of seizures, as demonstrated by patients who have seizures only while sleeping (nocturnal epilepsy) or during their menstrual period (catamenial epilepsy). If we could develop continuous monitoring methods to predict the timing of seizure generation (Box 58–2), acute intervention to deliver a drug or change neural activity patterns to prevent seizures might become a therapeutic option. However, EEG studies reveal great variability between patients in pre-ictal patterns. Continuous chronic stimulation of neural circuits is another method of modifying the excitability of epileptic circuits. As an example of this approach, implanted vagal nerve stimulators have been modestly successful in treating pharmaco-resistant epilepsy that does not respond to other treatments.

The Spread of Seizure Activity Involves Normal Cortical Circuitry

If activity in the seizure focus is sufficiently intense, the electrical activity begins to spread to other brain regions. Spread of seizure activity from a focus generally follows the same axonal pathways as does normal cortical activity. Thus, thalamocortical, subcortical, and transcallosal pathways can all become involved in seizure spread. Seizure activity can propagate from a seizure focus to other areas of the same hemisphere or across the corpus callosum to involve the contralateral hemisphere (Figure 58–10). Once both hemispheres become involved, a focal onset seizure has become secondarily generalized. At this point, the patient generally experiences loss of consciousness. The spread of a partial seizure usually occurs rapidly over a few seconds, but can also evolve over many minutes. Rapid generalization is more likely if a focal onset seizure begins in the neocortex than if it begins in the limbic system (in particular, the hippocampus and amygdala).

An interesting unanswered question is what terminates a seizure. Remarkably, few mechanisms for the self-limiting return to the interictal state have been defined with certainty. One definite conclusion at this point is that termination is not due to cellular metabolic exhaustion, because under severe conditions clinical seizures may continue for hours (see below). During the initial 30 seconds or so of a focal onset seizure that secondarily generalizes, neurons in the involved areas undergo prolonged depolarization and fire continuously (due to loss of the afterhyperpolarization that normally follows a paroxysmal depolarizing shift). As the seizure evolves, the neurons begin to repolarize and the afterhyperpolarization reappears. The cycles of depolarization and repolarization correspond to the clonic phase of the seizure (Figure 58–7A).

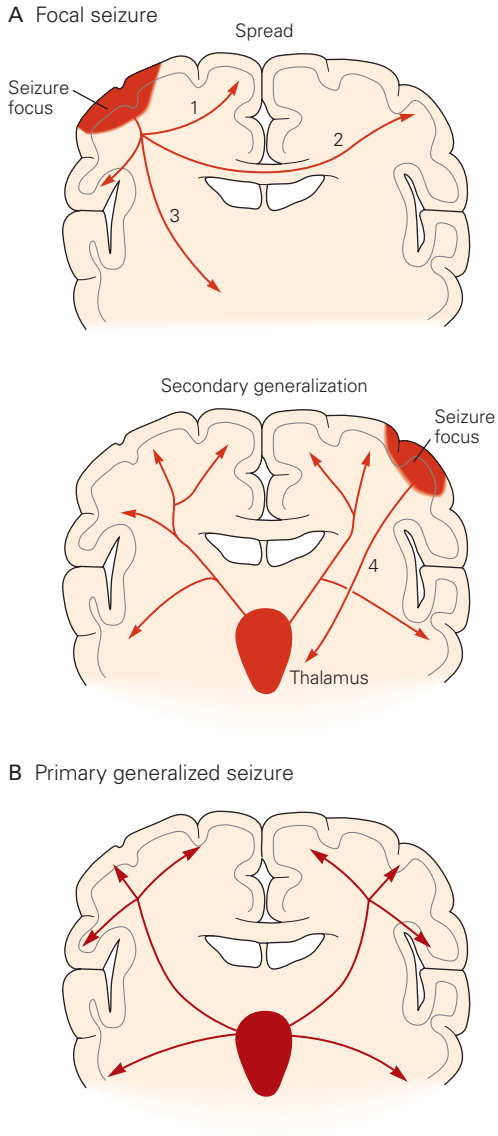


Figure 58–10 Focal and generalized onset seizures propagate via several pathways. (Adapted, with permission, from Lothman 1993b.)

A. Focal onset seizures can spread locally from a focus via intrahemispheric fibers (**1**) and more remotely to homotopic contralateral cortex (**2**) and subcortical centers (**3**). The secondary generalization of a focal onset seizure spreads to subcortical centers via projections to the thalamus (**4**). Widespread thalamocortical interconnections then contribute to rapid activation of both hemispheres.

B. In a generalized onset seizure, such as a typical absence seizure, interconnections between the thalamus and cortex are a major route of seizure propagation.

