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

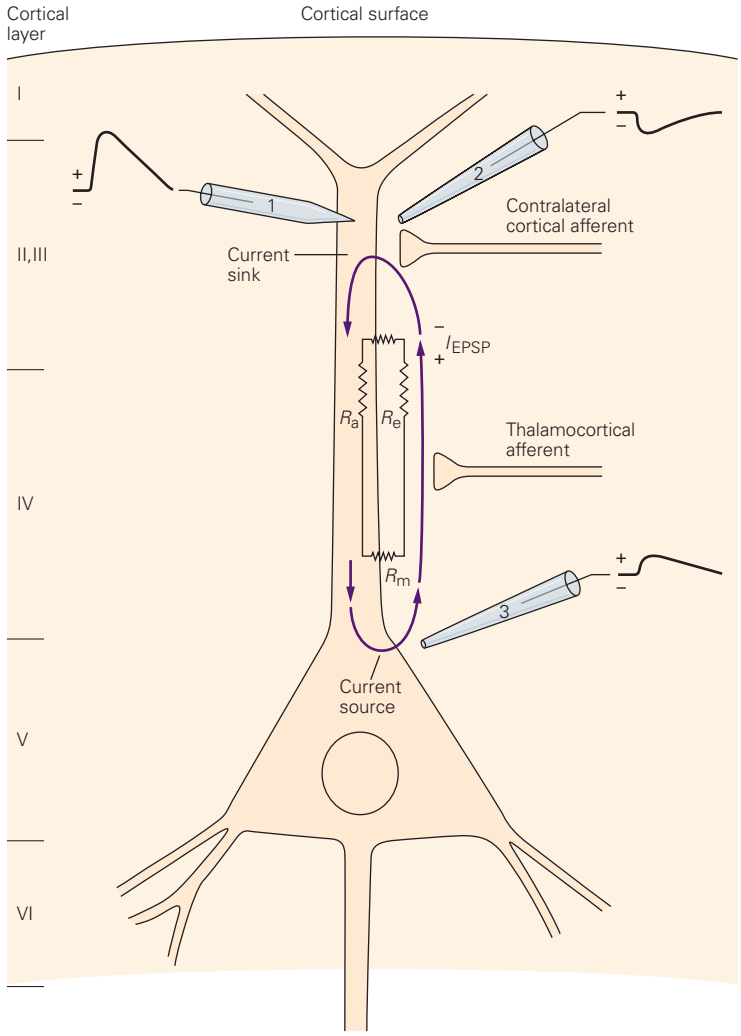

Figure 58–2 The pattern of electrical current flow for an excitatory postsynaptic potential (EPSP) initiated at the apical dendrite of a pyramidal neuron in the cerebral cortex. Activity is detected by three electrodes: an intracellular electrode inserted in the apical dendrite (**1**), an extracellular 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.

intracellular electrode (V_m) is also larger than the voltage at an extracellular electrode positioned near the current sink (V_e).

At the site of generation of an EPSP, the extracellular electrode detects the voltage change due to charge flowing away from the electrode into the cytoplasm as a negative voltage deflection. However, an extracellular electrode near the current source records a signal of opposite polarity (compare electrodes 1 and 3 in Figure 58–2). The situation is reversed if the site of the EPSP generation is on the basal segment of the apical dendrites.

In the cerebral cortex, excitatory axons from the contralateral hemisphere terminate primarily on dendrites in layers II and III, whereas thalamocortical axons terminate in layer IV (Figure 58–2). As a result, the activity measured by a surface EEG electrode will have opposite polarities for these two inputs even though the electrical event (membrane depolarization) is the same.

Similarly, the origin or polarity of cortical synaptic events cannot be unambiguously determined from surface EEG recordings alone. EPSPs in superficial layers and inhibitory postsynaptic potentials (IPSPs) in deeper layers both appear as upward (negative) potentials, whereas EPSPs in deeper layers and IPSPs in superficial layers have downward (positive) potentials (Figure 58–3).

