REVIEW ARTICLE

MECHANISMS OF DISEASE

Epilepsy

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Epilepsy is one of the most common neurologic problems worldwide. Approximately 2 million persons in the United States have epilepsy, and 3 percent of persons in the general population will have epilepsy at some point in their lives.[1] In recent years, important advances have been made in the diagnosis and treatment of seizure disorders.[2] However, our understanding of the cellular and molecular mechanisms by which epilepsy develops, or epileptogenesis, is still incomplete.

In this overview, we highlight some of the prevailing ideas about epileptogenesis by presenting examples of epilepsy syndromes and theories of their mechanisms of origin. Several recent reviews offer more specialized and comprehensive discussions of this topic.[3-5]

CLASSIFICATION OF EPILEPSY

The term "epilepsy" encompasses a number of different syndromes whose cardinal feature is a predisposition to recurrent unprovoked seizures. Although specific seizures can be classified according to their clinical features (e.g., complex partial seizures and generalized tonic–clonic seizures),[6] epilepsy syndromes can also be classified according to the type of seizure, the presence or absence of neurologic or developmental abnormalities, and electroencephalographic (EEG) findings.[7] For example, the syndrome of juvenile myoclonic epilepsy is characterized by the onset of myoclonic seizures, generalized tonic–clonic seizures, and less frequently absence seizures in adolescents who have normal intellectual function, with EEG findings of rapid, generalized spike-wave and polyspike-wave discharges.[8]

Epilepsy syndromes fall into two broad categories: generalized and partial (or localization-related) syndromes.[7,8] In generalized epilepsies, the predominant type of seizures begins simultaneously in both cerebral hemispheres. Many forms of generalized epilepsy have a strong genetic component; in most, neurologic function is normal. In partial epilepsies, by contrast, seizures originate in one or more localized foci, although they can spread to involve the entire brain. Most partial epilepsies are believed to be the result of one or more central nervous system insults, but in many cases the nature of the insult is never identified.

MECHANISMS OF GENERALIZED EPILEPSIES

ABSENCE EPILEPSY

Childhood absence epilepsy is a generalized epilepsy syndrome that begins between the ages of four and eight years with absence seizures and, more rarely, generalized tonic–clonic seizures.[9] During absence seizures, patients stare and cease normal activity for a few seconds, then return immediately to normal and have no memory of the event. Since these seizures can occur tens or hundreds of times a day, an incorrect diagnosis of attention-deficit disorder or daydreaming is frequently made. There is a classic EEG pattern of three-per-second, generalized spike-wave discharges in childhood absence epilepsy.

For many years, the anatomical origin of absence seizures and the accompanying EEG pattern were debated. The results of some experiments supported the hypothesis that absence seizures originated in the thalamus. For example, electrical stimulation of the thalamus in cats produced bilaterally synchronous EEG discharges that resembled the classic absence pattern.[10] Also, recordings from electrodes implanted in the thalamus of a child with absence epilepsy demonstrated three-per-second EEG discharges during typical seizures.[11] Other work, however, suggested that the cerebral cortex itself was the primary origin of these seizures. For example, similar EEG discharges could be produced by applying proconvulsant agents to the cortical surface bilaterally.[12]

The mechanism that generates absence seizures is now believed to involve an alteration in the circuitry between the thalamus and the cerebral cortex (Fig. 1).[13-15] Much has been learned from in vivo and in vitro electrophysiological recordings in animal models of absence epilepsy, both those that were experimentally induced and those that were genetically determined.[16-18] These and other studies have shown that thalamocortical circuits govern the rhythm of cortical excitation by the thalamus and underlie normal physiologic patterns such as those that occur during sleep.[19] Three neuronal populations are involved in this circuitry: thalamic relay neurons, thalamic reticular neurons, and cortical pyramidal neurons. The thalamic relay neurons can activate the cortical pyramidal neurons either in a tonic mode, which occurs during wakefulness and rapid-eye-movement (REM) sleep, or in a burst mode, which occurs during non-REM sleep. The burst mode is made possible by T-type calcium channels, which allow for low-threshold depolarizations on which bursts of action potentials (mediated by voltage-gated sodium channels) are superimposed.[20] The mode of thalamocortical activation — tonic or burst — is controlled largely by input from the thalamic reticular neurons, which hyperpolarize the relay neurons, allowing them to fire in bursts.[21] The reticular neurons can themselves be inhibited through recurrent collaterals from neighboring reticular neurons.[22] Both cortical pyramidal neurons and thalamic relay neurons project to the reticular neurons to complete the circuitry. In addition, ascending noradrenergic, serotonergic, and dopaminergic inputs to the thalamus modulate this circuit and affect the likelihood of a burst mode.[23]