The seizure is often followed by a period of decreased electrical activity, the postictal period, which may be accompanied by symptoms of confusion, drowsiness, or even focal neurological deficits such as a hemiparesis (Todd paralysis). A neurological exam in the postictal period can lead to insights about the locus of the seizure focus when there is prolonged depression of one brain region or function, once other brain regions have regained normal function.

Generalized Onset Seizures Are Driven by Thalamocortical Circuits

Unlike the typical focal onset seizure, a generalized onset seizure abruptly disrupts normal brain activity in both cerebral hemispheres simultaneously. Generalized onset seizures and their associated epilepsies vary both in their manifestations and etiologies. Although the cellular mechanisms of generalized onset seizures differ in a number of interesting respects from those of focal onset or secondarily generalized seizures, a generalized onset seizure can be difficult to distinguish clinically or by EEG from a focal onset seizure that rapidly generalizes.

The most studied type of generalized onset seizure is the typical absence seizure (petit mal), whose characteristic EEG pattern (the 3-Hz spike-and-wave pattern in Figure 58–11A) was first recognized by Hans Berger in 1933. F. A. Gibbs recognized the relationship of this EEG pattern to typical absence seizures (he aptly described the pattern as "dart and dome") and attributed the mechanism to generalized cortical disturbance. The distinctive clinical features of typical absence seizures have a clear correlation with the EEG activity.

The typical absence seizure begins suddenly, lasts 10 to 30 seconds, and produces impaired awareness with only minor motor manifestations such as blinking or lip smacking. Unlike a focal onset seizure that secondarily generalizes, generalized onset seizures are not preceded by an aura or followed by postictal symptoms. The spike-wave EEG pattern can be seen in all cerebral areas abruptly and simultaneously and is immediately preceded and followed by normal background activity. Very brief (1–5 seconds) runs of 3-Hz EEG activity without apparent clinical symptoms are common in patients with absence seizures, but if frequent, they can affect their ability to carry out normal activities such as school performance.

In contrast to Gibbs's hypothesis of diffuse cortical hyperexcitability, Penfield and Jasper noted that the EEG in typical absence seizures is similar to rhythmic EEG activity in sleep, so-called sleep spindles (Chapter 44). They proposed a "centrencephalic" hypothesis in which generalization was attributed to rhythmic activity (pacing) by neuronal aggregates in the upper brain stem or thalamus that project diffusely to the cortex.

Research on animal models of generalized onset seizures and studies of the genetics of generalized epilepsy suggest that elements of both hypotheses are correct. In cats, parenteral injections of penicillin, a weak $GABA_A$ antagonist, produce behavioral unresponsiveness associated with an EEG pattern of bilateral synchronous slow waves (generalized penicillin epilepsy). During such a seizure, thalamic and cortical cells become synchronized through the same reciprocal thalamocortical connections that contribute to normal sleep spindles during slow-wave sleep.

Such seizures could in theory represent a form of diffuse hyperexcitability in the cortex. Recordings from individual cortical neurons show an increase in the rate of firing during a depolarizing burst that in turn produces a powerful GABAergic inhibitory feedback that hyperpolarizes the cell for approximately 200 ms after each burst (Figure 58–11C). This depolarization followed by inhibition differs fundamentally from the paroxysmal depolarizing shift in focal onset seizures in that GABAergic inhibition is preserved. In the typical absence seizure, the summated activity of the bursts produces the spike while the summated inhibition produces the wave of the spike-wave EEG pattern.

What are the properties of cells and networks that facilitate this generalized and synchronous activity? An early clue came from studies of the intrinsic bursting of thalamic relay neurons. Henrik Jahnsen and Rodolfo Llinas found that these neurons robustly express the T-type voltage-gated Ca^{2+} channel that is inactivated at the resting membrane potential but becomes available for activation when the cell is hyperpolarized (Chapter 10). A subsequent depolarization then transiently opens the Ca^{2+} channel (thus its name, T-type), and the Ca^{2+} influx generates low-threshold Ca^{2+} spikes. Consistent with the hypothesis that T-type channels contribute to absence seizures, certain anticonvulsant agents that block absence seizures, such as ethosuximide (Zarontin) and valproic acid (Depakote), also block T-type channels. T-type channels are encoded by three related genes (*Cav3.1*–*Cav3.3*), with *Cav3.1* the predominant type in the thalamus.

