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Supplement Article

A Phase-by-Phase Review of Migraine Pathophysiology

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Migraine is a common, disabling neurological disorder characterized by multiple phases: premonitory, aura, headache, postdrome, and interictal. Our understanding of the pathophysiology of each phase of migraine has evolved over recent years. The premonitory phase begins as early as 3 days before the headache phase, and involves a complex interplay between various cortical and subcortical brain regions, including the hypothalamus and brainstem nuclei that modulate nociceptive signaling. The headache phase involves activation of the trigeminovascular system, a pathway that is well characterized. In one-third of patients, an aura phase may occur during some attacks and likely correlates with a cortical spreading depression-like event; a slowly propagating wave of neuronal and glial cell depolarization and hyperpolarization. Improved characterization of the pathophysiological processes involved at each stage of the migraine attack will aid the identification of new therapeutic targets for migraine prevention. This review provides an update on prevailing concepts of migraine pathophysiology.

Key words: migraine, pathophysiology, trigeminovascular pathway, aura, premonitory phase, cortical spreading depression

Abbreviations: ATP adenosine triphosphate, CDS cortical spreading depression, CGRP calcitonin gene-related peptide, CNS central nervous system, FHM familial hemiplegic migraine, GWAS genome-wide association studies, ICHD-3 International Classification of Headache Disorders 3rd edition, TCC trigeminal cervical complex, TNC trigeminal nucleus caudalis

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INTRODUCTION

Migraine is a common and debilitating neurological disorder experienced by approximately 10% of the global population.[1] The International Headache Society defines migraine as a recurrent primary headache disorder resulting in attacks that last 4-72 hours. Typically, the headache is unilateral, pulsating, moderate or severe in intensity, aggravated by routine physical activity, and associated with nausea or photophobia and phonophobia.[2] In approximately one-third of individuals with migraine, some attacks are associated with an aura phase, comprised of visual, sensory, and language or brainstem disturbances.[3,4] A premonitory phase, often lasting hours to days, almost always precedes the aura or headache.[2,3] Symptoms that occur during the premonitory phase are varied, but fatigue, neck discomfort, yawning, gastrointestinal disturbances, and mood changes are among the most commonly reported.[3,4] The disorder may be categorized according to the frequency of attacks; episodic migraine is defined as headache occurring on 1-14 days per month, whereas chronic migraine is diagnosed in those who experience headache on $\geq$15 days per month, at least 8 days of which fulfill criteria for migraine with or without aura.[2,5]

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The various symptoms and neurological disturbances observed during all phases of migraine are complex and wide-ranging. Disturbances of sensory function, of affect, and of cognitive and autonomic function may be experienced, suggesting involvement of multiple neural networks.[4] Over the last three decades, the peripheral and central pathways and relevant neuropeptides, neurotransmitters, and the receptors involved have come more sharply into focus. This article explores the current knowledge and proposed mechanisms underlying the various phases of the migraine attack.

PHASE 1: PREMONITORY

The Interplay Between Alterations in Homeostasis and the Onset of Migraine.—The premonitory phase of migraine can begin as early as 3 days before a migraine headache and allows some patients to correctly predict migraine headache up to 12 hours before its onset.[6] Common symptoms experienced during this phase, including fatigue, mood changes, food cravings, yawning, muscle tenderness, and photophobia, point to the involvement of the hypothalamus, brainstem, limbic system, and certain cortical areas during the early stages of an attack.[7-9] Migraine may also display a diurnal periodicity and is commonly triggered by alterations in homeostasis.[10] These findings suggest the involvement of chronobiological mechanisms in migraine pathogenesis and have led to the investigation of the hypothalamus as a potential site of origin of the migraine attack.[8,10]

Functional neuroimaging studies provide evidence of the involvement of the hypothalamus during the premonitory phase. In a positron emission tomography study using cerebral blood flow as a marker of neuronal activity in patients with glyceryl trinitrate-induced migraine attacks, activations were found in the posterolateral hypothalamus as well as in the midbrain tegmental area, periaqueductal gray, dorsal pons, and various cortical areas during the premonitory phase.[7] A second study used functional magnetic resonance imaging during the interictal phase (the period between migraine attacks). Imaging revealed stronger functional connections between the hypothalamus and areas of the brain related to pain transmission and autonomic function in patients with migraine compared with healthy controls, which may account for some of the autonomic symptoms experienced during the interictal and premonitory phases.[11] With evidence pointing toward the involvement of the hypothalamus during the early stage of migraine, it has been postulated that the hypothalamus may play a key role in facilitating or amplifying pain transmission during an attack. Two main theories for this mechanism exist; the first proposes that increased parasympathetic tone activates meningeal nociceptors, and the other involves modulation of nociceptive signals from the trigeminal nucleus caudalis (TNC) to supratentorial structures involved in pain processing.[12,13]

