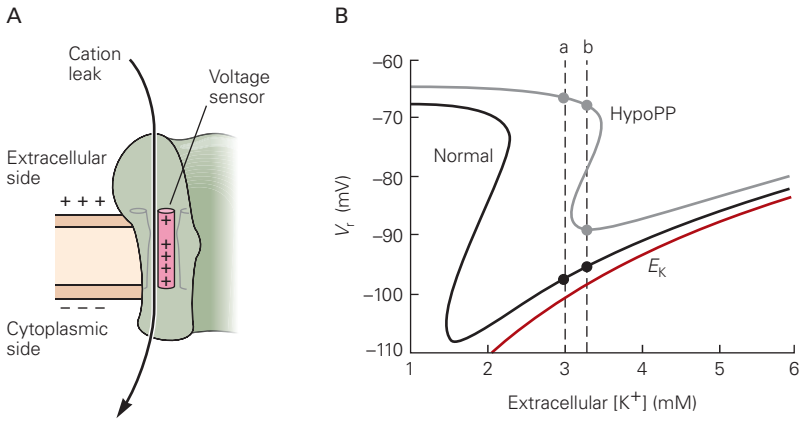

Figure 57–13 Hypokalemic periodic paralysis (HypoPP) is caused by leaky ion channels.

A. In HypoPP, missense mutations in the voltage-sensor domains create leaky Ca^{2+} or Na^+ channels that allow cation influx via an anomalous pathway separate from the channel pore.

B. Although this leak is small (~0.5% of the total resting membrane conductance), model simulations show that it causes an increased susceptibility to depolarization of resting potential (V_r), resulting in inexcitability and weakness as the external $[K^+]$ is lowered. This paradoxical depolarization of V_r diverges from the Nernst potential for K^+ (E_K) because of loss of the contribution from the inward rectifier K^+ channel in low $[K^+]$. Normally, this depolarization occurs only at extremely low $[K^+]$ (<2 mM) and is not seen in healthy people, but for patients with HypoPP, the cation leak shifts the depolarization point into the physiological range of $[K^+]$. For this simulation, in 3.3 mM $[K^+]$ (**line b**), excitability is preserved for normals (V_r = –95.6 mV), whereas HypoPP fibers may be excitable (V_r = –89 mV) or refractory and inexcitable (V_r = –67.7 mV). Reduction of $[K^+]$ to 3.0 mM (**line a**) results in complete loss of excitability for all HypoPP fibers (–66.3 mV) and retained excitability for normal fibers (V_r = –97.8 mV). (Adapted, with permission, from Cannon 2017.)

expressed in skeletal muscle. The resulting mutant Na^+ channels have inactivation defects. Subtle inactivation defects produce myotonia, whereas more pronounced defects result in chronic depolarization and loss of excitability with paralysis (Figure 57–12A–C). Hypokalemic paralysis is caused by missense mutations in the voltage-sensor domains of either Ca^{2+} channels or Na^+ channels in skeletal muscle. Disruption of the voltage-sensor domain allows an influx of ion current through an anomalous pathway, separate from the channel pore (Figure 57–13). This current "leak" in resting fibers produces a susceptibility to depolarization and loss of excitability in low extracellular K^+. A rare form of periodic paralysis that is characterized by weakness, developmental defects, and cardiac irritability is caused by primary mutations in an inwardly rectifying K^+ channel important for the resting potential (Figure 57–13).

In myotonia congenita, muscle stiffness is present from birth and is nonprogressive. Unlike myotonic dystrophy, there is no muscle wasting, permanent muscle weakness, or other organ involvement. Congenital myotonia is a consequence of mutations in the gene coding for the ClC-1 Cl^- channel in skeletal muscle membrane (Figure 57–14). The resultant decrease

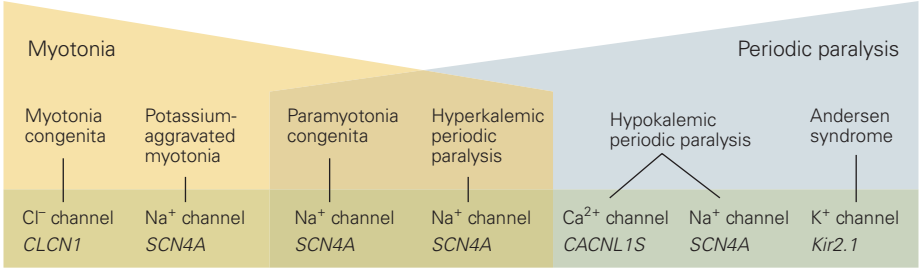

Figure 57–14 The myotonias and periodic paralyses are caused by mutations in genes that code for diverse voltage-gated ion channels in the skeletal muscle membrane. Some of these channel disorders are characterized only by myotonia, some by periodic paralysis without myotonia, and some by both myotonia and paralysis. Some clinical disorders (eg, hypokalemic periodic paralysis) can arise from defects in different channels in different individuals.

in Cl^- influx leads to membrane depolarization and repetitive firing. The disease is inherited as a dominant, semi-dominant, or recessive trait.

