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Migraine pathophysiology: anatomy of the trigeminovascular pathway and associated neurological symptoms, CSD, sensitization and modulation of pain

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Abstract

Scientific evidence support 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. Also, structural and functional alterations include the presence of subcortical white matter 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.

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, skipping meals 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 only limited to its multifactorial origin but also to 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].

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An estimate of 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 support 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.

Anatomical substrate of the trigeminovascular pain pathways

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 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 unmyelinated (C-fibers) and thinly myelinated (A δ 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].

That the vascular origin of the headache during migraine is a viable theory or not, has been debated for decades. In a recent study using magnetic resonance angiography on patients undergoing triggered attacks, Asghar and colleagues [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, the same group [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.

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 A δ and C nociceptive primary afferents terminate in the superficial layers (laminae I and II), and that some A δ 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.

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 (AH), lateral (LH) and perifornical (PeF) hypothalamic areas, lateral preoptic nucleus (LPO), zona incerta, and ventral posteromedial (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 (vIPAG), rostral trigeminal spinal nuclei, nucleus of the solitary tract, brainstem reticular areas, superior salivatory (SSN) and cuneiform nuclei [22; 39; 92].

Projections from thalamic trigeminovascular neurons to the cerebral cortex (Figure 1)

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 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].

Activation and sensitization of the trigeminovascular pathway: animal studies and clinical correlation

Cortical Spreading Depression and the activation of peripheral and central trigeminovascular neurons (Figure 2)

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 min) of cortical activity [116; 117]. First identified by Leão in the rabbit [67], 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 towards the surface of the cortex where they come in 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 only supported 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]. In addition, a potential mechanistic explanation on how meningeal nociceptors activation begins after CSD has been recently proposed [51]. In this study, various experimental approaches were performed in mice to demonstrate that CSD causes the opening of neuronal Panx1 megachannels, resulting in downstream cascade of events that leads to release of proinflammatory 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]. 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 show 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 show 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 TRESK potassium channels that regulate neuronal resting potential and excitability [61]. Altogether, these findings support the notion that neuronal excitability plays a pivotal role in the predisposition to develop the different forms of migraine.

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] (Figure 3), whereas sensitization of second-order neurons in the SpVC mediates cephalic allodynia as well as muscle tenderness [19; 21] (Figure 4). Until recently, no neural substrate had been proposed for the extracephalic allodynia during migraine. A recent study showed (a) that innocuous brush and heat stimuli induce larger BOLD signal in the pulvinar thalamic nucleus of patients exhibiting signs of whole-body allodynia (can't wear tight cloth, can't use heavy blanket, can't take shower) during migraine, as compared to pain-free state, and (b) that topical application of inflammatory molecules on the rat meninges sensitized thalamic trigeminovascular neurons located in VPM, Po and LP (Figure 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 humans and by the most dorsal and posterior part of the thalamus in animals (i.e., Po) [21].

Neural substrate of migraine-type photophobia

There are 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 to light, as the term "phobia" suggests, and have been associated with intracranial pathologies such as migraine, meningitis, subdural hemorrhage, 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.

Central mechanisms involved in exacerbation of headache by light, hypersensitivity to light and ocular discomfort/pain (Figure 6)

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 due to 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 due to severe degeneration of rod and cone photoreceptors [91]. Retinal projections to the brain constitute two functionally different pathways. The first 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 (ipRGCs) containing melanopsin photoreceptors [38; 56; 75]. Activation of ipRGCs 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 existing knowledge of the neurobiology of the trigeminovascular system and the anatomy of visual pathways, the following information is available: (a) light enhances the activity of thalamic trigeminovascular neurons; (b) a subgroup of light/dura-sensitive neurons located mainly in the LP/Po area of the posterior thalamus receive direct input from RGCs; and (c) 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 supporting the existence of such pathway in humans comes from imaging studies and probabilistic tractography that show blood oxygen-level dependent (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 on 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]. Additionally, a transgenic mice 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 following 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 photophobia, 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 SSN and the sphenopalatine ganglion which drives parasympathetically-controlled vasodilatation and mechanical deformation of ocular blood vessels that 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 question this scenario.