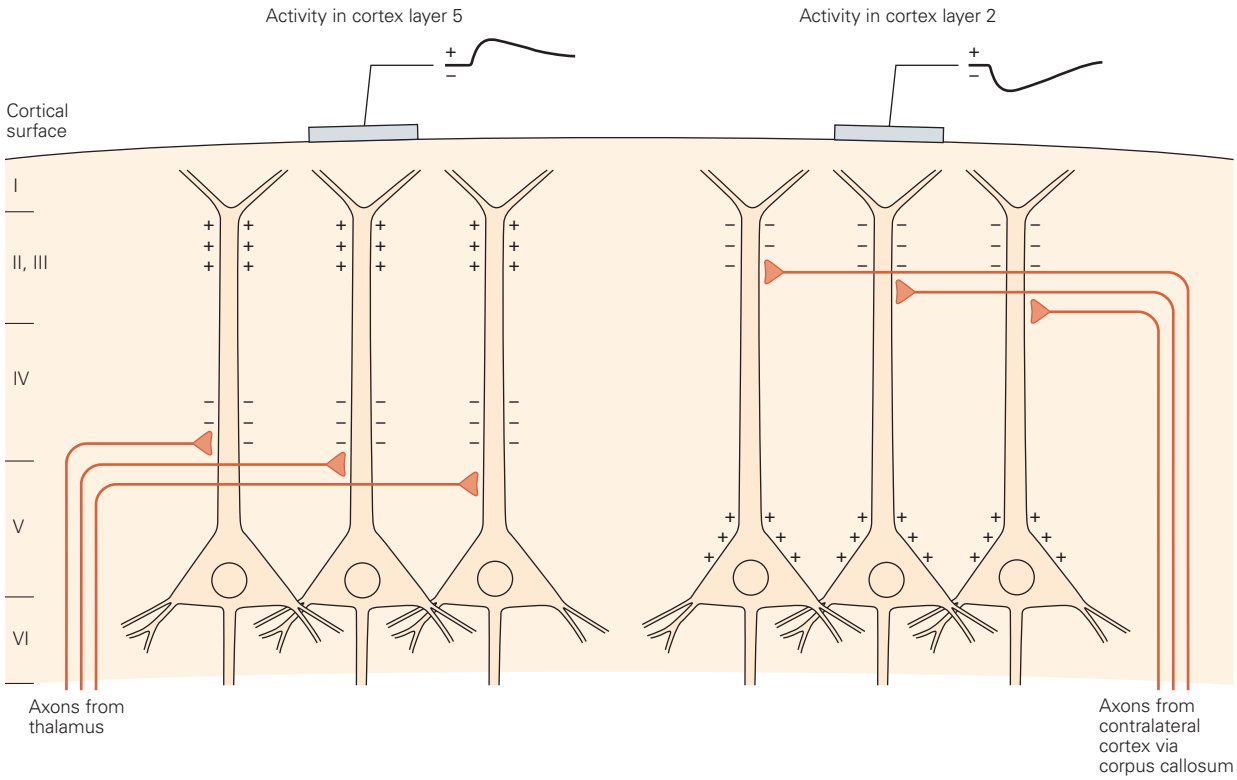

Figure 58–3 Surface electroencephalogram (EEG) recordings do not unambiguously indicate the polarity of synaptic events. The polarity of the surface EEG depends on the location of the synaptic activity within the cortex. A thalamocortical excitatory signal in layer V causes an upward voltage deflection at the surface EEG electrode because the electrode is nearer the current source. In contrast, an excitatory signal from the contralateral hemisphere in layer II causes a downward deflection because the electrode is nearer the sink.

