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Overview
Laboratory Animal Models of Temporal Lobe Epilepsy

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Temporal lobe epilepsy is a common human disease that is difficult to treat. The pathogenesis of temporal lobe epilepsy, which holds many unresolved questions, and opportunities for creating more effective treatments and preventative strategies are reviewed herein. Laboratory animal models are essential to meet these challenges. How models are created, how they compare with each other and with the disease in human patients, and how they advance our understanding of temporal lobe epilepsy are described.

After stroke, epilepsy, a condition characterized by spontaneous, recurrent seizures, is the most common neurologic disorder. Over 3% of the U.S. population living to the age of 80 will be diagnosed with a chronic epileptic disorder (66). Seizures are caused by uncontrolled, excess, and hypersynchronous neuronal activity, the timing of which is unpredictable. Therefore, common activities like driving, swimming, or climbing a ladder can be life-threatening risks for epileptic patients.

The International League Against Epilepsy has classified human epilepsies by seizure type as self-limited, continuous, or reflex, and as focal or generalized (67). Generalized seizures involve widespread regions of the cerebral cortex. Generalized, self-limited seizures are exemplified by tonic-clonic seizures, which begin with tonic extension of the limbs and trunk, evolve into rhythmic movements (clonus), and terminate spontaneously within a few minutes. Absence seizures also are generalized and self limited, characterized by brief episodes (about 10 sec) of staring and unconsciousness that can occur more than 100 times per day (165). In contrast, focal seizures arise from a focal region of the cerebral hemisphere, and their manifestations depend on the brain region(s) involved. A focal seizure in the limb region of the motor cortex, for example, can induce clonus of the contralateral limb. A focal seizure in the mesial temporal lobe induces automatisms, which are semi-purposeful coordinated movements. Most seizures are self limited, but continuous seizures—status epilepticus—sometimes occur. Reflex seizures are rare and are precipitated by visual stimuli, somatosensory stimuli, thinking, reading, or tooth brushing. The precipitating stimulus is specific for each patient.

The human classification scheme can be used to classify seizures in other species. Self-limited, generalized tonic-clonic seizures and status epilepticus occur in many species. Self-limited generalized absence seizures (characterized by sudden loss of consciousness associated with bilateral spike-and-wave discharges on the electroencephalogram) have been identified in Wistar Albino Glaxo rats (WAG/Rij) (52) and genetic absence epilepsy rats from Strasbourg (GAERS) (130). Reflex seizures occur in Mongolian gerbils with inherited epilepsy (122, 202), in which the optimal precipitating stimulus is exposure to a novel environment (127).

The International League Against Epilepsy has also classified epilepsies by cause as familial, idiopathic, or symptomatic. Familial epilepsies are inherited. Idiopathic epilepsies do not involve underlying structural brain lesions or other signs of neurologic dysfunction, and presumably have a genetic basis. Symptomatic epilepsies are caused by a structural lesion in the brain. Additionally, epilepsies can be associated with specific diseases or encephalopathies, including neurocutaneous disorders, malformations in brain development, tumors, chromosomal abnormalities, metabolic disorders, and infections (67).

More than 100 laboratory animal models of epilepsy have been reported (55, 75, 120). In this article, human temporal lobe epilepsy will be described, unresolved questions about its causes and treatment will be identified, and a review of how laboratory animal models are prepared and how they advance our understanding of temporal lobe epilepsy will be presented.

Temporal Lobe Epilepsy

Temporal lobe epilepsy is the most common type in humans, and many patients continue to have uncontrolled seizures despite treatment with anti-convulsant medications (68). It is associated with a specific structural lesion in the hippocampus, which may be surgically resected in medically intractable cases. Investigation of temporal lobe epilepsy is stimulated, in part, by involvement of the hippocampus, which has a simple organization compared with other parts of the cerebral cortex and plays a role in learning and memory. The role of the hippocampus in memory formation was shockingly evident historically, after bilateral temporal lobectomy was performed to treat medically refractory epilepsy. Surgery caused the immediate and permanent loss of a patient's ability to form new memories, while pre-surgical memories remained intact (185). Insights gained from studying temporal lobe epilepsy may be applied to other types of epilepsy and help reveal mechanisms of temporal lobe function.

Patients with temporal lobe epilepsy have approximately 2 to 30 self-limiting, focal seizures per month (68, 79). Seizures are unpredictable, and why a seizure begins is a persistent question in epilepsy research. The ability to accurately predict seizure onset would be a tremendous advance in helping patients to prepare. Seizures in patients with temporal lobe epilepsy typically

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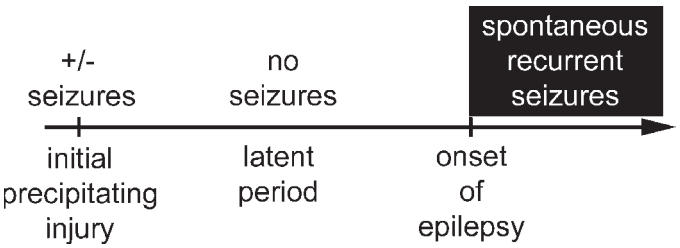

Figure 1. Time line illustrating the sequence of events in the development of temporal lobe epilepsy.

start with an aura (79, 110), during which the patient is conscious. The most common aura is a visceral sensation described as nausea, pressure, "butterflies," or epigastric rising (68, 79). It is followed closely by a focal motor seizure and loss of consciousness, which begins with motor arrest and staring and evolves to oral-alimentary automatisms (e.g., lip smacking, chewing, tooth grinding). Focal motor seizures sometimes progress to generalized tonic-clonic seizures. In either instance, seizures typically are followed by postictal depression. The mechanisms that terminate seizures and determine whether focal seizures will become generalized are of great investigational interest because, once better defined, they could provide targets for anti-convulsant therapies.