The circuitry of the thalamus seems ideally suited to the generation of generalized onset seizures. The pattern of thalamic neuron activity during sleep spindles suggests a reciprocal interaction between thalamic relay neurons and GABAergic interneurons in the thalamic reticular nucleus and perigeniculate nucleus (Figure 58–11B). Studies of thalamic brain slices by David McCormick and his colleagues indicate that

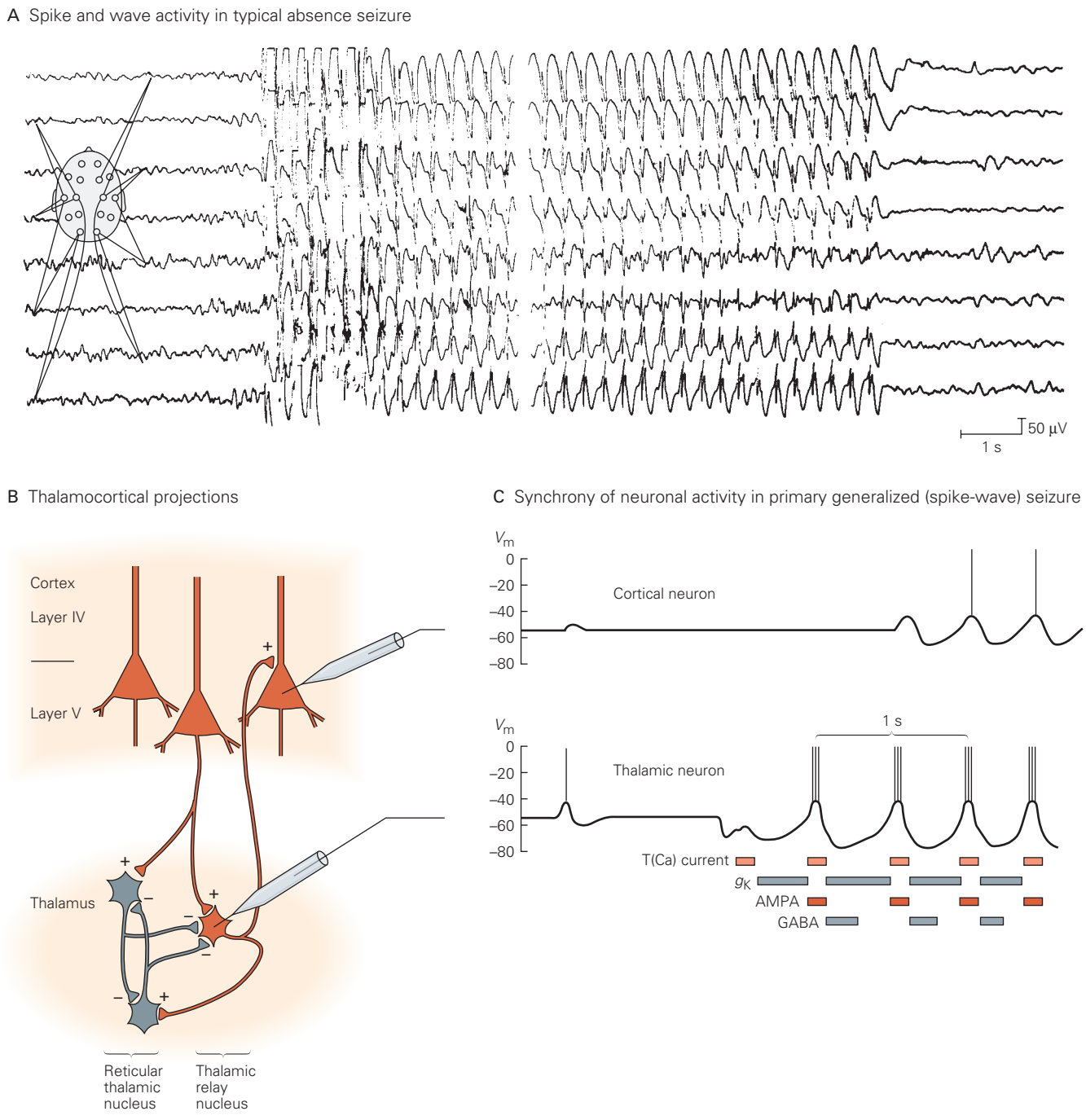


Figure 58–11 Generalized onset seizures have distinctive electroencephalogram (EEG) and single-neuron patterns.

A. This EEG from a 12-year-old patient with typical absence (petit mal) seizures shows the sudden onset of synchronous spikes at a frequency of 3 per second and wave activity lasting approximately 14 seconds. The seizure clinically manifested as a staring spell with occasional eye blinks. Unlike a focal onset seizure, there is no buildup of activity preceding the seizure and the electrical activity returns abruptly to the normal background level following the seizure. The discontinuity in the trace is due to removal of a 3-second period of recording. (Reproduced, with permission, from Lothman and Collins 1990.)

B. Thalamocortical connections that participate in the generation of sleep spindles (Chapter 44) are thought to be essential for the generation of generalized onset seizures. Pyramidal cells in the cortex are reciprocally connected by excitatory synapses with thalamic relay neurons. GABAergic inhibitory interneurons in the reticular thalamic nucleus are excited by pyramidal cells in the cortex and by thalamic relay neurons and inhibit the thalamic relay cells. The interneurons are also reciprocally connected.