Brain regions associated with modulation of migraine pain

Cerebral cortex as a major source of trigeminovascular modulation (Fig. 7)

Endogenous modulation of trigeminal nociception certainly originates from the cortex since most nociceptive relays within the central nervous system are under corticofugal control. A large and growing body of clinical and preclinical evidence point 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 the rat [30; 48; 89] and human [60]. 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].

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 one 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 [39; 44; 77; 79; 123] [110] 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 SSN in the brainstem [47; 118], suggesting that this circuit is contributing to the parasympathetic autonomic symptoms observed in migraine and cluster headache [41; 62].

Brainstem nuclei as unspecific migraine modulator

Since the first published report describing delayed migraine-like pain in patients undergoing electrodes 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. But evidence supporting the role of PAG as a headache generator are lacking (see refs in [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] in order to generate migraine-like pain. Functionally, activation of lateral and ventrolateral PAG neurons by direct ascending lamina I projections, produce non-selective, non-specific pain relief, cardiovascular (decrease in blood pressure), homeostatic (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]. Since 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]. 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 descendence 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 show however, activation in nearby nuclei in the dorsolateral pons (DLP) that 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.

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 on (a) activation of the trigeminovascular pathway by pain signals that originate in peripheral intracranial nociceptors, and (b) dysfunction of CNS structures involved in the modulation of neuronal excitability and pain. Because to date there is no evidence on paroxysmal conditions causing pain without peripheral afferent input, efforts to study this complex disorder must continue in order to incorporate additional elements and open the framework in which we conceptualize migraine pathophysiology.

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Ascending pathways of trigeminovascular system