Activation of Meningeal Nociceptors by Increased Parasympathetic Activity.—Many features of migraine, such as nausea, vomiting, and thirst, but also cranial autonomic symptoms such as lacrimation, nasal congestion, and rhinorrhea are indicative of altered autonomic function in the central nervous system (CNS).[11,14] As such, it has been shown that alterations in sympathetic and parasympathetic tone can be found from the premonitory phase through to postdrome.[15] One proposal is that migraine triggers, such as stress, awakening, or other changes in physiological or emotional

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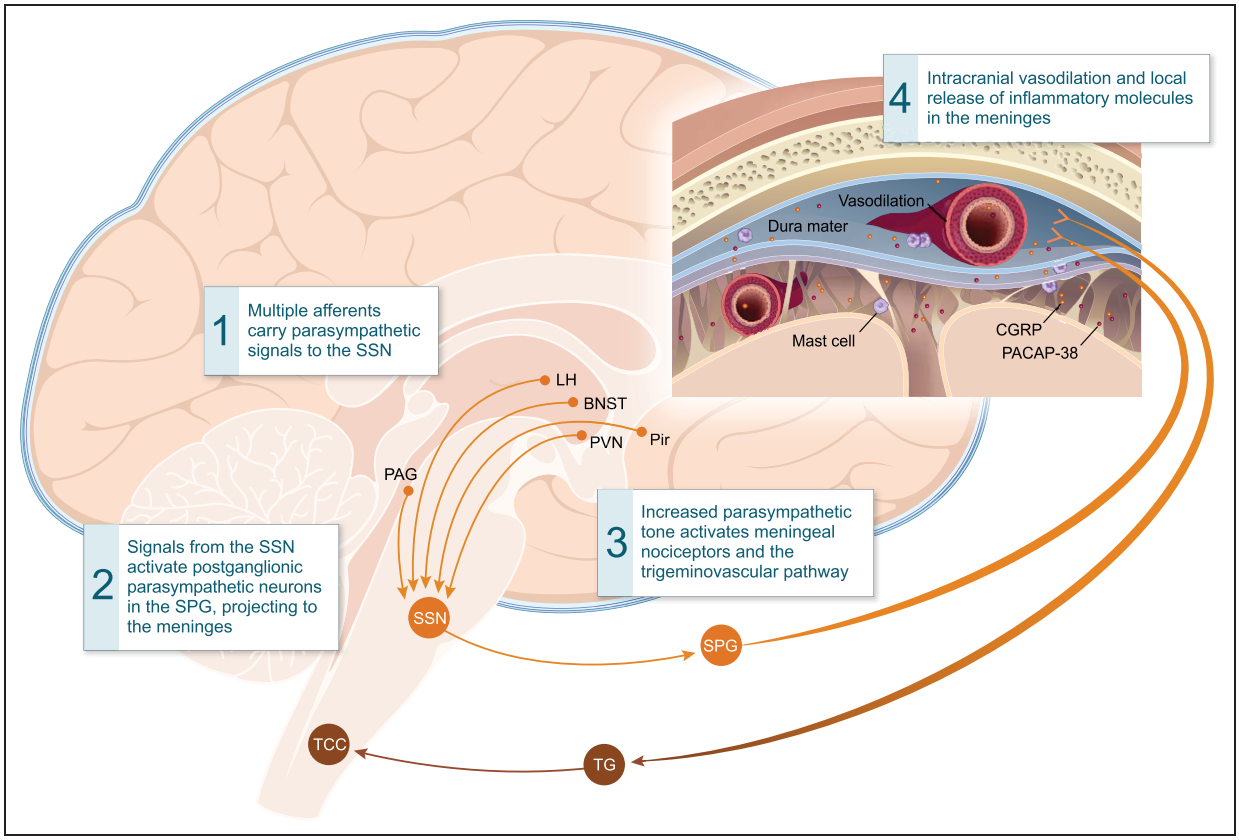

Fig. 1.—Activation of meningeal nociceptors by increased parasympathetic tone. BNST = bed nucleus of stria terminalis; LH = lateral hypothalamus; PAG = periaqueductal gray; Pir = piriform cortex; PVN = paraventricular hypothalamic nucleus; SPG = sphenopalatine ganglion; SSN = superior salivatory nucleus; TCC = trigeminal cervical complex; TG = trigeminal ganglion.

homeostasis, activate nociceptive pathways through increased parasympathetic tone.[12] Other pathways may also play a role in the provocation of migraine by stress. Sympathetic outflow into the meninges involving norepinephrine release has been shown in preclinical models to contribute to pronociceptive signaling through actions on dural afferents and dural fibroblasts.[16] Activation of the kappa-opioid system in response to stress-induced corticotropin-releasing hormone and dynorphin release may also play a role in stress-induced migraine.[17,18] These physiological mechanisms, involving networks which project to preganglionic parasympathetic neurons in the superior salivatory nucleus, may result in peripheral nociceptor activation through the release of neuropeptide transmitters contained within parasympathetic efferents that innervate the meninges and meningeal blood vessels (Fig. 1).[12]