In normal non-REM sleep, thalamic relay neurons in the burst mode activate the cortex in a rhythmic, bilaterally synchronous way, creating visible EEG patterns, such as sleep spindles.[19] This "sleep state" of the thalamocortical circuit is in contrast to the normal "awake state," in which the thalamic relay neurons are firing in the tonic mode and thalamocortical projections are transferring sensory information to the cortex in a nonrhythmic manner. In absence epilepsy, the abnormal circuit causes rhythmic activation of the cortex (typical of normal non-REM sleep) during wakefulness, which results in the characteristic EEG discharges and clinical manifestations of an absence seizure.[15] The precise abnormality of the circuit has yet to be determined, but there are multiple possibilities. Some data suggest that the T-type calcium channels may be the primary culprits.[24,25] Other work has emphasized the importance of altered γ-aminobutyric acid (GABA) receptor function.[26] A combination of factors may be involved, including changes in modulatory input from the brain stem.[23] The overriding concept, however, is that dysfunction of a neuronal circuit that produces a physiologic state of rhythmic cortical activation (sleep) can lead to abnormal paroxysmal episodes of rhythmic cortical activation (absence seizures).

This concept helps explain the unique pharmacologic treatment of absence epilepsy. Ethosuximide, a drug that suppresses absence seizures but not other types of seizures, appears to work by causing voltage-dependent blockade of T-type calcium currents.[27] This mechanism, as might be expected, is believed to inhibit the burst mode of thalamic-relay-neuron firing. Valproic acid, an antiepileptic drug used for absence seizures and other types of seizures, also acts on the T-type calcium channels, as well as other substrates.[28] Benzodiazepines that activate an inhibitory $GABA_A$ receptor subtype on thalamic reticular neurons can also be effective in suppressing absence seizures (although other types of benzodiazepines can worsen them).[29] Baclofen, an agonist of a GABA-receptor subtype that hyperpolarizes thalamic relay neurons and makes the burst mode more likely, clearly exacerbates EEG spike-wave discharges in animal models.[30]

GENERALIZED EPILEPSIES ASSOCIATED WITH ION-CHANNEL MUTATIONS

Although most generalized epilepsies have complex inheritance patterns, a few have a mendelian

