Chapter 41

Epilepsy*

Helen E. Scharfman[1,2], Allison Peterson[3] and Devin K. Binder[3]

[1]Departments of Child & Adolescent Psychiatry, Physiology & Neuroscience, Psychiatry New York University Langone Medical Center, New York, NY, United States; [2]The Nathan Kline Institute, Dementia Research, Orangeburg, NY, United States; [3]Division of Biomedical Sciences, School of Medicine, University of California, Riverside, CA, United States

Chapter outline

Introduction

History

Epilepsy is a disease with an extremely long history, suggesting that the causes of epilepsy have been present for centuries and are not related to the industrialized world. The first descriptions of individuals with seizures are found in texts from ancient civilization. For example, in a document from Mesopotamia, an individual having a seizure was described with " … a neck that turns left, hands and feet are tense and eyes wide open, froth flowing from the mouth and consciousness being lost … ."[1] Without the understanding of the nervous system that we have today, most of these behaviors were attributed to demons "seizing" an individual. In fact, the word "epilepsy" has its origin in the Greek word "epilambanein," which is a combination of "epi," meaning "upon" and "lambanein," which means "to seize" or "to take hold of." In Rome, epilepsy was known as a curse from the gods, and in Greece, epilepsy was referred to as the "Sacred Disease."[1] During the height of Christianity, over 40 patron saints were established for epilepsy, a number exceeded only by catastrophic illnesses such as the plague.[2] Few people realize that St. Valentine, who is famous as the patron saint of lovers and for whom Valentine's day is named, is also a patron

* Thoughts on teaching about the neurobiology of diseases section available at the beginning of the book and Index terms are available at the end of the book.

Neurobiology of Brain Disorders. https://doi.org/10.1016/B978-0-323-85654-6.00060-5

saint of epilepsy.[2] Exactly how this patron saint became associated with epilepsy is not clear, however. St. Valentine may have been a doctor who died on February 14, 273,[2] and an association was made with epilepsy for a reason that is currently unclear. Another suggestion is that St. Valentine "cured" epilepsy in his fiance, most likely because he witnessed remission of seizures, which occurs in some epilepsy syndromes that have historically been named "benign."

Hippocrates was the first to suggest that epilepsy was not a disease related to demons but a biological problem in the brain.[3] However, the association of epilepsy with evil spirits or demonic influence persisted. Remarkably, a negative conception of individuals with epilepsy, religious or not, still exists in some parts of the world today. Even in industrialized nations, patients with epilepsy often describe a stigma associated with the word "epilepsy" or "epileptic." This view has led to suggestions that alternate terms be used for "epilepsy," such as "seizure disorder," and "antiseizure drug" (ASD) instead of "antiepileptic drug." A great deal of effort has been spent to dispel negative views about epilepsy.[4–6]

Clinical overview

In general, epilepsy is defined by spontaneous seizures that occur intermittently and recurrently. The word "spontaneous" means that the seizure is unprovoked. However, there are epilepsy syndromes in which a person experiences a seizure whenever a specific stimulus occurs, such as flashing lights, a particular sound, or excessive alcohol intake. This type of epilepsy is called "provoked" or "reflex epilepsy."

There is some disagreement about the exact number of seizures necessary for the diagnosis of epilepsy. Until recently, epilepsy was defined by any number of seizures greater than one, because even two seizures that were unprovoked would discriminate an individual with epilepsy from other disorders. One of the reasons that this definition has been debated is that many conditions besides epilepsy can lead to a seizure, such as head injury, gastrointestinal illness accompanied by electrolyte depletion, or drug abuse. For these reasons and others, it was suggested in 2005 that only one spontaneous seizure be required for a diagnosis of epilepsy as long as there were signs that more seizures were likely to occur.[7] For example, an individual that had their first seizure could be diagnosed with epilepsy if neuroimaging showed a structural abnormality consistent with a type of epilepsy, such as a cortical tuber, which is the defining pathology in tuberous sclerosis. Once a physician has made the diagnosis of an epileptic seizure, they can diagnose the epilepsy syndrome using the multilevel classification, which was designed to aid in classifying epilepsy across diverse clinical settings.[8] When possible, a diagnosis at all three levels (seizure type, epilepsy type, and epilepsy syndrome) is recommended.

Terminology

One of the long-standing debates in the field of clinical epileptology, as well as basic research in epilepsy, relates to terminology. Not only are there debates about the exact definition for the term "epilepsy," but there also is some difficulty in defining the term "seizure." One definition of "seizure" is "hypersynchronous neuronal activity," but the term "hypersynchronous" is somewhat subjective because various types of synchronous neuronal activity are characteristic of the normal brain, such as alpha, theta, or delta rhythms. Some definitions include a long duration of hypersynchronous neuronal activity, such as >3 s, because some normal individuals may exhibit brief periods of EEG activity that are seizure-like, but long periods are extremely rare. Nevertheless, EEG manifestations of seizures are sometimes hard to differentiate from normal EEG activity. Therefore, seizures that are accompanied by convulsive movements are the easiest to define as seizures. These events may be called "convulsions" or "convulsive seizures" or, in the United Kingdom, "fits." Movements can be deceiving, however. Individuals who faint, for example, are similar to those individuals with atonic seizures—in each case, individuals suddenly lose postural tone and fall. Narcolepsy is an example of a condition where sudden falls are common, but in this case there is no EEG activity that resembles a seizure. Conditions where movements occur that are similar to a type of epilepsy (such as atonic seizures), but are not accompanied by EEG manifestations of seizures are called "non-epileptic seizures" or "psychogenic non-epileptic seizures (PNES)" (Table 41.1).

Other terms are also debated. For example, "anticonvulsant" was commonly used to refer to drugs used to treat epilepsy, until it was recognized that these medications can also reduce non-convulsive seizures. The term "antiepileptic drug" is widely used today but is not ideal either because these drugs are also used in some psychiatric disorders in which there may be no evidence of seizures by EEG. In these individuals, it may be that specific brain areas are overactive and therefore, benefit from a drug that reduces neuronal activity—which can occur even though the excessive activity is never sufficiently robust to be detected by EEG. As a result of these observations, and the stigma associated with the term "epileptic" (described above), the term "antiseizure drug" (ASD) has been suggested.

Incidence and prevalence

Epilepsy is extremely common and pervasive, affecting over 50 million individuals worldwide. In the United States, approximately 3 million adults and 470,000 children have epilepsy, a number comparable to that for diseases that typically are considered much more prevalent, such as Alzheimer's disease (2.5 million individuals) and schizophrenia (2.4 million). Likewise, whereas it is estimated that 1 in 88 children will develop autism, 1 in 26 will develop epilepsy.[9,10]

In the United States and other industrialized nations, the incidence, or the number of new cases of epilepsy per year, is between 40 and 70 per 100,000.[11–13] In developing countries, the incidence is higher: 100−190 per 100,000 individuals. As one might infer from the high incidence of epilepsy in developing countries, low socioeconomic status has been related to an increased risk of epilepsy.[14,15] Indeed, it has been estimated that 80% of the patients with epilepsy in the world live in

TABLE 41.1 Terminology.

Term (synonyms)	Definition
Absence seizure (petit mal)	A seizure that is accompanied by staring and unresponsiveness, with 2 Hz spike-and-wave discharges recorded from multiple EEG leads, bilaterally
Antiseizure drug	A drug that reduces seizures
Anticonvulsant drug	A drug that reduces convulsions
Antiepileptic drug	A drug that reduces the severity or frequency of seizures in epilepsy
Atonic	A sudden fall or loss of posture, often called a "drop" or "drop attack"
Benign epilepsy	Epilepsy that resolves with time
Clonic	Rhythmic muscular contractions and relaxations
Convulsions (behavioral seizures)	Movements that accompany epileptic seizures
Complex partial seizure (psychomotor)	A focal seizure that is accompanied by a loss of awareness or responsiveness
Epilepsy (seizure disorder)	Recurrent spontaneous (unprovoked) seizures
Epileptic	A subject (person or animal) with epilepsy
Epileptic seizures	Seizures that are accompanied by hypersynchronous neuronal activity
Epileptogenesis	The process whereby the normal adult brain becomes epileptic
Focal (localized, partial)	A seizure that occurs in one area of the brain
Generalized (diffuse, distributed)	A seizure that involves multiple brain areas in both hemispheres
High-frequency oscillations	Rhythmic potentials that are between 100 and 500 Hz; sometimes called ripples (usually ripples refer to oscillations <200 Hz) or fast ripples (typically >200 Hz)
Ictal	The period during which a seizure occurs
Interictal	The period between seizures
Interictal spikes	A transient voltage deflection on the EEG that occurs between seizures
Myoclonic	Involuntary twitching of a small subset of muscles
Non-epileptic (pseudo-, psychogenic) seizures	Behavior that is similar to epileptic seizures but the EEG is normal
Paroxysmal depolarization shift	A sudden, large depolarization of a neuron, usually with action potentials at the peak of the depolarization, and typically lasting <500 ms
Preictal	The period immediately before a seizure
Ripples or fast ripples	*See* high-frequency oscillations
Secondarily generalized	A partial seizure that changes to one that involves both hemispheres
Seizure	Hypersynchronous neural activity with an EEG pattern that is abnormal, typically lasting >10 s, except for absence seizures (which can be brief)
Simple partial seizure	A seizure that occurs primarily in one brain region, and awareness is unaffected
Spike-and-wave (spike–wave)	A rhythmic EEG pattern that is typically 3 Hz in humans, and >6 Hz in lower mammals, with a short voltage deflection (spike) and slow component (wave)
Tonic	Stiffness or rigidity reflecting persistent activity of extensor muscles
Tonic–clonic seizure (grand mal)	A seizure that is accompanied by tonic–clonic movements and both hemispheres in the EEG

A table is provided of terms used in the text with their synonyms in parentheses and definitions on the right. Abbreviations: *EEG*, electroencephalogram.

underdeveloped countries.[16] Epilepsy also disproportionally affects socioeconomically deprived populations in the United States, making epilepsy a significant public health problem.[17] Age is also a factor, with epilepsy mainly occurring in childhood or the elderly.[18–20]

The prevalence, or total number of individuals who have epilepsy out of the total number of individuals who were studied, is 5–10 per 1000. The lifetime prevalence, or fraction of individuals who at some point in their life will have epilepsy, has been estimated to be 3% in the United States.[21]

Mortality and sudden unexpected death in epilepsy

Although epilepsy is defined by seizures, mortality is a common outcome and often underappreciated.[9] The risk of premature death is 11 times more likely in people with epilepsy compared

with people that do not have epilepsy.[22] Many epilepsy-related deaths occur suddenly and unexpectedly, a phenomenon termed Sudden Unexpected Death in Epilepsy (SUDEP). It is estimated that one of every 10,000 new diagnoses of epilepsy will lead to SUDEP. The number is higher for patients who are refractory to medication and are eligible for surgery. Approximately nine of every 1000 of these patients have SUDEP.[9]

Cost burden

Not surprisingly, epilepsy is a disease associated with huge economic costs. There is not only a financial burden on patients, who typically face a lifetime coping with their illness, but a reduced quality of life, which is hard to define in dollars. There is also a cost to families, who may need to care for the patient and support them if the individual with epilepsy cannot drive or work. Furthermore, there is a cost to society related to lost productivity in the workforce. The annual direct medical care cost of epilepsy in the United States is more than $9.6 billion.[16] The total direct and indirect costs, i.e., medical care costs plus lost earnings and productivity, are approximately $15.5 billion.[23]

Classification of the seizures and the epilepsies

Seizures versus epilepsy

Defining epilepsy is difficult because it is not a single disorder but many, reflected by the term, "the epilepsies." Historically, characteristics of seizures have been used to define the type of epilepsy, with terms such as "petit mal" referring to staring spells or literally "absences," which led to the term "absence epilepsy" for patients with this type of seizure (Fig. 41.1A). In contrast to petit mal, "grand mal" refers to major movements of the limbs associated with repetitive contraction and relaxation. Both petit mal and grand mal seizures involve many sites in both hemispheres, i.e., the seizures are "generalized" in contrast to the term "focal," which refers to seizures that are confined to one portion of the brain (Table 41.2). In grand mal seizures, the rhythmic contractions and relaxations of the muscles are called tonic–clonic seizures or "generalized tonic-clonic seizures" (GTCS). A generalized tonic seizure is shown in Fig. 41.1B. Consciousness (often called "responsiveness" or "awareness") is lost in both absence seizures and GTCS, but the outcome to an observer is vastly different. In absence epilepsy, one cannot be sure that an individual is having a seizure without EEG because the individual usually sits quietly, staring into space. GTCS, which is the type of seizure most people associate with epilepsy, involves major movements of the limbs. Therefore, before the advent of the EEG in the first part of the 20th century, many individuals with absence epilepsy were probably undiagnosed. With EEG, categorization and diagnosis of the epilepsies became much more advanced (Tables 41.3 and 41.4). Grand mal and petit mal were common terms to describe seizures until International League Against Epilepsy (ILAE) released a new classification of seizure types and terminology in 2017,[8] Seizures are generally divided into two categories: focal (previously called partial seizures) versus generalized (also called diffuse or distributed and previously called primary generalized; Table 41.2). Focal seizures begin in one brain region, whereas generalized seizures occur in many brain areas in both hemispheres at the same time. However, some seizures start focally and then become generalized, called secondary generalization.

Seizures are also described based on a person's awareness during the seizure. It is crucial to understand a person's level of awareness during a seizure because this is one of the main factors that can affect a person's safety.

Motor symptoms can also assist in seizure classification. Focal motor seizures can involve twitching, jerking, or stiffening of a body part, whereas focal nonmotor seizures can involve symptoms prior to seizure onset (known as "auras") including changes in sensation, emotion, or experiences.

The EEG activity during seizures is extremely different, but within a given epilepsy syndrome it is similar. Therefore, the EEG activity plays a critical role in defining the type of epilepsy of any given patient. Fig. 41.1 makes this point by showing an example of a seizure from an individual with absence epilepsy beside an example of a seizure from a person with another type of epilepsy that had a tonic seizure. The absence seizure is distinguished by a very specific EEG pattern composed of a transient (spike) followed by a slow wave or "spike-and-wave" (Fig. 41.1A). There is an abrupt onset, at which time responsiveness is lost, and an abrupt termination, when awareness resumes. The spikes and slow waves occur repetitively at 3 Hz (Fig. 41.1A). The tonic seizure shown in Fig. 41.1B is very different: it does not begin simultaneously in all areas of the brain, but eventually all brain areas are generating fast rhythmic activity. A spike-and-wave cycle never occurs.

Until very recently, epilepsy was divided into three major categories and often still is: idiopathic, symptomatic and cryptogenic. Provoked or reflex epilepsies are a minor, fourth category (Table 41.3). Focal or generalized seizures are subdivisions within each of the three major categories (Table 41.3). "Idiopathic" is a term that refers to an epilepsy syndrome with an unknown cause, but presumably a genetic basis, with the gene (s) not yet identified. "Symptomatic" epilepsies, in contrast, are related to a known structural cause, such as a cortical malformation or a head injury. "Cryptogenic" is a term that reflected a cause that was unclear. In 2010, the ILAE, the largest international group that is dedicated to epilepsy, proposed a new set of guidelines for the definitions of seizure types and the epilepsies[24] (Tables 41.2 and 41.3). Regarding seizures, it was suggested that words such as "partial" seizure be deemphasized in favor of "focal." With respect to the classification of the epilepsies, it was suggested that the term "idiopathic" be replaced by "genetic," and instead of "symptomatic," the term "structural/metabolic" be adopted. "Unknown" was offered as a replacement for "cryptogenic," to be more direct and transparent with terms. Although these guidelines are not completely settled,[24] new ways to classify the epilepsies have already been suggested that take into account the new guidelines. One proposal is shown in Table 41.3.[25] In this classification, some of the older terms are still used, but there is a new emphasis that is consistent with the proposed guidelines. The ILAE guidelines also suggested a classification where epilepsies are divided into constellations of

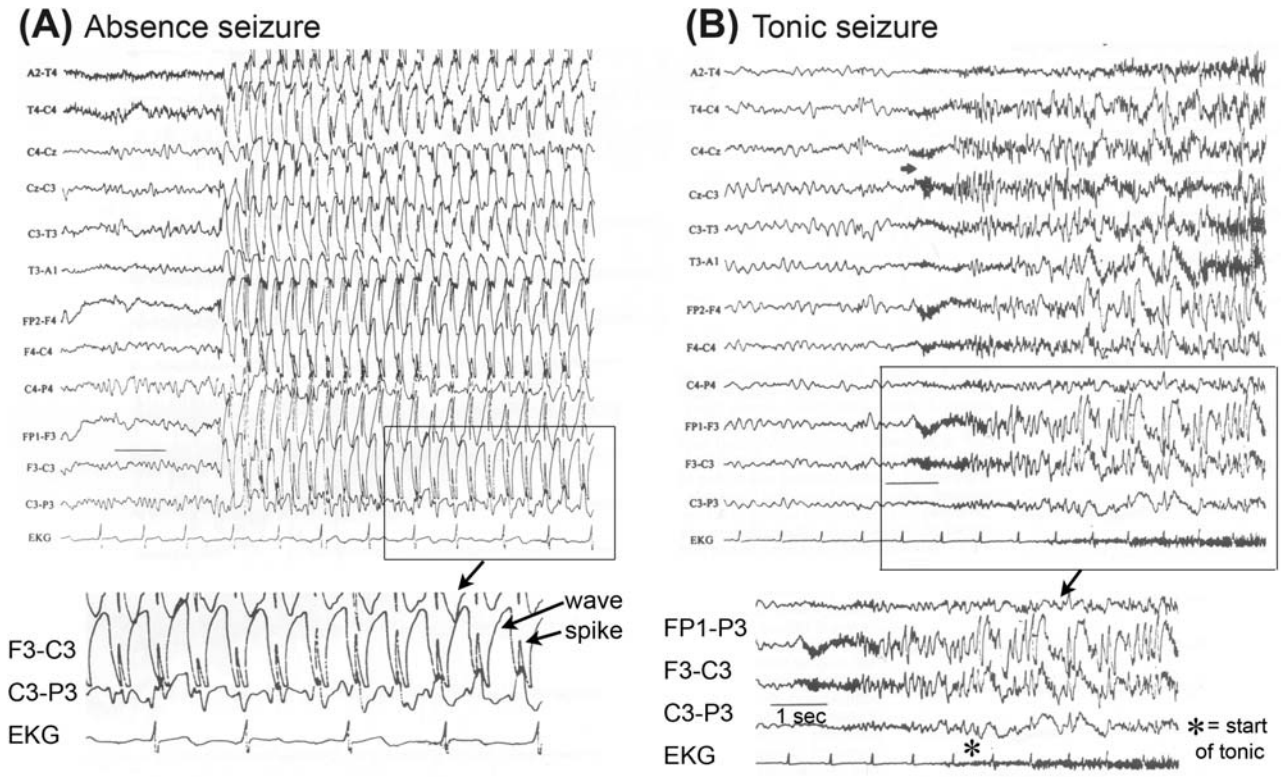

FIGURE 41.1 The use of EEG to distinguish types of epilepsy. A. An example of a seizure in absence epilepsy is shown. There is a repetitive spike-and-wave pattern approximately three spike-wave cycles per second. At the bottom, the area of the EEG that is boxed is enlarged. B. An example of a tonic seizure in a patient with a different kind of epilepsy than absence epilepsy. The EEG illustrates many differences from the absence seizure, such as the lack of a 3 Hz spike-wave pattern, and rhythmic activity that is faster than 3 Hz. At the bottom, the EKG is shown to illustrate that during the onset of the tonic seizure, muscular activity began. *Adapted from Ryvlin P. Avoid falling into the depths of the insular trap.* Epileptic Disord. *2006;8(Suppl 2):S37–S56.*[202]

symptoms called "electroclinical syndromes."[24] An electroclinical syndrome is defined as "a complex of clinical features, signs and symptoms that together define a distinctive, recognizable clinical disorder."[24] Divisions into constellations have been suggested before, as shown in Fig. 41.2. In this figure, the age of onset, severity, and focal versus generalized seizure types are distinguished in a way that establishes roughly four "constellations."

