PRIMARY AND SECONDARY MECHANISMS OF EPILEPTOGENESIS IN THE TEMPORAL LOBE: THERE IS A BEFORE AND AN AFTER

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Extensive data involving several animal models of temporal lobe epilepsy highlight synaptic alterations that likely act synergistically during acquired epileptogenesis. Most of this research has utilized experimental models in which intense electrical activity in adult animals, primarily involving status epilepticus, causes variable neuronal death in the hippocampus and other temporal lobe structures. Neuronal death, including principal cells and specific interneurons, likely has several roles in epileptogenesis after brain injury. Both reduction of GABA-mediated inhibition from selective interneuron loss and the progressive formation of new recurrent excitatory circuits after death of principal neurons enhance excitability and promote seizures during the development of epilepsy. These epileptogenic circuits hypothetically continue to undergo secondary epileptogenesis, which involves further modifications that contribute to a progressive, albeit variable, increase in the frequency and severity of spontaneous recurrent seizures.

Primary and Secondary Epileptogenesis: Seizure-Induced Neuron Death and Synaptic Reorganization

A substantial body of experimental data—from numerous investigators and using a variety of animal models and techniques—suggest that the occurrence of a long-lasting period of repetitive seizures (e.g., status epilepticus) produces a cascade of events that lead to a progressive and permanent modification of cortical neuronal networks. This scenario of modification of cortical circuits in animal models represents one form of the seizures beget seizures concept (1) in the sense that the repetitive seizures associated with the experimental status epilepticus lead to spontaneous recurrent seizures (i.e., epileptogenesis). Some of these synaptic alterations also contribute to, or possibly underlie, acquired epileptogenesis after other forms of brain injury.

An important question is whether the late spontaneous recurrent seizures of chronic epilepsy cause yet more spontaneous recurrent seizures. Does this process lead to a progressive worsening of the epilepsy over time (i.e., secondary epileptogenesis)? This review will summarize a sequence of events that occurs after repetitive seizures: 1) selective interneuron loss and chronic suppression (but not complete failure) of GABAergic inhibition (Figure 1) and 2) death of glutamatergic principal neurons, with subsequent axon sprouting by many of the remaining neurons (and neurogenesis, at least in some areas), which is followed by the formation of new recurrent glutamatergic excitatory circuits (Figure 2). The central hypothesis proposed here for secondary epileptogenesis is that the selective loss of specific GABAergic interneurons and the formation of new excitatory glutamatergic circuits *synergistically* augment excitability, which leads to the propensity for further seizures. The presence of the remaining GABAergic inhibition prevents recruitment of multisynaptic interactions via the newly formed recurrent excitatory circuits (2,3), so that seizures do not occur continuously; however, the labile nature of the diminished inhibition permits periodic expression of the recurrent excitation and multisynaptic activation of the network (4,5). In addition, newly formed synapses are aberrant in their location and have intrinsic features that reinforce the ease with which seizures are generated (6,7). Although this sequence may vary depending on different types of seizures or brain injury as well as on the specific cortical structure involved, it appears that this progression of events may be critical to the development of human temporal lobe epilepsy.

Selectivity of Neuronal Loss in Relation to Human Histopathological Data

Many adult animal models of induced repetitive seizures consistently show the development of epilepsy with spontaneous recurrent seizures. In animal models based on chemoconvulsant- or electrically induced status epilepticus, neuronal damage can either be quite limited (i.e., loss of only a few hundred neurons) or substantial (but highly variable) across structures and animals, even within a particular type of animal model (8,9).