C. Neuronal activity of cortical and thalamic neurons becomes synchronized during a generalized onset seizure. The depolarization is dependent on conductances in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (**AMPA**)-type glutamate receptor-channels and T-type voltage-gated Ca^{2+} channels. The repolarization is due to γ-aminobutyric acid (**GABA**)-mediated inhibition as well as voltage- and calcium-dependent K^+ conductances (g_K). (Adapted, with permission, from Lothman 1993a.)

the interneurons hyperpolarize the relay neurons, thus removing the inactivation of T-type Ca^{2+} channels. This action leads to an oscillatory response: A rebound burst of action potentials following each IPSP to which the T-type Ca^{2+} channels contribute stimulates the GABAergic interneurons, resulting in another round of relay neuron rebound firing. The relay neurons also excite cortical neurons, manifested in the EEG by a "spindle." Both the T-type Ca^{2+} channel and the $GABA_B$ receptor-channel play an important role in the generation of this activity, which resembles human absence seizures (Chapter 44).

Mutations in voltage-gated Ca^{2+} channels have produced several mouse models of generalized epilepsy, including the so-called *totterer* mouse, which bears a mutation in the P/Q-type calcium channels involved in neurotransmitter release. Studies of these mutants by Jeffrey Noebels and his colleagues have revealed that the animals develop generalized onset seizures when they reach adolescence. EEGs in these animals show a paroxysmal spike-wave discharge and seizures that are characterized by an arrest of behavior and blockade by ethosuximide, similar to typical absence seizures in children. Thalamic neurons in these mice have elevated T-type Ca^{2+} channels that favor rebound bursting. Mutations of over 20 different genes for this phenotype have now been described in mice. Remarkably, many encode ion channel subunits or proteins involved in presynaptic transmitter release.

Locating the Seizure Focus Is Critical to the Surgical Treatment of Epilepsy

The pioneering studies of Wilder Penfield in Montreal in the early 1950s led to the recognition that removal of the temporal lobe in certain patients with focal onset seizures of hippocampal origin could reduce the number of seizures or even cure epilepsy. As surgical treatment for such patients became more common, it became clear that the surgical outcome is directly related to the adequacy of the resection. Thus, precise localization of the seizure focus in cases of focal onset seizures is essential. Electrical mapping of seizure foci originally relied on the surface EEG, which we have seen is biased toward particular sets of neurons in the cortex immediately adjacent to the skull. However, seizures intractable to conventional medical management often begin in deep structures that show little or no abnormality on the surface EEG at the onset of the seizure. Thus, the surface EEG is somewhat limited in identifying the location of the seizure focus.

The development of magnetic resonance imaging (MRI) markedly improved the noninvasive anatomical mapping of seizure foci. This technique is now routine in the evaluation of epilepsies involving the temporal lobe, but also shows increasing promise for identifying seizure foci in other locations. The scientific basis of anatomical mapping of seizure foci by MRI was the observation that a majority of patients with intractable focal onset seizures with impaired awareness have atrophy and cell loss in the mesial portions of the hippocampal formation. There is a dramatic loss of neurons within the hippocampus (mesial temporal sclerosis), changes in dendritic morphology of surviving cells, and collateral sprouting of some axons. The anatomical resolution of modern MRI machines has allowed a noninvasive, quantitative assessment of the size of the hippocampus in epilepsy patients. Loss of volume of the hippocampus on one or another side of the brain generally correlates well with the localization of seizure foci in the hippocampus as determined by functional criteria using implanted depth electrodes.

The typical patient with mesial temporal epilepsy has unilateral disease, which leads to shrinkage of the hippocampus on one side that can be associated with apparent dilatation of the temporal horn of the lateral ventricle. Such a case is illustrated in Box 58–3. However, in many patients, abnormalities cannot be detected using anatomical MRI; thus, nonanatomical (functional) imaging techniques (fMRI) are used as well (Chapter 6).

Functional neuroimaging takes advantage of the changes in cerebral metabolism and blood flow that occur in the seizure focus during the ictal and interictal periods. The electrical activity associated with a seizure places a large metabolic demand on brain tissue. During a focal onset seizure, there is an approximately three-fold increase in glucose and oxygen utilization. Between seizures, the seizure focus often shows decreased metabolism. Despite the increased metabolic demands, the brain is able to maintain normal adenosine triphosphate (ATP) levels during a focal onset seizure. On the other hand, the transient interruption of breathing during a generalized motor seizure causes a decrease in oxygen levels in the blood. This results in a drop in ATP concentration and an increase in anaerobic metabolism as indicated by rising lactate levels. This oxygen debt is quickly replenished in the postictal period, and no permanent damage to brain tissue results from a single generalized seizure.

