

ON THE CELLULAR AND NETWORK BASES OF EPILEPTIC SEIZURES

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■ **Abstract** The highly interconnected networks of the mammalian forebrain can generate a wide variety of synchronized activities, including those underlying epileptic seizures, which often appear as a transformation of otherwise normal brain rhythms. The cerebral cortex and hippocampus are particularly prone to the generation of the large, synchronized bursts of activity underlying many forms of seizures owing to strong recurrent excitatory connections, the presence of intrinsically burst-generating neurons, ephaptic interactions among closely spaced neurons, and synaptic plasticity. The simplest form of epileptiform activity in these structures is the interictal spike, a synchronized burst of action potentials generated by recurrent excitation, followed by a period of hyperpolarization, in a localized pool of pyramidal neurons. Seizures can also be generated in response to a loss of balance between excitatory and inhibitory influences and can take the form of either tonic depolarizations or repetitive, rhythmic burst discharges, either as clonic or spike-wave activity, again mediated both by intrinsic membrane properties and synaptic interactions. The interaction of the cerebral cortex and the thalamus, in conjunction with intrathalamic communication, can also generate spike waves similar to those occurring during human absence seizure discharges. Although epileptic syndromes and their causes are diverse, the cellular mechanisms of seizure generation appear to fall into only two categories: rhythmic or tonic “run-away” excitation or the synchronized and rhythmic interplay between excitatory and inhibitory neurons and membrane conductances.

INTRODUCTION

Clinical epilepsy is a diverse disorder of which there are over 40 recognized types segregated into distinct epileptic syndromes (1). This diversity arises from both the numerous underlying cellular and molecular mechanisms, as well as from the spatial and temporal characteristics of the seizure. Most epileptic syndromes are grouped in two basic categories: partial and generalized. Partial seizures occur

within a localized area of the brain, whereas generalized seizures appear (at least on the level of the electroencephalogram) throughout the forebrain from the outset. If the partial seizure does not cause a disruption of consciousness or cognitive abilities, then it is said to be simple; if it does, then it is referred to as complex. There is great diversity in the pathologies leading to, and clinical manifestations of, the epileptic syndrome, yet it is thought that the actual generation of many of the different types of seizure may occur through common cellular mechanisms and networks. Although practically every part of the brain may generate an epileptic seizure, the investigation of the cellular and network mechanisms of epilepsy over the last several decades has focused largely on three structures: the cerebral cortex, the hippocampus (and related structures), and the thalamus. Investigation of the possible mechanisms for generation of partial, complex partial, and generalized seizures in these structures has demonstrated that every aspect of neuronal and glial function, from genes to synapses to networks, has at least a modulatory influence. Extensive and informative reviews of many of these aspects are available (see 2–14a). Here, we focus on the neurophysiological mechanisms for generation of epileptiform activity within thalamocortical, cortical, and hippocampal networks, with a particular emphasis on network mechanisms.

NEOCORTICAL AND HIPPOCAMPAL MECHANISMS OF EPILEPTIFORM ACTIVITIES

Both the neocortex and the hippocampus are prone to the generation of epileptiform activity and seizures. There are multiple factors contributing to the epileptogenicity of these structures, including the presence of massive recurrent excitatory connections, reliance upon inhibition for the regulation of excitability of this recurrent network, the ability of synaptic connections to strengthen or weaken with repetitive activation, the presence of intrinsically burst-generating cells, and finally a strong influence from ion regulation and perhaps other ephaptic (non-synaptic) interactions (reviewed in 5–7, 10, 14).

Single, Synchronized Bursts: Cellular Mechanisms of the Interictal Spike

The simplest identifiable unit of epileptiform activity in the central nervous system (CNS) is the interictal (between seizures) spike. Interictal spikes are brief (80–200 ms), large, sharp spikes in the EEG that occur in isolation on a background of otherwise normal activity (Figure 1A). They appear in a subpopulation of patients with focal epilepsy and are not, as individual events, associated with overt changes in cognitive abilities or behavior. Interictal spikes may serve to localize the epileptogenic focus, but they are not always detected from the primary focus from which seizures originate. The intracellular correlate of the interictal spike is an overt depolarization, called the paroxysmal depolarizing shift (PDS) (Figure 1B), that

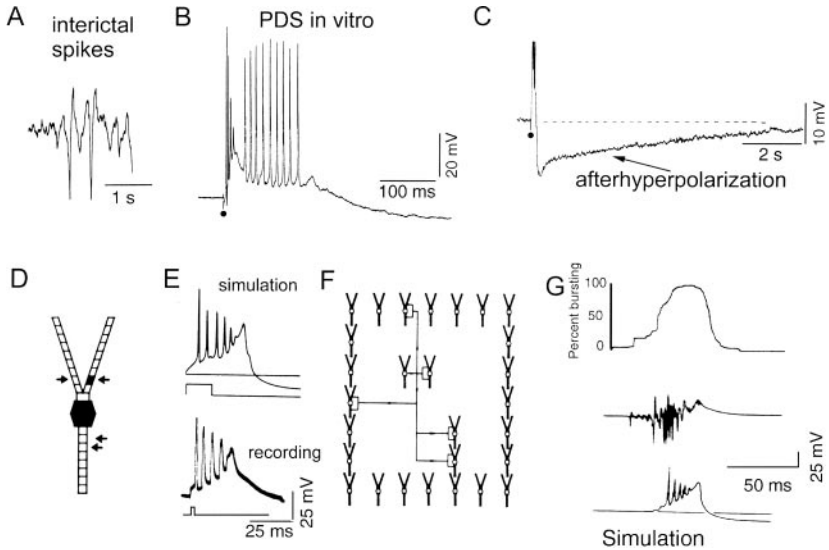


Figure 1 Interictal spike generation in hippocampus and cortex. (A) Example of two interictal spikes in the human EEG. Interictal spikes are brief (~ 0.1 s) events typically localized to a particular region of the forebrain. (B) Intracellular recording in a human cortical pyramidal cell maintained in a cortical slice *in vitro* during the generation of an epileptiform burst similar to that underlying the generation of interictal spikes. The depolarization underlying the epileptiform activity is termed a paroxysmal depolarization shift (PDS) and results in the initiation of a high-frequency burst of action potentials. (C) The PDS in the human cortical neuron is followed by a prolonged after-hyperpolarization that is generated by the activation of various K^+ currents. (D) Compartmental model of a single CA3 burst-generating pyramidal neuron. Arrows indicate location of excitatory inputs to modeled cells. (E) Intracellular injection of a short-duration depolarizing current pulse in a CA3 pyramidal neuron (bottom traces) or in the model of one of these cells (top traces) results in an intrinsic burst of action potentials. (F) Diagrammatic illustration of the modeled network of CA3 burst-generating pyramidal cells. Each pyramidal neuron synaptically excites multiple pyramidal cells. (G) Simulation of a synchronized burst of epileptiform activity in the stimulated network of CA3 pyramidal neurons. Initially, a few pyramidal neurons synchronously discharge, and this activity rapidly recruits other neurons into the epileptiform burst. The network activity fails as the percentage of neurons generating action potentials decreases dramatically, owing to spike inactivation and/or hyperpolarization. The simulated EEG (local field potential) includes high-frequency components from the synchronous action potential discharge of the neurons. The bottom trace is the membrane potential of one representative neuron (B and C from 43; D-G from 152).

last tens of milliseconds and can be so large that it leads to sodium-spike inactivation. The mechanisms for generation of interictal spikes derive from a basic and ubiquitous operation of neocortical and hippocampal networks: the activation of brief periods dominated by synaptic excitation between pyramidal cells followed by a period dominated by synaptic inhibition and/or activation of intrinsic hyperpolarizing conductances. Indeed, in cortical structures, most if not all epileptic activities derive from some type of imbalance between depolarizing and hyperpolarizing influences (synaptic, ion concentration regulation, or intrinsic membrane properties) in a large interconnected network of neurons. This imbalance in cortical networks can be experimentally induced by a variety of methods. Examples include reducing the efficiency of GABAergic inhibition through the application of GABA_A receptor antagonists, increasing the excitability of neuronal elements and reducing the effectiveness of hyperpolarizing conductances by raising the extracellular concentration of K⁺, and enhancing synaptic transmission by reducing some K⁺ currents with the application of 4-aminopyridine. Additional methods such as modifying synaptic strength through repetitive electrical stimulation (e.g. kindling), enhancing excitatory synaptic transmission through NMDA receptors and reducing GABA_A receptor-mediated inhibition by removing Mg²⁺ from the extracellular medium, and other manipulations may also induce epileptiform activities (see 5, 6, 10, 11). In all models of cortical epileptogenesis, except for the generation of epileptiform activity through ephaptic interactions (see below), the generation of seizures is completely dependent upon neurotransmission.

