Introduction
This chapter provides a brief overview of seizures and epilepsy, with emphasis on pathophysiological mechanisms that determine seizure generation and how these differ from the mechanisms underlying paroxysmal neurologic events that are not epileptic in nature. Detailed discussion about the pathophysiology of epilepsy can be found in numerous reviews, so the question arises: why consider this topic in a book that focuses on the practical approach to seizure management? There are two major reasons. First, the choice of antiepileptic drug (AED) is often crucially dependent on the seizure type or epilepsy syndrome, and hence an understanding of the underlying pathophysiology can direct medication choice. Second, burgeoning knowledge of epilepsy genetics is revealing more and more syndromes with specific mutations that determine the seizure phenotype, sometimes suggesting drugs that should or should not be selected. In this chapter, important terms are defined, and some basics of seizure pathophysiology are discussed as an aid for the practicing physician. It is important to recognize that epilepsy is not a singular disease, but is heterogeneous in terms of clinical expression, underlying etiologies, and pathophysiology.

Definitions
A seizure is a temporary disruption of brain function due to the hypersynchronous, abnormal firing of cortical neurons. Sometimes, the term epileptic seizure is used to distinguish it from a nonepileptic seizure such as a psychogenic (“pseudo”) seizure (Chapter 6), which involves abnormal clinical behavior that might resemble an epileptic seizure but is not caused by hypersynchronous neuronal firing. The clinical manifestations of a seizure depend upon the specific region and extent of brain involved and may include an alteration in motor function, sensation, alertness, perception, autonomic function, or some combination of these. Anyone might experience a seizure in the appropriate clinical setting (e.g., meningitis, hypoglycemia, toxin ingestion), attesting to the innate capacity of a “normal” brain to support epileptic activity in certain circumstances. More than 5% of people will experience a seizure at some point during their lifetimes.

Epilepsy is the condition of recurrent, unprovoked seizures (i.e., two or more seizures). Epilepsy occurs when a person is predisposed to seizures because of a chronic pathological state (e.g., brain tumor, cerebral dysgenesis, or post-traumatic scar) or a genetic susceptibility. Approximately 1% of the population suffers from epilepsy, making it the second...
most common neurologic disorder (after stroke), affecting more than two million persons in the United States.

An epilepsy syndrome refers to a group of clinical characteristics that occur together consistently, with seizures as a primary manifestation. Syndrome features might include similar seizure type, age of onset, electroencephalogram (EEG) findings, precipitating factors, etiology, inheritance pattern, natural history, prognosis, and response to AEDs. Examples of epilepsy syndromes are infantile spasms, Lennox–Gastaut syndrome, febrile seizures, childhood absence epilepsy, rolandic epilepsy, and juvenile myoclonic epilepsy. Many of these syndromes are discussed in Chapter 21.

Finally, epileptogenesis refers to the events by which the normal brain becomes capable of producing epileptic seizures, that is, the process by which neural circuits are converted from normal excitability to hyperexcitability. This process may take months or years, and its mechanisms are poorly understood. None of the currently available AEDs have robust antiepileptogenic effects. Clearly, the development of antiepileptogenic therapies is a research priority.

Classification of seizures and epilepsies

Epileptic seizures are broadly divided into two groups, depending on their site of origin and pattern of spread. Focal (or partial) seizures arise from a localized region of the brain, and the associated clinical manifestations relate to the function ordinarily mediated by that area. A focal seizure is called “simple” if the patient’s awareness or responsiveness is retained, and “complex” if those functions are impaired during the seizure. Focal discharges can spread locally through synaptic and nonsynaptic mechanisms or distally to subcortical structures, as well as through commissural pathways to involve the whole brain, in a process known as secondary generalization (Figure 1.1). For example, a seizure arising from

![Figure 1.1](https://example.com/figure1.png)

Figure 1.1. Coronal sections of the brain indicating patterns of seizure origination and spread. (A) Primary generalized seizure begins deep in brain (thalamus) with spread to superficial cortical regions (arrows). (B) Focal onset seizure begins in one area of the brain (star) and may spread to nearby or distant brain regions. (C) A focal onset seizure “secondarily generalizes” by spreading first to thalamus (left panel) then to widespread cortical regions (right panel).
the left motor cortex may cause rhythmic jerking movements of the right upper extremity; if the epileptiform discharges subsequently spread to adjacent areas and eventually encompass the entire brain, a secondarily generalized tonic–clonic convulsion may ensue.