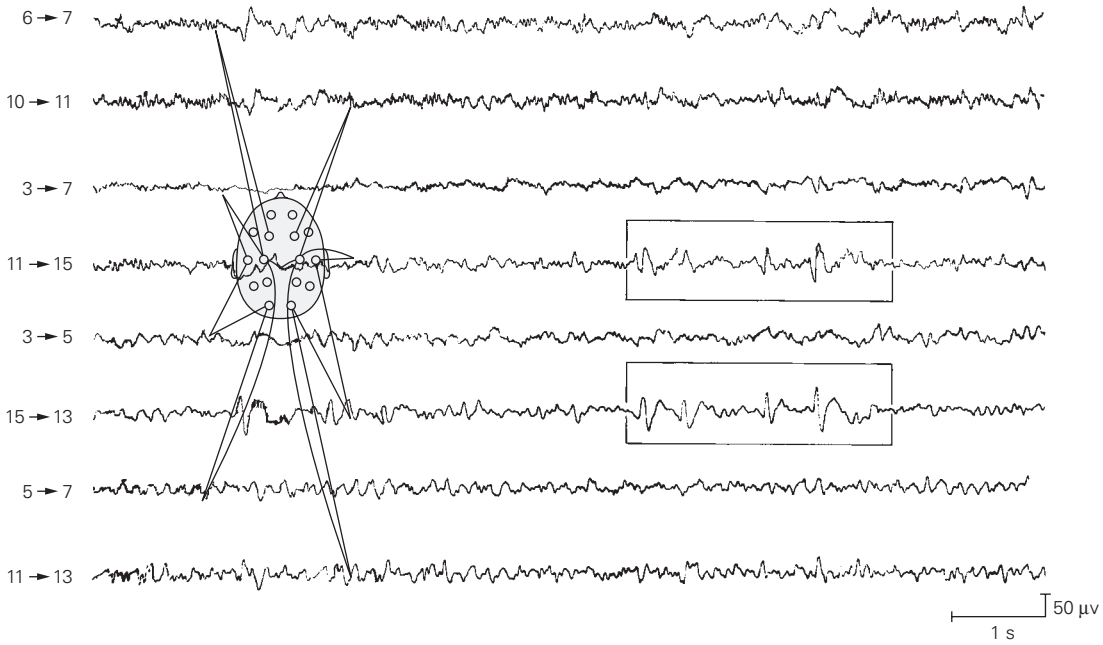

Figure 58–4 The electroencephalogram (EEG) can provide clues to the location of a seizure focus. Each trace represents the electrical activity between pairs of scalp electrodes as indicated in the electrode map. For example, electrode pairs 11–15 and 15–13 measure activity from the right temporal area. EEG activity in a patient with epilepsy shows sharp waves in the electrodes over the right temporal area (record enclosed in boxes). Such paroxysmal activity arises suddenly and disrupts the normal background EEG pattern. The focal abnormality may indicate that the seizure focus in this patient is in the right temporal lobe. Because the patient had no clinical seizures during the recording, these are interictal spikes (see Figure 58-7). (Adapted, with permission, from Lothman and Collins 1990.)

wave or EEG spike can also provide a clue to the location of a seizure focus in a patient with epilepsy (Figure 58–4). New recording and analytical methods such as spectral analysis of the EEG are increasingly being used to detect abnormal zones of synchrony (fast ripples) within a seizure focus.

Focal Onset Seizures Originate Within a Small Group of Neurons

Despite the variety of clinically defined seizures, important insights into the generation of seizure activity can largely be understood by comparing the electrographic patterns of focal onset seizures with those of generalized onset seizures.

The defining feature of focal onset seizures is that the abnormal electrical activity originates from a *seizure focus*. The seizure focus is considered to be nothing more than a small group of neurons, perhaps 1,000 or so, that have enhanced excitability and the ability to occasionally spread that activity to neighboring regions and thereby cause a seizure. The enhanced excitability (epileptiform activity) may result from many different factors such as altered cellular properties, glial dysfunction, or altered synaptic connections caused by a local scar, blood clot, or tumor. The development of a focal onset seizure can be arbitrarily divided into four phases: (1) the interictal period between seizures followed by (2) synchronization of activity within the seizure focus, (3) seizure spread, and finally, (4) secondary generalization. Phases 2 to 4 represent the ictal phase of the seizure. Different factors contribute to each phase.

Much of our knowledge about the electrical events during seizures comes from studies of animal models of focal onset seizures. A seizure is induced in an animal by focal electrical stimulation or by acute injection of a convulsant agent. This approach along with in vitro studies of tissue from these animal models has provided a good understanding of electrical events within the focus during a seizure as well as during the onset of the interictal period.

Neurons in a Seizure Focus Have Abnormal Bursting Activity

How does electrical activity in a single neuron or group of neurons lead to a focal onset seizure? Each neuron

within a seizure focus has a stereotypic and synchronized electrical response, the paroxysmal depolarizing shift, a depolarization that is sudden, large (20–40 mV), and long-lasting (50–200 ms), and that triggers a train of action potentials at its peak. The paroxysmal depolarizing shift is followed by an afterhyperpolarization (Figure 58–5A).

The paroxysmal depolarizing shift and afterhyperpolarization are shaped by the intrinsic membrane properties of the neuron (eg, voltage-gated Na^+, K^+, and Ca^{2+} channels) and by synaptic inputs from excitatory and inhibitory neurons (primarily glutamatergic and GABAergic, respectively). The depolarizing phase results primarily from activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)- and *N*-methyl-D-aspartate (NMDA)-type glutamate receptor-channels (Figure 58–5A), as well as voltage-gated Na^+ and Ca^{2+} channels. NMDA-type receptor-channels are particularly effective in enhancing excitability because depolarization relieves Mg^{2+} blockage of the channel. Removal of the blockage increases current through the channel, thus enhancing the depolarization and allowing additional Ca^{2+} to enter the neuron (Chapter 13).

The normal response of a cortical pyramidal neuron to excitatory input consists of an excitatory postsynaptic potential (EPSP) followed by an inhibitory postsynaptic potential (IPSP) (Figure 58–5B). Thus, the paroxysmal depolarizing shift can be viewed as a massive enhancement of these depolarizing and hyperpolarizing synaptic components. The afterhyperpolarization is generated by voltage-dependent and Ca^{2+}-dependent K^+ channels as well as by a γ-aminobutyric acid (GABA)-mediated Cl^- conductance (ionotropic $GABA_A$ receptors) and K^+conductance (metabotropic $GABA_B$ receptors) (Figure 58–5A). The Ca^{2+} influx through voltage-dependent Ca^{2+} channels and NMDA-type receptor-channels triggers the opening of calcium-activated channels, particularly K^+ channels. The afterhyperpolarization limits the duration of the paroxysmal depolarizing shift, and its gradual disappearance is the most important factor in the onset of a focal onset seizure, as discussed later.