Modulation of Nociceptive Signals from the Thalamus to the Cortex and the Threshold Set by Cyclical Brainstem Activity.—Nociceptive trigeminovascular signals reaching the thalamus may be modulated by the release of excitatory and inhibitory neuropeptides/neurotransmitters from hypothalamic and brainstem neurons.[8] The balance of these neurotransmitters regulates the firing of relay trigeminovascular neurons. If the neurotransmitter is excitatory, it can shift the firing of thalamic trigeminovascular neurons from burst to tonic mode; if the neurotransmitter is inhibitory, the shift is from tonic to burst mode.[13] The converging inputs from hypothalamic and brainstem neurons can therefore provide high and low set points for the allostatic load (the amount of physiological or emotional stress that can be managed by the brain) in patients who experience migraine,

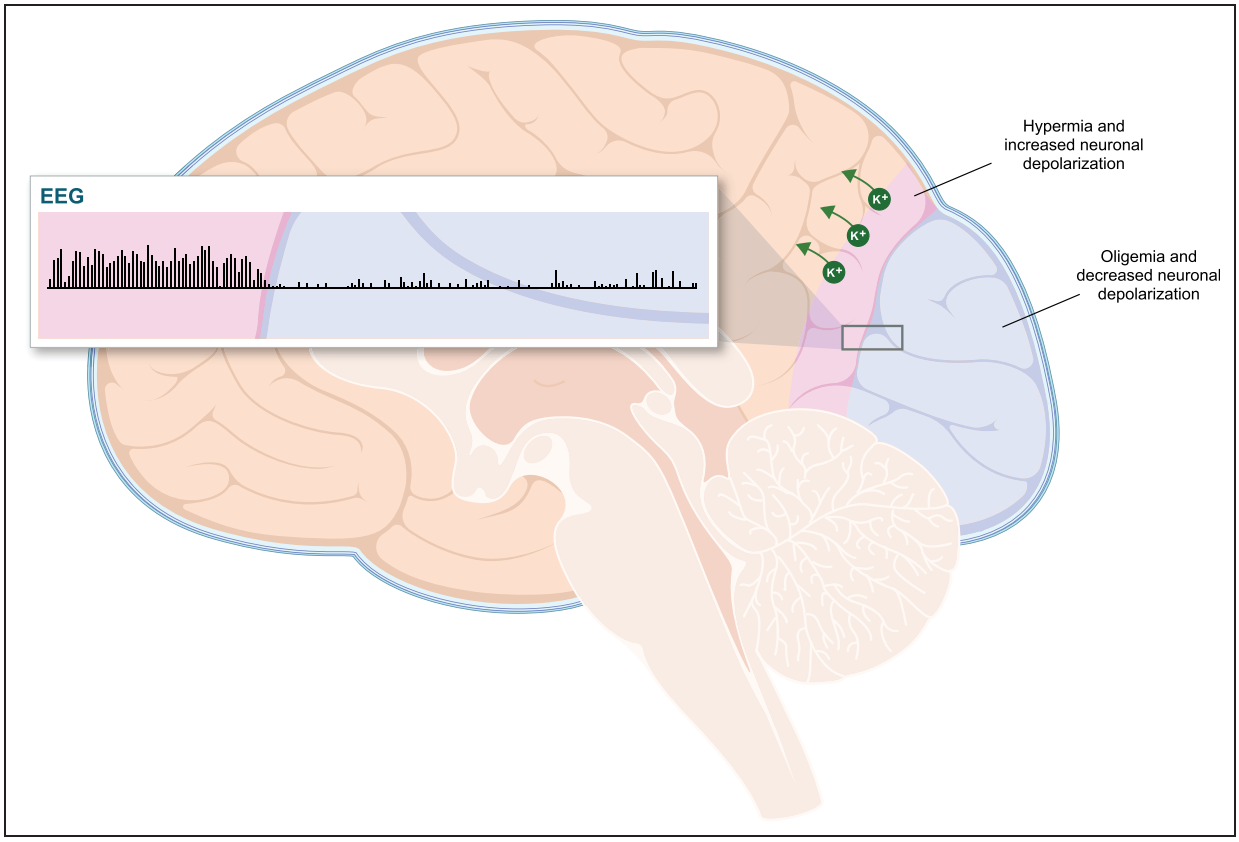

Fig. 2.—Cortical spreading depression. EEG = electroencephalogram; K^+ = potassium.

and thus determine whether nociceptive signals are transmitted to the cortex.[8,19]

