Journal of Neuroscience Research

Journal of Neuroscience Research 90:913–924 (2012)

Review

Understanding the Basic Mechanisms Underlying Seizures in Mesial Temporal Lobe Epilepsy and Possible Therapeutic Targets: A Review

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Despite years of research, epilepsy remains a poorly understood disorder. In the past several years, work has been conducted on a variety of projects with the goal of better understanding the pathogenesis and progression of mesial temporal lobe epilepsy (MTLE), in particular, and how to exploit those properties to generate innovative therapies for treatment of refractory epilepsies. This review seeks to give an overview of common morphological and biochemical changes associated with epilepsy and proposed treatments to address those changes. Furthering the understanding of ictogenesis and epileptogenesis remains an important goal for scientists seeking to find more effective treatments for MTLE.

Key words: temporal lobe epilepsy; calpain; epileptogenesis; cytokines

Mesial temporal lobe epilepsy (MTLE) is a chronic disease characterized by spontaneous, progressive seizures. In many patients, MTLE is initiated by a traumatic event (status epilepticus [SE], trauma, febrile seizures), which is often followed by a latency period of 5–10 years before onset of spontaneous seizures (de Lanerolle et al., 2003; Pitkanen and Sutula, 2002; Sharma et al., 2007; Bae et al., 2010; Yang et al., 2010). Several histological and biochemical changes have become recognized as hallmarks of MTLE. Most commonly, MTLE is associated with hippocampal changes, including diminished size and hardening of the hippocampus, with neuron loss and lesions in CA1, 3, and 4 regions (de Lanerolle et al., 2003; Sharma et al., 2007; Bae et al., 2010). Additionally, MTLE is characterized by axonal sprouting of the granule neurons of the dentate gyrus (Sloviter, 1996; Wieser, 2004). MTLE is also linked to changes in glial morphology and function. These changes, both individually and collectively, have been implicated in the maintenance and progression of MTLE over an individual's lifetime.

Clinical presentation of MTLE seizures often includes auras, particularly epigastric or abdominal auras, alteration of consciousness, amnesia, aphasia, automatisms, and motor symptoms (Wieser, 2004). Quality of life issues are important and complex for patients with MTLE. Poorly controlled seizures may lead to loss of autonomy, and the progressive nature of the disease may lead to cognitive decline (Pitkanen and Sutula, 2002). Unfortunately, current treatment modalities are often only transiently effective and are usually aimed at symptomatic control rather than stopping or reversing the events leading to spontaneous seizures (Sharma et al., 2007; Linard et al., 2010). To understand the mechanism of epilepsy, much work is currently being conducted to elucidate the mechanisms behind the genesis of MTLE and other epilepsies and to use new information to design more effective treatment options for patients suffering from this difficult disease. Several animal models have been developed to study epileptogenesis (Table I). Here, we discuss currently understood mechanisms of epileptogenesis and new research that is leading to a clearer understanding of MTLE. Additionally, we discuss

Contract grant sponsor: National Institute of Neurological Disorders and Stroke; Contract grant number: NS-31622; Contract grant number: NS-38146; Contract grant number: NS-41088.

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Received 11 August 2011; Revised 5 October 2011; Accepted 9 October 2011

Published online 8 February 2012 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/jnr.22829