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Epilepsy Currents, Vol. 10, No. 5 (September/October) 2010 pp. 118–125
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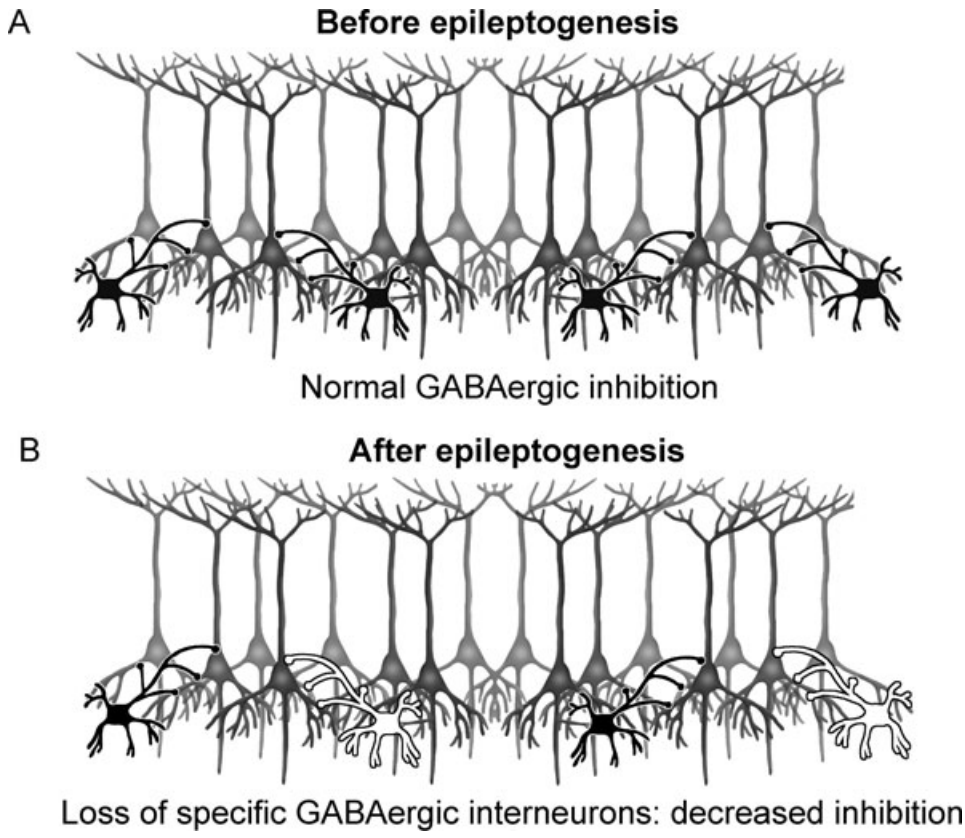

FIGURE 1. Loss of interneurons and decreased GABAergic inhibition in the hippocampus during epileptogenesis. Schematic diagram showing hippocampal CA1 pyramidal cells and interneurons before (A) and after (B) epileptogenesis has occurred. The diagrams illustrate the hypothesis that the hippocampus either from the brain of a patient or from an animal model of temporal lobe epilepsy loses specific, but not all, interneurons.

The areas with neuronal damage typically include several regions traditionally damaged in temporal lobe epilepsy, such as CA1, CA3, and the dentate hilus of the hippocampus, but the damage also extends to extrahippocampal regions, such as the entorhinal and pyriform cortices or the amygdala (10–13). The amount and pattern of neuronal death depends on: 1) the type, dose, and route of administration (e.g., intraperitoneal or intracranial) of the chemoconvulsant, 2) the potential use and timing of pharmacological agents (e.g., diazepam) to suppress the repetitive seizures, and 3) many other variables (e.g., animal strain, particularly in mice), but generally definable, features of the study protocol. The severity of the seizures, as evident in the electrographic components of the seizures, directly determines the extent of brain damage (8,9). The many patterns of neuronal death, however, show similarities to mesial temporal sclerosis in human temporal lobe epilepsy, which can also be quite variable across patients (14).