In the neocortex, cortical pyramidal cells in all layers project both locally and to other layers of the cortex, contacting other pyramidal cells (or spiny stellate neurons in layer IV) as well as local GABAergic interneurons. Typically, only one or a few synaptic contacts are made between each pyramidal cell and each of its target neurons (see 15), keeping the influence of most neurons on any other particular neuron relatively weak. However, each cortical neuron receives a large number (thousands) of excitatory synaptic inputs from a wide variety of sources, most of which are other cortical neurons, and therefore there is much divergence and convergence in cortical networks. The synaptic output of cortical pyramidal cells is often densest near the cell of origin, although patchy horizontal connections to functionally relevant and neighboring regions of cortex are also prominent (16, 17). Long-range and extensive connections to other cortical areas are characteristics of a subpopulation of cortical pyramidal cells (18), and functionally related cortical areas are highly interconnected, allowing for the rapid dissemination of neuronal activity (19). Each subclass of GABAergic interneuron exhibits its own unique connectivity (reviewed in 20), and each of the different types of synaptic connections within the cerebral cortex, both inhibitory and excitatory, have their own unique temporal properties (21, 22) that may be specifically modulated with experience and neurotransmitters (23). In addition to synaptic interactions, GABAergic neurons in the cortex also form gap junctions with other select subgroups of GABAergic cells, allowing for the fast synchronization of local networks (24–26).

Like the neocortex, the hippocampus contains a network of richly interconnected excitatory cells (e.g. pyramidal neurons) that are regulated by a wide diversity of inhibitory interneurons (reviewed by 27). In addition to the classic trisynaptic loop, from dentate granule cells, to CA3 pyramidal neurons, to CA1 pyramidal cells, there are also extensive associational connections (particularly within CA3), longitudinal connections along the length of the hippocampus, and commissural fibers connecting the two hippocampi, as well as extensive excitatory connections with related cortical structures such as the subiculum and entorhinal cortex.

The great complexity of cortical and hippocampal networks allows them to perform their varied tasks. However, one consequence of the massive interconnectivity of excitatory cells in both structures is the generation of “runaway” excitation if the recurrent excitation inherent in these networks is left unchecked. This is apparently the case, at least to some degree, in the generation of interictal spikes. The recurrent network of excitatory connections, both within the neocortex and hippocampus, results in a rapid excitation of other excitatory cells through the activation of non-NMDA and NMDA glutamatergic ionotropic receptors, causing a rapid recruitment of neurons into the epileptiform event (Figure 1D–G). Although all layers of the cerebral cortex and regions of the hippocampus appear to be capable of generating epileptiform activity, the cells that appear to discharge first during the generation of the so-called paroxysmal depolarizing shifts that underlie interictal spikes are layer V pyramidal neurons (28). Similarly, in the hippocampus, the CA3 field of pyramidal neurons exhibits a particular propensity to generate this pattern of abnormal activity (see 5, 10). This propensity, within layer V of the neocortex and CA3 of the hippocampus, relies not only on the excitatory interconnectivity of pyramidal neurons, but also on the presence of intrinsically burst-generating cells (Figure 1E).

Burst-Generating Cells in the Cortex and Hippocampus A subset of layer V neocortical neurons and CA3 pyramidal cells can intrinsically generate bursts of 2 to 5 action potentials at 200–350 Hz upon activation by a brief depolarization (Figure 1E). These burst discharges are generated through the activation in the dendrites of slow action potentials that are mediated by Na^+ and Ca^{2+} currents (29, 30) and provide a prolonged depolarization of the soma and axon initial segment, thus promoting repetitive firing during the burst. The generation of burst discharges is not unidirectional from the dendrite to the soma because action potentials generated in the soma can back-propagate into the dendrites, and trigger dendritic spikes (31). Similarly, CA1 pyramidal neurons in the hippocampus and superficial (layer 2, 3) pyramidal cells of the cerebral cortex may generate high-frequency bursts of action potentials, under particular circumstances, through an interaction between the activation of traditional action potentials in the soma/initial segment and the activation of Na^+ -dependent after-depolarizations following each action potential through the electrogenic properties of the dendrite (32–34). Recent investigations have confirmed earlier studies that CA1 pyramidal cells may also generate intrinsic bursts of spikes in response to strong or prolonged depolarization of the

dendrites through the activation of a dendritic Ca^{2+} spike (35, 36). These pyramidal neurons exhibit a relatively uniform distribution along the soma-dendritic axis of both Na^+ and Ca^{2+} channels (although individual subtypes are distributed non-homogeneously), but with a striking non-uniformity in the distribution of K^+ channels (reviewed in 36). Near the soma of CA1 pyramidal cells, there is a high density of BK Ca^{2+} -activated K^+ channels; the dendrites appear to have a higher density of transient K^+ channels (such as I_A and I_D). This distribution of depolarizing and hyperpolarizing channels limits the back-propagation of action potentials from the soma to the dendrites (owing to the strong activation of BK channels and transient K^+ channels by action potentials), while at the same time allowing the dendrites to generate $\text{Na}^+/\text{Ca}^{2+}$ spikes in response to dendritic depolarization (owing to the presence of Na^+ and Ca^{2+} channels and the reduced concentration of BK channels in the dendrites). Thus strong or prolonged depolarization of CA1 pyramidal cells, such as during a seizure, may result in the generation of intrinsic burst discharges in these cells, while less synchronous or weaker depolarizations may result in trains of single spikes only.

A general mechanism for the generation of burst-discharges in cortical pyramidal neurons therefore appears to be through a “ping-pong” interaction between somatic and dendritic compartments (36a). Whether cortical cells generate action potential bursts is dependent upon both the neuromodulators being released onto the cell and the recent electrophysiological history of the neuron (see 34). Known burst-promoting states include slow-wave sleep for layer V pyramidal cells (reviewed in 37), repetitive and prolonged stimulation and increases in $[\text{K}^+]_o$ in at least superficial cortical pyramidal cells (34), and dendritic depolarization for CA1 hippocampal pyramidal cells (see 35). Changes in the prevalence of burst discharges in cortical neurons may contribute to the state dependence of some forms of epileptic seizures *in vivo*. Likewise, the generation of epileptiform activity may promote the generation of burst discharges, at least in some cortical neurons, thereby forming a positive feedback mechanism for the initiation of paroxysmal events.

The functional consequence of burst generation in cortical neurons is the amplification of inputs. The excitation of these cells with a short duration excitatory postsynaptic potential (EPSP) may result in the activation of several postsynaptic EPSPs, which, being generated at a relatively high frequency, will summate temporally and may increase synaptic reliability, owing to the low probability of neurotransmitter release at many cortical synapses (reviewed by 15, 30). Physiological and anatomical evidence suggests that burst-generating neurons may excite other such neurons through local axonal collaterals (see 38), giving rise to a network of cells that can generate powerful recurrent excitation. Indeed, following the block of inhibition in CA3 *in vitro*, bursting in a single CA3 pyramidal cell can evoke, if occurring at the right time, a synchronized burst throughout the population (38a).

The termination of burst discharges in cortical and hippocampal neurons appears to be largely achieved through the activation of outward K^+ currents and possibly through the inactivation of inward currents (39). Of the many different subtypes

of K^+ channels distinct from one another in their voltage dependence, kinetics, and sensitivity to second messengers, those that are activated by increases in $[Ca^{2+}]_i$ (such as I_C and I_{AHP}) (40) and/or voltage are particularly important in the termination of single cell and network (e.g. interictal spike) burst discharges (Figure 1C). The discovery of K^+ channels that are sensitive to increases in $[Na^+]_o$ raises the possibility that they are also involved in the generation of prolonged (seconds) periods of hyperpolarization of cortical pyramidal neurons following the generation of intense bursts of activity (41, 42) and, therefore, could contribute to the termination of single cell or network burst discharges.