In contrast, in a generalized seizure, abnormal electrical discharges begin in both hemispheres simultaneously and involve reciprocal thalamocortical connections (Figure 1.1). The EEG signature of a primary generalized seizure is bilateral synchronous spike-wave discharges seen across all scalp electrodes. The manifestations of such widespread epileptiform activity can range from brief impairment of responsiveness (as in an absence seizure) to a full-blown convulsion with rhythmic jerking movements of all extremities accompanied by loss of posture and consciousness.

Epilepsy syndromes have been divided historically by etiology (symptomatic vs. idiopathic; the majority of idiopathic epilepsies have a genetic basis) and site of seizure onset (generalized vs. focal or “localization-related”). This classification is being revised based on rapidly accumulating knowledge about the molecular genetic basis of epilepsies and new information gleaned from modern neuroimaging, as well as the realization that many epilepsy syndromes include both focal and generalized seizures. The newer classification scheme (Chapter 2) uses etiologic categories: genetic, structural/metabolic, and unknown. Undoubtedly, this scheme will be refined as further knowledge is gained. From the pathophysiological perspective, some mechanisms are likely to operate across epilepsy categories, and other mechanisms may be specific to certain epilepsy syndromes.

**Pathophysiology**

At the cellular level, the two hallmark features of epileptiform activity are neuronal hyperexcitability and neuronal hypersynchrony. **Hyperexcitability** refers to the heightened response of a neuron to stimulation, so that a cell might fire multiple action potentials rather than single ones in response to a synaptic input. **Hypersynchrony** reflects increased neuron firing within a small or large region of cortex, with cells firing in close temporal and spatial proximity.

While there are differences in the mechanisms that underlie focal versus generalized seizures, at a simplistic level it is still useful to view any seizure activity as a perturbation in the normal balance between inhibition and excitation in a localized region, in multiple discrete areas (seizure “foci”), or throughout the whole brain (Figure 1.2). This imbalance likely involves a combination of increased excitation and decreased inhibition (Table 1.1).

In addition to the traditional concept of excitation/inhibition imbalance, novel pathophysiological mechanisms for the epilepsies are also being discovered. For example, in febrile seizures, release of inflammatory mediators such as cytokines could contribute to neuronal hyperexcitability, an observation that might open new avenues of treatment.

**Seizure mimics**

Many conditions resemble seizures clinically yet have a distinct etiology and therefore warrant treatment other than AEDs. Such seizure mimics are typically paroxysmal and recurrent, like seizures. Representative examples, listed in Table 1.2, illustrate the wide diversity of mechanisms and hence treatment modalities.

Distinguishing epileptic from nonepileptic episodes relies on a detailed clinical history including precipitating triggers; careful description of the patient’s behavior before, during, and after the episode; whether ictal movements can be suppressed manually; and the ability of the patient to recall the spell.

Response of a suspected seizure event to an AED does not necessarily mean that the episode was epileptic, as the ability of AEDs to reduce neuronal excitability are well recognized. Recording such an event on EEG or, preferably, video-EEG is often helpful in differentiating a seizure from a nonepileptic event. However, some epileptic seizures have a subtle or minimal electrographic correlate, especially if the focus is deep in the brain, such as in the temporal lobe. Therefore, a detailed clinical description should be combined with appropriately selected laboratory investigations in the evaluation of a seizure-like event.
Table 1.1. Examples of pathophysiological processes leading to epilepsy.

<table>
<thead>
<tr>
<th>Level of dysfunction</th>
<th>Disorder</th>
<th>Pathophysiological mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ion channels</td>
<td>Benign familial neonatal convulsions</td>
<td>Potassium channel mutations: impaired repolarization</td>
</tr>
<tr>
<td></td>
<td>Dravet syndrome</td>
<td>Sodium channel mutations: enhanced excitability</td>
</tr>
<tr>
<td>Synapse development</td>
<td>Neonatal seizures</td>
<td>Depolarizing action of GABA early in development</td>
</tr>
<tr>
<td>Neurotransmitter receptors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excitatory</td>
<td>Nonketotic hyperglycinemia</td>
<td>Excess glycine leads to over-activation of NMDA receptors</td>
</tr>
<tr>
<td>Inhibitory</td>
<td>Angelman syndrome</td>
<td>Abnormal GABA receptor subunits</td>
</tr>
<tr>
<td>Neurotransmitter synthesis</td>
<td>Pyridoxine (vitamin B6) dependency</td>
<td>Decreased GABA synthesis; B6 is a cofactor of GAD</td>
</tr>
<tr>
<td>Neuron structure</td>
<td>Down syndrome and other disorders with intellectual impairment and seizures</td>
<td>Abnormal structure of dendrites and dendritic spines: altered current flow in neuron</td>
</tr>
<tr>
<td>Neuronal network</td>
<td>Cerebral dysgenesis; post-traumatic scar; mesial temporal sclerosis (in TLE)</td>
<td>Altered neuronal circuits: formation of aberrant excitatory connections (sprouting)</td>
</tr>
</tbody>
</table>

