

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

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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

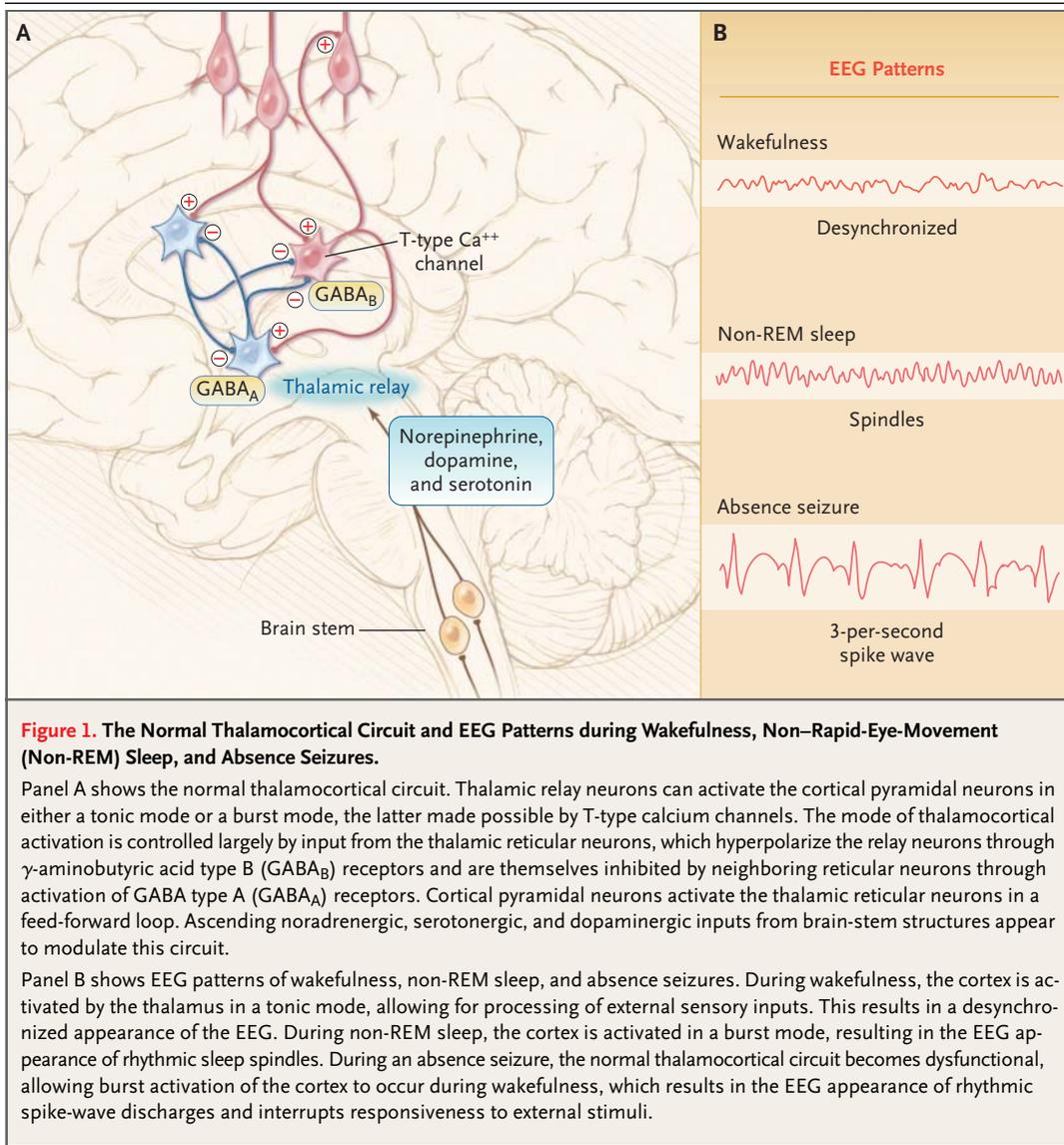
dopaminergic inputs to the thalamus modulate this circuit and affect the likelihood of a burst mode.²³

