Deciphering migraine

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Migraine is an episodic headache disorder affecting as many as 10% of people worldwide. Familial hemiplegic migraine (FHM) is an autosomal dominant subtype of severe migraine accompanied by visual disturbances known as aura. Migrainous aura is caused by cortical spreading depression (CSD) — a slowly advancing wave of tissue depolarization in the cortex. More than half of FHM cases are caused by mutations in the *CACNA1A* gene, which encodes a neuronal $Ca_v2.1$ Ca^{2+} channel, resulting in increased Ca^{2+} flow into dendrites and excessive release of the excitatory neurotransmitter glutamate. In this issue of the *JCI*, Eikermann-Haerter et al. show that transgenic mice with FHM-associated mutations in *Cacna1a* have increased susceptibility to CSD compared with wild-type animals, likely due to augmentation of excitatory neurotransmission (see the related article, doi:10.1172/JCI36059). Additional as-yet-undefined channel mutations may similarly render the migraine brain more susceptible to the initiation of CSD, with implications not only for the genesis of migraine but also for the hypoxic injury that accompanies its worst manifestation, complicated migraine.

Cortical spreading depression as a trigger of migraine pain

Written accounts of migraine are nearly as old as writing itself. Descriptions of headaches, dating to roughly 3000 BCE, have been found in the ruins of the ancient Sumerian civilization. When people lacked the understanding of the human body that modern medicine grants us, migraine pain was ascribed to the will of evil spirits or malevolent gods — doctors of the time recommended cranial trepanation as a way to release "unholy forces." In the early seventeenth century, European clinicians first proposed the vascular hypothesis, which long dominated our views of migraine. Patients' descriptions of the pulsating character of migraine pain led to the concept that the vasculature might play a central role in the severe headache typical of migraine (1).

It was the Canadian psychologist Peter Milner who, in 1958, first noted the striking similarities between the progression of migraine aura and cortical spreading depression (CSD). CSD is a self-propagating wave of tissue depolarization that migrates without a loss in depolarization amplitude and is followed by a prolonged period of suppressed neural activity (2). Milner saw the connection between this and the migraine aura, because it was known that the scintillating scotomata (often manifesting as flashes of light in a geometric pattern that slowly move across the visual field) that precede and accompany migraine pain propagate at a rate of about 3 mm/min through the visual cortex (3). It is now generally accepted that CSD constitutes the biological basis of most, if not all, types of migraine. Approximately 30% of migraine patients experience this aura (4). The idea that CSD is the endogenous trigger of migraine was initially met with considerable skepticism; one article of the time called this theory "ingenious, if absurd" (quoted in ref. 5). One obvious issue noted was that the brain itself is not capable of sensing pain. Thus, how might a transient wave of cortical depolarization give rise to the prolonged state of pain that clearly involves the vasculature? Insight came from Moskowitz and coworkers, who showed that CSD induces long-lasting changes in extracranial blood flow, including dilatation of the middle meningeal artery and extravasation of plasma protein (6). In short, CSD disrupted the blood-brain barrier, resulting in MMP9-dependent pathway–mediated extravasation of blood-borne factors, which in turn activated the nociceptive nerve afferent fibers around meningeal vessels (6) (Figure 1). Additional pathways, including those involving gap junctions, cytokines, and NO release, may contribute to the activation of trigeminal ganglion nerve afferents and to the prolonged pain associated with migraine headaches (7, 8). Migraine without aura may result from advancement of CSD waves in regions (such as cerebellum) where the tissue depolarization is not perceived by the patient.