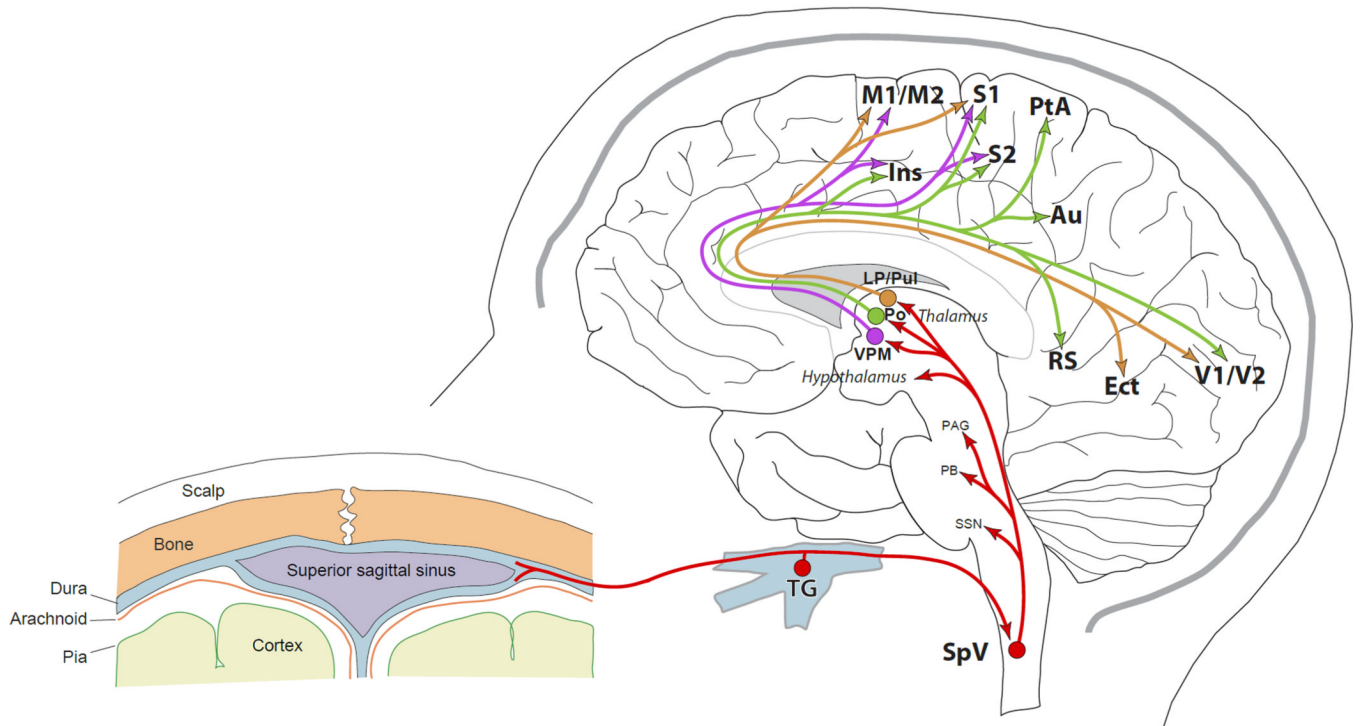


Figure 1. Schematic representation of ascending neuronal pathways of the trigeminovascular system that are involved in the different aspects of migraine.