During network burst discharges, the activation of GABAergic inhibitory conductances, both $GABA_A$ and $GABA_B$, contribute to the termination of these synchronized events or PDSs (43, 44), and the block of these receptors may result in the generation of prolonged periods of after-discharges (see below). Interictal spikes, therefore, appear to be generated through a brief period of runaway excitation that spreads rapidly through a large local network of neurons, lasting ~ 80 – 200 ms and being terminated largely by the activation of inhibitory synaptic conductances and intrinsic K^+ currents (Figure 1) (39). Recent evidence suggests that an additional factor in the termination of burst discharges is a decrease in excitatory synaptic transmission owing to depletion of the readily releasable vesicles in presynaptic terminals (45). If this hypothesis is true, then the generation of prolonged discharges would be achieved by virtue of the large number of synapses involved, of which any single one might release transmitter only occasionally.

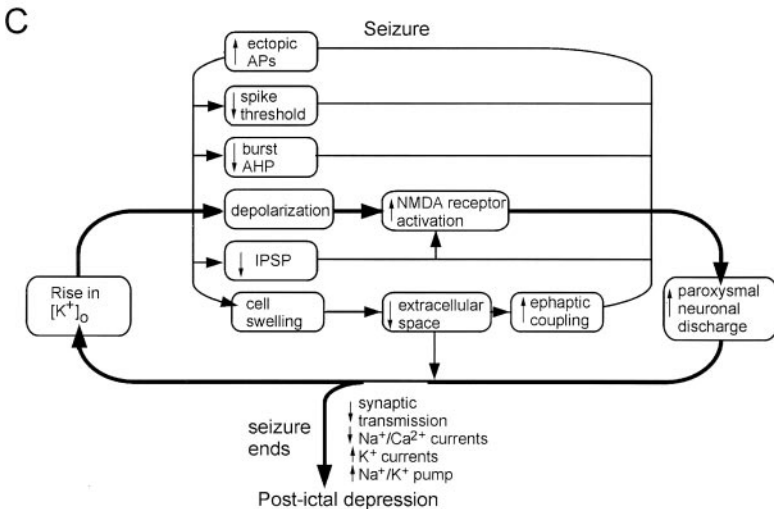
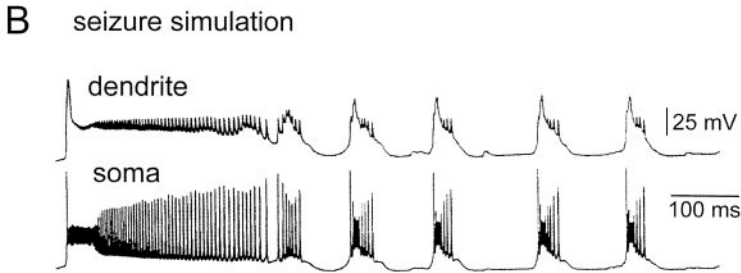
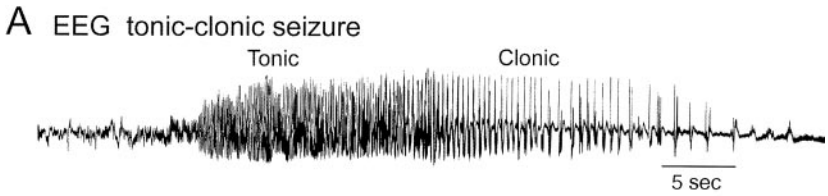
Another influence identified in the generation of synchronous discharges, especially in the CA1 field of the rodent hippocampus, is ephaptic (non-synaptic) interactions. The close proximity of cell bodies and dendrites in the hippocampus results in direct activation of neighbor cells by currents circulating in the extracellular space (referred to as an electrical field effect; see 6). The entry of positive charge into one neuron results in a negative charge in the extracellular space, thereby causing a decrease in the potential difference (e.g. depolarization) across the membrane of neighboring neurons. This apparent depolarization may then influence the timing of action potential generation in neighboring cells and therefore bring the network into synchrony. It is not yet clear how significant these electrical field effects are in the human hippocampus or neocortex, where pyramidal cell bodies are not as closely spaced as in the rodent hippocampal CA1 region.

Another form of non-synaptic interaction is the change in the extracellular concentration of ions. Periods of intense activity, from brief synchronized bursts of action potentials in a population of neurons to more prolonged discharges, result in significant increases in $[K^+]_o$ and decreases in $[Ca^{2+}]_o$. These changes in ion concentration may significantly increase neuronal excitability and promote epileptogenesis (Figure 2C) (46–48) (see below). Finally, changes in the extracellular space may facilitate these electrical field and ionic influences on synchronized burst generation and epileptogenesis. Decreases in the size of the extracellular space increase the electrical field effects and exacerbate increases in $[K^+]_o$ with activity (see 6). The interaction of these varied factors in positive feedback loops

may lead to the generation of repetitive barrages of activity that qualify as the generation of epileptic seizures.

Sustained, Synchronized After-Discharges: Cortical Mechanisms for the Generation of Seizures

Interictal spikes denote a local disruption of normal function in cortical circuits and as such are useful in the diagnosis and localization of the underlying pathology



generating epileptic seizures. In addition to interictal spikes, epileptiform activity can also appear as the generation of after-discharges following the initial spike, as well as full tonic or tonic-clonic seizures (49). The transition from the generation of single PDSs during interictal spikes to full seizures *in vivo* has been associated with the gradual loss of the burst after-hyperpolarization and the progressive appearance of repetitive bursts of activity during a more and more prolonged after-depolarization (49, 50). The transition to a full seizure is associated with the maintained or tonic depolarization of the membrane potential and repetitive generation of action potentials at a few to tens of Hz (e.g. Figure 2*B*). This period of tonic activity is often followed by a period of irregular periodic bursts of action potentials (Figure 2*B*; the clonic phase), with relatively little synaptic or action potential activity in between synchronized bursts. Finally, as the clonic period of activity ends, there is a relatively quiet and hyperpolarized membrane potential corresponding to a period of “post-ictal depression.”

Slice preparations, often of the hippocampus, have been utilized to develop models of repetitive after-discharges and electrographic seizures. Many of the manipulations that generate brief burst discharges in hippocampal slices also initiate seizure-like events. These include the block of GABA_A receptor-mediated inhibition, induction of rapid kindling through repetitive local electrical stimulation of synaptic pathways, raising $[K^+]_o$, application of the K⁺ channel blocker 4-aminopyridine, and reduction of $[Mg^{2+}]_o$ to very low levels (see 5, 6, 10, 13, 51–54). Additional manipulations that can generate prolonged after-depolarizations

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Figure 2 Possible mechanisms of tonic-clonic seizures. (A) Single EEG trace from a curare-treated patient undergoing a tonic-clonic seizure. Note that the tonic portion of the seizure is associated with high-frequency discharge in cortical networks and that this high-frequency discharge gradually gives way to the lower-frequency synchronized discharges of the clonic portion of the seizure. (B) Simulated tonic-clonic seizure in a network of hippocampal pyramidal neurons induced by block of GABA_A receptors. The tonic component is associated with the prolonged depolarization of both the dendritic and somatic compartments of the cell, which results in the generation of high-frequency action potential discharge, whereas the clonic component is associated with synchronized rhythmic burst generation mediated by the activation of slow spikes in the dendrites. (C) The importance of $[K^+]_o$ regulation and feedback mechanisms in the generation of seizures. Increases in $[K^+]_o$ initially promote the generation of epileptiform activity through multiple mechanisms including the enhancement of ectopic action potentials, decreases in action potential threshold, decreases in the amplitude of after-hyperpolarizations that terminate action potential bursts, depolarization of neurons, decreases in inhibitory synaptic potentials, and cell swelling. Secondary consequences include the increased activity of NMDA receptors and increased ephaptic coupling between neighboring neurons. All these events promote the generation of paroxysmal activity, which again increases $[K^+]_o$. Epileptiform activity fails when there is sufficient build up of decreases in synaptic transmission, the amplitude of Na⁺ and Ca²⁺ currents, and through the activation of K⁺ currents and electrogenic ion pumps (A from 153; B from 154; C modified from 47).

and/or electrographic seizures in hippocampal slices include the prior administration of tetanus toxin (which acutely disrupts synaptic transmission by cleaving synaptobrevin), the prolonged administration of cAMP analogues or stimulants of adenylyl cyclase (see 5), and the activation of group I metabotropic glutamate receptors (55).