Thus, it is not surprising that many convulsants act by enhancing excitation or blocking inhibition. Conversely, anticonvulsants can act by blocking excitation or enhancing inhibition. For example, the benzodiazepines diazepam (Valium) and lorazepam (Ativan) enhance $GABA_A$-mediated inhibition and are used in the emergency treatment of prolonged repetitive seizures. The anticonvulsants phenytoin (Dilantin) and carbamazepine (Tegretol) and several others reduce the opening of voltage-gated Na^+ channels that underlie the action potential. Molecular models of the Na^+ channel indicate that these drugs are more effective when the channel is in the open or activated state.

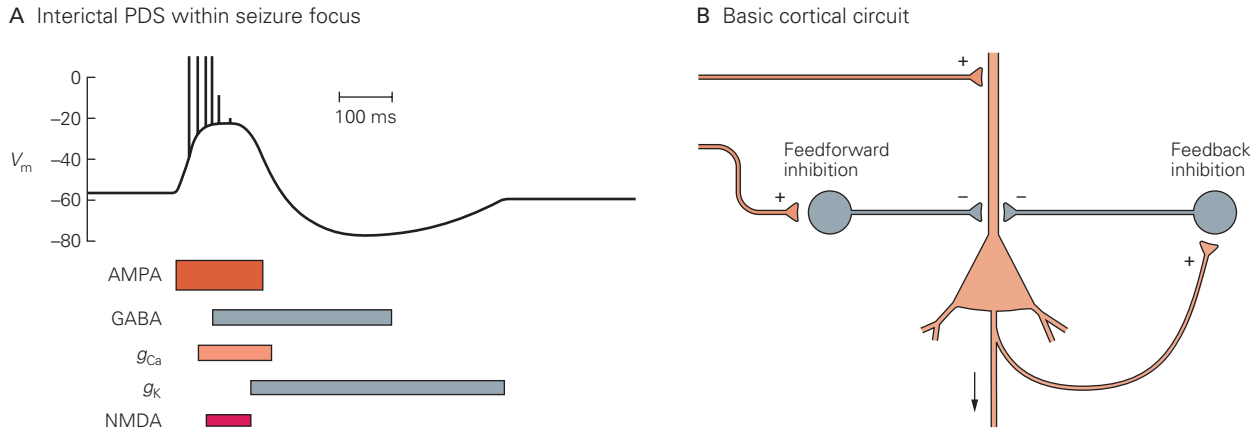

Figure 58–5 The conductances that underlie the paroxysmal depolarizing shift of a neuron in a seizure focus.

A. The paroxysmal depolarizing shift (**PDS**) is largely dependent on α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (**AMPA**)- and *N*-methyl-D-aspartate (**NMDA**)-type glutamate receptor-channels whose effectiveness is enhanced by the opening of voltage-gated Ca^{2+} channels (g_{Ca}). Following the depolarization, the cell is hyperpolarized by activation of γ-aminobutyric acid (**GABA**) receptors (both ionotropic $GABA_A$ and metabotropic $GABA_B$) as well as by voltage-gated and calcium-activated K^+ channels (g_K). (Adapted, with permission, from Lothman 1993a.)

B. Recurrent axon branches activate inhibitory neurons and cause feedback inhibition of the pyramidal neuron. Extrinsic excitatory inputs can also activate feedforward inhibition. The PDS represents exaggerated excitation in a seizure focus, whereas the inhibitory circuitry forms the basis of surround inhibition, important in restricting interictal activity to the seizure focus.

Thus, fittingly, the ability of these drugs to block Na^+ channels is enhanced by repetitive activity associated with seizures; that is, the greatest effect is in those neurons that need to be silenced the most.

The Breakdown of Surround Inhibition Leads to Synchronization

As long as the abnormal electrical activity is restricted to a small group of neurons, there are no clinical manifestations. The synchronization of neurons in a seizure focus is dependent not only on the intrinsic properties of each individual cell but also on the number and strength of connections between neurons. During the interictal period, the abnormal activity is confined to the seizure focus by inhibition of the surrounding tissue.

This "inhibitory surround," initially described by David Prince, is particularly dependent on feedforward and feedback inhibition by GABAergic inhibitory interneurons (Figure 58–6A). Although inhibitory circuits in the cerebral cortex are often represented by simple diagrams (Figure 58–6B), the morphology and connectivity of cortical inhibitory neurons are actually quite complex and a topic of continuing investigation with many new methods such as cell type–specific viral labeling and optogenetic stimulation.