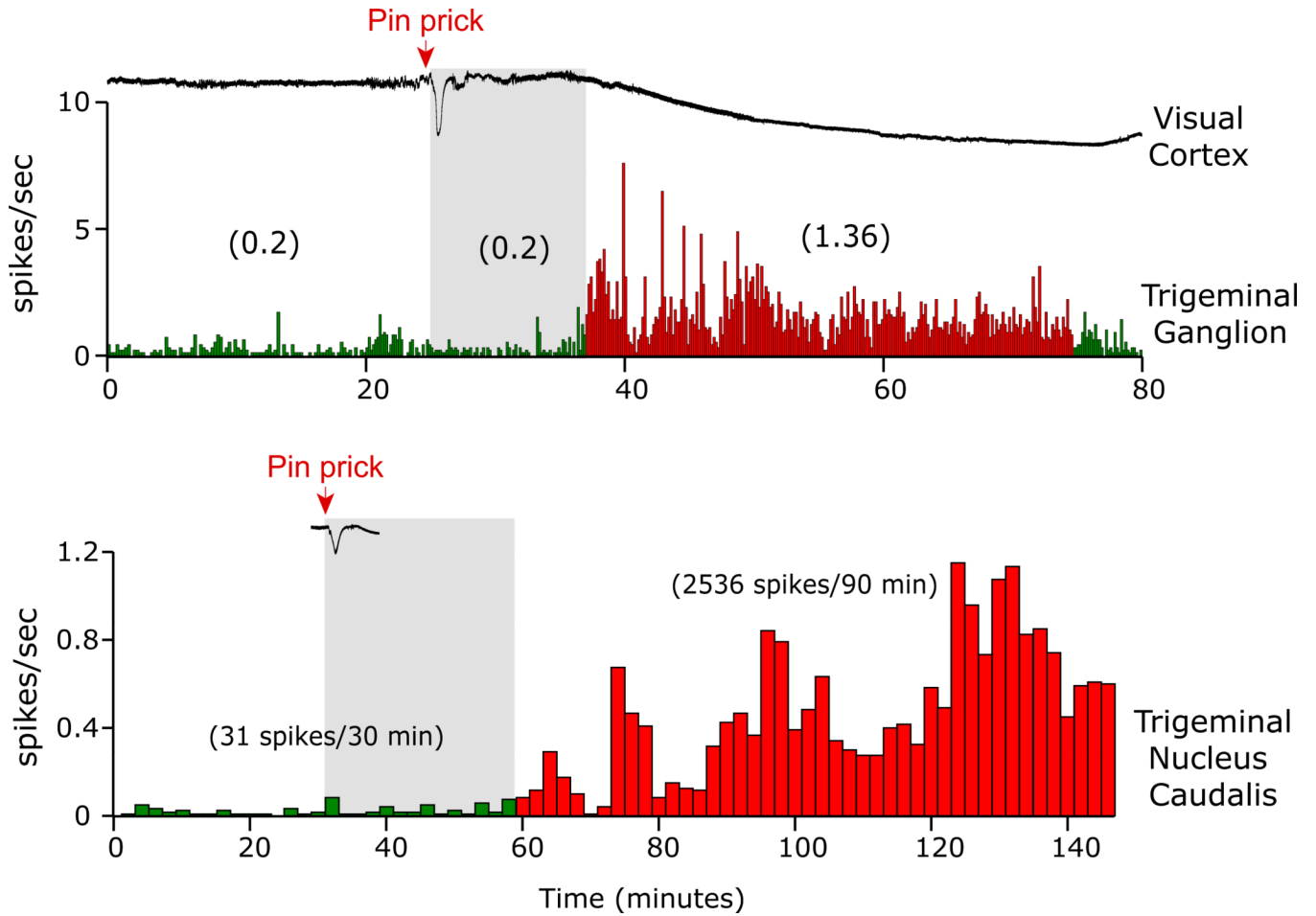


Figure 2. Electrophysiological recordings showing delayed activation of meningeal nociceptors (top panel) and SpVC trigeminovascular neurons (bottom panel) by cortical spreading depression. (Adapted from Zhang et al., J Neurosci 2010; and Zhang et al., Ann Neurol 2011)