In many of these models (reduction of GABA_A inhibition, increases in $[K^+]_o$, repetitive stimulation), the initial burst of epileptiform action potential activity is blocked only by antagonism of both non-NMDA and NMDA receptors, whereas the repetitive bursts of action potentials that follow this initial burst (Figure 2B) are sensitive to block of NMDA receptors alone (see 10). In contrast, both the primary and secondary bursts that occur in low $[Mg^{2+}]_o$ are abolished by block of NMDA receptors (51). Computational models of the generation of these after-depolarizations in a network of CA3 pyramidal cells by Traub et al (56) suggest that they are generated as a network of coupled oscillators in which the activation of NMDA receptors provides a prolonged depolarization of the dendrites of these cells, resulting in regenerative dendritic Na^+/Ca^{2+} spikes at 10–20 Hz, which then drive the repetitive bursts of action potentials at the soma (Figure 2B). The periodic activation of AMPA receptors at the synaptic connections between this pool of modeled pyramidal cells provides the timing signal that synchronizes the network.

During the generation of after-depolarizations and repetitive burst discharges, $[K^+]_o$ may increase considerably, from a normal level of approximately 3 mM up to 10 to 12 mM (e.g. 57). Initially, increases in $[K^+]_o$ will result in epileptogenic changes in network mechanisms by providing a depolarizing influence, decreasing the hyperpolarizing influence of compensatory K^+ currents, decreasing inhibitory synaptic transmission, decreasing action potential threshold, and increasing ephaptic interactions (Figure 2C) (see 47). However, strong increases in $[K^+]_o$ can also lead to decreases in neuronal and axonal excitability and, indeed, axonal conduction may become blocked (57a). Additionally, long-term changes in functional synaptic connections induced by bursts may also play a significant role in epileptogenesis (58, 59). These functional changes include the potentiation of excitatory synapses between pyramidal neurons, as well as potential functional decreases in inhibitory synaptic connections (51).

The generation of antidromic action potentials in the axon terminals of excitatory cells is important in the transition of single, interictal-like bursts to repetitive burst discharges, both in vivo (60, 61) and in vitro (62–64). Ectopic action potentials may travel throughout the axonal arbor and invade local and distal synaptic terminals, generating either a burst of synaptic transmitter release, or, on the population level, a periodic increase in excitation of the neurons in the network. Increases in ectopic action potential generation are often the consequence of increases in $[K^+]_o$, although other mechanisms are possible (Figure 2C) (62, 63). Ectopic action potentials, either following an initial burst of neuronal activity or during periods of intense neuronal firing, may be prevalent and facilitate the

continuation of reverberating excitatory activity, thus promoting the transition from interictal spikes to seizures.

Local Propagation of Epileptiform Activity in Cortical Networks

Interictal spike-like epileptiform activity and associated after-discharges, generated in response to reduction of inhibition, propagate locally in hippocampal and cortical networks at a rate of approximately 70 to 200 mm/s (65a, 66). This propagation rate is substantially below that of axon conduction velocities and most likely is limited by the integration time required to bring each successive neuron to firing threshold. Thus the more quickly each neighboring neuron in the cortical slice is depolarized, the quicker the epileptiform burst may propagate (56). Obviously, the rate of depolarization of each neuron will be strongly influenced by many factors that include the strength and axonal length of excitatory and inhibitory connections in the network, the distance to firing threshold, the generation of burst discharges, and the membrane time constant. Epileptiform activity generated in response to lowering $[Mg^{2+}]_o$ propagates at a significantly lower rate than that following block of GABA_A receptor-mediated inhibition, presumably owing to the intact nature of inhibitory interactions and their ability to slow the rapid depolarization of each successive neuron in the network (67). The propagation of primary and secondary (after-discharges) bursts of action potentials in hippocampal networks may not, however, follow the same rules. While primary bursts typically propagate in an orderly fashion away from the site of initiation, secondary bursts may jump to more distal points and propagate in a reverse direction, presumably in relation to the gradient of some important variable such as the density of excitatory or inhibitory connections (56).

Propagation of epileptiform activity in neocortical slices reveals a periodicity that depends on the direction of travel (66) and is indicative of some type of periodic functional connectivity, presumably related to functional columns in the neocortex. Isolation of different layers of cortex reveal that epileptiform activity may propagate through any layer, although it shows a preference for layer V (68).

These results reveal that epileptiform activities similar to those occurring in vivo during partial or complex-partial seizures may be generated on a local scale within small networks of hippocampal and cortical neurons. However, in vivo, it is expected that much larger networks of neurons are involved in the generation of each seizure that expresses itself clinically. Seizures in vivo may be partial, and therefore localized and limited to a particular cortical region, or may be initiated as apparently generalized, or become secondarily generalized, throughout the fore-brain. It seems likely that in all these seizures, the epileptiform activity is initiated in a single location, and in all but the most localized forms of epileptiform activity, the abnormal discharges spread to involve multiple cortical and sub-cortical regions. The mechanisms by which seizure activity spreads and synchronizes

between these multiple regions is still only poorly understood, although it is clear that corticocortical connections, as well as the interaction of cortical and subcortical structures, are highly involved. Thalamocortical interactions have received particular attention in the generation of certain types of seizures, especially in the primary generalized seizures of absence.

THALAMOCORTICAL MECHANISMS AND EPILEPTIC SEIZURES

One form of generalized epilepsy that has received particular attention during the last two decades is absence (or petit-mal) epilepsy (69). Typical absence seizures are characterized in the EEG by a few seconds or more of sudden generalized and bilaterally synchronous spike-wave discharges at 2.5–3.5 Hz (Figure 3B), most often occurring in 2–16-year old children, and associated with a loss of cognitive abilities and behavioral arrest. One of the characteristics of absence seizures is that immediately following the ictal event there appears to be little if any disruption of either cognitive abilities or neurophysiological activities in the forebrain (70). This is in marked contrast to tonic-clonic or complex-partial seizures involving the neocortex or hippocampus, where both a behavioral and neurophysiological post-ictal depression is characteristic.

When discussing the cellular mechanisms of absence seizures and its associated EEG pattern of 3 Hz spike wave, it must be remembered that although typical absence seizures are always associated with spike-wave activity, the opposite is not true because there are multiple forms of spike-wave activity that are not associated with clinical absence and appear during other types of seizures (71). Therefore, it is particularly important in animal models of absence seizures to examine not only the spike-wave components of the EEG but also the behavioral and pharmacological aspects of these seizures. Two animal models of human absence are of particular note: the feline penicillin-generalized epilepsy (FPGE) model (reviewed in 72, 73) and the GAERS or WAG/Rij rat models (reviewed in 74–76). Spike-wave seizures in these animal models are similar to human absence attacks in that they exhibit a sudden onset and offset associated with behavioral arrest and lack of attentiveness. These seizures can be interrupted by an increase in arousal or by a sensory stimulus, and the frequency of attacks is decreased in response to drugs typically used to treat this type of epilepsy in humans (however, significant differences do exist, see below). Studies using these and other animal models, as well as human investigations, have implicated an abnormality in cortical and thalamic activity in the generation of spike-wave seizures (e.g. 4, 77, 78). For example, field potential recordings from cortical and thalamic loci in humans during absence seizures have shown spike-wave activity in both structures (reviewed in 9), and recent examinations of regional blood flow in thalamic structures using PET scans indicate an increase in thalamic activity during typical absence attacks (79).

