Common Pathophysiologic Mechanisms in Migraine and Epilepsy

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Migraine and epilepsy are comorbid episodic disorders that have common pathophysiologic mechanisms. Migraine attacks, like epileptic seizures, may be triggered by excessive neocortical cellular excitability; in migraine, however, the hyperexcitability is believed to transition to cortical spreading depression rather than to the hypersynchronous activity that characterizes seizures. Some forms of epilepsy and migraine are known to be channelopathies. Mutations in the same genes can cause either migraine or epilepsy or, in some cases, both. Given the likely commonalities in the underlying cellular and molecular mechanisms, it is not surprising that some antiepileptic drugs, including valproate, topiramate, and gabapentin, are effective antimigraine agents. Ionotropic glutamate receptors play roles in both migraine and epilepsy, with NMDA receptors that are critical to cortical spreading depression of particular importance in migraine. Greater understanding of the shared mechanisms of epilepsy and migraine can provide a basis for the development of improved treatment approaches that may be applicable to both conditions. *Arch Neurol. 2008;65(6):709-714*

Patients with epilepsy and migraine are often cared for by different subspecialists in neurology and there is little communication among researchers in the 2 disciplines. We think of epileptic seizures as arising because of a disturbance in brain electrical excitability, whereas migraine has traditionally been viewed as a type of chronic pain syndrome that is fundamentally vascular in nature. Nevertheless, epilepsy and migraine share 1 essential and defining attribute that distinguishes them from other common neurological disorders: they are both characterized by paroxysmal symptoms and are therefore episodic disorders. Affected individuals are ordinarily symptom-free between attacks until they experience a time-limited ictus of more or less sudden onset from which they recover completely. In recent years, migraine researchers have developed an increasingly sophisticated understanding of the basis of the migraine attack. This new knowledge has led to a convergence between theories of epilepsy and migraine pathophysiology. In the future, there may be good reason to consider epilepsy and migraine as part of a family of disorders in which understanding of pathophysiologic mechanisms in either type of disorder can inform a shared understanding and suggest therapeutic strategies that may be broadly applicable across the family. Herein, I provide an update on the pathophysiology of migraine and point out its similarities with epilepsy.

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WOLFF'S VASCULAR THEORY OF MIGRAINE

During the 1940s, the neurologist Harold G. Wolff, MD, developed the vascular theory of migraine. He hypothesized that migraine attacks are initiated by vasoconstriction in the cranial vasculature leading to oligemia and a reduction in cerebral blood flow that could be severe enough to generate an aura.[1] Compensatory vasodilation occurring in intracranial or extracranial blood ves-

