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Is Epilepsy a Preventable Disorder? New Evidence from Animal Models

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Abstract

Epilepsy accounts for 0.5% of the global burden of disease, and primary prevention of epilepsy represents one of the three 2007 NINDS Epilepsy Research Benchmarks. In the past decade, efforts to understand and intervene in the process of epileptogenesis have yielded fruitful preventative strategies in animal models. This article reviews the current understanding of epileptogenesis, introduces the concept of a “critical period” for epileptogenesis, and examines strategies for epilepsy prevention in animal models of both acquired and genetic epilepsies. We discuss specific animal models, which may yield important insights into epilepsy prevention including kindling, poststatus epilepticus, prolonged febrile seizures, traumatic brain injury, hypoxia, the tuberous sclerosis mouse model, and the WAG/Rij rat model of primary generalized epilepsy. Hopefully, further investigation of antiepileptogenesis in animal models will soon enable human therapeutic trials to be initiated, leading to long-term epilepsy prevention and improved patient quality of life.

Keywords

epileptogenesis; prevention; activity dependent; animal models; acquired epilepsy; idiopathic generalized epilepsy

Epilepsy is a disorder characterized by chronically recurring seizures without clear precipitants. The age-adjusted prevalence of epilepsy is in the range of 4 to 10 per 1000 people in most locations (Sander 2003; Forsgren and others 2005). The burden associated with epilepsy is great, both for the individual with epilepsy and for society at large. Epilepsy can negatively impact cognitive function, is a source of social stigma and legal marginalization, causes increased mortality, economically contributes 0.5% of the global burden of disease, and is associated with an increased risk of psychiatric disorder (de Boer and others 2008). As such, epilepsy prevention is one of the three 2007 NINDS Epilepsy Research Benchmarks (Kelley and others 2009).

Work on epilepsy prevention can for the most part be parsed into prevention of epilepsy after a known inciting event (acquired epilepsy), and prevention of epilepsy in genetic

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models where the time of epilepsy development is well characterized and may be dependent on a transient developmental milieu. Both of these approaches rest upon identification of epileptogenesis, understanding of the underlying mechanisms of epilepsy development, and intervention targeted to these mechanisms in an appropriate time period. While prevention of epilepsy in human subjects has been largely unsuccessful to this point, recent studies in animal models have been encouraging and show certain treatments to be efficacious. In this article, we focus on the prevention of epilepsy in animal models of acquired epilepsy, including kindling, poststatus epilepticus, prolonged febrile seizures, traumatic brain injury, and hypoxia, as well as in genetic models including tuberous sclerosis and a model of primary generalized epilepsy.

What Is Epileptogenesis and Can It Be Prevented?

Epileptogenesis is the process by which a “normal” brain becomes epileptic. Most work on epileptogenesis has focused on acquired forms of epilepsy, in which there is an inciting event such as injury or prolonged seizure, followed by a clinically latent period during which the brain undergoes repair and reorganization to a hyperexcitable state, succeeded by a clinically epileptic phenotype. Throughout epileptogenesis, modulating factors such as genetics, age, and the inherent structural and functional plasticity of the brain in question help to determine the progression to chronic or refractory epilepsy (Fig. 1).

In humans, events that may incite acquired epileptogenesis include traumatic brain injury, stroke, central nervous system infection, neoplasm, intracerebral hemorrhage, complex febrile seizures, and status epilepticus (Shinnar and others 2000; Herman 2002). One inciting event may be sufficient, or multiple “hits” may be required for the development of epilepsy (Dichter 2009a). Factors that have been shown to modulate progression to epilepsy include family history of seizure, age, gender, existing organic brain disease, and psychiatric comorbidity (Hauser and Annegers 1991; Hesdorffer and others 2000; Frey 2003). In experimental models, repeated subthreshold electrical stimulation (kindling), drug- or electrical stimulus-induced status epilepticus, prolonged hyperthermia-induced seizures, traumatic brain injury, and ischemia are among the mechanisms used to induce epileptogenesis.

Recent work suggests that a similar process of epileptogenesis may also occur in genetic forms of epilepsy. In such disorders, there is an underlying genetic predisposition that initiates epileptiform events. However, even in genetic forms of epilepsy, recurrent epileptiform events may lead to abnormal activity-dependent plasticity, which can both contribute to further tendency for seizures, and to other adverse chronic changes in the nervous system (Massa and others 2001; Staley and others 2005; Nicolai and others 2007).

Cellular and Electrical Mechanisms of Epileptogenesis

As the brain becomes epileptic, a combination of cell loss, increased excitability, and formation of abnormal circuits occurs. Cellular mechanisms of epileptogenesis are numerous and include cell loss, gliosis, increased expression of intermediate-early genes c-fos and c-jun, as well as growth factors, neurogenesis, synaptogenesis, alterations in glutamate and GABA signaling, inflammatory mediators, changes in voltage-gated ion currents, and excitotoxic antibodies (Ransom and Blumenfeld 2007).

In tandem with the cellular changes of epileptogenesis, there are often electroencephalographic (EEG) changes that occur prior to the full development of epilepsy. These nonseizure EEG changes include interictal spikes, which have been shown to occur immediately after brain injury and prior to the first spontaneous seizure (Hellier and others 1999), and which are correlated with spontaneous seizures (Sundaram and others 1999).

Interictal spikes are transient EEG discharges that occur when paroxysmal depolarizations of cortical neuron membrane potential cause a series of action potentials (Matsumoto and Marsan 1964). Spikes have been hypothesized to be both the result of cellular changes during epileptogenesis and the cause of further cellular changes, serving to reinforce and maintain epileptogenesis (Staley and others 2005; Staley and Dudek 2006). Brain injury and subsequent disinhibition of dentate granule cells, as seen after epileptogenic events, have been shown to produce spikes (Prince 1968; Kobayashi and Buckmaster 2003). In turn, spiking has been causally associated with some of the processes that underlie epileptogenesis. Spiking has been shown to cause long-term potentiation (LTP) (Bains and others 1999), drive activity-dependent gene expression (Rakhade and others 2007), and provide synchronous activity that may guide axon growth (Hanson and Landmesser 2004).

Epileptogenesis as a Critical Period

In development, there are certain transient periods of time, known as “critical periods,” during which particular stimuli cause irreversible changes in brain function. During critical periods, certain neural circuits have increased plasticity and undergo experience-dependent architectural remodeling, resulting in a highly stable pattern of connectivity (Knudsen 2004). Critical periods have been shown to occur in learning processes such as filial imprinting (Horn 2004), ocular representation in the visual cortex (Wiesel and Hubel 1965), and language acquisition (Arshavsky 2009). While critical periods are generally conceptualized as times of developmentally normal learning, they also represent an increased susceptibility to abnormal learning. There are certain sensitive time windows during development when an initial insult is more likely to initiate epileptogenesis, and in genetic forms of epilepsy, age of seizure onset is often stereotyped (Ben-Ari and Holmes 2006). This likely represents a specific developmental milieu, which renders the brain more susceptible to abnormal learning and formation of aberrant neural circuitry. Likewise, in older animals, the period soon after epileptogenic insult represents a time of increased plasticity when aberrant neuronal networks that serve to facilitate seizures are formed and strengthened (Bragin and others 2000). By intervening to block the cellular and electrical mechanisms at work during the critical period for epileptogenesis, it may be possible to prevent epilepsy.