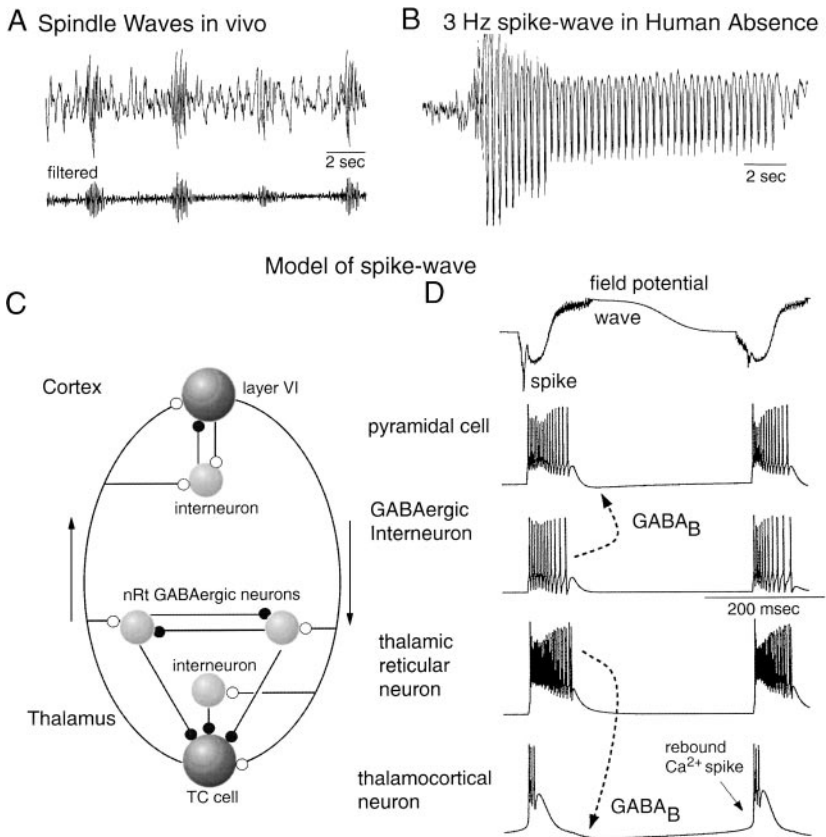


Figure 3 Possible cellular mechanisms of the generation of spike-wave seizures in human absence. (A) Spindle waves during slow-wave sleep in the normal EEG are intermixed with delta waves and recur once every few seconds. (B) Single EEG trace during an absence attack illustrating the striking 3-Hz spike-wave activity that characterizes this state. This spike-wave activity is widely synchronized throughout the EEG (not shown). (C) Simplified diagram of thalamocortical interactions proposed to underlie the generation of some forms of spike-wave activities. Cortical pyramidal cells and thalamocortical cells form mutually excitatory connections (open circles) that are regulated through the activation of GABAergic interneurons within the thalamus and cortex and thalamic reticular nucleus (inhibitory synaptic connections are denoted with filled circles). (D) Simulation of one cycle of a spike-wave seizure in corticothalamic networks. A burst of spikes in a thalamocortical neuron activates the cortical network, which generates a strong burst of action potentials through intracortical recurrent excitatory connections. This activity strongly activates both local GABAergic neurons and thalamic reticular neurons. The buildup of K^+ currents, including the activation of $GABA_B$ receptors and the inactivation of the depolarizing currents such as the low-threshold Ca^{2+} spike in thalamocortical cells, results in the cessation of activity in the network. The generation of a rebound Ca^{2+} spike in the thalamocortical cell, ~ 300 ms later, initiates the next cycle of the oscillation (A from 155; B from 156; D from 157).

Of particular relevance to the cellular mechanisms of absence seizures in humans and other primates is the observation that these paroxysmal EEG events are typically much more numerous during slow-wave sleep than during waking or rapid-eye-movement sleep (80, 80a). Indeed, animal models indicate that spike-wave seizures may be generated through a perversion of the normal cellular and network mechanisms underlying the generation of a normal slow-wave sleep EEG rhythm: the spindle wave (72, 73).

Spindle Waves and Their Relation to Spike-Wave Activity

Spindle waves are epochs of 6–15 Hz oscillation in the EEG that wax and wane over a period of 1 to 2 s and recur approximately once every 5 to 10 s during the early stages of slow-wave sleep (Figure 3A). Spindle waves are generated in the thalamus (reviewed in 3, 81), with neurons in the cerebral cortex being relatively weakly activated owing to the presence of strong feed-forward inhibition. Spindle waves are generated as an interaction between the GABAergic neurons of the thalamic reticular nucleus and thalamocortical neurons in which a brief burst of action potentials in the GABAergic cells hyperpolarizes their target thalamocortical cells through the activation of a Cl^- conductance mediated by GABA_A receptors (see 3, 81). This hyperpolarization can be rather large because the equilibrium potential for Cl^- in thalamocortical cells is relatively negative, and burst firing in thalamic reticular cells results in both temporal summation of the unitary inhibitory postsynaptic potentials (IPSPs) and facilitation of these events (82, 83). The summated IPSP may result in the removal of inactivation of enough low-threshold Ca^{2+} current in the recipient thalamocortical cell to result in a rebound low-threshold spike (LTS) (84, 85) which then activates a burst of 1 to 4 Na^+ action potentials. Because thalamocortical and thalamic reticular cells are reciprocally connected (86, 87), the burst of action potentials in thalamocortical cells once again excites the thalamic reticular cells, thereby initiating the next cycle of the spindle oscillation (Figure 3C). The frequency of spindle-wave generation (6–15 Hz) appears to be dictated mainly by the cycle time required to complete a loop of activity between thalamic reticular and thalamocortical neurons (~ 70 –150 ms) (88, 89). Local GABAergic neurons within the thalamus are not excited by thalamocortical cells but may participate in the generation of spindle waves *in vivo* owing to their excitation by corticothalamic axons. Present evidence suggests that local GABAergic neurons in the thalamus are either only weakly or not inhibited by thalamic reticular cells (88–90), although this finding remains to be explored.

The generation of spindle waves requires that both thalamocortical cells and thalamic reticular cells be in a relatively hyperpolarized membrane potential so that the low threshold Ca^{2+} current may be activated. In thalamocortical cells, low-threshold Ca^{2+} spikes are initiated by the rising phase of IPSPs, whereas in thalamic reticular cells, these Ca^{2+} spikes are initiated by EPSPs from thalamocortical neurons mediated via NMDA and non-NMDA receptors (88, 89, 91). This difference between the two cell types arises largely from the different subtypes

of low-threshold Ca^{2+} currents present: The voltage dependence of the subtype of I_T present in thalamic reticular neurons is shifted to more depolarized levels (see 92) and probably has a more dendritic localization than in thalamocortical cells (93). The requirement for a hyperpolarized membrane potential for the generation of spindle waves explains the suppression of these by arousal. Increased activity in ascending and descending activating systems that underlie arousal results in a net depolarization of thalamocortical, thalamic reticular, and some cortical neurons through the reduction of K^+ conductances and, at least for thalamocortical cells, the enhancement of the h-current (reviewed in 37). Importantly, thalamic reticular neurons inhibit each other through dendrodendritic and axonal synaptic connections that activate mainly GABA_A , but also, longer lasting GABA_B receptor-mediated IPSPs (94, 95). This lateral inhibition controls the amplitude and duration of excitation of these cells by thalamic and cortical activity (88, 89), which may have important consequences for the generation of some forms of spike-wave activity (96, 97).

Thalamic GABA_B mechanisms are not only involved in the generation of spindle waves, but also at least some forms of spike-wave seizures. In particular, intrathalamic injection of GABA_A or GABA_B (98) receptor agonists in the GAERS or WAG/Rij rat models of spike-wave seizures *in vivo* result in an enhancement of this epileptiform activity in these animals, presumably through hyperpolarization of thalamocortical neurons and promotion of the rebound oscillatory state. Administration of GABA_B antagonists results in a marked reduction in these seizures in epileptic mice (99), suggesting that the activation of GABA_B receptors may be particularly important. Extracellular recordings during spike-wave seizures reveal robust activity in thalamocortical and thalamic reticular neurons during these paroxysmal events, and lesions of the thalamic reticular nucleus abolish spike-wave seizures throughout the thalamocortical system (100, 101).

In vitro investigations of ferret thalamic slices suggest possible cellular and network mechanisms involved in the generation of paroxysmal 2–4 Hz thalamocortical activity (reviewed in 80). Dual intracellular recordings between thalamic reticular and thalamocortical neurons *in vitro* reveal that a physiological burst of 2 to 6 action potentials in reticular thalamic cells activates IPSPs predominately through GABA_A receptors similar to those underlying the generation of spindle waves. Increasing the train of action potentials in these cells to >10 results in the additional activation of GABA_B receptors and consequently a slow IPSP through a G protein-mediated increase in K^+ conductance (Figure 3D) (96). The requirement for strong release of GABA for the activation of GABA_B receptor-mediated IPSPs by thalamic reticular neurons suggests that these receptors may be extrasynaptic (see 102) because their sensitivity to exogenous GABA itself appears similar or even higher than that of GABA_A receptors (103). However, an additional explanation is that the opening of the K^+ channels activated by GABA_B receptors requires the binding of multiple (four?) G proteins, such as one G protein to each receptor subunit (104). Functionally, the activation of GABA_B receptors results in a slowing of the reverberatory activity between thalamic reticular

and thalamocortical neurons, owing to the slow kinetics and prolonged duration (150–300 ms) of these IPSPs. In thalamic slices maintained *in vitro*, the block of GABA_A receptors results in a pronounced increase in action potential activity in thalamic reticular neurons, presumably from disinhibition from other reticular neurons (88, 89). Following disinhibition from each other, thalamic reticular cells respond to barrages of EPSPs with the generation of a prolonged burst of action potentials and subsequently activate slow, GABA_B-mediated IPSPs in their postsynaptic thalamocortical cells (88, 89, 96, 105, 106). Following the near complete block of GABA_A receptors, the time to complete a loop of activity between thalamic reticular cells and thalamocortical neurons lengthens to ~300–400 ms, and therefore the network generates a rhythmic oscillation at ~2–3 Hz. Because this frequency is similar to that at which thalamocortical cells prefer to endogenously oscillate, owing to the properties of I_T and the pacemaker current I_h (107, 108), the thalamocortical cells discharge with several action potentials on every cycle of the network oscillation (Figure 3D). The block of GABA_A receptors in the thalamus may therefore result in the transformation of spindle waves into a paroxysmal event at 2–3 Hz, in which thalamocortical and thalamic reticular neurons discharge strongly and in synchrony. This manipulation provides a model for how the same diencephalic network can generate oscillations at two different frequencies characteristic of spindles (6–15 Hz) and absence-like events (2–3 Hz).