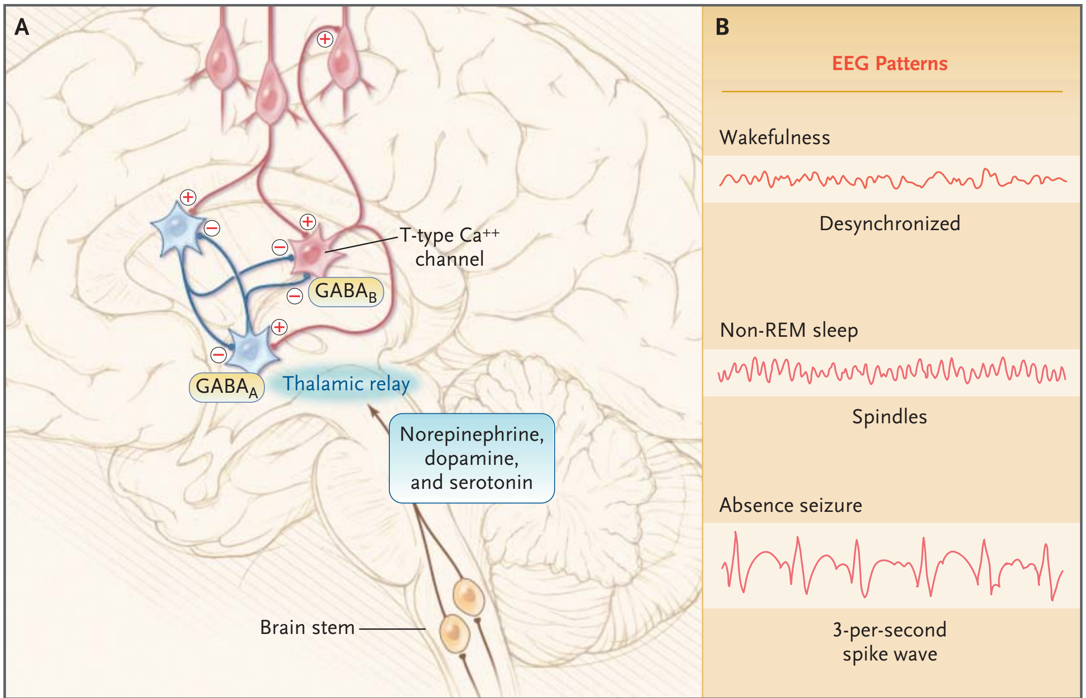

Figure 1. The Normal Thalamocortical Circuit and EEG Patterns during Wakefulness, Non–Rapid-Eye-Movement (Non-REM) Sleep, and Absence Seizures.

Panel A shows the normal thalamocortical circuit. Thalamic relay neurons can activate the cortical pyramidal neurons in either a tonic mode or a burst mode, the latter made possible by T-type calcium channels. The mode of thalamocortical activation is controlled largely by input from the thalamic reticular neurons, which hyperpolarize the relay neurons through γ-aminobutyric acid type B ($GABA_B$) receptors and are themselves inhibited by neighboring reticular neurons through activation of GABA type A ($GABA_A$) receptors. Cortical pyramidal neurons activate the thalamic reticular neurons in a feed-forward loop. Ascending noradrenergic, serotonergic, and dopaminergic inputs from brain-stem structures appear to modulate this circuit.

Panel B shows EEG patterns of wakefulness, non-REM sleep, and absence seizures. During wakefulness, the cortex is activated by the thalamus in a tonic mode, allowing for processing of external sensory inputs. This results in a desynchronized appearance of the EEG. During non-REM sleep, the cortex is activated in a burst mode, resulting in the EEG appearance of rhythmic sleep spindles. During an absence seizure, the normal thalamocortical circuit becomes dysfunctional, allowing burst activation of the cortex to occur during wakefulness, which results in the EEG appearance of rhythmic spike-wave discharges and interrupts responsiveness to external stimuli.

inheritance pattern and are associated with single-gene mutations (Table 1).[42-44] Almost all these mutations have been found in genes encoding ion-channel proteins (Fig. 2). Functional studies of the mutant channels have revealed potential mechanisms for some of these disorders.

For example, "generalized epilepsy with febrile seizures plus" is a genetic syndrome consisting of febrile seizures plus at least one other type of seizure (absence, myoclonic, atonic, or afebrile generalized tonic–clonic seizures).[45] Pedigree analysis has suggested that the inheritance pattern is autosomal dominant with incomplete penetrance and linkage to chromosome 19q. In this disorder, there is a mutation in the gene for the voltage-gated sodium channel $\beta 1$ subunit (*SCN1B*), which modifies the gating and inactivation properties of the channel.[31] The mutant channel protein, when expressed in oocytes of the frog genus xenopus, allows passage of an increased sodium current. In neurons, the mutation promotes depolarization and neuronal hyperexcitability. Since generalized epilepsy with febrile seizures plus was initially described, phenotypically similar families have been identified with mutations in sodium channel subunits SCN1A and SCN2A and the $GABA_A$ receptor subunit, GABRG2.[32-34]

Another generalized epilepsy syndrome, benign familial neonatal convulsions, has also been linked

Table 1. Epilepsy Syndromes Associated with Single-Gene Mutations.