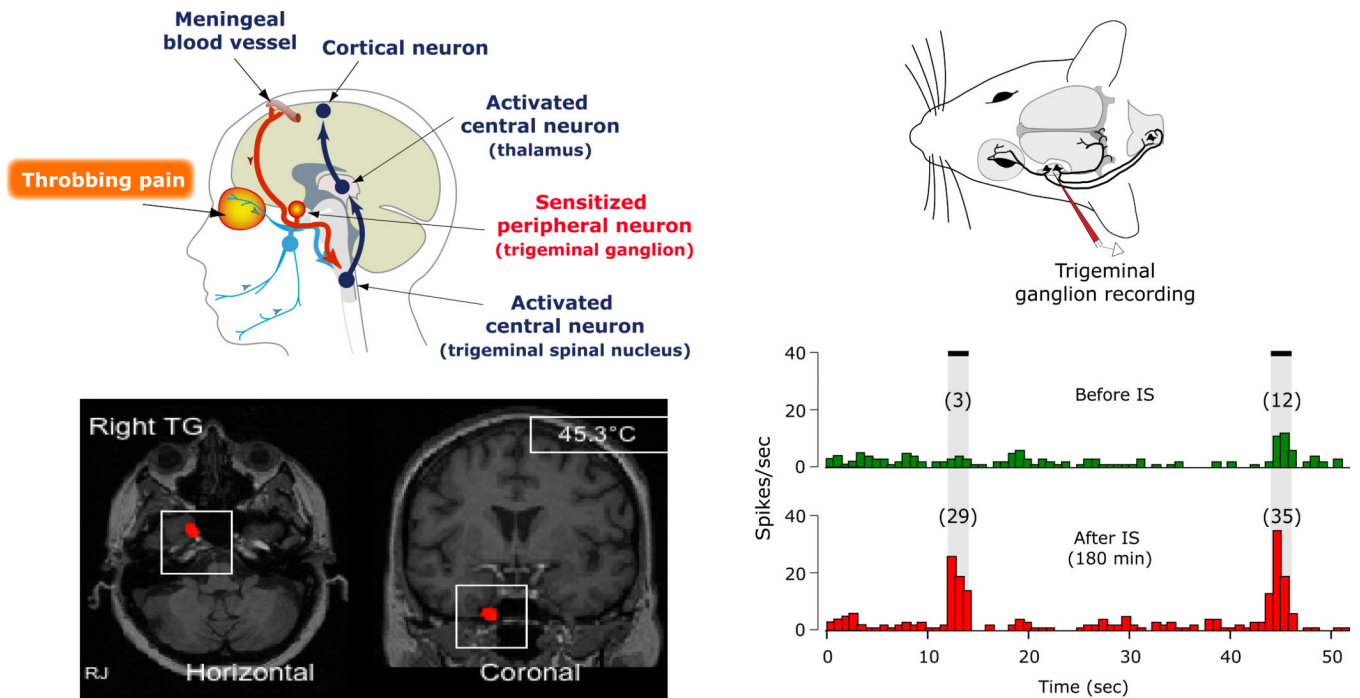


Figure 3. Sensitization of meningeal nociceptors believed to mediate the throbbing nature of migraine pain. Left panel: Schematic representation of peripheral sensitization and periorbital throbbing pain in the human; fMRI evidence showing activation of the trigeminal ganglion during migraine. Right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

