Migraine and Epilepsy—Shared Mechanisms within the Family of Episodic Disorders

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Chapter 73

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INTRODUCTION

In 1906, the British neurologist Sir William R. Gowers delivered a clinical lecture at the National Hospital for the Paralysed and Epileptic, Queen Square, London, in which he pointed out the resemblance between migraine and epilepsy. He argued that migraine is a borderland disease to epilepsy: “near it but not of it.” Gowers recognized that migraine and epilepsy often occur together in the same patient and that the two conditions are similar in their “character and nature.” In recent years, the association between migraine and epilepsy as comorbid conditions has been confirmed. Moreover, migraine and epilepsy are now recognized to be key members of a large family of episodic disorders that also includes periodic paralyses, cardiac arrhythmias, and episodic movement disorders. Studies of the pathophysiological mechanisms underlying the generation of migraine aura and focal seizures indicate remarkable similarities. The identification of genes responsible for both conditions is perhaps the strongest evidence for shared underlying mechanisms.

Fred Andermann, in the introduction to the book Migraine and Epilepsy, published in 1987, proposed the following possible explanations for the comorbidity between migraine and epilepsy: (1) both are common and therefore will co-occur by chance, (2) they are
causally related, with one leading to the other, and (3) there is a shared pathophysiological or genetic basis. In this chapter, I examine the evidence for and against these alternatives, focusing on recent advances in physiology and genetics that support Andermann's third possibility.

**COMORBIDITY OF EPILEPSY AND MIGRAINE**

Migraine and epilepsy are both common neurological disorders, although migraine is more frequent. Numerous studies have observed an association between the two disorders. Most studies of comorbidity have examined the incidence of migraine in cohorts of subjects with epilepsy. The prevalence of migraine in populations of individuals with epilepsy is estimated at 8%–24%, so that the risk of migraine is approximately twice that in the normal population. Recently, the incidence of epilepsy was examined in a large series of children with headache. In this study, children with migraine had a 3.2-fold increased risk of epilepsy compared with those with tension-type headache. Although prior studies have found an association only with migraine with aura, this more recent study observed an increased incidence of epilepsy in subjects with migraine both with aura and without aura. In the majority of cases, epilepsy preceded migraine with aura. Overall, the prevalence of epilepsy in individuals with migraine has been reported to be in the range of 1%–17%, with a median of 5.9%, which is higher than the population prevalence of about 0.5%–1%. There is a small increase in the risk of migraine in those with partial onset seizures compared with generalized onset seizures (relative risk, L.3). Migraine is particularly frequent in those with epilepsy caused by head trauma, where the relative risk compared with idiopathic or cryptogenic epilepsy is 1.8. The strong association between post-traumatic epilepsy and migraine is believed to occur because head injury is a risk for both conditions.

Apart from the observation that head trauma may lead to both epilepsy and migraine, there are several possible explanations for the general comorbidity between the two conditions. Migraine attacks could be epileptogenic and over time could lead to the development of epilepsy; alternatively, recurrent seizures could lead to the development of migraine. Epidemiological data indicate that these explanations are unlikely. If migraine caused epilepsy, for example by inducing brain injury, the incidence of an epilepsy diagnosis should be increased in individuals with preexisting migraine. The epidemiological results demonstrate that there is an excess risk of epilepsy both before and after the onset of migraine, leading to the rejection of the unidirectional causality hypothesis. A similar argument suggests that epilepsy does not lead to the development of migraine.

**Do Migraine Attacks Trigger Seizures?**

The association between migraine and epilepsy could arise not because migraine attacks are epileptogenic (i.e., cause a permanent change in the brain to an epileptic state), but because migraine attacks may simply trigger seizures. Indeed, in 1960, William G. Lennox and his daughter Margaret A. Lennox, in their book *Epilepsy and Related Disorders*, recognized a condition they termed *migralepsy*, in which "ophthalmic migraine with perhaps nausea and vomiting [is] followed by symptoms characteristic of epilepsy." In recent years, the International Headache Society has included migralepsy in its classification scheme. However, it has been noted that the differentiation of occipital seizures from migraine aura is difficult, leading to the frequent erroneous diagnosis of migralepsy. Indeed, a review of the literature suggested that migralepsy is extremely rare. In contrast, occipital seizures are often associated with postictal headache that is often indistinguishable from migraine. Therefore, according to Panayiopoulos, in the majority of cases, occipital epilepsy is the correct diagnosis. An alternative perspective is that there are pathophysiological similarities between migraine and epilepsy that make the sharp distinction between the two disorders artificial. In some cases of occipital epilepsy, migraine mechanisms may come into play, inasmuch as there is an overlapping brain substrate. A particularly extreme example of the concept that shared pathophysiological
A Hypothesis for Comorbidity

Acknowledging that seizures often trigger headache, which may have migraine-like features, there remains an increased risk of migraine attacks, unassociated with seizures, in persons with epilepsy and vice versa. Given that there is little evidence to support the unilateral causality concept, it might be concluded that shared genetic risk factors are the underlying explanation for the comorbidity. This simple explanation was not supported in the epidemiological study of Ottman and Lipton. Indeed, their result might have been expected from the observation noted above that head trauma is a risk factor for both epilepsy and migraine. Ottman and Lipton therefore discarded the simple genetic risk hypothesis and instead proposed that a state of brain hyperexcitability, which can either be produced by genetic factors or can be acquired (such as in a head injury), increases the risk of both migraine and epilepsy, thus leading to the comorbid association. As discussed below, this concept is supported by a wide range of physiological evidence.