Positron emission tomography (PET) scans of patients with focal onset seizures originating in the mesial temporal lobe frequently show interictal hypometabolism, with metabolic changes extending to the lateral temporal lobe, ipsilateral thalamus, basal ganglia, and frontal cortex. PET scans using nonhydrolyzable glucose analogs have been particularly helpful

Box 58–3 Surgical Treatment of Temporal Lobe Epilepsy

A 27-year-old woman had episodes of decreased responsiveness beginning at age 19. At first, she would stare off and appear confused during the episodes. Later, she developed an aura consisting of a feeling of fear. This fear was followed by altered consciousness, a wide-eyed stare, tightening of the left arm, and a scream that lasted for 14 to 20 seconds (Figure 58–12).

These spells were diagnosed as complex partial seizures. The seizures occurred several times a week despite treatment with several antiepileptic drugs. She was unable to work or drive due to frequent seizures. She had a history of meningitis at age 6 months, and throughout childhood she had experienced brief episodes of altered perception described as "like someone threw a switch."

Based on an evaluation summarized in Figures 58–13 and 58–14, a right amygdalohippocampectomy was performed. The patient was seizure-free following the operation and returned to full-time employment.

Figure 58–12 The patient is shown reading quietly in the period preceding the seizure (A), during the period when she reported a feeling of fear (B), and during the period when there was alteration of consciousness and an audible scream (C). (Reproduced, with permission, from Dr. Martin Salinsky.)

in identifying seizure foci in patients with normal MRI scans and in some early childhood epilepsies. Unfortunately, for unclear reasons, PET has been less reliable in localizing seizure foci in extratemporal areas such as the frontal lobe. An additional limitation is the expense of the PET scan and the short half-life of the isotopes (a nearby cyclotron is required). PET scanning can also be used to look for functional changes in neurotransmitter receptor binding and transport related to seizure activity.

A related technique that measures cerebral blood flow, single-photon emission computed tomography (SPECT), has been used more frequently than PET. SPECT does not have the resolution of PET but can be performed in the nuclear medicine department of many large hospitals. Injection of radioisotopes and SPECT imaging at the time of a seizure (ictal SPECT) reveal a pattern of hypermetabolism followed by hypometabolism in the seizure focus and surrounding tissue. Magnetoencephalography and functional MRI also offer further advantages in the mapping of seizure foci.

With rigorous selection of patients for epilepsy surgery, the cure rate for epilepsy with a well-defined

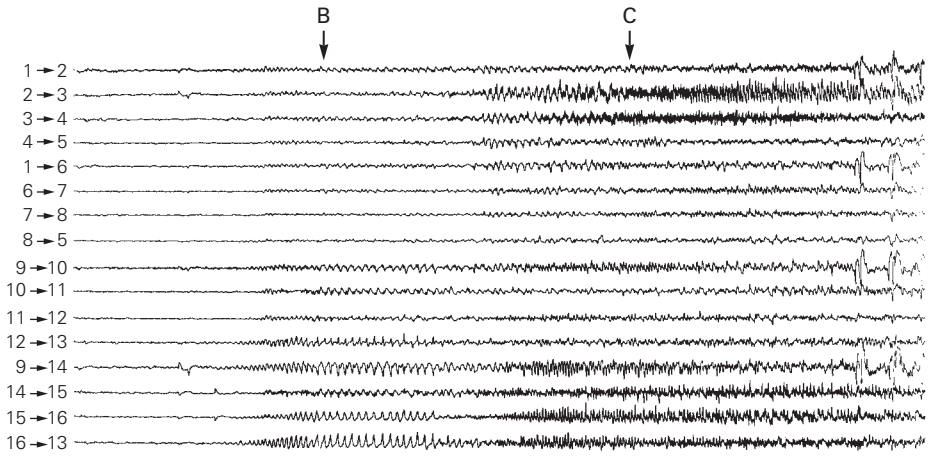


Figure 58–13 The electroencephalogram (EEG) at the time of the photographs in Figure 58–12. Low-amplitude background rhythms occur in the beginning (*left*). At the point when the patient reported fear (**B**), there is a buildup of EEG activity at the onset of a focal onset seizure with impaired awareness, but this activity is confined to the EEG electrodes over the right hemisphere (electrodes 9–16). At the point awareness is altered (**C**), the seizure activity has spread to the left hemisphere (electrodes 1–8). EEG spike-waves are particularly prominent in lead 9 over the right anterior temporal region. (Reproduced, with permission, from Dr. Martin Salinsky.)