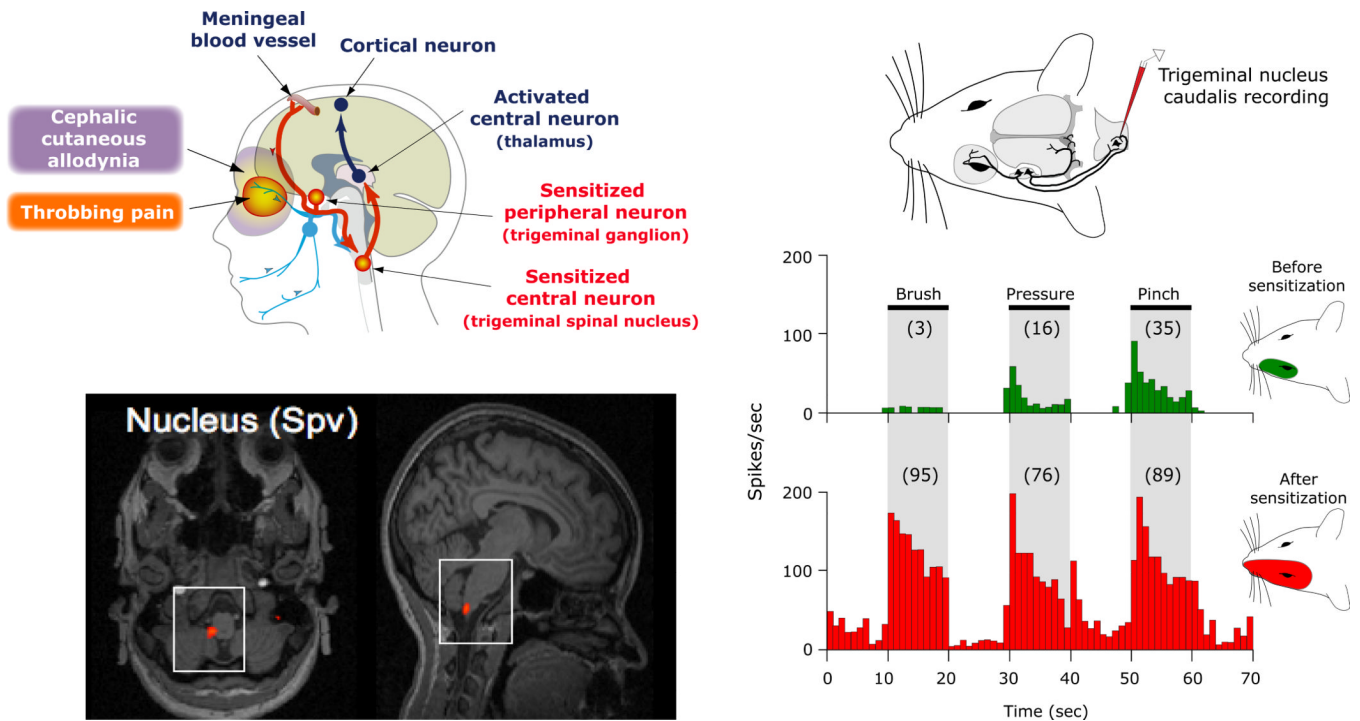


Figure 4. Sensitization of central trigeminovascular neurons in the trigeminal nucleus caudalis believed to mediate cephalic cutaneous allodynia during migraine. Left panel: Schematic representation of central sensitization of SpVC trigeminovascular neurons and cephalic cutaneous allodynia in the human; fMRI evidence showing activation of the spinal trigeminal nucleus during migraine. Right panel: 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.

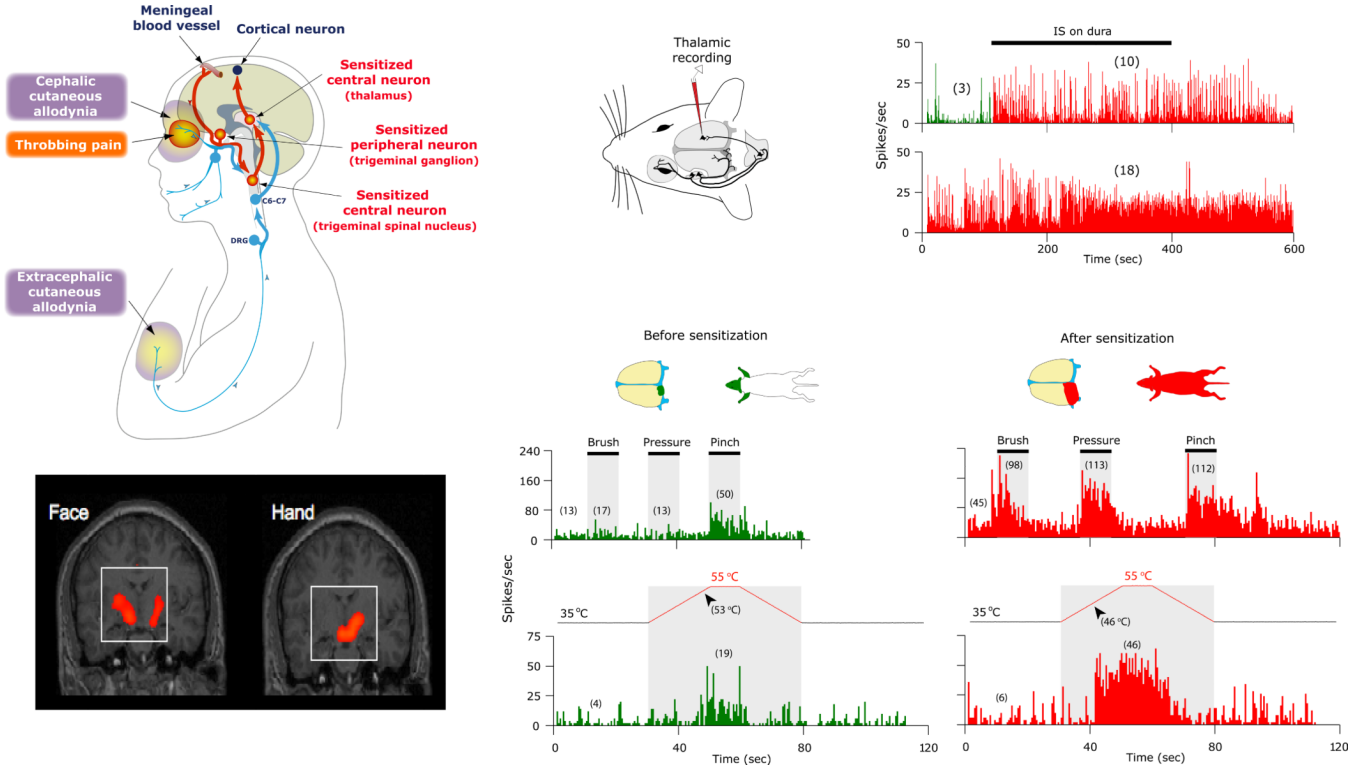


Figure 5. Sensitization of central trigeminovascular neurons in the thalamus believed to mediate the extracerebral (whole-body) cutaneous allodynia during migraine. Left panel: Schematic representation of central sensitization of thalamic trigeminovascular neurons and extracerebral cutaneous allodynia in the human; fMRI evidence showing activation of the thalamus during migraine. Right panel: 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.