Whether the premonitory phase transitions into the headache phase may also be determined by the current circadian phase of cyclical brainstem activity.[4,8,9,19] If cyclical brainstem activity is high, the threshold is raised for transmission of nociceptive trigeminovascular signals, and nociceptive signals are inhibited. If cyclical brainstem activity is low, the threshold is lowered for the transmission of nociceptive signals, and thus a migraine headache may occur.[8,19] This may in part explain why identical migraine triggers (both external and internal) do not always cause an attack, as this may largely depend on the present stage of cyclic brainstem rhythm and on the degree of modulation of trigeminovascular nociceptive signals.[8]

PHASE 2: AURA

Approximately one-third of migraine attacks are preceded by aura.[20] The International Classification of Headache Disorders 3rd edition (ICHD-3) defines migraine with aura as recurrent attacks, lasting minutes, of unilateral, fully reversible, visual, sensory or other CNS symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms.[2] The most prevalent aura symptoms are visual disturbances; however, other common symptoms include sensory, speech/language, and motor disturbances, as well as disruption of higher cortical function.[2,21]

Initiation and Propagation of Cortical Spreading Depression (CSD).—CSD is thought to be the neurophysiological correlate of migraine and was first described by Aristides Leão in 1944.[22,23] It is characterized by a slowly (2-6 mm/min) propagating wave of depolarization in neuronal and glial cell membranes that is followed by inhibition of cortical activity for up to 30 minutes, coinciding with the initiation and progression of aura symptoms (Fig. 2).[23-26] This wave of spreading depression is

also associated with a wave of hyperemia, followed by a prolonged phase of cortical oligemia.[27,28] CSD is initiated by local elevations in extracellular potassium (K^+) that chronically depolarize neurons for approximately 30-50 seconds.[25] It has been suggested that the initial accumulation of extracellular K^+ occurs as a result of repeated depolarization and repolarization of hyperexcitable neurons in the cerebral cortex, and that this accumulation of extracellular K^+ then further depolarizes the cells from which it was released.[23,25,29] This large efflux of K^+ is associated with a major disruption of cell membrane ionic gradients, influx of sodium (Na^+) and calcium (Ca^{2+}), and release of glutamate.[30] The propagation of CSD is still not fully understood, and several hypotheses exist. Originally, the interstitial diffusion of either K^+ or glutamate was thought to lead to the propagation of CSD, but later hypotheses suggest that the propagation is mediated via gap junctions between glial cells or neurons.[24] Increasing evidence from animal studies supports the assumption that CSD can activate trigeminal nociception, and thus trigger headache mechanisms.[23,31,32]

PHASE 3: HEADACHE

The characteristic throbbing pain of migraine headache is widely accepted to be the result of trigeminovascular pathway activation. The trigeminovascular pathway is well characterized and its anatomy and physiology explain the distribution of pain seen in migraine.[8]

The Trigeminovascular Pathway.—The trigeminovascular pathway conveys nociceptive information from the meninges to the central areas of the brain, and subsequently to the cortex. Nociceptive fibers originating from the trigeminal ganglion innervate the meninges and large cerebral arteries.[4,8] This nociceptive innervation occurs mainly through the ophthalmic branch of the trigeminal nerve.[4] Afferent projections from the trigeminal ganglion converge with inputs from adjacent skin, pericranial, and paraspinal muscle, and other C1-C2 innervated tissues before synapsing on second-order neurons in the trigeminal cervical complex (TCC), which encompasses the TNC and the dorsal horn of the upper cervical spinal cord (C1-C2).[4,20,33-35] The convergence of afferent projections with neurons from extracranial structures accounts for referred pain perception in the periorbital, occipital, and cervical-neck regions.[34] Ascending pathways from the TCC transmit signals to multiple brainstem, thalamic, hypothalamic, and basal ganglia nuclei.[36] These nuclei project to multiple cortical areas including the somatosensory, insular, motor, parietal association, retrosplenial, auditory, visual, and olfactory cortices that are involved in processing the cognitive, emotional, and sensory-discriminative aspects of the nociceptive signals and give rise to some of the associated symptoms that are characteristic of the attacks and the syndrome, such as photophobia, phonophobia, cognitive dysfunction, osmophobia, and allodynia (Fig. 3).[8,37]