TABLE I. Current Experimental Models for Epilepsy

Model	Basic administration	Mechanism of action	Pros	Cons
Kainic acid	High or repeated doses of KA administered i.p., i.v., or directly to brain	Induces SE	Changes mimic human MTLE: CA1 and −3 neuron loss Aberrant MF sprouting, astrogliosis and microgliosis (Zheng et al., 2011)	High mortaltity rate with higher doses; source of damage drug toxcitiy or seizure activity? (Zheng et al., 2011; Sharma et al., 2007)
Pilocarpine	Administered with lithium either i.p. or directly	Induces SE	Changes mimic human MTLE	Lesions are more prominent in the neocortex (Sharma et al., 2007)
Electrical stimulation	Electrial pulse trains administered to specific brain areas to produce self-sustaining seizures	Induces SE	Can be either unilateral or bilateral; changes mimic human MTLE (Gorter et al., 2003)	Special equipment and time requirements for electrode implantation (Gorter et al., 2003)
Kindling	Repeated small electrical or chemical stimulation to the brain	Repeated subconvulsant stimulation leads to envokable, but not spontaneous, seizures	Seizure onset can be controlled; specific sites can be individually stimulated (Sharma et al., 2007)	No spontaneous seizures are generated; lesion pattern is not as predictable (Sharma et al., 2007)
Tetanus toxin	Sterotaxic administration into brain	Blocks neurotransmitter release	Causes spontaneous motor seizures (Sharma et al., 2007)	Weak or temporary seizures; lesions differ from human MTLE; limited information on the model (Sharma et al., 2007)
Hyperthermia	Rats 1–2 weeks old are subjected to ambient hyperthermia, heated air stream, or microwaves to induce hyperthermia	Hyperthermia leads to febrile convulstions in young rats	Attempts to mimic febrile convulsions that are often part of TLE patient histories (Wieser et al., 2004)	No spontaneous seizures are generated; few neuropathologic changes occur (Hayashi et al., 2011)
Fluid percussion Injury	Injury is induced by exposing the dura and using a fluid percussion instrument to deliver a traumatic force	Lesion formation leads to cellular changes	Produces spontaneous seizures; useful for studying post-TBI epilepsy (Kharatishvili et al., 2006)	Seizures originate from frontal-parietal cortex and progress to mesial temporal cortex; damage and seizure generation are highly heterogenic (Pitkanen et al., 2009)

treatment options, both currently available and potentially useful.

EPILEPTOGENESIS

Onset and Mechanisms of Damage

MTLE is often associated with previous injuries, including trauma, SE, febrile seizures, and infection (Kharatishvili and Pitkanen, 2010; Yang et al., 2010). Typically, a standard course of events occurs leading to epileptic status. After the initial insult, a latency period of 5–10 years is characterized by freedom from symptoms or complications (Wieser, 2004; Boison, 2008). The latency period ends when the patient begins to suffer from spontaneous seizures. At the onset of spontaneous seizure activity, seizures are often controllable with medication. This period is known as the silent period. As the disease progresses, however, patients commonly develop intractable symptoms that cannot be managed with the current antiepileptic drugs (Wieser, 2004).

The latent period associated with epileptogenesis is thought to involve structural and biochemical changes that lead to spontaneous seizure onset. These changes, presumably, are initiated by the primary insult and occur over an extended time course (Sharma et al., 2007). A plethora of changes have been observed in epileptic tissue. Most notably, lesions created by astroglial scarring and astrogliosis as well as neuronal death and aberrant mossy fiber sprouting have been strongly correlated with epileptic tissue both in animal models (Crespel et al., 2002; Pitkanen and Sutula, 2002; Kharatishvili et al., 2006; Sharma et al., 2007; Pitkanen et al., 2009; Hayashi et al., 2011; Zheng et al., 2011) and in resected human tissue (Sloviter, 1996; Pitkanen and Sutula, 2002; de Lanerolle et al., 2003; Bae et al., 2010; Yang et al., 2010). The biochemical pathways leading to neuron degeneration, gliosis, and mossy fiber sprouting remain unclear, but many studies indicate that the initial seizure or insult directly causes primary structural changes (Sloviter, 1996; Sharma et al., 2007). However, several authors have proposed that these changes continue to accumulate over the course of the disease with each new insult (Pitkanen and Sutula, 2002; Wieser, 2004; Yang et al., 2010). In addition to these macrostructural changes, many biochemical and signaling changes have been reported both for animal models and for collected human tissue.

Although it is convenient to discuss molecular mechanisms in terms of one or more initiating causes leading to the effect of chronic seizures, disparate yet convincing opinions prevent a clear picture of epilepto-

genesis from taking shape. Adenosine fluxes have been studied extensively in resected human tissue and in animal models of epilepsy, with the prevailing hypothesis suggesting that insulted astrocytes initially increase adenosine levels before an overcompensation event results in constitutively upregulated adenosine kinase (ADK) activity (Gouder et al., 2004; Boison, 2008; Aronica et al., 2011). Once a threshold for ADK activity/production is exceeded, it is thought that irregular synaptic excitability becomes inevitable. Likewise, upregulation of inflammatory indicators in patients as well as in animal models suggests a role for anti-inflammatory therapies (Crespel et al., 2002; Yang et al., 2010; Ravizza et al., 2011). Proinflammatory cytokines might also have a role to play, with the observed increases in μ-calpain, interleukin (IL)-1β, IL-6, and transforming growth factor (TGF)-β1 in resected human anterior temporal lobe specimens (Feng et al., 2011). Further supporting the inflammatory hypothesis, downstream COX-2 inhibition in epileptic rats using celecoxib (Jung et al., 2006), parecoxib (Polascheck et al., 2010), and SC58236 (Holtman et al., 2009) is found to reduce seizure onset, severity, and frequency while preserving neurons.