What the current classifications of the epilepsies do not specify is the relative proportions of the different types of epilepsies and how many of the epilepsies are treatable or—regrettably—still lack a therapeutic approach that stops seizures. The most common epilepsy syndrome is temporal lobe epilepsy. These individuals have focal seizures that start in the temporal lobe and are accompanied by a loss of awareness; secondarily generalized seizures can occur. There are characteristics that suggest a "symptomatic" categorization is best for this type of epilepsy, because there is usually a loss of neurons in a particular pattern in hippocampus, originally called Ammon's horn or hippocampal sclerosis.[26] After it was shown that more areas than hippocampus were typically damaged, a term with a broader scope was invoked: mesial temporal sclerosis (MTS;[26]). The damage is highly variable, however, and some patients even lack an identifiable lesion; in these individuals, the cause may be genetic.[27–29] Therefore, there may be types of temporal lobe epilepsy that are genetic, and types that are structural/metabolic and are associated with MTS. Many of these individuals are successfully treated by antiseizure drugs, but approximately 20%–30% continue to have seizures. Individuals who have seizures that are not controlled by ASDs are called "drug-resistant" or "refractory," and are a major clinical concern.[30]

Comorbidities

Seizures are the major symptom in epilepsy but not the only symptom. The additional symptoms may be dysfunction associated with interruption of normal activity in the part of the brain where seizures occur. For example, in temporal lobe epilepsy, memory loss can occur because the temporal lobe is critical to memory. Although the seizures could be causally related to these "comorbidities," it is often hard to prove cause and effect. In some cases, the seizures do seem causally related to the comorbid condition, such as instances of malnutrition. In these cases, the comorbidity (malnutrition) may be the cause of the seizures. Symptoms in patients on medications are especially hard to interpret because of interactions between seizures, medications, and the comorbidity. For example, some medications increase appetite, which may contribute to a comorbid condition—obesity. According to the 2013 IOM report,[9] a comorbidity is defined as "the co-occurrence of two supposedly separate conditions at above

TABLE 41.2 Classification of seizures.

Before 2010[a]	After 2010[b]
I. Focal (partial)	**I. Focal**
Simple partial	With or without aura
Complex partial	With or without awareness
Secondary generalized	With or without motor/autonomic manifestations With or without evolution to both hemispheres
II. Generalized	**II. Generalized**
Absence	Absence
Myoclonic	– Typical
Clonic	– Atypical
Tonic	– Absence with special features (myoclonic, eyelid myoclonia)
Tonic–clonic	Myoclonic
Atonic	– Myoclonic – Myoclonic atonic – Myoclonic tonic Tonic Tonic–clonic Atonic **III. Unknown or unclear** Epileptic spasms

Two classifications of seizures are shown. On the left is the standard classification, and on the right is the classification that was suggested by the International League Against Epilepsy (ILAE) in 2010.
[a]*Standard classification.*
[b]*Classification suggested by the International League Against Epilepsy (ILAE) in 2010.*[24]

TABLE 41.3 Classification of the epilepsies.

(a) Before 2010[a]		After 2010[b]
Idiopathic	→	Genetic
Symptomatic	→	Structural/metabolic
Cryptogenic	→	Unknown
(b) Engel (2001)[c]		**Shorvon (2011)[d]**
I. Localization-related		**I. Idiopathic/genetic**
A. Idiopathic		A. Pure epilepsies due to single gene disorders
B. Symptomatic		B. Pure epilepsies with complex inheritance
C. Cryptogenic		
II. Generalized		**II. Symptomatic/structural–metabolic**
A. Idiopathic		A. Predominantly genetic or developmental
B. Symptomatic or cryptogenic		B. Predominantly acquired
C. Symptomatic		
III. Undetermined whether focal or generalized		**III. Cryptogenic/unknown cause**
A. Both		
B. Equivocal		
IV. Special syndromes		**IV. Provoked**
Situation-related		A. Provoking factors B. Reflex epilepsies

Top: The major categories used to classify the epilepsies are shown. On the left are the standard categories used prior to 2010, and the 2010 guidelines from the ILAE are shown on the right.
Bottom: A detailed classification is shown for the standard categories and subcategories and a recent view that takes into account 2010 suggestions from the ILAE.
[a]*Standard categories used before 2010.*
[b]*2010 guidelines from the International League Against Epilepsy (ILAE).*
[c]*Detailed classification of standard categories and subcategories.*[173]
[d]*A recent view that takes into account 2010 suggestions from the ILAE.*[25]
From Engel J, Jr. Classification of epileptic disorders. *Epilepsia* 2001;42:316.[201]
From Shorvon SD. The etiologic classification of epilepsy. *Epilepsia* 2011;52:1052–1057.[25]

chance levels" and are distinguished into categories (Table 41.5). Guidelines proposed by the ILAE and American Epilepsy Society[31] suggest the following four types of comorbidities:

1. Essential comorbidity: When two conditions share an underlying causal factor. For example, a cortical malformation may impair development and also cause seizures.
2. Secondary comorbidity: When one condition directly contributes to mechanisms involved in producing another condition. For example, temporal lobe seizures may lead to functional impairments related to the temporal lobe, such as memory impairment.
3. "Iatrogenic" comorbidity: When the treatment of epilepsy leads to or exacerbates another condition. An example would be side effects of an antiseizure drug, such as sedation.
4. "Situational or contextual" comorbidity: This refers to social–environmental factors which, as a consequence of epilepsy, may lead to a comorbid condition. An example would be the loss of the ability to drive in individuals with epilepsy, which could lead to social isolation and possibly depression.

Mechanisms underlying seizures

Understanding seizures by their EEG correlates

The interictal spike and ictal events

Prior to the 1960s, mechanisms underlying seizures were poorly defined. Various hypotheses for epilepsy had been proposed, but until the foundations of modern neurophysiology were in place, most hypotheses were vague. Two methodological advances made a great difference: (1) the ability to record from single neurons to clarify the neurophysiological correlates of EEG seizures, and (2) the first methods for experimental induction of seizures in laboratory animals. Using topical application of penicillin to the cortical surface, Ayala and colleagues made some of the first intracellular recordings of cortical neurons during a seizure (Fig. 41.3). They recorded activity of cortical neurons during "interictal spikes" as well as the "ictal period." Interictal spikes are large transient voltage deflections, ~50–100 msec long, which occur rhythmically in the period of time between seizures; the seizure itself is the "ictus" or ictal period (Figs. 41.3 and 41.4). Ayala and colleagues learned that during the interictal spike, there was a sudden (paroxysmal) large depolarization shift (paroxysmal depolarization shift; PDS) in cortical principal cells. The depolarization triggered a

TABLE 41.4 Classification of the epilepsies—expanded

Engel (2001)	Shorvon (2011)
I. Localization-related	**I. Idiopathic/genetic**
A. Idiopathic Benign childhood epilepsy with centrotemporal spikes Childhood epilepsy with occipital paroxysms Primary reading epilepsy	A. Pure epilepsies due to single gene disorders Benign neonatal febrile convulsions Severe myoclonic epilepsy in infancy Autosomal dominant frontal lobe epilepsy
B. Symptomatic Temporal lobe epilepsy, frontal lobe epilepsy, parietal lobe epilepsy, occipital lobe epilepsy	B. Pure epilepsies with complex inheritance Idiopathic generalized epilepsy
C. Cryptogenic	
II. Generalized	**II. Symptomatic/structural—metabolic**
A. Idiopathic Benign neonatal febrile convulsions Benign myoclonic epilepsy in infancy Juvenile absence epilepsy Juvenile myoclonic epilepsy Epilepsy with generalized tonic–clonic seizures or myoclonic absences	A. Predominantly genetic or developmental Childhood epilepsy syndromes (West syndrome, Lennox–Gastaut syndrome) Progressive myoclonic (Unverricht–Lundborg disease, Lafora) Neurocutaneous (tuberous sclerosis, Sturge–Weber syndrome) Other neurological single-gene disorders (Angelman syndrome, Rett syndrome) Disorders of chromosome function (Down syndrome, fragile X syndrome)
B. Symptomatic or cryptogenic West syndrome Lennox–Gastaut syndrome Epilepsy with myoclonic–astatic seizures or myoclonic absences	Developmental anomalies of cerebral development (focal cortical dysplasia)
	B. Predominantly acquired Mesial temporal lobe sclerosis (acquired temporal lobe epilepsy) Perinatal or infantile causes (neonatal seizures, cerebral palsy)
C. Symptomatic	Cerebral trauma (head injury)
Nonspecific etiology (early myoclonic encephalopathy with suppression burst)	Cerebral infection (meningitis, encephalitis)
Engel (2001)	**Shorvon (2011)**
Specific syndromes	Cerebral immunological disorders
	Degenerative or other neurological conditions (Alzheimer disease)

Continued

TABLE 41.4 Classification of the epilepsies—expanded—cont'd

Engel (2001)	Shorvon (2011)
III. Undetermined whether focal or generalized	**III. Cryptogenic**
A. Both Neonatal Severe myoclonic epilepsy in infancy Epilepsy with continuous spike–waves during slow-wave sleep Landau–Kleffner syndrome B. Equivocal	
IV. Special syndromes (situation-related)	**IV. Provoked/unknown cause**
Febrile convulsions	A. Provoking factors Fever, sleep–wake cycle B. Reflex epilepsies Photostimulation, auditory
Isolated status epilepticus	

Table 41.3 is presented in more detail, with examples of epilepsy syndromes provided for each subcategory. Note that all epilepsy syndromes are not listed.

high-frequency burst of action potentials on its peak, and then action potentials decayed, with resting potential ultimately restored (Fig. 41.3). During ictal periods, a PDS initially occurred, and the depolarization was greatly prolonged (Fig. 41.3). These observations led to the view that the PDS was central to seizure generation. It was hypothesized that neurons that exhibited the PDS either were altered intrinsically, i.e., cortical principal cells became "epileptic neurons" or the interactions between cortical neurons were altered, creating an "epileptic aggregate."[32–36] Ultimately, it was suggested that the PDS was caused by a "giant" synaptic potential. This giant synaptic potential was larger than a normal synaptic potential, but due to similar underlying mechanisms, i.e., glutamate release from afferent fibers, acting at ionotropic glutamate receptors (AMPA/Kainate and NMDA receptors[37]). Like normal glutamatergic transmission, the initial depolarization of the PDS was mediated by AMPA receptors, and the slower component of the depolarization was attributed to NMDA receptors.[38] However, it should be noted that the idea of "epileptic neurons" continues to be raised.[39]

The research that followed the initial studies of the PDS pursued the mechanisms underlying seizures in more detail, using recordings from both cortical or hippocampal principal cells and the GABAergic interneurons located nearby, which are primarily responsible for synaptic inhibition of the principal cells. A major question was the neurobiological basis of the transition from the interictal to ictal state—the transition to seizure. From the recordings, three states were described: (1) the interictal period, (2) the preictal period, which is the period immediately before the onset of a seizure, (3) and the ictal period (Figs. 41.3 and 41.4). What has changed over the last decades is the idea that there is a silent preictal period (compare Figs. 41.3 and 41.4). The view of the silent period changed after recordings from GABAergic

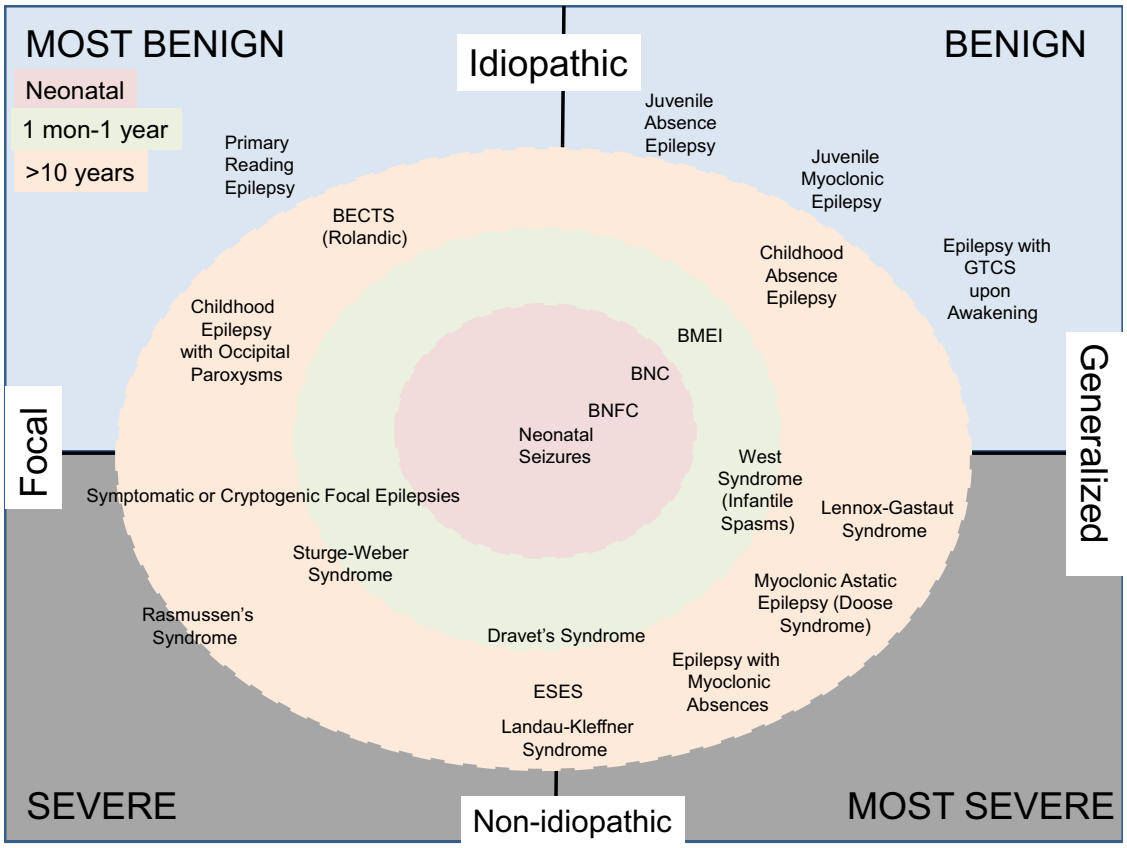

FIGURE 41.2 The epilepsy solar system. A perspective on epilepsy classification is shown. This depiction of four quadrants, each including several epilepsy syndromes that are similar (e.g., upper right: idiopathic and generalized) is similar to the idea of the ILAE[24] that the epilepsies should be considered as constellations of syndromes with common characteristics. Typical age of onset is denoted by the concentric circles, with neonatal onset near the center and older ages further from the center. Abbreviations: SMEI, severe myoclonic epilepsy in infancy; BMEI; benign myoclonic epilepsy in infancy; BNC, benign neonatal convulsions; BFNC, benign familial neonatal convulsions; EIEE, early infantile epileptic encephalopathy; EME, early myoclonic epilepsy; ESES, electrical status epilepticus in sleep; BECTS, benign epilepsy with centrotemporal spikes. *Adapted from Tich SN, Pereon Y. Semiological seizure classification.* Epilepsia *1999;40:531.*[203]

neurons showed that during the preictal period there is an increase in GABAergic neuron firing causing $GABA_A$ receptor-mediated inhibition of principal cells. There also is a gradual increase in excitation of principal cells by glutamatergic inputs (Fig. 41.4;[40,41]). Therefore, there is no silent period necessarily. Another important event during the preictal period is a gradual increase in the extracellular concentration of potassium ($[K^+]_o$). The increase in $[K^+]_o$, and possibly other factors, leads to a shift in chloride flux through $GABA_A$ receptors, which normally is inward, and normally causes hyperpolarization of the cell. Increased $[K^+]_o$ affects $K^+ Cl^-$ cotransporters (e.g., KCC2;[42]) so that chloride flux is outward instead of inward, and a depolarization occurs in principal cells in response to GABA.[43] In addition, there may be a gradual failure of GABA release during the preictal period because of persistent GABAergic neuron firing, causing depolarization block.[44] However, postsynaptic $GABA_A$ receptors do not appear to change.[40,41]

The depolarizing effects of GABA, reduced GABA release, and persistent glutamatergic activity[40,41] herald the onset of the seizure. Elevated $[K^+]_o$ could also play a role by depolarizing principal neurons, which can change their firing behavior from a tonic to a bursting mode.[45] A bursting mode would be consistent with the type of firing at the onset of the seizure. As the onset of the ictal period begins, the failure of local GABAergic inhibition and presence of recurrent collaterals between principal cells could be sufficient to cause hypersynchrony[46] and potentially explain how seizures spread from one brain area to adjacent regions.[47–49] Other mechanisms may be important also, such as dendritic potentials in principal cells, related to GABAergic innervation of dendrites or dendritic ion channels governing backpropagation of action potentials.[50]

Seizure termination

One of the fundamental aspects of epilepsy is that most patients have seizures only a small fraction of the time. Also, when seizures occur, they last only a brief time (seconds–minutes), because there are inherent mechanisms for seizures to "self-terminate," meaning they stop on their own. These observations suggest that there are inherent mechanisms that are extremely effective in stopping a seizure. Therefore, many investigators have attempted to understand the endogenous mechanisms that stop seizures, because it may lead to new drugs to treat epilepsy. However, understanding the termination of seizures has been difficult. Although our understanding of potential mechanisms for seizure termination is extensive, the endogenous mechanisms that stop an ictal event, and ways to enhance them, are still

TABLE 41.5 Comorbidities.

Somatic	Neurological	Psychiatric	Intellectual/Cognitive	Infectious/Immune	Nutritional/Dietary
Anemia	Cerebral palsy	ADHD	Down syndrome	Encephalitis	Malnutrition
Asthma	Chronic pain	Alzheimer disease	Fragile X syndrome	Glioma	Obesity
Diabetes	Migraine	Autism	Intellectual disability (MR)	Meningitis	
Fibromyalgia	Stroke	Depression	Memory loss	Neurocysticercosis	
Gastrointestinal	Rett syndrome	Schizophrenia			
	Hearing loss	Substance abuse			
	Vision loss Sleep disorders	Suicidality			

The types of comorbidities that are found in epilepsy are shown. Abbreviations: *ADHD,* attention deficit hyperactivity disorder; *MR,* mental retardation.