Most patients with temporal lobe epilepsy have a history of brain injury. Age at time of the injury is quite variable, but averages about 3 years (134). Up to two-thirds of patients have a history of febrile seizures (70, 79, 207). Although many infants have febrile seizures, only a small proportion develop epilepsy (4, 156). Thus, it is unclear why similar febrile seizures result in temporal lobe epilepsy in some patients, but not in others. One possibility is that an unidentified factor predisposes patients to febrile seizures and temporal lobe epilepsy. Other precipitating injuries include head trauma, infections (e.g., bacterial meningitis and viral encephalitis), status epilepticus, hypoxia/ischemia, birth trauma, and toxins (45, 79, 136, 161). Many, but not all, precipitating events involve seizures at the time. After recovery from the initial precipitating injury, patients begin a seizure-free latent period. The duration of the latent period varies from negligible to decades, the average being six to nine years (79, 134). After the latent period, spontaneous, recurrent seizures develop, which typically continue throughout life (Fig. 1).

Although some patients with temporal lobe epilepsy have tumors or vascular malformations in the temporal lobe, the most common lesion, in 70% of patients, is hippocampal sclerosis highlighted by a specific pattern of neuronal loss (68). The most vulnerable neurons are in the CA1 region and in the hilus of the dentate gyrus, whereas the least vulnerable neurons are the granule cells in the dentate gyrus and the CA2 pyramidal cells (131). Other features include loss of specific classes of inhibitory interneurons and synaptic reorganization of dentate granule cells (58, 97, 128, 135, 191, 196, 221). Lesions also develop outside of the hippocampus. For example, magnetic resonance imaging (MRI) has revealed brain volume loss, and histologic examination has revealed neuron loss in subregions of the amygdala and entorhinal cortex (19, 42, 46, 61, 98, 106, 219). Nevertheless, the hippocampus is the most consistently severely affected region (7, 30, 71, 84, 108, 131, 176).

The reason for the high incidence of temporal lobe epilepsy in humans is unclear, but it is suggested that there are predisposing, species-specific factors. Although epilepsy is common in dogs, it is not consistent with temporal lobe epilepsy, because dogs rarely develop hippocampal sclerosis (38). Hippocampal sclerosis has been described in cats with epilepsy (183). Although epilepsy is not diagnosed in cats as often as in dogs, mild behavioral seizures that involve automatisms but not obvious convulsions might not be recognized as epileptic seizures (54).

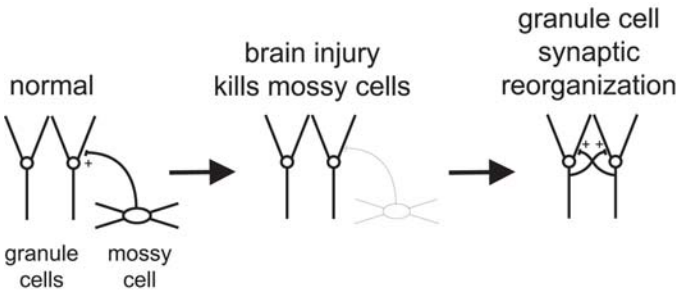

Figure 2. Schematic of the recurrent excitation hypothesis of temporal lobe epilepsy.

The relationship of hippocampal sclerosis to seizures has been debated since 1825 (23). Some evidence suggests that the hippocampal lesion generates seizures. Electroencephalographic recordings indicate that seizures begin in mesial temporal lobe structures (100, 101), and surgical removal of the affected hippocampus (and other structures of the anteriomesial temporal lobe) eliminates seizures in 80 to 90% of patients with medically refractory temporal lobe epilepsy (68). If hippocampal lesions generate seizures, hippocampal sclerosis should precede development of epilepsy. In fact, severe seizure activity, which is one type of precipitating injury, induces hippocampal sclerosis within days in rodents (80, 111), monkeys (143), and humans (81, 161, 199, 207). Since the seizure-free latent period is long, hippocampal sclerosis is likely to be present during the latent period and, therefore, may contribute to seizure generation when epilepsy begins. However, hippocampal sclerosis alone is insufficient to explain seizures, because patients do not have seizures during the latent period.

This leads to the important question of what happens during the latent period. Many hypotheses of temporal lobe epileptogenesis focus on the hippocampal dentate gyrus, which is thought to serve as a seizure-suppressing filter or gate (53, 124). The dentate gyrus contains dramatic lesions featuring loss of hilar neurons (131), and it may not function properly. Neuronal loss includes excitatory mossy cells (8, 10, 21, 152) and inhibitory interneurons (58, 128, 135, 191, 221). Excitatory dentate granule cells survive, and normally are inhibited by γ-aminobutyric acidergic (GABAergic) synaptic input (65, 194). The loss of interneurons may reduce inhibition of granule cells, making them hyperexcitable and lowering the seizure threshold (58, 111).

Another hypothesis contends that the loss of mossy cells results in axon sprouting and synaptogenesis, inducing an aberrant positive-feedback circuit between dentate granule cells that generates seizures (155) (Fig. 2). Mossy cells are the predominant neurons in the hilus (1, 36, 119) and concentrate their glutamatergic axon terminals in the inner molecular layer of the dentate gyrus where they form excitatory synaptic contacts with granule cells (39, 180, 216). Mossy cells are exquisitely sensitive to a wide range of insults (37, 190). When they die, their axon