The difficulty faced by all of the inflammatory hypotheses is that, although childhood inflammation of the brain can precede adult epilepsy, adult-onset epileptics also present with inflammatory indicators in the epileptic focus, but not necessarily in response to a previous inflammatory event (Ravizza et al., 2011). Further complicating the situation, Jaworsk-Adamu and others have suggested that lipopolysaccharide-induced CNS inflammation in vivo does not mirror pilocarpine-induced astroglial changes (Jaworska-Adamu et al., 2011). However, other experimental models have reproduced cytokine-mediated findings (Paradiso et al., 2011), and a good review of the balance between cytokine regulation and growth factor expression in epilepsy was published by Jankowsky and Patterson (2001). Inflammatory factors play some role in excitatory and presynaptic inhibitory receptor activation, insofar as they modulate glutamate and kainate receptor activities (Matute, 2010; Frasca et al., 2011). Finally, ion channel restructuring as found in human patients and animal models (Galanopoulou, 2007) likely shares responsibility for MTLE expression and, ultimately, synaptic restructuring (Epsztein et al., 2005). Perhaps the best hope for resolving these arguments is in the FEBSTAT study (Shinnar et al., 2008), which has already shown that childhood inflammation leading to SE is a strong indicator of future epilepsy susceptibility; however, the patients currently being followed are not yet adults. As the FEBSTAT study patients mature, hopefully so will our understanding of epileptogenesis.

Although the molecular mechanisms of epilepsy and epileptogenesis have been and continue to be aggressively studied, and although refinement of previous therapies has greatly enhanced the physician's and the patient's ability to avoid unwanted side effects from therapy, there is still no cure for epilepsy. What is it about an early-childhood CNS infection or a 5-year-old traumatic injury that predisposes some to epilepsy but not others (Wieser, 2004)? When should preventive medical treatment begin? It remains unclear what deleterious event precedes the next to result in full-blown MTLE. Furthermore, understanding what happens during the latency period is complicated by variable time courses (some patients have brief latency periods) and inconsistent development of symptoms. Important advances must be made in early identification of epilepsy risk and interventional therapies in order to optimize treatment and make curing epilepsy an attainable goal. The rest of this review is devoted to analyzing in greater detail both the macrostructural and the molecular targets of current research as well as exploring common themes for future therapeutic interventions.

Neuronal Degeneration

Neuronal degeneration was one of the first recognized hallmarks of MTLE. In the earliest characterizations of the disease, hippocampal changes including decreased size and hardening were recorded. In 1880, Sommer examined a diseased hippocampus under the microscope and noted that neurons were lost preferentially in CA1, CA3, and the hilus (CA4) of the hippocampus, whereas CA2 and the dentate nucleus seemed to be spared (de Lanerolle et al., 2003). Even today, these findings are consistent with observations from resected human tissue (de Lanerolle et al., 2003; Bae et al., 2010) and animal models (Sharma et al., 2007; Zheng et al., 2011). Extrahippocampal neuron loss has also been observed in MTLE in the entorhinal cortex, pyriform cortex, and amygdala (Ben-Ari and Dudek, 2010).

The role and mechanism of neuronal degeneration in MTLE remain unclear. Some research has shown that damage occurs during a precipitating event, which then leads to epileptogenesis (Gorter et al., 2003), but other studies indicate that neuron loss is progressive as a result of repetitive seizures (Ben-Ari and Dudek, 2010). Still others have shown that, particularly in childhood-onset epilepsy, cell death is not necessary for seizure onset (Baram et al., 2011), Additionally, the role of cell loss in MTLE onset and severity has been questioned after observations on rat models led to the conclusion that there is no correlation between hippocampal cell damage and seizure severity or frequency (Gorter et al., 2001). However, the same study did indicate that bilateral cell loss leads to progressive epilepsy, whereas unilateral loss usually results in nonprogressive epilepsy following SE. These varied findings indicate that neuronal loss might not play as clear a role in epileptogenesis as previously believed. These differences could be due to the highly ambiguous nature of epilepsy onset and the variety of precipitating events that can lead to MTLE.

