U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Rogawski MA. Migraine and Epilepsy—Shared Mechanisms within the Family of Episodic Disorders. In: Noebels JL, Avoli M, Rogawski MA, et al., editors. Jasper's Basic Mechanisms of the Epilepsies [Internet]. 4th edition. Bethesda (MD): National Center for Biotechnology Information (US); 2012.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

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

Michael A. Rogawski[1,*]

Migraine and epilepsy are episodic disorders that share many clinical features and underlying pathophysiological mechanisms. Cortical spreading depression (CSD), a wave of profound cellular depolarization, is believed to underlie migraine aura and to be a trigger for the headache pain in migraine. However, the initial event preceding CSD is cellular hyperexcitability associated with localized epileptiform discharges. Glutamate is a critical mediator of the hyperexcitability in both focal seizures and migraine. In focal epilepsy, seizure generation and spread is mediated by synaptically released glutamate acting on AMPA receptors, whereas triggering of CSD depends on NMDA receptors and spread does not require synaptic transmission. Some antiepileptic drugs prevent the occurrence of migraine attacks, supporting the view that neuronal hyperexcitability is an initiating event. Epidemiological studies demonstrate that epilepsy and migraine are comorbid conditions. This is likely due to shared genetic or environmental factors (such as head injury) that lead to brain hyperexcitability. Strong support for a shared genetic basis comes from familial hemiplegic migraine (FHM), an autosomal dominant syndrome characterized by severe migraine, that arises as a result of mutations in genes for the membrane ion transport proteins *CACNA1A* (P/Q-type voltage-gated calcium channel), *ATP1A2* (Na^+-K^+ ATPase), and *SCN1A* (voltage-gated sodium channel). Allelic mutations in all three genes also cause generalized and in some cases focal epilepsy. Certain mutations in each of the genes are associated with the co-occurrence of FHM and seizures in the same family members; in some cases, seizures occur during migraine attacks ("migralepsy"). While hypersynchronous neuronal discharges are present in seizures and migraine attacks, a key unanswered question is why hypersynchronous activity propagates in epilepsy and transitions to CSD in migraine. Insights into commonalities in the pathophysiology of epilepsy and migraine may suggest new treatment approaches for both conditions.

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.[1] He argued that migraine is a borderland disease to epilepsy: "near it but not of it." Gowers recognized

Author Affiliation: 1 Department of Neurology, School of Medicine and Center for Neuroscience, University of California, Davis, Sacramento, California 95817, USA.

* Addresses for correspondence: Michael A. Rogawski, M.D., Ph.D., Department of Neurology, School of Medicine, University of California, Davis, 4860 Y Street, Suite 3700, Sacramento, CA 95817; E-mail: rogawski@ucdavis.edu

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.[2] 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%,[3] so that the risk of migraine is approximately twice that in the normal population.[4,5] Recently the incidence of epilepsy was examined in a large series of children with headache.[3] In this study, children with migraine had a 3.2-fold increased risk of epilepsy when compared with tension-type headache. Although prior studies have found an association only with migraine with aura,[6] this more recent study observed an increased incidence of epilepsy in subjects both with migraine 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 to 1%. In general, partial epilepsies, particularly cryptogenic epilepsies, are associated with higher rates of migraine than idiopathic epilepsy. However, the increase in rate for those with partial-onset versus generalized onset seizures is small (relative risk, 1.3),[7] except for cases of epilepsy caused by head trauma where the relative risk is 1.8. The strong association between posttraumatic epilepsy and migraine is believed to occur because head injury is a risk for both conditions.[7]

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 lead to the development of epilepsy, or, alternatively, recurrent seizures could lead to the development of migraine. Epidemiological data indicate that this explanation is unlikely.[7,8] 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 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 writing in their book *Epilepsy and Related Disorders* recognized a condition they termed "migralepsy" in which "opthalmic migraine with perhaps nausea and vomiting [is] followed by symptoms characteristic of epilepsy." [9] 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.[10,11] Indeed, a review of the literature suggested that migralepsy is extremely rare.[12] In contrast, occipital seizures are often associated with postictal headache that is often indistinguishable from migraine.[10,13] Therefore, according to Panayiotopoulos,[11] 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 mechanisms may underlie migraine and epilepsy in the same patient is in familial hemiplegic migraine, discussed in detail below, in which migraine attacks and seizures can occur together.[14] In some instances in familial hemiplegic migraine, true migralepsy occurs in which migraine does trigger a seizure. Also, it should be noted that seizures may be caused by migrainous cerebral infarction or possibly also in basilar artery migraine although the latter has been disputed.[15]

While triggering of a seizure by migraine is unusual, headache is often associated with seizures. Preictal and ictal headaches occur rarely but postictal headache is common and may have migraine-like features.[7] Not only does migraine-like postictal headache occur following occipital seizures, it also occurs following generalized tonic–clonic seizures[16] and can also occur following temporal lobe seizures, however, it is less likely following frontal lobe seizures or simple partial seizures.[13] Case reports indicate that postictal headache can respond to sumatriptan.[17] Therefore, it has been proposed that seizures can in some instances trigger trigeminovascular pain mechanisms as occurs in migraine.