terminals degenerate, leaving vacant postsynaptic sites on the proximal dendrites of granule cells (155, 162). This deafferentation triggers or permits granule cell axon reorganization (115). Granule cells sprout axon collaterals that invade the inner molecular layer—a region they usually avoid (35, 50)—and form synapses to fill the vacated synaptic sites. Anatomic evidence from patients with temporal lobe epilepsy supports the view that granule cell axons reorganize to form a positive-feedback circuit (58, 76, 97, 99, 196, 220), and the extent of granule cell axon sprouting correlates with the extent of hilar neuron loss (9, 133). It has been proposed that the seizure-free latent period is attributable to the time it takes for synaptic reorganization to establish a sufficient degree of recurrent excitation to surpass the seizure threshold (63). However, if neuron loss in the hilus is present shortly after the initial precipitating injury, synaptic reorganization is likely to develop within several months, as it does in rodent models of temporal lobe epilepsy to be discussed (137, 145, 163, 215). Therefore, the extensive latent period in many patients does not correlate with the short time expected for synaptic reorganization. Nevertheless, it would be useful experimentally and perhaps therapeutically to develop methods to block synaptic reorganization following an epileptogenic injury. Currently, such treatments do not exist to the author's knowledge. Currently prescribed epilepsy medications are seizure-suppressing anti-convulsants, but they are not anti-epileptogenic. In other words, they temporarily treat the symptoms by reducing the probability of seizures, but they do not permanently block or reverse the development of epilepsy (200, 201). Creating anti-epileptogenic treatments is an important goal of epilepsy research.

The aforedescribed hypotheses provide a conceptual link between hippocampal sclerosis and epilepsy. However, they do not adequately account for the long seizure-free latent period in patients. Other hypotheses, alone or in combination, also do not provide a satisfying explanation of the underlying mechanisms and clinical manifestations of temporal lobe epilepsy. They include: inhibition of inhibitory neurons (167), excess excitatory conductance through N-methyl-D-aspartic acid (NMDA)-type glutamate receptors (148), reduced excitatory synaptic drive to inhibitory neurons (190), impaired release of GABA (64), altered $GABA_A$-receptor subunit expression with zinc-induced collapse of inhibition (40), acquired abnormalities in potassium channel function (18, 47), and hypersynchrony mediated by inhibitory neurons (10). Therefore, fundamental questions regarding cause and pathogenesis persist. Study of brain tissue obtained at surgery or autopsy can be helpful, but is limited in quantity, quality, and experimental versatility, and control tissue frequently is unavailable. Therefore, laboratory animal models are essential to help identify causes of temporal lobe epilepsy and translate such findings into better treatments for patients.

Animal Models of Temporal Lobe Epilepsy

Because temporal lobe epilepsy commonly develops after brain injury, most models involve use of this factor. Unfortunately, this raises animal welfare issues because palliative treatment during experimentation may block the pathophysiologic processes that are the focus of study. Investigators and laboratory animal veterinarians must, therefore, choose and use models wisely and humanely to address experimental questions, while minimizing pain, distress, and discomfort. Some of the methods used to create models will be described, because they are important for animal welfare concerns and for encouraging refinement.

Table 1. Features displayed by various rodent models of temporal lobe epilepsy

Model	Hippocampal neuron loss	Granule cell synaptic reorganization	Spontaneous seizures
Neonatal hyperthermia	—	±	±
Neonatal hypoxia	—	—	—
Neonatal hypoxia + ischemia	+	+	+
Percussive brain injury	+	+	±
Tetanus toxin	±	±	+ (transient)
Kindling	—	±	—
Over-kindling	+	+	+
Status epilepticus	++	++	++

Absence of a feature is indicated by —, presence by +, and strong presence by ++. Uncertain or conflicting data, or special circumstances are indicated by ±. *See* text for details and references.

Neonatal hyperthermia. Most patients with temporal lobe epilepsy have history of febrile seizures (79). Hyperthermia has been used to develop several rat models that can be used to investigate the long-term effects of febrile seizures (94, 96, 150). For example, heated air is used to raise the core temperature of 10- to 11- (postnatal) day-old rats to 41°C for 30 min, causing seizures lasting approximately 14 min (12). After treatment, rat pups are placed on a cool surface for 15 min before being returned to their home cage. Mortality is about 10%. One week later, the seizure threshold is reduced and the hippocampus is hyperexcitable (62). Unlike patients with temporal lobe epilepsy, however, the hippocampus does not display neuron loss and there is little evidence of granule cell synaptic reorganization (15). Preliminary results suggest that hyperthermia-treated rats can develop spontaneous, recurrent seizures (11), but they do not appear to become epileptic as consistently and reliably as do other models of temporal lobe epilepsy (Table 1).

Neonatal hypoxia ± ischemia. Neonatal hypoxia/ischemia is associated with increased risk of developing epilepsy (16), stimulating development of rat models of neonatal hypoxia (49). For example, 10- to 12- (postnatal) day-old rats were exposed to 3 to 4% oxygen for 15 to 20 min (104). The treatment reduced blood oxygen pressure and saturation, causing acidosis and seizures (103). Up to at least 110 days later, the seizure threshold was reduced (49, 138), and the hippocampus was hyperexcitable (105), but did not display neuron loss (164). Currently there is no evidence that spontaneous, recurrent seizures develop. Thus, like the febrile seizure model, the hypoxia model does not induce hippocampal sclerosis and is not epileptogenic (Table 1).

More severe treatments involve combined hypoxia with ischemia in rats (95). For example, 7-day-old rats were anesthetized with isoflurane, and the right common carotid artery was ligated prior to return to the dam (217). Two hours later, the pups were placed in a warm, humidified chamber filled with 8% oxygen and 92% nitrogen for 2 h. During that time, the pups displayed seizure-like behavior; mortality was 20%. Rats treated with hypoxia plus ischemia developed hippocampal sclerosis, granule cell synaptic reorganization, and spontaneous seizures (Table 1). The extent of synaptic reorganization was less than that found in status epilepticus models and patients with temporal lobe epilepsy. The seizure-free latent period was longer and seizure frequency was about 20 times lower than that of status epilepticus models. Nevertheless, to the author's knowledge, this is the only current model of perinatal brain injury that induces

substantial hippocampal sclerosis and eventual development of epilepsy. However, the hypoxia plus ischemia treatment is likely to cause a clinical syndrome and neuropathologic changes that extend beyond the temporal lobe and resemble those in patients with epilepsy and cerebral palsy (91, 114).