Gliosis

Gliosis has long been recognized as a standard finding in human and animal epileptic tissue (Pitkanen and

Sutula, 2002; Sharma et al., 2007), which can show up to a tenfold increase in activated microglia (Yang et al., 2010). However, the role of gliosis in epileptogenesis remains unclear. The epileptogenic glial scar hypothesis purports that reactive astrocytes release trophic factors that lead to axonal sprouting, synapse formation, and hyperexcitability (Crespel et al., 2002). Multiple studies have measured increases in glial fibrillary acidic protein, a molecule associated with astrocyte hypertrophy and proliferation, in epileptogenic tissue (Pitkanen and Sutula, 2002). This hypothesis has been supported by several recent studies that have identified upregulated cytokines and growth factors in both animals and humans following SE.

Several important factors relate directly to gliosis in epilepsy. An increase in nuclear factor-κB (NFκB) has also been recorded, but its role in protection from or progression to epilepsy remains unclear and controversial (Crespel et al., 2002; Pitkanen and Sutula, 2002; Yang et al., 2010). In one study, activation of both microglia and astrocytes during acute SE led to an increase in IL-1β (Yang et al., 2010). Additionally, Yang and colleagues noted the substantial and chronic changes in astrocytes leading to prolonged IL-1β increase, upregulation of ADK, and upregulation of cytokines including macrophage colony-stimulating factor (M-CSF) and granulocyte macrophage colony-stimulating factor (GM-CSF) and adhesion molecules including VCAM and ICAM. These factors have all been implicated in sclerosis of the hippocampus in MTLE (Gouder et al., 2004; Lee et al., 2004; Eid et al., 2005; Aronica et al., 2011; Strohschein et al., 2011).

Excessive hyperpolarization as seen in MTLE suggests either dysregulation of neurotransmitter recycling at the synaptic cleft or, more likely, overwhelming of such systems. Both scenarios would result in astroglial modification either directly or indirectly. Gliosis has also been linked to excessive glutamate release, which may directly contribute to hyperexcitability (Tian et al., 2005; Takahashi et al., 2010; Yang et al., 2010), but why should astrocytes begin to release excess glutamate, and why would glutamate activation of inhibitory interneurons not result in a decrease in excitatory transmission?

The beginnings of an answer may lie in the complex mechanisms of gliosis. Astroglial ADK upregulation as seen in MTLE tissue (Gouder et al., 2004; Aronica et al., 2011) could indicate an increase in vesicle recycling activities in response to transmitter buildup in the cleft. Another possibility is that ADK upregulation potentiates the sclerosis of the hippocampus as it facilitates VCAM and ICAM presentation and, thus, glial motility (Yang et al., 2010). Yet another possibility is that ADK is facilitating changes in gap junctions between astrocytes as well as aquaporin (AQP) channel expression in response to astroglial buffering activities. Osmolarity changes and glial swelling in epilepsy are related directly to AQP expression (Lee et al., 2004; Eid et al., 2005). Both studies linked AQP4 upregulation directly to Kir4.1 (an inwardly rectifying K^+ channel), which suggests that astrocytes can increase K^+ influx by actively reducing internal [K^+]. Additionally, intracellular water uptake is thought to be involved with motility, which would account for the relocation of AQP4 from vessel-associated astrocyte end feet to other regions of the cell membrane (Eid et al., 2005). This correlates with previously mentioned findings on VCAM and ICAM.

Altogether these findings paint a picture in which chronic astroglial activation increases inflammatory cytokine production, potentiates excessive synaptic activity (directly or indirectly), and induces a "traveling effect" as activated astrocytes migrate to the epileptic focus, resulting in sclerosis. Whether these effects are responsive to MTLE or inducers of MTLE has yet to be answered.