An 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 visa 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.[8] 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 be produced either 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.[5] 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.[18] 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 muscle, episodic channelopathies also affect the brain. Ryan and Ptáček[18] 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 common characteristics and a presumption that the underlying pathohysiology 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 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.[18] This concept implies that unaffected individuals (that is, 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 also for migraine. Seizures can be provoked in nonepileptic 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.[19] In addition to the immediate headache that occurs in all individuals, in migraine sufferers, glyceryl trinitrate can trigger a delayed headache of greater intensity and with a greater number of migraine-like features than in non-migrainurs.[20,21] Usually, this is without aura even in migraineurs that experience aura although migraine with visual aura can be triggered in some cases.[22] Histamine infusion can produce similar effects.[23] Secondary migraine headache can also be triggered in non-migraineurs by many factors, such as intense physical exercise, head injury, hypoglycemia, chronic renal failure, dialysis, and sickle cell disease.[24]

In addition to both 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 let-down 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.[25] The gabapentinoids gabapentin and pregabalin may also be effective in migraine therapy.[26,27] Other AEDs that have been reported to be useful in migraine prophylaxis are levetiracetam and zonisamide.[28–30] Interestingly, while the limited clinical trial data available does not indicate that lamotrigine reduces the frequency of migraine attacks overall, there is evidence that it may reduce the frequency, duration and intensity of migraine aura; in many patients who responded with a reduction in aura, there was a reduction in headache frequency.[31] 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.[32] AEDs reduce neuronal hyperexcitability by various mechanisms.[33] Consequently, these results are consistent with the concept that hyperexcitability is responsible for triggering 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 act primarily 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."[1] 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 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.[34] 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.[34,35] 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 ends his classic 1944 paper with the statement: "The depression and 'tonic-clonic' activity of experimental cortical epilepsy seem to be closely related phenomena."[35] 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.[36,37] Recording from small isolated slabs of cortex in *cerveau 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.[38] 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.[39] Although neuronal somata become electrically unresponsive during CSD, recent studies indicate that parts of the dendritic tree maintain electrical excitability.[40] The membrane conductances that participate in CSD are not fully defined.[41] Potassium currents, including transient A-type currents and 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 follows the DC shift.[42,43] 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, Makarov et al.[41] 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 conductance is a major determinant of the cellular depolarization in CSD.

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 center and propagates to peripheral zones within 10 to 15 min. Function returns to normal within another 10 to 15 min.[44] 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[45] 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 rate of spread of symptoms along the sensory homunculus occurs at a similar rate.

Numerous neuroimaging studies in humans have supported the concept that spreading depression-like phenomena in neocortex occur with migraine aura.[46–48] 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.[47] 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.[48]

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,[36,38] 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 spatial extent of current flows are insufficiently broadly distributed 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/sec). In contrast, the spread of epileptiform activity occurs over a wide range of rates that spans three orders of magnitude.[49] 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 (for example, with $GABA_A$ receptor blocking agents), neocortical slices exhibit discharges that propagate at 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 electroencephalographic recordings indicate that human cortical seizures can spread at low or high rates (<200 μm/s to >10,000 μm/s).[49,50] 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.[49] 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.[51] Therefore, in general, it appears that epileptiform activity associated with enhanced excitatory neurotransmission propagates at rates comparable to 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 where seizures are generated by excessive activation of ionotropic glutamate receptors and 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 Fifková in the 1970s that glutamate can trigger CSD.[52] 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-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP), have been shown to inhibit CSD.[53–56] Therefore, NMDA receptors are a critical trigger for CSD. In contrast, AMPA receptor antagonists are generally ineffective.[53] 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.[57] An exception is the low magnesium model associated with excessive activation of NMDA receptors, where NMDA receptor antagonists do abolish the epileptiform discharges.[58]

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 prodromal oscillations and raise the threshold to initiate CSD but do not prevent CSD propagation once initiated.[55] 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 inciting 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,[59,60] more recent evidence raises doubt.[61] A schematic illustration of the related but distinct pathways leading to an ictal event in migraine and epilepsy is presented in Figure 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 Figure 2. Ordinarily, seizure and migraine mechanisms are not considered as occurring together. However, the clinical evidence presented in the first part of this chapter suggest that there are many instances, such as migralepsy 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[62,63] 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.[64] In contrast, while tetrodotoxin may inhibit the triggering of CSD in some situations, it has generally not been found to inhibit CSD propagation.[65–67] 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 the case of 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.[68] 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 generalized or local cortical

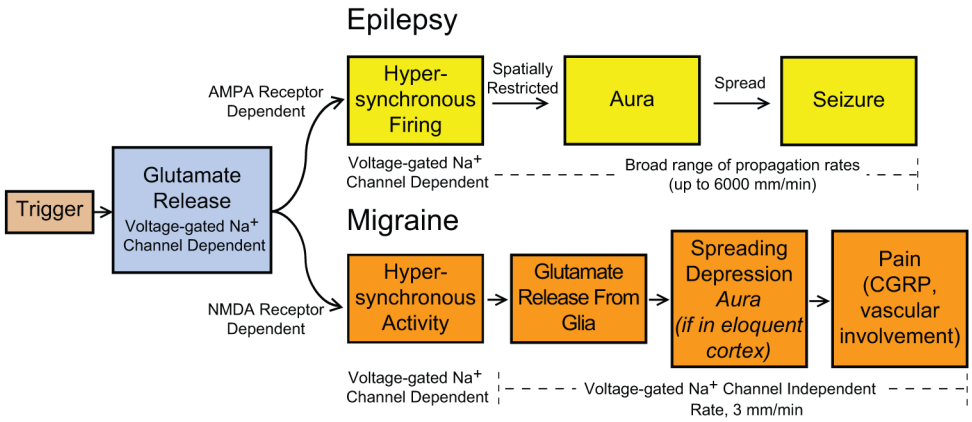

Figure 1. Schematic illustration of the putative chain of cellular events in the evolution of an epileptic seizure and migraine attack, highlighting the similarities and differences. In epilepsy, synaptic glutamate release acting through AMPA receptors is a trigger factor and synaptic activity is required (in most instances) for propagation. In migaine, 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.