Epilepsy Syndrome	Gene	Gene Product*	Study
Generalized epilepsy with febrile seizures plus	*SCN1B*	Sodium-channel subunit	Wallace et al.[31]
	SCN1A	Sodium-channel subunit	Escayg et al.[32]
	SCN2A	Sodium-channel subunit	Sugawara et al.[33]
	GABRG2	$GABA_A$-receptor subunit	Baulac et al.[34]
Benign familial neonatal convulsions	*KCNQ2*	Potassium channel	Biervert et al.,[35] Singh et al.[36]
	KCNQ3	Potassium channel	Charlier et al.[37]
Autosomal dominant nocturnal frontal-lobe epilepsy	*CHRNA4*	Neuronal nicotinic acetylcholine–receptor subunit	Steinlein et al.[38]
	CHRNB2	Neuronal nicotinic acetylcholine–receptor subunit	Fusco et al.[39]
Childhood absence epilepsy and febrile seizures	*GABRG2*	$GABA_A$-receptor subunit	Wallace et al.[40]
Autosomal dominant partial epilepsy with auditory features	*LGI1*	Leucine-rich transmembrane protein	Kalachikov et al.[41]

*$GABA_A$ denotes γ-aminobutyric acid type A.

to single-gene mutations. In this autosomal dominant disorder, seizures that are not associated with neurologic or metabolic abnormalities begin in the first few days of life and usually remit within a few weeks, with or without treatment.[46] Mutations have been identified in *KCNQ2* and *KCNQ3*, the genes for potassium channels on chromosomes 20q and 8q.[35-37] Functional studies have shown that the mutant channels allow passage of significantly less potassium current than wild-type channels.[35] Since potassium currents are the primary force behind repolarization of the neuronal membrane after depolarization, these mutations would be expected to prolong depolarization, thereby increasing neuronal hyperexcitability.

In these pure epilepsy syndromes, then, mutations in genes encoding ion-channel proteins lead to hyperexcitability of cortical neurons through alterations in channel function. Since these genes are expressed throughout the brain, it is plausible that the effect of the mutations is diffuse and therefore confers a predisposition to a generalized seizure disorder. Similar ion-channel mutations have been identified in a variety of disorders now termed "channelopathies." These conditions, which are characterized by paroxysmal episodes of neurologic or cardiac dysfunction, include episodic ataxia, periodic paralysis, familial hemiplegic migraine, and the long-QT syndrome.[47] Two recent reports describe calcium-channel mutations in patients with a combination of episodic ataxia and a mixed-seizure syndrome.[48,49] These reports raise the prospect that calcium-channel mutations will be found in pure epilepsy syndromes and emphasize the possibility that various paroxysmal neurologic disorders share common underlying mechanisms.

UNANSWERED QUESTIONS

Our understanding of generalized epileptogenesis remains far from complete. Why, for example, do persistent alterations in neuronal circuits or excitability result in a paroxysmal disorder such as epilepsy? A better understanding of the molecular and cellular circumstances that predispose a person to a seizure at a particular time could have implications for the prevention of seizures. It is also unclear why many seizure syndromes have an age-dependent onset and why some remit spontaneously. These features suggest that developmental changes in the nervous system have an important role in the clinical expression of generalized epilepsy syndromes that are genetically determined.[50]

MECHANISMS OF PARTIAL EPILEPSIES

MESIAL TEMPORAL-LOBE EPILEPSY

We know much less about the mechanisms underlying partial-seizure disorders than we do about generalized epileptogenesis, even though partial seizures are the most common seizure disorder in adults, often stemming from focal lesions such as