Kindling Model

The kindling model of epileptogenesis involves repeated electrical stimulation of limbic regions of the brain. While the electrical stimulus initially causes only subclinical afterdischarge, over time, the neuronal response is greater, resulting in generalized seizures of greater duration (Goddard and others 1969; Racine 1972).

Cellular Mechanisms of Kindling

In terms of mechanism, kindling has been shown to cause activity-dependent facilitation via functional plasticity as well as recruitment of networks outside of the stimulus focus. Changes associated with kindling are numerous and include changes in intracellular signaling pathways, neurotransmitter function, ion channel expression, and neuronal morphology and ultrastructure. For example, kindling has been associated with increased BDNF in the hippocampus, hypothalamus, neocortex, and striatum (Sato and others 1996; Mhyre and Applegate 2003), which has been shown to cause hyperexcitability in hippocampal slices (Scharfman 1997); increased NGF (Scharfman 1997), which hastens both mossy fiber sprouting and kindling when injected intraventricularly (Adams and others 1997); and tyrosine receptor kinase B (Trk B) phosphorylation in the mossy fiber pathway and CA3 stratum oriens (Binder and others 1999a; He and others 2002), which has been associated with LTP at the mossy fiber–CA3 pyramid synapse (Huang and others 2008). Kindling has also been shown to have effects on LTP; the lateral amygdala and CA1 of

hippocampus in kindled rats have faster saturation of LTP, consistent with less capacity for further synaptic strengthening, and theta pulse stimulation of kindled rats causes LTP, while it causes LTD in control animals (Schubert and others 2005). Progressive mossy fiber sprouting is a well-known ultrastructural change, which has been observed in kindling, and may contribute to abnormal excitability by forming recurrent excitatory synapses in the dentate gyrus (Sutula and Dudek 2007). On a network level, kindling results in increased connectivity as measured by both ictal and interictal EEG signal coherence between limbic and neocortical regions, specifically between the amygdala and the frontal cortex and medial thalamus (Blumenfeld and others 2007). GABA(A) receptor density is progressively increased in the dentate gyrus and acutely downregulated but chronically upregulated in CA1 and CA3 (Liu and others 2009). Finally, changes in ion channel expression have also been shown to occur in kindling, including increased expression of hippocampal CA3 Nav1.6, which causes increased persistent sodium current, and may contribute to enhanced excitability (Blumenfeld and others 2009).

Prevention of Kindling

In general, prevention of kindling can occur via increased afterdischarge threshold, requiring greater current to initiate epileptogenesis, or via an increased number of stimuli required for development of the epileptic phenotype. Some of the aforementioned cellular mechanisms of kindling have provided fruitful epilepsy prevention strategies, while others have not. Notably, targeting the TrkB pathway can prevent kindling, targeting certain ion channels or other mediators can slow the rate of kindling, and interventions such as anticonvulsant medications tend to raise afterdischarge threshold but do not affecting the rate of kindling once the threshold is exceeded.

We recently found that heterozygous Nav1.6 knockout mice had both resistance to the initiation of kindling, requiring nearly double the stimulus current to produce an afterdischarge, and delayed rates of kindling, with a mean of 65 stimuli required for full kindling versus a mean of 27 for wild-type animals (Blumenfeld and others 2009) (Fig. 2). These findings imply that kindling is dependent on normal levels of Nav1.6 expression for the baseline network excitability required for initiation as well as on increased Nav1.6 expression for the long-term hyperexcitability seen in kindled animals. Consistent with these findings, mutation of Nav1.6 causes resistance to seizure in the kainite and flurothyl mouse models of epileptogenesis as well as in a model of severe myoclonic epilepsy of infancy (Martin and others 2007).

A more dramatic effect on kindling prevention is seen by targeting the neurotrophin/TrkB pathway. There is a great deal of evidence that neurotrophin signaling occurs through the TrkB receptor (McNamara and others 2006). Kindling development and associated mossy fiber sprouting were delayed by anti-NGF antisera infusion in ventricles (Funabashi and others 1988; Van der Zee and others 1995), and BDNF heterozygotes had delayed kindling (Kokaia and others 1995). However, BDNF deletion only delayed but did not prevent epileptogenesis or the associated increases in TrkB activation (He and others 2004). Similarly, intraventricular infusion of TrkB receptor body, which inhibits Trk receptor activation by sequestering neurotrophin ligand, caused delayed kindling with no change in afterdischarge threshold (Binder and others 1999b). In contrast, deletion of TrkB has been shown to fully prevent epileptogenesis without preventing capability for afterdischarge generation (He and others 2004) (Fig. 3). These disparate effects of BDNF and TrkB, where TrkB is necessary for epileptogenesis but BDNF is not, raise the question of how TrkB, a neurotrophin receptor, is activated in epileptogenesis independent of BDNF. While conflicting studies have found that BDNF is indeed necessary for TrkB activation in poststatus epileptogenesis (Danzer and others 2004), the findings in He and others (2004) show that BDNF is necessary for neither TrkB phosphorylation nor epileptogenesis. This

may be in part explained by a recent study, which found that TrkB phosphorylation and epileptogenesis occur via an activity-regulated, zinc-mediated increase in Src family kinase activity; LTP at the hippocampal mossy fiber–CA3 pyramid synapse is thus increased by exogenous zinc and decreased by zinc chelation with CaEDTA (Huang and others 2008). This pathway shows promise for antiepileptogenesis and merits further investigation. Paradoxically, some studies have found that BDNF and GDNF actually delay kindling (Larmet and others 1995; Kanter-Schlifke and others 2007a). These disparate effects require further study.

Some interventions increase resistance to kindling initiation. For example, sodium channel–blocking medications cause increased afterdischarge threshold but do not ultimately slow or prevent kindling (Ehle 1980; Albertson and others 1984; Post and others 1984; Weiss and Post 1987). Other interventions do not change the after-discharge threshold but rather slow the rate of kindling. These rate-delaying interventions include glutamate receptor blockers (Cain and others 1988; Sato and others 1988; Kodama and others 1999; Rogawski and others 2001), noradrenaline (Bengzon and others 1990; Lindvall and others 1990), levetiracetam (Loscher and others 1998), the neuroprotective agent gamma-vinyl-GABA (GVG) known also as vigabatrin (Shin and others 1986; Jolkkonen and others 1996), and intracranial implants of adenosine-releasing polymer (Wilz and others 2008). As with the Nav1.6 knockout mice (Figure 2), despite the delay in rate of kindling, these interventions have not been shown to ultimately prevent epileptogenesis.