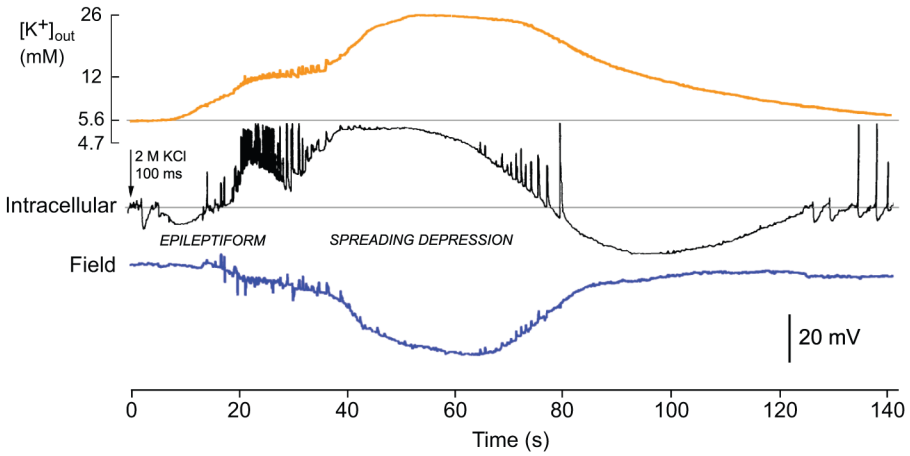

Figure 2. Seizure activity and spreading depression can occur together in the same brain substrate. The example shown is from a brain slice recording in hippocampal CA3 region of a young rabbit. A local micropressure application of 2 M KCl was made at time 0 (arrow). *Top trace* shows extracellular K^+ level as recorded by an ion sensitive microelectrode. *Middle trace* is intracellular recording from a CA3 neuron. *Bottom trace* shows extracellular field. There is an initial ictal discharge (depolarization and increased action potential generation) followed by a 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], with permission.

hyperresponsivity in susceptible individuals that predisposes to the triggering of attacks. There is a voluminous literature on the sensitivity to sensory stimuli in migraineurs.[69] The techniques that have been used include psychophysical studies; visual, auditory and somatosensory evoked potentials; magentoencephalography; 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 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.[70] Some studies have found such effects only in subjects that experience migraine with aura whereas other have found that the visual cortical hyperexcitability extends to subjects that experience migraine without aura.[71,72] 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] 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, heminanesthesia, 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 hemparesis. Attacks of non-hemiplegic 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 α_{1A}-subunit ($Ca_V2.1$) of neuronal P/Q-type calcium channels.[75] 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 $Ca_V2.1$ 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[75] notes that a consistent effect seen in studies of the single-channel properties of human $Ca_V2.1$ channels with FHM1 mutations is enhanced channel open 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^{2+} flux through the mutant $Ca_V2.1$ 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 with the R192Q mutation, in accordance with the more severe phenotype of the S218L mutation.[77,78] R192Q mice exhibit a reduced threshold and increased velocity of CSD[77]; 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 was 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^{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 fast spiking 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 *CACNA1A* is associated with idiopathic generalized epilepsy.[80] Moreover, mutations in homologs of the gene can cause absence-like seizures in rodents.[81,82] Interestingly, in mice with these mutations (*tottering* and *leaner*), there is actually a marked

resistance to CSD.[82] Among the FHM types, mutations in *CACNA1A* is least likely to be associated with epilepsy. However, seizures (including seizures occurring during headache) have been reported with some mutations including the S218L mutation[14,76,83] as well as I1710T,[84] where a 14-year-old girl had recurrent FHM episodes with status epilepticus.[85] Childhood absence epilepsy (with generalized tonic-clonic seizures) has been associated with a non-FHM-causing point mutation in *CACNA1A* (C5733T).[86] Therefore, diverse mutations in *CACNA1A* can cause migraine without epilepsy, epilepsy without migraine, or both. The underlying pathophysiological mechanisms of absence epilepsy are distinct from those in partial epilepsy. The evidence presented here for a commonality between epilepsy and migraine does not extend to absence epilepsy. Indeed, absence epilepsy mutations in *CACNA1A* are not associated with FHM and absence epilepsy mutations in *Cacna1a*, the mouse homolog of *CACNA1A*, not only do not promote CSD, but actually markedly inhibit it.[82]

Sodium-Potassium Transporter

The second FHM gene to be described was *ATP1A2*, which encodes the α2 isoform of the main catalytic subunit of Na^+-K^+-ATPase (Na^+-K^+ transporter).[87] 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,[88] benign familial infantile convulsions (BFIC),[89] and febrile seizures.[90] Epilepsy and migraine can co-occur in the same mutation carriers;[90] in some cases, seizures occur during migraine attacks, representing true migralepsy.[91] Na^+-K^+-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^+-K^+-ATPase activity in astrocytes accounts for FHM2. Na^+-K^+-ATPase plays a fundamental role in the maintenance of the resting potential of all cells, including astrocytes. The pump, which transports three Na^+ out of the cell in exchange for the countertransport of two K^+ into the cell, allows extracellular K^+ levels to be maintained at a low level. In addition, the Na^+ gradient produced by Na^+-K^+-ATPase is required for clearance of extracellular glutamate by astrocytes.[92] Glutamate uptake in astrocytes is mediated by glutamate transporters, predominantly GLAST (EAAT1) and GLT-1 (EAAT2). These transporters are expressed along with Na^+-K^+-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^+ (and also one H^+) down the electochemical gradient in exchange for one K^+. Recent evidence indicates that the transporters and Na^+-K^+-ATPase are physically associated in the same protein complex.[93] Impairment in the pump function of Na^+-K^+-ATPase is expected to reduce the ability of astrocytes to remove K^+ that accumulates extracellularly during high frequency neuronal firing. This in itself would promote hyperexcitability (and seizure activity) and CSD. In addition, elevated external K^+ causes reversal of glutamate transporters, so that intracellular glutamate is released into the extracellular space, which would further enhance excitability and predispose to CSD. FHM mutations in *ATP1A2*, of which more than 36 have now been described, lead to complete inactivation of the protein in some cases[94] whereas in other cases there is altered kinetics, altered cation affinity, reduced membrane trafficking or reduced protein stability.[92,95,96] FHM2 is an autosomal dominant condition and it is likely that FHM2 mutations lead to haploinsufficiency with reduced but not absent Na^+-K^+-ATPase. Indeed, *ATP1A2* knockout mice die at birth but heterozygous animals grow normally.[97] Overall, impairment of astrocytic K^+ and glutamate handing are likely to account for the CSD and seizures in FHM2. To the extent that α2 Na^+-K^+-ATPase is expressed in neurons, the neuronal resting potential may be depolarized, which would also enhance excitability. It is noteworthy that both seizures[98,99] and CSD[66,100] can be produced by pharmacological inhibition of Na^+-K^+-ATPase with ouabain, a nonselective inhibitor of astrocytic and also neuronal Na^+-K^+-ATPase.