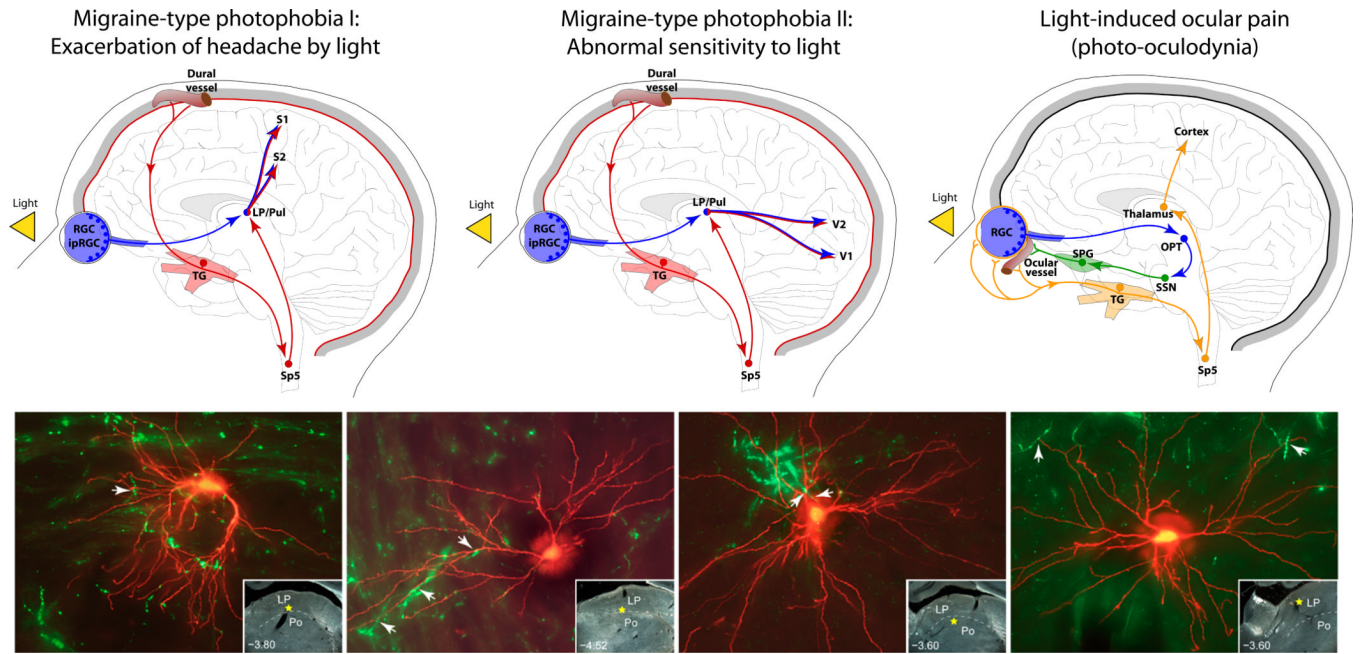


Figure 6. Mechanisms of Photophobia. Top panel: Proposed mechanism for exacerbation of headache by light, hypersensitivity to light in migraine patients and ocular pain induced by light (Adapted from Noseda and Burstein, *Curr Opin Neurol* 2011). Bottom panel: dura/light-sensitive neurons (red) closely apposed to retinal afferents (green) in the posterior thalamus (Adapted from Noseda et al., *Nat Neurosci* 2010)