Percussive brain injury. Head trauma is the second most common risk factor for developing temporal lobe epilepsy (79, 213). There are several methods for inducing traumatic brain injuries. One type uses fluid percussion to generate injurious mechanical force and has been done in cats (92, 195), rabbits (118), and rats (59). For example, McIntosh and co-workers (140) developed a lateral fluid-percussion injury model in which a pressurized [approx. 2 atm (1 atm = 101.29 kPa)] pulse (about 20 milliseconds) of saline was injected against cranial dura mater of anesthetized or recovering rats (56, 140, 195, 204). The injury caused transient unconsciousness in rats recovering from anesthesia and longer-lasting motor and memory deficits (56, 140, 192). Mortality was approximately 10% after a pulse at moderate pressure, but increased with higher impact pressures.

Fluid-percussion injury induces a lesion at the site of impact in the neocortex. Although the hippocampus is remote from the impact site, the treatment induces neuron loss, mild degree of granule cell synaptic reorganization, and lasting hyperexcitability in the hippocampus (56, 86, 126, 177, 204). Currently there is no evidence that an injury inflicted by use of moderate impact causes spontaneous recurrent seizures. After more severe injuries induced with approximately 3 to 4 atm of impact pressure, some rats developed spontaneous behavioral seizures (57, 160). However, it is unclear whether seizures were initiated in the neocortex or hippocampus, or both. The neocortical lesion was not typical of that of temporal lobe epilepsy, and it is a confounding factor for experiments investigating the role of the hippocampus in epileptogenesis.

The most persuasive attributes of the aforementioned injury models are their link to risk factors for developing temporal lobe epilepsy, including effects on the hippocampus. However, they all fall short of mimicking key aspects of human temporal lobe epilepsy. Of at least equal importance, they induce considerable morbidity and mortality, which makes their use problematic from an animal welfare perspective.

Tetanus toxin. Loss of inhibitory neurons in patients with temporal lobe epilepsy (58, 135, 191) may make remaining excitatory neurons more likely to generate seizures. Tetanus toxin blocks neurotransmitter release, and preferentially affects GABA (17). Therefore, inhibition was reduced by injecting tetanus toxin into the hippocampus of rats (102, 144). They began having spontaneous seizures about seven days later. Seizure rate maximized at 10 to 15 days after treatment, then subsided, none being observed after 31 days. Neuron loss and granule cell synaptic reorganization in the hippocampus were absent or minor (3, 146, 147). Tetanus toxin also has been used to induce seizures initiated in the neocortex (28) and the hippocampus of infant rats (9 to 10 days old) (116). Although the tetanus toxin model does not induce hippocampal sclerosis or permanent epilepsy, it may be useful for studying the effects of selective loss of inhibition. Other models of temporal lobe epilepsy involve multiple, simultaneous changes (Table 1). With multiple variables, it is difficult to determine which are the most important for generating seizures. More selective deficits, like those induced by tetanus toxin, can be useful for testing specific mechanisms.

Kindling. Kindling entails repeated, mild, electrical stimulation of the amygdala, olfactory regions, hippocampus, or other brain regions to induce a progressive and permanent seizure response (85). For example, Racine (170) stereotaxically implanted an electrode in the amygdala of anesthetized rats. Unrestrained rats were then stimulated daily using a 1-sec train of electrical pulses of 60 Hz and one-millisecond duration. The stimulus intensity was set just high enough so that an afterdischarge was evoked (i.e., the tissue continued to discharge for a few seconds after stimulation ceased). At first, there was no behavioral response to stimulation. With repeated stimulation, afterdischarges lengthened and rats began displaying seizure behaviors, despite unaltered stimulation parameters. There are five cumulative stages (classes) of seizure development: 1) mouth and facial movements, 2) head nodding, 3) forelimb clonus, 4) rearing, and 5) rearing and falling. The Racine scale is a common way for investigators to describe seizure behavior in rodent models of epilepsy.

The number of stimulations required to kindle an animal—so that, for example, class-4 or class-5 seizures are evoked consistently—depends on several parameters, including the species used. A wide variety of species has been kindled, including frogs (151), lizards (172), rodents (85), cats (212), dogs (214), macaques (210), and baboons (211), and different species kindle at different rates. Rodents kindle quickly, primates slowly, and carnivores at intermediate rate. For example, an average of 14 stimulations is required for amygdala kindling in rats, 25 in cats, and 196 in rhesus macaques (209).

There also are differences within species. For example, of rat strains tested, Lewis rats require the most stimulations for amygdala kindling, Sprague-Dawley and Brown Norway rats require the fewest, and Wistar, Fischer 344, ACI, and Wistar-Kyoto rats need an intermediate number (121). Additionally, different brain regions kindle at different rates. In rats, the amygdala requires an average of 11 stimulations, and the hippocampus requires an average of 27 (170). The long time required to kindle an animal with single, daily stimulations is undesirable for some experiments. Consequently, accelerated kindling protocols have been developed (125). A long-term stimulating electrode is implanted in the ventral hippocampus of rats (20). At least one week later, animals are stimulated by use of a 10-sec train of one-millisecond pulses at 400 μA and 50 Hz. A total of 72 stimulus trains are delivered every 5 min to kindle rats in just over 6 h.

One advantage of the kindling model is that specific brain regions can be treated more selectively. However, as kindling progresses, afterdischarges and seizures propagate beyond the targeted region. Another advantage is that kindled animals can help resolve one of the major problems in epilepsy experiments: determining whether a difference between an epileptic and control group is a cause or an effect of seizures. For example, one study included a control group, an epileptic group, and a kindled group (137). The number of spontaneous seizures in epileptic rats was recorded, and the same number of seizures was evoked in kindled rats. The kindled rats, therefore, served as a control for the effect of seizures (without epilepsy). If a difference between the control and epileptic groups is only a side effect of seizure activity, the kindled group should resemble the epileptic group.