Another target that has been investigated for kindling prevention is long-term potentiation (LTP). Recent studies have found that blockade of the brain-specific protein kinase C isoform known as protein kinase M zeta (PKM ζ) with the selective pseudosubstrate inhibitor ZIP reverses existing LTP both in vitro and in vivo (Shema and others 2007). However, Heida and others (2009) found that PKM ζ administration did not affect afterdischarge threshold or rate of kindling, nor did PKM ζ reverse kindling retention in animals that had already been kindled. Thus, while kindling affects LTP, blocking LTP alone was not sufficient for prevention or treatment of kindling. It should be noted that in these experiments, ZIP was administered locally in the hippocampus, while kindling may have persisted due to abnormally enhanced excitability in a more widely distributed network including other structures.

Poststatus Epilepticus Models

In humans, acute status epilepticus is associated with the development of epilepsy. Acute symptomatic status epilepticus confers greater risk for future unprovoked seizures than acute symptomatic seizures, with a 41% versus 13% risk for future unprovoked seizures at 10 years (Hesdorffer and others 1998). In the poststatus epilepticus animal models of epilepsy, a single episode of status epilepticus is used to incite epileptogenesis. First, an episode of self-sustained status epilepticus is induced in previously healthy animals. After a latency period of 3 to 4 weeks, recurrent spontaneous behaviorally apparent seizures develop (electrical epileptiform events may occur earlier). Methods of status epilepticus induction are typically either electrical or chemical in nature (Loscher 2002). They include electrical stimulation of the hippocampus, perforant path, or amygdala; injection of the glutamate analog kainite; and injection of the muscarinic agonist pilocarpine. While investigators typically interrupt status epilepticus at 90 to 120 minutes to decrease mortality, if status epilepticus is terminated by diazepam and pentobarbital at 30 minutes, spontaneous seizures do not develop (Lemos and Cavalheiro 1995). In a model related to status epilepticus, prolonged hyperthermia-induced seizures have been used to mimic prolonged febrile convulsions in children, leading to chronic spontaneous seizures in rodent models (Dube and others 2009).

Cellular Mechanisms of Epileptogenesis Poststatus Epilepticus

Proposed mechanisms of epileptogenesis poststatus epilepticus include cell death, alterations in ion channel function, changes in neurotransmitter receptor subunit composition, and synaptic reorganization. A pathway that may mediate many of these changes is the mammalian target of rapamycin (mTOR) signaling pathway, which is activated in a biphasic manner in the hippocampus and neocortex 3 hours after kainite-induced status and then only in the hippocampus 3 days after status (Zeng and others 2009). Status epilepticus also causes calcium influx via NMDA channels and voltage-gated ion channels, which triggers cell death (Fujikawa and others 2000; Niquet and others 2005), and studies have shown poststatus loss of inhibitory GABA-ergic interneurons in the hippocampus (Sloviter 1987; Kobayashi and Buckmaster 2003) and entorhinal cortex (Kumar and Buckmaster 2006), which would contribute to hyperexcitability. Also causing increased excitability, dendritic HCN channels in CA1 pyramidal neurons progressively decrease after pilocarpine-induced status (Jung and others 2007). The subunit composition of the GABA_A receptor, which mediates fast synaptic inhibition, changes in the dentate granule; $\alpha 1$ subunit expression decreases, $\alpha 4$ increases, nonsynaptic δ subunit decreases, and $\gamma 2$ shifts from synaptic to perisynaptic locations, causing impairment of tonic and phasic inhibition (Brooks-Kayal and others 1998; Zhang and others 2007). GABA_A receptor subunit expression has been found to be regulated by the BDNF, JAK-STAT, CREB-ICER, and Egr3 signaling pathways (Brooks-Kayal and others 2009). On a structural level, dentate mossy fibers sprout and form new recurrent excitatory synapses on the granule cells of the fascia dentate, which have been implicated in the development of recurrent limbic seizures (Perez and others 1996; Wuarin and Dudek 1996; Esclapez and others 1999; Rao and others 2006). This synaptic reorganization has been hypothesized to be driven by activity-dependent changes in semaphorin expression (Yang and others 2005). There is also growing evidence that inflammatory mediators such as interleukins, and damage to the blood-brain barrier may play a crucial role in epileptogenesis following prolonged hyperthermia-induced seizures, status epilepticus, and other acute brain insults (Dube and others 2009; Vezzani and others 2008).

Prevention of Epileptogenesis After Status Epilepticus

Consistent with the theory that transient mTOR activation poststatus mediates many of the cellular mechanisms of epileptogenesis in this model, inhibition of seizure-induced mTOR activation with 3 days of rapamycin pretreatment prior to kainite-induced status was found to prevent development of spontaneous seizures at 7 weeks in 3 of 8 mice and to decrease the seizure frequency as well as to increase latency (Zeng and others 2009). Rapamycin pretreatment also decreased cell death, dentate granule neurogenesis, and mossy fiber sprouting. Post-treatment for 6 consecutive days followed by every other day, starting at 24 hours after kainate injection, decreased seizure frequency at up to 6 weeks poststatus and decreased mossy fiber sprouting but did not impact neuronal death or neurogenesis. These findings imply that rapamycin treatment inhibits epileptogenesis by preventing the effects of transient mTOR activation after status.

Although cell death is a hallmark of status epilepticus, neuroprotective strategies have not been shown to prevent epileptogenesis. NMDA receptor blockade after status in the kainite model protects against limbic brain damage but does not prevent epileptogenesis (Brandt and others 2003). Similarly, GVG is neuroprotective in CA3 and CA1 but does not prevent or slow epileptogenesis in the lithium-pilocarpine model (Andre and others 2001), and long-term treatment with pregabalin in the lithium-pilocarpine model is neuroprotective of basal cortices and delays but does not prevent seizures (Andre and others 2003).