Highlights

1. Distinct disorders arise from pathology in different components of the motor unit. Pure motor diseases such as amyotrophic lateral sclerosis or spinal muscular atrophy are caused by loss of motor neurons, whereas combined motor and sensory features are present in most peripheral nerve disorders. These disorders usually spare eye movements and the eyelids.
2. Pure motor weakness, sometimes highly variable in severity over time, is also caused by disorders of the neuromuscular junction, which may begin early in life (congenital or neonatal myasthenia) or in childhood or adulthood (commonly autoimmune myasthenia gravis). The latter often involves eyelids and facial muscles.
3. Many forms of weakness are caused by mutations in genes that are important in skeletal muscle. These disorders usually become evident in infancy or childhood, involve the proximal more than the distal muscles, and progress relentlessly. Some (eg, Duchenne muscular dystrophy) also entail degeneration of cardiac muscle.
4. Inherited diseases of skeletal muscle with transient episodes of weakness (periodic paralysis) or involuntary after-contractions lasting seconds (myotonia) are caused by missense mutations in voltage-gated ion channels. During an episode of weakness, muscle fibers are depolarized and refractory from conducting action potentials. This intermittent failure to maintain the resting potential may arise from gain-of-function mutations in Na^+ channels, loss-of-function mutations in K^+ channels, or anomalous leakage currents in Na^+ or Ca^{2+} channels. Myotonia is a hyperexcitable state of skeletal muscle caused by Cl^- channel loss-of-function or Na^+ channel gain-of-function mutations.
5. Studies of the diseases of the peripheral nervous system show the powerful synergy between clinical and basic neuroscience. For most of the disorders inherited as Mendelian traits, molecular genetic analyses have led to the description of causative defects in muscle and nerve proteins, beginning only with the clinical data in affected families and DNA from family members.
6. Small animal models of many of these disorders, with precisely defined genetic defects, are proving invaluable for the analysis of mechanisms of disease pathogenesis and studies of new treatments. Combined with innovation in new biological therapies (gene therapy, gene silencing), these models have led to transformative successes in human trials (eg, spinal muscular atrophy).
7. In several of these disorders, a new generation of molecular therapies (eg, antisense oligonucleotides or viral-mediated gene delivery) that augment function of the mutant genes is substantially improving clinical outcomes.

Robert H. Brown
Stephen C. Cannon
Lewis P. Rowland

Selected Reading

Brown RH, Al-Chalabi A. 2017. Amyotrophic lateral sclerosis. N Engl J Med 377:162–172.

Cannon SC. 2015. Channelopathies of skeletal muscle excitability. Compr Physiol 5:761–790.

Engel AG, Shen X-M, Selcen D, et al. 2015. Congenital myasthenic syndromes: pathogenesis, diagnosis, and treatment. Lancet Neurol 14:420–434.

Fridman V, Reilly MM. 2015. Inherited neuropathies. Semin Neurol 35:407–423.

Gilhus NE, Verschuuren JJ. 2015 Myasthenia gravis: subgroup classification and therapeutic strategies. Lancet Neurol 14:1023–1036.

Ranum LP, Day JW. 2004. Pathogenic RNA repeats: an expanding role in genetic disease. Trends Genet 20:506–512.

References

Bromberg MB. 2002. Acute and chronic dysimmune polyneuropathies. In: WF Brown, CF Bolton, MJ Aminoff (eds). *Neuromuscular Function and Disease*, p. 1048, Fig. 58–2. New York: Elsevier Science.

Bromberg MB, Smith A, Gordon MD. 2002. Toward an efficient method to evaluate peripheral neuropathies. J Clin Neuromuscular Dis 3:172–182.

Brown RH Jr, Amato AA. 2002. Inherited peripheral neuropathies: classification, clinical features and review of molecular pathophysiology. In: WF Brown, CF Bolton, MJ Aminoff (eds). *Neuromuscular Function and Disease*, p. 624, Fig. 35–2. New York: Elsevier Science.