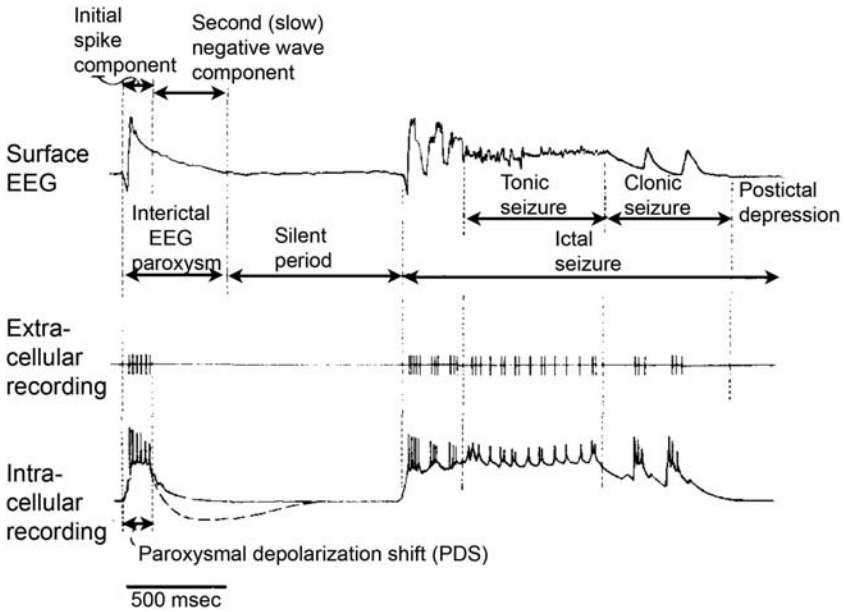

FIGURE 41.3 The cellular correlates of interictal spikes and seizures. A recording of the EEG from the surface of the brain (top), near cortical neurons (center, extracellular recording), and inside a cortical neuron (bottom, intracellular recording). Recordings were made from a cat where the convulsant penicillin had been applied to the cortical surface to create an area where spontaneous seizures occurred periodically. During a spike that occurred between seizures (an interictal spike), cortical neurons fired action potentials on a large, sudden depolarization called a paroxysmal depolarization shift (PDS). During the seizure (the ictal event), a prolonged depolarization with action potentials occurred. Together these recordings explained the activity of cortical neurons during spikes and seizures that were recorded at the cortical surface. *Adapted from Ayala GF, Dichter M, Gumnit RJ, Matsumoto H, Spencer WA. Genesis of epileptic interictal spikes. New knowledge of cortical feedback systems suggests a neurophysiological explanation of brief paroxysms.* Brain Res. *1973;52:1–17.*[204]

debated. Below are four different mechanisms that are considered to contribute to seizure termination.

a. Action potential repolarization and voltage-dependent K^+ channels. Mechanisms that repolarize neurons after action potential generation are a logical place to look for mechanisms that stop seizures. The vast majority of repolarization after action potentials is attributed to voltage-gated K^+ channels.[51] The A-type K^+ channel and delayed rectifier-type of K^+ channels are primarily responsible for repolarization after a single action potential. During a persistent depolarizing input, M-type K^+ channels also contribute by slowing action potential firing frequency, which is called "spike frequency adaptation." Interesting, the "M current" appears to decrease its expression in some of the neurons that have been studied in animal models of epilepsy, and the antiseizure drug retigabine exerts its effect by opening these channels.[52] K^+ currents that are regulated by Ca^{2+} (Ca^{2+}- dependent K^+ currents) are also important in regulating the hyperpolarizations that follow action potentials (after-hyperpolarizations;[53]).

b. The Na^+-K^+ pump and other mechanisms that regulate $[K^+]_o$. After prolonged depolarizations, such as those that occur during ictal discharges, extracellular K^+ rises, and the Na^+/K^+ pump is a primary mechanism for restoring $[K^+]_o$. Cellular energy depletion inhibits the pump because it

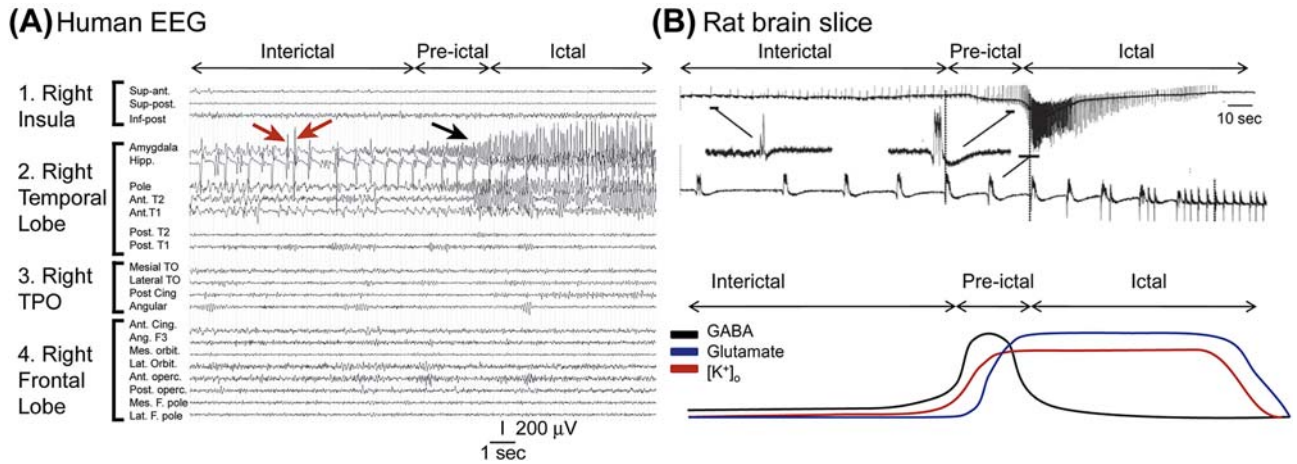

FIGURE 41.4 Mechanisms underlying the transition from normal brain activity to seizures. A. An example of a focal seizure that started in the temporal lobe. The black arrow points to the start of the seizure, called the ictal period. The red arrows point to interictal spikes, which change frequency before the seizure begins, during the preictal period. B. Top: An example of a seizure-like event in a slice of hippocampus of a rat, exposed to the convulsant 4-aminopyridine. Parts of the seizure (designated by the horizontal bars) are expanded below. Bottom: A schematic illustrates the changes in the activity of GABAergic neurons (black), glutamatergic principal cells (blue), and the concentration of extracellular K^+ ($[K^+]_o$; red) during the transition between interictal, preictal, and ictal periods. During the preictal period, GABAergic neurons increase their firing rate. $[K^+]_o$ rises and glutamatergic neurons become depolarized. Glutamatergic neurons increase their activity as GABAergic inhibition becomes depolarizing instead of hyperpolarizing, and GABA release fails (either because of GABA depletion, depolarization block, or other mechanisms). At this point the seizure begins. At the end of the seizure, mechanisms that normally control excitability of glutamatergic and GABAergic neurons are restored, such as the normal $[K^+]_o$ by the Na + -K + -ATPase. *(A) Adapted from Sperling MR, Clancy RR. Ictal EEG. In: Engel J, Pedley TA, ed. E*pilepsy: A Comprehensive Textbook. *Philadelphia: Lippincott-Raven; 1997:849–885.*[205] *(B) Adapted from Zhang ZJ, Valiante TA, Carlen PL. Transition to seizure: from "macro"- to "micro"-mysteries.* Epilepsy Res. *2011;97:290–299;*[40] *Zhang ZJ, Koifman J, Shin DS, et al. 2012. Transition to seizure: ictal discharge is preceded by exhausted presynaptic GABA release in the hippocampal CA3 region.* J Neurosci. *2012;32:2499–2512.*[41]

depends on ATP. Inhibitors of the Na^+-K^+ pump, such as ouabain, promote seizure activity in hippocampal slices, particularly at young ages.[54,55] The susceptibility of young ages suggested that a vulnerability of the Na^+-K^+ pump may be one of the reasons that children are susceptible to seizures.[54,55] Astrocytes are a major regulator of $[K^+]_o$ also, which is discussed further below.

c. GABAergic inhibition. If release of GABA becomes impaired during the onset of a seizure, restoring GABA by either enhanced GABA reuptake into the GABAergic nerve terminal or increasing GABA synthesis could help restore GABAergic function. In addition, the mechanisms that control the preferred direction of chloride flux through $GABA_A$ receptors are important. Carbonic anhydrase plays an important role, as the enzyme that catalyzes the hydration of CO_2. There are five families of carbonic anhydrases (α–ε) with the α family primarily responsible for mammalian forms. Of the >15 types of α carbonic anhydrases, many are expressed in the brain and implicated in seizures. Inhibition of carbonic anhydrase in brain slices or deletion in transgenic mice has proconvulsant effects, which are likely to be mediated by acidification of the extracellular milieu, which can facilitate actions of glutamate at NMDA receptors.[56] In addition, water balance is disrupted by carbonic anhydrase inhibition, which is potentially important because neuronal swelling increases excitability.[57] However, carbonic anhydrase may also be an indirect regulator of KCC2 because of its effects on the concentration of HCO_3^-, which influences the direction of chloride flux through $GABA_A$ receptors.[42,43] The restoration of the normal direction for chloride flux through $GABA_A$ receptors, into the cell, has been suggested to be responsible for termination of seizures.[58] For this reason, carbonic anhydrase inhibition is one potentially important mechanism of action of several antiseizure drugs, acetazolamide being the most well-known (see Treatment of epilepsy, below).

d. Brain "gates." There are several sites in the brain where seizure activity is normally difficult to induce, and it has been proposed that these areas act as barriers or "gates" to seizure propagation. The gates can stop a seizure from developing, truncate seizures if they have begun, or preventing them from reaching parts of the brain that control movement. As a result, seizures do not trigger convulsive behaviors.
The locations where these gates are located are diverse—they include the substantia nigra, subthalamic nucleus, superior colliculus, reticular activating system, thalamus,[59] and dentate gyrus.[60] What causes the gating behavior is not clear, but in the case of the reticular activating system, it is suggested that the widespread innervation of cortical areas is the reason for its robust effects on seizures. In the dentate gyrus, it has been proposed that there are several inherent mechanisms in principal cells of the region, the granule cells, which make the dentate gyrus operate like a gate to seizures. These include intrinsic properties of granule cells such as a very hyperpolarized resting potential and strong spike frequency adaptation, as well as robust GABAergic inhibition of granule cells.[61,62] Because the granule cells are situated in the circuitry between cortex and area CA3 of hippocampus, if the granule cells do not discharge action potentials, area CA3 will not either, stopping cortical seizure activity from affecting area CA3.[60]

e. Neuromodulators. The brain synthesizes many potent anticonvulsant molecules, often packaged in dense core vesicles in GABAergic neurons, preferentially released during high-

frequency activity (the type of activity that would occur during a seizure). One example is neuropeptide Y (NPY), which acts on five types of NPY receptors, located pre- and postsynaptically.[63] Actions at Y2 and Y5 receptors inhibit glutamate release from hippocampal pathways involved in seizure propagation, and infusion or overexpression of NPY leads to a reduced susceptibility or fewer seizures.[63,64] Interestingly, NPY synthesis normally occurs in a subset of GABAergic neurons, and increases after seizures in both the GABAergic neurons that normally synthesize NPY and other cells that normally do not produce NPY.[65] Therefore, it has been proposed that upregulation of NPY is an endogenous anticonvulsant response of the CNS to seizures.[66] As a result, gene therapy to increase synthesis of NPY has been proposed as a therapeutic strategy for epilepsy.[67] Other endogenous molecules that have anticonvulsant effects include somatostatin,[68] adenosine,[69] and endocannabinoids.[70]

The brain also produces neuromodulators that have excitatory effects and promote neuronal outgrowth. In the context of the normal brain, these neuromodulators may be beneficial by supporting neuronal activity and plasticity. In the context of epilepsy, blocking their receptors may be therapeutic. One example is the neurotrophin brain-derived neurotrophic factor (BDNF), which acts at TrkB receptors to support synaptic plasticity (long-term potentiation) and structural plasticity (increased dendritic spine density, axon sprouting;[71,72]). BDNF infusion into the hippocampus of an adult rat induces seizures,[73] suggesting that blockade of TrkB could be therapeutic in epilepsy.[74]

3 Hz spike-and-wave rhythms

The EEG of an individual with absence epilepsy distinguishes it from virtually all other types of epilepsy, as described above. What causes this rhythm has been of great interest because of the potential that understanding the cause can lead to better treatment. Experiments in animals first established that the 3 Hz spike-and-wave rhythm was produced by oscillations in thalamocortical circuitry, where cortical principal cells excite thalamic GABAergic neurons in the reticular nucleus of the thalamus, which inhibit the thalamic relay cells that project back to cortex (Fig. 41.5). Neurophysiological recordings from the primary cell types in the thalamocortical circuit established that the 3 Hz rhythm is caused by action potentials of the corticothalamic and thalamocortical neurons during the "spike" of the spike-and-wave discharge; the "wave" is associated with a hyperpolarization of the neurons (Fig. 41.5). A critical first step in producing the spike-and-wave rhythm appears to be increased cortical excitability (Fig. 41.5;[75,76]). The increased activity of cortical neurons causes the GABAergic neurons of the reticular nucleus to fire more intensely, releasing more GABA onto thalamic relay cells (Fig. 41.5). The increase in GABA release activates not only $GABA_A$ receptors but also $GABA_B$ receptors, which leads to a longer period of inhibition of the thalamic relay cells (Fig. 41.4). As inhibition wanes, the unique ion channels of the relay cell, including a T-type calcium channel, cause the relay cell to exhibit a "rebound" burst discharge. The T-type channel is normally inactivated at resting potential but deinactivates with

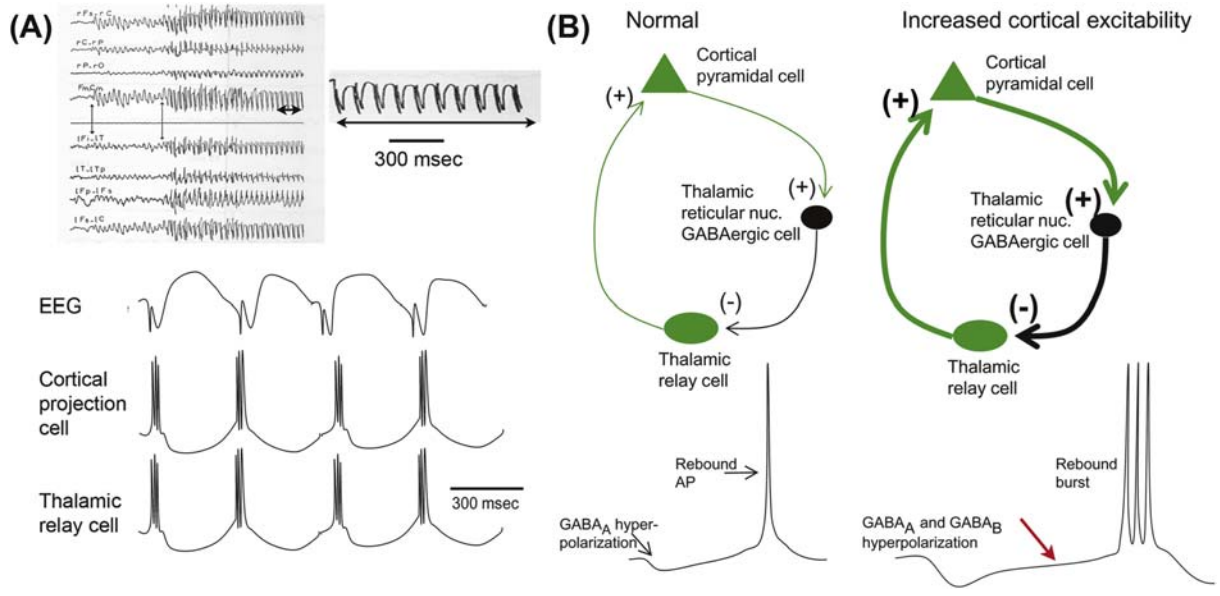

FIGURE 41.5 The neuronal correlates of 3 Hz spike-and-wave discharge. A. Top: An example of an absence seizure with 3 Hz spike-and-wave discharge is shown. The part of the recording indicated by the double-sided arrow is expanded on the right. Bottom: A schematic of the neuronal activity in corticothalamic principal cells and thalamocortical relay cells during a spike-and-wave discharge. During the "spike," there is neuronal discharge and during the "wave" are hyperpolarizations. B. A schematic of some of the circuitry involved in spike-and-wave discharge illustrates the corticothalamic neuron, typically a cortical pyramidal cell, innervates GABAergic neurons of the thalamic reticular nucleus, which innervate glutamatergic thalamic relay cells. The relay cells project back to cortex. When there is increased cortical excitability, the corticothalamic cell excites GABAergic neurons more, leading to greater release of GABA on thalamic relay cells. In contrast to the normal situation, where GABA release primarily activates $GABA_A$ receptors on the relay cells, there is activation of $GABA_A$ and $GABA_B$ receptors on the relay cell, causing a larger and more prolonged hyperpolarization in the relay cell (red arrows). When the hyperpolarization increases, there is a more effective deinactivation of T-type calcium channels of the relay cell. As a result, there is a greater T-type calcium current when the hyperpolarization decays, leading to enhanced firing of the relay cell. The relay cell then activates the corticothalamic cell, leading to a cycle of hyperpolarization and burst firing at approximately 3 Hz.[206,207] *(A) Top: Adapted from Gastaut H.* Epilepsy—the Electroclinical Correlates. *Oxford: Blackwell; 1954.*[208]

hyperpolarization; the consequence of activation is calcium entry into the relay cell, leading to a depolarization. Because of the particular combination of ion channels expressed by the relay cell, including T-type calcium channels and also hyperpolarization-activated cyclic nucleotide-gated cation channels (I_h), the relay cell oscillates at about 3 Hz. This rhythmic firing of relay cells entrains the cortical cells, so that the entire thalamocortical circuitry begins to oscillate at a 3 Hz spike-and-wave rhythm. For this reason, absence seizures are exacerbated by drugs that enhance GABAergic inhibition. In contrast, drugs that block the T-type calcium channel, such as ethosuximide, are highly effective.

High-frequency oscillations (HFOs)

The normal brain exhibits spontaneous EEG rhythms at many frequencies, from relative slow oscillations (<1 Hz) to higher frequencies (>100 Hz). In normal adults, these rhythms are well characterized, including the well-known alpha, beta, and delta rhythms. In the last decades, the mechanisms underlying faster oscillations have been characterized, such as the cellular mechanisms for gamma oscillations (30−120 Hz). Synchronous discharges of GABAergic interneurons appear to be responsible for gamma oscillations, because they synchronously hyperpolarize principal cells (Fig. 41.6A). During synchronous hyperpolarizations