Activation of the Trigeminovascular Pathway.—The activation of migraine pain begins peripherally when nociceptive neurons that innervate the dura mater are stimulated and release vasoactive neuropeptides such as calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating polypeptide-38, causing signaling along the trigeminovascular pathway – the extent to which arterial vasodilatation, mast cell degranulation and plasma extravasation are involved remains unclear.[38-40] Some believe that CSD initiates the activation of meningeal nociceptors.[23] Molecules such as ATP, glutamate, K^+, hydrogen ions, CGRP, and nitrous oxide that are released locally during a CSD are thought to diffuse toward and activate meningeal nociceptors.[20] Evidence from animal studies supports this idea. Focal stimulation of the rat visual cortex was shown to induce CSD and lead to long-lasting activation of meningeal nociceptors. In addition, this neuronal activation occurred approximately 14 minutes after the induced CSD, consistent with the time delay between onset of aura and onset of migraine headache.[32] It has also been shown that CSD can lead to ongoing increased activity in central trigeminovascular neurons in the spinal trigeminal nucleus of anesthetized rats, supporting the theory that CSD results in sequential activation of peripheral and then central trigeminovascular neurons.[41] Preclinical evidence also suggests that CSD may directly activate or

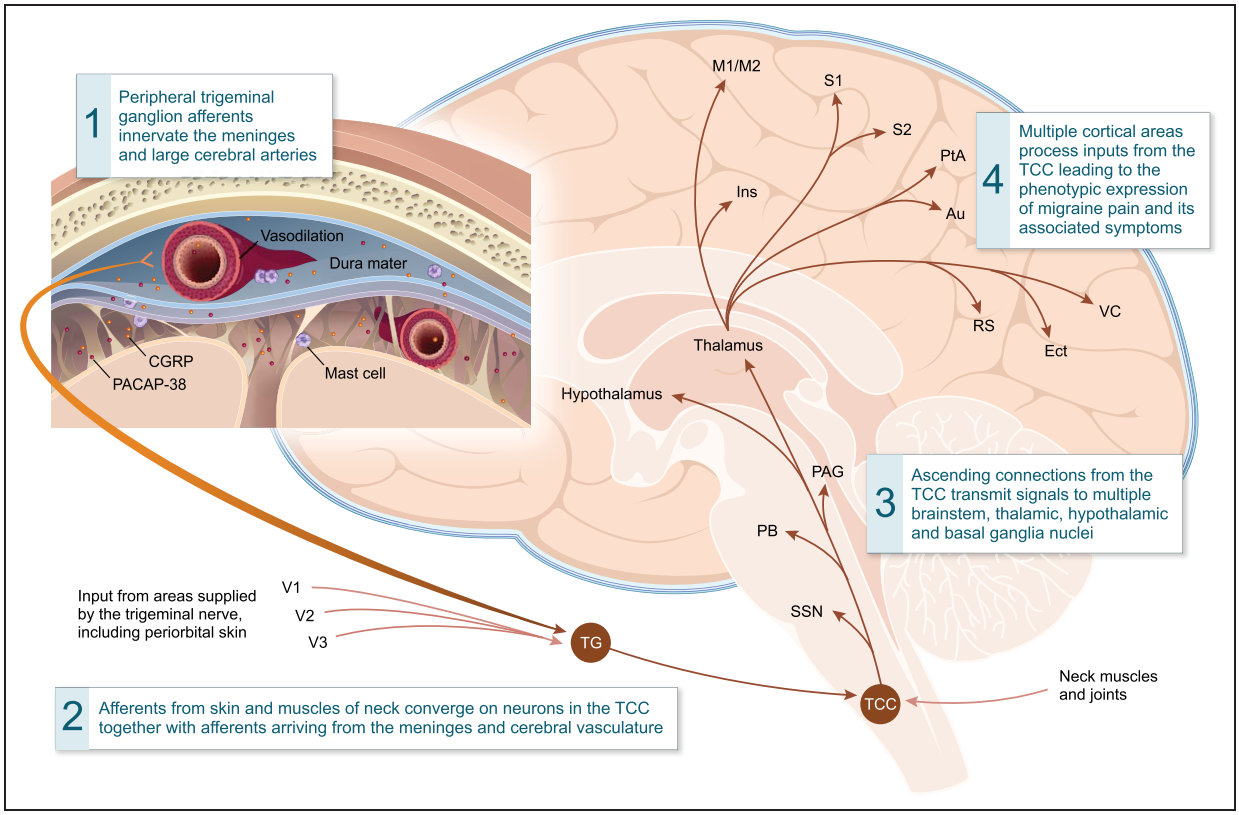

Fig. 3.—The triggering of pain via the trigeminovascular pathway. Au = auditory; Ect = ectorhinal; Ins = insula; M1/M2 = motor cortices; PAG = periaqueductal gray; PB = parabrachial nucleus; PtA = parietal association; RS = retrosplenial; S1/S2 = somatosensory cortices; SSN = superior salivatory nucleus; TCC = trigeminal cervical complex; TG = trigeminal ganglion; VC = visual cortices; V1 = ophthalmic branch of trigeminal nerve; V2 = maxillary branch of trigeminal nerve; V3 = mandibular branch of trigeminal nerve.

disinhibit central trigeminal sensory neurons by a mechanism intrinsic to the CNS. In these experiments, sensory blockade of the trigeminal ganglion did not disrupt CSD-induced activation of second-order trigeminovascular neurons in the TCC.[42] This suggests that CSD does not act to increase central trigeminovascular traffic by a peripheral action alone, and that, therefore, the pain of migraine may also arise by a central mechanism.[42] This may explain, eg, several clinical observations including the development of mechanical allodynia (neck discomfort) prior to the development of headache that occurs in some patients.