Brown RH, Mendell J. 2005. Muscular dystrophy. In: *Harrison's Principles of Internal Medicine*. New York: McGraw-Hill.

Cannon SC. 2010. Voltage-sensor mutations in channelopathies of skeletal muscle. J Physiol (Lond) 588:1887–1895.

Cannon SC. 1996. Ion channel defects and aberrant excitability in myotonia and periodic paralysis. Trends Neurosci 19:3–10.

Cannon SC. 2017. Sodium channelopathies of skeletal muscle. Handb Exp Pharm 246:309–330.

Cannon SC, Brown RH Jr, Corey DP. 1991. A sodium channel defect in hyperkalemic periodic paralysis: potassium-induced failure of inactivation. Neuron 64:619–626.

Cannon SC, Brown RH Jr, Corey DP. 1993. Theoretical reconstruction of myotonia and paralysis caused by incomplete inactivation of sodium channels. Biophys J 66:270–288.

Chamberlain JR, Chamberlain JS. 2017. Progress toward molecular therapy for Duchenne muscular dystrophy. Mol Ther 25:1125–1131.

Cull-Candy SG, Miledi R, Trautmann A. 1979. End-plate currents and acetylcholine noise at normal and myasthenic human endplates. J Physiol (Lond) 86:353–380.

Drachman DB. 1983. Myasthenia gravis: immunology of a receptor disorder. Trends Neurosci 6:446–451.

Finkel RS, Mercuri E, Darras BT, et al. 2017. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. N Engl J Med 377:1723–1732.

Gilhus NE, Verschuuren JJ. 2015. Myasthenia gravis: subgroup classification and therapeutic strategies. Lancet Neurol 14:1023–1036.

Hoffman EP, Brown RH, Kunkel LM. 1987. Dystrophin: the protein product of the Duchenne muscular dystrophy locus. Cell 51:919–928.

Hoffman EP, Kunkel LM. 1989. Dystrophin in Duchenne/Becker muscular dystrophy. Neuron 2:1019–1029.

Lisak RP, Barchi RL. 1982. *Myasthenia Gravis*. Philadelphia: Saunders.

Lupski JR. 1998. Molecular genetics of peripheral neuropathies. In: JB Martin (ed). *Molecular Neurology*, pp. 239–256. New York: Scientific American.

Mendell JR, Al-Zaidy S, Shell R, et al. 2017. Single-dose gene-replacement therapy for spinal muscular atrophy. N Engl J Med 377:1713–1722.

Mendell JR, Goemans N, Lowes LP, et al. 2016. Longitudinal effect of etiplersen versus historical control on ambulation in Duchenne muscular dystrophy. Ann Neurol 79:257–271.

Milone M. 2017. Diagnosis and management of immune-mediated myopathies. Mayo Clin Proc 92:826–837.

Newsom-Davis J, Buckley C, Clover L, et al. 2003. Autoimmune disorders of neuronal potassium channels. Ann NY Acad Sci 998:202–210.

Patrick J, Lindstrom J. 1973. Autoimmune response to acetylcholine receptor. Science 180:871–872.

Rahimov F, Kunkel LM. 2013. Cellular and molecular mechanisms underlying muscular dystrophy. J Cell Biol 201:499–510.

Rosen DR, Siddique T, Patterson D, et al. 1993. Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. Nature 362:59–62.

Rowland LP, Hoefer PFA, Aranow H Jr. 1960. Myasthenic syndromes. Res Publ Assoc Res Nerv Ment Dis 38:548–600.

Taylor JP, Brown RH, Cleveland DW. 2016. Decoding ALS: from genes to mechanisms. Nature 539:197–206.

58

Seizures and Epilepsy

Until quite recently, the function and organization of the human cerebral cortex—the region of the brain concerned with perceptual, motor, and cognitive functions—has eluded both clinicians and neuroscientists. In the past, the analysis of brain function relied largely on observations of loss of brain functions resulting from brain damage and cell loss caused by strokes or trauma. These natural experiments provided much of the early evidence that distinct brain regions serve specific functions, or as the famous American neurologist C. Miller Fisher said, "We learn about the brain 'stroke by stroke.'" Observation of patients with seizures and epilepsy has been equally important in the study of brain function because the behavioral consequences of these disorders of neural *hyperactivity* inform clinicians how activation affects the brain regions from which they originate.