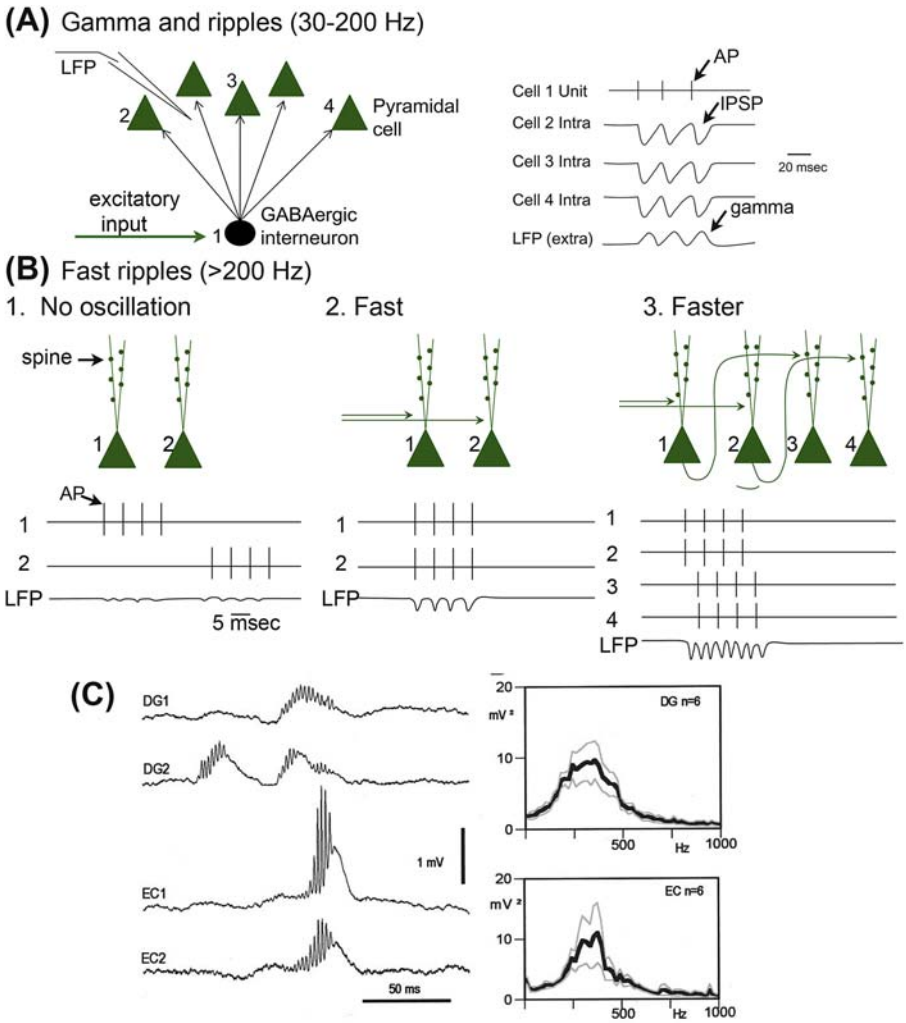

FIGURE 41.6 High-frequency oscillations and their underlying mechanisms. A. High-frequency oscillations refer to several types of oscillations, typically over 100 Hz. Gamma oscillations are between 30 and 100 Hz. Ripples typically refer to oscillations between 100 and 200 Hz. The underlying mechanisms are generally attributed to the effects of synchronized GABAergic neurons on principal cells, as shown. A shared glutamatergic input is one way that the GABAergic neurons are synchronized. Because GABAergic neurons innervate multiple principal cells, they can silence principal cell activity synchronously. The effects that are detected extracellularly (the local field potential; LFP) are shown on the right. When the GABAergic neurons fire (indicated by extracellular recordings of action potentials; AP), synchronized IPSPs occur in the principal cells (cells #2−4). As chloride ions enter $GABA_A$ receptors on the principal cells, positive waves occur in the LFP. B. Fast ripples are higher-frequency oscillations, typically 200−500 Hz, and are considered to be a hallmark of epileptic tissue. Mechanisms for high-frequency oscillations are typically nonsynaptic because synapses would slow the oscillation to a frequency <200 Hz. Instead, glutamatergic afferents that are divergent, innervating many principal cells may synchronize them (compare B1 to B2). The influx of Na+ during APs would be detected as negative oscillations (ripples) in the LFP, and the frequency of the ripples would reflect the frequency of synchronous firing of the principal cells. Faster frequencies could theoretically occur by a mechanism shown schematically in B3, where glutamatergic principal cells sprout onto principal cells nearby. C. A high-frequency oscillation is shown from a recording from the dentate gyrus (DG) and entorhinal cortex (EC) with power spectral analyses on the right, showing peak frequencies between 200 and 500 Hz. *(C) From Bragin A, Mody I, Wilson CL, Engel J, Jr. Local generation of fast ripples in epileptic brain.* J Neurosci. *2002;22:2012−2021.*[80] *Copyright [2002] Society for Neuroscience.*

of principal cells, extracellular recordings near the principal cell bodies show an oscillation at approximately gamma rhythm, corresponding to the repetitive inward flux of chloride during each GABAergic hyperpolarization (also called inhibitory postsynaptic potentials or currents; IPSPs or IPSCs; Fig. 41.6A). Higher-frequency "ripples" (100–200 Hz) also are considered to be a result of GABAergic mechanisms, but other mechanisms contribute, such as gap junctions.[77]

Extremely fast ripples are often called higher-frequency oscillations (HFOs; 200–500 Hz), and they have captured attention because they are recorded in patients with epilepsy as well as animal models of epilepsy,[78–82] but HFOs are normally rare. The literature is confusing because sometimes the term fast ripple is used and sometimes the term is HFOs. Regardless, oscillations >200 Hz are too fast to be explained by synaptic mechanisms. Using normal hippocampal slices exposed to elevated $[K^+]_o$, Dzaha and Staley[83] suggested that intrinsic mechanisms that allow the principal cells to fire at 200–500 Hz are responsible for the extremely fast oscillations (Fig. 41.6;[83,84]).

When action potentials from adjacent pyramidal cells are synchronous, a fast oscillation would be generated extracellularly at a frequency proportional to the interspike interval and reflect the repetitive inward Na^+ currents during the action potentials (Fig. 41.6). There are several potential reasons why such fast oscillations might be found preferentially in epileptic tissue, such as an increase in the number of recurrent excitatory connections between principal cells, a result of axon outgrowth or "sprouting" (Fig. 41.6; sprouting is discussed further below). In this case, the action potentials in the synchronized population of neurons could trigger action potentials in other neurons that are not innervated by the original glutamatergic afferents. Although the glutamatergic synapses may contribute, ultimately the fast oscillation would be due to intrinsic properties governing interspike interval. Synaptic and intrinsic mechanisms may also interact to produce very fast oscillations, such as variability in the onset of action potentials activated by glutamatergic inputs.[85]

A great deal of interest has been generated by the finding that the epileptic brain may be characterized by very fast oscillations (>200 Hz) that is rarely detected under normal conditions. One reason is that the fast oscillation can be a useful "biomarker" of the disease, which can be helpful in diagnosis and treatment. Another reason is that the mechanisms that underlie fast oscillations may provide targets for new antiseizure drugs. These ideas have led investigators to study various mechanisms related to HFOs, and it has been suggested that drugs that block gap junctions may be therapeutic because they would block HFOs.[86,87]

Understanding seizures by principles of neuronal excitability: the balance of excitation and inhibition

A common perspective on seizures is that they represent an imbalance between excitation and inhibition. This general idea is useful because it allows one to appreciate the diverse ways that the brain can produce seizures, leading to many ideas for new drugs to stop seizures. Table 41.6 provides a summary of the current methods to induce seizures in laboratory animals, and Table 41.7 lists the tests that are commonly used to assess efficacy of new ASDs.

Although the concept that a seizure arises when there is an imbalance between excitation and inhibition has been useful in epilepsy research, one could argue that an imbalance between excitation and inhibition is an oversimplification, because seizures in individuals with epilepsy are often rare, occurring once a day, once a week, or even once a month. If there was simply an imbalance, for example, excessive excitation, one would expect seizures would occur most of the time. Furthermore, some types

TABLE 41.6 Experimental models of seizures.

In Vitro models of seizure-like activity[a]		*In Vivo* models of seizures	
Preparations	**Treatments**	**Preparations**	**Treatments**
Tissue culture	Convulsants	Lower species	Convulsants
– Primary cultures	Other chemicals	– Zebrafish	Other chemicals
– Organotypic cultures	Altered extracellular	– Invertebrates	Altered CSF/plasma
Brain slices	– Ion concentrations	Rodents (mice, rats, other)	– pH
Isolated brain preparations	– pH	– Anesthetized	– Osmolarity
– Perfused Guinea pig brain	– Osmolarity	– Unanesthetized	– Immune stimulus
– Isolated hippocampus	Electrical stimulus	Other lower mammals	– Change to blood–brain barrier
	Optogenetics	Nonhuman primates	Electrical stimulus
	Transgenic tissue	– Monkey	Optogenetics
	Viral injection[b]	– Photosensitive baboon	Transgenic tissue Viral injection

In vitro and in vivo models of seizures are presented. In vitro preparations do not exhibit seizures in the clinical sense, so the phrase "seizure-like activity" is often used instead. Viral injection refers to the use of viral vectors to alter gene expression.
[a]*In vitro* preparations do not exhibit seizures in the clinical sense, so the phrase "seizure-like activity" is often used instead.
[b]*Use of viral vectors to alter gene expression.*

TABLE 41.7 Standardized tests for anticonvulsant drug screening.

Seizure model[a]	Clinical seizure type[b]
Pentylenetetrazol (metrazol) administration	Myoclonic/clonic seizures
Maximal electroshock test	Generalized tonic–clonic seizures
Rodents with absence epilepsy (genetic)	Absence seizures
γ-Hydroxybutyrate administration	Absence seizures
Kindling model	Focal seizure with secondary generalization
Kainic acid– or pilocarpine-induced epilepsy	Focal seizure with secondary generalization (drug-resistant)

On the left are models of experimental seizures used in tests of potential anticonvulsant drugs at the National Institutes of Health. For each seizure model (left), the response to a drug is considered predictive of the effect that drug would have on the type of clinical seizure it simulates (right).
[a]*Models of experimental seizures used in tests of potential anticonvulsant drugs at the National Institutes of Health.*[3].
[b]For each seizure model, the response to a drug is considered predictive of the effect that drug would have on the type of clinical seizure it simulates.

of epilepsy are associated with many complex changes in the brain—including changes in glia and vasculature. Indeed, most ASDs have multiple sites of action (see below). This has been one reason to develop animal models to study epileptogenesis and epilepsy that are different from the methods to study seizures (Table 41.8).

Neuronal properties: ions, ion channels, and "channelopathies"

Intrinsic properties of neurons in the CNS are diverse, but there are some generalizations that can be made. For example, the major ions that pass through ligand- or voltage-gated ion channels are distributed so that Na^+, Ca^{2+}, and Cl^- are concentrated extracellularly and K^+ is concentrated intracellularly. The consequence is a −60 mV resting membrane potential. Therefore, conditions where electrolyte balance becomes impaired (such as severe diarrhea after cholera) may result in seizures.[88] Mg^{2+} is an important example of a critical mineral, because it normally maintains a voltage-dependent block of NMDA receptors. There also is a potential consequence of perturbations in pH and osmolarity; acidic pH influences NMDA receptors and can exacerbate hypersynchronous events[89]; a disruption of osmolarity can lead to neuronal swelling and nonsynaptic interactions that facilitate seizures.[57]

It is also relevant to consider the voltage-gated ion channels that are required for action potential generation. Mutations in the subunits of the voltage-gated sodium channels, which are responsible for fast depolarization during the rising phase of the action potential, are the basis for several genetic forms of epilepsy in childhood, including severe myoclonic epilepsy in infancy (SMEI, also called Dravet syndrome;[90]). This type of epilepsy is often called a "channelopathy" because it is considered to be the only defect in the disease—and the defect is a loss-of-function mutation in a gene that normally gives rise to an ion channel. Other "channelopathies" that give rise to epilepsy also exist. For example, mutations in the *KCNQ* gene family, encoding Kv7 channels, lead to abnormal K^+ channels and disruption of the M current. *KCNQ* mutations are responsible for a type of epilepsy in childhood called generalized epilepsy with febrile seizures plus (GEFS+; Table 41.8; Fig. 41.8B;[91]). Voltage-gated ion channels are not the only examples of channelopathies; a mutation in the genes responsible for subunits of the nicotinic acetylcholine receptor leads to an epilepsy syndrome called autosomal dominant frontal lobe epilepsy (ADFLE; Table 41.8;[92]).

Synaptic properties: glutamate, GABA, and other neurotransmitters

Many aspects of synaptic transmission are targets for antiseizure drugs or are related to causes of epilepsy. In fact, virtually every component of synaptic transmission is a target, including trafficking of neurotransmitters and their receptors to the nerve terminal or dendrites, transmitter release and reuptake, postsynaptic receptor expression and function, and postsynaptic signaling pathways and their regulation. This applies to the major neurotransmitters in the CNS, glutamate and GABA, as well as other neurotransmitters such as acetylcholine and norepinephrine.

Properties of neuronal circuits

From the discussion above, there already would seem to be sufficient vulnerabilities in the nervous system to explain the diversity of seizures and epilepsy, but there is more to consider in the circuit organization of the CNS. Many forms of epilepsy arise from defects in the essential structure of the brain, such as inability to form the normal pattern of lamination in the neocortex. Some of these developmental disorders are caused by single gene mutations, such as lissencephaly, where *Lis1* is mutated and the normal gyri and sulci of the neocortex are absent.[93] Other developmental disorders give rise to malformation such as tubers in Tuberous sclerosis, where the mammalian target of rapamycin (mTOR) pathway is disrupted.[94] Additional examples are discovered regularly by investigators who introduced a novel mutation in a transgenic mouse to study a specific question in neurobiology and were surprised to find that seizures occur; these mice may provide insight into the many types of epilepsy that have been considered "idiopathic" in the past (Table 41.8).

Nonneuronal mechanisms of seizures

Another perspective on seizure generation deemphasizes the typical neuron-centric view of the CNS and considers other cells/processes that are essential to normal brain function, such as astrocytes, the vasculature, the immune system, and subcellular energy metabolism.

Astrocytes are glial cells in the CNS that play a role in blood–brain barrier (BBB) permeability, ion homeostasis,

TABLE 41.8 Experimental models of epileptogenesis and epilepsy.

Type of epilepsy	Animal model
I. Genetic	
BNC, BFNC	*KCNQ* mutations
SMEI, GEFS+	*SCN1A/B* mutations
ADFLE	*CHRNA/B* mutations
Absence epilepsy	Spontaneous mutations in mice(e.g., *tottering*)
Absence epilepsy	Inbred rat strains (GAERS, Wag/Rij)
Neocortical epilepsy	EL mouse
II. Structural/metabolic	
A. Predominantly genetic or developmental	
1. West syndrome (infantile spasms)	CRH injection, betamethasone/NMDA, doxorubin/LPS/chlorophenyalanine, neonatal tetrodotoxin, *ARX* knockout mice
2. Progressive myoclonic	
Unverricht–Lundborg disease	*CSTB* (Cystatin B) knockout mice
Lafora disease	*EPM2A* (Laforin) knockout mice
3. Neurocutaneous	
Tuberous sclerosis	*TSC1/2* knockout mice, Eker rat
4. Other single-gene disorders	
Angelman syndrome	*Ube3a* or *GABRB3* knockout mice
Rett syndrome	*MECP2* knockout mice
5. Disorders of chromosome function	
Down syndrome	Ts65Dn transgenic mice
Fragile X syndrome	*Fmr1* knockout mice
6. Developmental anomalies of cerebral development	
Focal cortical dysplasia	Prenatal irradiation of MAM, p35 knockout mice
Polymicrogyria	Neonatal freeze lesion
Heterotopias	*Lis1* knockout mouse
B. Predominantly acquired	
1. Mesial temporal sclerosis/TLE	Experimental status epilepticus
2. Perinatal or infantile causes	Neonatal febrile seizures or hypoxia
3. Cerebral trauma	Fluid percussion injury, cortical undercut, focal alumina gel, penicillin or tetanus toxin
4. Cerebral infection	Lipopolysaccharide infection, viral encephalitis
5. Cerebral immunological disorders	
Rasmussen encephalitis	Antibodies to GluR3
6. Other degenerative or neurological conditions	
Stroke	Carotid occlusion, vascular manipulations
Alzheimer disease	APP, tau, PS1 mutations/overexpression
III. Cryptogenic	Transgenic mice with epilepsy but unclear etiology

Continued

TABLE 41.8 Experimental models of epileptogenesis and epilepsy.—cont'd

Type of epilepsy	Animal model
IV. Provoked	Kindling (electrical. Chemical)
Auditory stimulation	Audiogenic seizure-susceptible (DBA) mice
Photic stimulation	Photosensitive baboon (*Papio papio*)
Drug-induced	Alcohol withdrawal
Hormonal	Mild status epilepticus, female rats

Experimental models of epileptogenesis and epilepsy are listed with the same classification scheme as the categorization of the epilepsies in Table 41.4. All types of epilepsy and all animal models are not listed. Abbreviations: *ADFLE,* autosomal dominant frontal lobe epilepsy; *APP,* amyloid precursor protein; *BNC,* benign neonatal convulsions; *BNFC,* benign neonatal familial convulsions; *CHRNA/B,* the gene encoding the α and β subunits of the nicotinic cholinergic receptor; *CRH,* corticotropin releasing hormone; *DBA,* Dilute Brown Non-Agouti; *EL,* EL/Suz; *GAERS,* genetic absence epilepsy rats from Strasbourg; *GEFS+,* generalized epilepsy with febrile seizures plus; *KCNQ,* the gene encoding the Kv7 potassium channel family; *MAM,* methoxymethanol; *NMDA,* N-methyl-D-aspartate; *PS1,* presenilin 1; *SCN1A/B,* the gene encoding the α and β subunits of the Nav1.1 voltage-dependent sodium channel; *SMEI,* severe myoclonic epilepsy in infancy; *TLE,* temporal lobe epilepsy; *TSC,* tuberous sclerosis; *WAG/Rij,* wistar-albino-glaxo from Rijswijk.

volume regulation, and synaptogenesis. There are many ways astrocytes contribute to the regulation of seizures, and evidence has suggested that changes in astrocytes could contribute to the development of epilepsy.[95–108] Astrocytes express membrane-bound transporters, which are critical for efficient excitatory neurotransmission permitting high signal-to-noise ratio in glutamate signaling. Their presence at synapses limits the spatial and temporal exposure of synapses to neurotransmitter. Astrocytes express high-affinity glutamate transporters, glutamate transporter-1 (GLT-1) and glutamate aspartate transporter (GLAST). GLT-1 is responsible for approximately 90% of the total glutamate clearance in the dorsal forebrain.[109] Transgenic mice that lack GLT-1 succumb to lethal spontaneous generalized seizures at an early age.[110] Conversely, transgenic mice that overexpress GLT-1 have lower seizure frequency and decreased poststatus epilepticus mortality compared to WT control mice when challenged with the cholinomimetic convulsant pilocarpine.[111] These findings suggest that GLT-1 plays a role in both seizure generation and seizure maintenance. GLT-1 has been shown to be reduced at epileptic foci in patients and preclinical models of TLE.[98,112–114] *De novo* mutations of SLC1A2, the human homolog of GLT-1, have been identified in patients and families with early-onset multiple seizure types.[115] Mice deficient in GLAST have significantly longer seizure times suggesting that this transporter also plays a role in seizure susceptibility.[116] GLAST protein levels have been shown to be downregulated in patients with TLE.[98] Glutamine synthetase is responsible for the conversion of glutamate to glutamine in astrocytes and is critical for the regulation of glutamatergic neurotransmission in the human brain. Loss of glutamine synthetase has also been observed in patients with TLE.[99] These findings suggest that disruptions in astrocyte glutamate transport and metabolism could contribute to ictogenesis in the epileptic brain.

Another critical role of astrocytes is maintaining extracellular K^+ homeostasis. Potassium spatial buffering involves the redistribution of K^+ ions from areas of high to low concentration through astrocytic gap junctions. Potassium spatial buffering is critical for rapidly displacing high levels of K^+ following repolarization of neurons. Kir4.1 channels are the major inwardly rectifying (Kir) K^+ channels found on astrocytes responsible for this phenomenon.[117,118] Patients with TLE have been reported to have significantly lower levels of Kir4.1 expression suggesting that spatial K^+ buffering is impaired in the epileptic hippocampus.[102,108] Kir4.1 is also found to colocalize at astrocytic "end-feet" with the bidirectional water channel, aquaporin-4 (AQP4). AQP4 expression levels have been shown to be altered in patients with TLE, which could disrupt water homeostasis, which is essential in the CNS to prevent both cytotoxic and vasogenic edema.[119,120] Astrocytic "end-feet" support the integrity of BBB through maintenance of tight junctions with endothelial cells, and BBB dysfunction can be involved in seizure generation.

BBB disruption is involved in many diseases involving the CNS including epilepsy. The BBB tightly regulates the transport of nutrients and other molecules in and out of the brain while acting as physical barrier between the circulatory system and the brain extracellular fluid. Following epileptogenic brain insults, macromolecules and immune cells typically excluded from entering the brain can infiltrate, leading to increased inflammation and activation of nonneuronal cells in the CNS including astrocytes and microglia. Albumin extravasation has been observed in astrocytes and neurons at early and chronic stages of epileptogenesis in patients and preclinical models of TLE.[121] A positive correlation between BBB permeability and seizure frequency has also been shown in epileptic rats suggesting that drugs targeting BBB repair could be a potential avenue to treat refractory epilepsies. Notably, BBB dysfunction may not only be the result of seizure activity but it may be the cause. For example, BBB integrity is compromised following traumatic brain injury (TBI). BBB breakdown can cause edema and an increase in intracranial pressure, which can result in secondary brain injury following TBI. Secondary brain injury can lead to a cascade of events leading to the manifestation of seizures months to years following the initial trauma. In the area of injury, astrocytes invade and transform the local environment, often creating a scar-like region ("gliosis"), which impedes regrowth in the local area and creates an impasse for entry of ASDs into the region. Thus, oral administration of ASDs in this patient population may be unsuccessful because drug concentration in the area of gliosis

is too low. Posttraumatic epilepsy accounts for approximately 10%–20% of symptomatic epilepsy in the general population.[122] Although BBB breakdown can lead to the infiltration of unwanted components from the circulatory system, it also allows opportunity for alternative antiepileptic therapies that under normal physiological conditions would be hindered entry into the CNS.