Sodium Channel

The third FHM gene is *SCN1A*, which encodes the pore-forming α1-subunit of neuronal type I voltage-gated sodium channel $Na_V1.1$.101–103 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 Portugese family, the L263V mutation was found to be associated not only with FHM but also with generalized tonic-clonic and complex partial seizures.[103] Family members with the mutation invariably had FHM and some also exhibited seizures that occurred separately from the migraine attacks. Studies with recombinant human $Na_V1.1$ channels bearing the mutations have demonstrated that the pure FHM mutations Q1489K and L1649Q caused biophysical changes in the Na^+ current that were interpreted as predominantly of the loss-of-function type.[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.[104] Whether these results, which were obtained with recombinant channels expressed in non-neuronal 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 $Na_V1.1$ have impaired function of GABAergic inhibitory neurons, which leads to enhanced circuit excitability. In cases where there is gain of function in $Na_V1.1$, 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.[105,106] 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 or 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.

FHM is a 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. CSD leads to the release of mediators that elicit headache pain. 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 FHM mutations support 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.

ACKNOWLEDGMENT

I thank Jeffrey L. Noebels for thoughtful comments.

REFERENCES

1. Gowers WR. Clinical lectures on the borderland of epilepsy. III.—Migraine. Brit Med J. 1906;2(2397):1617–1622. PubMed PMID: 20762970.
2. Anderman F. Clinical features of migraine-epilepsy syndromes. In: Anderman F, Lugaresi E, editors. Migraine and epilepsy. Boston: Butterworths; 1987. p. 30.
3. Toldo I, Perissinotto E, Menegazzo F, Boniver C, Sartori S, Salviati L, Clementi M, Montagna P, Battistella PA. Comorbidity between headache and epilepsy in a pediatric headache center. J Headache Pain. 2010;11:235–240. PubMed PMID: 20112041.
4. Ottman R, Lipton RB. Comorbidity of migraine and epilepsy. Neurology. 1994;44:2105–2110. PubMed PMID: 7969967.
5. Haut SR, Bigal ME, Lipton RB. Chronic disorders with episodic manifestations: focus on epilepsy and migraine. Lancet Neurol. 2006;5:148–157. PubMed PMID: 16426991.
6. Ludvigsson P, Hesdorffer D, Olafsson E, Kjartansson O, Hauser WA. Migraine with aura is a risk factor for unprovoked seizures in children. Ann Neurol. 2006;59:210–213. PubMed PMID: 16374824.
7. Silberstein SD, Lipton RB, Haut S. Migraine. In: Engel J Jr, Pedley TA, editors. Epilepsy: a comprehensive Textbook. 2nd edition. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008. pp. 2733–2743.
8. Ottman R, Lipton RB. Is the comorbidity of epilepsy and migraine due to a shared genetic susceptibility. Neurology. 1996;47:918–924. PubMed PMID: 8857719.
9. Lennox WG, Lennox MA. Epilepsy and related disorders. Boston: Little, Brown & Company, Boston; 1960.
10. Panayiotopoulos CP. Visual phenomena and headache in occipital epilepsy: a review, a systematic study and differentiation from migraine. Epileptic Disord. 1999;1:205–216. PubMed PMID: 10937155.
11. Panayiotopoulos CP. "Migralepsy" and the significance of differentiating occipital seizures from migraine. Epilepsia. 2006;47:806–808. PubMed PMID: 16650152.
12. Sances G, Guaschino E, Perucca P, Allena M, Ghiotto N, Manni R. Migralepsy: a call for a revision of the definition. Epilepsia. 2009;50:2487–2496. PubMed PMID: 19694799.
13. Ito M, Adachi N, Nakamura F, Koyama T, Okamura T, Kato M, Kanemoto K, Nakano T, Matsuura M, Hara S. Characteristics of postictal headache in patients with partial epilepsy. Cephalalgia. 2004;24:23–28. PubMed PMID: 14687009.
14. Zangaladze A, Asadi-Pooya AA, Ashkenazi A, Sperling MR. Sporadic hemiplegic migraine and epilepsy associated with CACNA1A gene mutation. Epilepsy Behav. 2010;17:293–295. PubMed PMID: 20071244.
15. Panayiotopoulos CP. The Epilepsies. Seizures, Syndromes and Management. Oxfordshire (UK): Bladon Medical Publishing; 2005.
16. Schon F, Blau JN. Post-epileptic headache and migraine. J Neurol Neurosurg Psychiatry. 1987;50:1148–1152. PubMed PMID: 3117978.
17. Jacob J, Goadsby PJ, Duncan JS. Use of sumatriptan in post-ictal migraine headache. Neurology. 1996;47:1104.
18. Ryan DP, Ptáček LJ. Episodic neurological channelopathies. Neuron. 2010;68:282–292. PubMed PMID: 20955935.
19. Stevenson T, editor. Taylor's Principles and Practices of Medical Jurisprudence. 3rd edition. Philadelphia: Henry C Lea's Son & Co. 1883.
20. Iversen HK. Human migraine models. Cephalalgia. 2001;21:781–785. PubMed PMID: 11595013.
21. Olesen J. Nitric oxide-related drug targets in headache. Neurotherapeutics. 2010;7:183–190. PubMed PMID: 20430317.