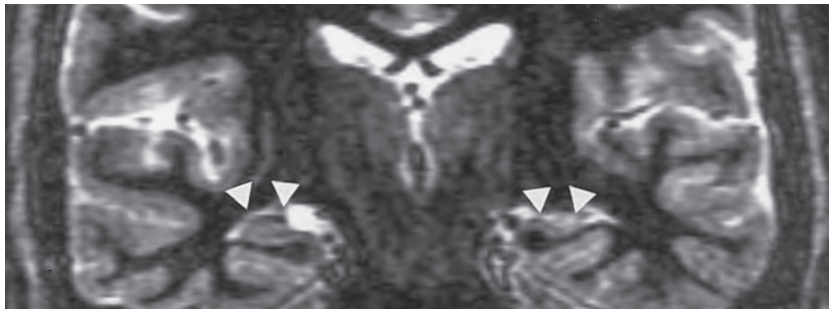


Figure 58–14 Enhanced magnetic resonance imaging reveals atrophy of the right hippocampus (arrows on the right) and a normal left hippocampus (arrows on the left). (Reproduced, with permission, from Dr. Martin Salinsky.)

seizure focus in the temporal lobe can approach 80%. Patients with complicating factors (eg, multiple foci) have lower success rates. However, even among these patients, the number and severity of seizures are usually reduced. Patients who have been "cured" of seizures may still experience cognitive problems such as memory loss and social problems such as adjustments to more independent living and limited employment opportunities. These factors emphasize the need for treatment as early in life as feasible.

Prolonged Seizures Can Cause Brain Damage

Repeated Convulsive Seizures Are a Medical Emergency

As noted above, brain tissue can compensate for the metabolic stress of a focal onset seizure or the transient decrease in oxygen delivery during a single generalized tonic-clonic seizure. In a generalized seizure, stimulation of the hypothalamus leads to massive

activation of the "stress" response of the sympathetic nervous system. The increased systemic blood pressure and serum glucose initially compensate for increased metabolic demand, but these homeostatic mechanisms fail during prolonged seizures. The resulting systemic metabolic derangements, including hypoxia, hypotension, hypoglycemia, and acidemia, lead to a reduction in high-energy phosphates (ATP and phosphocreatine) in the brain and thus can be devastating to brain tissue.

Systemic complications such as cardiac arrhythmias, pulmonary edema, hyperthermia, and muscle breakdown can also occur. The occurrence of repeated generalized seizures without return to full consciousness between seizures, called *status epilepticus*, is a true medical emergency. This condition requires aggressive seizure management and general medical support because 30 or more minutes of continuous convulsive seizures leads to brain injury or even death. Status epilepticus can involve nonconvulsive seizures for which the metabolic consequences are much less severe.

In addition to the dangers of status epilepticus, patients with poorly controlled seizures are also at risk for sudden death (sudden unexpected death in epilepsy [SUDEP]), the leading cause of death in patients with uncontrolled seizures. The underlying mechanisms for SUDEP are not completely understood, but recent studies by Richard Bagnall and colleagues as well as others suggest that cases of SUDEP have clinically relevant mutations in the genes implicated in cardiac arrhythmia and epilepsy. Such data support an association between SUDEP and cardiac arrhythmias or interruption of brain stem circuits involved in respiratory control. This topic is appropriately the focus of intense current investigation.

Excitotoxicity Underlies Seizure-Related Brain Damage

Repeated seizures can damage the brain independently of cardiopulmonary or systemic metabolic changes, suggesting that local factors in the brain can result in neuronal death. The immature brain appears particularly vulnerable to such damage, perhaps because of greater electrotonic coupling between neurons in the developing brain, less effective potassium buffering by immature glia, and decreased glucose transport across the blood–brain barrier.

In 1880, Wilhelm Sommer first noted the vulnerability of the hippocampus to such insults, with preferential loss of the pyramidal neurons in the CA1 and CA3 regions. This pattern has been duplicated in experimental animals by electrical stimulation of afferents to the hippocampus or by injection of excitatory amino acid analogs such as kainic acid. Interestingly, kainic acid causes local damage at the site of injection and also at the site of termination of afferents originating at the injection site.

These observations suggest that release of the excitatory transmitter glutamate during excessive stimulation such as a seizure can itself cause neuronal damage, a condition termed *excitotoxicity*. Because it has been difficult to detect increases in extracellular glutamate during status epilepticus, it appears that excitotoxicity results more from excessive stimulation of glutamate receptors than from tonic increases in extracellular glutamate. The histological appearance of acute excitotoxicity includes massive swelling of cell bodies and dendrites, the predominant locations of glutamate receptors and excitatory synapses.