Similar results are obtained *in vivo*, by intrathalamic injections of the GABA_A receptor antagonist bicuculline (109). Injection of bicuculline into the thalamus of otherwise intact cats greatly increases the number of spikes and the duration of burst discharges both in reticular thalamic and thalamocortical cells. This increase in burst activity is concomitant with a progressive decrease in the frequency of rhythmic activity from ~10 Hz down to 2–3 Hz and a parallel increase in the synchrony among thalamic cells.

However, one important difference between the spike-wave seizures generated in rodents and those associated with human absence seizures, or the abnormal activity generated in thalamic slices, is their respective frequencies. Whereas the spike-wave activity in the EEG during human absence seizures is typically around 2.5 to 3.5 Hz, those spontaneously occurring in the rodent are ~6–9 Hz, a frequency that would seem too high to be driven by IPSP through the activation of GABA_B receptors in thalamocortical neurons. Indeed, intracellular recordings in rodent thalamocortical neurons reveal typical fast IPSPs, presumably mediated by GABA_A receptors during the generation of these seizures (110). One possible solution to this apparent paradox has been suggested by computational modeling of both the 2–3 Hz thalamic rhythm and the 6–9 Hz oscillation (111). By reducing the strength of GABA_B receptor activation (but not blocking it completely), the higher frequency oscillation may be generated. This rhythm still depends critically on the activation of GABA_B receptors because this activation provides a prolonged hyperpolarization of thalamocortical cells that keeps these neurons in the range for the generation of rebound low-threshold Ca^{2+} spikes in response to the large GABA_A receptor-mediated IPSPs. Thus the block of GABA_B receptors would be

expected to result in the cessation of these seizures, as observed, even though it is the activation of GABA_A receptors that drives the oscillation with each cycle.

There are multiple possible reasons for the frequency differences between absence-like seizures in humans and rodents. Perhaps one of the most prominent is the general lack of local GABAergic circuit neurons in the rodent thalamus (see 91). In the primate, approximately 20–30% of neurons within each of the primary relay nuclei are local circuit GABAergic neurons, which are strongly innervated by corticothalamic inputs (see 91). These local circuit neurons activate both GABA_A and GABA_B receptor-mediated IPSPs (112) and therefore may contribute to the generation of large, slow IPSPs in thalamocortical neurons, thus facilitating the generation of 3-Hz spike-wave seizures in higher species. One implication of this is that the cognitive disruption associated with absence seizures is not related to the frequency of the spike-wave discharge per se but rather to the brain structures involved.

Investigations of spike-wave seizures in cats have emphasized the important role of abnormal discharge in the cerebral cortex and the interaction of this discharge with thalamocortical mechanisms. In the FPGE model of absence epilepsy, the intramuscular injection of a weak GABA_A receptor antagonist, penicillin, results in the gradual transformation of spindle waves into spike-wave seizures (reviewed in 73). The critical locus for action of penicillin appears to be the cerebral cortex, since injection of this agent into the thalamus directly did not initiate spike-wave seizures in the EEG (although the spread of intrathalamic injections of penicillin are limited), whereas the topical application of penicillin directly to the cerebral cortex can initiate spike-wave events as long as the thalamocortical networks are intact. During the transition from spindle waves to spike-wave seizures with the systemic administration of penicillin, cortical neurons, including corticothalamic cells, undergo marked increases in action potential discharges. Initially, these cells discharge only weakly and intermittently in response to each phase of the spindle wave, while the development of spike-wave discharges is associated with strong bursts of action potentials in these cells during the spike and with hyperpolarization during the wave.

Results from systemic (i.v.) injections of bicuculline in cats in which the cerebral cortex had been completely removed from one hemisphere showed that seizures only occurred in the intact hemisphere, indicating that the thalamus cannot generate seizures alone (109). Furthermore, removal of the cortex in the seizing hemisphere caused the underlying thalamus to generate normal spindle waves without seizures. Because the lack of effect in thalamus of the systemic injections could be the result of an increased threshold for seizures in isolated thalamic networks, large injections of bicuculline were made intrathalamically. This resulted in the progressive substitution of sleep spindles by high-amplitude oscillations at 2–3 Hz that had characteristics intermediate between normal spindle waves and spike-wave seizures (109).

These studies indicate that disinhibition of neuronal activities in either the cerebral cortex or thalamus may result in abnormal 2–4 Hz activities in the EEG

in both structures, with disinhibition of the neocortex resulting in activity that is most similar to spike-wave activities in human epilepsies (73, 113). One possibility is that the abnormal discharge of corticothalamic neurons, owing to an imbalance of excitation and inhibition in the cerebral cortex, results in the strong phasic excitation of thalamic reticular, thalamocortical, and local GABAergic neurons. Thus the strong activation of the corticothalamic pathway may result in both the direct excitation of thalamocortical cells and the hyperpolarization of these cells through disynaptic inhibition via thalamic reticular and local GABAergic cells (91, 114). Although this disynaptic inhibition may silence some thalamocortical cells, others generate rebound low-threshold Ca^{2+} spikes and bursts of action potentials that may initiate the next cycle of paroxysmal activity (Figure 3D) (115). Thus the critical feature in the transition from normal spindle wave to paroxysmal 2–3 Hz activity in the thalamus may be the initiation of prolonged barrages of action potentials simultaneously in many thalamic reticular GABAergic neurons. Indeed, the spike bursts of reticular neurons increase substantially in duration in the transition from normal sleep rhythms to spike-wave activity and become tightly related to the spike component of the seizure (115).

In vitro (116, 116a) and in vivo (116b) studies confirm the ability of strong synchronous activation of thalamic reticular cells by corticothalamic (or thalamocortical) afferents to convert the thalamic network from one generating normal spindle waves to one generating 2–3 Hz paroxysmal discharges. Again, these thalamic oscillations depend critically on the activation of GABA_B receptor-mediated IPSPs for their generation (116, 116a). Therefore, even if thalamocortical mechanisms are responsible for the generation of 3-Hz spike-wave activity in human absence, the primary deficit need not be localized to the thalamus, but rather may occur within the cerebral cortex. The abnormal activity of cortical networks may then lead to pronounced discharge, followed by periods of silence and hyperpolarization, in both cortical and of thalamic cells (Figure 3D). At this point, the suggested mechanisms for the generation of abnormal spike-wave activities are the loss of GABA_A receptor-mediated inhibition between thalamic reticular cells (97), the abnormally strong activation of thalamic GABAergic neurons by corticothalamic or thalamocortical afferents (e.g. 116, 116a), the loss of K^{+} currents regulating burst length in thalamic reticular neurons, or the enhancement of the low threshold Ca^{2+} current (117).

Some of the cellular actions reported for one of the drugs typically used in the treatment of absence seizures, ethosuximide, are consistent with this model of these seizures. In particular, application of ethosuximide and related compounds reduces the amplitude of the low threshold Ca^{2+} current in thalamocortical neurons (reviewed in 118), although this effect is not seen by all investigators (119). In addition, the critical role of GABAergic inhibition in the generation of this form of spike-wave seizures is also consistent with the well known seizure-promoting side effects of barbiturates (which enhance GABAergic synaptic transmission) in patients with absence epilepsy (120).