However, the majority of migraine attacks are not preceded by clinical symptoms of aura; aura may occur after the headache phase has already begun, and patients may experience aura but not the subsequent headache.[28] In a prospective study of the time course of aura and headache symptoms, it was found that many patients reported migraine symptoms such as nausea (51%), photophobia (88%), phonophobia (73%), and headache (73%) during the aura phase, and 11% reported the headache as starting simultaneously with the aura.[43] It has been suggested therefore, that aura may instead be the result of an aberrant "brain state" that occurs in a genetically susceptible individual during a migraine attack, and that physiological events occurring during the premonitory phase (which occurs earlier than aura) may be the primary cause of both trigeminovascular pathway activation and cortical neuronal/glial activity.[7,28]

Peripheral Sensitization.—Once activated by endogenous mediators, peripheral trigeminovascular neurons become sensitized to dural stimuli, meaning their threshold for response decreases and

the magnitude of their response increases.[8] Peripheral sensitization is considered to be responsible for the characteristic throbbing pain of migraine, and the exacerbation of pain by bending over or coughing.[8] This increased sensitivity to sensory stimulation is thought to be caused by hyper-responsiveness within primary afferent fibers and/or central neurons.[23] The precise inflammatory mediators that promote activation and sensitization of peripheral trigeminovascular neurons remains to be fully understood.[23] Studies of trigeminovascular activation in the rat have shown that mast cell degranulation produces long-lasting activation and sensitization of dural nociceptors.[44] Several animal studies implicate CGRP release in the initiation and maintenance of peripheral sensitization.[45,46] In a study of repeated CGRP injection into rats' paws, the response threshold to a noxious mechanical stimulus was significantly lowered as a result of peripheral sensitization.[46]

Central Sensitization.—Sensitization of central trigeminovascular neurons in the TCC and thalamic nuclei are responsible for cephalic and extracephalic allodynia.[8] Sensitization causes an increase in spontaneous neuronal activity and a heightened response to innocuous cephalic and extracephalic stimuli.[8] Cephalic allodynia, resulting from sensitization in the spinal trigeminal nucleus, includes signs of scalp and cephalic muscle tenderness and an aversion to touch that develops over 30-60 minutes, reaching a maximum after approximately 120 minutes.[8] Thalamic sensitization develops after approximately 2-4 hours and is responsible for extracephalic allodynia.[8] There is evidence that cutaneous allodynia may be a risk factor for migraine progression.[47,48] It is thought that this may occur through repeated activation and sensitization of the central trigeminovascular pathways, and eventually persistent central sensitization, elevating the risk for developing chronic migraine.[49]

NEURONAL HYPEREXCITABILITY AND ITS GENETICS

Neuro-physiological studies have shown that the migraine brain is characterized by general neuronal hyperexcitability.[50] Evoked and event-related potential studies have shown increased excitability in patients with migraine in response to a wide range of stimuli including visual, somatosensory, and auditory, as well as brainstem reflexes in response to nociceptive stimuli.[50-52] Such studies show that individuals with migraine exhibit a lack of habituation in response to repetitive stimulation, in contrast to nonmigraine controls.[53] Functional imaging studies have also shown that the migraine brain is hyper-responsive to sensory stimuli during the interictal phase.[54,55] It is thought that this general neuronal hyperexcitability may explain the increased sensitivity to sensory stimuli seen in patients with migraine during the interictal phase.[56] It has also been proposed that this hyper-responsiveness may contribute to the development of central sensitization, since patients with migraine show greater activation in pain-facilitating regions, and decreased activation in pain-inhibiting regions at resting state and in response to painful stimuli, compared to healthy controls.[56,57] Some genetic variations found to be possibly associated with migraine may provide insights into the mechanism(s) for the generalized neuronal hyperexcitability seen in these patients.[58,59]

