE, Sawyer WB, Wada H, Platt KB, Loewy AD. CNS projections to the pterygopalatine parasympathetic preganglionic neurons in the rat: a retrograde transneuronal viral cell body labeling study. Brain Res 1990;534:149–69.
[119] Stankewitz A, Aderjan D, Eippert F, May A. Trigeminal nociceptive transmission in migraineurs predicts migraine attacks. J Neurosci 2011;31:1937–43.
[120] Strassman AM, Mason P, Moskowitz M, Maciewicz RJ. Response of medullary trigeminal neurons to electrical stimulation of the dura. Brain Res 1986;379:242–50.
[121] Strassman AM, Mineta Y, Vos BP. Distribution of fos-like immunoreactivity in the medullary and upper cervical dorsal horn produced by stimulation of dural blood vessels in the rat. J Neurosci 1994;14:3725–35.
[122] Strassman AM, Raymond SA, Burstein R. Sensitization of meningeal sensory neurons and the origin of headaches. Nature 1996;384:560–4.
[123] Swanson LW, McKellar S. The distribution of oxytocin- and neurophysin-stained fibers in the spinal cord of the rat and monkey. J Comp Neurol 1979;188:87–106.
[124] Tfelt-Hansen PC. History of migraine with aura and cortical spreading depression from 1941 and onwards. Cephalalgia 2010;30:780–92.
[125] Tottene A, Conti R, Fabbro A, Vecchia D, Shapovalova M, Santello M, van den Maagdenberg AM, Ferrari MD, Pietrobon D. Enhanced excitatory transmission at cortical synapses as the basis for facilitated spreading depression in Ca(v)2.1 knockin migraine mice. Neuron 2009;61:762–73.
[126] Uddman R, Edvinsson L, Ekman R, Kingman T, McCulloch J. Innervation of the feline cerebral vasculature by nerve fibers containing calcitonin gene-related peptide: trigeminal origin and co-existence with substance P. Neurosci Lett 1985;62:131–6.
[127] van den Maagdenberg AM, Pietrobon D, Pizzorusso T, Kaja S, Broos LA, Cesetti T, van de Ven RC, Tottene A, van der Kaa J, Plomp JJ, Frants RR, Ferrari MD. A Cacna1a knockin migraine mouse model with increased susceptibility to cortical spreading depression. Neuron 2004;41:701–10.

[128] Vecchia D, Pietrobon D. Migraine: a disorder of brain excitatory-inhibitory balance? Trends Neurosci 2012;35:507–20.
[129] Wager TD, Scott DJ, Zubieta JK. Placebo effects on human mu-opioid activity during pain. Proc Natl Acad Sci USA 2007;104:11056–61.
[130] Wahl M, Schilling L, Parsons AA, Kaumann A. Involvement of calcitonin gene-related peptide (CGRP) and nitric oxide (NO) in the pial artery dilatation elicited by cortical spreading depression. Brain Res 1994;637:204–10.
[131] Weiller C, May A, Limmroth V, Juptner M, Kaube H, Schayck RV, Coenen HH, Diener HC. Brain stem activation in spontaneous human migraine attacks. Nat Med 1995;1:658–60.
[132] Welty TE, Horner TG. Pathophysiology and treatment of subarachnoid hemorrhage. Clin Pharmacol 1990;9:35–9.
[133] Werhahn KJ, Wiseman K, Herzog J, Forderreuther S, Dichgans M, Straube A. Motor cortex excitability in patients with migraine with aura and hemiplegic migraine. Cephalalgia 2000;20:45–50.
[134] Yirmiya R, Ben-Eliyahu S, Shavit Y, Marek P, Liebeskind JC. Stimulation of the hypothalamic paraventricular nucleus produces analgesia not mediated by vasopressin or endogenous opioids. Brain Res 1990;537:169–74.
[135] Zagami AS, Lambert GA. Stimulation of cranial vessels excites nociceptive neurones in several thalamic nuclei of the cat. Exp Brain Res 1990;81:552–66.
[136] Zhang X, Levy D, Kainz V, Noseda R, Jakubowski M, Burstein R. Activation of central trigeminovascular neurons by cortical spreading depression. Ann Neurol 2011;69:855–65.
[137] Zhang X, Levy D, Noseda R, Kainz V, Jakubowski M, Burstein R. Activation of meningeal nociceptors by cortical spreading depression: implications for migraine with aura. J Neurosci 2010;30:8807–14.