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



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 mu-

tation in the gene for the voltage-gated sodium channel β 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 | <i>SCN1B</i> | Sodium-channel subunit | Wallace et al. ³¹ |
| | <i>SCN1A</i> | Sodium-channel subunit | Escayg et al. ³² |
| | <i>SCN2A</i> | Sodium-channel subunit | Sugawara et al. ³³ |
| | <i>GABRG2</i> | GABA _A -receptor subunit | Baulac et al. ³⁴ |
| Benign familial neonatal convulsions | <i>KCNQ2</i> | Potassium channel | Biervert et al. ³⁵ Singh et al. ³⁶ |
| | <i>KCNQ3</i> | Potassium channel | Charlier et al. ³⁷ |
| Autosomal dominant nocturnal frontal-lobe epilepsy | <i>CHRNA4</i> | Neuronal nicotinic acetylcholine–receptor subunit | Steinlein et al. ³⁸ |
| | <i>CHRN2</i> | Neuronal nicotinic acetylcholine–receptor subunit | Fusco et al. ³⁹ |
| Childhood absence epilepsy and febrile seizures | <i>GABRG2</i> | GABA _A -receptor subunit | Wallace et al. ⁴⁰ |
| Autosomal dominant partial epilepsy with auditory features | <i>LG11</i> | 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-sei-

zure 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

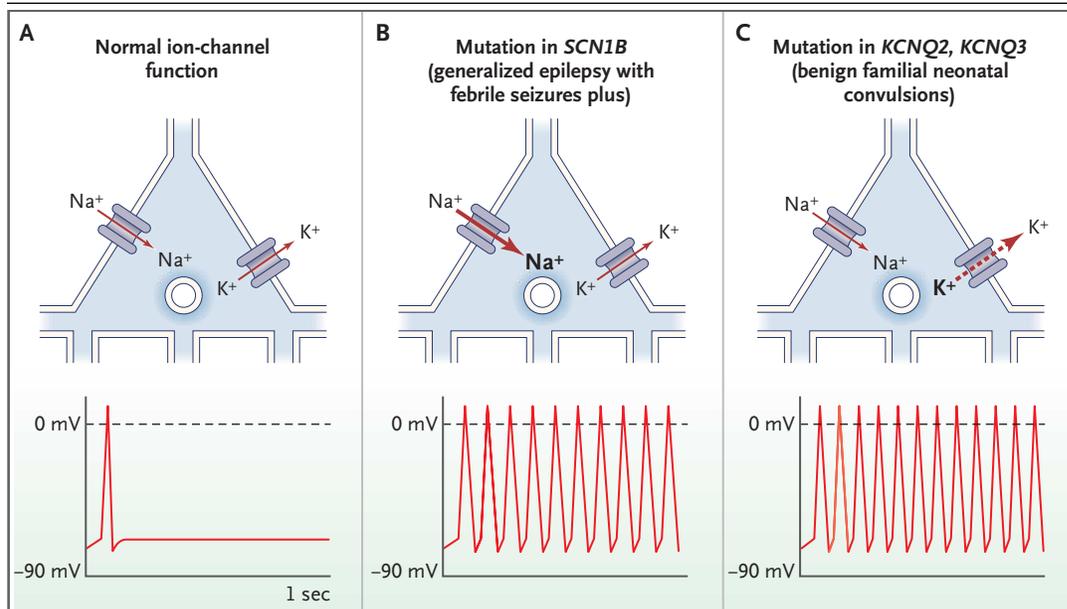


Figure 2. Examples of Ion-Channel Dysfunction Associated with Inherited Forms of Epilepsy.

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 epilepsy⁶⁰ and epilepsy that follows febrile seizures or other brain insults early in life,⁶¹ as well as in animal models of head injury⁶² 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.