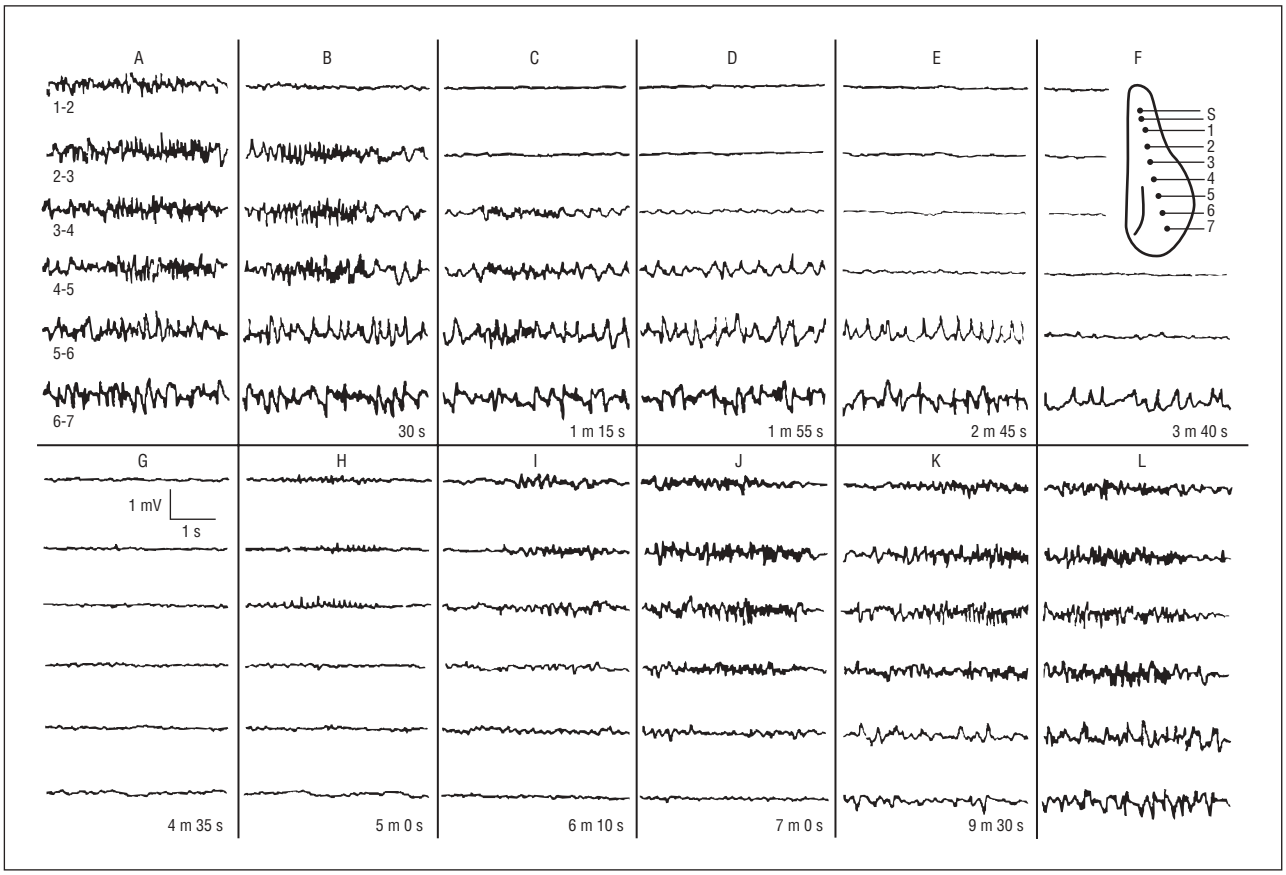

Figure 1. Demonstration of the spread of cortical spreading depression in the rabbit neocortex from Leão's original article.[4] Simultaneous recordings from several pairs of electrodes showing slow, gradual directional spread of cortical spreading depression (nearly absent electrical activity) and slow recovery in the opposite direction. Cortical spreading depression was elicited by tetanic electrical stimulation (3-5 seconds) applied via an electrode at S (topmost position in inset diagram). Used with permission from the American Physiological Society.

sels after vasoconstriction was assumed to result in perivascular edema and inflammation that, in turn, triggered headache pain. Whereas most of the brain is insensitive to pain, meningeal blood vessels are highly innervated by pain fibers. Blood vessel dilation was presumed to activate the trigeminal sensory nerves that surround the meningeal blood vessels, causing pain. Wolff's theory was accepted for nearly 50 years. However, Jes Olesen's careful measurements of regional cerebral blood flow during migraine attacks using xenon 133 single-photon emission computed tomography demonstrated that while there was a reduction in blood flow at the time of aural symptoms, blood flow could remain decreased during the headache.[2] Blood flow might then become abnormally high without a change in the headache. The lack of correlation between the changes in blood flow and migraine symptoms raised doubts about the vascular etiology of migraines and opened the door for the neural theory.