EPISODIC NEUROLOGICAL DISORDERS

Although epilepsy and migraine have distinct clinical manifestations, an important similarity is that they are both episodic disorders in which patients are affected with symptoms sporadically and the interictal interval between the appearance of symptoms is variable; between attacks, affected individuals may be symptom free. Episodic disorders comprise a large group of clinically important conditions that affect excitable tissues in various organs and have diverse outward manifestations that depend upon the organ affected, such as seizures, headache, cardiac arrhythmias, episodic movements, and periodic paralysis. A hallmark of episodic disorders is that they often are due to defects in ion channels or, more generally, ion-translocating transmembrane proteins including Na⁺,K⁺-ATPase. Paradigmatic of the episodic channelopathies are conditions affecting skeletal muscle that lead to transitory weakness or paralysis, including the periodic paralyses and myotonias. Other well-recognized episodic disorders are the various forms of the long QT syndrome that can cause ventricular tachyarrhythmias and sudden death. In addition to affecting skeletal and cardiac muscles, episodic channelopathies affect the brain. Ryan and Ptáček have defined three broad categories of such episodic disorders: paroxysmal movement disorders (episodic ataxias and paroxysmal dyskinesias), epilepsies, and headache disorders. As episodic disorders, epilepsy and migraine share certain characteristics and a presumption that the underlying pathophysiology relates to alterations in ion channels or ion transporters.

FEATURES THAT CHARACTERIZE EPISODIC DISORDERS

Episodic channelopathies exhibit similar clinical features. The hallmark of all episodic disorders is their paroxysmal nature. A trigger factor of some kind causes the system to assume an
aberrant state that is expressed as an aberrant phenotype. An individual with the disease has a reduced barrier to entry into the aberrant state. In episodic disorders, alterations in the structure of ion channels (more generally, ion transport proteins) decrease the safety margins so that a normally innocuous stressor overcomes homeostatic mechanisms that prevent entry into a pathological state, such as a seizure or migraine attack. This concept implies that unaffected individuals (i.e., individuals who do not enter the aberrant state in the normal course of their daily lives) may enter the aberrant state with sufficient provocation. This is certainly the case for epilepsy and possibly for migraine. Seizures can be provoked in non-epileptic individuals by head trauma, chemical convulsant agents, electrical stimulation (as in electroconvulsive therapy), or metabolic derangements. Headache can also be provoked by certain chemical agents. For example, glyceryl trinitrate (nitroglycerin) has been known from the time of its discovery to produce intense headache. In addition to the immediate headache that occurs in all individuals, migraine sufferers glyceryl trinitrate can trigger a delayed headache of greater intensity and with a greater number of migraine-like features than occurs in nonmigraineurs. Usually, this is without an aura even in migraineurs who experience an aura, although migraine with a visual aura can be triggered in some cases. Histamine infusion can produce similar effects. Secondary migraine headache can also be triggered in nonmigraineurs by many factors, such as intense physical exercise, head injury, hypoglycemia, chronic renal failure, dialysis, and sickle cell disease.

In addition to being members of the family of episodic disorders and often existing together in the same individual, epilepsy and migraine have other similarities. Seizures and migraine attacks may evolve in four comparable stages, with prodromal symptoms, an aura, an ictus (seizure or headache), and a postdromal or postictal phase. Occasionally, the attacks fail to stop, resulting in status epilepticus or status migrainosus. Although there may be a greater diversity of trigger factors for migraine than for epilepsy, there are a surprisingly large number of similar triggers, such as stress (or letdown from stress), factors related to sleep, photic stimulation, hormonal changes such as those occurring during menstruation, and alcohol or dietary factors. How these factors bring on a migraine attack or epileptic seizures is not well understood. However, there is evidence for enhanced cortical responsiveness to diverse stimuli in migraine as well as in epilepsy, as discussed later in this chapter.

**ANTIEPILEPTIC DRUGS IN MIGRAINE**

A further similarity between migraine and epilepsy that strongly supports the notion that there are shared underlying mechanisms is that some antiepileptic drugs (AEDs) are useful in both conditions. There is extensive evidence from randomized controlled clinical trials that divalproex sodium (valproate) and topiramate are effective in preventing migraine attacks, and both drugs are approved by the U.S. Food and Drug Administration for this indication. The gabapentinois gabapentin and pregabalin may also be effective in migraine therapy.