Detailed studies of the morphologic changes in hippocampal sclerosis have led to several hypotheses about the mechanism of epileptogenesis in this condition (Fig. 3). The best-described change is the sprouting of mossy-fiber axons from dentate granule cells.⁶⁴ Normally, excitatory input to the hippocampus comes directly to the hippocampal dentate granule cells from the neighboring entorhinal cortex, whereas inhibitory input arises locally from interneurons in the inner molecular layer. The dentate granule cells sprout mossy-fiber axons, which extend to pyramidal neurons as part of the hippocampal output pathway. Normal dentate granule cells appear to be relatively resistant to hypersynchronous activation and may actually serve to inhibit the propagation of seizures from the entorhinal cortex.⁵¹ In hippocampal sclerosis, however, these cells sprout mossy-fiber axons that are directed back into the inner molecular layer,^{60,65,66} possibly because the neurons to which they usually extend have been lost. There is some evidence that these aberrant mossy fibers instigate a recurrent excitatory circuit by forming synapses on the dendrites of neighboring dentate granule cells.^{67,68} Although such a circuit is a plausible explanation for hyper-

excitability, the causative role of mossy-fiber sprouting in epileptogenesis is still largely speculative. There is, for example, strong evidence that newly sprouted axons also form synapses on inhibitory interneurons as part of a feedback mechanism, rather than simply increase excitation.⁶⁹⁻⁷¹

Some investigators have suggested that the selective vulnerability of certain neurons may be a mechanism of epileptogenesis in hippocampal sclerosis. In animal models, excitatory interneurons located within the dentate gyrus, which normally activate inhibitory interneurons, appear to be selectively lost.⁷² Loss of these excitatory cells would be expected to impair the inhibitory feedback and feed-forward mechanisms that act on dentate granule cells, resulting in hyperexcitability.⁷³ This explanation is plausible, but the evidence that dentate granule cells can project directly onto inhibitory interneurons raises the possibility of a compensatory mechanism. For these reasons, the implications of selective cell loss in the hippocampus, although highly suggestive of a mechanism of epileptogenesis, are still not completely understood.

An intriguing hypothesis lies in the phenomenon of neurogenesis. Almost all neurons in the brain

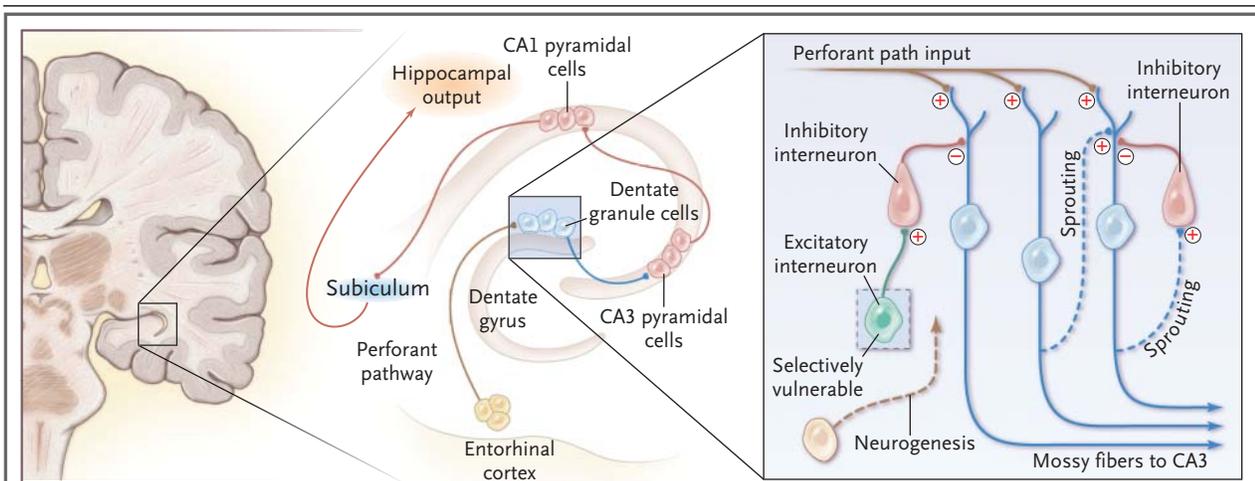


Figure 3. Hippocampal Sclerosis.