CORTICAL SPREADING DEPRESSION

Cortical spreading depression (CSD) is becoming increasingly accepted as the likeliest basis for migraine aura and the trigger for headache pain. Cortical spreading depression is characterized by rapid and nearly complete depolarization of a sizable population of cortical neurons with massive efflux of potassium ions from intracellular to extracellular compartments.[3] The process represents a regenerative all-or-none process that propagates slowly as a wave in brain tissue. Cortical spreading depression was discovered in the 1940s by a Brazilian doctoral student Aristides A.P. Leão while working in the Department of Physiology at Harvard Medical School.[4] Leão had set out to study the response of cortical tissue to electrical stimulation in an attempt to understand the basis of cortical electroencephalography in a model of experimental epilepsy. His experiments were performed in the exposed cortex of rabbits and a few pigeons and cats. Following a brief period (1-5 seconds) of repetitive electrical stimulation of the cortex or a few light touches with a small glass rod, he noticed a "marked, enduring depression" of the spontaneous electrical activity in the electroencephalogram signal that spread out slowly in all directions from the region stimulated (**Figure 1**). The velocity of spread was about 3 mm/min.

The initial suggestion that CSD is responsible for migraine aura was based on a comparison between the rates of aural progression and spreading depression. Migraine aura is any transient neurological disturbance that appears shortly before or during the development of a migraine headache. Most commonly, the aura arises in the primary visual cortex and typically involves spreading scintillating scotomata with a characteristic distribution of fortification figures. The disturbance usually starts at the center of the visual field and propagates to peripheral zones within 10 to 15 minutes. Function re-

turns to normal within another 10 to 15 minutes.[5] The rate of development of the visual symptoms suggests that there is a front of hyperactivation in the visual cortex that moves at a speed of approximately 3 mm/min. Milner[6] noted that the speed of propagation of the visual symptoms was the same as that of CSD, leading to the hypothesis that CSD is the physiologic basis for the aura. Interestingly, in individuals experiencing somatosensory symptoms, the spread of symptoms along the sensory homunculus occurs at a similar rate. Numerous neuroimaging studies in humans have supported the concept that CSD-like phenomena in the neocortex occur with migraine aura.[7] In particular, by using functional magnetic resonance imaging, it has been possible to demonstrate slowly propagating neurovascular changes in the visual cortex that occur with visual symptoms in patients experiencing visual aura.[8]

Given these various lines of evidence, there is a consensus that CSD accounts for migraine aura. However, in view of the lack of pain fibers in the brain parenchyma, it has been difficult to understand how the alterations in brain tissue excitability of spreading depression induce the intense pain that follows. A recent study of blood flow in the rat cortex following the induction of CSD may provide the link.[9] These studies have shown that CSD in rats is associated with changes in extracerebral cephalic blood flow as a result of vasodilation within the middle meningeal artery. It is hypothesized that the intrinsic neurophysiologic events occurring in the brain during CSD irritate axon collateral nociceptors in pia and dura mater leading to trigeminal and parasympathetic activation. Trigeminal pain afferents originating in the meningeal vessels pass through the trigeminal ganglion and synapse on second-order neurons in the trigeminocervical complex. These nociceptive neurons, in turn, project through the trigeminal nucleus and, after decussating in the brainstem, form synapses with neurons in the thalamus. While migraine with aura is believed to originate in the neocortex, hippocampal spreading depression can also activate the trigeminal nucleus; however, the role of the hippocampus in migraine has not been well characterized. It is possible that migraine without aura, in at least some cases, may originate in the hippocampus.