Other AEDs that have been reported to be effective in migraine prophylaxis are levetiracetam and zonisamide. Interestingly, while the limited clinical trial data available do not indicate that lamotrigine reduces the frequency of migraine attacks overall, there is evidence that it may reduce the frequency, duration, and intensity of the migraine aura; in many patients who responded with a reduction in aura, there was a reduction in headache frequency. An effect on aura was also found for the investigational AED tonabersat, which produced a reduction in the number of aura attacks (either isolated aura or aura followed by headache) but not a reduction in the number of migraine headache days. The AEDs reduce neuronal hyperexcitability by various mechanisms. Consequently, these results are consistent with the concept that hyperexcitability is responsible for triggering the aura and the subsequent headache. However, they raise the question of whether, in migraine without aura, different trigger mechanisms may be at play. Some AEDs, including phenytoin, oxcarbazepine, vigabatrin, and clonazepam, are not effective in migraine prophylaxis. Thus, AEDs that primarily act via use-dependent block of voltage-gated sodium channels or that act via GABAergic mechanisms appear to influence
hyperexcitability mechanisms that are not relevant to migraine (perhaps related to the spread of hypersynchronous activity). In any case, it is noteworthy that in both epilepsy and migraine, a proportion of patients are pharmacoresistant (around 30% in both conditions).

CORTICAL SPREADING DEPRESSION

When speaking about migraine in his 1906 lecture on the borderland of epilepsy, Gowers noted, "a peculiar spreading disturbance of the nerve structures is evident." He remarked on the similarity with the Jacksonian march in epilepsy but recognized the different time course in that "The epileptic aura occupies a few seconds," whereas "the premonition of migraine is almost always many minutes, often twenty, in its deliberate course." Gowers' description of the slow spread of the migraine aura is remarkable in that it foreshadows the current view that cortical spreading depression (CSD), a propagating wave of cellular depolarization, is the basis for the aura in migraine and the trigger for the subsequent headache pain.

The phenomenon of CSD was first described by Aristides Leão, who was attempting to develop a model of "experimental epilepsy" by electrically stimulating the cortical surface of the rabbit. Instead, he found that weak electrical (and later mechanical) stimulation elicited a decrease in the spontaneous activity (depression of the electrocorticogram signal) at the stimulated region that slowly spread in all directions at a rate of 3 to 5 mm/min. Recovery of the initial pattern of spontaneous activity occurred over 5 to 10 min. Leão found that epileptiform discharges elicited by electrical stimulation, strychnine, or acetylcholine were suppressed by spreading depression. In addition, he noted that various types of discharges occurred in conjunction with the wave of depression, including electrographic events that resembled tonic-clonic seizure discharges. The spreading depression and the tonic-clonic seizure activity involved the same cortical elements. Moreover, Leão ended his classic 1944 paper with the statement "The depression and 'tonic-clonic' activity of experimental cortical epilepsy seem to be closely related phenomena." Although Leão considered the cortical discharges and the suppression of neuronal activity to be independent, Grafstein's subsequent work demonstrated that the depression is actually preceded by neural activation. Recording from small, isolated slabs of cortex in cerebri isolé (midbrain-transected) cats, Grafstein was able to confirm Leão's observation that spreading depression is associated with a slow negative direct current (DC) shift and depressed neural activity. However, she observed that there is a brief (2-3 s) burst of action potential activity at the initiation of the DC negativity. More recent studies have confirmed the existence of fast, rhythmic discharges in the front of a CSD wave; the discharges are synchronized over considerable distances in the tissue and occur for several seconds before the negative DC shift. Initially, there are subthreshold field oscillations that give rise to a high-frequency (60-70 Hz) burst of populations spikes.

The mechanisms that underlie the initiation and propagation of CSD are still not fully defined. Neurons become silent during the passage of CSD, and recordings from neuronal somata have revealed that the negative DC shift of CSD is associated with collapse of the membrane potential to zero and a severe loss of membrane input resistance. Although neuronal somata become electrically unresponsive during CSD, recent studies indicate that parts of the dendritic tree maintain electrical excitability. The membrane conductances that participate in CSD are not fully defined. Potassium currents, including transient A-type currents, M-type (KV7/KCNQ) current, and also, to a lesser extent, delayed rectifier current, certainly become activated by the depolarization, leading to large transitory increases in extracellular potassium to 30-60 mM that closely follow the DC shift. Ionotropic glutamate receptor channels have also been proposed to play a role. AMPA receptors rapidly desensitize and therefore do not contribute substantially. NMDA receptors are ordinarily blocked by magnesium at resting potential, but the depolarization of CSD is expected to relieve the block. Based on modeling, Makarova et al. have argued that while NMDA receptors do contribute, their contribution is relatively small, particularly since NMDA receptors are inhibited by elevated extracellular potassium concentrations. These authors have proposed that a large, but as yet unidentified, dendritic...
The concept that spreading depression is responsible for migraine aura is based on a comparison between the rates of progression of the two phenomena. Most commonly, migraine aura arises in the primary visual cortex and is associated with visual symptoms. The disturbance usually starts at the center of the visual field and propagates to peripheral zones within 10 to 15 min. Function returns to normal within another 10 to 15 min. 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 et al. noted that the speed of propagation of the visual symptoms was the same as that of the wave of spreading depression, leading to the hypothesis that CSD is the physiological basis for the aura. In subjects experiencing somatosensory symptoms, the spread of symptoms along the sensory homunculus occurs at a similar rate.