Mossy Fiber Sprouting

Evidence of mossy fiber, or granule cell axon, sprouting is well documented in analyses of human and animal tissues (Gorter et al., 2001; Jankowsky and Patterson, 2001; Pitkanen and Sutula, 2002; Sharma et al., 2007; Bae et al., 2010; Yang et al., 2010). Sprouting is characterized by dentate granule cell axons forming synapses with cells in the granule cell layer and inner molecular layer rather than in the CA3 region of Ammon's horn (Sharma et al., 2007).

The environmental changes deriving from seizures that drive sprouting are currently unknown. Proposed mechanisms revolve around gliosis and the release of growth factors, cytokines, and adhesion molecules from activated astrocytes and microglia (Yang et al., 2010). It seems clear that sprouting is progressive and is brought on by recurrent seizures (Pitkanen and Sutula, 2002); however, the specific factors involved remain elusive. Paradiso et al. (2011) recently found that increased fibroblast growth factor-2 (FGF2) and brain-derived nurotrphic factor (BDNF) decreased mossy fiber sprouting in rat epilepsy models.

How this sprouting affects epileptogenesis is greatly debated. Proponents of the recurrent excitation hypothesis purport that dentate granule cells become hyperexcitable as a result of recurrent sprouting (Sharma et al., 2007). This hypothesis is supported by the fact that mossy fibers are glutamatergic axons and by evidence of excitatory circuit formation within the inner molecular layer (Sharma et al., 2007). The likelihood of mossy fibers playing a proepileptic role is further strengthened by the finding that treatment with cytosine-β-D-arabinofuranose (an antimitotic agent) decreases seizure activity (Bae et al., 2010). Conversely, some investigators believe that mossy fiber sprouting serves to reform inhibitory circuits that are lost during the initial damage to neurons (Gorter et al., 2001). Proponents of this hypothesis are backed by findings that mossy fibers synapse primarily on inhibitory interneurons in control animals (Gorter et al., 2001). Additionally, it has been noted that mossy fiber sprouting occurs secondary to neuron loss

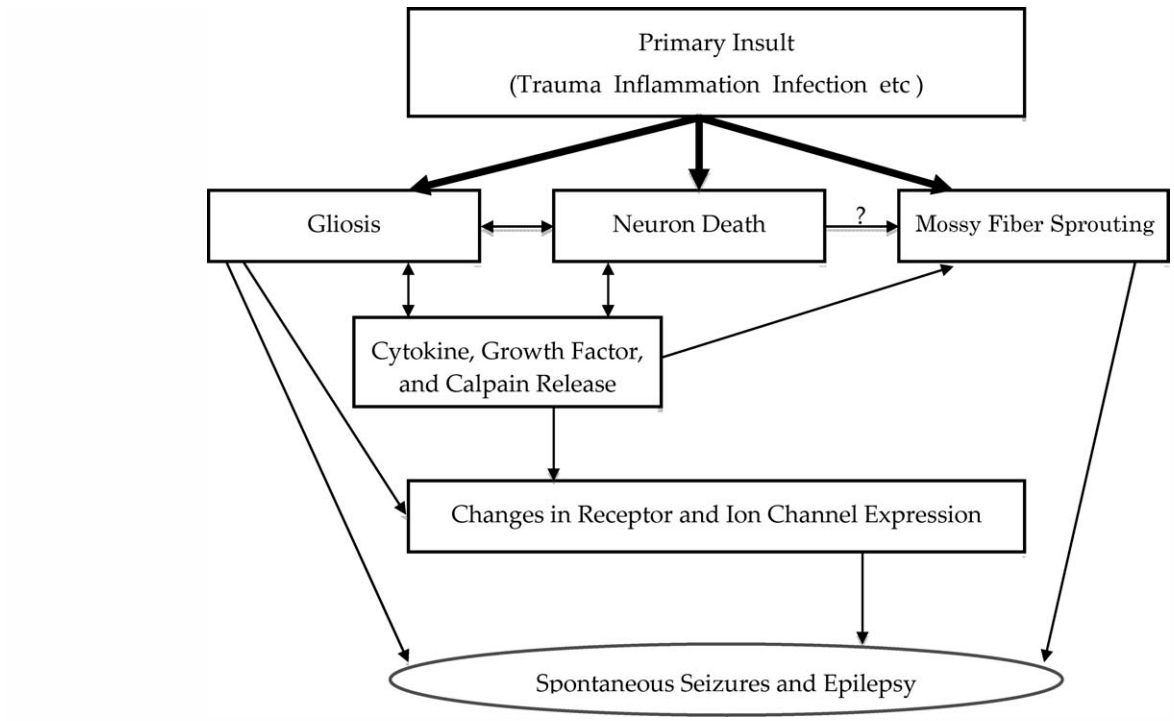

Fig. 1. Schematic representation of factors leading to epileptogenesis.