NEURONAL HYPEREXCITABILITY AT THE ONSET OF CORTICAL SPREADING DEPRESSION

Following the work of Leão, there have been numerous investigations into the physiologic basis of CSD. It has been found that in addition to the classical electrical and mechanical triggers, the phenomenon can be induced by elevated extracellular potassium, glutamate, and inhibition of Na^+/K^+ adenosine triphosphatase (ATPase). Grafstein's early studies on the ionic basis of CSD are particularly relevant to the issue of the commonality between migraine and epilepsy.[10,11] Studying small isolated slabs of cortex in cerveau isolé (midbrain-transected) cats, Grafstein was able to confirm Leão's observation that CSD is associated with a slow negative direct current (DC) shift and depressed neural activity. Importantly, however, she observed that there is a brief (2-3 seconds) burst of action potential activity at the initiation of the DC negativity (**Figure 2**) and she hypothesized that the intense neuronal activity caused potassium elevations in the interstitial space that led to the depolarization and excitation of adjacent neurons, which in turn are "thrown into intense activity and liberate more K^+."[10] However, Herraras' recent studies[12] have questioned the potassium hypothesis, at least as far as investigating its central role in the spread of the depressed neural activity. Indeed, tetrodotoxin blockade of neuron firing fails to interfere with CSD in some situations, so intense neuronal activity does not seem to be required. Seconds before the neuronal activity is recorded and millimeters ahead of it, subthreshold pacemaker field oscillations that are resistant to synaptic transmission blockade can be detected. Thus, as an alternative to the potassium hypothesis, Herraras has suggested that neuronal synchronization and field oscillations that precede the front of depolarization play a critical role in extending the zone of depressed activity. The synchronization has been hypothesized to be caused by nonsynaptic interactions between neurons possibly mediated by the excitatory neurotransmitter glutamate or through gap junctional interactions. Recently, glia have been implicated as the source of glutamate.[13] These ideas are intriguing given the recent demonstration that calcium signaling in astrocytes may lead to the induction of epileptiform hypersynchronous activity in adjacent neuronal networks as a result of glutamate released from the astrocytes.[14] Several antiepileptic drugs (AEDs), including valproate and gabapentin, with demonstrated activity in migraine prophylaxis effectively suppress calcium signaling in astrocytes. The activity of valproate and gabapentin is more robust than that of phenytoin, which has not been demonstrated to be active in migraine. Thus, it seems plausible that astrocytes are an important target for AEDs in migraine prophylaxis. However, it is noteworthy that CSD can occur even when intracellular calcium waves are eliminated.[15] Presently, the contribution of astrocytes to CSD

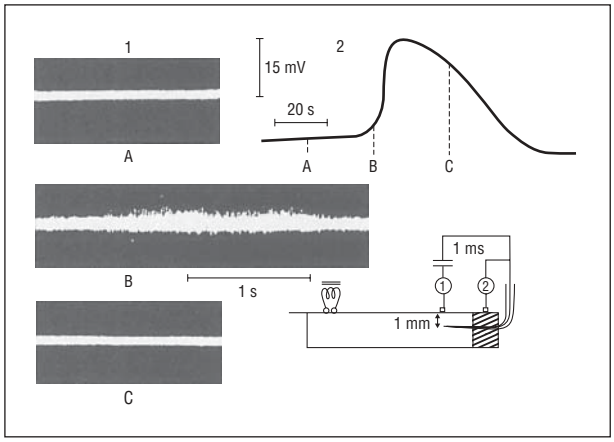

Figure 2. Grafstein's[10] classic demonstration of enhanced single neuron firing at the onset of cortical spreading depression in the isolated cortex of a cat. Slow cortical potential (2) with samples of unit activity preceding negative potential wave (1A), as negativity begins (1B), and after peak of wave (1C). There is a brief period of intense firing activity (1B) as the wave begins that precedes the depression of neural activity (1C). Grafstein noted that interference with the cortical activation (such as seen in 1B) could arrest the spread of depression and she therefore proposed that "the phase of neuronal excitation is an essential link in the spreading depression mechanism." Used with permission from the American Physiological Society.

is incompletely defined; additional evidence is needed to characterize how and when they play a role, if any. It is tantalizing to speculate that suppression of the high-frequency firing noted by Grafstein to be associated with the onset of CSD accounts for the ability of AEDs to protect against migraine attacks. However, the recognition that nonsynaptic mechanisms may trigger CSD suggests that this view is probably too simplistic. Rather, it is more plausible that AEDs that are effective in migraine may suppress the synchronizing mechanisms that Herraras has proposed are critical to CSD. However, experimental support for this hypothesis is required.