Numerous neuroimaging studies in humans support the concept that spreading depression-like phenomena in neocortex occur with migraine aura. In particular, using functional magnetic resonance imaging, it has been possible to demonstrate slowly propagating neurovascular changes in visual cortex that occur together with visual symptoms in patients experiencing visual aura. Although CSD has been assumed to be relevant only to migraine with aura, there is an increasing body of evidence that CSD-like changes in cerebral blood flow also occur in migraine without aura, providing a unified theory of migraine pathogenesis.

HYPEREXCITABILITY IN CSD AND FOCAL SEIZURES

Given that the propagating wave of CSD is led by oscillatory field activity and the discharge of synchronous field responses, it is reasonable to compare the hyperexcitability of CSD with that occurring in a focal seizure discharge. In both cases there is hypersynchronous activity in cortical neural aggregates, although in the case of migraine the current flows are insufficiently broadly distributed spatially to be detected by scalp EEG recordings. Although the way in which CSD generates migraine aura symptoms is poorly understood, the positive symptoms presumably derive from active zones with hypersynchronous activity, whereas negative symptoms (such as scotomas) result from depressed zones; the headache is also generated by depressed cortex. In contrast, in epilepsy, the hypersynchronous activity itself generates the aura and the ictus. The spread of CSD occurs at a stereotypical rate of 3–5 mm/min (50–83 μm/s). In contrast, the spread of epileptiform activity occurs over a wide range of rates that spans three orders of magnitude. Ordinarily, the rate of epileptiform propagation is assumed to be faster than that of CSD. However, in in vitro brain slice models, the speed of propagation depends on the specific model. When synaptic inhibition is reduced (e.g., with GABA receptor-blocking agents), neocortical slices exhibit discharges that propagate at a rate of 2–10 mm/s. In contrast, in the low-magnesium model, in which seizures arise as a result of the enhanced activity of NMDA receptors, seizures propagate at rates of approximately 100–250 μm/s, which is in the same range as the rate of propagation of CSD. Similarly, measurements from EEG recordings indicate that human cortical seizures can spread at low or high rates (<200 μm/s to >10,000 μm/s). Thus, the rate of propagation of epileptiform discharges that are elicited by unblocking NMDA receptors is similar to that of CSD. Potassium channel blockade with 4-aminopyridine (4-AP) can also induce slowly propagating seizure discharges. These seizures, which are largely due to excessive glutamate-mediated excitatory neurotransmission, are not sensitive to NMDA receptor antagonists but are blocked by AMPA receptor antagonists. Therefore, in general, it appears that epileptiform activity associated with enhanced excitatory neurotransmission propagates at rates comparable to those of CSD, whereas epileptiform activity caused by reduced inhibition propagates much faster.

ROLE OF GLUTAMATE

The evidence presented so far indicates that there are similarities in the physiology of the early stages of the evolution of a migraine attack and a focal epileptic seizure. Both begin with
hypersynchronous activity, and both spread as a wave from the region of detonation. For some types of seizure discharges—specifically, those generated by excessive activation of ionotropic glutamate receptors and where GABAergic inhibition is intact—the rate of spread is similar to that occurring in CSD. Ionotropic glutamate receptors appear to play a special role as a trigger in both instances. Indeed, it has been known since the work of van Harreveld and Friliková in the 1970s that glutamate can trigger CSD. Moreover, in their earliest study, glutamate-induced CSD was found to be inhibited in the presence of high magnesium ion concentrations (10–15 mM). We now know that these concentrations of magnesium are sufficient to block NMDA receptors. Indeed, diverse NMDA receptor antagonists, including MK-801, ketamine, memantine, and 3-(2-carboxypropyl-4-yl)propyl-l-phosphonic acid (CPP), have been shown to inhibit CSD. Therefore, NMDA receptors are a critical trigger for CSD. In contrast, AMPA receptor antagonists are generally ineffective. The relative importance of NMDA and AMPA receptors in triggering CSD mimics their relative roles in generating the large DC shift of CSD. The opposite situation applies for most in vitro seizure models, where AMPA receptor antagonists effectively inhibit epileptiform activity but NMDA antagonists do not. An exception is the low-magnesium model associated with excessive activation of NMDA receptors, where NMDA receptor antagonists do abolish the epileptiform discharges.