(Jankowsky and Patterson, 2001). Observations of reinnervation of dormant basket cells by mossy fibers and of collateral sprouts from interneurons forming inhibitory feedback to granule cells also supports the antiepileptogenic hypothesis (Ben-Ari and Dudek, 2010). Recently, Sharma and colleagues (2007) noted that aberrant sprouting precedes seizure onset in rats exposed to kianic acid. This observation does not clarify the question of the role of mossy fibers, unfortunately, because whether the sprouting itself leads to seizure production or the inability to sprout further leads to seizure production is unclear. Clarifying the role that mossy fibers play in epileptogenesis is an important step in better understanding epilepsy and epileptogenesis and may lead to new treatment options.

The types of synapses formed during sprouting have also been examined, and similarities and differences between newly formed synapses have been noted, including an increase in kianic acid receptors in new synapses, whereas old synapses tend to have predominately AMPA receptors (Epsztein et al., 2005; Ben-Ari and Dudek, 2010). How this affects activation and regulation of neuronal circuits remains unclear and is an exciting area for further research. The changes leading to formation of mossy fibers remain to be determined, but it seems clear that mossy fibers play some role in epileptogenesis. Some purport that this role is minimal or nonexistent, but the reliability and reproducibility of this phenomenon indicate that there is more to be learned about sprouting and its roles in seizure activation or prevention.

MOLECULAR MECHANISMS OF HYPEREXCITATION

Over the past decade, much attention has been shifted toward understanding the molecular factors that play a role in the macroscopic changes observed in epilepsy, such as those listed above. Some of the most promising changes associated with epileptic activity include the role of inflammatory cytokines in acute and chronic seizures, adenosine homeostasis within the brain, and ion channel regulation (Fig. 1).

Role of Inflammation and Cytokines in Epileptogenesis

IL-1β. Extensive studies have been conducted to identify potential cytokine targets for attenuation of epilepsy. One prominent proinflammatory cytokine of interest is IL-1β. IL-1β has been associated with kindling progression in rodents (Ravizza et al., 2011). The review by Ravizza and others goes on to discuss how several studies have found that IL-1β is upregulated in hippocampal tissue as soon as 30 min following pilocarpine-induced SE. IL-1β upregulation is then maintained for weeks following SE. The prolonged expression of IL-1β is attributed to astrocyte activation (Vezzani et al., 2008). The mechanisms of action of IL-1β are numerous; IL-1β has been shown to increase blood–brain barrier permeability (this promotes angiogenesis and may affect neurotransmitter and ion concentrations), inhibit γ-aminobutyric acid (GABA)-mediated Cl^- flux, enhance N-mthyl-D-aspartate (NMDA) receptor-mediated Ca^{2+}

flux, and promote angiogenesis (Vezzani and Granata, 2005; Vezzani et al., 2008; Ravizza et al., 2011). Additionally, IL-1β at low doses has been shown to increase neuron growth factor, ciliary neurotrophic factor, and insulin-like growth factor expression as well as to activate antioxidant pathways and increase manganese superoxide dismutase and calbindin (Vezzani and Granata, 2005). These paradoxical actions of IL-1β have led to further dose-dependent studies to clarify the role of IL-1β in epilepsy. Several investigators have concluded that, at the levels observed in post-SE rats, IL-1β's actions serve mainly to increase oxidative stress, inflammation, and ion flux, leading to hyperexcitability and cell death (Vezzani et al., 2008). The same study suggested that these effects were accompanied by a remarkable increase in IL-1β activity possibly resulting from a decrease in IL-1ra (an endogenous IL-1 antagonist) release as well as a delayed release of IL-1ra (Vezzani et al., 2008).