Temporary disruptions of brain function resulting from abnormal, excessive neuronal activity are called seizures, whereas the chronic condition of repeated seizures is called epilepsy. For centuries, understanding the neurological origins of seizures was confounded by the dramatic, and sometimes bizarre, behaviors associated with seizures. The chronic condition of epilepsy was widely associated with possession by evil spirits, yet seizures also were thought to be a sign of oracular, prescient, or special creative powers.

The Greeks in the time of Hippocrates (circa 400 BC) were aware that head injuries to one side of the brain could cause seizure activity on the opposite side of the body. In those earlier times, the diagnosis of epilepsy was probably much broader than the contemporary definition. Other causes of episodic unconsciousness, such as syncope as well as mass hysteria and

psychogenic seizures, were almost certainly attributed to epilepsy. Moreover, historical writings typically describe generalized convulsive seizures involving both cerebral hemispheres; thus, it is likely that seizures involving a very limited area of the brain were misdiagnosed or never diagnosed at all. Even today, it can be difficult for physicians to distinguish between episodic loss of consciousness and the various types of seizures. Nevertheless, as our ability to treat and even cure epilepsy continues to improve, these diagnostic distinctions take on increasing significance.

The early neurobiological analysis of epilepsy began with John Hughlings Jackson's work in London in the 1860s. Jackson realized that seizures need not involve loss of consciousness but could be associated with localized symptoms such as the jerking of an arm. His observation was the first formal recognition of what we now call partial (or focal) seizures. Jackson also observed patients whose seizures began with focal neurological symptoms, then progressed to convulsions with loss of consciousness by steadily involving adjacent regions in an orderly fashion (the so-called Jacksonian march). His observations gave rise to the concept of the motor homunculus (the anatomical map representing the body organization or "wiring diagram" over the cortical surface) long before functional organization was established using electrophysiological techniques (Chapter 4).

Another pioneering development that presaged modern therapy was the first surgical treatment for epilepsy in 1886 by the British neurosurgeon Victor Horsley. Horsley resected cerebral cortex adjacent to a depressed skull fracture and cured a patient with focal motor seizures. Related medical innovations include the first use of phenobarbital as an anticonvulsant in 1912 by Alfred Hauptmann, the development of electroencephalography by Hans Berger in 1929, and the discovery of the anticonvulsant properties of phenytoin (Dilantin) by Houston Merritt and Tracey Putnam in 1937. The birth of routine surgical treatment for epilepsy dates to the early 1950s, when Wilder Penfield and Herbert Jasper in Montreal stimulated the cortex and pinpointed the motor and sensory maps before removing the epileptic focus. As in any chronic disease, the physiological features of seizures are not the only consideration in the care and management of patients with epilepsy. Psychosocial factors are also extremely important. The diagnosis of epilepsy has consequences that can affect all aspects of everyday life, including educational opportunities, driving, and employment. Although many societal limitations imposed on epileptics are appropriate—most would agree that patients with epilepsy should not be commercial pilots—a diagnosis of epilepsy can result in inappropriately negative effects on educational opportunities and employment. To improve this situation, physicians have a duty to educate themselves and the public on the underlying science of epilepsy and its major comorbidities, including cognitive problems and depression.

Classification of Seizures and the Epilepsies Is Important for Pathogenesis and Treatment

Not all seizures are the same. Thus, the pathogenesis and classification of seizures must take into account their clinical characteristics as well as acquired and genetic factors in each patient. Seizures and the chronic condition of repetitive seizures (epilepsy) are common. Based on epidemiological studies in the United States, 1% to 3% of all individuals living to the age of 80 will be diagnosed with epilepsy. The highest incidence occurs in young children and the elderly.

In many respects, seizures represent a prototypic neurological disease in that the symptoms include both "positive" and "negative" sensory or motor manifestations. Examples of positive signs that can occur during a seizure include the perception of flashing lights or the jerking of an arm. Negative signs reflect impairments of normal brain function such as an impairment of consciousness and cognitive awareness or even transient blindness, speech arrest, or paralysis. These examples underscore a general feature of seizures: The signs and symptoms depend on the location and extent of brain regions that are affected. Finally, the manifestations of seizures result in part from synchronous activity triggered in surrounding tissue with normal cellular and network properties. The latter activity is particularly important in the spread of a seizure beyond its original boundaries—seizures quite literally hijack the normal functions of the brain.

Seizures Are Temporary Disruptions of Brain Function

Seizures have been classified clinically into two categories, focal or generalized, based on their onset (Table 58–1). This classification is conceptually simple, but because several terms have been used over the years to refer to the same condition, the binary nature may have been obscured. Nonetheless, this classification of seizures has proven extremely useful to clinicians, and anticonvulsant medications are targeted to one or the other type.