Hippocampal sclerosis is the most common identified pathological feature in cases of mesial temporal-lobe epilepsy. Normally, input to the hippocampus comes from the entorhinal cortex to the dentate granule cells through the perforant path. Dentate granule cells project to the CA3 sector as the first step in the hippocampal output pathway. A close-up of the dentate granule-cell layer reveals several morphologic changes characteristic of hippocampal sclerosis that may play a part in epileptogenesis. Newly sprouted mossy fibers from dentate granule cells can synapse on dendrites of neighboring dentate granule cells, resulting in a recurrent excitatory circuit. They can also sprout onto inhibitory interneurons. Excitatory interneurons, which normally activate inhibitory interneurons, may be selectively vulnerable to brain insults. Finally, neurogenesis of new dentate granule cells continues into adult life, and these neurons may integrate themselves into abnormal circuits.

are postmitotic and do not divide in adults, but progenitor cells in the dentate gyrus of the hippocampus are known to divide. Postnatal neurogenesis in the hippocampus can occur throughout life.⁷⁴ In an animal model of temporal-lobe epilepsy induced with the use of pilocarpine, seizures can trigger increased mitotic activity in a proliferative area of the dentate gyrus, resulting in the differentiation of new dentate granule cells.⁷⁵ This process may be independent of mossy-fiber sprouting, which appears to involve mature dentate granule cells rather than newly differentiated ones.⁷⁶ The functional significance of neuronal generation in the hippocampus after a brain insult is uncertain, although some evidence suggests that new dentate granule cells become abnormally integrated into neuronal circuits.⁷⁷ The potential clearly exists for an imbalance between excitation and inhibition as new neurons differentiate and form synaptic connections. Since the genesis of dentate granule cells recapitulates similar processes early in the development of the nervous system, this mechanism could be relevant to epileptogenesis both early and later in life.

In addition to these morphologic features, changes at the molecular level may also be important. The most prominent of these are alterations in the composition and expression of GABA_A receptors on the surface of hippocampal dentate granule cells. Normally, GABA_A receptors in adults, which consist of five subunits, serve as inhibitors, hyperpolarizing the neuron by allowing passage of chloride ions when activated. In the pilocarpine model of temporal-lobe epilepsy, however, the expression of various GABA_A-receptor subunits in dentate granule cells is altered, and these altered receptors have heightened sensitivity to zinc, which is abundant in mossy-fiber terminals.⁷⁸ Because this molecular change precedes the onset of spontaneous seizures, it is a plausible mechanism of epileptogenesis. Such findings have implications for treatment, since various anticonvulsant drugs act through the GABA_A receptor.

In summary, hippocampal sclerosis, the most widely studied pathologic lesion underlying partial epilepsy, has features of structural reorganization, selective neuronal loss, and neurogenesis. The nature of these changes supports hypotheses that predict the development of local hyperexcitability and a predisposition to partial seizures. However, the actual contributions of these factors, if any, to the development of an epileptic state have not been de-

termined. Moreover, molecular alterations, such as changes in neurotransmitter receptors, are also likely to be important. What this research indicates is that changes in local circuits are compatible with the development of focal hyperexcitability, which may be the basis of some partial epilepsy syndromes.

UNANSWERED QUESTIONS

Although studies of mesial temporal-lobe epilepsy have yielded useful information, there are other plausible mechanisms of partial epileptogenesis that are not suggested by this syndrome. Some partial epilepsies, for example, are genetically determined. Autosomal dominant nocturnal frontal-lobe epilepsy, in which single-gene mutations have been identified, has turned out to be a channelopathy that affects the neuronal nicotinic acetylcholine receptor, which serves as a ligand-gated sodium channel.³⁸ Why mutations in this receptor, which is widely expressed throughout the brain, should cause partial seizures in the frontal lobe is just one of many mysteries. Some genetically determined partial epilepsies, such as benign epilepsy with centrotemporal spikes (also called benign rolandic epilepsy), are age-limited syndromes, suggesting the importance of developmental influences.^{8,50,79} For many patients with partial epilepsy, there may be an underlying genetic predisposition that becomes manifest only after a sufficient environmental insult. Obviously, understanding what molecular mechanisms are at work in patients with such a predisposition is of considerable clinical interest.