Descendent modulation of trigeminovascular system

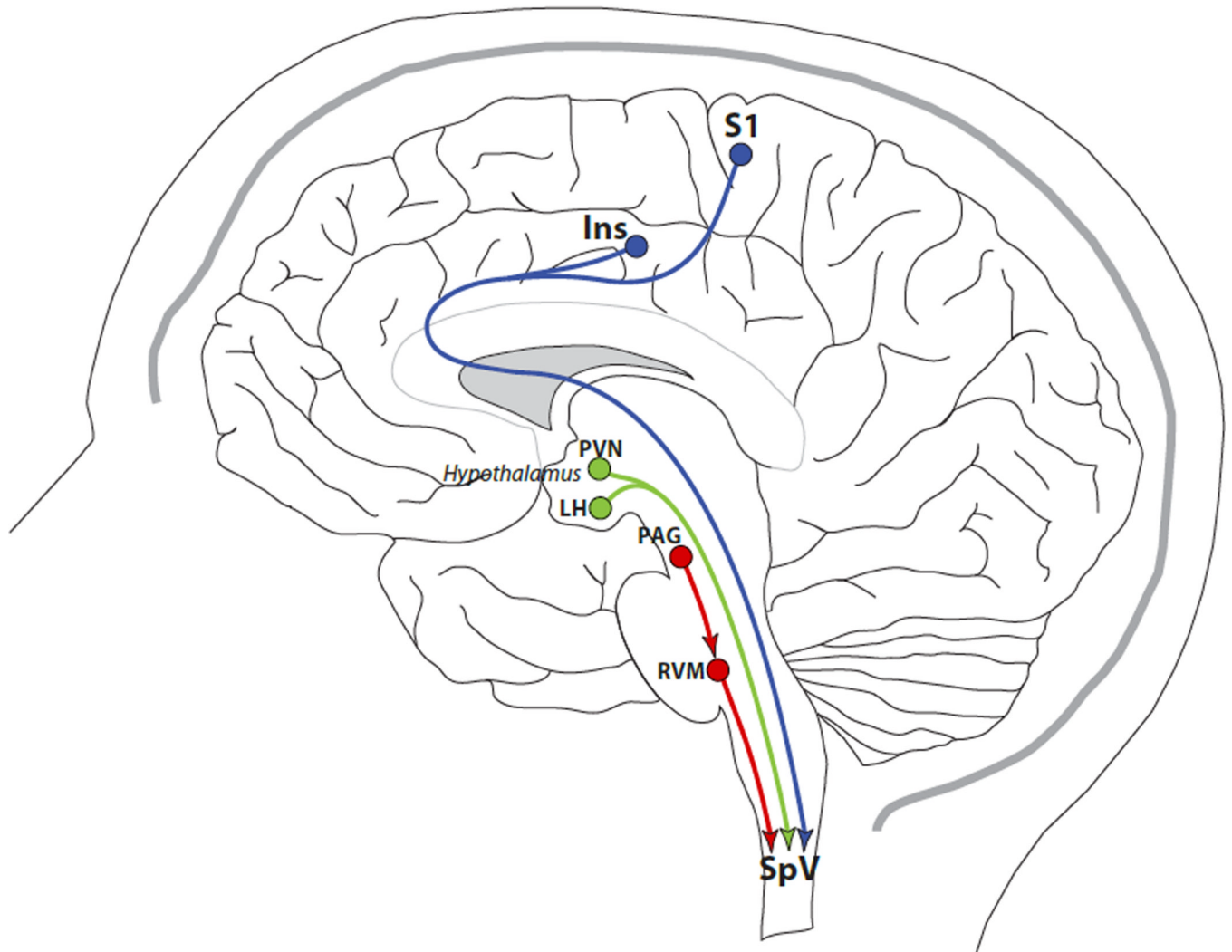


Figure 7. Schematic representation of descending neuronal pathways that modulate trigeminovascular nociceptive transmission in the SpVC.