CORTICAL HYPEREXCITABILITY IN MIGRAINE

As is the case for many episodic disorders, including epilepsy, the precise trigger for migraine attacks is enigmatic. Many clinical factors such as diet, alterations in sleep, and stress are known to predispose individuals to attacks. It is particularly intriguing that photic stimulation can trigger both migraine attacks and epileptic seizures. How these factors bring on a migraine attack is not known. However, there is evidence for enhanced cortical responsiveness to diverse stimuli in migraineurs. The techniques that have been used to generate this evidence include psychophysical studies; visual, auditory, and somatosensory evoked potentials; magnetoencephalography; and transcranial magnetic stimulation of the motor cortex. In all cases, there is evidence of heightened reactivity between migraine attacks. Results from transcranial magnetic stimulation of the occipital (visual) cortex have been particularly compelling.[16] Most but not all studies have observed that migraineurs have a reduced threshold for induction of phosphenes (the experience of light with nonluminous stimulation) compared with controls. This phenomenon appears to be equally present in individuals who experience migraines with and without aura. Thus, a pathologically low threshold for activation of cortical hyperexcitability may characterize both migraine and epilepsy.

SOME FORMS OF MIGRAINE AND EPILEPSY ARE CHANNELOPATHIES

Migraine and epilepsy share many characteristics with the broader group of episodic disorders that include the various forms of the congenital long QT syndrome (disorders of cardiac muscle) and different myotonias and periodic paralyses (disorders of skeletal muscle).[17] Although they affect diverse organ systems and have different outward manifestations, such episodic disorders have a number of common features. They often occur in otherwise healthy individuals and the attacks may be precipitated by factors such as stress, fatigue, or diet. Episodic disorders often have a genetic component and are first experienced in infancy, childhood, or adolescence. As the genetic bases of the syndromes have been identified, it has become clear that many episodic disorders are caused by defects in membrane ion channels or, more broadly, ion (or neurotransmitter) transport molecules. Disorders associated with defects in ion channels have become known as *channelopathies*. Since ion channels are the principal mediators of cellular excitability properties, it can be presumed that the underlying pathophysiologic basis of diverse channelopathies is altered cellular excitability. For some episodic disorders—for example, some genetic epilepsies, long QT syndromes, and periodic paralyses—it has been possible to define the specific nature of the change in cellular excitability that results from the mutations that cause the disorders. Often this is a gain-of-function increase in excitability, but in some instances there may be a reduction in excitability in a specific cell population (for example, in inhibitory interneurons) that leads to a net increase in circuit excitability (as in severe myoclonic epilepsy in infancy[18]). Additional evidence for a common pathophysiologic basis among the episodic disorders is that they may occur together. In particular, there is strong evidence of comorbidity between migraine and epilepsy.[19] Moreover, in at least 1 episodic disorder, childhood epilepsy with occipital paroxysms, the attacks have features of both migraine and epilepsy. In this syndrome, partial seizures begin with a visual migrainelike aura and in some cases are followed by postictal migrainelike headache. The comorbidity does not necessarily imply that epilepsy and migraine share a common genetic basis in all instances.[20] Rather, in cases in which there are environmental contributions to the pathogenesis (for example, in a head injury, which is a risk factor for both epilepsy and migraine), it is possible that the state of brain hyperexcitability causes some individuals to manifest both epileptic seizures and migraine attacks. It is also the case that migraine attacks may, albeit rarely, trigger epileptic seizures (preictal headache), and seizures often initiate headache (postictal headache), which patients may recognize as similar to their migraines.