This line of thought led to a series of investigations into the effects of inhibiting IL-1β activity. Seizure onset and severity induced by pilocarpine injections can be significantly reduced by the IL-1β receptor antagonist IL-1ra or by pretreatment of rats with dexamethasone (Marchi et al., 2009, 2011). Even more interesting is the fact that Marchi and others were able to compare data from pediatric epileptic patients who took steroids or anti-inflammatory agents regularly with the similar effect of reduced seizure load. Perhaps more interesting were the findings from Sayyah and others (2005) that indicated an antiepileptogenic effect of low-dose (~0.01 ng/ml) IL-1β directly injected into the hippocampus of kindled rats. However, the later findings by the Vezzani group and others indicate that the protective effects are expected at such low doses and may be irrelevant in the context of more severe chemotherapeutic models of epilepsy.

TNFα. TNFα has also been identified as a possible player in epileptogenesis. It is also overexpressed following SE, but its levels typically decline in the hours following SE and are not maintained over a long period (Ravizza et al., 2011). The mechanism of action of TNFα depends on which receptor is stimulated. Stimulation of the p55 receptor is associated with increased synaptic expression of AMPA receptors that lack GluR2, $GABA_A$ endocytosis, increased vascular permeability, and angiogenesis (Vezzani et al., 2008; Ravizza et al., 2011). Activation of TNFα receptor p75 has, conversely, been shown to provide a protective effect in regions of exposure and to lead to delayed epileptogenesis. TNFα, along with IL-6, has been overexpressed in transgenic mice, indicating that a chronic inflammatory state in the brain predisposes animals to seizures and neuronal cell loss (Vezzani et al., 2008).

COX-2. The role of COX-2 has also been thoroughly studied in relation to seizure activity. After seizures, COX-2 has been observed in increased quantities in neurons and glia. Prostaglandins D2, E2, and F2α have all shown increased expression associated with different stages of epileptogenesis (Vezzani and Granata, 2005). These findings have led to testing of a COX-2 inhibitor post-SE in rats. Experimental findings have varied, ranging from cellular protection leading to decreased seizure frequency and duration with celecoxib treatment (Ravizza et al., 2011) to cellular protection without changes in seizure onset or frequency with parecoxib treatment (Polascheck et al., 2010). At least one study has even suggested that COX-2 inhibition by SC58236 in a kindling model of epilepsy is potentially lethal (Holtman et al., 2009). However, more recent work refutes this claim by showing that nonspecific COX inhibitors and the COX2 inhibitor SC58236 showed no significant difference in neuronal protection or seizure onset or frequency but exhibited some anticonvulsant activity (Ravizza et al., 2011).

NFκB. Significant research has also been conducted in relation to NFκB, a factor known to be involved in the inflammatory process. Although its role remains unclear, upregulation of NFκB is clearly defined in epileptic models related to neuronal loss and reactive gliosis. Interestingly, NFκB production seems to come solely from astrocytes and neurons (Crespel et al., 2002). NFκB is found in increased quantities in surviving neurons, whereas neurons lacking NFκB undergo apoptosis, indicating that presence of NFκB provides protection for neurons (Vezzani and Granata, 2005). However, increased production of NFκB in glial cells has also been linked to reactive gliosis, increased production of cell adhesion molecules, intermediate filaments, and neurotrophins, which may lead to glial scar formation and neuronal sprouting (Crespel et al., 2002). In addition to its conflicting role in epilepsy, NFκB upregulation has been linked to other neurodegenerative diseases (Arganaraz et al., 2008).

Jankowsky and Patterson (2001) have written a more comprehensive review outlining current knowledge on inflammation factors and cytokines and their role in epilepsy. Inflammatory factors seem to play an important role in epileptogenesis; however, which factors contribute to which cellular changes remains unclear. Future studies are needed to delineate more clearly the role of individual factors in the generation and perseveration of epilepsy.

Adenosine Kinase Hypothesis of Epileptogenesis

Recently, attention has turned to upregulation of ADK as a possible contributor to hyperexcitability associated with seizures in the CNS. Studies of rat model tissue and resected human tissue have shown an upregulation of ADK in astrocytes of epileptic animals and patients (Gouder et al., 2004; Aronica et al., 2011). ADK upregulation is thought to be associated with astrogliosis secondary to proinflammatory molecule release as found in rodent models of epilepsy and extrapolated to patient findings (Aronica et al., 2011). Upregulation of ADK leads to downregulation of extracellular adenosine, an endogenous signaling buffer, and disinhibits neuronal firing (Boison, 2008). Interestingly, it has been observed that the upregulation of ADK occurs before gross morphological changes in the hippocampus

occur, indicating that it may offer therapeutic potential (Gouder et al., 2004). ADK inhibitor 5-iodotubercidin is currently being studied for possible therapeutic potential in patients whose epilepsy cannot be controlled by currently available medications (Gouder et al., 2004; Boison, 2008). The future of therapy targeting ADK is promising. Clinical studies to determine efficacy in humans still have to be pursued in addition to studies to identify other compounds that may be useful in antagonizing ADK.