Table 58–1 International Classification of Seizures

Seizures
Focal onset
Aware versus impaired awareness
Motor versus nonmotor onset
Focal to bilateral tonic-clonic
Generalized onset
Motor
Tonic-clonic (formerly grand mal)
Other motor
Nonmotor (absence)
Unknown onset
Motor
Tonic-clonic
Other motor
Nonmotor
Unclassified

Source: Commission on Classification and Terminology of the International League Against Epilepsy, 2017.

Focal onset (also called partial) seizures originate in a small group of neurons (the seizure focus), and thus the symptoms depend on the location of the focus within the brain. Focal onset seizures can occur either without alteration of consciousness (often called simple partial) or with alteration of consciousness (often called complex partial). A typical focal onset seizure might begin with jerking in the right hand and progress to clonic movements (ie, jerks) of the entire right arm. If a focal onset seizure progresses further, the patient may lose consciousness, fall to the ground, rigidly extend all extremities (tonic phase), then have convulsive jerking in all extremities (clonic phase).

A focal onset seizure can be preceded by telltale symptoms called *auras*. Common auras include unprovoked and often vivid sensations such as a sense of fear, a rising feeling in the abdomen, or even a specific odor. The novelist Fyodor Dostoyevsky described his auras as a "feeling … so strong and sweet that for a few seconds of such bliss I would give ten or more years of my life, even my whole life perhaps." The aura is a product of electrical activity in the seizure focus and thus represents the earliest seizure manifestation. The time after a seizure but before the patient returns to his or her normal level of neurological function is called the post-ictal period.

Generalized onset seizures constitute the second main category. They begin without an aura or focal onset and involve both hemispheres from the onset. Thus, they are sometimes called primary generalized seizures to avoid confusion with seizures that secondarily generalize following a focal onset. Generalized onset seizures can be further divided into motor (convulsive) or nonmotor types depending on whether the seizure is associated with tonic-clonic movements.

The prototypic nonmotor generalized onset seizure is the *typical absence seizure* in children (formerly called petit mal). These seizures begin abruptly, usually last less than 10 seconds, are associated with staring and sudden cessation of all motor activity, and result in loss of awareness but not loss of posture. Patients appear as if in a trance, but the episodes are so brief that their occurrence can be missed by a casual observer. Unlike a focal onset seizure, there is no aura before the seizure or confusion after the seizure (the post-ictal period). Patients may exhibit mild motor manifestations such as eye blinking, but do not fall or have tonic-clonic movements. Typical absence seizures have very distinctive electrical characteristics on the electroencephalogram (EEG) known as a spike-and-wave pattern.

Some generalized onset seizures involve only abnormal (myoclonic, clonic, or tonic) movements or a sudden loss of motor tone (atonia). The most common motor type of generalized onset seizure is the tonic-clonic (formerly called *grand mal*) seizure. Such seizures begin abruptly, often with a grunt or cry, as tonic contraction of the diaphragm and thorax forces expiration. During the tonic phase, the patient may fall to the ground in a rigid posture with clenched jaw, lose bladder or bowel control, and become blue (cyanotic). The tonic phase typically lasts 30 seconds before evolving into clonic jerking of the extremities lasting 1 to 2 minutes. This active phase is followed by a post-ictal phase during which the patient is sleepy, disoriented, and may complain of headache and muscle soreness.

A generalized onset tonic-clonic seizure can be difficult to distinguish on purely clinical grounds from a focal seizure with a brief aura, which then rapidly progresses to a generalized tonic-clonic seizure. This distinction is not academic, as it can be vital to pinpointing the underlying cause and choosing the proper treatment. However, some seizures are simply difficult to classify because of undetermined onset.

Epilepsy Is a Chronic Condition of Recurrent Seizures

Recurrent seizures constitute the minimal criterion for the diagnosis of epilepsy. The oft-quoted clinical rule, "A single seizure does not epilepsy make," emphasizes this point, and even repeated seizures in response to a provocation such as alcohol withdrawal are not considered epilepsy. Various factors that contribute to a clinical pattern of recurrent seizures—the

underlying etiology of the seizures, the age of onset, or family history—are ignored in the classification scheme for seizures in Table 58–1. The classification of the epilepsies evolved primarily based on clinical observation rather than a precise cellular, molecular, or genetic understanding of the disorder. The factors influencing seizure type and severity can often be recognized as patterns of signs and symptoms, referred to as *epilepsy syndromes*. Such factors include the age of seizure onset, whether the seizures are inherited, and certain patterns on the EEG. The recognition of these syndromes has played a role in the recent discovery of single gene mutations as a cause of seizure disorders.