INSIGHTS FROM FAMILIAL HEMIPLEGIC MIGRAINE

Familial hemiplegic migraine (FHM) is a rare subtype of migraine with aura that is inherited in a mendelian autosomal dominant fashion. Three different genes are now known to be responsible for forms of FHM. The first to be described was *CACNA1A* (GenBank NM_000068), which encodes the pore-forming subunit of neuronal P/Q-type calcium channels ($Ca_V2.1$).[21] Familial hemiplegic migraine mutations in *CACNA1A* cause an increase in the calcium flux of single channels but there is paradoxically a decrease in the maximal $Ca_v2.1$ current density in neurons.[22] Thus, precisely how the FHM mutations influence cellular excitability is obscure. Interestingly, mutations in *CACNA1A* are also associated with the episodic ataxia syndrome EA-2, the spinocerebellar ataxia syndrome SCA-6, and idiopathic generalized epilepsy.[23] Moreover, mutations in homologs of the gene can cause absencelike seizures in rodents.[24]

The second FHM gene to be described was *ATP1A2* (GenBank NM_000702), which encodes the $\alpha 2$ subunit of Na^+/K^+ ATPase.[25] In 1 family, a mutation in the *ATP1A2* gene was not only associated with FHM but also with benign familial infantile convulsions.[26] Other allelic conditions include alternating hemiplegia of childhood, basilar-type migraine, and migraine without aura.[27] Familial hemiplegic migraine mutations in *ATP1A2* lead to complete inactivation of the protein.[28] Seizures can be pro-

duced by inhibition of Na^+/K^+ ATPase,[29] presumably because of diminished capacity to maintain the neuronal resting membrane potential so that neurons can more easily be brought to threshold and excited. A similar increased excitability mechanism is likely to account for the FHM attacks.

The third FHM gene is *SCN1A* (GenBank NM_006920), which encodes the pore-forming α1 subunit of neuronal voltage-gated sodium channel $Na_v1.1$.[30] Mutations in this gene have been associated with generalized epilepsy with febrile seizures plus (GEFS+) and severe myoclonic epilepsy of infancy (SMEI). The FHM mutation in *SCN1A* is believed to accelerate recovery from sodium channel fast inactivation, which would be expected to be permissive to pathologically high-frequency spike firing. Indeed, inhibition of sodium channel inactivation with scorpion toxins can produce seizures,[31] and sodium channel AEDs have an opposing action.[32]

There are 2 important lessons that can be derived from the recent advances in the understanding of FHM. First, the remarkable fact that mutations in the same genes can cause either migraine or epilepsy (or in some cases both), supports the commonality of epilepsy and migraine suggested by the observation that they are both episodic disorders with substantial comorbidity and similarities in cellular physiologic mechanisms. Second, it is apparent that the known FHM genes encode proteins that are ion channels or, in the case of *ATP1A2*, that regulate the level of membrane potential and thus indirectly influence ion channel gating and function. This supports the notion that migraine, like epilepsy, is fundamentally a disorder of altered neuronal excitability.

ROLE OF GLUTAMATE

Synaptically released glutamate acting on ionotropic glutamate receptors is well recognized as playing a critical role in most, if not all, forms of interictal and ictal epileptiform activity. Similarly, there is strong evidence that glutamate release contributes to the triggering of CSD. This release could be from neurons, though as previously discussed, the intriguing possibility that astrocytes are a source of the glutamate has recently been advanced.[12] (Astrocytic glutamate release has also been implicated in the generation of epileptiform activity.[14]) The observation that glutamate can trigger CSD was first made by Van Harreveld in 1959.[33] Subsequently, it was found that Mg^{2+}, which is now recognized as an NMDA receptor channel blocker, can selectively inhibit glutamate-induced spreading depression.[34] Numerous other studies have demonstrated that NMDA receptor antagonists of various types—including the noncompetitive channel blocking antagonists ketamine and MK-801 (dizocilpine) and competitive glutamate-recognition site antagonists such as DL-2-amino-7-phosphonoheptanoate—can inhibit spreading depression in the parietal and occipital corticies.[35] These NMDA receptor antagonists are powerful anticonvulsants in animal models. Interestingly, neither phenytoin, a sodium channel–blocking anticonvulsant, nor diazepam, an anticonvulsant that acts as a positive modulator of $GABA_A$ receptors, was able to inhibit CSD.[35] It is noteworthy that neither of these latter agents are recognized as having antimigraine activity in humans. Although NMDA receptors were the first type of ionotropic glutamate receptor for which selective pharmacological antagonists were available, it is now recognized that AMPA receptors are responsible for the bulk of synaptic excitation at central nervous system synapses. However, NMDA receptors seem to be specifically involved in mediating CSD, as antagonists of AMPA receptors cannot inhibit the phenomenon.[36] Thus, NMDA receptors seem to play a critical role in triggering CSD, and it is reasonable to infer that they could represent targets for the development of antimigraine agents.

