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INVITED LECTURE

Neural substrate of depression during migraine

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Abstract Migraine headache is triggered by and associated with a variety of hormonal, emotional, nutritional and physiological changes. The perception of migraine headache is formed when nociceptive signals originating in the meninges are conveyed to the somatosensory cortex through the trigeminal ganglion, medullary dorsal horn and thalamus. We propose that different migraine triggers activate a wide variety of brain areas that impinge on parasympathetic neurons innervating the meninges. According to this hypothesis, migraine triggers such as stress activate multiple hypothalamic, limbic and cortical areas, all of which contain neurons that project to the preganglionic parasympathetic neurons in the superior salivatory nucleus (SSN). The SSN, in turn, activates postganglionic parasympathetic neurons in the sphenopalatine ganglion, resulting in vasodilation and local release of inflammatory molecules that activate meningeal nociceptors. We propose that trigeminovascular projections from the medullary dorsal horn to selective areas in the midbrain, hypothalamus, amygdala and basal forebrain are functionally positioned to produce migraine symptoms such as irritability, loss of appetite, fatigue, depression and the quest for solitude. The network of bidirectional trafficking by which the trigeminovascular system can activate the same brain areas that have triggered its own activity in the first place provides an attractive mechanism of perpetual feedback that drives a migraine attack for many hours and even days.

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Introduction

Migraine is a recurring neurological disorder commonly described as unilateral throbbing headache, readily aggravated by routine activities. Similar to other pain pathways, the sensory discriminative aspect of migraine pain is believed to be mediated by activation and modulation of nociceptive trigeminothalamic tract by peripheral drivers and central modulators, respectively. In the case of the trigeminothalamic tract, the role of driver is played by meningeal nociceptors, whereas modulation is provided by inhibitory and facilitatory neurons in the brainstem. Evidence for the driving role of meningeal nociceptors comes from studies in which awake patients experienced headache in response to electrical stimulation of their dura [1, 2]. Evidence for descending modulation comes from studies that examined the effects of electrical stimulation of the periaqueductal gray (PAG) and rostral ventromedial medulla on nociceptive spinal neurons. Whereas electrical brainstem stimulation per se did not induce any activity in the spinal nociceptive neurons when they were quiet, it clearly increased or decreased their response magnitude to noxious and innocuous stimulation of their cutaneous and visceral receptive fields [3].

The initiation of migraine headache is commonly associated with a wide variety of circumstances, such as hormonal milieu, periods of stress, post-stress periods, skipping a meal, lack of sleep, olfactory stimulation and several types of aura [4, 5]. These associations raise the possibility that a migraine attack originates in brain areas that are not directly involved in nociception, but are wired

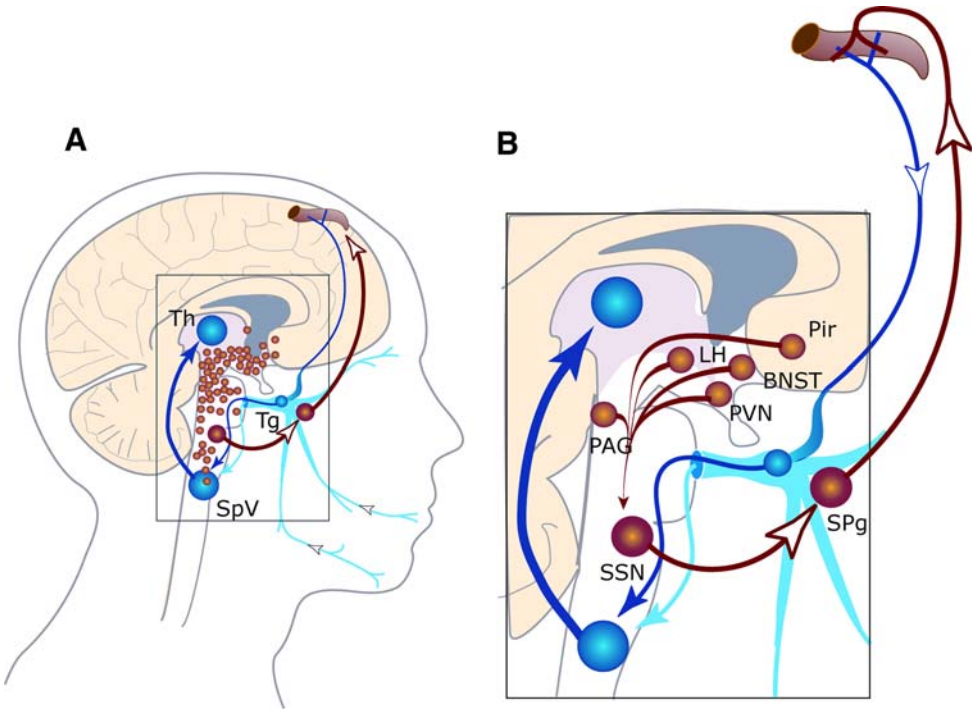

Fig. 1 A proposed parasympathetic pathway for the activation of meningeal nociceptors. Preganglionic parasympathetic neurons in the superior salivatory nucleus (SSN) can trigger intracranial vasodilation and the release of nitric oxide in the meninges through postganglionic parasympathetic neurons in the sphenopalatine ganglion (SPG). **a** The SSN receives input from over 50 limbic and hypothalamic brain areas (*red dots*) whose activity may be influenced by common migraine triggers. **b** Examples of SSN afferents proposed to be involved in migraine triggering by olfactory stimuli (Pir), food and sleep deprivation (LH), stress or post stress (PVN, BNST, PAG). *BNST* bed nucleus stria terminalis, *LH* lateral hypothalamus, *PAG* periaqueductal gray, *Pir* piriform cortex, *PVN* paraventricular hypothalamic nucleus