During the development of a focal seizure, the excitation in the circuit overcomes the inhibitory

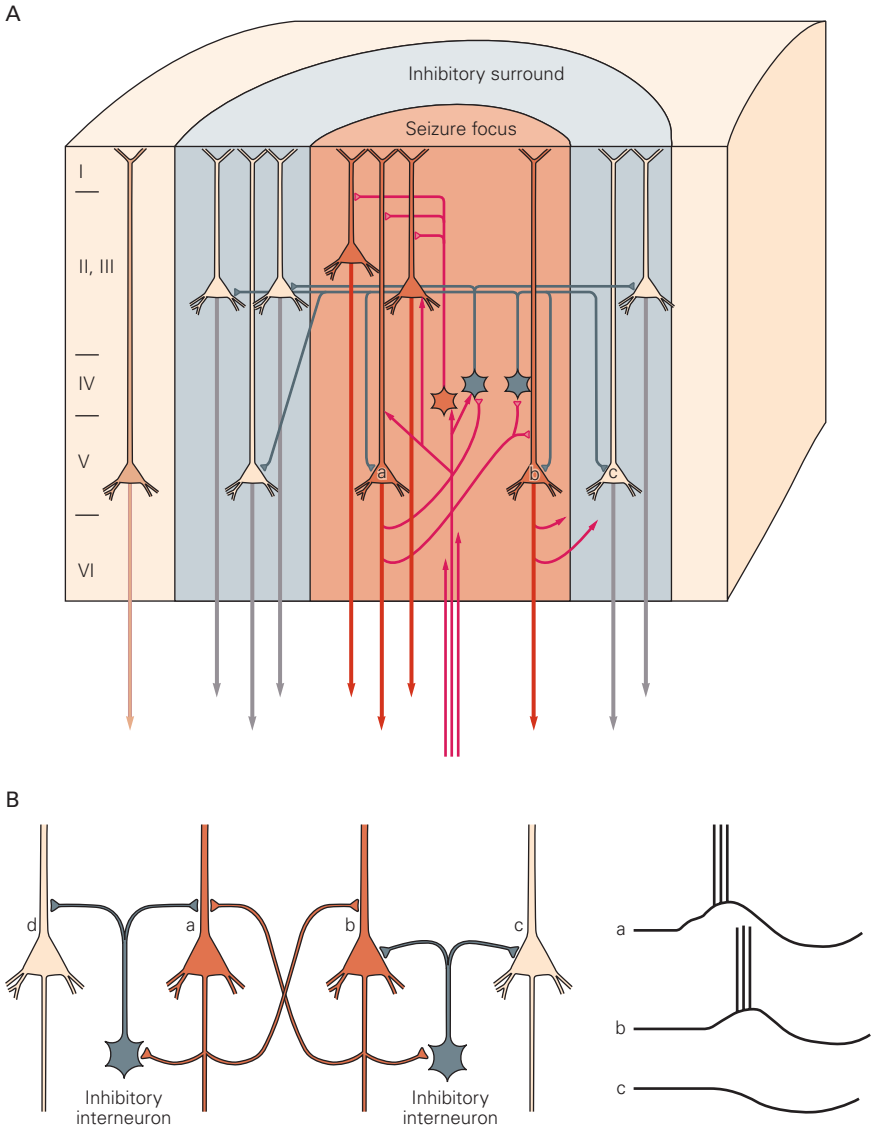

Figure 58–6 The spatial and temporal organization of a seizure focus depends on the interplay between excitation and inhibition of neurons in the focus.

A. The pyramidal cell *a* shows the typical electrical properties of neurons in a seizure focus (see part **B**). Excitation in cell *a* activates another pyramidal cell (*b*), and when many such cells fire synchronously, a spike is recorded on the electroencephalogram. However, cell *a* also activates γ-aminobutyric acid (GABA)-ergic inhibitory interneurons (**gray**). These interneurons can reduce the activity of cells *a* and *b* through feedback inhibition, thus limiting the seizure focus temporally, as well as prevent the firing of cells outside the focus, represented here by cell *c*. This latter phenomenon creates an inhibitory surround that acts to contain the hyperexcitability to the seizure focus during interictal periods. When extrinsic or intrinsic factors alter this balance of excitation and inhibition, the inhibitory surround begins to break down and the seizure activity spreads, leading to seizure generation. (Adapted, with permission, from Lothman and Collins 1990.)

B. The synaptic connections and activity patterns for cells *a*, *b*, and *c* shown in part **A**. Cells *a* and *b* (within the seizure focus) undergo a paroxysmal depolarizing shift, whereas cell *c* (in the inhibitory surround) is hyperpolarized due to input from GABAergic inhibitory interneurons.