Although the cellular and molecular mechanisms of excitotoxicity are still not fully understood, several features are clear. Overactivation of glutamate receptors leads to an excessive increase in intracellular Ca^{2+} that can activate a self-destructive cellular cascade involving calcium-dependent enzymes, such as phosphatases, proteases, and lipases. Lipid peroxidation can also cause production of free radicals that damage vital cellular proteins and lead to cell death. The role of mitochondria in Ca^{2+} homeostasis and in control of free radicals may also be important. The pattern of cell death was first thought to reflect necrosis due to the autolysis of critical cellular proteins. However, the activation of "death genes," characteristic of programmed cell death (apoptosis), may also be involved.

Seizure-related brain damage or excitotoxicity can be specific to certain types of cells in particular brain regions, perhaps due to protective factors, such as calcium-binding proteins in some cells and sensitizing factors, such as the expression of calcium-permeable glutamate receptors in other cells. For example, excitotoxicity induced in vitro by excessive activation of AMPA-type glutamate receptors preferentially affects interneurons that express AMPA-type receptors that have high Ca^{2+} permeability, providing a possible mechanism for their selective vulnerability.

Several outbreaks of "amnestic" shellfish poisoning provide a vivid example of the consequences of overactivation of glutamate receptors. Domoic acid, a glutamate analog not present in the brain, is a natural product of certain species of marine algae that flourish during appropriate ocean conditions. Domoic acid can be concentrated by filter feeders such as shellfish. Ingestion of domoic-contaminated shellfish sporadically causes outbreaks of neurological damage, including severe seizures and memory loss (amnesia).

The area most sensitive to damage is the hippocampus, providing further support for the excitotoxicity hypothesis and the critical role of the hippocampus in learning and memory.

The Factors Leading to Development of Epilepsy Are Poorly Understood

A single seizure does not warrant a diagnosis of epilepsy. Normal people can have a seizure under extenuating circumstances such as after drug ingestion or extreme sleep deprivation. Clinicians look for possible causes of seizures in such patients but usually do not begin treatment with anticonvulsants following a single seizure. Unfortunately, our understanding of what factors contribute to susceptibility to epilepsy is still rudimentary. However, progress on this front is increasing rapidly with the advent of experimental mutagenesis in animal models and clinical neurogenetics in patients including whole-exome sequencing.

Some forms of epilepsy have long been considered to result in part from a genetic predisposition. For example, infants with febrile seizures often have a family history of similar seizures. The role of genetics in epilepsy is supported by the existence of familial epileptic syndromes in humans as well as seizure-prone animal models with such exotic names as *Papio papio* (a baboon with photosensitive seizures), audiogenic mice (in which loud sounds induce seizures), and spontaneous single-locus mutations such as *reeler* and *totterer* mice (names alluding to the clinical manifestations of cerebellar mutations in these animals). Even with a genetic predisposition or a structural lesion, the evolution of the epileptic phenotype often involves maladaptive changes in brain structure and function.

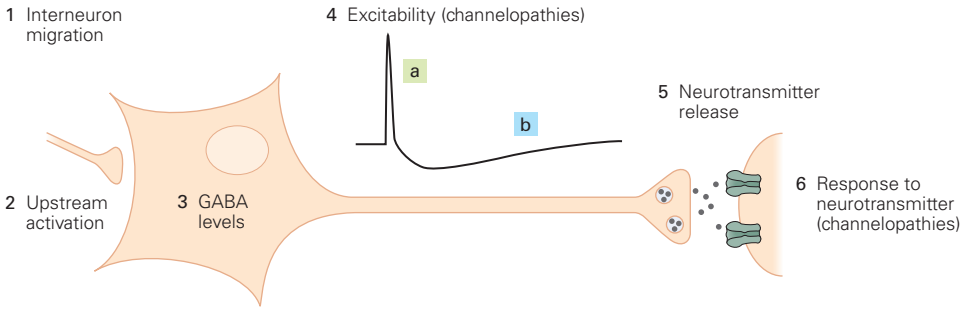
Mutations in Ion Channels Are Among the Genetic Causes of Epilepsy

Recent studies have provided a wealth of new information concerning the molecular genetics of epilepsy. At present, more than 120 genes have been linked to an epileptic phenotype; approximately half of these were discovered in humans and the others in animals, mostly mice. The affected proteins include ion channel subunits, proteins involved in synaptic transmission such as transporters, vesicle proteins, synaptic receptors, and molecules involved in Ca^{2+} signaling. For example, seizures in the *totterer* mutant mouse are due to a spontaneous mutation in the gene that encodes the $Ca_V2.1$ or α_{1A}-subunit of the P/Q-type voltage-gated Ca^{2+} channel. That a mutation in these classes of proteins can cause epilepsy is perhaps not unexpected given the dependence of seizures on synaptic transmission and neuronal excitability.