Antiepileptic drugs poststatus have had mixed results. While phenobarbital reverses the change in I(h) current caused by HCN1 and HCN2 channel loss, it does not prevent the HCN1 or HCN2 channel loss associated with epileptogenesis after status epilepticus (Jung and others 2007). In the kainite model, valproate treatment for 30 days followed by a 10-day taper after status was found to prevent spontaneous seizures at 30 to 40 days after status (Bolanos and others 1998). However, at 30 to 40 days poststatus, animals were still receiving 300 mg/kg valproate IP Q12 for 5 days followed by 300 mg/kg IP QD. While dosing was likely subtherapeutic, the effects of valproate on poststatus epileptogenesis after complete drug washout in the kainite model remain to be determined. In contrast, another study that treated with valproate for 4 weeks after electrical-induced status epilepticus found that treatment did not prevent spontaneous seizures or affect seizure frequency or severity (Brandt and others 2006). A drug that has shown some promise poststatus is levetiracetam (Margeanu and others 2008). Animals treated with levetiracetam for 21 days poststatus followed by a 3-day washout showed dose-dependent reduction in the increased population spike amplitude in the dentate gyrus (Fig. 4). Treated animals also had reduced paired-pulse inhibition in CA1 compared to untreated animals (Margeanu and others 2008) (Fig. 5). However, another study found that levetiracetam was neither neuroprotective nor antiepileptogenic after electrical-induced status (Brandt and others 2007). Some have argued that this study may have been limited by dosing and recording difficulties (Dudek and others 2008).

Alteration of gene expression has been effective in the prevention of poststatus epileptogenesis. Modulation of GABA_A receptor subunit composition by gene transfer is one approach that has been effective. Rats that received an injection to the dentate gyrus of a viral vector containing the $\alpha 1$ subunit 2 weeks prior to induction of status epilepticus, thereby increasing $\alpha 1$ subunit expression, showed both increased latency time and decreased rates of seizure development, with only 39% of treated animals developing spontaneous seizures (Raol and others 2006) (Fig. 6). Other antiepileptogenic changes in gene expression include overexpression of galanin (Kanter-Schlifke and others 2007b), neuropeptide Y (Noe and others 2008), and ICER (Kojima and others 2008) (for review, see Brooks-Kayal and others 2009). Further modulation of GABA_A receptor subunit expression and upstream regulators should be investigated for antiepileptogenic effect. Another intervention that has been tried is pretreatment with electroshocks, which causes prolonged latency prior to spontaneous seizures. It has been postulated that this delay may be due to decreased C-fos expression or electroshock damage to the substantia nigra pars reticulata, entorhinal cortex, and perirhinal cortex, making it more difficult to establish the abnormal epileptic circuit (Andre and others 2000). While the mechanism of this treatment merits further study, its application for epilepsy prevention may be limited.

Mossy fiber sprouting as a target for epilepsy prevention has had mixed results. The ketogenic diet is associated with reduction in both mossy fiber sprouting and spontaneous seizures (Muller-Schwarze and others 1999). However, inhibition of mossy fiber sprouting may not be sufficient for prevention of poststatus epileptogenesis; while administration of the protein synthesis inhibitor cycloheximide blocked mossy fiber sprouting after either pilocarpine or kainite, spontaneous seizures developed with the same frequency (Longo and Mello 1997). While other studies have found cycloheximide to be less efficacious for preventing mossy fiber sprouting, they have also found that poststatus spontaneous seizures could develop without mossy fiber sprouting as detected by Timm staining (Williams and others 2002).

Prevention of cellular proliferation following status epilepticus has shown some promise for epilepsy prevention. Infusion of the antimitotic agent cytosine-b-D-arabinofuranoside (Ara-C) after pilocarpine-induced status was associated with reduced development of ectopic

granule cells in the hilus and reduced glial proliferation in the CA1 area as well as reduction in the number of animals that went on to develop spontaneous recurrent seizures (Jung and others 2004).

Posttraumatic Epilepsy

Epilepsy after head injury is a major concern in humans. Posttraumatic epilepsy (PTE) occurs in 16.7% of patients with severe head injury (Annegers and others 1998), and soldiers with missile head injuries have a 50% incidence of epilepsy (Lowenstein 2009). Animal models of PTE include neocortical islands, fluid percussion, controlled cortical impact (CCI), iron injection, weight drop, and penetrating ballistic-like injury (Pitkanen and others 2009). In the neocortical island model, an area of neocortex with intact blood supply is isolated both via transcortical lesioning and white matter undercutting (Echlin and Battista 1963). Lesioning is succeeded by a 1- to 2-week latency period, followed by spontaneous seizures (Hoffman and others 1994). In the fluid percussion model, a single pressure pulse on the dura replicates closed-head injury without cortical damage (McIntosh and others 1989). Electrographic, subclinical seizures develop as early as 2 weeks after trauma in some animals, and clinical seizures are seen in a subset of the animals at 7 weeks to 1 year (D'Ambrosio and others 2004; Kharatishvili and others 2006). The CCI model involves contusion to intact dura with a pneumatic device, allowing for modulation of injury depth (Lighthall 1988). Clinical seizures are seen after 6 to 10 weeks in 20% to 36% of animals (Hunt and others 2009).

Mechanisms of Posttraumatic Epileptogenesis

Pathogenesis of PTE can be divided into primary damage, which incites immediate molecular and ionic changes, and secondary damage, including gliosis, axonal injury + sprouting, neurodegeneration + neurogenesis, and vascular damage + angiogenesis (Pitkanen and others 2009). In the neocortical island model, changes in gene expression have been seen within the first 24 hours, including increased levels of neuronal activity-related pentraxin (Narp) (Song and others 2002), which has been shown to promote excitatory synaptogenesis (O'Brien and others 1999) and neurite outgrowth (Tsui and others 1996). At 3 days postlesioning, there is increased immunoreactivity of growth associated protein 43 (GAP43), and at 3 weeks, there is increased 68-kDa neurofilament immunoreactivity (Prince and others 2009). Chronically, larger axonal arbors and increased synaptic bouton density in layer V pyramidal neurons have been seen (Salin and others 1995). In the fluid percussion model, there is reactive gliosis (Hill-Felberg and others 1999), which has been correlated with epilepsy (D'Ambrosio and others 2004). Hippocampal sclerosis has been observed after fluid percussion (Hicks and others 1996), along with increased hippocampal BDNF and TrkB, and decreased hippocampal neurotrophin-3 (Hicks and others 1999). Animals that exhibited seizures after CCI exhibited reduction in paired-pulse ratios and increased spontaneous and hilar-evoked epileptiform activity in the dentate gyrus. These animals also had mossy fiber sprouting ipsilateral to the CCI (Hunt and others 2009).

Recently, it has been hypothesized that disruption of the blood-brain barrier (BBB) plays a primary role in both posttraumatic brain injury and poststatus epilepticus epileptogenesis (Friedman and others 2009). The degree of BBB permeability after status has been correlated with seizure frequency, and opening the BBB with mannitol was found to increase seizure frequency in epileptic rats (van Vliet and others 2007). It has been theorized that BBB disruption induces epileptogenesis by allowing albumin leak, causing astrocyte activation via binding to the transforming growth factor-beta (TGF- β) receptor and subsequent release of inflammatory mediators (Vezzani and others 2008) and impairment of buffering capacity and glutamate metabolism (Friedman and others 2009). Supporting this hypothesis, TGF- β receptor activation with TGF- β 1 has been shown to be sufficient for

epileptiform activity and results in similar gene expression patterns to BBB breakdown or albumin exposure (Cacheaux and others 2009).