The kindling model has been used to develop novel hypoth-

eses. One hypothesis is that temporal lobe epileptogenesis is attributable to excess excitatory conductance through NMDA-type glutamate receptors on dentate granule cells. The NMDA receptors are glutamate-gated ion channels that are permeable to sodium and calcium ions. When activated, NMDA channels depolarize the cell and trigger calcium-dependent second-messenger signal transduction cascades. Compared with granule cells from controls, those from kindled rats have NMDA receptors that open more easily and more often (112), which makes previously subthreshold excitatory inputs capable of triggering action potentials and perhaps seizure activity (148). However, NMDA receptor conductance decreases to control values within a month after kindling stimulations cease (13, 14, 179), whereas the kindling-induced increase in seizure response is permanent (85, 212). Therefore, NMDA receptors may be important for induction of kindling, but not for maintenance of the seizure-sensitive state.

Zinc-induced collapse of inhibition is another hypothesis of temporal lobe epilepsy developed using the kindling model. Zinc is concentrated in synaptic vesicles of granule cell axons (166). The hypothesis contends that granule cells change their expression of $GABA_A$ receptors, so that they can be blocked by zinc ions released by sprouted granule cell axons (29, 40). Unlike $GABA_A$ receptors from control rats, the $GABA_A$ receptors on granule cells from kindled rats, pilocarpine-induced epileptic rats, and patients with temporal lobe epilepsy are blocked by exogenously applied zinc (40, 188). However, whether endogenous zinc ions are released at concentrations sufficient to diffuse to and effectively block $GABA_A$ receptors is questionable (107, 149).

Bragin and co-workers (25) hypothesized that kindling accounts for the latent period in patients. They proposed that, after an initial precipitating injury, hippocampal sclerosis and granule cell synaptic reorganization form small clusters of pathologically interconnected neurons that gradually kindle the hippocampus by generating hypersynchronous bursts of action potentials. If so, anti-convulsant treatment during the latent period would prevent development of epilepsy by blocking hypersynchronous bursts of action potentials. Contrary to this prediction, anti-convulsant drugs administered during the latent period do not prevent or delay the development of epilepsy (168).

In the kindling model, seizures are evoked, and are not spontaneous. Animals receive stimulation treatments until they reliably display class-4 or class-5 seizures, then kindled animals are compared with unstimulated controls. Kindled animals do not have spontaneous seizures, so they are not truly epileptic. Futhermore, kindled animals do not have hippocampal sclerosis. Therefore, their relevance to humans with temporal lobe epilepsy is questionable. However, animals can be "over-kindled" so that they exhibit more features of temporal lobe epilepsy. Spontaneous seizures develop after many kindling stimulation treatments, but this requires at least approximately 100 class-5 seizures in rats (178). After repeated stimulation, rats gradually display progressive neuron loss and mild degree of synaptic reorganization in the hippocampus (43, 44), but not to the same extent as that in status epilepticus models (Table 1) or patients with temporal lobe epilepsy.

Status epilepticus. Patients with temporal lobe epilepsy frequently have a history of a precipitating injury that involves prolonged seizures (79, 136) and sometimes status epilepticus (161). Status epilepticus is rapidly repeated or continuous seizure activity. In animal models, it can be initiated by use of electrical stimulation or chemical convulsants.

(i) Electrical induction. Electrical stimulation of the hippocampus, its afferents (139, 187, 189, 208), or the amygdala (141) has been used to initiate status epilepticus. For example, stimulating electrodes were implanted in the hippocampus of adult rats (123). One week later, awake rats were stimulated with 1-millisecond pulses at 400 μA and 50 Hz—a train of stimuli is on for 10 sec and off for 1 sec—that continued for 90 min. Ninety percent of treated rats developed self-sustaining status epilepticus that continued for at least 30 min and longer (6 to 12 h) in some instances. Over 80% of the rats that developed status epilepticus for at least 6 h sustained neuronal loss, had evidence of hyperexcitability in the hippocampus, and developed spontaneous recurrent seizures after a latent period (129).

Status epilepticus can be induced by electrically stimulating the lateral nucleus of the amygdala (158). Adult rats with implanted electrodes were stimulated by use of 100-millisecond pulses at 400 μA and 60 Hz every 0.5 sec for 20 min. If status epilepticus began—evident by head nodding and/or clonus of the limbs—stimulation was stopped. If status epilepticus did not begin, stimulation was resumed, and the rat was evaluated for status epilepticus 5 min later. This cycle was repeated a second time, if necessary. The treatment induced neuronal loss in the hippocampus and granule cell synaptic reorganization; spontaneous seizures developed after a latent period in over 85% of the rats that experienced status epilepticus; however, mortality was 20%.

(ii) Chemical induction. Chemical convulsants such as pilocarpine (206) and kainic acid (153), can initiate status epilepticus. Pilocarpine is a muscarinic acetylcholine receptor agonist. Activation of these receptors has many effects in the brain, and blocking a class of potassium channels is likely to contribute to increased neuronal excitability and seizures. Kainic acid is a glutamate receptor agonist that excites neurons to produce seizures. It is structurally related to domoic acid, which is the toxin responsible for shellfish poisoning. Ingestion of domoic acid causes seizures (sometimes status epilepticus) and hippocampal sclerosis, and survivors develop memory impairment and temporal lobe epilepsy (45, 199).