22. Afridi S, Kaube H, Goadsby PJ. Occipital activation in glyceryl trinitrate induced migraine with visual aura. J Neurol Neurosurg Psychiatry. 2005;76:1158–1160. PubMed PMID: 16024898.
23. Lassen LH, Thomsen LL, Olesen J. Histamine induces migraine via the H1-receptor. Support for the NO hypothesis of migraine. Neuroreport. 1995;6:1475–1479. PubMed PMID: 7579128.
24. Abend NS, Younkin D, Lewis DW. Secondary headaches in children and adolescents. Semin Pediatr Neurol. 2010;17:123–133. PubMed PMID: 20541105.
25. Rogawski MA. Antiepileptic drugs and migraine. In: Olesen J, Ramadan N, editors. Innovative Drug Development for Headache Disorders (Frontiers in Headache Research Volume 16). Oxford University Press; 2008. pp. 153–178.
26. D'Amico D. Pharmacological prophylaxis of chronic migraine: a review of double-blind placebo-controlled trials. Neurol Sci. 2010;31(Suppl 1):S23–28. PubMed PMID: 20464578.
27. Calandre EP, Garcia-Leiva JM, Rico-Villademoros F, Vilchez JS, Rodriguez-Lopez CM. Pregabalin in the treatment of chronic migraine: an open-label study. Clin Neuropharmacol. 2010;33:35–39. PubMed PMID: 19935409.
28. Drake ME, Greathouse NI, Armentbright AD, Renner JB. Levetiracetam for preventative treatment of migraine. Cephalalgia. 2001;373:Abst P2-I13.
29. Bermejo PE, Dorado R. Zonisamide for migraine prophylaxis in patients refractory to topiramate. Clin Neuropharmacol. 2009;32:103–106. PubMed PMID: 18978487.
30. Villani V, Ciuffoli A, Prosperini L, Sette G. Zonisamide for migraine prophylaxis in topiramate-intolerant patients: an observational study. Headache. 2011;51:287–291. PubMed PMID: 21284610.
31. Lampl C, Katsarava Z, Diener HC, Limmroth V. Lamotrigine reduces migraine aura and migraine attacks in patients with migraine with aura. J Neurol Neurosurg Psychiatry. 2005;76:1730–1732. PubMed PMID: 16291905.
32. Hauge AW, Asghar MS, Schytz HW, Christensen K, Olesen J. Effects of tonabersat on migraine with aura: a randomised, double-blind, placebo-controlled crossover study. Lancet Neurol. 2009;8:718–723. PubMed PMID: 19570717.
33. Macdonald RL, Rogwski MA. Cellular effects of antiepileptic drugs. In: Engel J Jr, Pedley TA, editors. Epilepsy: a comprehensive textbook. Wolters: Kluwer/Lippincott Williams & Wilkins; 2008; pp. 1433–1445.
34. Somjen GG. Aristides Leão's discovery of cortical spreading depression. J Neurophysiol. 2005;94:2–4. PubMed PMID: 15985690.
35. Leão AAP. Spreading depression of activity in the cerebral cortex. J Neurophysiol. 1944;7:359–390.
36. Grafstein B. Mechanism of spreading cortical depression. J Neurophysiol. 1956;19:154–171. PubMed PMID: 13295838.
37. Strong AJ. Dr. Bernice Grafstein's paper on the mechanism of spreading depression. J Neurophysiol. 2005;94:5–7. PubMed PMID: 15985691.
38. Herreras O, Largo C, Ibarz JM, Somjen GG, Martín del Río R. Role of neuronal synchronizing mechanisms in the propagation of spreading depression in the in vivo hippocampus. J Neurosci. 1994;14(11 Pt 2):7087–7098. PubMed PMID: 7965100.
39. Snow RW, Taylor CP, Dudek FE. Electrophysiological and optical changes in slices of rat hippocampus during spreading depression. J Neurophysiol. 1983;50:561–572. PubMed PMID: 6311993.
40. Canals S, Makarova I, López-Aguado L, Largo C, Ibarz JM, Herreras O. Longitudinal depolarization gradients along the somatodendritic axis of CA1 pyramidal cells: a novel feature of spreading depression. J Neurophysiol. 2005;94:943–951. PubMed PMID: 15800073.
41. Makarova J, Ibarz JM, Canals S, Herreras O. A steady-state model of spreading depression predicts the importance of an unknown conductance in specific dendritic domains. Biophys J. 2007;92:4216–4232. PubMed PMID: 17400694.
42. Brinley FJ Jr, Kandel ER, Marshall WH. Potassium outflux from rabbit cortex during spreading depression. J Neurophysiol. 1960;23:246–256. PubMed PMID: 13804482.