The first genetic association with migraine to be identified was familial hemiplegic migraine (FHM), a rare form of migraine that is inherited in an autosomal dominant pattern.[60,61] It is characterized by migraine attacks accompanied by a transient unilateral motor weakness.[60] The genes identified for FHM all encode for proteins that ultimately modulate the availability of glutamate at synaptic terminals, thus increasing neuronal excitability.[60] Three types of FHM have been identified. FHM type 1 (FHM1) is caused by mutations in *CACNA1A* on chromosome 19p13 that encodes for the α1 subunit of voltage-gated Ca^{2+} channels that control neurotransmitter release at synapses.[60,62] FHM2 is caused by mutations in *ATP1A2* on chromosome 1q23 which encodes for the α2 subunit of Na^{+}/K^{+}-ATPase which is expressed in the glial cells of adults and aids reuptake of glutamate from the synaptic cleft.[60,62] Both FHM1 and FHM2 mutations result in hyperexcitatory neurotransmission through the unregulated release or reduced

reuptake of glutamate from the synaptic cleft.[60,62] FHM3 results from a mutation in *SCN1A* on chromosome 2q24 that encodes for the α1 subunit of voltage-gated Na^+ channels which are expressed on inhibitory interneurons; FHM3 mutations cause unregulated firing of excitatory neurons.[60,62] Since the identification of the FHM genes, 12 genetic loci have been identified that are associated with increased susceptibility for migraine, with or without aura, three of which increase activity in glutamatergic systems.[58,63-65] Such activity leads to increased transmission of pain signals, allodynia, and central sensitization.[8,66]

The underlying basis for hyperexcitability in migraine is not clear, but genetic factors appear to play a key role.[8] Large genome-wide association studies (GWAS) have identified genetic loci that predict for susceptibility to migraine with and without aura.[58,59] Among the identified susceptibility gene variants, some may regulate glutamate neurotransmission (*MTDH, LRP1*, and *MEF2D*),[63-65] while others regulate synaptic development and plasticity (*ASTN2* and *FHL5*)[59,65] and ion channels (*KCNK5* and *TRPM8*)[59] as well as ion homeostasis (*SLC24A3*, near *ITPK1*, and near *GJA1*).[59] In a meta-analysis of 22 GWAS, a number of migraine-associated single nucleotide polymorphisms were identified that are involved in both arterial and smooth muscle function, suggesting that alterations in vascular and smooth muscle function are likely to play a role in migraine pathogenesis.[59] This is consistent with the increased risk of vascular disease (ischemic stroke and cardiovascular disease) in migraine, especially with aura.[59] This is also consistent with the primacy of the central neuronal mechanisms involved in migraine given the intimate anatomical and physiological relationship between the blood vessel and neuronal and glial cells within the neurovascular unit.[67]

CGRP

CGRP is a 37 amino acid neuropeptide encoded by the calcitonin gene (CALCA) which plays a role in cardiovascular, digestive, and sensory functions.[45,68] CGRP and its receptor are expressed throughout the body, particularly in the central and peripheral nervous systems, the cardiovascular system and the gastrointestinal system.[3,45] The somatosensory function of CGRP has been implicated in the development of neuronal sensitization and pain generation, most notably in migraine.[45]

Considerable evidence points towards CGRP as a key player in migraine pathogenesis: (1) CGRP is a potent vasodilator, and is present in afferents innervating meningeal blood vessels;[3,69] (2) CGRP is a neurotransmitter that can enhance synaptic transmission mediated by glutamatergic signaling;[3] (3) Elevations of CGRP can be detected in jugular venous blood during migraine attacks;[70] (4) Intravenous injection of CGRP triggers migraine in patients with migraine, but not in healthy volunteers.[71,72]

CGRP is thought to act at multiple sites along the trigeminovascular pathway. Peripheral release of CGRP in the meninges causes arterial vasodilatation, and may result in sterile inflammation and activation of meningeal nociceptors.[3,40] CGRP acts indirectly in the periphery to cause plasma extravasation by further increasing substance P release (although the relevance of this action is unclear in migraine), and CGRP acts centrally within the trigeminal ganglion, where it may be involved in signaling between trigeminal ganglion neurons.[40,73] In addition, CGRP has also been implicated in neuronal-glial cell signaling within the trigeminal ganglion, which may contribute to peripheral sensitization.[74] Release of CGRP in the TCC may facilitate nociceptive transmission by increasing the release of neurotransmitters from adjacent primary afferent terminals (Fig. 4).[40]

THE UNMET NEED IN THE TREATMENT OF MIGRAINE

While there have been significant advances in our knowledge of the complex mechanisms involved in migraine pathophysiology, there remains an unmet need for more effective treatments for the disease.[75] Currently available acute treatments for migraine result in sustained and complete relief of pain within 2 hours in only a minority of patients, and have been associated with medication overuse headache when used frequently (more than 10 days per month).[75-77] The success of acute therapy is further hindered by treatment discontinuation due to tolerability issues,