The pilocarpine-induced status epilepticus rat model may be the most widely used model of temporal lobe epilepsy. Initially, peripheral cholinergic side effects are blocked by administration of atropine methylbromide (5 mg/kg of body weight, i.p.). Twenty minutes later, pilocarpine is administered (380 mg/kg, i.p.) to evoke status epilepticus. Behavioral seizure activity typically begins in 10 to 30 min. After a period of status epilepticus, seizures are suppressed by use of an anticonvulsant (for example, two to four diazepam treatments, each 10 mg/kg, i.p., at 2- to 3-h intervals as needed). It is critical that status epilepticus be of sufficient duration (approx. 2 h) to induce a brain injury that will result in the temporal lobe epilepsy phenotype. If status epilepticus is blocked or curtailed prematurely, neuronal loss is prevented and synaptic reorganization and epilepsy fail to develop (27, 80, 117, 197). To help rats recover, supportive care should be provided (subcutaneous fluids, monitor and control body temperature, as needed). Body weight decreases after status epilepticus, but recovers to pretreatment value in approximately one week (206). The aforementioned protocol has been used extensively in 32- to 63-day-old male Harlan Sprague-

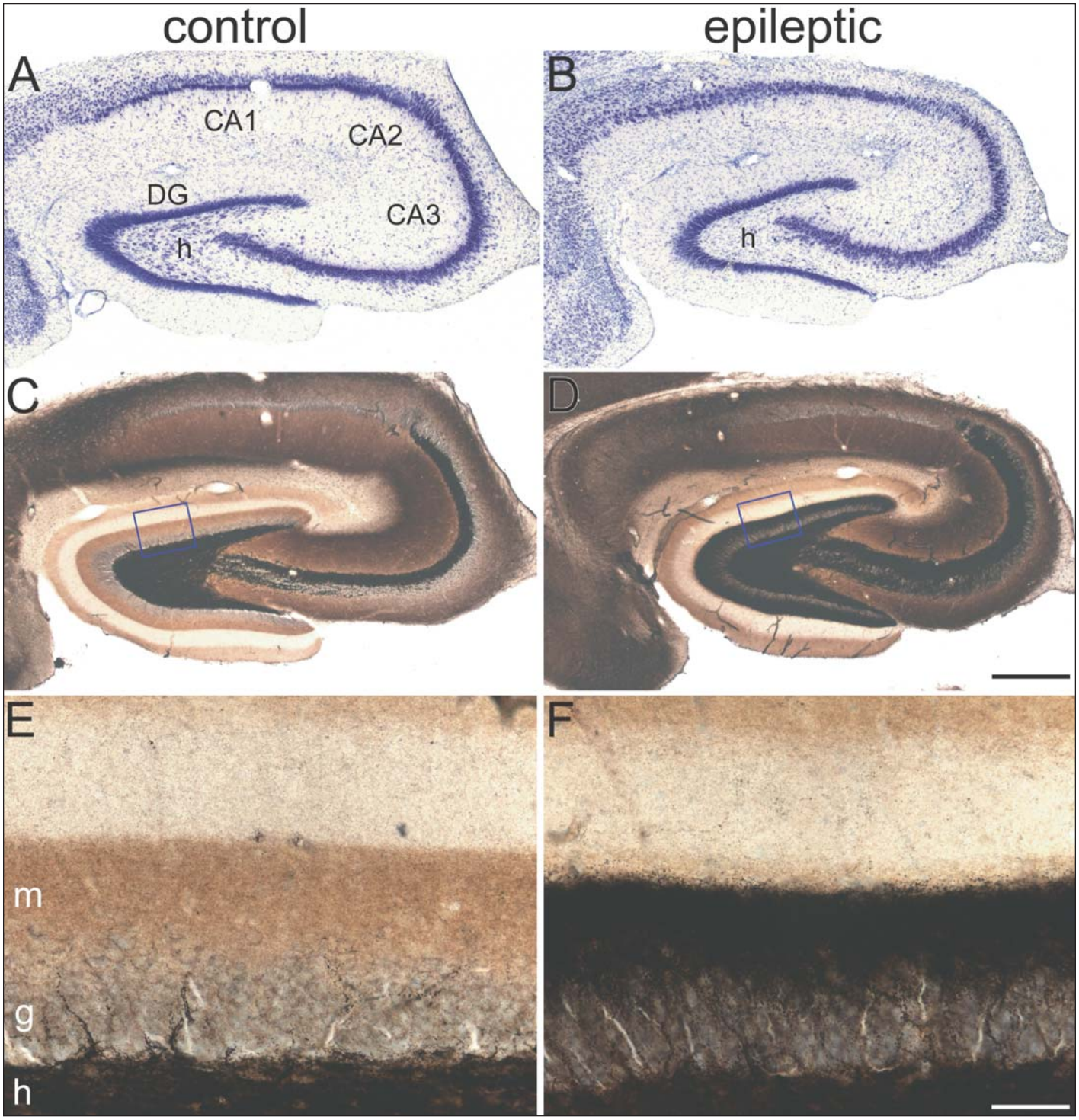

Figure 3. Photomicrographs of the hippocampus of an age-matched, vehicle-treated control (A, C, E) and an epileptic rat 40 days after pilocarpine-induced status epilepticus (B, D, F). (A and B) Nissl-stained sections reveal the dentate gyrus (DG) and the major subfields of Ammon's horn (CA1, CA2, and CA3). The hilus of the dentate gyrus (h) contains many large, scattered neurons in the control, but not in the epileptic rat. (C and D) Timm staining labels axon terminals that concentrate zinc. Granule cell axon terminals are black. The hilus and a layer in (CA3) are black because that is where granule cell axons normally project. The boxed regions are shown at higher magnification in (E and F). Black Timm staining extends from the hilus (h) into the granule cell layer (g) and inner molecular layer (m) in the epileptic but not in the control rat. Bars: (A-D) = 500 μm; (E and F) = 50 μm.