43. Chang JC, Shook LL, Biag J, Nguyen EN, Toga AW, Charles AC, Brennan KC. Biphasic direct current shift, haemoglobin desaturation and neurovascular uncoupling in cortical spreading depression. Brain. 2010;133(Pt 4):996–1012. PubMed PMID: 20348134.
44. Lauritzen M. Cortical spreading depression in migraine. Cephalalgia. 2001;21:757–760. PubMed PMID: 11595007.
45. Milner PM. Note on a possible correspondence between the scotomas of migraine and spreading depression of Leao. Electroencephalogr Clin Neurophysiol. 1959;10:705.
46. Olesen J, Friberg L, Skyhøj Olsen T, Iversen HK, Lassen NA, Andersen AR, Karle A. Timing and topography of cerebral blood flow aura, and headache during migraine attacks. Ann Neurol. 1990;28:791–798. PubMed PMID: 2285266.
47. Hadjikhani N, Sanchez Del, Rio M, Wu O, Schwartz D, Bakker D, Fischl B, Kwong KK, Cutrer FM, Rosen BR, Tootell RB, Sorensen AG, Moskowitz MA. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. Proc Natl Acad Sci USA. 2001;98:4687–4692. PubMed PMID: 11287655.
48. Schwedt TJ, Dodick DW. Advanced neuroimaging of migraine. Lancet Neurol. 2009;8:560–568. PubMed PMID: 19446275.
49. Trevelyan AJ, Sussillo D, Yuste R. Feedforward inhibition contributes to the control of epileptiform propagation speed. J Neurosci. 2007;27:3383–3387. PubMed PMID: 17392454.
50. Jasper HH. Mechanisms of propagation: extracellular studies. In: Jasper HH, Ward AA, Pope A, editors. Basic mechanisms of the epilepsies. Boston: Little Brown; 1969. pp. 421–440.
51. Yamaguchi S, Donevan SD, Rogawski MA. Anticonvulsant activity of AMPA/kainate antagonists: comparison of GYKI 52466 and NBOX in maximal electroshock and chemoconvulsant seizure models. Epilepsy Res. 1993;15:179–184. PubMed PMID: 7693450.
52. Van Harreveld A, Fifková E. Mechanisms involved in spreading depression. J Neurobiol. 1973;4:375–387. PubMed PMID: 4724814.
53. Psarropoulou C, Avoli M. CPP, an NMDA-receptor antagonist, blocks 4-aminopyridine-induced spreading depression episodes but not epileptiform activity in immature rat hippocampal slices. Neurosci Lett. 1992;135:139–143. PubMed PMID: 1347414.
54. Peters O, Schipke CG, Hashimoto Y, Kettenmann H. Different mechanisms promote astrocyte Ca^{2+} waves and spreading depression in the mouse neocortex. J Neurosci. 2003;23:9888–9896. PubMed PMID: 14586018.
55. Larrosa B, Pastor J, López-Aguado L, Herreras O. A role for glutamate and glia in the fast network oscillations preceding spreading depression. Neuroscience. 2006;141:1057–1068. PubMed PMID: 16713108.
56. Peeters M, Gunthorpe MJ, Strijbos PJ, Goldsmith P, Upton N, James MF. Effects of pan- and subtype-selective N-methyl-D-aspartate receptor antagonists on cortical spreading depression in the rat: therapeutic potential for migraine. J Pharmacol Exp Ther. 2007;321:564–572. PubMed PMID: 17267580.
57. Rogawski MA. Revisiting AMPA receptors as an antiepileptic drug target. Epilepsy Curr. 2011;11:56–63. PubMed PMID: 21686307.
58. Köhr G, Heinemann U. Effects of NMDA antagonists on picrotoxin-, low Mg^{2+}- and low Ca^{2+}-induced epileptogenesis and on evoked changes in extracellular Na^{+} and Ca^{2+} concentrations in rat hippocampal slices. Epilepsy Res. 1989;4:187–200. PubMed PMID: 2575519.
59. Tian GF, Azmi H, Takano T, Xu Q, Peng W, Lin J, Oberheim N, Lou N, Wang X, Zielke HR, Kang J, Nedergaard M. An astrocytic basis of epilepsy. Nat Med. 2005;11:973–981. PubMed PMID: 16116433.
60. Rogawski MA. Astrocytes get in the act in epilepsy. Nat Med. 2005;11:919–920. PubMed PMID: 16145568.
61. Fellin T, Gomez-Gonzalo M, Gobbo S, Carmignoto G, Haydon PG. Astrocytic glutamate is not necessary for the generation of epileptiform neuronal activity in hippocampal slices. J Neurosci. 2006;26(36):9312–9322. PubMed PMID: 16957087.
62. Schweitzer JS, Patrylo PR, Dudek FE. Prolonged field bursts in the dentate gyrus: dependence on low calcium, high potassium, and nonsynaptic mechanisms. J Neurophysiol. 1992;68:2016–2025. PubMed PMID: 1337101.