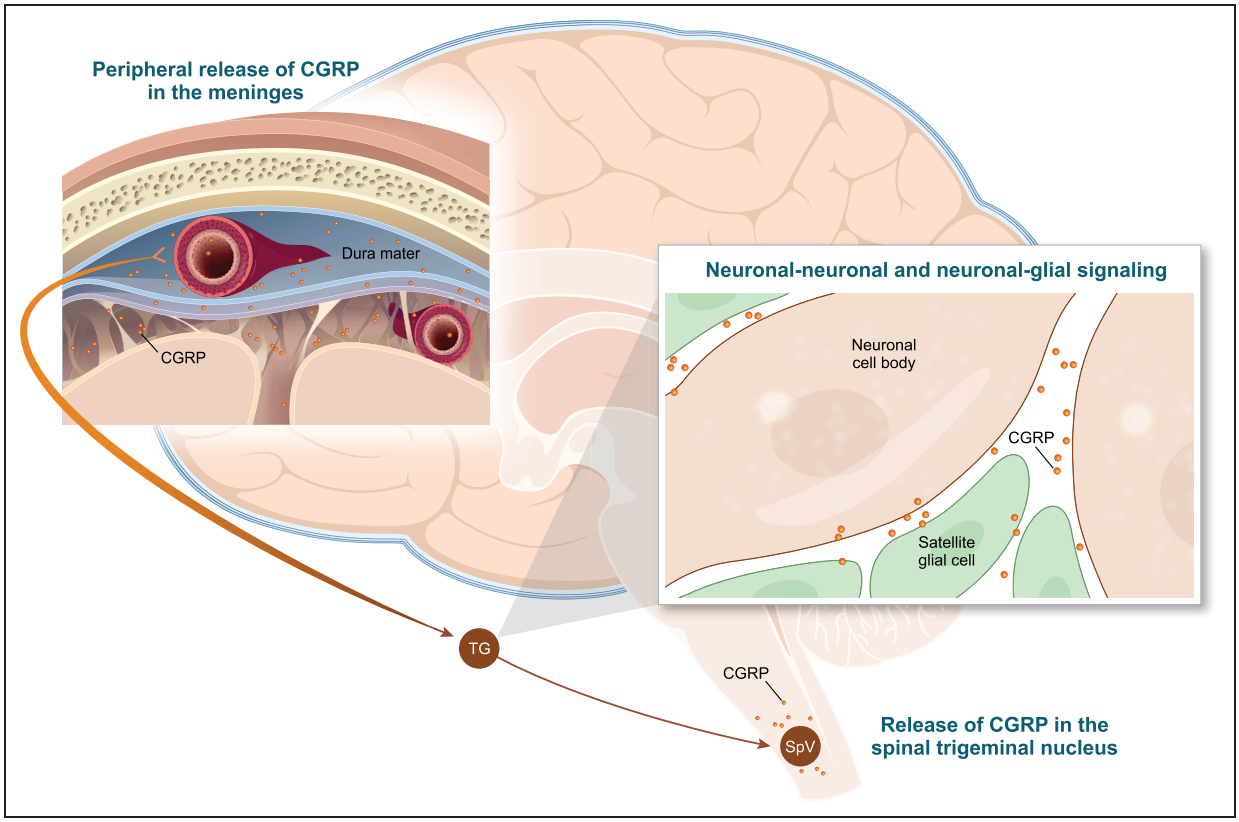

Fig. 4.—CGRP signaling in the trigeminovascular system. CGRP = calcitonin gene-related peptide; SpV = spinal trigeminal nucleus; TG = trigeminal ganglion.

or by contraindications due to the presence of cardiovascular disease or significant risk.[78,79]

Prophylactic treatment would provide the opportunity to prevent an attack from occurring, obviate the need for the use of acute therapies, and potentially mitigate progression which occurs in up to 3% of patients annually (though the latter requires longitudinal prospective studies).[48] At present, available pharmacological approaches to prevention are effective in only a limited number of patients with migraine, and there is an unmet need for better approaches.[75] This suboptimal efficacy, combined with poor tolerability, results in low adherence rates.[80-82] For example, in one study, low adherence rates were observed at 6 and 12 months after starting oral preventive drug treatment.[79]

Integrating our knowledge of migraine pathophysiology, and translating pathophysiological concepts into developing better treatments and patient management approaches, are important goals in the field of migraine research.

CONCLUSION

Migraine is an inherited neurological disorder characterized by an underlying state of increased responsiveness of cortical and subcortical networks that amplify the intensity of sensory stimuli. Migraine attacks are evolutive and generally involve a premonitory, headache pain, and postdromal phase, and in about one-third, reversible visual, sensory, and language symptoms (aura phase). The premonitory phase appears to involve the hypothalamus and its functional connections to specific brainstem nuclei and cortical regions, whereas migraine headache pain involves increased sensory processing within peripheral and central trigeminovascular pathways.

While many aspects of migraine pathophysiology remain unclear, a great deal of research has been conducted over recent years to increase our understanding of the complex processes involved in all stages of the migraine attack, which has subsequently informed the identification of therapeutic targets.

CGRP, which is involved in the activation and transmission of sensory signals within trigeminovascular pathways, is one such target that has been validated as an effective therapeutic target for both acute and preventive treatment.

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