to activate the trigeminovascular pathway. The trigeminovascular pathway consists of first-order nociceptors in the trigeminal ganglion that innervate the meninges; second-order trigeminothalamic tract neurons that receive sensory inputs from the meninges, periorbital skin and neck muscles; third-order thalamocortical neurons that process incoming pain signals from the trigeminal nerve, including the meninges; and cortical neurons located in the first somatosensory cortex.

Activation of the trigeminovascular pathway by the limbic system and hypothalamus

The observation that visual aura precedes the onset of headache by several minutes promoted extensive research on the neural substrate by which cortical spreading depression can result in activation of meningeal nociceptors. Evidence suggests that in the wake of cortical spreading, depression the blood brain barrier becomes more permeable [6, 7], allowing potassium and hydrogen ions to diffuse from the surface of the cortex to the pia where they activate C-fiber meningeal nociceptors [8]. This activation appears to involve direct depolarization by potassium ions, and action of hydrogen ions through the vallinoid receptor (Caterina et al. 1997) or the acid-sensitive ion channel receptor (Waldmann et al. 1997). Consequently, the activated meningeal nociceptors release calcitonin-gene-related peptide [9] from their peripheral branches, resulting in neurogenic inflammation in the dura [10].

In contrast to the ongoing effort, to understand how aura triggers activity in meningeal nociceptors, little attention was given to the mechanisms by which brain areas involved in regulation of stress could activate meningeal nociceptors and trigger the headache. Is there a common pathway that activates meningeal nociceptors for a variety of migraine triggers? We are proposing that such a pathway involves pre- and postganglionic parasympathetic neuron in the superior salivatory nucleus (SSN) and sphenopalatine ganglion (SPG), respectively. According to our hypothesis, migraine triggers either activate or originate in a number of brain areas whose projections converge on the SSN. The SSN, in turn, stimulates the release of acetyl choline, vasopressin intestinal peptide and nitric oxide from meningeal terminals of SPG neurons, resulting (directly or indirectly) in a cascade of events that include the dilation of intracranial blood vessels, plasma protein