Similarities and differences among the models of temporal lobe epilepsy in adult animals (with or without status epilepticus) that develop spontaneous recurrent seizures have been debated in the literature. One of the most long-standing animal models is kindling, which does not typically lead to spontaneous recurrent seizures but, instead, is defined by enhanced seizure susceptibility to electrical stimulation. The kindling model has generally been reported to lack neuronal death, at least compared to the models based on status epilepticus; however, histopathological data suggest that even a single kindled seizure in adult rats can lead to the death of a small number of neurons (15). Furthermore, some investigators have reported that rats that have undergone extensive kindling not only have loss of neurons (including specific GABAergic interneurons) and prominent axonal sprouting, they may also have spontaneous recurrent seizures (16). Another model, which involves the repetitive electrical stimulation of the perforant pathway in anesthetized animals without frank status epilepticus (17), reportedly causes highly specific neuronal death (i.e., severe damage to the hilus in particular, but also to CA3 and CA1), although neuronal damage in this model may also extend to extrahippocampal regions when performed in awake rodents (18,19). Most of the available data are consistent with the concept that the combination of interneuron loss and increased recurrent excitation—not only in the dentate gyrus but in other areas, such as CA1, as well—is a common theme among these temporal lobe epilepsy models and may account for the

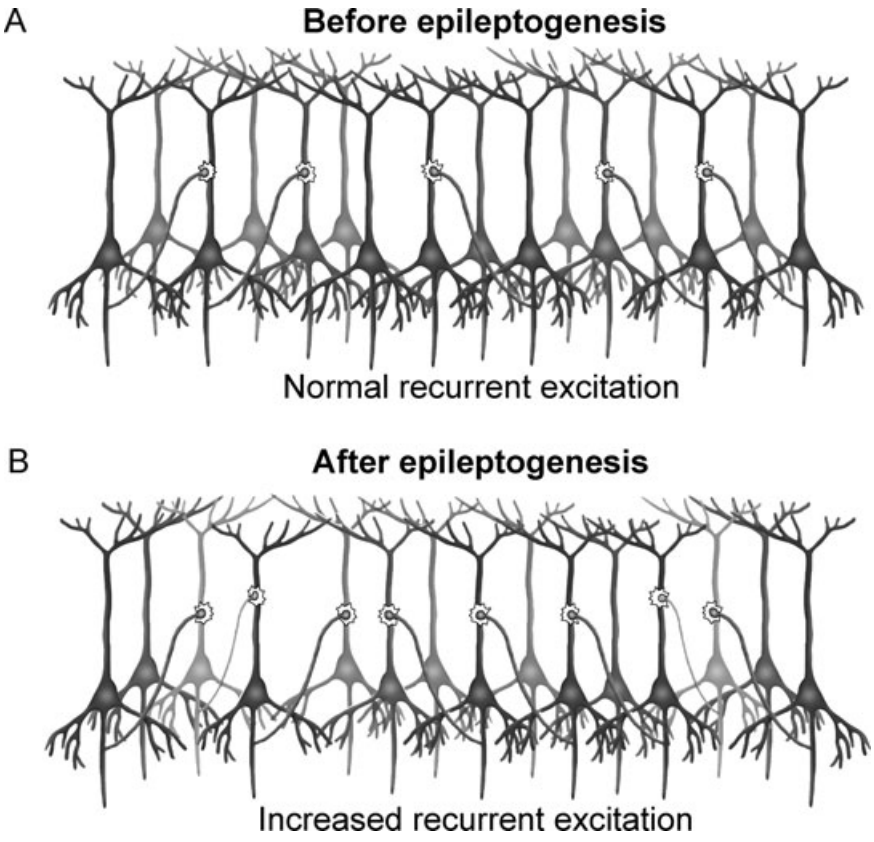

FIGURE 2. Axon sprouting and increased recurrent excitation in the hippocampus during epileptogenesis. The diagram shows glutamatergic pyramidal cells (e.g., CA1 area of the hippocampus) before (A) and after (B) epileptogenesis. The diagrams illustrate the hypothesis that although recurrent excitation is normally present among some pyramidal cells before epileptogenesis, recurrent excitation increases during epileptogenesis (B).

progressive epileptogenesis that follows repetitive seizures in limbic structures, particularly for those models that have demonstrated spontaneous recurrent seizures. It is interesting to speculate that this positive feedback loop (i.e., seizures begetting neuronal death, begetting more seizures) in the CA1 area progressively kills all of the neurons in that area (i.e., Sommer's sector).