The initial skepticism surrounding CSD as an endogenous trigger of migraine pain has vanished in recent years, because functional MRI imaging of changes in blood oxygen level–dependent (BOLD) signal have shown that the visual aura of migraine is temporally linked to a slowly advancing wave of BOLD signal, which propagates across the visual cortex. The pattern of changes of BOLD signals a patient experienced during visual aura proved identical to those that were observed in experimentally elicited CSD (9). Additional evidence was obtained by magnetoencephalography, which documented that visual scotomata were accompanied by slow changes in the cortical magnetic field, and these were indistinguishable from those recorded during CSD (10). An important question thereby arose: What is the nature of the trigger for spontaneous waves of CSD, antecedent to or accompanying a migraine episode? Experimentally, strong focal stimulation is needed to evoke CSD. Various approaches have been used, including inserting a needle into the exposed cortex, electrical stimulation, or topical application of high K^+ concentrations or glutamate agonists (e.g., NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA]) (11). It is also known that multiple waves of CSD often are spontaneously elicited in the setting of acute neurological injury, including stroke or head trauma (12). Interestingly, the CSD waves last longer in the ischemic brain, and the frequency with which they are generated correlates with the degree of ischemic damage (13). However, stroke or head trauma is not responsible for the CSD waves in patients with migraine, making it difficult to explain how and why CSD is initiated in the absence of focal stimulation.

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Nonstandard abbreviations used: BOLD, blood oxygen level–dependent; CACNA1A, voltage-gated $Ca_v2.1$ Ca^{2+} channel, α_{1A} subunit; CSD, cortical spreading depression; FHM, familial hemiplegic migraine.

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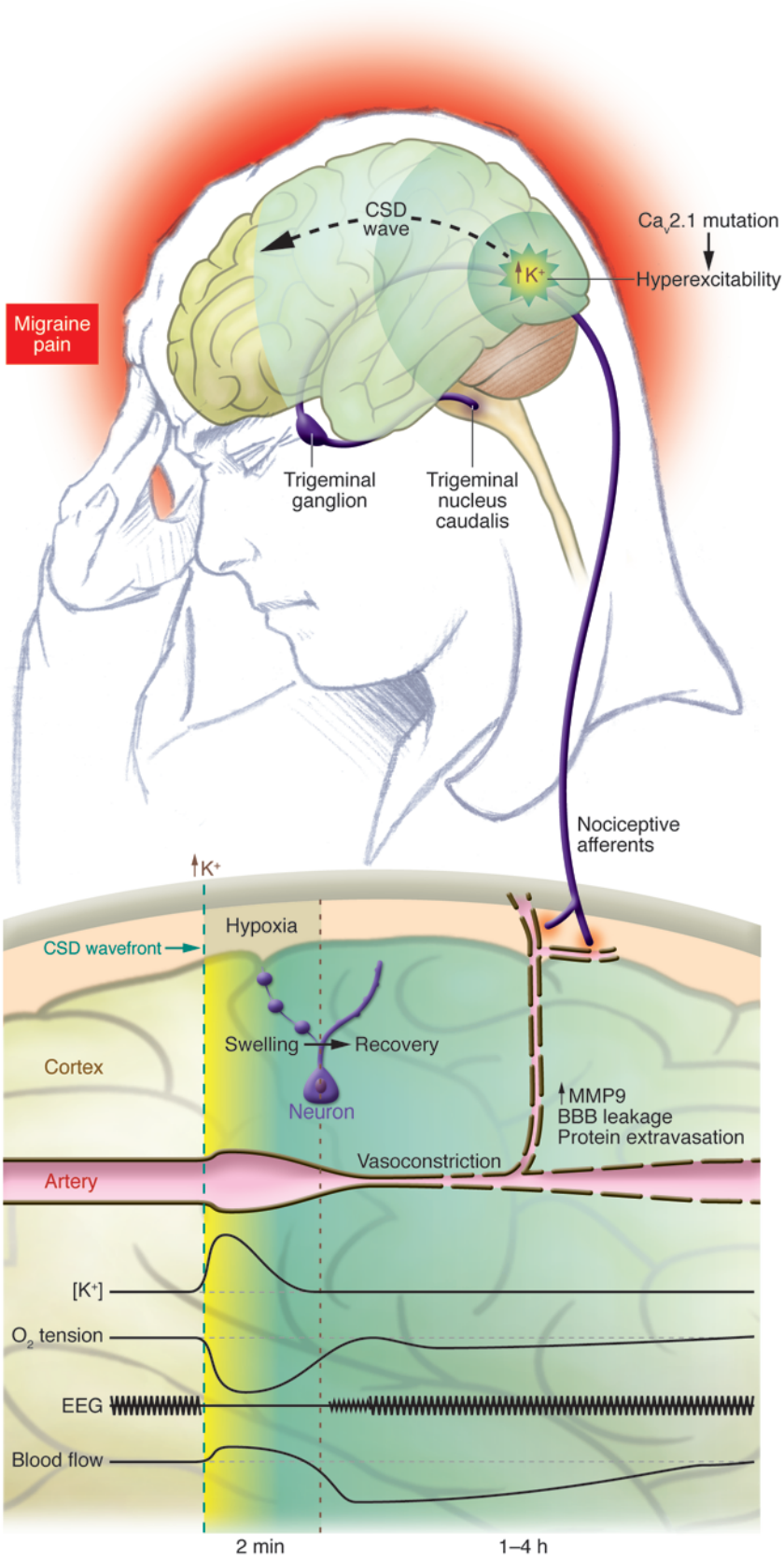