The primary variables in the classification of the epilepsies are whether or not a focal brain abnormality can be identified (localization-related versus generalized epilepsies) and whether there is an identifiable cause (symptomatic) or not (unknown, often called idiopathic). The great majority of adult-onset epilepsies are classified as symptomatic localization-related epilepsies. This category includes such causes as trauma, stroke, tumors, and infections. A large number of individuals have adult-onset epilepsies without a clearly defined cause.

Unfortunately, despite the usefulness of this classification scheme, many epilepsy syndromes do not fit neatly. One expects (and hopes) that this classification will be greatly refined as criteria include the underlying etiologies rather than just clinical phenotype.

The Electroencephalogram Represents the Collective Activity of Cortical Neurons

Because neurons are excitable cells, it should not be surprising that seizures result directly or indirectly from a change in the excitability of single neurons or groups of neurons. This view dominated early experimental studies of seizures. To study such effects, electrical recordings of brain activity can be made with intracellular or extracellular electrodes. Extracellular electrodes sense action potentials in nearby neurons and can detect the synchronized activity of ensembles of cells called *field potentials*.

At the slow time resolution of extracellular recording (hundreds of milliseconds to seconds), field potentials can appear as single transient changes called spikes. These spikes reflect action potentials in many neurons and should not be confused with spikes in recordings of single neurons, which are individual action potentials that last only 1 or 2 ms. The EEG thus represents a set of field potentials as recorded by multiple electrodes on the surface of the scalp (Figure 58–1).

Because the electrical activity originates in neurons in the underlying brain tissue, the waveform recorded by the surface electrode depends on the orientation and distance of the electrical source with respect to the electrode. The EEG signal is inevitably distorted by the filtering and attenuation caused by intervening layers of tissue and bone that act in the same way as resistors and capacitors in an electric circuit. Thus, the amplitude of EEG signals (measured in microvolts) is much smaller than the voltage changes in a single neuron (millivolts). High-frequency activity in single cells, such as action potentials, is filtered out by the EEG signal, which primarily reflects slower voltage changes across the cell membrane, such as synaptic potentials.

Although the EEG signal is a measure of the extracellular current caused by the summated electrical activity of many neurons, not all cells contribute equally to the EEG. The surface EEG reflects predominately the activity of cortical neurons in close proximity to each of the set of EEG electrodes on the scalp. Thus, deep structures such as the base of a cortical gyrus, mesial walls of the major lobes, hippocampus, thalamus, or brain stem do not contribute directly to the surface EEG. The contributions of individual nerve cells to the EEG are discussed in Box 58–1.

The surface EEG shows patterns of activity—characterized by the frequency and amplitude of the electrical activity—that correlate with various stages of sleep and wakefulness (Chapter 44) and with some pathophysiological processes such as seizures. The normal human EEG shows activity over the range of 1 to 30 Hz with amplitudes in the range of 20 to 100 μV. The observed frequencies have been divided into several groups: alpha (8–13 Hz), beta (13–30 Hz), delta (0.5–4 Hz), and theta (4–7 Hz).

Alpha waves of moderate amplitude are typical of relaxed wakefulness and are most prominent over parietal and occipital sites. During intense mental activity, beta waves of lower amplitude are more prominent in frontal areas and over other regions. Alerting relaxed subjects by asking them to open their eyes results in so-called desynchronization of the EEG with a reduction in alpha activity and an increase in beta activity (Figure 58–1B). Theta and delta waves are normal during drowsiness and early slow-wave sleep; if they are present during wakefulness, it is a sign of brain dysfunction.