Dissociative anestheticlike NMDA receptor antagonists such as ketamine and MK-801 cause substantial neurobehavioral adverse effects and would not be of practical utility in migraine prophylaxis, though there is a report that aura in some patients with FHM may be terminated by acute intranasal ketamine.[37] However, certain so-called low affinity channel-blocking NMDA receptor antagonists such as memantine are well tolerated even with serum levels that are predicted to cause substantial block of brain NMDA receptors.[38] In this regard, it is intriguing that Peeters et al[39] have recently shown that systemically administered memantine inhibits the frequency and amplitude of spreading depression events induced by potassium chloride in the rat parietal cortex. Indeed, there is evidence from open-label trials and anecdotal reports that memantine is effective in migraine prophylaxis.[40] Unlike the more abundant NR1 NMDA receptor subunit, which is expressed throughout the brain, NR2B subunits are largely restricted to the forebrain. It has therefore been suggested that NR2B selectivity would be useful for an NMDA antagonist to be used in migraine treatment, since the CSD implicated in triggering migraine attacks is a forebrain phenomenon. Indeed, NR2B-selective NMDA receptor antagonists can inhibit spreading depression[39] and it will be of interest to determine if NR2B agents have clinical utility in migraine. There is a hope that these antagonists will be better tolerated than nonselective agents, though as yet there is little evidence to support this proposition.[36]

Kainate receptors, the third type of ionotropic glutamate receptors, may also play a role in migraine and could represent a target for antimigraine therapies. Kainate receptors containing the GluR5 subunit regulate pain transmission in the spinal cord, and GluR5 kainate-receptor subunits and functional GluR5 kainate receptors are expressed in the sensory trigeminal neurons that transmit headache pain signals. Moreover, GluR5 antagonists are active in migraine models[41] and intravenous LY293558 (tezampanel), an antagonist of AMPA and GluR5 kainate receptors, was found to dramatically improve headache in a small controlled clinical trial in acute migraine.[42] Topiramate, which is widely used for migraine prophylaxis, is a functional antagonist of GluR5 kainate receptors (and also AMPA receptors).[43] Thus, GluR5 kainate receptors along with NMDA receptors represent attractive targets for migraine therapy. Unlike the situation for NMDA receptor antagonists in which the putative antimigraine action is presumably through inhibition of triggering mechanisms (interference with CSD), in the case of GluR5 kainate-receptor antagonists, the effects

on migraine are likely caused by an action on trigeminovascular pain mechanisms. There is no evidence that GluR5 kainate-receptor blockade affects CSD.

COMMENT

Although rare forms of epilepsy and migraine that are inherited in a mendelian fashion are in many instances caused by defects in ion channels or ion transport molecules, the molecular pathogenesis in the sporadic forms of the disorders that constitute the bulk of clinical cases is obscure. Nevertheless, there is evidence that complex genetic factors contribute to the risk for both sporadic epilepsy and sporadic migraine. Indeed, it is well recognized that migraine aggregates in families, so that the risk of migraine is 50% greater in relatives of migraineurs than in relatives of controls. There is considerable interest in the possibility that genetic polymorphisms in ion channels and other excitability molecules contribute to epilepsy susceptibility. Sporadic migraine susceptibility may be related to polymorphisms in the same or different excitability molecules. When the molecular similarities and differences between epilepsy and migraine are better understood, it will be possible to address why cortical hyperexcitability leads to seizure phenomena characterized by hypersynchronous firing in epilepsy and why it becomes CSD, which leads to headache pain in migraine.

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