Figure 1
The link between CSD and migraine pain. CSD is most often initiated in the occipital cortex of patients with visual migraine aura. It is believed that CSD is ignited by local elevation of extracellular K^+ levels in pockets of intense excitatory transmission. When K^+ levels reach a critical threshold of 10–12 mM, a self-propagating CSD wave is initiated and advances across the cortex with a slow velocity of 3 mm/min. The threshold for CSD initiation is reduced in FHM patients with mutations in the $Ca_v2.1$ Ca^{2+} channel because the higher Ca^{2+} level in dendrites facilitates glutamate release and thereby increases the likelihood that K^+ levels will reach the CSD threshold. A combination of stress and food intake may be sufficient to ignite CSD in patients with FHM, whereas stronger stimulation is required in the rest of the population. The lower diagram depicts the cortical events linking CSD to migraine pain. The high extracellular K^+ level at the edge of the CSD wavefront is key for wave propagation. K^+ is normalized within minutes, but the restoration of normal membrane potential of neurons and glial cells is a high energy–demanding process. The cortical tissue experiences a minutes-lasting period of severe reduction of tissue O_2 tension (hypoxia) during CSD because O_2 consumption transiently exceeds the vascular supply of O_2. This hypoxia has several consequences: (a) Neurons exhibit severe morphological distortions, swelling, and transient loss of dendritic spines. Normal dendritic structures are reestablished 15–20 minutes later, coinciding with the reappearance of a normal EEG pattern. This hypoxic phase is followed by prolonged vasoconstriction and reduction of local blood flow. (b) The CSD wave activates MMP9, resulting in opening of the blood-brain barrier (BBB) and extravasation of plasma protein. The leakage of blood-borne factors activates nociceptive afferent neurons from trigeminal ganglion innervating meningeal arteries, connecting to trigeminal nucleus caudalis, triggering the migraine pain. (c) CSD triggers preconditioning — an endogenous mechanism of neuroprotection that raises ischemic tolerance.

Strong genetic component of migraine

Analysis of genetic data from patients with familial hemiplegic migraine (FHM), an autosomal dominant subtype of migraine with aura associated with hemiparesis (weakening or paralysis of one side of the body), has in recent years proven to be a powerful tool to determine why CSD typically manifests in patients with migraines. FHM is a heterogeneous genetic disease, but up to 50% of the patients have a mutation in the *CACNA1A* gene, which encodes the α_{1A} subunit of the neuronal, voltage-gated $Ca_v2.1$ Ca^{2+} channel (14). $Ca_v2.1$ channels are primarily located in presynaptic terminals and are important regulators of neurotransmitter release in excitatory synapses (7). An analysis of the single-channel properties of 8 types of mutant $Ca_v2.1$ channels reported in individuals with FHM showed that channel activation in cerebellar granule cells was shifted to lower voltages as a result of all mutations, resulting in a greater influx of Ca^{2+} in cerebellar granule cells (15). Although the functional significance of these changes in the intact brain is not completely understood, a likely scenario is that the increased Ca^{2+} influx augments release of the neurotransmitter glutamate from excitatory neurons in FHM patients, thus increasing the likelihood of triggering CSD. In fact, in a knock-in mouse model carrying the R192Q mutation in *Cacna1a* (the same mutation observed in individuals with FHM), the animals exhibited a reduced threshold for experimentally elicited CSD; in addition, the waves propagated faster once evoked (16).