Prevention of Posttraumatic Epileptogenesis

In the neocortical island model, tetrodotoxin (TTX) has been shown to prevent epileptogenesis (Graber and Prince 1999; Prince and others 2009) (Fig. 7A). Work with TTX has supported the existence of a critical period for epilepsy prevention following injury; only TTX treatment initiated less than 4 days postlesion and lasting for at least 3 days was found to prevent epileptogenesis (Graber and Prince 2004) (Fig. 7B, C). TTX, which blocks voltage-gated sodium channels, has been posited to decrease excitability and thus reduce the expression of activity-dependent genes involved in epileptogenesis. TTX after cortical injury has been shown to reduce axonal sprouting (Carmichael and Chesselet 2002), and TTX treatment after neocortical island lesioning reduced both GAP43 immunoreactivity at 3 days and 68-kDa neurofilament immunoreactivity at 3 weeks (Prince and others 2009) (Fig. 7D).

Large-scale clinical studies of prophylactic antiepileptics after brain injury have been disappointing. Treatment for 1 year with prophylactic phenytoin, starting within 24 hours of head trauma, reduced seizure incidence during the first week but did not decrease rates of seizure development at 2 years (Temkin and others 1990). Other medications that have failed to prevent epilepsy include phenobarbital, carbamazepine, valproate, and magnesium (Temkin 2009). Consistent with these findings, a meta-analysis of 6 randomized controlled trials found that prophylactic antiepileptics after traumatic brain injury reduced early seizures but did not significantly reduce late seizures or improve rates of death and disability (Schierhout and Roberts 2001). One possible reason that these medications have failed to prevent the development of epilepsy following injury is that they do not block interictal spikes, which may play an important role in epileptogenesis (Staley and Dudek 2006).

Recently, blockade of the TGF- β receptor was found to prevent TGF- β and albumin-induced epileptiform activity in vitro as well as the characteristic gene expression changes at 24 hours (Cacheaux and others 2009). These results show great promise for antiepileptogenesis after BBB disruption. The mechanisms of BBB disruption and subsequent epileptogenesis may be important for both treatment and prevention of epilepsy and should be further elucidated.

Tuberous Sclerosis Complex Model

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder caused by mutation in either *TSC1* or *TSC2*. It is characterized by multiple dermatological manifestations, multiorgan hamartomas, and intracranial manifestations such as cortical tubers, subependymal nodules, subependymal giant-cell tumors, cerebral cortical dysplasia, and white-matter radial migration lines. Neuropsychiatric manifestations include epilepsy, mental retardation, and autism (Crino and others 2006). One model of TSC is the *Tsc1*^{GFAP}CKO mouse, which has conditional inactivation of the *Tsc1* gene in glia. Seizures appear at 4 to 6 weeks of age and increase in frequency until death, which typically occurs before 3 months of age (Erbayat-Altay and others 2007).

Cellular Mechanisms of Epileptogenesis in Tuberous Sclerosis

The *TSC* gene products form a complex, which inhibits the mammalian target of rapamycin (mTOR) signaling pathway (Gao and others 2002; Inoki and others 2002; Tee and others 2002). *TSC* mutation results in increased mTOR activation, which causes cell proliferation, growth, and tumorigenesis. Among other abnormalities, the *Tsc1*^{GFAP}CKO model has been shown to have astrogliosis and abnormal cortical organization (Uhlmann and others 2002) as

well as impaired astrocyte glutamate transport, with decreased expression of GLT-1 and GLAST glutamate transporters, leading to elevated extracellular glutamate levels that may cause increased excitotoxic cell death (Zeng and others 2007). This model also exhibits altered expression of astrocyte inward rectifier potassium channel subunits and decreased inward rectifier potassium current, with increased potassium-induced epileptiform activity. Interestingly, these potassium current changes were reversed by roscovitine or retinoic acid, which decrease CDK2 activity, but not by inhibition of the mTOR pathway with rapamycin (Jansen and others 2005).

Prevention of Epilepsy in the Tuberous Sclerosis Model

Continuous blockade of mTOR pathway activation with rapamycin starting at postnatal day 14 has been found to completely prevent epilepsy development in *Tsc1*^{GFAP}CKO mice, as well as prevent astrogliosis, cortical disorganization, GLT-1 reduction, and premature death (Zeng and others 2008) (Fig. 8). However, in this study, prevention of epileptogenesis was dependent on continuous treatment with rapamycin; mice switched off of rapamycin treatment at 6 months of age developed clinical seizures, as well as astrogliosis and hippocampal pyramidal neuron dispersion, which mice kept on treatment did not. Thus, while continuous rapamycin started at P14 prevented epileptogenesis, the period of time during which the *Tsc1*^{GFAP}CKO mouse is susceptible to epileptogenesis extends after 6 months and may be indefinite, necessitating lifetime treatment with rapamycin. While use of rapamycin for seizure control in humans has so far been limited, one case report found that rapamycin decreased seizure frequency from 5 to 10 seizures daily with weekly seizure clusters to 1 to 5 seizures daily with cessation of seizure clusters in a 10-year-old girl with TSC (Muncy and others 2009). In the future, it will be important to investigate early rapamycin treatment in patients with tuberous sclerosis in a more systematic fashion. It will also be important to ascertain whether the decrease in astrocyte inward rectifying potassium current and abnormalities in channel subunit composition are prevented by rapamycin and if roscovitine or retinoic acid has any impact on epileptogenesis.

Hypoxia Model

In human infants, hypoxia is the most common cause of seizures (Jensen 2006). Although neonatal seizures often do not immediately progress to chronic epilepsy, they do cause increased susceptibility to seizures and risk of epilepsy later in life (Silverstein and Jensen 2007). Thus, neonatal seizures can be thought of as the first hit in a multihit process, where neonatal seizures initiate epileptogenesis, but a second hit is required to trigger subsequent seizures and chronic epilepsy. In a mouse model of this 2-hit process, hypoxia-induced seizures at 10 days of age are followed by stimulation with fluorothyl, hypoxia, or kainate at 14 to 75 days of age (Jensen and others 1995; Sanchez and others 2001; Koh and others 2004). Epileptogenesis induced by the initial hypoxic seizure in this model is inferred by seizure susceptibility, as quantified by latency to seizure and severity of seizure after kainate stimulation, rather than by spontaneous seizures.