Given the ability of glutamate to trigger CSD, it has been proposed that glutamate release is responsible for the advancing wave front of CSD. This glutamate could come from neurons, but recently glia have been implicated. At least partial support for this idea is provided by studies showing that NMDA receptor antagonists influence the synchronous population oscillations and raise the threshold required to initiate CSD but do not prevent CSD propagation once initiated. It is concluded that NMDA receptors contribute to but are not essential for the spatial spread of CSD; their role is mainly prior to the massive neuronal depolarization, and they contribute little to this depolarization. In any case, it is interesting to draw a parallel between epileptic activity and CSD/migraine, where fast glutamate-mediated excitation is the initiating event in both instances. In CSD, glia may be a major source of this glutamate. In epilepsy, however, while it had been speculated that glia might release glutamate that generates synchronized epileptic discharges, more recent evidence raises doubt. A schematic illustration of the related but distinct pathways leading to an ictal event in migraine and epilepsy is presented in Fig. 73-1. An example of a situation in an experimental model where seizure activity and spreading depression occur in the same brain networks following a triggering event (a brief pulse of potassium) is shown in Fig. 73-2. Ordinarily, seizure and migraine mechanisms are not considered as occurring together. However, the clinical evidence presented in the first part of this chapter suggests that there are many instances, such as migraine or more commonly seizure-induced headache, where both mechanisms may come into play.

### REQUIREMENT FOR SYNAPTIC TRANSMISSION

An important difference between seizure discharges and CSD is the role of synaptic mechanisms. In most but perhaps not all epilepsy models, ictal activity is blocked by the voltage-gated sodium channel blocker tetrodotoxin and therefore appears to require action potential-dependent synaptic transmission (see ref. 61). Inhibitory transmission, which is also tetrodotoxin sensitive, provides an obligatory synchronizing influence. In contrast, while tetrodotoxin may inhibit the triggering of CSD in some situations, it has generally not been found to inhibit CSD propagation. Therefore, one hypothesis to explain the difference between the physiology of CSD and focal seizure activity is that in CSD nonsynaptic glutamate release from glia is a major factor, whereas in epileptic discharges synaptic glutamate release from neurons is required. In addition, in epilepsy there is a predominant dependence on AMPA receptors, whereas triggering of CSD is mainly dependent on NMDA receptors. Once CSD is initiated, other channel mechanisms come into play.

### CORTICAL HYPERRESPONSIVITY IN MIGRAINE

While it appears that hyperexcitability is critical to seizures and CSD, this does not explain
the susceptibility of some individuals to clinical attacks of migraine. One possibility is that there is a generalized or local cortical hyperresponsivity in susceptible individuals that predisposes the triggering of attacks. There is a voluminous literature on the sensitivity to sensory stimuli in migraineurs. The techniques that have been used include psychophysical studies; visual, auditory, and somatosensory evoked potentials; magnetoencephalography; and transcranial magnetic stimulation (TMS) of the motor cortex. Although a broad range of results have been obtained, the preponderance of evidence supports the view that there is cortical

Figure 73–1. Schematic illustration of the putative chain of cellular events in the evolution of an epileptic seizure and a migraine attack, highlighting the similarities and differences. In epilepsy, synaptic glutamate release acting through AMPA receptors is a trigger factor and synaptic activity is required (in most instances) for propagation. In migraine, synaptic glutamate acting through NMDA receptors is a trigger factor. Once established, synaptic activity may no longer be necessary and glutamate release from glia is the predominant factor that drives the advancing front of spreading depression. The spreading depression wave triggers the release of mediators that activate the trigeminovascular system, resulting in headache pain. Voltage-gated Na⁺ channel dependence (tetrodotoxin sensitivity) implies the involvement of synaptic mechanisms. CGRP, calcitonin gene-related peptide.

Figure 73–2. Seizure activity and spreading depression can occur together in the same brain substrate. The example shown is from a brain slice recording in the hippocampal CA3 region of a young rabbit. A local micropressure application of 2 M KCl was made at time 0 (arrow). The top trace shows the extracellular K⁺ level as recorded by an ion-sensitive microelectrode. The middle trace is an intracellular recording from a CA3 neuron. The bottom trace shows the extracellular field. There is an initial ictal discharge (depolarization and increased action potential generation) followed by full-blown spreading depression with a large negative field potential in conjunction with strong membrane depolarization and a marked increase in extracellular K⁺. Adapted from ref. 100.
hypersensitivity to external stimuli in patients with migraine during and between attacks. For example, most but not all studies have shown reduced phosphene thresholds in the visual cortex of migraineurs with TMS.\(^79\) Some studies have found such effects only in subjects who experience migraine with aura, whereas other have found that the visual cortical hyper-excitability extends to subjects who experience migraine without aura.\(^2,5\) Interestingly, the preponderance of TMS data supports the view that untreated patients with generalized epilepsy syndromes also have enhanced cortical excitability.\(^73\)