The exact pattern of neuronal death in the temporal lobe and elsewhere likely is not a critical factor in epileptogenesis, since the location and amount of neuronal death in human temporal lobe epilepsy can be quite variable across patients, as it can be across animal models. Most (but not all) of the experimental research on the patterns of neuronal death in animal models of temporal lobe epilepsy as well as those seen in the histopathological studies of resected human tissue have been qualitative rather than quantitative or quite limited in scope (i.e., dependent of the size of the resection and the availability of tissue; obtained from autopsy specimens). Thus, many of the arguments in the field supporting one particular hypothesis or another concerning specific hippocampal injury (or lack thereof) have not been based on comprehensive, well-powered analyses with quantitative, volume-corrected stereological techniques. This caveat applies to a variety of animal models with protocols of chemical or electrical stimulation to produce repetitive discharges, seizures, or even status epilepticus. Similarly, a wide diversity of structural damage and neuronal loss is seen with human temporal lobe epilepsy. For example, even some of the classic neuropathological work, which is often cited to argue that human temporal lobe epilepsy is uniquely defined by a highly specific pattern of hippocampal neuronal damage (i.e., endfolium sclerosis or mesial temporal sclerosis), emphasized "the need to see beyond the temporal lobes and to take into account the possible importance of damage in other parts of the brain as well" (20). Finally, numerous clinical imaging studies have highlighted the fact that temporal lobe epilepsy involves pathology beyond the hippocampus (21). Thus, it is likely that the patterns of neuronal death and synaptic reorganization are quite variable in animal models as well as humans with temporal lobe epilepsy, but the principles previously outlined concerning neuronal loss and synaptic reorganization appear to be important contributors, if not fundamental mechanisms, to both.

Time Scale for Epileptogenesis in Temporal Lobe Epilepsy

One important problem in analyzing specific patterns of hippocampal damage and neuronal loss in animal models (based on status epilepticus or other approaches) is that many studies rely on a relatively short time period between the insult and the histopathological analysis, sometimes only days, often weeks, and rarely more than a month or two. Because of the progressive changes that often characterize acquired epilepsy

(22–26) and the long period of time between the precipitating insult and the pathological examination in humans (usually many years, if not tens of years), pathological data from neither experimental animal models nor human surgical tissue can, by themselves, be used to demonstrate causality. In addition, as many of the structures within or even beyond the temporal lobe are highly interconnected, they are probably activated during status epilepticus, repetitive electrical stimulation, or other treatments and injuries. Thus, in interpreting data, there is a need not only to consider the variance across different animal models or across individual animals for a particular model, but also to incorporate the concept that many (if not most) animals and humans with temporal lobe epilepsy may undergo continuous or periodic neuronal loss and synaptic reorganization, as possible components or integral parts of temporal lobe epilepsy and of many other forms of acquired epilepsy. A failure to observe progressive changes in a data set could represent a false negative result that is simply due to the variability in the models.

Chronic Failure of Inhibition: Death of Interneurons

In virtually all of the animal models (including pilocarpine, kainate, and electrical stimulation) and human tissue studies, some GABAergic interneurons degenerate (see Figure 1), which results in a permanent reduction of inhibitory drive to principal neurons (16,27–33). The somatostatin-containing interneurons in the outer molecular layer are among the most vulnerable (27). Whole-cell recordings from dentate granule cells and CA1 pyramidal cells have shown a reduction in the frequency of miniature IPSCs (mIPSCs) after status epilepticus, kindling, and other models (28,30,34,35). Direct electrical recordings from the dendrites and somata of CA1 pyramidal cells provide evidence that dendritic inhibition accounts for most of this reduction in GABAergic inhibition (28). This finding is important because dendritic and somatic inhibition control the inputs and outputs of the hippocampal networks, respectively, and yet, as previously mentioned, the fact that a substantial component of inhibition remains operative is most likely one reason why seizures are not continuous in animal models and human temporal lobe epilepsy.

Chronic Failure of Inhibition: Dormant Interneurons?