Dawley rats, with 67% developing status epilepticus and surviving, 11% developing fatal status epilepticus, and 21% not developing status epilepticus. Published protocols indicate that 15 to 40% of treated rats fail to develop status epilepticus (51, 80, 83, 111, 145, 162). If induction rates are low, expect some non-responders and factor them into the experimental design instead of increasing the convulsant dose, thereby increasing mortality. Non-responder rats can also be considered for a drug-treated

control group. After status epilepticus, treated rats display hippocampal neuron loss, especially in the hilus of the dentate gyrus, and they develop granule cell synaptic reorganization (34, 88, 159, 203) (Fig. 3). After an average latent period of approximately 26 days, over 90% of post-status epilepticus rats display spontaneous, recurrent seizures of Racine class 3 or greater, which continue for life.

There are variations in the pilocarpine-treatment protocol. For example, methylscopolamine (1 to 2 mg/kg, i.p.) can be used to antagonize the peripheral cholinergic side effects of pilocarpine. It is important to choose an antagonist that is effective in the periphery, but does not cross the blood-brain barrier easily, or it will block the intended seizure activity. Some protocols call for pretreatment with terbutaline (1 to 2 mg/kg, i.p.), an α_2-adrenergic agonist and bronchodilator that is thought to help with respiration. Various anticonvulsants can be used to suppress seizure activity after 2 h of status epilepticus. Benzodiazepines and/or barbiturates (e.g., 50 mg of pentobarbital/kg, i.p.) have been used as anticonvulsants. Failure to suppress seizures will result in high mortality after pilocarpine treatment.

Another variation of pilocarpine use is pretreatment with lithium. When lithium (3 mEq/kg, s.c.) is administered 24 h earlier, only a small dose of pilocarpine (30 mg/kg) is needed to evoke status epilepticus (51). Some protocols call for administration of a convulsant directly into the hippocampus or into the lateral cerebral ventricle. Pilocarpine and kainic acid can be injected directly into the hippocampus (24, 82, 154, 155). Intracerebral injections tend to induce a more focal lesion, longer seizure-free latent periods, and lower seizure frequencies than do systemic treatments.

Early protocols for systemic treatment with kainic acid called for administration of a single high dose (12 to 18 mg/kg, s.c., i.v., or i.p.). Mortality was high, and a low and variable proportion of rats developed spontaneous, recurrent seizures. To address these issues, a multiple low-dose protocol was developed, which permits individual dosing on the basis of how each animal responds (93). Kainate (5 mg/kg, i.p.) is administered to rats every hour, and seizure activity is scored according to the Racine scale. Injections are delayed or discontinued if a rat becomes unusually inactive or excessively active (continual circling, pacing, or jumping). Treatment ceases after three continuous hours with at least one class-4 or class-5 seizure per hour, and the cumulative kainate dose is 20 to 50 mg/kg. This approach reduced mortality to 15% and increased production of epileptic rats to over 95% of those surviving status epilepticus. A multiple low-dose protocol for pilocarpine treatment produces results similar to those of the aforementioned single high-dose pilocarpine-treatment (83).

Advantages of status epilepticus models include robust development of hippocampal sclerosis and granule cell synaptic reorganization, a latent period, and permanent epilepsy once it is established (Table 1). The latent period is important experimentally, because it provides a window of opportunity to test antiepileptogenic treatments (31). It also presents a pre-epileptic state that can help distinguish between causes and effects of chronic epileptic seizures (111). Most importantly, status epilepticus models have advanced understanding of human temporal lobe epilepsy. For example, Nadler and co-workers (154) were the first to recognize that rats treated with kainic acid display a pattern of neuron loss similar to that of hippocampal sclerosis found in human patients. They reported synaptic reorganization of granule cells, and proposed the recurrent excitation hypothesis (155, 198) (Fig. 2). Prompted by these findings in kainate-treated rats, other investigators evaluated hippocampal tissue from patients with temporal lobe epilepsy and found the same sort of abnormal rewiring of granule cells (58, 97, 196).

Nevertheless, status epilepticus models have limitations, as noted for other epilepsy models. The pattern of neuronal loss is not identical to that found in human patients, in that the loss in animal models is more symmetric. Systemic treatment, focal stimulation, and intracerebral injection induce a substantial degree of bilateral neuron loss, in part because of the extensive commissural connectivity of the hippocampus in rodents compared with primates (2). Compared with primate status epilepticus models (143) and patients (7, 30, 42, 71, 84, 131, 176, 219), rodent status epilepticus models also tend to have more neuron loss in regions outside of the hippocampus. The olfactory cortex is one of the largest regions of extrahippocampal damage in rodent status epilepticus models (26, 48, 51, 80, 141, 158, 184, 193, 205). It is highly developed in rodents and may play a disproportionate role in epileptogenesis of rodent models. Furthermore, the loss of CA1 pyramidal cells is less consistent in rodent models. To address this deficiency, a model combining ischemia and kainate-treatment was developed, and treated rats displayed substantial neuron loss in CA1, CA3, and the hilus (77). Additional differences include short latent period and older age at which the initial precipitating injury is sustained in models compared with patients. The severity of status epilepticus as a precipitating injury in models might contribute to their short latent period and more extensive extrahippocampal neuron loss.

Species, Strain, Sex, and Age Affects Results of Epileptogenic Treatments

Variability in the mortality and the proportion of animals that develop status epilepticus and chronic epilepsy can be attributed in part to sex, strain, and age differences. For example, estradiol increases susceptibility to kainate-induced seizures (157); thus, female rats will respond to kainite treatment, in part, on the basis of their estrous cycle. There also are strain-specific differences in kainate sensitivity. After systemic kainite treatment, adult (70- to 90-day-old) male Wistar-Furth and Fisher 344 rats, both inbred strains, display more sensitivity and more reliable behavioral seizure responses than do the outbred rat strains, Sprague-Dawley and Long Evans Hooded (87). Aged rats (24 months old) are less vulnerable to kainate-induced excitotoxicity than are 3- to 20-month-old rats (109). Juvenile rats (35 to 40 days old) are more sensitive and display more consistent behavioral seizures after kainite treatment than do adult rats (70 to 90 days old) (87). When young rats (up to approx. 25 days old) are subjected to the same pilocarpine or kainite treatment protocols as adults, they develop acute seizures, but their hippocampal neurons survive and synaptic reorganization and spontaneous recurrent seizures fail to develop (90, 169, 218). However, after lithium-pilocarpine combination treatment, some rats as young as 20 to 21 days old develop epilepsy (175), and some of these do so without hippocampal neuron loss or granule cell synaptic reorganization (171). In response to electrically induced status epilepticus, 100% of 35-day-old rats become epileptic, but only 11% of 21-day-old rats develop epilepsy (175). These findings indicate that using 35- to 60-day-old rats for status epilepticus models will reduce mortality and improve consistency.