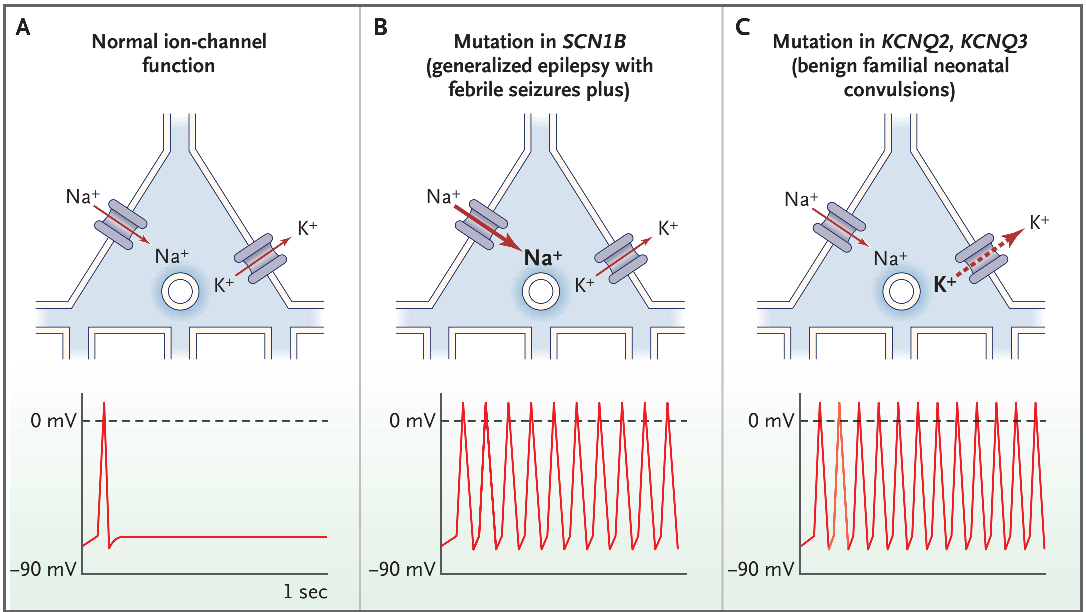

Figure 2. Examples of Ion-Channel Dysfunction Associated with Inherited Forms of Epilepsy.

Panel A shows normal neuronal-ion-channel function and the action potential. Sodium and potassium channels are responsible for the primary components of the action potential, which involve a depolarizing phase mediated by sodium-channel opening and a repolarizing phase due to potassium-channel opening and sodium-channel inactivation. Other potassium channels contribute to a longer-term repolarization that helps prevent repetitive firing of the neuron. Mutations in *SCN1B,* which encodes a voltage-gated sodium-channel subunit, are associated with generalized epilepsy with febrile seizures plus (Panel B). The apparent effect of these mutations is to allow passage of an increased sodium current, which would lead to a greater depolarization during the action potential and an increased tendency to fire repetitive bursts. Mutations in *KCNQ2* and *KCNQ3,* which both encode potassium channels, are associated with benign familial neonatal convulsions (Panel C). These mutations, which appear to decrease the potassium outflow underlying the longer-lasting "M current," are likely to cause a loss of spike-firing adaptation and therefore an increase in neuronal firing frequency.

head trauma, strokes, and tumors.[1] The most prevalent of these syndromes features complex partial seizures arising from the mesial temporal lobe.[8,51] Recordings from intracranial depth electrodes have clearly demonstrated an ictal onset in mesial temporal structures such as the hippocampus, amygdala, and adjacent parahippocampal cortex; surgical resection of these areas in suitable patients usually abolishes the seizures.[52] These seizures can begin with olfactory or gustatory hallucinations, an epigastric sensation, or psychic symptoms such as déjà vu or depersonalization. Once the seizures progress to a loss of awareness, the patients may stare blankly, speak unintelligibly, or exhibit lip smacking, picking at clothing, or other automatisms.[53]

The most common lesion in surgically resected tissue from patients with mesial temporal-lobe epilepsy is hippocampal sclerosis, a well-described entity whose cause remains elusive.[54-56] In hippocampal sclerosis, there is selective loss of neurons in the dentate hilus and the hippocampal pyramidal-cell layer, with relative preservation of dentate granule cells and a small zone of pyramidal cells (in the cornu ammonis, field 2, of the hippocampus). The dense gliosis that accompanies the loss of neurons causes shrinkage and hardening of tissue. The term "mesial temporal sclerosis" has also been used for this lesion, because often there is neuronal loss in the neighboring entorhinal cortex and amygdala.[57]

There is a vigorous debate about whether hippocampal sclerosis is a cause or an effect of seizures.[58,59] It has been seen in a wide variety of epileptic conditions, including cryptogenic temporal-lobe epilepsy[60] and epilepsy that follows febrile seizures or other brain insults early in life,[61] as well as in animal models of head injury[62] and seizures induced by chemicals.[63] It is possible that hippocampal sclerosis represents a pathologic final common pathway to partial epilepsy from a number of different causes.

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