As neuronal ensembles become synchronized, as when a subject relaxes or becomes drowsy, the summated currents become larger and can be seen as abrupt changes from the baseline activity. Such "paroxysmal" activity can be normal, eg, the episodes of high-amplitude activity (1–2 seconds, 7–15 Hz) that occur during sleep (sleep spindles). However, a sharp

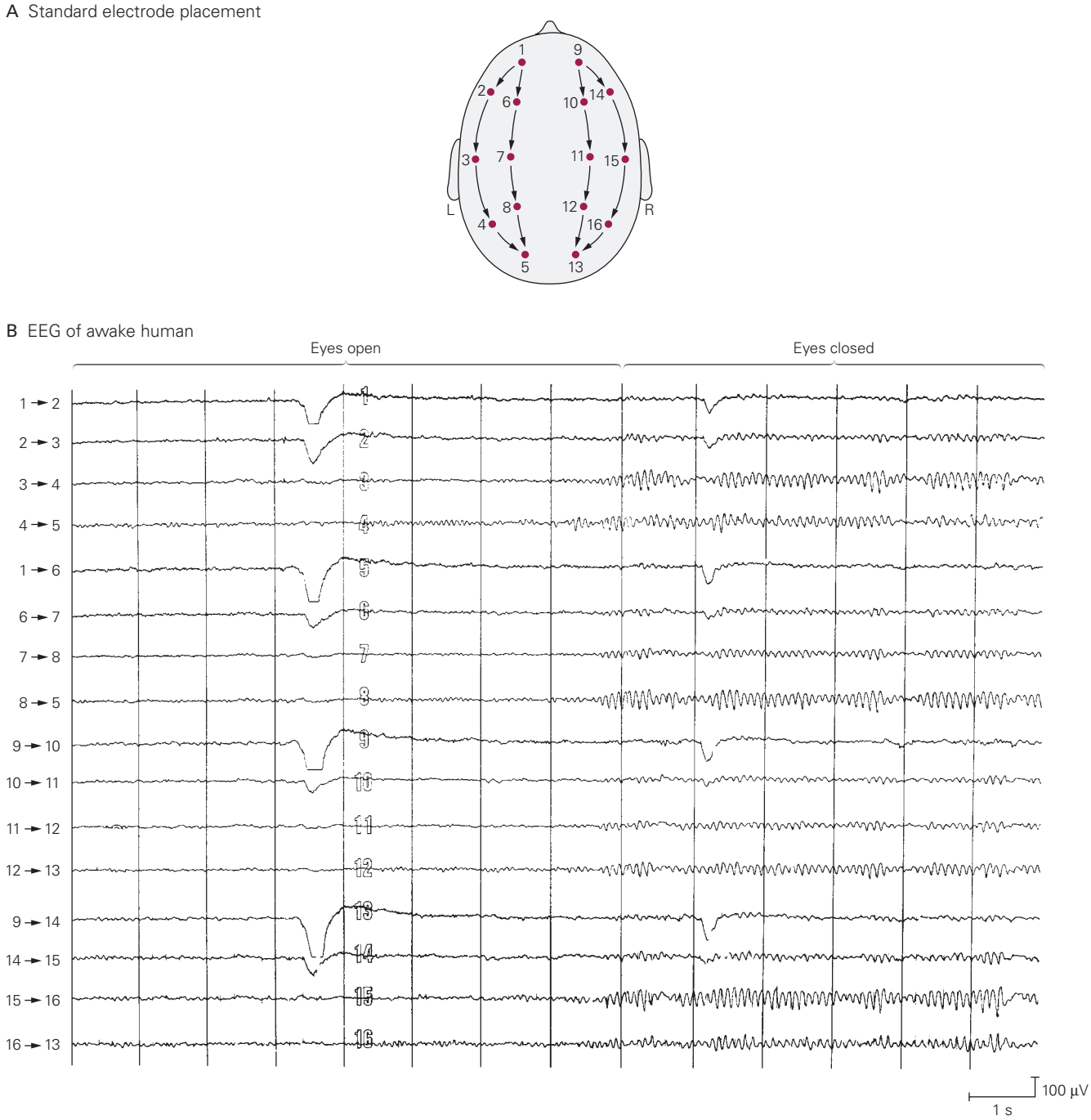

Figure 58–1 The normal electroencephalogram (EEG) in an awake human subject.

A. A standard set of placements (or montage) of electrodes on the surface of the scalp. The electrical response at each site reflects the activity between two of the electrodes.

B. At the beginning of the recording, the EEG shows low-voltage activity (~20 µV) over the surface of the scalp. The **vertical lines** are placed at 1-second intervals. During the first 8 seconds, the subject was resting quietly with eyes open, and then the subject was asked to close his eyes. With the eyes closed, larger-amplitude activity (8–10 Hz) develops over the occipital region (sites 3, 4, 8, 12, 15, and 16). This is the normal alpha rhythm characteristic of the relaxed, wakeful state. Slow large-amplitude artifacts occur at 3.5 seconds when the eyes blink and at 9 seconds when the eyes close.