63. Dudek FE, Yasumura T, Rash JE. 'Non-synaptic' mechanisms in seizures and epileptogenesis. Cell Biol Int. 1998;22(11–12):793–805. PubMed PMID: 10873292.
64. Khazipov R, Holmes GL. Synchronization of kainate-induced epileptic activity via GABAergic inhibition in the superfused rat hippocampus in vivo. J Neurosci. 2003;23:5337–5341. PubMed PMID: 12832559.
65. Sheardown MJ. The triggering of spreading depression in the chicken retina: a pharmacological study. Brain Res. 1993;607:189–194. PubMed PMID: 8097663.
66. Wu J, Fisher RS. Hyperthermic spreading depressions in the immature rat hippocampal slice. J Neurophysiol. 2000;84:1355–1360. PubMed PMID: 10980008.
67. Akerman S, Holland PR, Goadsby PJ. Mechanically-induced cortical spreading depression associated regional cerebral blood flow changes are blocked by Na^+ ion channel blockade. Brain Res. 2008;1229:27–36. PubMed PMID: 18656463.
68. Gorelova NA, Koroleva VI, Amemori T, Pavlík V, Burěs J. Ketamine blockade of cortical spreading depression in rats. Electroencephalogr Clin Neurophysiol. 1987;66:440–447. PubMed PMID: 2435524.
69. Coppola G, Pierelli F, Schoenen J. Is the cerebral cortex hyperexcitable or hyperresponsive in migraine. Cephalalgia. 2007;27:1427–1439. PubMed PMID: 18034686.
70. Aurora SK, Ahmad BK, Welch KM, Bhardhwaj P, Ramadan NM. Transcranial magnetic stimulation confirms hyperexcitability of occipital cortex in migraine. Neurology. 1998;50:1111–1114. PubMed PMID: 9566403.
71. Siniatchkin M, Reich AL, Shepherd AJ, van Baalen A, Siebner HR, Stephani U. Peri-ictal changes of cortical excitability in children suffering from migraine without aura. Pain. 2009;147:132–140. PubMed PMID: 19796876.
72. Chronicle EP, Pearson AJ, Mulleners WM. Objective assessment of cortical excitability in migraine with and without aura. Cephalalgia. 2006;26:801–808. PubMed PMID: 16776694.
73. Theodore WH. Transcranial Magnetic Stimulation in Epilepsy. Epilepsy Curr. 2003;3:191–197. PubMed PMID: 15346149.
74. Schürks M. Genetics of migraine in the age of genome-wide association studies. J Headache Pain. 2012;13(1):1–9. Epub 2011; doi 10.1007/s10194-011-0399-0 . PubMed PMID: 22072275.
75. Pietrobon D. $Ca_V2.1$ channelopathies. Pflugers Arch. 2010;460:375–393. PubMed PMID: 20204399.
76. Debiais S, Hommet C, Bonnaud I, Barthez MA, Rimbaux S, Riant F, Autret A. The FHM1 mutation S218L: a severe clinical phenotype? A case report and review of the literature. Cephalalgia. 2009;29:1337–1339. PubMed PMID: 19438926.
77. van den Maagdenberg AMJM, Pietrobon D, Pizzorusso T, Kaja S, Broos LAM, Cesetti T, van de Ven RCG, Tottene A, van der Kaa J, Plomp JJ, Frants RR, Ferrari MD. A *Cacna1a* knockin migraine mouse model with increased susceptibility to cortical spreading depression. Neuron. 2004;41:701–710. PubMed PMID: 15003170.
78. van den Maagdenberg AMJM, Pizzorusso T, Kaja S, Terpolilli N, Shapovalova M, Hoebeek FE, Barrett CF, Gherardini L, van de Ven RC, Todorov B, Broos LA, Tottene A, Gao Z, Fodor M, De Zeeuw CI, Frants RR, Plesnila N, Plomp JJ, Pietrobon D, Ferrari MD. High cortical spreading depression susceptibility and migraine-associated symptoms in $Ca_v2.1$ S218L mice. Ann Neurol. 2010;67:85–98. PubMed PMID: 20186955.
79. Tottene A, Conti R, Fabbro A, Vecchia D, Shapovalova M, Santello M, van den Maagdenberg AM, Ferrari MD, Pietrobon D. Enhanced excitatory transmission at cortical synapses as the basis for facilitated spreading depression in $Ca_v2.1$ knockin migraine mice. Neuron. 2009;61:762–773. PubMed PMID: 19285472.
80. Chioza B, Wilkie H, Nashef L, Blower J, McCormick D, Sham P, Asherson P, Makoff AJ. Association between the α_{1a} calcium channel gene *CACNA1A* and idiopathic generalized epilepsy. Neurology. 2001;56:1245–1246. PubMed PMID: 11342703.
81. Tokuda S, Kuramoto T, Tanaka K, Kaneko S, Takeuchi IK, Sasa M, Serikawa T. The ataxic groggy rat has a missense mutation in the P/Q-type voltage-gated Ca^{2+} channel α_{1A} subunit gene and exhibits absence seizures. Brain Res. 2007;1133:168–177. PubMed PMID: 17196942.