**INSIGHTS FROM GENETICS**

Migraine has long been known to have a strong inherited component, but until recently, no accepted linked genetic marker variants have been established for the common forms; a similar lack of information applies to the common forms of epilepsy. Recently, genome-wide association studies have begun to identify genetic variants that confer increased risk for migraine.\(^74\) Some of the variants (such as in the gene for metadherin) have been proposed to influence glutamate signalling although this is still speculative. In contrast, for both migraine and epilepsy, rare Mendelian forms are recognized and single-gene mutations have been identified whose functional implications are better defined. The rare monogenic forms of migraine are of the familial hemiplegic migraine (FHM) subtype. In FHM, attacks typically begin in youth (age range, 5 to 30 years) and include hemiparesis and, in some cases, hemianesthesia, paresthesia, hemianopic visual field disturbances, aphasia, and variable degrees of drowsiness, confusion, or coma. In addition, there is migraine-like unilateral headache that is usually contralateral to the hemiparesis. Attacks of nonhemiplegic migraine without aura can occur in FHM patients and family members, which has been interpreted as indicating that FHM is part of the spectrum of migraine.

**Calcium Channel**

Three different genes cosegregate with FHM. Epilepsy has been reported in all three FHM types. The first to be described was CACNA1A, which encodes the pore-forming \(\alpha_1\)-subunit (Ca\(_{\,2.1}\)) of neuronal P/Q-type calcium channels.\(^73\) Mutations in CACNA1A account for about one-half of all cases of FHM. In addition to FHM1, mutations in CACNA1A are associated with episodic ataxia type 2 (EA2) and spinocerebellar ataxia type 6 (SCA6). All of the 21 FHM1 mutations reported to date produce substitutions of conserved amino acids in important functional regions of the Ca\(_{\,2.1}\) channel, including the pore lining and the voltage sensors. Studies in heterologous expression systems show that the FHM1 mutations generally are associated with a gain of function of the channel represented as enhanced channel gating. Different studies have revealed a variety of complex effects on channel inactivation. However, Pietrobon\(^79\) notes that a consistent effect seen in studies of the single-channel properties of human Ca\(_{\,2.1}\) channels with FHM1 mutations is enhanced channel-opening probability at a wide range of membrane potentials, mainly due to hyperpolarizing shifts in channel activation. These changes in the biophysical properties of single channels result in greater Ca\(_{\text{ii}}\) flux through the mutant Ca\(_{\,2.1}\) channels, which is confirmed by measurements of whole-cell currents in heterologous expression systems and transfected neurons. In addition, while most FHM1 mutations cause a decreased density of functional channels, in some cases the mutations may cause enhanced channel expression, such as with the S218L mutation, which is associated with a particularly severe form of FHM1.\(^76\) Studies of FHM1 knockin mice carrying two different mutations (R192Q and S218L) have confirmed the gain of function observed with recombinant receptors in heterologous expression systems. The gain of function with the S218L mutation was larger than that with the R192Q mutation in accordance with the more severe phenotype of the S218L mutation.\(^72,73\) R192Q mice exhibit a reduced threshold and an increased velocity of CSD; S218L mice are far more sensitive to CSD. These results provide compelling support for the link between CSD and migraine. The functional consequences of the R192Q mutation were studied in neuronal cultures and brain slices from homozygous R192Q knockin mice.\(^79\) There was a gain of function of excitatory neurotransmission between cortical pyramidal cells and between
pyramidal cells and fast-spiking interneurons manifest as increased synaptic strength due to increased action potential-evoked Ca\textsuperscript{2+} influx through mutant P/Q calcium channels. Overall, the results are consistent with the idea that hemiplegic migraine resulting from the R192Q mutation is due to enhanced cortical excitatory neurotransmission. Indeed, inhibitory neurotransmission mediated by fastspiking interneurons was unaffected. Despite the altered balance between excitation and inhibition, the R192Q mutation is not associated with seizures. However, a genetic marker association study has indicated that CACNAIA is associated with idiopathic generalized epilepsy.\textsuperscript{56} Moreover, mutations in homologs of the gene can cause absence-like seizures in rodents.\textsuperscript{89,90} Interestingly, in mice with these mutations (tollering and learner), there is actually a marked resistance to CSD.\textsuperscript{91,92} Among the FHM types, mutations in CACNAIA are least likely to be associated with epilepsy. However, seizures (including seizures occurring during headache) have been reported with some mutations, including S218L,\textsuperscript{93,94} as well as I1710T,\textsuperscript{95} where a 14-year-old girl had recurrent FHM episodes with status epilepticus.\textsuperscript{96} Childhood absence epilepsy (with generalized tonic-clonic seizures) has been associated with a non-FHM-causing point mutation in CACNAIA (G5733T).\textsuperscript{97} Therefore, diverse mutations in CACNAIA can cause migraine without epilepsy, epilepsy without migraine, or both. The underlying pathophysiological mechanisms of absence epilepsy are distinct from those of partial epilepsy. The evidence presented here for a commonality between epilepsy and migraine does not extend to absence epilepsy. Indeed, absence epilepsy mutations in CACNAIA are not associated with FHM, and absence epilepsy mutations in Ca\textsuperscript{3+}IA, the mouse homolog of CACNAIA, not only do not promote CSD but actually markedly inhibit it.\textsuperscript{98}