The vasculature in the area of gliosis is also a potential problem in drug delivery. In resected tissue from patients with drug-resistant epilepsy, the new blood vessels that grow in the epileptic brain are often contorted or have abnormal characteristics.[123] Related to this point is the critical role of the BBB and its changes in epilepsy. During acute seizures, the BBB is weakened, and proteins from the periphery can enter the brain. Some of these proteins can exert adverse effects. For example, when serum albumin enters the brain, it can be removed by astrocytes, which decrease K^+ uptake as a result, increasing excitability.[121,124] Normally transporters such as p-glycoprotein and MDR (multidrug resistance proteins) are present to prevent entry of toxic substances into the brain. In epilepsy, these transporters may be upregulated at the BBB, leading to drug resistance.[125]

Another important factor in epilepsy that is not regulated directly by neurons is inflammation and the immune response of the brain.[126,127] A series of studies in animal models of epilepsy and later corroborated with tissue specimens from patients with epilepsy have shown that seizures cause a dramatic proinflammatory signal mediated by microglia secreting cytokines such as interleukins. Interleukin-1β has been shown to mediate several effects that are proconvulsant, either indirectly or directly acting on neurons.[127] Antagonism of the receptor of interleukin-1β is anticonvulsant and has been suggested as a new target for antiseizure drugs. Interleukin-1β, released from activated microglia, can also downregulate tight-junction proteins leading to further disruption of the BBB.[128] Many types of epilepsy appear to be associated with chronic inflammation, suggesting that antiinflammatory drugs could be therapeutic. One example is Rasmussen's encephalitis, where antibodies against glutamate receptors are present in the brain.[129] Proinflammatory mediators also play a role in the onset of seizures in epilepsies not caused by autoimmune processes. For example, reactive astrocytes in the hippocampi of patients with TLE have been shown to overexpress the inflammatory transcription factor NFκB.[130] TNF-α, a proinflammatory cytokine involved in the release of astrocytic glutamate, is rapidly induced during seizures.[131] Although using antibodies to neutralizing TNF-α has been reported to reduce seizure-induced neuronal death,[132] others reported that administration of recombinant TNF-α prior to kainate-induced SE can reduce seizure frequency and duration.[133]

Subcellular metabolism is another component of CNS function that is involved in epilepsy, which has been discussed since the time of Galen, who promoted the idea that decreased food intake would cure individuals of epilepsy.[134] It is still unclear what causes alterations in energy metabolism to be anticonvulsant, but several hypotheses have been proposed, discussed further below (see below, Ketogenic diet). There are other aspects of cellular metabolism that are potentially important to epilepsy besides those that govern the production of energy substrates. For example, there are epilepsy syndromes caused by single gene defects in enzymes responsible for lysosomal metabolism of macromolecules, leading to their accumulation. In neuronal ceroid lipofuscinosis (NCL), lipofuscin accumulates inside cells due to autosomal recessive mutations in CLN genes. Mutations in CLN3, which produces the lysosomal enzyme battenin, causes a form of NCL called Batten's disease. One of the progressive myoclonic epilepsies is due to a mutation in CLN8. Niemann–Pick disease, type C, where there are mutations in either the NPC1 or NPC2 genes, is often associated with seizures; NPC1 and NPC2 normally contribute to lysosomal transport of cholesterol and other lipids.[135,136]

Mechanisms of epileptogenesis and epilepsy

Mechanisms of epileptogenesis based on the kindling model

Although research into the basic mechanisms underlying seizures has provided important information, a number of scientists have focused instead on the following question: how does a normal brain become capable of producing repeated seizures—i.e., epileptogenesis and epilepsy? Individuals with epilepsy may have a genetic predisposition for epilepsy from birth, and only when there are a sufficient number of additional changes or "second hits" will a seizure to occur. A "second hit" could be a brain injury, or a time of life when changes in the body (hormones, aging) increase the likelihood of a seizure. Indeed, many individuals are diagnosed with epilepsy late in life, after steroid hormones such as estrogen, progesterone, and testosterone decline. The metabolites of progesterone and testosterone are so-called "neurosteroids," which bind to $GABA_A$ receptors and facilitate actions of GABA.[137]

In 1967, one of the first methods to study epileptogenesis was discovered by Graham Goddard and colleagues while attempting to understand the process in the brain that underlies memory.[138] In stimulating the brain repeatedly, intending to simulate what might occur during learning, they found that animals exhibited a gradual increase in response to the stimulus that ultimately was manifested by a convulsive seizure.[138] This process, called "kindling" because of the resemblance to kindling a fire, became a major area of research in epilepsy.[139]

One of the insights that was revealed by studies of kindling was the fact that kindling could occur by many mechanisms, for example, by stimulating various parts of the brain on a daily basis with an indwelling electrode (electrical kindling), or infusing a chemical into the brain on a regular basis using an implanted cannula (chemical kindling). These studies suggested that repeated excitation in the brain could initiate changes (plasticity) and suggested that neural plasticity was a key element of epileptogenesis.[140,141] In addition, chemicals were identified that were extremely effective in kindling, and areas of the brain were defined where kindling was easier to elicit. Identifying chemicals and areas of the brain that were susceptible to kindling was useful because they suggested where there were neurochemical vulnerabilities and neuroanatomical sites of vulnerability.[139]

Mechanisms of epilepsy based on animals with recurrent spontaneous seizures

Kindling was criticized as a model of epilepsy because stimulation was required to elicit a seizure. In epilepsy, it has been argued, seizures are spontaneous—or at least that is true for the vast majority of patients. To address epilepsy, investigators had few methods initially, except for topical application of convulsants to neocortex, creating a localized focus. A major advance was made when John Olney and colleagues discovered that a chemical called kainic acid, injected systemically or directly into the brain, could cause a lesion to the brain in laboratory rats that was similar to what is observed in temporal lobe epilepsy.[142,143] Kainic acid caused severe seizures and neuronal death in area CA1, CA3, and the dentate gyrus hilus, with sparing of the dentate gyrus granule cell layer. This pattern of neuronal loss was similar to MTS in temporal lobe epilepsy. Remarkably, the animals developed spontaneous recurrent seizures after several weeks, and the seizures persisted for the rest of their life span. This "animal model of temporal lobe epilepsy" has provided numerous experimentalists an ideal opportunity to ask how an animal can become epileptic.[144]

Before discussing the benefits of this animal model and the lessons learned from the experiments, it should be noted that the model is not without criticism. One criticism, for example, is that the period of seizures induced by kainic acid is very severe—status epilepticus (SE), a period of continuous seizures. Areas of the brain that are not always affected in temporal lobe epilepsy are damaged in the animals. In addition, adult rodents are typically used. However, temporal lobe epilepsy is typically considered to be a disease that begins in response to an injury or insult early in life, and SE may not occur. One counter argument is that the induction of SE is merely a tool to cause a lesion similar to temporal lobe epilepsy. Some investigators began to use anticonvulsants shortly after the onset of SE, to decrease the severity of SE, in order to decrease the extent of brain damage, but the debate continues. Notably, Turski, Cavalheiro, and colleagues found another compound that is an alternative to kainic acid, called pilocarpine, a muscarinic cholinergic agonist.[145,146] The pilocarpine model produces a slightly different pattern of damage than kainic acid, but the ultimate emergence of epilepsy occurs nevertheless, making it an extremely useful alternative. Other investigators have produced additional animal models, using methods that simulate one of risk factors for temporal lobe epilepsy, such as complex febrile seizures, neonatal hypoxia/ischemia, and traumatic brain injury.[147] Remarkably, it has been difficult to induce epilepsy in aged rodents, although epilepsy often develops late in life in humans.[148] Therefore, species differences are an important consideration in epilepsy research using laboratory animals.

Once it had been established that a pattern of hippocampal neuronal loss similar to patients with temporal lobe epilepsy could be induced in a rat by SE, a valuable animal model was established to understand underlying mechanisms of epileptogenesis and epilepsy. It was assumed that the neuronal loss in the rats caused the epilepsy, since rats that had SE exhibited neuronal damage within days, but spontaneous recurrent seizures (i.e., the epilepsy) did not develop until afterward. For this reason, many investigators tried to clarify why a particular pattern of neuronal loss occurred. First, the pattern of damage in the rat was better defined, and it was agreed that certain neurons in hippocampus were vulnerable ("selective vulnerability"), whereas others were relatively resistant. Several hypotheses for neuronal vulnerability and resistance were developed, including the idea that neurons were vulnerable if they had a weak capacity to buffer intracellular calcium,[149] which was later disputed.[150] Certain molecules such as STAT3 appear to be weakly expressed in neurons, which are vulnerable,[151] suggesting other molecular mechanisms. Possible causes of selective vulnerability are still debated.

At the same time, the assumption that neuronal loss caused epilepsy was questioned. One reason was that many animal models of temporal lobe epilepsy were developed where neuronal loss was negligible. For example, animal models are now established where young rats are subjected to elevated temperature to simulate febrile seizures, or a period of hypoxia, which are common precipitating factors for temporal lobe epilepsy in children. The extent of neuronal loss was modest, but the animals developed seizures later in life.[152] On the other hand, the seizures in these animals are not associated with robust convulsive movements and are infrequent compared to the rats that experience SE in adulthood. When neonatal insults are induced to produce more neuronal injury, a more robust convulsive epilepsy is induced in long term.[153]

A more detailed examination of the hippocampus after SE has led to some great insights. For example, it was noted that one hallmark of neuronal loss in hippocampus was a pattern of axonal outgrowth of granule cells in the dentate gyrus called mossy fiber sprouting. Mossy fiber sprouting has now been identified both in the SE models and in tissue resected from patients with drug-resistant temporal lobe epilepsy.[154] Using anatomical and physiological analyses of the sprouted axons, it was shown that mossy fiber sprouting reflected a novel excitatory circuit where granule cells axons developed synaptic connections with other granule cells (recurrent excitatory circuitry). The idea that epilepsy was a product of increased recurrent excitatory circuitry became popular. It was an idea that has been repeatedly shown to be relevant to epilepsy, because recurrent excitation appears to increase in other brain regions besides the dentate gyrus and other animal models of epilepsy such as kindling.[155] Increased recurrent excitation provides an explanation for the emergence of fast ripples in epilepsy (Fig. 41.6). However, there also are studies that suggested that mossy fiber sprouting may not be as important as once thought, or at least it is more complicated that initially suggested. For example, strategies to reduce mossy fiber sprouting do not necessarily stop epilepsy, although drugs with ideal specificity have not yet been tested. In addition, some investigators have found that mossy fiber sprouting is associated with increased inhibition, not increased excitation, because the abnormal sprouted axons innervate GABAergic neurons.[156] As more work has been done, the complexity of the changes in GABAergic inhibition of the granule cells in the dentate gyrus after SE has become very complex, with alterations in the presynaptic GABAergic neurons and the postsynaptic GABA receptors.[157,158]

Some advances in our understanding of epileptogenesis after SE have come with improved technology—video and EEG can

be monitored in rats in their home cage continuously, for weeks or even months. From detailed studies of seizures over time, it has become clear that the brain is not silent between SE and the emergence of epilepsy. Instead, there is a gradual increase in abnormal neuronal activity, and it continues to rise even after epilepsy is established.[159,160] These findings have led to the idea that there is a progressive change in the brain during epileptogenesis that starts with an initial insult and continues potentially for life. The implications are diagrammed in Fig. 41.7. At the start of the timeline is a person exposed to one of many potential risk factors for temporal lobe epilepsy, such as a birth injury, infection, febrile seizures, or perinatal hypoxia. Then there are a series of rapid and slower changes that occur, with the initial effects triggering the later alterations. The process may be accelerated or prolonged depending on genetic predisposition, the presence of a second injury, and the environment (e.g., stressful living conditions). Essentially the plasticity inherent in the brain leads to a process that ultimately lowers seizure threshold sufficiently for a spontaneous seizure to occur. As shown in Fig. 41.7B1-2, this process may not stop. Instead, any time a seizure occurs, it can initiate another period of changes. One of the underlying reasons is that many genes are regulated by neuronal activity, with an increase in neuronal activity increasing transcription/translation or decreasing it.[161,162]

The specific changes that occur on the fastest and increasing slower timescales are depicted in Fig. 41.7C1-3. After the initial period of SE, animals have dramatic changes caused by the large rise in intracellular calcium that accompanies high-frequency neuronal activity. There are alterations in some cells that are "excitotoxic" and lead to swelling and neuronal death. The surviving neurons exhibit a number of changes in gene expression and are influenced by the parallel changes in the extracellular milieu, astrocytes, and openings in the BBB that allow molecules to enter the neuropil from the peripheral circulation. Secondary changes ensue, including the alteration of astrocytes in the area of the injured neurons, becoming "reactive glia." The changes in gene expression lead to new proteins synthesized in surviving neurons and redistribution of proteins along the dendrites and axons. Over the course of days to weeks, new circuits form from existing neurons that grow new collaterals, refine dendrites and dendritic spines, and reorganize circuitry. Then there are responses to these new circuits, an attempt to reestablish homeostasis. In some individuals who develop epilepsy after a precipitating insult in childhood, it is suspected that there may be a malfunction in these homeostatic mechanisms, which differentiates them from other children who may have a similar injury, but for some reason never develop epilepsy. Even in rodents where genetic and environmental factors are less variable, there can be animal-to-animal variability.[163]

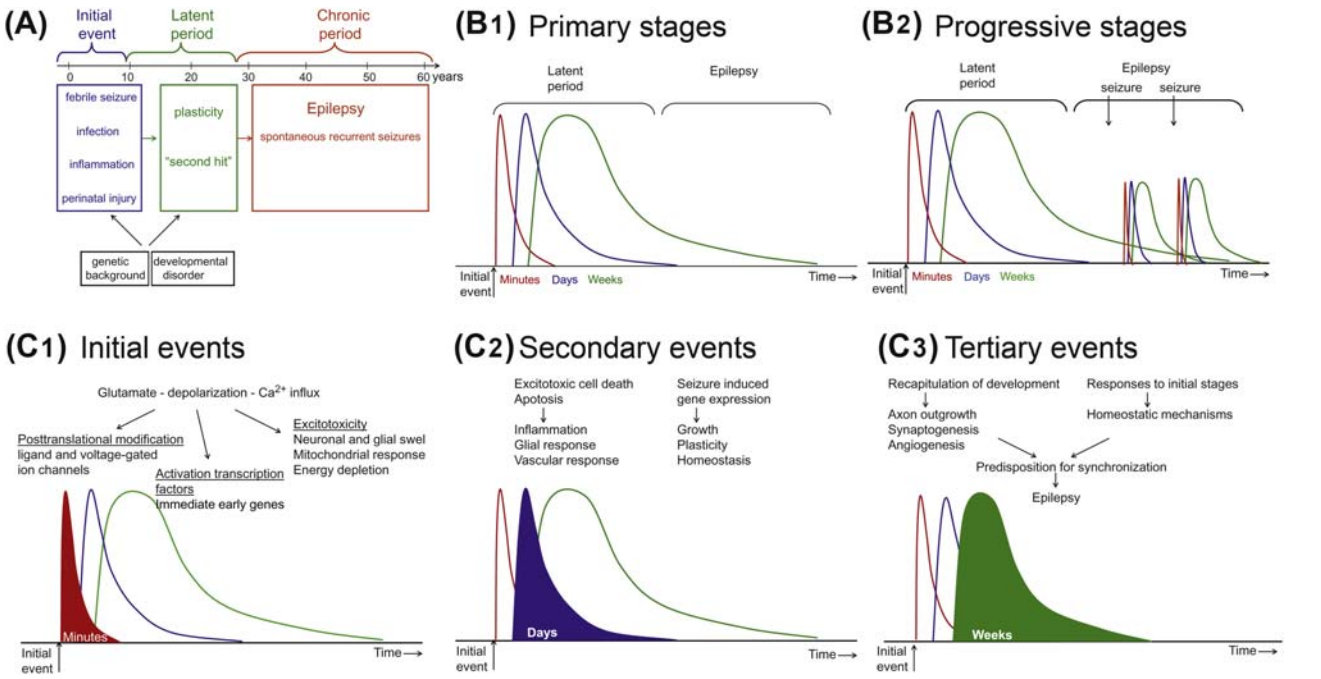

FIGURE 41.7 Stages of epileptogenesis after an insult or injury. A. A schematic shows the stages of epileptogenesis that are thought to follow a brain insult or injury early in life, ultimately causing temporal lobe epilepsy. On the x axis is age in years. Below the timeline, from left to right are three stages: Blue, the initial stage where a precipitating event occurs; Green, a latent period when responses of the CNS to an early life injury occur and may include a second "hit" (second insult/injury not necessarily the same as the first); Red, a chronic stage where spontaneous recurrent seizures occur (epilepsy). These stages are influenced by genes and development, indicated at the bottom. Genetic predisposition may lead to a more rapid and severe progression; abnormal development (biological or environmental) may also lead to a more rapid onset of epilepsy. B. 1. The effects of the initial precipitating insult or injury in A are shown in more detail. There are rapid responses and slower responses to the initial precipitating insult or injury with short timescales (minutes, days, weeks) in experimental animals but in humans the stages are more protracted, requiring decades in temporal lobe epilepsy. 2. The chronic period (epilepsy) is diagrammed. Notably, there is potential for chronic seizures to initiate additional changes in the brain other than those that occurred earlier. C. The specific changes in the brain caused by the initial insult or injury shown in A-B are illustrated. (1) Rapid changes, occurring within minutes in the rodent brain; (2) Delayed effects in response to the rapid changes, occurring within days in the rodent brain; (3) Effects that occur in the weeks that follow the initial insult, which may be compensatory.

Treatment of epilepsy

Antiseizure drugs (ASDs)

One might think that after a seizure, almost anyone would be prescribed a medication to stop it from occurring again. However, many seizures are not accompanied by long-term risk for more seizures and are simply a result of a specific situation, such as hypoglycemia. Therefore, drugs are the first line treatment of epilepsy, but there are established guidelines when to administer ASDs. According to guidelines of the American Academy of Neurology, the decision to treat should be made on the basis of the risk of recurrence, which is established after diagnostics such as neuroimaging. A high risk is usually suggested by a structural abnormality that is consistent, for example, with temporal lobe epilepsy.[164,165]

ASDs have been in use since 1857 when Charles Locock discovered potassium bromide. Potassium bromide acts by simulating chloride, passing through the chloride channel coupled to the $GABA_A$ receptor. Therefore, potassium bromide enhances the effects of GABA at $GABA_A$ receptors. In 1912, phenobarbital was introduced, which also acts by facilitating actions of GABA at $GABA_A$ receptors, but by another mechanism. The barbiturates and benzodiazepines bind to particular subunits of the $GABA_A$ receptor, and when bound, GABA has greater effects. Importantly, severe seizures can cause these subunits to change, and the subunit where benzodiazepines bind is replaced by another. Therefore, at the onset of SE, benzodiazepines are often the drug of choice, but have diminishing efficacy with time.[166]

Phenobarbital was the standard for epilepsy care until Tracy Putnam and H. Houston Merritt discovered the beneficial effects of phenytoin in 1939, which was a major advance because phenytoin caused less sedation than phenobarbital. The next decades brought a wave of new medications for epilepsy: the benzodiazepines, other GABAergic drugs such as primidone (1952), drugs that acted primarily on calcium channels (ethosuximide, 1955), or drugs that had multiple effects (carbamazepine, 1963; valproic acid, 1967) and novel effects, such as inhibition of carbonic anhydrase (acetazolamide, 1953). After the advent of the anticonvulsant screening program in the United States in 1971 at the National Institutes of Health, and growth at academic centers and pharmaceutical companies throughout the world, another "generation" of antiseizure drugs became available: oxcarbazepine (1990); felbamate (1993); gabapentin (1993); lamotrigine (1990); topiramate (1995); tiagabine (1996); levetiracetam (1999); zonisamide (2000); pregabalin (2004); eslicarbazepine acetate (2009).