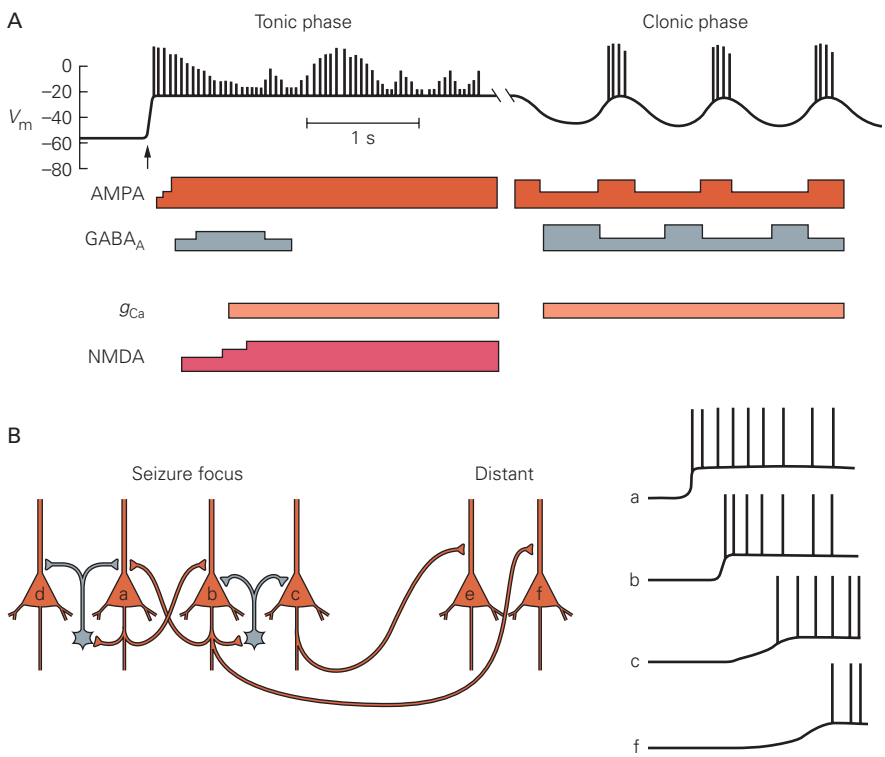

Figure 58–7 A focal onset seizure begins with the loss of the afterhyperpolarization and surround inhibition. (Adapted, with permission, from Lothman 1993a.)

A. With the onset of a seizure (**arrow**), neurons in the seizure focus depolarize as in the first phase of a paroxysmal depolarizing shift. However, unlike the interictal period, the depolarization persists for seconds or minutes. The γ-aminobutyric acid (**GABA**)-mediated inhibition fails, whereas excitatory activity in the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (**AMPA**)- and *N*-methyl-D-aspartate (**NMDA**)-type glutamate receptors is functionally enhanced. This activity corresponds to the tonic phase of a secondarily generalized tonic-clonic seizure. As the GABA-mediated inhibition gradually returns, the neurons in the seizure focus enter a period of oscillation corresponding to the clonic phase.

B. As the surround inhibition breaks down, neurons in the seizure focus become synchronously excited and send trains of action potentials to distant neurons, thus spreading the abnormal activity from the focus. Compare this pattern of activity in cells *a* to *c* with that during the interictal period (Figure 58–6B).

surround, and the afterhyperpolarization in the neurons of the original focus gradually disappears. As a result, a nearly continuous high-frequency train of action potentials is generated, and the seizure begins to spread beyond the original focus (Figure 58–7).

An important factor in the spread of focal onset seizures appears to be that the intense firing of the pyramidal neurons results in a relative decrease in synaptic transmission from the inhibitory GABAergic interneurons, although the interneurons remain viable. Whether this decrease results from a presynaptic change in the release of GABA or a postsynaptic change in GABA receptors is still not understood and may not be the same in all cases. Other factors that may contribute to the loss of the inhibitory surround over time include changes in dendritic morphology, the density of receptors or channels, or a depolarizing shift in E_K caused by extracellular K^+ ion accumulation. Prolonged firing also transmits action potentials to distant sites in the brain, which in turn may trigger trains of action potentials in neurons that project back to neurons in the seizure focus (backpropagation). Reciprocal connections between the neocortex and thalamus may be particularly important in this regard.

Despite our understanding of such mechanisms, we still do not know what causes a seizure to occur at any particular moment. The inability to predict when a seizure will occur is perhaps the most debilitating aspect of epilepsy. New approaches to this dilemma are discussed in Box 58–2. Some patients learn to recognize the triggers most critical for them, such as sleep deprivation or stress, and thus adjust their lifestyle to avoid these circumstances. But in many individuals, seizures do not follow a predictable pattern.