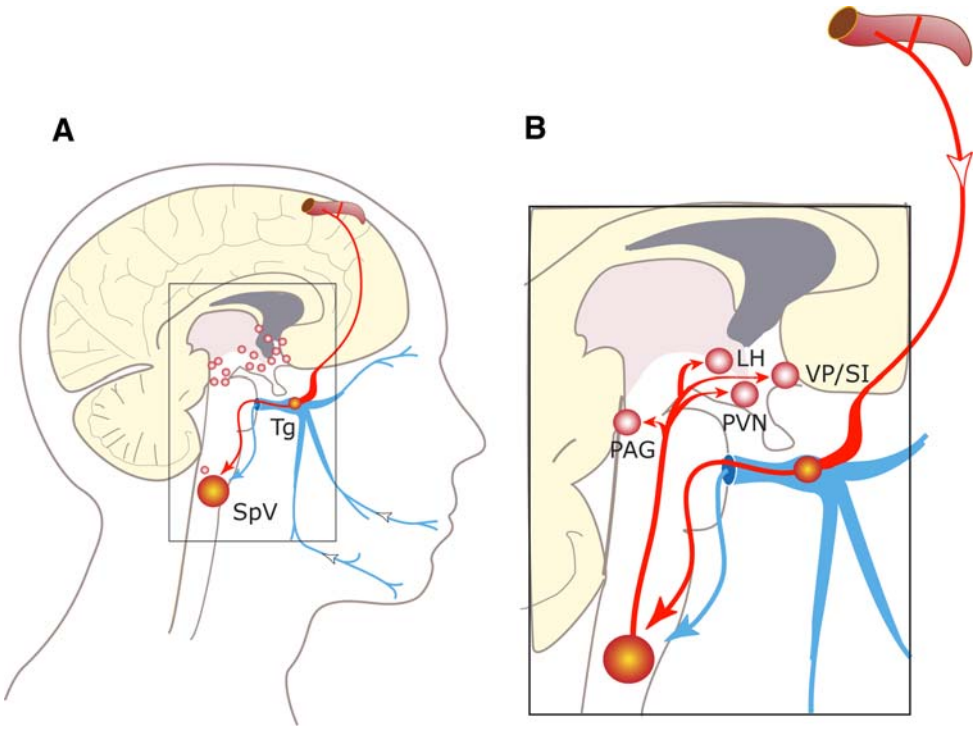

Fig. 2 Proposed mechanism for the initiation of symptoms commonly associated with migraine headache by ascending trigeminovascular pathways to the brainstem, hypothalamus and basal ganglia. **a** Trigeminovascular neurons in the spinal trigeminal nucleus (SpV) project to multiple limbic and hypothalamic brain areas (*red dots*) whose activity my underlie common migraine symptoms. **b** Examples of SpV projections proposed to be involved in stress (PVN), decreased motivational state (VP/SI), pursuit of solitude (PAG), sleepiness, irritability and loss of appetite (LH). *LH* lateral hypothalamus, *PAG* periaqueductal gray, *PVN* paraventricular hypothalamic nucleus, *VP/SI* ventral pallidum/substantia innominata

extravasation, and local release of inflammatory molecules that activate adjacent terminals of meningeal nociceptors (Fig. 1).

Several lines of evidence support this parasympathetic hypothesis: (1) meningeal blood vessels are densely innervated by parasympathetic fibers [11–13]; (2) preganglionic parasympathetic neurons in the SSN increase their activity after activation of meningeal nociceptors [14]; (3) ongoing activity in meningeal nociceptors appears to depend on enhanced activity in the SPG [15]; (4) parasympathetic tone is enhanced during migraine, as evidenced by lacrimation, teary eyes, nasal congestion [5]; (5) blockade of the SPG provides partial or complete relief of migraine pain [16–25].

The SSN receives extensive input from more than 50 brain areas distributed throughout the forebrain, diencephalon, midbrain, pons and medulla [26]. SSN-projecting neurons located in some of these brain areas are theoretically positioned to mediate the onset of a migraine by means of their involvement in emotional responses (Fig. 1a). The bed nucleus of stria terminalis (BNST), the paraventricular hypothalamic nucleus (PVN) and the PAG are all involved in the circuitry that regulates "stress response". BNST neurons, which regulate hypothalamic-pituitary-adrenal axis, appear to mediate long-lasting behavioral responses during sustained stress, which persist long after the termination of stress [27, 28]; such neurons may be involved in stress-induced migraine and also in migraine triggered after the termination of stress. Parvocellular PVN neurons that project to sympathetic and parasympathetic preganglionic neurons in the brainstem and spinal cord promote the autonomic part of the stress response [29, 30], which includes localized cerebrovascular vasodilation in the early phase of the migraine attack [31]. Ventrolateral PAG neurons involved in passive emotional coping with inescapable stressors such as repeated defeat in social encounters [32, 33] may mediate onset of increase migraine frequency associated with a long period of social stress such as divorce.

Activation of the hypothalamus and limbic system by the trigeminovascular pathway

The most frequently reported symptoms associated with migraine are depression, stress, irritability, fatigue, sleepiness, exaggerated emotional responses, nausea and loss of appetite. To elicit these symptoms, pain signals that originate in the trigeminovascular pathway during migraine must reach and alter the activity of hypothalamic and limbic structures that integrate sensory, physiological and cognitive signals that drive behavioral, affective and autonomic responses. Brain areas involved in the execution of such responses include the parabrachial complex, PAG, hypothalamus, amygdala, septum, nucleus accumbens, bed nucleus of the stria terminalis and basal ganglia [34–46]. Many of these brain areas receive direct inputs from laminae I–II and V neurons located in the ventrolateral area of

the upper cervical and medullary dorsal horn (Fig. 2)—an area containing the majority of second-order trigeminovascular neurons [47–56].

We propose that these ascending pathways are functionally positioned to produce irritability, loss of appetite, sleepiness, fatigue, chill, stress, depression, emotional arousal, decreased motivation, the quest for solitude and lethargy during migraine (Fig. 2b). For example, loss of appetite, sleepiness and irritability during migraine may be mediated by trigeminovascular projections to the lateral hypothalamus; in this area, neurons expressing melanin-concentrating hormone or hypocretin regulate food and water intake, sleep and arousal [36, 37, 57] through widespread projections to the cerebral cortex, brainstem and spinal cord [58–62]. Migraine-associated stress may be mediated by trigeminovascular projections to the paraventricular nucleus of the hypothalamus; this nucleus contains neurons expressing corticotrophin-releasing hormone and oxytocin which regulate stress responses [63]. Emotional arousal and decreased motivation during migraine may be mediated by trigeminovascular projections to forebrain nuclei such as the ventral pallidum and substantia innominata; these areas can alter endocrine, autonomic and somatomotor functions to match different emotional and motivational states [64].

The pursuit of solitude during migraine may be mediated by the ventrolateral PAG; this area receives more input from trigeminal neurons locate in C1-3 and nucleus caudalis than from the entire spinal cord [32, 54, 55]. The input to the ventrolateral PAG originates mainly in visceral and deep somatic tissues [65, 66]. Trigeminovascular projections to the ventrolateral PAG can activate neurons that mediate responses to deep, inescapable pain, such migraine pain [32, 67].

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Conflict of interest statement The authors declare that they have no conflict of interest related to the publication of this manuscript.

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