Another possible explanation for reduced inhibition, termed the "dormant basket cell hypothesis," has been proposed and involves a loss of excitatory input to basket cell interneurons (36,37), but the hypothesis is based primarily on indirect measures of inhibition (i.e., light-microscopic studies or paired-pulse suppression with field-potential recordings) that are not reliable measures of the potency of GABAergic inhibition and would not detect the loss of dendritic inhibition (38). The parameter measured in paired-pulse suppression experiments—that is, the reduction of a field potential of synchronous action potentials (i.e., the population spike) compared to a preceding one—reflects many independent mechanisms, such as the excitability of axons, dendrites, and somata; alterations in the probability of transmitter release; accumulation of extracellular potassium and decrease of extracellular calcium; in addition to feed-forward and recurrent inhibition. Furthermore, without carefully defined control of the stimulus intensity (and particularly with repetitive, paired pulses), one can obtain a wide range of outcomes from the same animal, and the technique is highly prone to bias, because the amount of suppression is a function of stimulus intensity, which has to be measured in relative terms. Paired-pulse suppression can actually be enhanced when GABAergic inhibition is suppressed pharmacologically (39). The dormant basket cell hypothesis has also been challenged by direct recordings from interneurons in an animal model of temporal lobe epilepsy showing that interneurons are not dormant after chronic seizures and, in fact, interneurons discharge at a high firing rate (40,41). Inferences on the state of GABAergic inhibition without due regard to these multiple levels of complexity may produce misleading, if not spurious, conclusions.

Axon Sprouting and Formation of New Excitatory Synapses

The mossy fibers of the dentate granule cells sprout and form novel aberrant synapses in several animal models and in humans (4,5,12,42,43). Most importantly, these new connections are functional and aberrant in their new locations, as they form excitatory synapses on neurons that they do not normally innervate, and they do not exist in the naive brain. Interestingly, the new synapses also operate in part via kainatergic receptors, whereas naive ones only rely on AMPA receptors (6,7). This finding has major consequences, because kainate-receptor–mediated EPSCs have slow kinetics and activate a phenytoin-sensitive, voltage-gated current (i.e., INap) known to play an important role in the epilepsies (44); furthermore, these seizures are blocked by kainate-receptor antagonists, thus possibly paving the way for the development of a novel and selective blockade of temporal lobe epilepsy (45). Also of interest is the fact that the distribution of kainate-receptor mediated synapses in the brain fits well with the location of brain areas known to be susceptible to damage after seizures, suggesting that one reason why kainate generates seizures and causes neuronal damage is related to activation of normal synaptic signaling. Interneurons and CA3 pyramidal cells that degenerate after seizures are also well endowed with kainate-receptor mediated synapses (46,47).

Although considerable attention has focused on mossy fiber sprouting, neurogenesis, and the formation of new recurrent excitatory synapses among dentate granule cells, a more realistic perspective may be that the dentate gyrus, although a unique if not strategically located structure, is *a model* of synaptic reorganization in other hippocampal and limbic structures. For example, several researchers have developed anatomic and cellular electrophysiological evidence for axon sprouting and the formation of new recurrent excitatory circuits among CA1 pyramidal cells (48–52). Although the CA1 area is a particularly vulnerable portion of the hippocampus and CA1 damage is a classic component of mesial temporal sclerosis, synaptic reorganization in the CA1 area may be best viewed as a model of the type of alterations that comprise synaptic reorganization throughout the limbic system. The concept of extensive changes in the hippocampus and elsewhere fits with an important but underappreciated result developed in a status epilepticus model in which seizure onsets are variable across animals and even within an individual animal, supporting the hypothesis that a constellation of reorganizational mechanisms are widespread throughout the limbic system and potentially other brain areas (53). Thus, temporal lobe epilepsy is essentially a network phenomenon, with reorganizational mechanisms (i.e., loss of vulnerable interneurons and subsequent axon sprouting with formation of recurrent excitatory circuits) that are seen in other types of acquired epilepsy, including perinatal and adult stroke (54,55) as well as in posttraumatic epilepsy (56).