**Sodium-Potassium Transporter**

The second FHM gene to be described was ATP1A2, which encodes the α2 isomorph of the main catalytic subunit of Na\textsuperscript{+}-K\textsuperscript{+}-ATPase (Na\textsuperscript{+}-K\textsuperscript{+} transporter).\textsuperscript{99} Among the forms of FHM, this type has the most frequent association with epilepsy (approximately 20% of families). There have been associations with partial seizures,\textsuperscript{88} benign familial infantile convulsions (BFIC),\textsuperscript{90} and febrile seizures.\textsuperscript{96} Epilepsy and migraine can co-occur in the same mutation carriers;\textsuperscript{92} in some cases, seizures occur during migraine attacks, representing true migraine.\textsuperscript{91} Na\textsuperscript{+}-K\textsuperscript{+}-ATPase is a highly conserved membrane protein that is expressed in virtually all cells. There are four different isoforms of the catalytic subunit (α1–α4). The α2 isoform is predominantly expressed in astrocytes and skeletal muscle, although it may be expressed in neurons in early development. Therefore, altered Na\textsuperscript{+}-K\textsuperscript{+}-ATPase activity in astrocytes accounts for FHM2. Na\textsuperscript{+}-K\textsuperscript{+}-ATPase plays a fundamental role in the maintenance of the resting potential of all cells, including astrocytes. The pump, which transports three Na\textsuperscript{+} out of the cell in exchange for the countertransport of two K\textsuperscript{+} into the cell, allows extracellular K\textsuperscript{+} to be maintained at a low level. In addition, the Na\textsuperscript{+} gradient produced by Na\textsuperscript{+}-K\textsuperscript{+}-ATPase is required for clearance of extracellular glutamate by astrocytes.\textsuperscript{92} Glutamate uptake in astrocytes is mediated by glutamate transporters, predominantly GLAST (L-glutamate/L-aspartate transporter; EAAT1) and GLT-1 (glutamate transporter 1; EAAT2). These transporters are expressed along with Na\textsuperscript{+}-K\textsuperscript{+}-ATPase in astrocytic processes surrounding glutamatergic synapses. There is tight functional coupling between the transporters and the pump proteins: the uptake of a glutamate molecule is driven by the entry of three Na\textsuperscript{+} (and also one H\textsuperscript{+}) down the electrochemical gradient in exchange for one K\textsuperscript{+}. Recent evidence indicates that the transporters and Na\textsuperscript{+}-K\textsuperscript{+}-ATPase are physically associated in the same protein complex.\textsuperscript{96} Impairment in the pump function of Na\textsuperscript{+}-K\textsuperscript{+}-ATPase is expected to reduce the ability of astrocytes to remove K\textsuperscript{+} that accumulates extracellularly during high-frequency neuronal firing. This in itself would promote hyperexcitability (and seizure activity) and CSD. In addition, elevated external K\textsuperscript{+} causes reversal of glutamate transporters, so that intracellular glutamate is released into the extracellular space, which would further enhance excitability and predispose to CSD. The FHM mutations in ATP1A2, of which more than 36 have now been described, lead to complete inactivation of the protein in some cases,\textsuperscript{94} whereas in other cases there is altered kinetics, altered cation affinity, reduced
membrane trafficking, or reduced protein stability.\textsuperscript{89,90,95} Familial hemiplegic migraine 2 is an autosomal dominant condition, and it is likely that FHM2 mutations lead to loss-of-function with reduced but not absent Na\textsuperscript{+}-K\textsuperscript{+}-ATPase. Indeed, ATP1A2 knockout mice die at birth but heterozygous animals grow normally.\textsuperscript{97} Overall, impairment of astrocytic K\textsuperscript{+} and glutamate handling are likely to account for the CSD and seizures in FHM2. To the extent that \( \alpha_2 \) Na\textsuperscript{+}-K\textsuperscript{+}-ATPase is expressed in neurons, the neuronal resting potential may be depolarized, which would also enhance excitability. It is noteworthy that both seizures\textsuperscript{89,90} and CSD\textsuperscript{98,100} can be produced by pharmacological inhibition of Na\textsuperscript{+}-K\textsuperscript{+}-ATPase with ouabain, a nonselective inhibitor of astrocyte and also neuronal Na\textsuperscript{+}-K\textsuperscript{+}-ATPase.