Cellular Mechanisms of Epileptogenesis after Hypoxic Seizure

After hypoxia-induced seizure, AMPA receptor subunit composition is rapidly altered, leading to hyperexcitability. As early as 1 hour after seizure, hippocampal AMPA receptor subunits GluR2 S880 and GluR1 S831 and S845 are phosphorylated, and there is a concurrent increase in AMPA receptor excitability (Rakhade and others 2008). It has been postulated that hypoxic seizures cause calcium influx and a subsequent increase in the activity of CaMKII, PKA, and PKC, followed by phosphorylation of the aforementioned AMPA receptor subunit sites, leading to increased GluR1 delivery to synapses and GluR2 internalization, and ultimately resulting in increased excitability and synaptic potentiation

(Rakhade and others 2008). At 72 to 96 hours after seizure, expression of the GluR2 subunit is further decreased (Sanchez and others 2001).

CA1 pyramidal neurons also have decreased GABAergic inhibition at 1 hour after hypoxic seizure (Sanchez and others 2005). This decreased inhibition was found to be concomitant with GABA_A receptor dephosphorylation and dependent on calcineurin and AMPA receptor-mediated calcium current, implying that seizure causes AMPA receptor-mediated calcium influx, activating calcineurin, which subsequently dephosphorylates the GABA_A receptor and downregulates GABAergic inhibition (Sanchez and others 2005).

Prevention of Epileptogenesis in the Hypoxia Model

Given the proposed AMPA receptor-mediated mechanisms of epileptogenesis in this model, the AMPA receptor is a major target for intervention. Pretreatment with the AMPA receptor antagonist NBQX decreases the severity of the initial hypoxia-induced seizure and prolongs latency to flurothyl-induced seizure at postnatal day 75 (Jensen and others 1995).

Posttreatment in the first 48 hours after seizure decreased kainate-induced seizure susceptibility at up to 45 days as well as the second-hit seizure-induced neuronal injury (Koh and others 2004). Posttreatment with AMPA receptor antagonists NBQX, topiramate, and talampanel (GYKI-53773) was also found to block the increased seizure susceptibility at 72 hours as well as the increased excitability, GluR1 phosphorylation, and CaMKII, PKC, and PKA activation thought to underlie postseizure epileptogenesis (Rakhade and others 2008). More recently, talampanel pretreatment has been found to suppress initial hypoxia-induced seizures and reduce kainate seizure-induced neuronal injury at postnatal day 30, although interestingly, it did not reduce seizure susceptibility as measured by latency (Aujla and others 2009).

Post-hypoxia-induced seizure treatment with calcineurin inhibitor FK-506, which is used clinically as an immunosuppressant, also significantly decreases seizure susceptibility and duration at 24 hours after hypoxia (Sanchez and others 2005). Seizure susceptibility in FK-506-treated mice at greater than 24 hours after hypoxia has not yet been revealed; this pathway shows great promise and warrants further investigation.

Epileptogenesis in Primary Generalized Epilepsy

Although primary generalized epilepsy by definition does not have a clear-cut inciting event, as do the aforementioned models of acquired epilepsy, certain animal models of primary generalized epilepsy do have a defined period of epileptogenesis, when abnormal cellular changes occur in association with seizure development. In the WAG/Rij rat, a model of absence epilepsy, the period of seizure development occurs between the ages of 2 to 4 months. On EEG, spike-wave discharges (SWDs) appear and increase in frequency during this time, and there is a corresponding upregulation of cortical voltage-gated sodium channels Nav 1.1 and 1.6 within the facial somatosensory cortex (Klein and others 2004). This upregulation of cortical Nav 1.1 and 1.6 may be a cellular mechanism of epileptogenesis in this model, with self-reinforcing activity-dependent changes similar to those seen in kindling (Blumenfeld and others 2009). Voltage-gated sodium channels (VGSCs) determine neuronal excitability and contribute to burst firing, which plays an important role in SWD generation (Blumenfeld and McCormick 2000). Supporting the epileptogenic nature of this local VGSC increase, the area of seizure onset in the WAG/Rij rats has also been localized to the facial region of the somatosensory cortex (Meeren and others 2002).

Also in the somatosensory cortex at greater than 2 months, there is a decrease in HCN1 protein expression and a corresponding reduction in the h current density and rate of

activation, which would contribute to hyper-excitability (Strauss and others 2004). Like the changes in sodium channel expression, this HCN1 reduction and resulting hyperexcitability is most likely an activity-dependent, self-reinforcing process. In organotypic hippocampal slice cultures, HCN1 expression was decreased by kainate-induced seizure-like activity via AMPA receptor-mediated calcium influx and subsequent calcium/calmodulin-dependent protein kinase II activation (Richichi and others 2008). Other changes in ion channel expression and in dendritic morphology have also been described in WAG/Rij rats compared to nonepileptic controls (Karpova and others 2005).

In terms of imaging markers of epileptogenesis, 8-month-old adult WAG/Rij rats had reduced fractional anisotropy with increased perpendicular diffusivity in the anterior corpus callosum, indicating reduced myelin and/or axon fiber density in pathways connecting epileptic somatosensory cortex. These changes were not seen in WAG/Rij rats prior to seizure onset at 1.7 months of age (Chahboune and others 2009).

Given the defined cellular and EEG changes occurring in the WAG/Rij rats between 2 and 4 months and imaging changes between 1.7 and 8 months, this represents a critical period of epileptogenesis during which blockade of either the cellular or electrical mechanisms of epileptogenesis could prevent development of the epileptic phenotype.

Prevention of Epileptogenesis in Primary Generalized Epilepsy

Not only is there an epileptogenic period of identifiable EEG, cellular, and imaging change during which the WAG/Rij brain transitions from a normal to epileptic phenotype, but this process can be modulated by exogenous factors. Rats with enriched housing from 1 to 3 months of age were found to have an increased number and duration of SWD at 3 months of age (Schridde and van Luijtelaar 2004). WAG/Rij rats that underwent maternal deprivation or neonatal handling from P1 to P21 had 35% less SWD at >4.5 months and greater HCN1 expression than control WAG/Rij rats (Schridde and others 2006) (Fig. 9).

Further confirming that WAG/Rij rats do indeed undergo epileptogenesis and supporting the hypothesis that epilepsy can be prevented if the process of epileptogenesis is blocked, we found that seizure suppression with ethosuximide from ages p21 to 5 months suppressed seizure frequency long term when medication was halted and prevented the corresponding increases in Nav1.1 and 1.6 and decrease in HCN1 expression (Blumenfeld and others 2008) (Figs. 10 and 11). While other attempts to prevent epilepsy have focused on preventing the cellular mechanisms of epileptogenesis, this study shows that it may be sufficient at least in some cases to prevent the electrical component of epileptogenesis and thereby halt activity-dependent changes. Furthermore, this study indicates that changes in VGSC and HCN1 expression are likely activity dependent rather than a primary cause of epilepsy, as they are expressed at normal levels in animals where seizures were suppressed during the usual period of seizure development. In additional support of these findings, a recent study found that early ethosuximide treatment prevents depression-like behavioral changes in WAG/Rij rats, providing hope that early treatment strategies may eventually prevent similar comorbidities of primary generalized epilepsy in human patients (Sarkisova and others 2009). Ongoing work in other rodent models of primary generalized epilepsy such as genetic absence epilepsy rats of Strasbourg (GAERS) and mouse models will also be important for further understanding of epileptogenesis (Bouilleret and others 2009; Depaulis and van Luijtelaar 2005; Ellens and others 2009).