Chemically induced status epilepticus in mice is associated with profound strain differences. For example, mouse strains differ in their seizure thresholds. Thus, electroconvulsive stimulation evokes seizures more easily in DBA/2J than in C57BL/6J mice (74, 78). There also are strain-dependent differences in seizure sensitivity to chemical convulsants (69, 73, 113, 132, 142, 174). Mature (9- to 10-week-old) DBA/2J mice are more vulnerable than are CBL/6J mice to induction of behavioral seizures after systemic kainite treatment (72). Although kainic acid at sufficient doses evokes seizures in all tested strains, there are strain differences in neuronal loss. The DBA/2J, FVB/N, and 129/SvEMS mice (like rats) have extensive hippocampal neuron loss and synaptic reorganization after kainate-induced status epilepticus, whereas C57BL/6, BALB/c, C3H, ICR, 129/SvJ, and SJL are resistant to neuronal loss (142, 181, 182). These strain differences are particularly problematic because C57BL/6 and 129/SvJ mice are commonly used as stock for gene-targeting experiments. To induce neuronal loss by use of kainic acid in resistant strains, focal injection into the hippocampus is preferable to systemic treatment (5). Alternatively, pilocarpine instead of kainic acid can be used systemically (41). After pilocarpine-induced status epilepticus, C57BL/6 mice sustain neuron loss and develop synaptic reorganization and spontaneous, recurrent seizures (186).

There may also be vendor-specific differences within strains. For example, pilocarpine-induced status epilepticus results in high mortality in C57BL/6 mice from The Jackson Laboratories but, for reasons that are unclear, not in C57BL/6 mice from Charles River Laboratory (22). These few examples illustrate that selection of epilepsy models must be done with care to obtain useful results while minimizing the impact on animal subjects. Laboratory animal veterinarians can provide important advice to investigators in this regard.

Primate Models of Temporal Lobe Epilepsy

Because of their small neocortex, rodents lack a well-defined temporal lobe, but have the homologous structures. Neurons in the hippocampus and nearby entorhinal cortex of rodents and primates are similar in many respects, but there also are differences in neuronal anatomy and function that are potentially important for temporal lobe epilepsy (6, 32, 33). This raises questions about the suitability of rodents for modeling some aspects of human temporal lobe epilepsy. To address this issue, nonhuman primate models of temporal lobe epilepsy have been developed.

An alumina gel injection model of temporal lobe epilepsy was developed in rhesus macaques (173). Young adults were anesthetized, and 0.1 to 0.2 ml of alumina gel was injected stereotaxically into one to three sites in a temporal lobe. After 12 to 14 days, animals given injections in the hippocampus developed severe, spontaneous seizures that required euthanasia. After 2 to 3 weeks, animals given injections in the entorhinal cortex developed less severe seizures. After injection in the amygdala, spontaneous behavioral seizures developed even more slowly, over 3 to 6 weeks, and remained mild over a long period. All affected animals developed behavioral, electrographic seizures and pathologic features (hippocampal neuron loss and granule cell synaptic reorganization), similar to those in patients with temporal lobe epilepsy.

A status epilepticus model of temporal lobe epilepsy has been developed in infant (6 to 7 months old) pigtailed macaque monkeys (89). A chronic, stereotaxic guide-tube cranial platform (60) was used to give unilateral intracerebral injections of the $GABA_A$ receptor antagonist bicuculline at each of three sites in the entorhinal cortex of awake animals. The infusions caused acute status epilepticus, consisting of facial twitching, chewing movements, drooling, unresponsiveness, tremors, rhythmic eye movements, erratic heart rate, vomiting, pallor, and contralateral head turning. After 1 h, status epilepticus was terminated by administration of diazepam. The MRI and histologic findings obtained 4 to 10 months later resembled those of patients with unilateral temporal lobe epilepsy. The hippocampus was shrunken, neuron loss occurred, and granule cell synaptic reorganization developed. However, none of five treated animals developed spontaneous recurrent seizures through 10 months. Whether they would have developed epilepsy eventually is not clear.

Conclusion and Future Directions

There is no doubt that temporal lobe epilepsy is a devastating human disease compounded by many unresolved questions about cause, pathogenesis, and treatment. To investigate injuries that initiate temporal lobe epileptogenesis, neonatal hyperthermia, neonatal hypoxia ± ischemia, and percussive brain injury models are useful. Status epilepticus models are useful to address questions about hippocampal sclerosis, the latent period, and the chronic epileptic state, and to test anti-epileptogenic and anti-convulsant treatments. The kindling model provides insights into an epileptogenic process. More selective and specific treatment, like that induced by tetanus toxin, is useful for dissecting out the complex, multiple effects of epileptogenic injuries. Studies in nonhuman primates may be useful in learning why the human hippocampus is predisposed to epileptic injuries and in identifying epileptogenic factors that develop during the long latent period.

Because epilepsy research requires an intact nervous system, animal models will remain an essential component toward better understanding and treatment. As illustrated here, currently available models mimic, to variable degrees, the biological features of human epilepsy, but they also entail induction of substantial neurologic deficits. Although careful selection of the appropriate model, species, strain, sex, and age can reduce contemporary impacts on animals, development of more refined models is clearly an important scientific and humane priority of epilepsy research.

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