NEWER AREAS OF RESEARCH

CORTICAL MALFORMATIONS

A rapidly expanding area of investigation in epileptogenesis is the study of malformations of cortical development, disorders in which the normal process of development in the cerebral cortex is disrupted. These malformations range from microscopic dysplasias to global abnormalities such as lissencephaly (smooth brain) or subcortical band heterotopia (double cortex)⁸⁰ and can be classified as disorders of neuronal proliferation, neuronal migration, or cortical organization.⁸¹ Many such malformations are associated with refractory epilepsy and are increasingly recognized as a common cause of epilepsy that was previously believed to be cryptogenic.⁸² In numerous cases, magnetic resonance imaging with high resolution has identified small

cortical malformations in patients without any other obvious causes of epilepsy.

Malformations of cortical architecture are useful for investigating the cellular and network changes that underlie the development of epilepsy.⁸²⁻⁸⁴ Although work in this area is still in its infancy, recent studies have provided us with a glimpse of what lies ahead. For example, in an animal model of hippocampal heterotopias the heterotopic neurons lack a particular potassium channel that in normal hippocampal neurons subserves a voltage-activated fast potassium current.⁸⁵ This defect would be expected to lead to hyperexcitability. Other investigators have shown in a rat model that neurons within dysplastic areas have impaired GABA-mediated inhibitory synaptic transmission, another defect that could lead to a predisposition to seizures.⁸⁶

THE ROLE OF GLIAL CELLS

Decades of research in epileptogenesis, including much of the work highlighted in this review, have focused on the intrinsic properties and network connections of neurons. Glial cells, although long considered to be merely supporting cells in the central nervous system, may also have an important role.⁸⁷ Glia perform key buffering functions that help to maintain the uptake of potassium and glutamate and other aspects of the extracellular milieu of neurons. Theoretically, disruption of these glial functions could cause neuronal hyperexcitability, since increased levels of extracellular potassium decrease the threshold for neuronal firing and increased levels of glutamate could increase neuronal activation. Preliminary evidence from an animal model of cortical malformation indicates that astrocytes (a subtype of glia) near the dysplastic region have a profound reduction in inward potassium currents.⁸⁸ Thus, a change in the neuronal microenvironment may be another mechanism of epileptogenesis.

CONCLUSIONS

Our aim in understanding how epilepsy develops is to prevent it. Clinically, there is often a "silent interval" between the occurrence of a neurologic insult and the appearance of recurrent seizures in many acquired forms of epilepsy. In addition, most genetically determined epilepsy syndromes do not become clinically manifest until well after birth. Both these facts suggest that epileptogenesis is a gradual process that can be specifically targeted. Ideally, we would like to have a drug that prevents the development of epilepsy, rather than one that merely suppresses seizures. Unfortunately, none of the available anticonvulsant agents appear to have a prophylactic effect in patients who are at risk for the development of a seizure disorder.⁸⁹

It is likely that generalized and partial epilepsy syndromes arise from different mechanisms. Current evidence suggests that generalized epilepsies originate from alterations in either neuronal networks, as in absence seizures, or intrinsic neuronal function, as in channelopathies. Partial epilepsy syndromes presumably stem from a focal lesion. Intensive studies of hippocampal sclerosis, the most common pathological finding in adults with the most common partial epilepsy, have demonstrated many local changes, but their causative role, if any, in epileptogenesis is still unknown. Newer avenues of study (such as cortical malformations) and newer conceptual mechanisms (such as the role of glial cells and the neuronal microenvironment) are likely to yield future insights into this complicated field. For now, however, while prevention is still elusive, our clinical goals must remain the treatment and cure of epilepsy.

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