Future Directions

If epileptogenesis represents a critical period for epilepsy development during which intervention may prevent epilepsy, then there is a need for biomarkers of epileptogenesis,

which could be used to identify people at high risk who would benefit from treatment. As a corollary, there is also a need to monitor whether treatment is working to prevent epileptogenesis. Neuroimaging would be an ideal technique for screening and evaluation of treatment efficacy, based on its minimally invasive nature. Thus far, magnetic resonance imaging (MRI) is a promising imaging modality for this purpose. On diffusion MRI of the lateral fluid percussion model of traumatic brain injury, decreased hippocampal diffusion at 3 hours postinjury and increased diffusion at 23 days postinjury were associated with both lower PTZ-induced seizure threshold at 12 months postinjury and increased mossy fiber sprouting (Kharatishvili and others 2007). Quantitative T2 measurements on MRI 3 days after TBI can be used to differentiate mild and severe TBI in the lateral fluid percussion model, which could be investigated for predictive value in terms of epileptogenesis (Kharatishvili and others 2009). Retrospective imaging of epileptic patients has been done, but it is unknown when many of the changes observed have occurred. Studies have shown a variety of interictal imaging changes in patients with established epilepsy, including syndrome-specific metabolite changes and networks by MRS (Savic and others 2004; Lin and others 2009), numerous areas of hypometabolism or hypermetabolism on FDG-PET (Kim and others 2005; Nishida and others 2008; la Fougere and others 2009), and many structural findings on MRI (Urbach 2005). Diffusion tensor imaging has been shown in many cases to detect structural and functional changes with greater sensitivity than conventional MRI (Luat and Chugani 2008), and it may be a good modality for detecting subtle changes in early epileptogenesis. Diffusion tensor tractography on one patient with mesial temporal sclerosis and intractable epilepsy posttrauma showed decreased fiber number, length, volume, and density in the perforant path and increased mean diffusivity bilaterally (Diaz-Arrastia and others 2009).

Electroencephalography is another source of potential biomarkers of epileptogenesis. As mentioned earlier, interictal spikes are seen in the latent period in the kainate poststatus model (Hellier and others 1999) and are predictive of future seizures in patients presenting with new-onset seizures (Holt-Seitz and others 1999). Interictal high-frequency oscillations (HFOs) at 250 to 600 Hz, which are felt to represent field potentials of population spikes from synchronously bursting neurons, are seen during the poststatus latent period in rats that go on to develop seizures (Bragin and others 2004) and in epileptogenic areas in patients with medial temporal lobe epilepsy (Engel and others 2009). As they have been detected both during epileptogenesis in animal models and interictally in epileptic patients, interictal spikes and HFOs are candidates for EEG markers of epileptogenesis. In terms of screening regimes, some have suggested implanted electrodes after a known high-risk inciting event in order to perform continuous recording and automatic identification of spikes, HFOs, and microseizures (Dichter 2009b).

In order to intervene during epileptogenesis and prevent the development of chronic epilepsy, in addition to identifying susceptible individuals, it is necessary to further define the time period in which epileptogenesis occurs. Based on the sigmoid curve of seizure frequency with time, epileptogenesis may very well continue for some time after the initial clinical seizure (Williams and others 2009). Although several models have found that the critical period for prevention occurs soon after the inciting event and prior to the initial seizure (Graber and Prince 2004; Zeng and others 2008; Zeng and others 2009), the critical period likely varies greatly by model and should be elucidated further.

Summary and Conclusions

In short, epilepsy in many animal models can be prevented by blocking either the cellular or electrical mechanisms of epileptogenesis. This is consistent with the conceptualization of epileptogenesis as a critical period for activity-dependent changes. In the kindling model,

TrkB deletion is effective in preventing epileptogenesis (He and others 2004), and modulation of this pathway via BDNF and zinc shows great promise (Huang and others 2008). Heterozygous Nav1.6 knockouts show increased afterdischarge threshold and delayed kindling, and Nav1.6 may be an important pharmacological target in antiepileptogenesis (Blumenfeld and others 2009). In the poststatus epilepticus model, mTOR inactivation with rapamycin has been successful (Zeng and others 2009), levetiracetam has had mixed results (Brandt and others 2007; Dudek and others 2008; Margineanu and others 2008), and electroshock (Andre and others 2000) and the antimitotic Ara-C (Jung and others 2004) have antiepileptogenic effects. Gene transfer in the poststatus epilepticus model has shown antiepileptogenic effect, both via GABA_A subunit modulation (Raol and others 2006) and several other targets (Brooks-Kayal and others 2009). Tetrodotoxin given within a critical period after trauma models has been shown to block activity-dependent changes (Prince and others 2009), and TGF- β receptor blockade has been found to prevent abnormal gene expression and epileptiform activity in models of BBB disruption (Cacheaux and others 2009). In the tuberous sclerosis complex mouse, early, continuous treatment with rapamycin has been found to prevent both epilepsy and premature death (Zeng and others 2008). The 2-hit hypoxia model has shown reduction in epileptogenesis after hypoxic seizures with the AMOA antagonists NBQX, topiramate, and talampanel (Rakhade and others 2008; Aujla and others 2009) and with the calcineurin inhibitor FK-506 (Sanchez and others 2005). While primary generalized epilepsy lacks a clear epileptogenic event, early environmental alterations have been shown to have an effect on the number of seizures in adult animals (Schridde and others 2006), and early treatment with ethosuximide prior to the development of clinical or EEG seizures has been found to suppress seizures up to 90 days after cessation of treatment. These findings support the theory that epileptogenesis can be halted and represents a critical period for epilepsy development (Blumenfeld and others 2008). However, many of these studies are limited by treatment starting prior to the inciting event, which confounds the issue of prevention of an inciting event versus intervention in already established epileptogenesis. Some are also limited by insufficient washout after treatment and short follow-up time. Furthermore, many of these strategies in antiepileptogenesis must be generalized to other models and the critical period for intervention better defined. In the future, it will be important to identify biomarkers for epileptogenesis and to translate methods for risk detection and epilepsy prevention to human patients.

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Figure 1.
Schematic of epileptogenesis. Reproduced with permission from White and others 2002.