In a few patients, sensory stimuli such as flashing lights can trigger seizures, suggesting that repeated excitation of some circuits causes a change in excitability. For example, NMDA-type glutamate receptor activity and GABAergic inhibition can undergo changes dependent on the frequency of firing of the presynaptic neuron. This provides one possible molecular mechanism for such changes in network excitability. On a longer time scale, circadian rhythms and hormonal patterns may also influence the likelihood

Box 58–2 New Approaches to Real-Time Seizure Detection and Prevention

Perhaps the most disabling aspect of seizures and epilepsy is the uncertainty of it all—when will the next seizure occur? As you can imagine, this impacts employment, driving, and recreation and often prevents the development of an individual's full potential. Patients with epilepsy sometimes have a brief warning or aura, but rarely do they have enough time to institute a therapeutic intervention such as a pill or an injection in order to abort the seizure.

Clinicians and epilepsy researchers have long recognized the importance of real-time seizure *detection* and real-time seizure *prevention* as a goal of therapy. Of course, acute detection must precede an acute treatment. However, in general, this approach has only been possible in patients undergoing EEG monitoring either with surface EEG electrodes or implanted electrodes. Several technologies are now emerging that allow new hope for detection, and thus enable efforts to abort or prevent an imminent seizure. Most are still in the experimental phase in animal models, but a few have reached clinical trials and even, in the case of vagal nerve stimulators, clinical practice. Seizure prevention can be imagined in two general ways: either altering the excitability of large regions of brain or somehow interrupting activity within a seizure focus. These two approaches can also be considered in engineering terms as open-loop or closed-loop strategies, respectively.

The first approach led to the development in 1997 of the vagal nerve stimulator, implanted in the neck and powered by a pacemaker-style battery (Figure 58–8). The

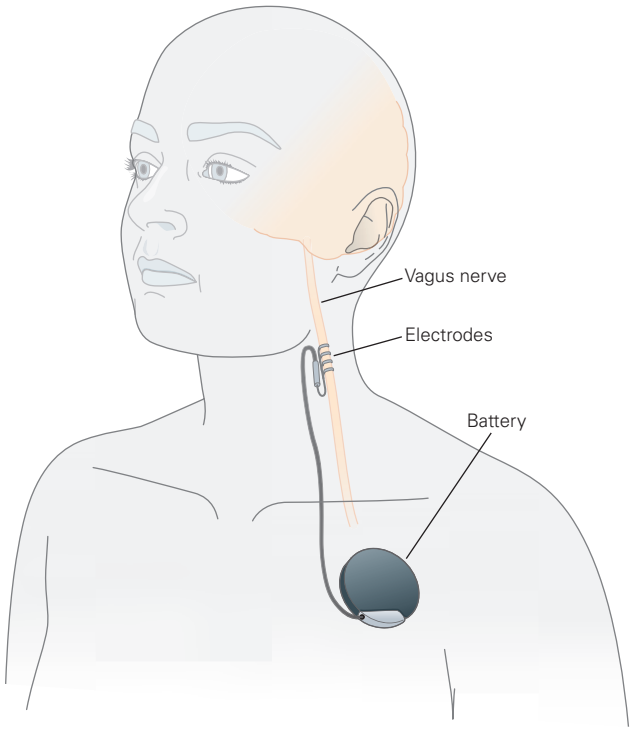

Figure 58–8 Vagal nerve stimulation. Schematic of placement of electrodes on the left vagus nerve powered by a battery implanted subcutaneously in the chest wall. The stimulation can be programmed at regular intervals (eg, every 30 seconds) and can also be activated on demand by placing a magnet over the chest. (Adapted from Stacey and Litt 2008.)

resulting chronic, intermittent stimulation of the vagus nerve has been effective in reducing seizure frequency in some patients. The patient can also activate the stimulator with a hand-held magnet during an aura to see if acute stimulation can prevent a seizure. The exact mechanism of seizure reduction by vagal nerve stimulation is still unclear, but presumably involves activation of the autonomic nervous system, and thus, this form of stimulation has limited specificity to particular brain regions.

Because many patients with intractable epilepsy have seizures that originate from one or more discrete foci in the brain, it would obviously be ideal to be able to detect abnormal activity within a seizure focus, and thus through some sort of feedback mechanism deliver a stimulus that would abort the spread of epileptiform activity from that focus. This goal has been an active area of investigation over the past decade, leading to a clinical trial the results of which were recently published. The device tested was a chronically implanted neurostimulator (RNS System, Neuropace) that directly stimulates the seizure focus when epileptiform activity is detected (Figure 58–9).