Box 58–1 The Contribution of Individual Neurons to the Electroencephalogram

The contribution of the activity of single neurons to the electroencephalogram (EEG) can be understood by examining a simplified cortical circuit and some basic electrical principles. Pyramidal neurons are the major projection neurons in the cortex. The apical dendrites of these cells, which are oriented perpendicular to the cell surface, receive a variety of synaptic inputs. Thus, synaptic activity in the pyramidal cells is the principal source of EEG activity.

To understand the contribution of a single neuron to the EEG, consider the flow of charge produced by an excitatory postsynaptic potential (EPSP) on the apical dendrite of a cortical pyramidal neuron (Figure 58–2). Ionic current enters the dendrite at the site of generation of the EPSP, creating what is commonly called a current sink. It then must complete a loop by flowing down the dendrite and back out across the membrane at other sites, creating a current source.

The voltage signal created by a synaptic current is approximately predicted by Ohm's law ($V = IR$, where V is voltage, I is current, and R is resistance). Because the membrane resistance (R_m) is much larger than that of the salt solution that constitutes the extracellular medium (R_e), the voltage recorded across the membrane with an

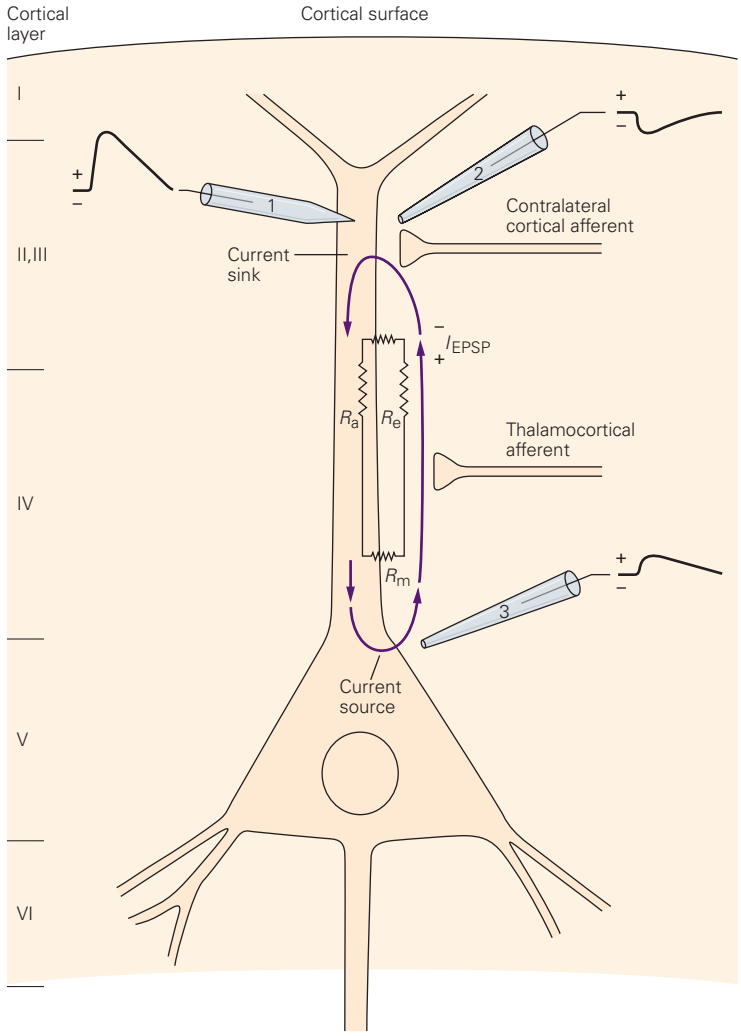

Figure 58–2 The pattern of electrical current flow for an excitatory postsynaptic potential (EPSP) initiated at the apical dendrite of a pyramidal neuron in the cerebral cortex. Activity is detected by three electrodes: an intracellular electrode inserted in the apical dendrite (**1**), an extracellular electrode positioned near the site of the EPSP in layer II of the cortex (**2**), and an extracellular electrode near the cell body in layer V (**3**). At the site of the EPSP (current sink), positive charge flows across the cell membrane (I_{EPSP}) into the cytoplasm, down the dendritic cytoplasm, and then completes the loop by exiting through the membrane near the cell body (current source). The potentials recorded by the extracellular electrodes at the sink and at the source have opposite polarity; the potentials recorded by the intracellular electrode have the same polarity regardless of the site. R_m, R_a, and R_e are the resistances of the membrane, cytoplasm, and extracellular space, respectively.