82. Ayata C, Shimizu-Sasamata M, Lo EH, Noebels JL, Moskowitz MA. Impaired neurotransmitter release and elevated threshold for cortical spreading depression in mice with mutations in the α1A subunit of P/Q type calcium channels. Neuroscience. 2000;95:639–645. PubMed PMID: 10670432.
83. Chan YC, Burgunder JM, Wilder-Smith E, Chew SE, Lam-Mok-Sing KM, Sharma V, Ong BK. Electroencephalographic changes and seizures in familial hemiplegic migraine patients with the *CACNA1A* gene S218L mutation. J Clin Neurosci. 2008;15:891–894. PubMed PMID: 18313928.
84. Kors EE, Melberg A, Vanmolkot KR, Kumlien E, Haan J, Raininko R, Flink R, Ginjaar HB, Frants RR, Ferrari MD, van den Maagdenberg AM. Childhood epilepsy, familial hemiplegic migraine, cerebellar ataxia, and a new *CACNA1A* mutation. Neurology. 2004;63:1136–1137. PubMed PMID: 15452324.
85. Beauvais K, Cavé-Riant F, De Barace C, Tardieu M, Tournier-Lasserve E, Furby A. New CACNA1A gene mutation in a case of familial hemiplegic migraine with status epilepticus. Eur Neurol. 2004;52:58–61. PubMed PMID: 15240985.
86. Jouvenceau A, Eunson LH, Spauschus A, Ramesh V, Zuberi SM, Kullmann DM, Hanna MG. Human epilepsy associated with dysfunction of the brain P/Q-type calcium channel. Lancet. 2001;358(9284):801–807. PubMed PMID: 11564488.
87. De Fusco M, Marconi R, Silvestri L, Atorino L, Rampoldi L, Morgante L, Ballabio A, Aridon P, Casari G. Haploinsufficiency of *ATP1A2* encoding the Na^+/K^+ pump α2 subunit associated with familial hemiplegic migraine type 2. Nat Genet. 2003;33:192–196. PubMed PMID: 12539047.
88. Deprez L, Weckhuysen S, Peeters K, Deconinck T, Claeys KG, Claes LR, Suls A, Van Dyck T, Palmini A, Matthijs G, Van Paesschen W, De Jonghe P. Epilepsy as part of the phenotype associated with *ATP1A2* mutations. Epilepsia. 2008;49:500–508. PubMed PMID: 18028407.
89. Vanmolkot KR, Kors EE, Hottenga JJ, Terwindt GM, Haan J, Hoefnagels WA, Black DF, Sandkuijl LA, Frants RR, Ferrari MD, van den Maagdenberg AM. Novel mutations in the Na^+, K^+-ATPase pump gene *ATP1A2* associated with familial hemiplegic migraine and benign familial infantile convulsions. Ann Neurol. 2003;54:360–366. PubMed PMID: 12953268.
90. de Vries B, Stam AH, Kirkpatrick M, Vanmolkot KR, Koenderink JB, van den Heuvel JJ, Stunnenberg B, Goudie D, Shetty J, Jain V, van Vark J, Terwindt GM, Frants RR, Haan J, van den Maagdenberg AM, Ferrari MD. Familial hemiplegic migraine is associated with febrile seizures in an FHM2 family with a novel de novo *ATP1A2* mutation. Epilepsia. 2009;50:2503–2504. PubMed PMID: 19874388.
91. Lebas A, Guégan-Massardier E, Guyant-Maréchal L. Epilepsy and familial hemiplegic migraine. Genetic and clinical aspects. In: Parain D, Guerrini R, Hesdorffer D, Ryvlin P, editors. Epilepsy and Migraine, John Libby Eurotext. 2009.
92. Benarroch EE. Na^+, K^+-ATPase: functions in the nervous system and involvement in neurologic disease. Neurology. 2011;76:287–293. PubMed PMID: 21242497.
93. Rose EM, Koo JC, Antflick JE, Ahmed SM, Angers S, Hampson DR. Glutamate transporter coupling to Na,K-ATPase. J Neurosci. 2009;29:8143–8155. PubMed PMID: 19553454.
94. Koenderink JB, Zifarelli G, Qiu LY, Schwarz W, De Pont JJ, Bamberg E, Friedrich T. Na,K-ATPase mutations in familial hemiplegic migraine lead to functional inactivation. Biochim Biophys Acta. 2005;1669:61–68. PubMed PMID: 15843000.
95. Morth JP, Poulsen H, Toustrup-Jensen MS, Schack VR, Egebjerg J, Andersen JP, Vilsen B, Nissen P. The structure of the Na^+, K^+-ATPase and mapping of isoform differences and disease-related mutations. Philos Trans R Soc Lond B Biol Sci. 2009;364:217–227. PubMed PMID: 18957371.
96. Tavraz NN, Dürr KL, Koenderink JB, Freilinger T, Bamberg E, Dichgans M, Friedrich T. Impaired plasma membrane targeting or protein stability by certain ATP1A2 mutations identified in sporadic or familial hemiplegic migraine. Channels (Austin). 2009;3:82–87. PubMed PMID: 19372756.
97. Moseley AE, Lieske SP, Wetzel RK, James PF, He S, Shelly DA, Paul RJ, Boivin GP, Witte DP, Ramirez JM, Sweadner KJ, Lingrel JB. The Na,K-ATPase α2 isoform is expressed in neurons, and its absence disrupts neuronal activity in newborn mice. J Biol Chem. 2003;278:5317–5324. PubMed PMID: 12458206.
98. Pedley TA, Zuckermann EC, Glaser GH. Epileptogenic effects of localized ventricular perfusion of ouabain on dorsal hippocampus. Exp Neurol. 1969;25:207–219. PubMed PMID: 5345010.

99. Stone WE, Javid MJ. Interactions of phenytoin with ouabain and other chemical convulsants. Arch Int Pharmacodyn Ther. 1982;260:28–35. PubMed PMID: 7165420.
100. Haglund MM, Schwartzkroin PA. Role of Na-K pump potassium regulation and IPSPs in seizures and spreading depression in immature rabbit hippocampal slices. J Neurophysiol. 1990;63:225–239. PubMed PMID: 2313342.
101. Dichgans M, Freilinger T, Eckstein G, Babini E, Lorenz-Depiereux B, Biskup S, Ferrari MD, Herzog J, van den Maagdenberg AM, Pusch M, Strom TM. Mutation in the neuronal voltage-gated sodium channel *SCN1A* in familial hemiplegic migraine. Lancet. 2005;366(9483):371–377. PubMed PMID: 16054936.
102. Vanmolkot KR, Babini E, de Vries B, Stam AH, Freilinger T, Terwindt GM, Norris L, Haan J, Frants RR, Ramadan NM, Ferrari MD, Pusch M, van den Maagdenberg AM, Dichgans M. The novel p.L1649Q mutation in the *SCN1A* epilepsy gene is associated with familial hemiplegic migraine: genetic and functional studies. Mutation in brief #957. Hum Mutat. 2007;28:522.
103. Castro M-J, Stam AH, Lemos C, de Vries B, Vanmolkot KR, Barros J, Terwindt GM, Frants RR, Sequeiros J, Ferrari MD, Pereira-Monteiro JM, van den Maagdenberg AM. First mutation in the voltage-gated Nav1.1 subunit gene *SCN1A* with co-occurring familial hemiplegic migraine and epilepsy. Cephalalgia. 2009;29:308–313. PubMed PMID: 19220312.
104. Kahlig KM, Lepist I, Leung K, Rajamani S, George AL. Ranolazine selectively blocks persistent current evoked by epilepsy-associated $Na_V1.1$ mutations. Br J Pharmacol. 2010;161:1414–1426. PubMed PMID: 20735403.
105. Escayg A, Goldin AL. Sodium channel *SCN1A* and epilepsy: mutations and mechanisms. Epilepsia. 2010;51:1650–1658. PubMed PMID: 20831750.
106. Catterall WA, Kalume F, Oakley JC. $Na_V1.1$ channels and epilepsy. J Physiol. 2010;588(Pt 11):1849–1859. PubMed PMID: 20194124.

License