Some of the other genes linked to epilepsy in mice have been more surprising, such as the genes for centromere BP-B, a DNA binding protein, and the sodium/hydrogen exchanger, which is affected in the slow-wave epilepsy mouse. A wide variety of human genes cause neurological disorders, of which epilepsy is only one manifestation. For example, Rett syndrome, a disease associated with intellectual disability, autism, and seizures, is caused by mutations in *MECP2* (methyl-CpG-binding protein-2), a regulator of gene transcription. Although the exact links are not known, it is clear that mutations in many different genes may result in epilepsy.

In most cases, genetic epilepsy syndromes in humans have complex rather than simple (Mendelian) inheritance patterns, suggesting the involvement of many, rather than single, genes. Nevertheless, a number of monogenic epilepsies have been identified in studies of families with epilepsy. Ortrud Steinlein and colleagues reported in 1995 that a mutation in the α4-subunit of the nicotinic acetylcholine receptor-channel is responsible for autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), the first example of an autosomal gene defect in human epilepsy. Subsequently, other voltage- and ligand-gated channel proteins have been identified as critical genes for epilepsy. Mutations in ion channel genes (channelopathies) constitute a major cause of known monogenic epilepsies (Figure 58–15). Many more genes are being discovered by clinical exome analysis for de novo mutations. The large number of genes for K^+ channels and the critical role of these channels in balancing excitation and inhibition are important reasons for the expanding epilepsy genome.

In voltage-gated channels, mutations largely involve the main pore-forming subunit(s), but there are also examples of epilepsy-causing mutations in regulatory subunits. When examined in vitro, the mutant channel proteins are most commonly associated with either reductions in the expression of the channel on the surface of the plasma membrane (due to reduced targeting to the membrane or premature degradation) or altered kinetics of the channels. It is straightforward to consider how changes in ion channel gating might affect the excitability of neurons and their synchronization during seizure generation. However, ion channel mutations may also affect neuronal development and thus exert their epileptogenic effects through a



	Channel	Subunits affected	Epilepsy
a	Voltage-gated Na^+	Na_V 1.1, Na_V 1.2, β1	Generalized epilepsy with febrile seizures plus (GEFS+) Severe myoclonic epilepsy of infancy Benign infantile epilepsy
	Voltage-gated K^+	K_V 1.1	Temporal lobe epilepsy
	Ca^{2+}-activated K^+	Ca_V 1.1	Absence epilepsy
b	$GABA_A$ receptor	α1, β3, γ2	GEFS+ Juvenile myoclonic epilepsy Childhood absence epilepsy
	M-type K^+	KCNQ2/3	Benign neonatal epilepsy
	Voltage-gated Ca^{2+}	Ca_V 2.1	Absence epilepsy
	Cl^-	CLCN2	Juvenile myoclonic epilepsy

Figure 58–15 **Channelopathies are a major, but not the only, cause of monogenic human epilepsies.** The human epilepsy genes discovered so far can affect multiple phases of synaptic transmission including the migration of interneurons (**1**), upstream activation of interneurons (**2**), γ-aminobutyric acid (GABA) levels within interneurons (**3**), the excitability of excitatory and inhibitory neurons (**4**), the release of neurotransmitters (**5**), and the postsynaptic response to neurotransmitters (**6**). The inset shows that the impact of mutations in these genes on neuronal excitability can affect the shape of the action potential as well as the afterpotentials and synaptic events that follow. Mutations indicated near the spike (**a**) affect the repolarization of the action potential. Other mutations shown in (**b**) affect the afterhyperpolarization, synaptic conductances, or interspike interval.

secondary action on cell migration, network formation, or patterns of gene expression.

In the early days of research on epilepsy genes, it was widely expected that the genes would mostly underlie generalized epilepsies, based on the idea that a gene mutation (eg, in an ion channel) would be expected to affect most neurons. However, the very first autosomal dominant epilepsy gene discovered by Steinlein and colleagues caused a focal onset (frontal lobe) epilepsy, and another gives rise to seizures originating in the temporal lobe with an auditory aura. In retrospect, this should not be so surprising because channel subunits are rarely expressed uniformly in the brain, and some brain regions are more likely to generate seizures than other regions.

Timing of gene expression is also important. For example, *totterer* mice with mutations in the pore-forming $Ca_V2.1$ subunit of P/Q-type Ca^{2+} channels show spike-wave–type seizures that begin in the third postnatal week, presumably because N-type Ca^{2+} channels are the predominant functional isoform earlier in development, whereas P/Q-type Ca^{2+} channels predominate later. The neurological phenotype begins once the mutant channel is functionally required during development.

Moreover, one mutation can give rise to different epilepsy phenotypes, or different mutant genes can cause the same epilepsy phenotype. As an example of the latter, the ADNFLE syndrome, first discovered as a mutation in the α4-subunit of the nicotinic