Figure 2. Nav1.6 +/- mice kindle more slowly than wild-type littermates. (A) Behavioral severity of seizures (mean Racine score) increases more slowly in Nav1.6 +/- mice than in wild-type controls. (B) Nav1.6 +/- mice require more stimuli to reach each stage of kindling compared to wild-type controls. Reproduced with permission from Blumenfeld and others 2009.

Figure 3.

Kindling is inhibited in $TrkB^{-/-}$ mice. (A) $TrkB^{-/-}$ mice do not progress beyond a seizure class 0, and behavioral severity of seizures increases more slowly in $TrkB^{+/-}$ mice than in wild-type mice. (B) Seizure duration is persistently decreased in $TrkB^{-/-}$ mice. (C) For each stage of kindling, up to 50 stimulations do not cause $TrkB^{-/-}$ mice to progress beyond class 0 seizures, and $TrkB^{+/-}$ mice require more stimuli to reach each stage of kindling compared to wild-type controls. Reproduced with permission from He and others 2004.

Figure 4.

Rats treated with levetiracetam show a dose-dependent reduction in the increased population spike amplitude in the dentate gyrus as a function of perforant path stimulation current intensity (I_{stim}) after pilocarpine-induced status epilepticus. (A) Averaged evoked field potentials show increased population spike amplitude in untreated poststatus rats (middle) in comparison to control rats (top) and poststatus rats treated with levetiracetam (bottom). (B) Mean $\pm$ SEM values of population spike amplitude show a dose-dependent reduction with levetiracetam treatment. Reproduced with permission from Margineanu and others 2008.

Figure 5.

Rats treated with levetiracetam show an improvement in the reduced paired-pulse inhibition in CA1 seen after pilocarpine-induced status epilepticus. (A) Averaged traces evoked with paired pulses show reduced paired-pulse inhibition, as evidenced by greater second population spike amplitude, in untreated poststatus rats (middle) as compared with control rats (top) and poststatus rats treated with levetiracetam (bottom). (B) Mean values of paired-pulse population spike amplitude ratios show an increase in paired-pulse inhibition with levetiracetam treatment. Reproduced with permission from Margineanu and others 2008.

Figure 6. Gene transfer of the GABA_A receptor $\alpha 1$ subunit decreases the risk of seizure development and increases the length of latency following status epilepticus. (A) Treated rats show decreased rates of seizure development than untreated rats. (B) Treated rats are seizure free longer than untreated rats. Reproduced with permission from Raol and others 2006.

Figure 7.

Early tetrodotoxin (TTX) prevents epileptiform events and associated changes in immunoreactivity after neocortical isolation. (A) Tetrodotoxin inhibits epileptiform evoked field potentials after partial neocortical isolation. In a control-Elvax (vehicle)-treated animal (left), 3 of 4 stimuli evoke epileptiform events. In a TTX-Elvax-treated animal (right), equivalent stimuli fail to evoke epileptiform events. Reproduced with permission from Graber and Prince 1999. (B) Brief TTX treatment is more effective with 3 or more days of treatment duration. Treatment was started at the time of neocortical isolation. Activity was assessed at multiple sites per animal, and the percentage of those sites with epileptiform activity was calculated. Reproduced with permission from Graber and Prince 2004. (C)

Delayed TTX treatment is less effective when initiated more than 4 days after lesioning. Reproduced with permission from Graber and Prince 2004. (D) Tetrodotoxin treatment after neocortical isolation reduced immunoreactivity (IR) to growth-associated protein (GAP) 43 antibody at 3 days and to 68-kDa neurofilament at 3 weeks. (A', D') Control sections from layer V contralateral to the undercut. (B', E') Untreated undercuts. (C', F') Undercuts in animals treated with TTX. Calibrations: 50 μ m. Reproduced with permission from Prince and others 2009.

Figure 8.

Early rapamycin (Rap) treatment prevents the development of epilepsy and premature death in presymptomatic Tsc1GFAPCKO mice. (A) Rapamycin treatment prevents the development of seizures and premature death in Tsc1GFAPCKO mice compared with vehicle-treated Tsc1GFAPCKO mice. (B) Rapamycin treatment prevents the increase in interictal spike frequency with age. (C) Electroencephalographic (EEG) background activity rating scale: grade 1 being less abnormal, grade 4 being more abnormal. (D) Rapamycin treatment prevents the age-related increase in interictal EEG grade (as defined in C). (E) Untreated Tsc1GFAPCKO mice begin to lose weight after 7 weeks of age. Rapamycin-treated Tsc1GFAPCKO mice gained weight at a similar rate to rapamycin-treated controls.

(F) Rapamycin treatment prevents the premature death seen in Tsc1GFAPCKO mice. Reproduced with permission from Zeng and others 2008.

Figure 9. WAG/Rij rats that underwent early maternal deprivation (MD) or neonatal handling (NH) have less spike-wave discharges (SWDs) as adults. (A) Sample electroencephalographic (EEG) recordings from control, MD, and NH rats illustrate that control rats have more SWD than MD and NH rats. (B) Expanded from the control WAG/Rij rat EEG above at bar. (C) Rats that underwent MD or NH had less SWD as adults in a 4-hour recording period. (D) Mean $\pm$ SEM SWD duration was not significantly different between control, MD, and NH groups. Reproduced with permission from Schridde and others 2006.

Figure 10.

Abnormal ion channel expression in WAG/Rij rats is blocked by early ethosuximide (ESX) treatment. (A-D) Nav1.1 is increased in untreated WAG/Rij rats (C) compared to nonepileptic (NE) rats (A, B). This increase is blocked by ESX treatment (D). (E-H) Nav1.6 is increased in untreated WAG/Rij rats (G) compared to NE rats (E, F). This increase is blocked by ESX treatment (H). (I-L) HCN1 is decreased in untreated WAG/Rij rats (K) compared to NE rats (I, J). This decrease is blocked by ESX treatment (L). (M) Untreated WAG/Rij rats have significantly increased Nav1.1 and Nav1.6 and decreased HCN1 by quantitative optical intensity of immunocytochemistry, while NE rats and WAG/Rij rats treated with early ESX do not. Calibration: 50 μ m. Reproduced with permission from Blumenfeld and others 2008.

Figure 11.

Spike-wave discharges (SWDs) in WAG/Rij rats are persistently suppressed by early ethosuximide (ESX) treatment after cessation of treatment. (A) Electroencephalographic (EEG) recording from untreated WAG/Rij rat at 8 months has frequent SWD. (B) EEG recording from WAG/Rij rat treated with ESX from P21 to 5 months shows suppressed SWD at 8 months. (C) EEG recording from WAG/Rij rat continuing to receive treatment with ESX that started at P21 shows continued blockade of SWD at 8 months. (D) WAG/Rij rats treated with early ESX show persistent reduction in percentage of time in SWD at up to 90 days after cessation of treatment. Reproduced with permission from Blumenfeld and others 2008.