The study by Eikermann-Haerter and coworkers in this issue of the *JCI* sheds light on several key aspects of the basic biology of migraine headaches (17). The authors describe what is believed to be a novel phenotype in transgenic mice expressing the R192Q or S218L mutations in *Cacna1a*, both of which are associated with human FHM. Patients with the R192Q mutation suffer from FHM only, whereas the S218L mutation is associated with not only severe migraine but also risk of developing excessive edema in the setting of minor head injury (18). Eikermann-Haerter et al. show that both mutations decreased the threshold for eliciting CSD in mice, while increasing its rate of propagation, and this susceptibility was modulated by allele dosage (i.e., homozygotes > heterozygotes > wild-type). Both mutations lowered the threshold for the $Ca_v2.1$ channel opening and prolonged channel inactivation, but the S218L mutation was associated with more severe alterations in both channel activity and neurological deficits, compared with changes associated with the R192Q mutation. Interestingly, corticostriatal propagation of CSD was observed in the majority of mutant mice, and more serious and prolonged post-CSD neurological deficits followed, compared with those observed in wild-type mice. Moreover, the higher prevalence of migraine in females was replicated in the mutant mice. Female mutant mice were more susceptible to CSD, and their neurological deficits manifested more severely than those in their male equivalents. The sex difference was eliminated by ovariectomy and partially restored by estrogen replacement, suggesting that differences in CSD susceptibility between males and females involve the effect of ovarian hormones. Like any important study, this new work raises a number of questions: Only experimentally induced CSD was studied, and it is tempting to ask whether the mutant mice experience spontaneous waves of CSD. Moreover, FHM is a rare disease, and the current study does not directly address the pathogenesis of migraine with or without aura. Common migraine is a multifactorial polygenetic disease, and a genetic component can only been identified in about 50% of individuals with migraine. In these patients, recent genome-wide screens have pointed to several susceptibility loci, but no causative genes have been identified (7).

Long-term effect of migraine

Pain is an unpleasant and not easily overridden sensation of potential or actual danger to the body. Does migraine pain signify that the brain is in potential danger? Perhaps. Recent studies show that cortical tissue experiences a short-lasting episode of hypoxia during CSD, which may be similar to that exhibited during a transient ischemic attack (Figure 1) (19). The hypoxia is caused not by a reduction in blood flow, but by the enormous increase in O_2 utilization that is required to restore ion homeostasis following CSD. Neuronal and glial membrane potentials are almost zero following a wave of CSD, and the clearance of the high level of extracellular K^+ is associated with a sharp increase in O_2 consumption. As a consequence, neurons and glia can experience 1–2 minutes of hypoxia during CSD; tissue O_2 tension level falls below 4 mmHg, resulting in dendritic swelling and a transient loss of dendritic spines, likely contributing to the prolonged depression of EEG activity after CSD (19). The changes in neuronal structure are reversible, and neurons do recover, but whether repeated episodes of migraine might cause permanent neuronal damage remains an unanswered question. Several prospective studies have shown that migraine patients do not experience cognitive decline (20, 21). It is interesting to note, however, that all studies published to date document that long-term migraineurs consistently score lower than matched controls in the processing of visual information (22, 23). Thus, visual aura, which is initiated and advances through the occipital cortex, may impair cortical network function locally. Alternatively, the impairment of visual processing and the lower threshold for CSD might be somehow coassociated through a common etiology.

A recent study suggested that women with a lifetime history of migraine performed better on cognitive tests than did subjects without migraines (24). One possible explanation is that the migraine pain, similar to other types of pain, warned the patients and reinforced a healthier lifestyle that not only reduced migraine attack but also protected memory. Another possible explanation is that although the hypoxia-associated CSD represents an immediate danger, the long-term effect might be a strengthening of cortical circuits. A large body of literature documents that CSD is a preconditioning stimulus, similar to short-lasting episodes of ischemia (25). Thus, exposure to a wave of CSD might confer tolerance, allowing cortical neurons to survive an otherwise lethal subsequent episode of ischemia. The mechanism by which CSD increases ischemic tolerance is multifactorial and includes release of well-known trophic factors, including brain-derived neurotrophic factor (26). Thus, it is plausible that the beneficial effect of increased neuronal tolerance may, over the long term, outweigh the hypoxic stress associated with CSD.

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