At the present time, valproic acid is the most widely prescribed ASD and the first choice for GTCS; carbamazepine is the first-line drug for partial seizures, with levetiracetam and lamotrigine commonly used in partial epilepsy also (Table 41.9;[167]). Recommendations of the American Academy of Neurology suggest that in newly diagnosed patients, the following ASDs are useful: carbamazepine, phenytoin, valproic acid, phenobarbital, GABApentin, lamotrigine, oxcarbazepine, and topiramate. If the newly diagnosed patient has partial epilepsy or mixed seizures, GABApentin, lamotrigine, oxcarbazepine, and topiramate are recommended. In childhood, lamotrigine is suggested. In cases that are refractory to medications, seven ASDs are suggested: gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, zonisamide.[164,165]

Regrettably, 20%–30% of newly diagnosed patients are not seizure-free after being treated with ASDs.[167–169] Statistically, individuals who fail to have seizures controlled by the first two ASDs have a high risk of failure with subsequent ASDs,[170] leading some patients to be evaluated for surgical treatment or alternatives to pharmacotherapy. For patients who are pharmacologically "refractory," meaning that they do not have seizure control after several ASDs are tested, a localized focus with a structural lesion such as MTS indicates that they are candidates for surgical resection of the hippocampus (discussed further below, Surgical treatment).

As shown in Table 41.9, ASDs comprise a chemically diverse group of drugs, but the majority of these drugs, where the mechanism is known, appear to target four general neurobiological mechanisms: voltage-dependent sodium channels, voltage-dependent calcium channels, glutamatergic transmission, or GABAergic transmission. In Fig. 41.8, these four mechanisms are depicted schematically. Phenytoin is the prototypical antagonist of voltage-dependent sodium channels, and ethosuximide is the prototypical antagonist of calcium channels, blocking the T-type calcium channel. Although many drugs affect glutamatergic transmission, few only do so; in contrast, several drugs appear to act only at GABAergic synapses, interfering with GABA synthesis, GABA reuptake, or the $GABA_A$ receptor.

Surgery

Resective or disconnective surgery

For most patients, surgery is recommended only if ASDs fail. However, in many cases, surgery is an excellent option.[171] In individuals with MTS and drug-resistant epilepsy, removal of the hippocampus is suggested, with outcome much better if the seizure onset zone is in the area where pathology (i.e., MTS) exists, and secondary sites of pathology are not detected by neuroimaging. In a retrospective review of outcomes, patients with a localized lesion prior to surgery had the best long-term outcome. On the other hand, some reports are less favorable with respect to seizure control in long term. In patients with other types of epilepsy, such as tuberous sclerosis, removal of the tuber is associated with seizure control, and even when there is more than one tuber, a multistaged approach has been successful.[172] To standardize the outcomes from surgery, Jerome Engel Jr. suggested a classification, now known as the Engel classification. There are four classes: Class 1 is "freedom from disabling seizures "; Class II is "rare disabling seizures"; Class III is "worthwhile improvement"; and Class IV is "no worthwhile improvement."[173]

For specific epilepsy syndromes, such as hemimegalencephaly, chronic encephalitis, congenital hemiplegia, or Sturge–Weber syndrome, other surgical options exist, including hemispherectomy (removal of the majority of one hemisphere;[174]). Outcome is excellent, with over 85% of patients improved and 60% seizure-free; cognitive function also improves in many individuals. Another approach is to sever neuronal connections within a cortical area. This option is attractive when the seizure-onset zone is located in an area where preservation of critical functions would be lost if the area was removed. Frank Morrell pioneered the approach,

TABLE 41.9 Antiseizure drugs (ASDs).

		Voltage- dependent sodium channels	Voltage- dependent calcium channels	Glutamate receptors	GABA receptor	Other mechanism	Use
ACTH						Suppresses CRH	Infantile spasms
Aromatic allylic alcohols	Stiripentol				X		Sever myoclonic epilepsy in infancy
Barbiturates	Phenobarbital			X	X		Many types
Benzodiazepines	Clobazam				X		Many types
	Diazepam, Lorazepam				X		Status epilepticus
Benzoxazoles	Zonisamide	X	X	?	?	Carbonic anhydrase inhibitor?	Many types
Bromides	Potassium bromide				X		
Carbamates	Felbamate	?	X	NR2B	X		Focal seizures, Lennox−Gastaut
Carboxamides	Carbamazepine	X			X		Many types
Fatty acids	Valproic acid	X	X		X	HDAC inhibitor	Many types
Deoxybarbiturates	Primidone	X			X		Many types
GABA analogues	GABApentin		X		X		Many types
	Pregabalin		X			Inhibits transmitter release	Focal-onset seizures
	Vigabatrin				X		Many types, Lennox−Gastaut
Hydantoins	Phenytoin	X					Many types
Oxazolidinones	Trimethadione		X				Absence seizures
Piperidines	Tiagabine				X		Focal-onset seizures
Succinimides	Ethosuximide		X				Absence seizures
Sulfamate-substituted polysaccharides	Topiramate	X		X	X	Carbonic anhydrase inhibitor	Many types, Lennox−Gastaut
Sulfonamides	Acetazolamide					Carbonic anhydrase inhibitor	Absence and myoclonic seizures
Triazines	Lamotrigine	X	?	X		H Current	Many types
New	Retigabine					Opens KCNQ K^+ channels	Focal-onset seizures
	Perampanel			AMPA			Focal-onset seizures
	Ganaxalone				X		Many types

The major classes of ASDs are listed with examples, mechanistic information, and clinical use. Actions at voltage-dependent sodium channels, calcium channels, ionotropic glutamate receptors, $GABA_A$ receptors, or other mechanisms of action are designated by an X. A question mark indicates that the data are not clear either because of conflicting reports, results that are not easily interpreted, or generalization from experimental preparations to humans is not yet clear. Abbreviations: *HDAC,* histone deacetylase; *NR2B,* the NR2B subunit of the NMDA receptor.

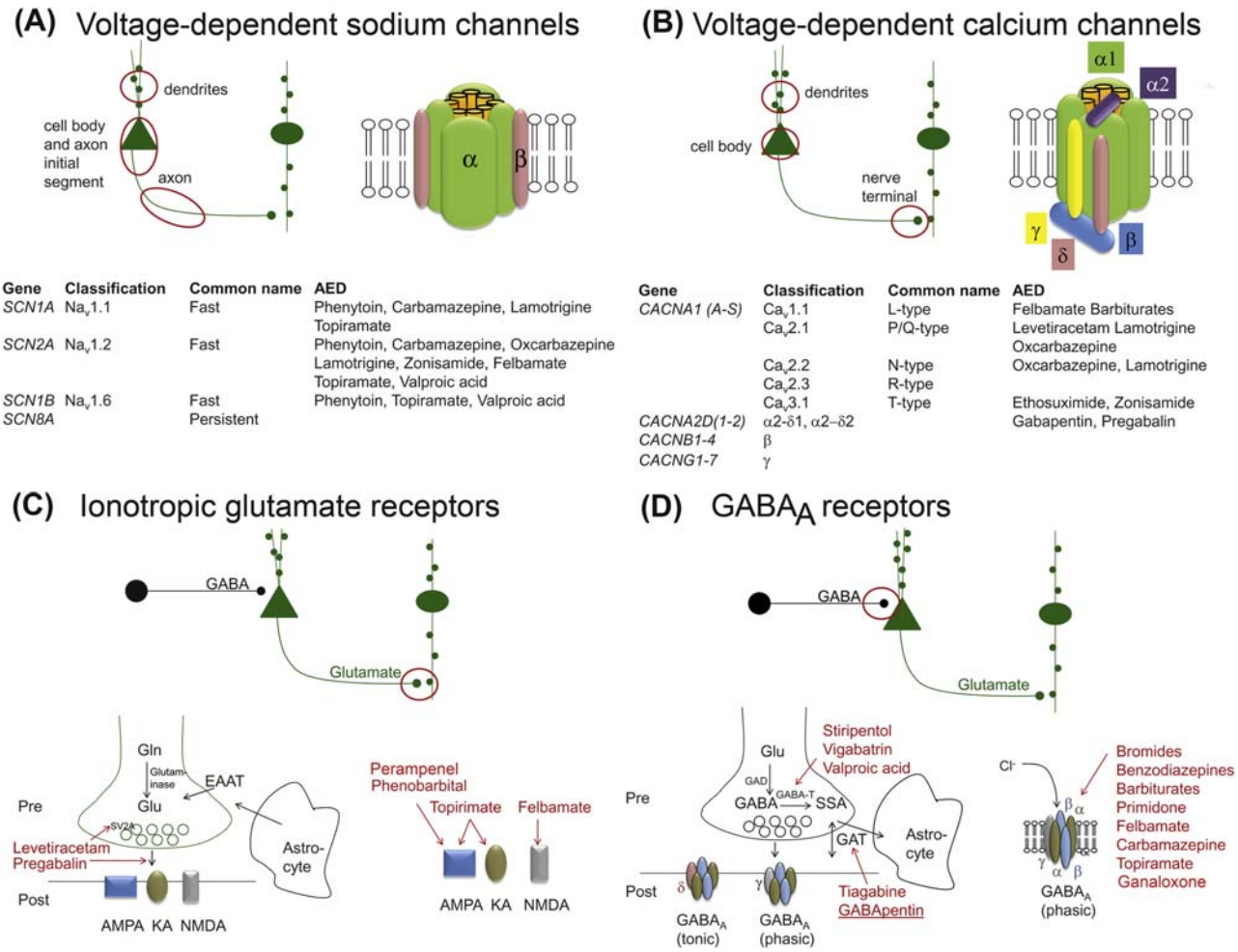

FIGURE 41.8 Mechanisms of action of antiseizure drugs (ASDs). A. One of the mechanisms of action of ASDs is inhibition of voltage-dependent sodium channels. Top left: the location of channels in the plasma membrane of typical cortical neurons is shown. Channels are primarily axonal, but some are also present on some dendrites. Top right: the structure of the sodium channel consists of multiple pore-forming α subunits (gold) and accessory β subunits (green). Bottom: the sodium channels that are targets of ASDs are listed, with the gene, numerical designation, and common name provided. Drugs that are known to act on these channels are listed on the right. B. Another mechanism of action of ASDs is inhibition of voltage-dependent calcium channels. Top left: voltage-dependent calcium channels are located in many parts of cortical neurons, including dendrites, somata, and the nerve terminal. Top right: the structure of voltage-dependent calcium channels consists of pore-forming subunits (α1, green) and several accessory subunits (α2, purple; β, blue; γ, yellow; δ, purple). Bottom: the nomenclature for calcium channels and examples of drugs that act on the channels are shown. C. ASDs that act on ionotropic glutamate receptors are shown. Top: Ionotropic glutamate receptors are located primarily at synapses. Some receptors are also present immediately outside the synapse (extrasynaptically) and on astrocytes (not shown). Bottom left: A drawing of a glutamatergic synapse, with sites of action of ASDs in red. Bottom right: The subtypes of ionotropic glutamate receptors are shown schematically with drugs that act on the receptors shown in red. Abbreviations: Gln, glutamine; Glu, glutamate; EAAT, excitatory amino acid transporter; SV2A, synaptic vesicle glycoprotein type 2A; AMPA, 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid; KA, kainic acid; NMDA, N-methyl-D-aspartate. D. ASDs that act on GABA receptors. Top: GABA receptors (primarily $GABA_A$ or $GABA_B$) are found at the synapses of GABAergic neurons and can be extrasynaptic. Bottom left: A schematic illustrates a GABAergic synapse and actions of ASDs in red. $GABA_A$ receptors are composed of multiple subunits (α–δ) and mediate phasic (synaptic) inhibition or tonic (nonsynaptic) inhibition depending on the presence of the δ subunit. $GABA_B$ receptors are not shown because antiseizure drugs do not influence them, although agonists facilitate absence seizures (e.g., γ-hydroxybutyrate). Bottom right: A $GABA_A$ receptor is shown, with drugs that act on the receptor in red. Barbiturates and benzodiazepines have specific binding sites. Abbreviation: GABA-T, GABA transaminase; GAD, glutamic acid decarboxylase; GAT, GABA transporter; SSA, succinic acid semialdehyde. *Adapted from Meldrum BS, Rogawski MA. Molecular targets for antiepileptic drug development.* Neurotherapeutics *2007;4:18–61.*[52]

where multiple subpial transections are made to sever connectivity as much as possible while preserving function. Corpus callosotomy is another method that attempts to block spread of seizures.

Laser interstitial thermal therapy (LITT)

A newer less invasive option for ablating epileptic foci is LITT. In this procedure, stereotactic techniques are used to place a probe into the target lesion, and laser ablation is performed at the tip of the probe. This has been used to treat brain tumors and also for drug-resistant lesional epilepsy.[175]

Vagus nerve stimulation (VNS)

In 1939, Bailey and Bremer found that the ECG of cats was altered upon stimulation of the vagus nerve. That observation was overlooked for some time because it was assumed that the effect

was related to hypotension, which ordinarily follows VNS. However, Zanchetti and colleagues[176] showed that the effect was not likely to be related to hypotension. It was subsequently shown that stimulation of the vagus nerve could desynchronize the EEG and stop seizures in dogs treated with the convulsant strychnine.[177] These findings led to the idea that stimulating the vagus nerve may prevent seizures in patients with epilepsy. In 1997, the FDA approved an implantable device for focal epilepsy. For practical reasons related to preservation of the battery, and safety precautions, a low frequency of stimulation was chosen. Despite concerns that cardiac and other peripheral side effects of vagal nerve stimulation would develop, the implantable stimulator has not been associated with a high frequency of side effects and has been a successful adjunct to ASD treatment of epilepsy.

The mechanism of action of VNS is still unclear. The vagus nerve is the 10th cranial nerve, releases acetylcholine, and is responsible for involuntary actions associated with the autonomic nervous system. It regulates the heart, gastrointestinal tract, and other organs. The vagus nerve also regulates sensory functions related to the ears and tongue. In the brain, the cell bodies of the vagus nerve are located in the brainstem. The mechanism of VNS stimulation may be related to the fact that seizure control often takes weeks, months, and typically continues to improve over years. The idea that the anticonvulsant effect takes time suggests that reorganization of neural circuits, either in the brainstem or in the forebrain where the brainstem systems project, is responsible for the efficacy of VNS. Other hypotheses include an increase in GABA levels and decreased inflammation.[178]

Other types of stimulation have also been studied in epilepsy. "Responsive stimulation" is a stimulation procedure that attempts to abort a seizure by stimulating shortly after it begins with an implanted electrode in the area where the seizure starts.[179] In the first published results of patients with drug-resistant focal epilepsy, there was a 38% reduction in seizures in the patients who were stimulated, compared to 17% in the control group.[180]

Deep brain stimulation (DBS)

DBS involves electrodes in structures such as the thalamus. A recent study where the anterior nucleus of the thalamus was stimulated showed efficacy for drug-resistant focal seizures with or without secondary generalization.[181] Like VNS, efficacy appeared to increase over time: after 3 months, there was a 40% median reduction of seizures, and after 2 years, it was 56%, compared to approximately 15% of controls. In April 2018, the FDA approved DBS of the thalamus for patients with medically refractory partial-onset seizures.

Other

Ketogenic diet

The ketogenic diet (KD) was first tested in individuals with epilepsy in 1921 by Russell Wilder,[134] but was used less often once phenobarbital and other antiseizure drugs were available. In the 1990s, there was a resurgence of the KD after the son of a well-known movie producer was successfully treated and several programs about the KD were televised. The KD is typically used in children with drug-resistant epilepsy. It is a treatment that is successful for diverse types of epilepsy, such as SMEI, tuberous sclerosis, and infantile spasms.[182]

The diet is a high-fat, low-carbohydrate, and low-protein diet, where the ratio of fat to carbohydrate and protein (in grams) is approximately 4 to 1. The response to the diet can be rapid in some patients, and in others several weeks may be necessary. The diet may be continued if seizures persist, and in those patients where seizures stop, recurrence of epilepsy occurs—remarkably—in only 20%.[183–185]

The reason for the efficacy of the KD is not entirely clear. It had been assumed that caloric restriction was an important component, because fasting can decrease seizures in patients with epilepsy[134] and laboratory animals.[186,187] Therefore, it had been recommended that the KD be administered with caloric restriction to 75% of the RDA. In addition, caloric restriction increases the production of ketones by the KD. Some studies suggest that calorie restriction is essential to the ability of the KD to stop seizures, but there are other factors to consider such as age.[188]

There are many hypotheses for the mechanism of action of the KD. The correlation of ketone levels with seizure control has led many to believe that ketones are directly responsible. In addition, it has been shown that the major ketone bodies, β hydroxybutyrate, acetyl-coA and acetone, all have actions that reduce seizures in laboratory animals. Another hypothesis is that the KD leads to greater production of mitochondria in neurons and more energy.[189] One of the reasons for increased mitochondria may be the effect of the KD to shift ATP production from glycolysis in the cytoplasm to mitochondria.[190] Increased mitochondria could support ATPases such as the Na^+K^+-pump and help neurons repolarize more quickly during seizures. As a consequence, seizures would be shortened.

A shift in cellular ATP production to mitochondria could prevent seizures in another way also, based on the idea that ATP produced by glycolysis is near ATP-dependent K^+ channels at the plasma membrane, but mitochondrial ATP production is not. Therefore, if glycolysis were reduced, ATP-mediated inhibition of the K^+ channel would be reduced. The consequence would be K^+ channel opening, causing hyperpolarization of the cell, reducing excitability.[190,191]

Another explanation for the effects of the KD is based on the increased production of GABA and reduced release of glutamate caused excess of the ketone body acetyl CoA, which causes a shunt in the Krebs cycle toward production of α ketoglutarate, which produces glutamate. One would think that an increase in glutamate levels would increase the likelihood of seizures, instead of having a protective effect, but there are two reasons why a reduction in seizures may occur instead: (1) glutamate is the precursor to GABA, so more GABA is produced, and (2) there may be a defect in the transport of glutamate into synaptic vesicles in the presence of the ketone body acetoacetate, because acetoacetate inhibits the vesicular glutamate transporter vGLUT 2.[190] The enhanced concentration of adenosine caused by the KD has also been suggested to mediate the effects of the diet on seizures, because adenosine is an endogenous compound with anticonvulsant actions.[69,192]

Cooling

Baldwin and colleagues were the first to describe the anticonvulsant effects of cooling.[193] These early reports were followed by many studies in diverse preparations showing that hot temperatures exacerbated seizures while cooling decreased them. Subsequently, devices to cool the brain have repeatedly shown efficacy in animals[194–196] and are starting to be used in people with epilepsy.

Stem cells

Use of transplanted cells to improve brain function has been proposed for many diseases. In epilepsy, the idea that transplantation would be effective was also tested, but met with little success initially. More recently, improved methods to implant GABAergic neurons into neocortical sites were made possible by selection of neurons from the medial ganglionic eminence, where they normally develop. Initial studies from several laboratories all show promise. In animals with neocortical transplantation, it was shown that the transplanted GABAergic neurons survive, have the ability to release GABA, and hyperpolarize adjacent neurons.[197] When the hippocampus was targeted, transplantation also gave rise to GABAergic neurons and efficacy to stop seizures.[198] However, other mechanisms may also be relevant besides those mediated by GABA, such as the ability to restore glial-derived neurotrophic factor (GDNF) expression to astrocytes, an "anticonvulsant" growth factor.[199] It was shown by Waldau and colleagues that GDNF is anticonvulsant and expressed widely by transplanted cells, but the expression of GABA was relatively weak.[200]

Summary

Epilepsy is one of the most complex neurological disorders. It requires a broad understanding of neurology and neuroscience—not only to understand the patient but to advance research so that better diagnostics and therapeutics can be developed. Here the current conceptions about clinical epilepsy have been summarized, starting with basic terminology, epidemiology, and categorization of the epilepsies. How seizures arise at the level of single neurons in cortical circuits has been summarized with a historical perspective, starting with the first observations of seizures using EEG and subsequent recordings from single neurons in anesthetized preparations or brain slices of experimental animals. From these studies and many others, we know now that seizures arise by diverse mechanisms, leading to the diversity of the epilepsies.