Axon Sprouting and Interneurons

Following chemoconvulsant or electrically evoked repetitive seizures, at least two forms of synaptic reorganization involving GABAergic interneurons have been proposed for the dentate gyrus, but they could also occur in other structures. First, sprouted mossy fiber collaterals of the granule cells have been hypothesized to reinnervate dormant basket cells and create progressively enhanced inhibition (57,58). A corollary to this modification of the dormant basket cell hypothesis is that shortly after the onset of seizures (i.e., after a minimal latent period), the dormant basket cells and the transient loss of inhibition (including selective loss of specific interneurons) create hyperexcitability that causes the onset of spontaneous recurrent seizures. Mossy fiber sprouting, as hypothesized on the basis of paired-pulse experiments and field-potential recordings, would then lead to augmented inhibition because the mossy fibers would form new synapses on basket cells.

Second, interneuron axons could sprout new collaterals and form inhibitory synapses onto granule cells (59,60). Evidence for reactive plasticity of GABAergic synapses is quite limited and generally indirect. Whole-cell recordings from dentate granule cells after kainate-induced status epilepticus showed a reduction in the frequency of mIPSCs shortly after the status epilepticus, and no recovery was present several months later when the animals were having spontaneous recurrent seizures (34). The sprouting of interneuron axons hypothesis predicts that the reduced frequency of mIPSCs in granule cells shortly after the insult should be recovered if interneuron axons reinnervate the granule cells. These data therefore appear to be inconsistent with the hypothesis that interneurons sprout axons that synapse on principal neurons. However, recent studies have provided more direct evidence for interneuron sprouting by demonstrating that the number of connections from interneurons to granule cells in the pilocarpine model is increased, thus possibly leading to partial compensation of at least one component of GABAergic inhibition (60). If mossy fiber axons sprout to interneurons or if interneurons sprout to principal neurons, any increase in inhibitory input would presumably lead to a *decrease* in frequency of seizures or at least to a lack of increase in seizure frequency over time. The epileptic state is generally not maximal immediately after an injury (as predicted by the sprouting and hyperinhibition hypotheses) and does not decrease with sprouting; rather, the opposite typically occurs. Thus, it is unclear what role synaptic reorganization of GABAergic interneuron circuits plays in epileptogenesis, but the possibility that the brain has compensatory mechanisms that counteract epileptogenic mechanisms deserves further investigation.

Secondary Epileptogenesis: Seizures Beget Seizures

The concepts of seizures beget seizures and of secondary epileptogenesis reflect the continuity and progressiveness of the process. A considerable body of data argue that acquired epileptogenesis is not a one-shot event (Figure 3A) that creates an all-or-none epileptic state. Numerous factors presumably contribute to the cascade of events that lead to acquired epilepsy. Epileptogenesis observed in the status epilepticus models is either always progressive (Figure 3B) or usually progressive, particularly when analyzed with long-term continuous monitoring (26). In those cases in which investigators either have not seen progressive epileptogenesis or have found some animals without progressive epileptogenesis, monitoring has usually occurred for a short time period (61). Epileptogenesis typically takes *several months* to be fully engaged in status epilepticus-treated rats and mice. Most investigators study kainate and pilocarpine animals after a relatively short period, such as a month or two after status epilepticus, when the animals are clearly having seizures, but when epileptogenesis is not fully developed (22,23,26,62,63). Although some of the damage characteristic of classic mesial temporal sclerosis can be created rapidly with bilateral electrical stimulation of the perforant path (17), most patients with mesial temporal sclerosis generally have had intractable epilepsy