Possible Mechanisms for the Waxing and Waning of Spindles and Thalamocortical Spike-Wave Seizures Both in vivo and in vitro spindle waves can recur with a remarkable periodicity at approximately once every 5 to 10 s (see Figure 3A) (121). The waxing or growth phase of the spindle wave and 2–3 Hz paroxysmal activity in vitro is explained by the cyclical recruitment of neurons into the oscillation, as well as the increasing strength of the oscillation in thalamocortical cells (represented by increasing amplitude of IPSPs and rebound Ca^{2+} spikes) and in thalamic reticular cells (involving increasing amplitude of EPSP barrages and low-threshold Ca^{2+} spike-mediated burst discharges). The mechanisms underlying waning of these network oscillations is less obvious. However, one clue is that in thalamocortical cells the waning of spindle waves is followed by the generation of a slow after-depolarization, the duration of which matches the duration of the inter-spindle interval (87). This after-depolarization is generated through the persistent activation of the hyperpolarization-activated cation current I_h and although small (1–4 mV) is large enough to reduce significantly the ability of IPSPs arriving in thalamocortical cells to generate rebound low-threshold Ca^{2+} spikes (87, 122, 123). The persistent activation of I_h following the generation of a network oscillation may involve the Ca^{2+} -dependent activation of a Ca^{2+} -sensitive adenylyl cyclase and, subsequently, an increase in $[\text{cAMP}]_i$ (124). Cyclic AMP appears to bind directly, in an allosteric manner, to single h-channels, and in so doing stabilizes the open state (124, 125), providing the prolonged depolarization that inhibits oscillatory activity in thalamocortical networks.

Could the cessation of spike-wave activity in thalamocortical networks during seizures also involve the persistent activation of the h-current? This intriguing hypothesis remains to be tested, but it is possible that the cessation of spike-wave seizures that require rebound burst firing in thalamocortical neurons may cease owing to the build up of I_h activation and depolarization of thalamocortical cells. If a similar mechanism occurs in absence seizures in children, then it would help explain the lack of post-ictal depression because the seizures would be followed by a slight depolarization of thalamocortical cells, which, if anything, should actually facilitate the operation of forebrain networks.

Synchronizing Mechanisms in Normal and Abnormal Thalamocortical Activity

All the cellular models of EEG rhythm and seizure generation have focused on the operation of relatively local neuronal circuits, yet generalized spike-wave seizures typically exhibit widespread synchronization and rapid generalization. How is it that neural networks come to oscillate in a widely coordinated manner? Since widespread synchronization is also exhibited by brain rhythms associated with slow-wave sleep and anesthesia, i.e. spindling, delta, and the slow (<1 Hz) oscillation (127–129), this intriguing question has begun to be addressed, by studying the mechanisms of synchronization of these normal thalamic and cortical rhythms.

Synchronization of Spindle Waves and Spike-Wave Seizures Recordings in vitro demonstrate that spindle waves in slices typically propagate along the horizontal plane at a slow rate (approximately 1 mm/s) as each adjacent portion is recruited into the network oscillation (126). Yet, recordings of these sleep rhythms in vivo often reveal spindle waves that appear almost simultaneously throughout the cerebral cortex, although local generation can still occur (127). This widespread synchronization is brought about by corticocortical and corticothalamocortical connections (127–129). Thus removal of the cerebral cortex leaves a thalamus that generates spindle waves that are only locally (within a couple of mm) coherent. On the other hand, when the cortex is present, local stimulation in the cerebral cortex results in spindle waves in the thalamus that are synchronized beyond the region stimulated (129). The mechanisms of this synchronization of thalamocortical rhythms is believed to rely largely on the divergence and convergence of axonal connections, including those between layer VI of the cerebral cortex and neurons in the thalamic reticular and relay nuclei (130), the divergence of axonal connections from the thalamic reticular nucleus to thalamocortical neurons (90, 131, 132), from the thalamus to the cerebral cortex, and within the cerebral cortex itself (19, 133).

Computational simulations of synchronization in thalamocortical circuits suggest that the activation of thalamic reticular neurons, with their divergent connections to multiple thalamocortical cells, may be a particularly powerful synchronizing mechanism (114). For example, the activation of a single GABAergic perigeniculate neuron, which is equivalent to a thalamic reticular neuron, may simultaneously inhibit 100 or more thalamocortical cells in the dorsal lateral geniculate nucleus that are separated by up to 1 mm (82). The subsequent rebound burst firing generated in these thalamocortical cells may then excite an even larger portion of the neocortex, and the subsequent feedback excitation from layer VI to the thalamus is expected to excite a considerably larger portion of the GABAergic neurons of the perigeniculate nucleus.

Severing the corpus callosum abolishes or severely reduces the inter-hemispheric synchrony of spindle waves as well as spike-wave seizures (73, 121). In contrast, local knife cuts through the depth of the cortex do not result in a loss of synchrony of spindle waves between the tissues on either side of the cut (129). Thus although local corticocortical connections are undoubtedly important in the synchronization of these thalamocortical rhythms, they are not necessary, whereas at least some long-range corticocortical connections are critical.

An important feature of synchronized rhythm generation in the thalamocortical system is the ability of these rhythms to be initiated in many different parts of the network. In thalamic slices, for example, spindle waves that propagate throughout the network can be initiated by the activation of a single GABAergic neuron (126). Thus the point of initiation of spindle waves, or of spike-wave seizures, may vary from event to event, depending on the state of the local network. The rapid generalization of these rhythms throughout the network and the inability to monitor the activity of all the neurons involved prevent the experimental or clinical detection of the true initiation and spread of these synchronized oscillations, which causes

them to appear as “generalized from the outset.” This synchronized, but distributed, nature of spike-wave activity is in marked contrast to the centrencephalic theory, which holds that a central pacemaker generates these seizures.

The synchronization of thalamocortical networks depends not only on anatomical connections, but also on the physiological state of the network. The deepening of slow-wave sleep or anesthesia is associated with increases in the synchronization of spindle waves and other slow rhythms (134). Hyperpolarization of the membrane potential of thalamic neurons, which occurs during deepening of sleep or anesthesia (see 37), markedly enhances slow rhythms in this structure, largely through the removal of inactivation of the low-threshold Ca^{2+} spike, but also through an increase in neuronal input resistance owing to the deactivation of various K^{+} currents (135). A similar enhancement of synchronized burst firing may also occur within the cerebral cortex (136), and this enhancement of the local cellular mechanisms for the generation of slow rhythms may then translate at a more global level into a marked enhancement of widespread synchrony of these rhythms (137). However, deepening the state of sleep and anesthesia may abolish the generation of some thalamocortical rhythms and promote the occurrence of others. Spindle waves are most pronounced in the early stages of sleep, while slower rhythms such as delta waves are more prominent during the deep stages of slow-wave sleep. Spike-wave seizures in the rodent model of absence epilepsy are also prevalent during the early stages of sleep, but abolished in the later stages (80). Again, these transitions appear to depend largely on the state of the membrane potential of thalamic and cortical neurons, in that strong hyperpolarization of these neurons reduces the ability of these cells to generate rebound low-threshold Ca^{2+} spikes in response to the arrival of barrages of IPSPs, while promoting the generation of intrinsic, slow oscillatory rhythms (138). In summary, absence may be facilitated by moderate but not extreme hyperpolarization of diencephalic neurons.

SLOW OSCILLATION IN THE CEREBRAL CORTEX AND ITS CONVERSION TO EPILEPTIC SEIZURES

During periods of anesthesia and slow-wave sleep, cortical and thalamocortical networks can generate recurrent synchronized activity at 0.1–0.9 Hz in animals and humans, the so-called slow oscillation (Figure 4A) (139–142). The slow oscillation is generated within the cerebral cortex because it survives complete lesions of the thalamus, isolation of cortical slabs from subcortical structures, and occurs in cortical slices maintained *in vitro* (143). However, the slow oscillation strongly influences activities in subcortical structures such as the caudate (144) and thalamus (139–141), and at least some EEG rhythms are generated through an interaction of the slow oscillation and other thalamocortical rhythms. For example, K-complexes, a normal human EEG rhythm occurring during slow-wave sleep, appear as the onset of a cycle of the slow oscillation in the cerebral cortex followed by the activation of a spindle wave within the thalamus (145).