GABA, gamma-aminobutyric acid; GAD, glutamic acid decarboxylase; NMDA, N-methyl-d-aspartate; TLE, temporal lobe epilepsy.
Recognizing Seizures and Epilepsy: Insights from Pathophysiology

Overview of medication mechanisms of action

Knowledge of pathophysiological mechanisms of seizures and epilepsy is helpful in choosing the best AED for a given seizure type or epilepsy syndrome. Many AEDs work at specific cellular or molecular targets (Table 1.3). For instance, agents that enhance γ-aminobutyric acid (GABA) function include benzodiazepines and phenobarbital. Other drugs, such as phenytoin, carbamazepine, and lacosamide, decrease repetitive neuronal firing by altering sodium channel function. Still others (e.g., valproate, topiramate) act at multiple sites, endowing the AED with a broad spectrum of action. In clinical practice, it is optimal to choose an AED that has a specific action in the given epilepsy syndrome, if possible (Chapter 11). For example, ethosuximide is preferable for absence seizures due to its blockade of a calcium channel subtype that underlies the rhythmic, reciprocal epileptic firing between neocortical neurons and thalamic neurons.

Table 1.2. Some common seizure mimics.

<table>
<thead>
<tr>
<th>Seizure mimic</th>
<th>Underlying pathophysiology</th>
<th>Representative treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign paroxysmal positional vertigo</td>
<td>Labyrinth dysfunction</td>
<td>Head repositioning procedures</td>
</tr>
<tr>
<td>Breath-holding spells</td>
<td>Vasovagal</td>
<td>Reduce precipitant, reassurance</td>
</tr>
<tr>
<td>Migraine</td>
<td>Spreading cortical depression, neurogenic inflammation</td>
<td>Serotonin receptor agonists</td>
</tr>
<tr>
<td>Paroxysmal movement disorders</td>
<td>Multiple types and genetic basis; most are channelopathies</td>
<td>AEDs (e.g., carbamazepine)</td>
</tr>
<tr>
<td>Psychogenic seizure</td>
<td>Unknown; unresolved psychological conflicts</td>
<td>Counseling, behavior therapy</td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>Multiple defects in regulation of arousal</td>
<td>Depends on type: e.g., reassurance for night terrors, arousal-promoting drugs for narcolepsy</td>
</tr>
<tr>
<td>Syncope</td>
<td>Vasovagal</td>
<td>Avoidance of triggers</td>
</tr>
<tr>
<td>Tics</td>
<td>Basal ganglia dysfunction</td>
<td>Dopamine receptor blockade</td>
</tr>
</tbody>
</table>

AED, antiepileptic drug.

**CAUTION!**

Epileptic seizures and seizure mimics can occur in the same patient, making their differentiation particularly challenging.

**TIPS AND TRICKS**

The best practice is to use a single agent (monotherapy) to avoid side effects due to multiple AEDs. If it is necessary to treat a patient with more than one AED, drugs with differing mechanisms of action should be chosen to minimize adverse effects and drug–drug interactions.

Two examples illustrate how knowledge of pathophysiological principles informs clinical practice. In neonates, there is a reversed chloride ion gradient across the neuronal membrane, such that binding of the neurotransmitter GABA to its receptor may paradoxically cause excitation rather than inhibition, as occurs in the mature brain. Thus, the clinical consequence of treating neonatal seizures with GABAergic agents (phenobarbital, benzodiazepines) might be to exacerbate seizures, due to increased excitation rather than inhibition. Alternative treatments for neonatal seizures are not yet validated, though bumetanide, a diuretic that speeds up the maturation of GABAergic inhibition, is undergoing clinical trials.

The second example is Dravet syndrome (DS), previously called severe myoclonic epilepsy of infancy. In DS, mutation of sodium channels results
in impaired closure of sodium channel gates and increased neuronal firing. In this disorder, agents that further block sodium channels are best avoided, and in fact, lamotrigine can worsen seizures in children with DS. Many other examples are likely to emerge whereby understanding the underlying epilepsy pathophysiology and pharmacological mechanisms of action will directly impact patient care. In addition, as more epilepsies yield to molecular genetic elucidation, the application of patient-specific pharmacogenetic profiles may guide therapy.

**Conclusion**

This book provides a practical approach to the diagnosis and management of seizures and epilepsy. The principles outlined in this introductory chapter stress the importance of understanding the pathophysiology of seizure generation for optimal management. Details can be found in the references, and many of the concepts introduced here are expanded on in subsequent chapters.

**Bibliography**