In this multicenter double-blinded trial, the device was implanted in patients with intractable focal onset seizures with one or two seizure foci. The patients were monitored for an average of 5 years. The device can be programmed by the clinician to match characteristics for each patient. The patients were randomized into two groups, responsive stimulation or sham stimulation groups, for the first 5 months, and then followed for up to 2 years. There was a 44% reduction in seizure frequency after 1 year and a 53% reduction after 2 years, suggestive of a progressive effect. The device was generally well tolerated. Thus, this approach has therapeutic potential for some patients and provides proof-of-concept evidence for closed-loop seizure detection and stimulation.

The RNS System uses electrical stimulation, but other strategies being studied in animals promise to refine methods of seizure prevention. These include neuronal stimulation or silencing using viral-mediated delivery of opto- or chemogenetic probes. In general, a replication-defective virus can be targeted to a specific cell type within a brain region. In the optogenetic approach, the virus is engineered to express ion channels or pumps that reduce neuron excitability when exposed to light. In the chemogenetic approach, a chemical is delivered systemically. This strategy has now been successfully employed in animal models of epilepsy.

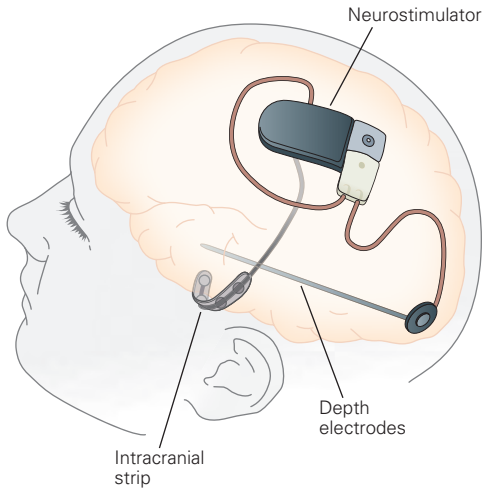

Figure 58–9 Closed-loop seizure detection and prevention. This schematic diagram of the closed-loop RNS System shows the intracranial strip and depth electrodes that detect seizure activity and subsequently deliver programmed stimulation to the seizure focus. (Adapted, with permission, from Heck et al. 2014.)

The optogenetic strategy is similar to the neurostimulator except that stimulation is delivered through a fiber optic light guide implanted near the seizure focus. The advantage of this approach is that the virus is engineered to deliver stimulation to a specific population of neurons. The chemogenetic approach has the advantage of noninvasive delivery of the chemical, but lacks the speed that can be achieved with optical or electrical stimulation. Even when optimized and tested in clinical trials, these invasive approaches are likely to be useful only in a subset of focal onset epilepsies that have stable and well-defined seizure foci. Thus, continuing and complementary efforts to understand the genetic mechanisms of epileptogenesis, as well as new technologies such as stem cell therapies, remain essential.

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

The Spread of Seizure Activity Involves Normal Cortical Circuitry

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

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

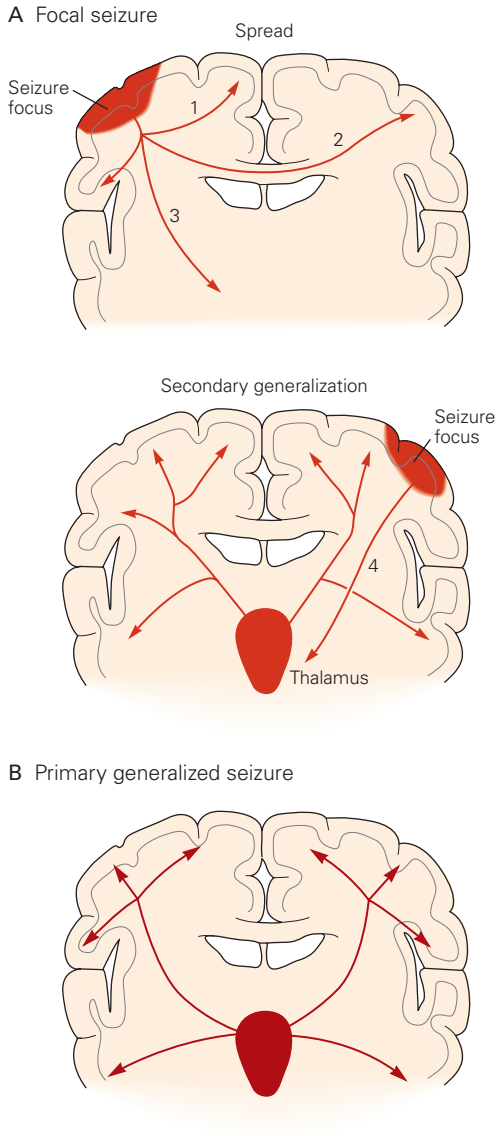

Figure 58–10 Focal and generalized onset seizures propagate via several pathways. (Adapted, with permission, from Lothman 1993b.)

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

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