**Sodium Channel**

The third FHM gene is SCN1A, which encodes the pore-forming \( \alpha_1 \) subunit of the neuronal type 1 voltage-gated sodium channel Na\textsubscript{1.1}.\textsuperscript{100,103} More than 600 sequence variants of this gene have been identified that have been associated with generalized epilepsy with febrile seizures plus (GEFS+) and severe myoclonic epilepsy of infancy (SMEI). To date, only three mutations have been associated with FHM. The first two to be described (Q1489K and L1649Q) cause pure FHM without epilepsy. More recently, in a multigenerational Portuguese family, the L263V mutation was found to be associated not only with FHM but also with generalized tonic-clonic and complex partial seizures.\textsuperscript{105} Family members with the mutation invariably had FHM, and some also exhibited seizures that occurred separately from the migraine attacks. Studies with recombinant human Na\textsubscript{1.1} channels bearing the mutations have demonstrated that the pure FHM mutations Q1489K and L1649Q caused biophysical changes in the Na\textsuperscript{+} current that were interpreted as predominantly of the loss-of-function type.\textsuperscript{104} In contrast, L263V was interpreted as causing gain of function because it produced delayed entry into and accelerated recovery from fast inactivation and increased persistent current as well as other changes in channel gating.\textsuperscript{104} Whether these results, which were obtained with recombinant channels expressed in nonneuronal cells, are relevant to the in vivo situation remains to be determined. However, it has generally been the case that mice with loss-of-function mutations in Na\textsubscript{1.1} have impaired function of GABAAergic inhibitory neurons, which leads to enhanced circuit excitability. In cases where there is gain of function in Na\textsubscript{1.1}, pathological effects may be mediated by the excessive excitability of principal (glutamatergic) neurons that do express the channel, albeit at lower relative levels than do GABAergic neurons.\textsuperscript{89,105} The observation that the gain-of-function L263V mutation is associated with both epilepsy and migraine is consistent with the notion that both disorders are triggered by hyperexcitability. Why attacks are manifest as seizures in some instances and as migraine in others remains to be determined.

Different loss-of-function SCN1A mutations cause pure epilepsy and pure FHM. This provides an opportunity to determine the factors that account for the tendency of circuit hyperexcitability to transition to seizures in one instance and CSD/migraine in the other.

Familial hemiplegic migraine is distinguished from typical migraine by its autosomal dominant Mendelian inheritance and by various clinical features that are not present in typical migraine. Nevertheless, there are sufficient similarities in headache characteristics and triggers to suggest that an understanding of the pathophysiological basis of FHM can shed light on the underlying mechanisms of the far more frequently encountered nonhemiplegic migraine syndromes. Moreover, nonhemiplegic migraine attacks can occur in FHM. It is remarkable that mutations in certain FHM genes can cause either migraine or epilepsy, or in some cases both, clearly demonstrating a commonality between FHM and epilepsy and supporting the notion that migraine generally, like epilepsy, is a disorder of neuronal hyperexcitability.

**CONCLUSIONS**

Epilepsy and migraine are both episodic functional disorders in which susceptible brain regions are hyperexcitable and attacks begin with hypersynchronous neuronal firing. In epilepsy, the hypersynchronous activity continues, whereas in migraine with aura (and possibly also in migraine without aura) there is CSD. If
CSD occurs in eloquent cortex, there are associated aura symptoms, pain. In both epilepsy and migraine, leads to the release of mediators that elicit headache pain. In both epilepsy and migraine, ionotropic glutamate receptor activation triggers the hyperexcitability. In epilepsy, AMPA receptors play a predominant role in mediating the generation and spread of seizure activity, whereas in migraine NMDA receptors are dominant in triggering CSD but the nature of the ionic conductance that leads to the massive but transitory neuronal depolarization in CSD is yet to be defined. In epilepsy and migraine, various factors can provoke attacks, but how these factors lead to neuronal hypersynchronous activity and the initiation of an attack is not understood. Evidence from human neurophysiology and functional studies of recombinant ion channels and animals with human FH M mutations supports the view that in migraine, as in epilepsy, excitability thresholds are reduced so that a normally innocuous stressor overcomes homeostatic mechanisms that prevent entry into the pathological state (migraine attack or seizure). Key unanswered questions are why some individuals are susceptible to migraine and others to epileptic seizures, and, in those susceptible to both migraine and seizures, why attacks manifest as one or the other at different times.

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DISCLOSURE STATEMENT

The author declares no relevant conflicts.

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