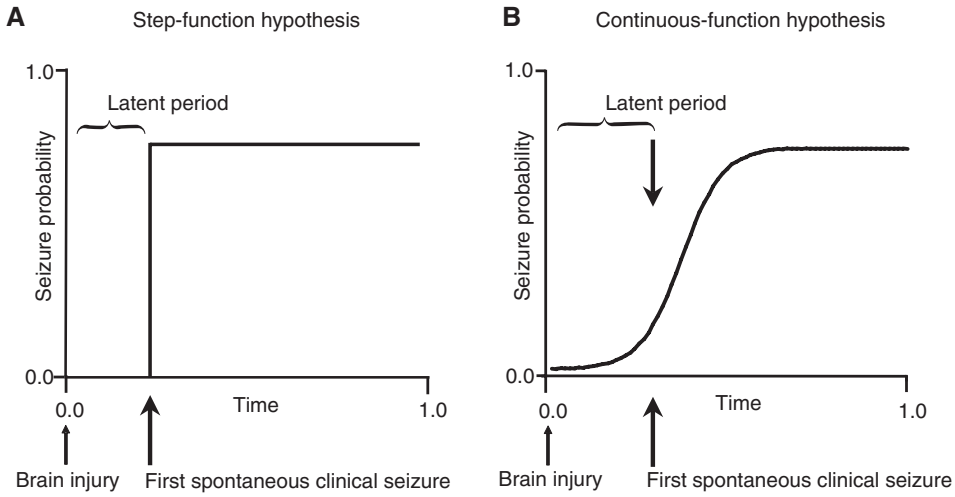

FIGURE 3. Step-function and continuous-function hypotheses of the time course of epileptogenesis. (A) A hypothetical graph illustrates the step-function hypothesis, involving two discrete states. The first state is a seizure-free period, which follows immediately after the initial brain insult (i.e., the latent period, when the process of epileptogenesis occurs and the brain does not experience spontaneous recurrent seizures). The second state is a period during which spontaneous recurrent seizures occur (i.e., epileptogenesis is mature). In the step-function hypothesis, the mechanisms responsible for generation of spontaneous recurrent seizures (i.e., epileptogenesis) are essentially complete by the time the first seizure has occurred. In this hypothesis, seizure rate abruptly reaches a steady state but may be variable, once reached. (B) A hypothetical graph illustrates the continuous-function hypothesis, which is consistent with but does not prove secondary epileptogenesis. In the continuous-function hypothesis, seizure frequency or probability continuously increases after a brain insult, until a steady state is achieved.

for months, years, or even decades before this pattern of neuronal loss is studied histopathologically. Therefore, data indicating that a model induces a pattern of epileptogenesis in a matter of hours or days may not be relevant to the clinical condition of long-term, progressive, human temporal lobe epilepsy, and, acquired epileptogenesis (including temporal lobe epilepsy) may be best viewed over a much longer time period than many *in vitro* mechanistic studies have considered. For example, epileptogenesis in a model of perinatal stroke shows extensive and progressive changes in seizure frequency and other features that continue for at least a year after the brain insult (25).

Conclusions

It has not been definitively established that the spontaneous recurrent seizures associated with chronic epileptogenesis in animal models of temporal lobe epilepsy directly lead to a worsening of the severity of the acquired epilepsy, but the overall constellation of experimental data strongly suggests that a process of *secondary epileptogenesis* is an integral part of the mechanism(s). The fact that intense repetitive seizures in myriad animal models, involving numerous techniques and protocols, result in a severe form of chronic epilepsy is a long-standing fact that supports the hypothesis of secondary epileptogenesis. The mechanism of selective interneuron loss could well be progressive and when combined with axonal sprouting and the formation of new recurrent excitatory circuits (which certainly develop slowly over time), could be the basis for the often seen progressive nature of acquired epileptogenesis. Much focus has been on the dentate gyrus, particularly on mossy fiber sprouting, but similar mechanisms almost certainly occur throughout the hippocampus, other temporal lobe structures, and even other neocortical areas after a brain injury, such as perinatal stroke. Future research in experimental epilepsy involving animal models may benefit from a perspective of acquired epileptogenesis as a slow, time-dependent process (see Figure 3B), rather than of a step-function (see Figure 3A) beginning with a simple latent period (25,26). Although a latent period often exists between a brain injury, such as status epilepticus, and the onset of spontaneous recurrent seizures in both humans and animal models, a large body of data from both *in vivo* recordings of spontaneous seizures and *in vitro* mechanistic experiments strongly suggest that acquired epileptogenesis should generally be viewed as a continuous process, (see Figure 3B) consistent with Gowers's century-old adage that seizures beget seizures (1).

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