With the tools provided by modern neuroscience and molecular biology, many of the initial conceptions about mechanisms have been expanded—or new explanations have been suggested. For example, many of the "idiopathic" epilepsies that were previously considered to have no clear cause are now recognized to have a genetic contribution or arise from mutations in single genes. New animal models have been developed and changed many of the prevailing views, such as the "neurocentric" view of seizures and epilepsy. Now it is well accepted that there are critical roles of astrocytes, microglia, the vasculature, and the BBB in seizures and epilepsy.

The chapter ends with a summary of the ASDs, the primary therapeutic approach for epilepsy. Surgery can be an effective treatment, however, and there is increasing interest in alternatives such as the KD. While an impressive armamentarium, much more research is needed because many epilepsy syndromes lack effective treatments or lead to debilitating side effects. In some of the epilepsies, where medication controls seizures in some individuals, there are others whose seizures are not controlled by available ASDs—called "drug resistance". These limitations of current clinical treatments are the priority for future research.

Acknowledgments

NIH and The New York State Office of Mental Health.

References

1. Temkin O. *The Falling Sickness*. Baltimore, MD: John Hopkins University Press; 1971.
2. Jankovic SM, Sokic DV, Levic ZM, Susic V, Stojsavljevic N, Drulovic J. [Epilepsy, eponyms and patron saints (history of Western civilization)]. *Srp Arh Celok Lek*. 1996;124:162–165.
3. NINDS. *Seizures and Epilepsy: Hope through Research*. 2010.
4. Amoroso C, Zwi A, Somerville E, Grove N. Epilepsy and stigma. *Lancet*. 2006;367:1143–1144.
5. Bandstra NF, Camfield CS, Camfield PR. Stigma of epilepsy. *Can J Neurol Sci*. 2008;35:436–440.
6. Jacoby A. Epilepsy and stigma: an update and critical review. *Curr Neurol Neurosci Rep*. 2008;8:339–344.
7. Fisher RS, van Emde Boas W, Blume W, et al. Epileptic seizures and epilepsy: definitions proposed by the international League against epilepsy (ILAE) and the international Bureau for epilepsy (IBE). *Epilepsia*. 2005;46:470–472.
8. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. *Epilepsia*. 2017;58:512–521.
9. IOM. *Epilepsy across the Spectrum: Promoting Health and Understanding*. Washington, DC: The National Academies Press; 2012.
10. Zack MM, Kobau R. National and state estimates of the numbers of adults and children with active epilepsy - United States, 2015. *MMWR Morb Mortal Wkly Rep*. 2017;66:821–825.
11. Benn EK, Hauser WA, Shih T, et al. Estimating the incidence of first unprovoked seizure and newly diagnosed epilepsy in the low-income urban community of Northern Manhattan, New York City. *Epilepsia*. 2008;49:1431–1439.
12. Hesdorffer DC, Logroscino G, Benn EK, Katri N, Cascino G, Hauser WA. Estimating risk for developing epilepsy: a population-based study in Rochester, Minnesota. *Neurology*. 2011;76:23–27.
13. Holden EW, Thanh Nguyen H, Grossman E, et al. Estimating prevalence, incidence, and disease-related mortality for patients with epilepsy in managed care organizations. *Epilepsia*. 2005;46:311–319.
14. Heaney DC, MacDonald BK, Everitt A, et al. Socioeconomic variation in incidence of epilepsy: prospective community based study in south east England. *BMJ*. 2002;325:1013–1016.
15. Hesdorffer DC, Tian H, Anand K, et al. Socioeconomic status is a risk factor for epilepsy in Icelandic adults but not in children. *Epilepsia*. 2005;46:1297–1303.
16. WHO. *Epilepsy*. 2009.
17. Kaiboriboon K, Bakaki PM, Lhatoo SD, Koroukian S. Incidence and prevalence of treated epilepsy among poor health and low-income Americans. *Neurology*. 2013;80:1942–1949.

18. Hauser WA. Seizure disorders: the changes with age. *Epilepsia*. 1992;33(Suppl 4):S6−S14.
19. Brodie MJ, Elder AT, Kwan P. Epilepsy in later life. *Lancet Neurol*. 2009;8:1019−1030.
20. Holmes GL, Milh MD, Dulac O. Maturation of the human brain and epilepsy. *Handb Clin Neurol*. 2012;107:135−143.
21. Hauser WA, Kurland LT. The epidemiology of epilepsy in Rochester, Minnesota, 1935 through 1967. *Epilepsia*. 1975;16:1−66.
22. Fazel S, Wolf A, Langstrom N, Newton CR, Lichtenstein P. Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study. *Lancet*. 2013;382:1646−1654.
23. CDC. www.cdc.gov/chronicdisease/resources/publications/AAG/epilepsy.htm; 2010.
24. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005−2009. *Epilepsia*. 2010;51:676−685.
25. Shorvon SD. The etiologic classification of epilepsy. *Epilepsia*. 2011;52:1052−1057.
26. Scharfman HE, Pedley TA. Temporal lobe epilepsy, p 349-369. In: Gilman S, ed. *The Neurobiology of Disease*. New York: Elsevier; 2006.
27. Lowenstein DH. Seizures and epilepsy, p 2498-2512. In: Fauci ASKD, Longo DL, eds. *Harrison's Principles of Internal Medicine*. 17th ed. New York: McGraw-Hill; 2008.
28. Hwang SK, Hirose S. Genetics of temporal lobe epilepsy. *Brain Dev*. 2012;34:609−616.
29. Noebels JL. The biology of epilepsy genes. *Annu Rev Neurosci*. 2003;26:599−625.
30. Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. *N Engl J Med*. 2011;365:919−926.
31. Brooks-Kayal A, Bath K, Berg A, et al. Issues related to symptomatic and disease modifying treatments affecting cognitive and neuropsychiatric comorbidities of epilepsy. *Epilepsia*. 2013;54(Suppl 4):44−60.
32. Ajmone Marsan C. Electrographic aspects of 'epileptic' neuronal aggregates. *Epilepsia*. 1961;2:22−38.
33. Ayala GF, Matsumoto H, Gumnit RJ. Excitability changes and inhibitory mechanisms in neocortical neurons during seizures. *J Neurophysiol*. 1970;33:73−85.
34. Dichter M, Spencer WA. Penicillin-induced interictal discharges from the cat hippocampus. II. Mechanisms underlying origin and restriction. *J Neurophysiol*. 1969;32:663−687.
35. Dichter M, Spencer WA. Penicillin-induced interictal discharges from the cat hippocampus. I. Characteristics and topographical features. *J Neurophysiol*. 1969;32:649−662.
36. Matsumoto H, Ayala GF, Gumnit RJ. Neuronal behavior and triggering mechanism in cortical epileptic focus. *J Neurophysiol*. 1969;32:688−703.
37. Johnston D, Brown TH. Giant synaptic potential hypothesis for epileptiform activity. *Science*. 1981;211:294−297.
38. Dingledine R, Hynes MA, King GL. Involvement of N-methyl-D-aspartate receptors in epileptiform bursting in the rat hippocampal slice. *J Physiol*. 1986;380:175−189.
39. Yaari Y, Beck H. "Epileptic neurons" in temporal lobe epilepsy. *Brain Pathol*. 2002;12:234−239.
40. Zhang ZJ, Valiante TA, Carlen PL. Transition to seizure: from "macro"- to "micro"-mysteries. *Epilepsy Res*. 2011;97:290−299.
41. Zhang ZJ, Koifman J, Shin DS, et al. Transition to seizure: ictal discharge is preceded by exhausted presynaptic GABA release in the hippocampal CA3 region. *J Neurosci*. 2012;32:2499−2512.
42. Kahle KT, Staley KJ, Nahed BV, et al. Roles of the cation-chloride cotransporters in neurological disease. *Nat Clin Pract Neurol*. 2008;4:490−503.
43. Staley KJ. Role of the depolarizing GABA response in epilepsy. *Adv Exp Med Biol*. 2004;548:104−109.
44. Ziburkus J, Cressman JR, Barreto E, Schiff SJ. Interneuron and pyramidal cell interplay during in vitro seizure-like events. *J Neurophysiol*. 2006;95:3948−3954.
45. Beck H, Yaari Y. Plasticity of intrinsic neuronal properties in CNS disorders. *Nat Rev Neurosci*. 2008;9:357−369.
46. Traub RD, Wong RK. Cellular mechanism of neuronal synchronization in epilepsy. *Science*. 1982;216:745−747.
47. Trevelyan AJ, Schevon CA. How inhibition influences seizure propagation. *Neuropharmacology*. 2012. https://doi.org/10.1016/j.neuropharm.2012.06.015. doi:S0028-3908(12)00273-0 [pii].
48. Trevelyan AJ, Sussillo D, Watson BO, Yuste R. Modular propagation of epileptiform activity: evidence for an inhibitory veto in neocortex. *J Neurosci*. 2006;26:12447−12455.
49. Trevelyan AJ, Sussillo D, Yuste R. Feedforward inhibition contributes to the control of epileptiform propagation speed. *J Neurosci*. 2007;27:3383−3387.
50. Yaari Y, Yue C, Su H. Recruitment of apical dendritic T-type Ca2+ channels by backpropagating spikes underlies de novo intrinsic bursting in hippocampal epileptogenesis. *J Physiol*. 2007;580:435−450.
51. Jan LY, Jan YN. Voltage-gated potassium channels and the diversity of electrical signalling. *J Physiol*. 2012;590:2591−2599.
52. Meldrum BS, Rogawski MA. Molecular targets for antiepileptic drug development. *Neurotherapeutics*. 2007;4:18−61.
53. Sah P. Ca(2+)-activated K+ currents in neurones: types, physiological roles and modulation. *Trends Neurosci*. 1996;19:150−154.
54. Haglund MM, Schwartzkroin PA. Seizure-like spreading depression in immature rabbit hippocampus in vitro. *Brain Res*. 1984;316:51−59.
55. 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.
56. Chesler M. Regulation and modulation of pH in the brain. *Physiol Rev*. 2003;83:1183−1221.
57. Hochman DW. The extracellular space and epileptic activity in the adult brain: explaining the antiepileptic effects of furosemide and bumetanide. *Epilepsia*. 2012;53(Suppl 1):18−25.
58. Bragin A, Penttonen M, Buzsaki G. Termination of epileptic afterdischarge in the hippocampus. *J Neurosci*. 1997;17:2567−2579.
59. Lado FA, Moshe SL. How do seizures stop? *Epilepsia*. 2008;49:1651−1664.
60. Hsu D. The dentate gyrus as a filter or gate: a look back and a look ahead. *Prog Brain Res*. 2007;163:601−613.
61. Scharfman HE. Differentiation of rat dentate neurons by morphology and electrophysiology in hippocampal slices: granule cells, spiny hilar cells and aspiny 'fast-spiking' cells. *Epilepsy Res Suppl*. 1992;7:93−109.
62. Mody I, Kohr G, Otis TS, Staley KJ. The electrophysiology of dentate gyrus granule cells in whole-cell recordings. *Epilepsy Res Suppl*. 1992;7:159−168.
63. Sperk G, Hamilton T, Colmers WF. Neuropeptide Y in the dentate gyrus. *Prog Brain Res*. 2007;163:285−297.
64. Vezzani A, Sperk G, Colmers WF. Neuropeptide Y: emerging evidence for a functional role in seizure modulation. *Trends Neurosci*. 1999;22:25−30.
65. Scharfman HE, Gray WP. Plasticity of neuropeptide Y in the dentate gyrus after seizures, and its relevance to seizure-induced neurogenesis. *EXS*. 2006:193−211.
66. Vezzani A, Hoyer D. Brain somatostatin: a candidate inhibitory role in seizures and epileptogenesis. *Eur J Neurosci*. 1999;11:3767−3776.
67. Noe F, Nissinen J, Pitkanen A, et al. Gene therapy in epilepsy: the focus on NPY. *Peptides*. 2007;28:377−383.
68. Tallent MK, Qiu C. Somatostatin: an endogenous antiepileptic. *Mol Cell Endocrinol*. 2008;286:96−103.

69. Theofilas P, Brar S, Stewart KA, et al. Adenosine kinase as a target for therapeutic antisense strategies in epilepsy. *Epilepsia*. 2011;52:589−601.
70. Chen K, Neu A, Howard AL, et al. Prevention of plasticity of endocannabinoid signaling inhibits persistent limbic hyperexcitability caused by developmental seizures. *J Neurosci*. 2007;27:46−58.
71. Harte-Hargrove L, Maclusky NJ, Scharfman HE. Brain-derived neurotrophic factor-estrogen interactions in hippocampal mossy fiber pathway: implications for normal brain function and disease. *Neuroscience*. 2013. https://doi.org/10.1016/j.neuroscience.2012.12.029. S0306-4522(12)01217-1 [pii].
72. Kramar EA, Babayan AH, Gall CM, Lynch G. Estrogen promotes learning-related plasticity by modifying the synaptic cytoskeleton. *Neuroscience*. 2013. https://doi.org/10.1016/j.neuroscience.2012.10.038. S0306-4522(12)01053-01056 [pii].
73. Scharfman HE, Goodman JH, Sollas AL, Croll SD. Spontaneous limbic seizures after intrahippocampal infusion of brain-derived neurotrophic factor. *Exp Neurol*. 2002;174:201−214.
74. McNamara JO, Scharfman HE. *Temporal Lobe Epilepsy and the BDNF Receptor*. TrkB. doi:NBK98186 [bookaccession]. 2012.
75. Timofeev I, Grenier F, Steriade M. The role of chloride-dependent inhibition and the activity of fast-spiking neurons during cortical spike-wave electrographic seizures. *Neuroscience*. 2002;114:1115−1132.
76. McCormick DA, Pape HC. Properties of a hyperpolarization-activated cation current and its role in rhythmic oscillation in thalamic relay neurones. *J Physiol*. 1990;431:291−318.
77. Traub RD, Draguhn A, Whittington MA, et al. Axonal gap junctions between principal neurons: a novel source of network oscillations, and perhaps epileptogenesis. *Rev Neurosci*. 2002;13:1−30.
78. Bragin A, Engel Jr J, Wilson CL, Fried I, Buzsaki G. High-frequency oscillations in human brain. *Hippocampus*. 1999;9:137−142.
79. Bragin A, Engel Jr J, Wilson CL, Fried I, Mathern GW. Hippocampal and entorhinal cortex high-frequency oscillations (100−500Hz) in human epileptic brain and in kainic acid–treated rats with chronic seizures. *Epilepsia*. 1999;40:127−137.
80. Bragin A, Mody I, Wilson CL, Engel Jr J. Local generation of fast ripples in epileptic brain. *J Neurosci*. 2002;22:2012−2021.
81. Fisher RS, Webber WR, Lesser RP, Arroyo S, Uematsu S. High-frequency EEG activity at the start of seizures. *J Clin Neurophysiol*. 1992;9:441−448.
82. Traub RD, Whittington MA, Buhl EH, et al. A possible role for gap junctions in generation of very fast EEG oscillations preceding the onset of, and perhaps initiating, seizures. *Epilepsia*. 2001;42:153−170.
83. Dzhala VI, Staley KJ. Mechanisms of fast ripples in the hippocampus. *J Neurosci*. 2004;24:8896−8906.
84. Kohling R, Staley K. Network mechanisms for fast ripple activity in epileptic tissue. *Epilepsy Res*. 2011;97:318−323.
85. Epsztein J, Represa A, Jorquera I, Ben-Ari Y, Crepel V. Recurrent mossy fibers establish aberrant kainate receptor-operated synapses on granule cells from epileptic rats. *J Neurosci*. 2005;25:8229−8239.
86. Gajda Z, Hermesz E, Gyengesi E, Szupera Z, Szente M. The functional significance of gap junction channels in the epileptogenicity and seizure susceptibility of juvenile rats. *Epilepsia*. 2006;47:1009−1022.
87. Samoilova M, Wentlandt K, Adamchik Y, Velumian AA, Carlen PL. Connexin 43 mimetic peptides inhibit spontaneous epileptiform activity in organotypic hippocampal slice cultures. *Exp Neurol*. 2008;210:762−775.
88. Riggs JE. Neurologic manifestations of fluid and electrolyte disturbances. *Neurol Clin*. 1989;7:509−523.
89. Tong CK, Chesler M. Endogenous pH shifts facilitate spreading depression by effect on NMDA receptors. *J Neurophysiol*. 1999;81:1988−1991.
90. Catterall WA, Kalume F, Oakley JC. NaV1.1 channels and epilepsy. *J Physiol*. 2010;588:1849−1859.
91. Burgess DL. Neonatal epilepsy syndromes and GEFS+: mechanistic considerations. *Epilepsia*. 2005;46(Suppl 10):51−58.
92. Lerche H, Shah M, Beck H, Noebels JL, Johnston D, Vincent A. Ion channels in genetic and acquired forms of epilepsy. *J Physiol doi:jphysiol*. 2012:240606 https://doi.org/10.1113/jphysiol.2012.240606.
93. Schwartzkroin PA, Walsh CA. Cortical malformations and epilepsy. *Ment Retard Dev Disabil Res Rev*. 2000;6:268−280.
94. Wong M. Mammalian target of rapamycin (mTOR) activation in focal cortical dysplasia and related focal cortical malformations. *Exp Neurol*. 2011. https://doi.org/10.1016/j.expneurol.2011.10.002. S0014-4886(11)00360-00368 [pii].
95. Tessler S, Danbolt NC, Faull RL, Storm-Mathisen J, Emson PC. Expression of the glutamate transporters in human temporal lobe epilepsy. *Neuroscience*. 1999;88:1083−1091.
96. Hubbard JA, Binder DK. *Astrocytes and Epilepsy*. Amsterdam, Netherlands: Elsevier; 2016.
97. Fedele DE, Gouder N, Guttinger M, et al. Astrogliosis in epilepsy leads to overexpression of adenosine kinase, resulting in seizure aggravation. *Brain*. 2005;128:2383−2395.
98. Proper EA, Hoogland G, Kappen SM, et al. Distribution of glutamate transporters in the hippocampus of patients with pharmaco-resistant temporal lobe epilepsy. *Brain*. 2002;125:32−43.
99. Eid T, Thomas MJ, Spencer DD, et al. Loss of glutamine synthetase in the human epileptogenic hippocampus: possible mechanism for raised extracellular glutamate in mesial temporal lobe epilepsy. *Lancet*. 2004;363:28−37.
100. Bordey A, Sontheimer H. Properties of human glial cells associated with epileptic seizure foci. *Epilepsy Res*. 1998;32:286−303.
101. Mathern GW, Mendoza D, Lozada A, et al. Hippocampal GABA and glutamate transporter immunoreactivity in patients with temporal lobe epilepsy. *Neurology*. 1999;52:453−472.
102. Hinterkeuser S, Schroder W, Hager G, et al. Astrocytes in the hippocampus of patients with temporal lobe epilepsy display changes in potassium conductances. *Eur J Neurosci*. 2000;12:2087−2096.
103. Bordey A, Spencer DD. Distinct electrophysiological alterations in dentate gyrus versus CA1 glial cells from epileptic humans with temporal lobe sclerosis. *Epilepsy Res*. 2004;59:107−122.
104. Hsu MS, Lee DJ, Binder DK. Potential role of the glial water channel aquaporin-4 in epilepsy. *Neuron Glia Biol*. 2007;3:287−297.
105. Takahashi DK, Vargas JR, Wilcox KS. Increased coupling and altered glutamate transport currents in astrocytes following kainic-acid-induced status epilepticus. *Neurobiol Dis*. 2010;40:573−585.
106. Binder DK. Astrocytes: stars of the sacred disease. *Epilepsy Current*. 2018;15:172−179.
107. Heuser K, Nome CG, Pettersen KH, et al. Ca2+ signals in astrocytes facilitate spread of epileptiform activity. *Cerebr Cortex*. 2018;28:4036−4048.
108. Heuser K, Eid T, Lauritzen F, et al. Loss of perivascular Kir4.1 potassium channels in the sclerotic hippocampus of patients with mesial temporal lobe epilepsy. *J Neuropathol Exp Neurol*. 2012;71:814−825.
109. Danbolt NC. Glutamate uptake. *Prog Neurobiol*. 2001;65:1−105.
110. Tanaka K, Watase K, Manabe T, et al. Epilepsy and exacerbation of brain injury in mice lacking the glutamate transporter GLT-1. *Science*. 1997;276:1699−1702.
111. Kong Q, Takahashi K, Schulte D, Stouffer N, Lin Y, Lin CL. Increased glial glutamate transporter EAAT2 expression reduces epileptogenic processes following pilocarpine-induced status epilepticus. *Neurobiol Dis*. 2012;47:145−154.
112. Hubbard JA, Szu JI, Yonan JM, Binder DK. Regulation of astrocyte glutamate transporter-1 (GLT1) and aquaporin-4 (AQP4) expression in a model of epilepsy. *Exp Neurol*. 2016;283:85−96.
113. Clarkson C, Smeal RM, Hasenoehrl MG, White JA, Rubio ME, Wilcox KS. Ultrastructural and functional changes at the tripartite synapse during epileptogenesis in a model of temporal lobe epilepsy. *Exp Neurol*. 2020;326:113196.