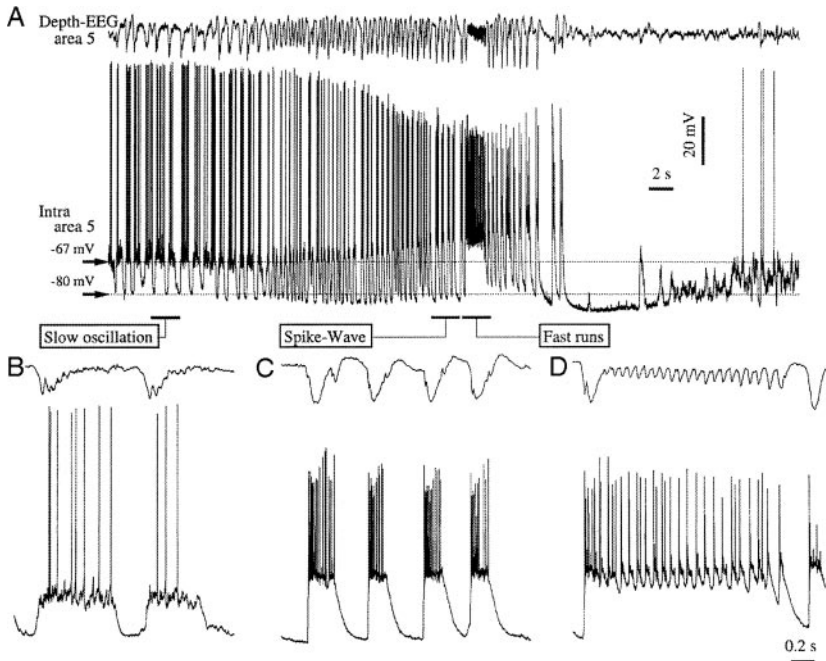


Figure 4 Cortical slow oscillations spontaneously develop into a seizure consisting of spike waves at 2–3 Hz and fast runs at ~15 Hz. (A) Intracellular recording from a regular-spiking cell and depth-EEG from neocortex area 5 in a cat under ketamine-xylozine anesthesia. The cortical slow oscillation is characterized by a depolarized up state at -67 mV and a hyperpolarized down state at -80 mV (expanded in *B* for detail). The transition to the seizure is associated with an increase in frequency of transitions between the up and down state, resulting in a spike-wave pattern in the EEG (expanded in *C*), that was interrupted by occasional fast runs of activity characterized by rhythmic 10–15 Hz activity riding on top of a sustained depolarization (expanded in *D*). The seizure lasted for ~25 s and was followed by an after-hyperpolarization and an apparent flattening of the EEG (from 113).

Intracellular recordings *in vivo* and *in vitro* reveal that the slow oscillation is characterized by the alternation between a depolarized “up” state and a hyperpolarized “down” state (Figure 4) (140, 143). Simultaneous recording of different identified cell types in the cerebral cortex and/or thalamus, as well as the local field potential or multiple unit activity, revealed that all cortical and thalamic neurons discharge during the up state and exhibit either no or reduced activity during the down state. Similarly, intracellular recordings from cortical pyramidal cells reveal that the up state is mediated by the arrival of barrages of both excitatory and inhibitory postsynaptic potentials, whereas the down state is associated with a relative reduction in the frequency of these events. These results indicate that the slow oscillation is generated by the initiation and failure of recurrent excitation

within cortical circuits, with the activation of inhibitory neurons regulating the intensity of discharges during the depolarized up state (139, 141, 143).

In vitro investigations of the slow oscillation reveal that it can occur throughout layers II-VI of the cerebral cortex but that layer V has the lowest threshold for generation, and therefore this oscillation often is initiated in this layer. Following the initiation of the slow oscillation, it then propagates horizontally through the slice at the relatively slow rate of approximately 10 mm/s (143). In vivo recordings of the slow oscillation also point to the generation of this activity throughout layers II-VI, and simultaneous recordings from widely spaced cortical regions reveal synchronization of this rhythm in a manner that is consistent with a propagation rate of approximately 100 mm/s (137), which is ten times faster than observed in vitro. The role of corticocortical connections in the synchronization of the slow oscillation is suggested by the finding that vertical knife cuts through the cortex, or the local block of activity with the application of lidocaine, abolish the synchronization of this rhythm between adjacent areas (137, 146). Thus, in contrast to spindle waves, the slow oscillation depends critically on local intracortical connections for synchronization and is not as capable in synchronizing different cortical regions through corticothalamocortical interactions.

The down state of the slow oscillation is generated largely through a failure of the recurrent excitatory activity that maintains the depolarized up state (139-143). Intracellular recordings in vivo and in vitro reveal that the down state is associated with a relatively hyperpolarized membrane potential in pyramidal neurons and a slow after-hyperpolarization similar to that generated following repetitive action potentials in these cells (140, 142). Thus the slow oscillation may be generated through the interaction between the depolarizing influence of the recurrent activity characteristic of corticocortical interactions and the slow build-up and dissipation of outward K^+ currents activated by this activity (143). Additionally, the activation of K^+ currents through the release of neuromodulators, such as adenosine, has been suggested to contribute to the down state (147).

In response to repetitive local electrical stimulation, injections of bicuculline, or spontaneously, the slow oscillation in vivo may convert to epileptic seizures. These seizures are characterized by periods of fast runs of 10-15 Hz activity and/or spike/polyspike-wave activity at 3-4 Hz (Figure 4) (4, 115). As with slow oscillation, these seizures survive thalamectomy and therefore can be generated intracortically (109). This pattern of seizure activity is similar to that occurring in the Lennox-Gastaut epileptic syndrome, which clinically is associated with frequent seizures, sudden falls, marked resistance to pharmacological therapy, and mental and behavioral disturbances. In Lennox-Gastaut syndrome, clinical and electrographic seizures are activated during sleep in a pattern consisting of diffuse slow spikes-waves and bursts of fast rhythms at 10 to 12 Hz.

The transition from the slow oscillation into a seizure is initially associated with a progressive increase in amplitude of the EEG slow waves followed by the appearance of runs of activity at 10-15 Hz that give way to sequences of spike/polyspike-wave complexes at 2 to 4 Hz. This gradual transformation of the cortical slow

wave into a spike-wave seizure is correlated with a marked increase in synchrony of activity between cortical areas as well as between cortical and thalamic regions (148, 149). Intracellularly, during the fast runs at 10–15 Hz, most cortical cells are tonically depolarized and discharge at high frequencies (Figure 4D); an exception is a special class of cortical cells named chattering (150) or fast repetitive bursting cells that fire rhythmic spike-bursts time locked with the 10–15 Hz EEG spikes (113). The intense, synchronized burst discharges of these neurons, which include superficial and deep lying pyramidal cells, suggest that they play an important role in the generation, synchronization, and propagation of these seizures.

Although these seizures can be generated entirely within the cerebral cortex, in intact animals the thalamus is also involved. Both thalamocortical and reticular thalamic cells are depolarized and discharge trains of spikes during the 10–15 Hz component of these seizures (115, 151). During spike/polyspike components, the GABAergic neurons of the thalamic reticular nucleus are strongly and phasically excited, discharging prolonged bursts of action potentials in phase with the EEG spikes. These bursts of action potentials in thalamic reticular cells generate either a sustained or cyclical inhibition of thalamocortical neurons, which results in a silencing of the activity of approximately 60% of these cells and the generation of rebound bursts of action potentials that are in synchrony with the EEG spikes in the remaining neurons (115). Therefore, although these seizures can be generated entirely within the cerebral cortex of athalamic cats, in the intact animal there is a marked synchronization of cortical, thalamic reticular, and a substantial fraction of thalamocortical neurons (109, 149). It is likely that this synchronization of corticocortical and thalamocortical activities reinforces the spread and generation of these seizures.

SUMMARY

The normal connectivity and functional properties of the neocortex, hippocampus, and thalamus give rise to the ability to generate either local or large-scale normal synchronized oscillations. The generation of epileptic seizures is also mediated by these same networks and cellular mechanisms and therefore often appear as perversions of normal rhythmic activities. Although there are many clinical epileptic syndromes, experimental models have revealed only a few forms of seizure-like activities. The first, which is a model of partial, complex-partial, and tonic-clonic seizures, is based on recurrent excitatory interactions between pyramidal cells in either the cerebral cortex or hippocampus; the second form, which is the leading model of human absence seizures, is based on the reverberation of oscillatory activity between excitatory and inhibitory neurons within the thalamus and cerebral cortex. Thus although the initiating insults that result in the development of epileptic seizures may be diverse, the cellular mechanisms underlying the expression of these seizures may be relatively similar and therefore form a reasonable target for pharmacological intervention.

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