114. Sarac S, Afzal S, Broholm H, Madsen FF, Ploug T, Laursen H. Excitatory amino acid transporters EAAT-1 and EAAT-2 in temporal lobe and hippocampus in intractable temporal lobe epilepsy. *APMIS*. 2009;117:291−301.
115. Consortium EK. De novo mutations in SLC1A2 and CACNA1A are important causes of epileptic encephalopathies. *Am J Hum Genet*. 2016;99:287−298.
116. Watanabe T, Morimoto K, Hirao T, Suwaki H, Watase K, Tanaka K. Amygdala-kindled and pentylenetetrazole-induced seizures in glutamate transporter GLAST-deficient mice. *Brain Res*. 1999;845:92−96.
117. Butt AM, Kalsi A. Inwardly rectifying potassium channels (Kir) in central nervous system glia: a special role for Kir4.1 in glial functions. *J Cell Mol Med*. 2006;10:33−44.
118. Kofuji P, Newman EA. Potassium buffering in the central nervous system. *Neuroscience*. 2004;129:1045−1056.
119. Lee TS, Eid T, Mane S, et al. Aquaporin-4 is increased in the sclerotic hippocampus in human temporal lobe epilepsy. *Acta Neuropathol*. 2004;108:493−502.
120. Nagelhus EA, Mathiisen TM, Ottersen OP. Aquaporin-4 in the central nervous system: cellular and subcellular distribution and coexpression with KIR4.1. *Neuroscience*. 2004;129:905−913.
121. van Vliet EA, da Costa Araujo S, Redeker S, van Schaik R, Aronica E, Gorter JA. Blood-brain barrier leakage may lead to progression of temporal lobe epilepsy. *Brain*. 2007;130:521−534.
122. Verellen RM, Cavazos JE. Post-traumatic epilepsy: an overview. *Therapy*. 2010;7:527−531.
123. Marchi N, Lerner-Natoli M. Cerebrovascular remodeling and epilepsy. *Neuroscientist*. 2012. https://doi.org/10.1177/1073858412462747. doi:1073858412462747 [pii].
124. Ivens S, Kaufer D, Flores LP, et al. TGF-beta receptor-mediated albumin uptake into astrocytes is involved in neocortical epileptogenesis. *Brain*. 2007;130:535−547.
125. Sills GJ. The multidrug transporter hypothesis of refractory epilepsy: corroboration and contradiction in equal measure. *Epilepsy Current*. 2006;6:51−54.
126. Devinsky O, Vezzani A, Najjar S, De Lanerolle NC, Rogawski MA. Glia and epilepsy: excitability and inflammation. *Trends Neurosci*. 2013. https://doi.org/10.1016/j.tins.2012.11.008. doi:S0166-2236(12)00205-6 [pii].
127. Vezzani A, French J, Bartfai T, Baram TZ. The role of inflammation in epilepsy. *Nat Rev Neurol*. 2010;7:31−40.
128. da Fonseca AC, Matias D, Garcia C, et al. The impact of microglial activation on blood-brain barrier in brain diseases. *Front Cell Neurosci*. 2014;8:362.
129. Granata T. Rasmussen's syndrome. *Neurol Sci*. 2003;24(Suppl 4):S239−S243.
130. Crespel A, Coubes P, Rousset MC, et al. Inflammatory reactions in human medial temporal lobe epilepsy with hippocampal sclerosis. *Brain Res*. 2002;952:159−169.
131. Balosso S, Ravizza T, Aronica E, Vezzani A. The dual role of TNF-alpha and its receptors in seizures. *Exp Neurol*. 2013;247:267−271.
132. Shinoda S, Skradski SL, Araki T, et al. Formation of a tumour necrosis factor receptor 1 molecular scaffolding complex and activation of apoptosis signal-regulating kinase 1 during seizure-induced neuronal death. *Eur J Neurosci*. 2003;17:2065−2076.
133. Balosso S, Ravizza T, Perego C, et al. Tumor necrosis factor-alpha inhibits seizures in mice via p75 receptors. *Ann Neurol*. 2005;57:804−812.
134. Wheless JW. History and origins of the ketogenic diet. In: Stafstrom CE, Rho JM, eds. *Epilepsy and the Ketogenic Diet*. New York: Humana; 2004.
135. Infante RE, Wang ML, Radhakrishnan A, Kwon HJ, Brown MS, Goldstein JL. NPC2 facilitates bidirectional transfer of cholesterol between NPC1 and lipid bilayers, a step in cholesterol egress from lysosomes. *Proc Natl Acad Sci U S A*. 2008;105:15287−15292.
136. Subramanian S, Balch WE. NPC1/NPC2 function as a tag team duo to mobilize cholesterol. *Proc Natl Acad Sci U S A*. 2008;105:15223−15224.
137. Reddy DS. Role of anticonvulsant and antiepileptogenic neurosteroids in the pathophysiology and treatment of epilepsy. *Front Endocrinol*. 2011;2:38.
138. Goddard GV. Development of epileptic seizures through brain stimulation at low intensity. *Nature*. 1967;214:1020−1021.
139. McIntyre DC, Gilby KL. Kindling as a model of human epilepsy. *Can J Neurol Sci*. 2009;36(Suppl 2):S33−S35.
140. Sutula TP. Mechanisms of epilepsy progression: current theories and perspectives from neuroplasticity in adulthood and development. *Epilepsy Res*. 2004;60:161−171.
141. Scharfman HE. Epilepsy as an example of neural plasticity. *Neuroscientist*. 2002;8:154−173.
142. Olney JW, Fuller T, de Gubareff T. Acute dendrotoxic changes in the hippocampus of kainate treated rats. *Brain Res*. 1979;176:91−100.
143. Olney JW, Rhee V, Ho OL. Kainic acid: a powerful neurotoxic analogue of glutamate. *Brain Res*. 1974;77:507−512.
144. Bertram E. The relevance of kindling for human epilepsy. *Epilepsia*. 2007;48(Suppl 2):65−74.
145. Turski WA, Cavalheiro EA, Schwarz M, Czuczwar SJ, Kleinrok Z, Turski L. Limbic seizures produced by pilocarpine in rats: behavioural, electroencephalographic and neuropathological study. *Behav Brain Res*. 1983;9:315−335.
146. Cavalheiro EA, Leite JP, Bortolotto ZA, Turski WA, Ikonomidou C, Turski L. Long-term effects of pilocarpine in rats: structural damage of the brain triggers kindling and spontaneous recurrent seizures. *Epilepsia*. 1991;32:778−782.
147. Pitkanen A, Moshe SL, Schwartzkroin PA. *Models of Seizures and Epilepsy*. New York: Elsevier; 2006.
148. Kelly KM. Aging models of acute seizures and epilepsy. *Epilepsy Curr*. 2010;10:15−20.
149. Sloviter RS. Calcium-binding protein (calbindin-D28k) and parvalbumin immunocytochemistry: localization in the rat hippocampus with specific reference to the selective vulnerability of hippocampal neurons to seizure activity. *J Comp Neurol*. 1989;280:183−196.
150. Bouilleret V, Schwaller B, Schurmans S, Celio MR, Fritschy JM. Neurodegenerative and morphogenic changes in a mouse model of temporal lobe epilepsy do not depend on the expression of the calcium-binding proteins parvalbumin, calbindin, or calretinin. *Neuroscience*. 2000;97:47−58.
151. Choi YS, Lin SL, Lee B, et al. Status epilepticus-induced somatostatinergic hilar interneuron degeneration is regulated by striatal enriched protein tyrosine phosphatase. *J Neurosci*. 2007;27:2999−3009.
152. Baram TZ, Jensen FE, Brooks-Kayal A. Does acquired epileptogenesis in the immature brain require neuronal death. *Epilepsy Current*. 2011;11:21−26.
153. Kadam SD, White AM, Staley KJ, Dudek FE. Continuous electroencephalographic monitoring with radio-telemetry in a rat model of perinatal hypoxia-ischemia reveals progressive post-stroke epilepsy. *J Neurosci*. 2010;30:404−415.
154. Buckmaster PS. Mossy fiber sprouting in the dentate gyrus. In: Noebels JLAM, Rogawski MA, Olsen RW, Delgado-Escueta AV, eds. *Jasper's Basic Mechanisms of the Epilepsies [Internet*. 4th ed. Bethesda, MD: National Center for Biotechnology Information (US); 2012, 2012/07/13 ed doi:NBK98174 [bookaccession].
155. Sutula TP, Dudek FE. Unmasking recurrent excitation generated by mossy fiber sprouting in the epileptic dentate gyrus: an emergent property of a complex system. *Prog Brain Res*. 2007;163:541−563.
156. Sloviter RS, Zappone CA, Harvey BD, Frotscher M. Kainic acid-induced recurrent mossy fiber innervation of dentate gyrus inhibitory interneurons: possible anatomical substrate of granule cell hyper-inhibition in chronically epileptic rats. *J Comp Neurol*. 2006;494:944−960.
157. Coulter DA. Epilepsy-associated plasticity in gamma-aminobutyric acid receptor expression, function, and inhibitory synaptic properties. *Int Rev Neurobiol*. 2001;45:237−252.

158. Zhang W, Buckmaster PS. Dysfunction of the dentate basket cell circuit in a rat model of temporal lobe epilepsy. *J Neurosci*. 2009;29:7846−7856.
159. Williams PA, Hellier JL, White AM, Staley KJ, Dudek FE. Development of spontaneous seizures after experimental status epilepticus: implications for understanding epileptogenesis. *Epilepsia*. 2007;48(Suppl 5):157−163.
160. Williams PA, White AM, Clark S, et al. Development of spontaneous recurrent seizures after kainate-induced status epilepticus. *J Neurosci*. 2009;29:2103−2112.
161. Scharfman HE. Seizure-induced neurogenesis in the dentate gyrus and its dependence on growth factors and cytokines, p 1-40. In: Binder DK, Scharfman HE, eds. *Growth Factors and Epilepsy*. Hauppauge: Novasciences; 2006.
162. Lukasiuk K, Dabrowski M, Adach A, Pitkanen A. Epileptogenesis-related genes revisited. *Prog Brain Res*. 2006;158:223−241.
163. Bolkvadze T, Pitkanen A. Development of post-traumatic epilepsy after controlled cortical impact and lateral fluid-percussion-induced brain injury in the mouse. *J Neurotrauma*. 2011;29:789−812.
164. French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs, II: treatment of refractory epilepsy: report of the TTA and QSS Subcommittees of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia*. 2004;45:410−423.
165. French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs, I: treatment of new-onset epilepsy: report of the TTA and QSS Subcommittees of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia*. 2004;45:401−409.
166. Goodkin HR, Joshi S, Kozhemyakin M, Kapur J. Impact of receptor changes on treatment of status epilepticus. *Epilepsia*. 2007;48(Suppl 8):14−15.
167. Goldenberg M. Overview of drugs used for epilepsy and seizures. *P T*. 2010;35:393−415.
168. Patsalos PN, Sander JW. Newer antiepileptic drugs. Towards an improved risk-benefit ratio. *Drug Saf*. 1994;11:37−67.
169. Hwang H, Kim KJ. New antiepileptic drugs in pediatric epilepsy. *Brain Dev*. 2008;30:549−555.
170. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med*. 2000;342:314−319.
171. Wiebe S, Blume WT, Girvin JP, Eliasziw M. Effectiveness, efficiency of surgery for temporal lobe epilepsy study G (2001) A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med*. 2001;345:311−318.
172. Hidalgo ET, Frankel HG, Rodriguez C, et al. Invasive monitoring after resection of epileptogenic neocortical lesions in multistaged epilepsy surgery in children. *Epilepsy Res*. 2018;148:48−54.
173. Engel J. *Surgical Treatment of the Epilepsies*. New York: Raven Press; 1987.
174. Binder DK, Schramm J. Multilobar resections and hemispherectomy. In: Pedley JETA, ed. *Epilepsy: A Comprehensive Textbook*. 2nd ed. Philadelphia, PA: Lippincott-Raven; 2007:1879−1890.
175. Landazuri P, Shih J, Leuthardt E, et al. A prospective multicenter study of laser ablation for drug resistant epilepsy - one year outcomes. *Epilepsy Res*. 2020;167:106473.
176. Zanchetti A, Wang SC, Moruzzi G. The effect of vagal afferent stimulation on the EEG pattern of the cat. *Electroencephalogr Clin Neurophysiol*. 1952;4:357−361.
177. Chase MH, Nakamura Y, Clemente CD, Sterman MB. Afferent vagal stimulation: neurographic correlates of induced EEG synchronization and desynchronization. *Brain Res*. 1967;5:236−249.
178. Tracey KJ. Reflex control of immunity. *Nat Rev Immunol*. 2009;9:418−428.
179. Sun FT, Morrell MJ, Wharen Jr RE. Responsive cortical stimulation for the treatment of epilepsy. *Neurotherapeutics*. 2008;5:68−74.
180. Morrell MJ. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology*. 2011;77:1295−1304.
181. Salanova V, Witt T, Worth R, et al. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. *Neurology*. 2015;84:1017−1025.
182. Kossoff EH, Hartman AL. Ketogenic diets: new advances for metabolism-based therapies. *Curr Opin Neurol*. 2012;25:173−178.
183. Gasior M, Rogawski MA, Hartman AL. Neuroprotective and disease-modifying effects of the ketogenic diet. *Behav Pharmacol*. 2006;17:431−439.
184. Kossoff EH. International consensus statement on clinical implementation of the ketogenic diet: agreement, flexibility, and controversy. *Epilepsia*. 2008;49(Suppl 8):11−13.
185. Martinez CC, Pyzik PL, Kossoff EH. Discontinuing the ketogenic diet in seizure-free children: recurrence and risk factors. *Epilepsia*. 2007;48:187−190.
186. Eagles DA, Boyd SJ, Kotak A, Allan F. Calorie restriction of a high-carbohydrate diet elevates the threshold of PTZ-induced seizures to values equal to those seen with a ketogenic diet. *Epilepsy Res*. 2003;54:41−52.
187. Greene AE, Todorova MT, McGowan R, Seyfried TN. Caloric restriction inhibits seizure susceptibility in epileptic EL mice by reducing blood glucose. *Epilepsia*. 2001;42:1371−1378.
188. Bough KJ, Valiyil R, Han FT, Eagles DA. Seizure resistance is dependent upon age and calorie restriction in rats fed a ketogenic diet. *Epilepsy Res*. 1999;35:21−28.
189. Appleton DB, DeVivo DC. An animal model for the ketogenic diet. *Epilepsia*. 1974;15:211−227.
190. Lutas A, Yellen G. The ketogenic diet: metabolic influences on brain excitability and epilepsy. *Trends Neurosci*. 2013;36:32−40.
191. Ma W, Berg J, Yellen G. Ketogenic diet metabolites reduce firing in central neurons by opening K(ATP) channels. *J Neurosci*. 2007;27:3618−3625.
192. Masino SA, Kawamura M, Ruskin DN, Gawryluk J, Chen X, Geiger JD. Purines and the anti-epileptic actions of ketogenic diets. *Open Neurosci*. 2010:58.
193. Baldwin M, Frost LL. Effect of hypothermia on epileptiform activity in the primate temporal lobe. *Science*. 1956;124:931−932.
194. Smyth MD, Han RH, Yarbrough CK, et al. Temperatures achieved in human and canine neocortex during intraoperative passive or active focal cooling. *Ther Hypothermia Temp Manag*. 2015;5:95−103.
195. Smyth MD, Rothman SM. Focal cooling devices for the surgical treatment of epilepsy. *Neurosurg Clin*. 2011;22:533−546. vii.
196. D'Ambrosio R, Eastman CL, Darvas F, et al. Mild passive focal cooling prevents epileptic seizures after head injury in rats. *Ann Neurol*. 2013;73:199−209.
197. Anderson SA, Baraban SC. *Cell Therapy Using GABAergic Neural Progenitors*. 2012. NBK98214 [bookaccession].
198. Maisano X, Carpentino J, Becker S, et al. Embryonic stem cell-derived neural precursor grafts for treatment of temporal lobe epilepsy. *Neurotherapeutics*. 2009;6:263−277.
199. Kanter-Schlifke I, Georgievska B, Kirik D, Kokaia M. Seizure suppression by GDNF gene therapy in animal models of epilepsy. *Mol Ther*. 2007;15:1106−1113.
200. Waldau B, Hattiangady B, Kuruba R, Shetty AK. Medial ganglionic eminence-derived neural stem cell grafts ease spontaneous seizures and restore GDNF expression in a rat model of chronic temporal lobe epilepsy. *Stem Cell*. 2010;28:1153−1164.
201. Engel Jr J. Classification of epileptic disorders. *Epilepsia*. 2001;42:316.
202. Ryvlin P. Avoid falling into the depths of the insular trap. *Epileptic Disord*. 2006;8(Suppl 2):S37−S56.
203. Tich SN, Pereon Y. Semiological seizure classification. *Epilepsia*. 1999;40:531.
204. Ayala GF, Dichter M, Gumnit RJ, Matsumoto H, Spencer WA. Genesis of epileptic interictal spikes. New knowledge of cortical feedback systems suggests a neurophysiological explanation of brief paroxysms. *Brain Res*. 1973;52:1−17.
205. Sperling MR, Clancy RR. Ictal EEG. In: Engel J, Pedley TA, eds. *Epilepsy: A Comprehensive Textbook*. Philadelphia: Lippincott-Raven; 1997, 849−885.
206. Destexhe A. Spike-and-wave oscillations based on the properties of GABAB receptors. *J Neurosci*. 1998;18:9099−9111.
207. Destexhe A, Contreras D, Steriade M. Mechanisms underlying the synchronizing action of corticothalamic feedback through inhibition of thalamic relay cells. *J Neurophysiol*. 1998;79:999−1016.
208. Gastaut H. *Epilepsy−the Electroclinical Correlates*. Oxford: Blackwell; 1954.