Ion Channel and Receptor Regulation in Epileptogenesis and Seizure Propagation

Glutamate receptors. Of the three main types of glutamate receptors (AMPAR, NMDAR, and KAR), NMDAR has long been the focus of epilepsy research. Strong evidence suggests that NMDAR is involved in epileptogenesis (de Moura et al., 2010). Long-used folk remedies with *Searsia* plants from South Africa have recently been found to contain compounds that act as NMDAR antagonists (Marchetti et al., 2011), indicating a role of NMDAR in hyperexcitability and seizure propagation. Upregulation of NMDA receptors has been observed in epileptic tissue, and NMDR subunit NR1 has been hypothesized to contribute to neuronal hyperexcitability, synchronization, and seizure generation (de Moura et al., 2010). Additionally, a dual role of BDNF-TrkB-NO signaling has been observed in the brain. This axis seems to provide neuroprotective effects to the cerebrocortex via downregulation of NMDAR but in the hippocampus shows neurodegenerative effects (Sandoval et al., 2011).

Recently, several studies have begun to examine the role of kainic acid (KA) receptors in epileptogenesis, particularly in association with mossy fiber sprouting. The most widely studied KA receptor subunits are GluK1 (GluR5) and GluK2 (GluR6). GluK1 has been implicated in presynaptic regulation of glutamate release. Its regulation seems to be multifaceted and dependent on agonist concentration, synapse type, glutamate source, and activation of modulator GPRCs. Repetitive release of glutamate may activate GluK1 and propagate further release, but ambient glutamate does not seem to regulate GluK1 action (Chamberlain et al., 2011). GluK1 has been observed to be upregulated in MTLE patient tissue samples, indicating its involvement in generation and perseveration of spontaneous seizures (Li et al., 2010). Although the role of GluK2 is even less well understood, it has been identified as a potential player in postsynaptic response to glutamate release and may also be involved in GABA release modulation (Chamberlain et al., 2011). GluK2 seems to be involved in seizure propagation and cell death specifically as an upregulator of Bcl-2 degradation (Zhang et al., 2011). KA receptor involvement in MTLE seems to be related to mossy fiber sprouting. Aberrant sprouts have been shown to have increased KA receptor expression compared with normal mossy fibers, suggesting that upregulation of KA receptors helps to propagate epileptic activity (Epsztein et al., 2005; Ben-Ari and Dudek, 2010). Clearly, epilepsy is a complex disorder characterized by a variety of changes on the cellular and molecular levels. Further understanding of glutamate receptor roles is necessary for a comprehensive model of epileptogenesis.

GABA receptors. Changes in $GABA_A$ receptors have long been implicated in epileptogenesis, with ancient herbal remedies relying on GABA receptor agonists to treat epilepsy (Marchetti et al., 2011); however, the specific changes associated with epileptogenesis remain unclear. Some purport that GABA signaling is simply decreased as part of the epileptogenic mechanism, which allows glutamate signaling to continue out of control, but recent studies have indicated that epileptic deregulation is actually a more complicated process involving qualitative and quantitative changes in GABA receptor subunits (Fritschy et al., 1999), GABA modulation by other neurotransmitters and second messengers (Oliveira et al., 2010; Chamberlain et al., 2011), and phenotypic changes in GABA receptor types that create depolarizing rather than hyperpolarizing reactions to GABA (Galanopoulou, 2007).

Recent work has elucidated the dual function of GABA receptors. Immature GABA receptors encourage cell depolarization and seem to play an important role in young brain development. Adult GABA receptors, conversely, tend to hyperpolarize cells. A change in dominant receptor type from the hyperpolarization subtype (KCC2) to the depolarization subtype (NKCC1) has been observed after trauma, hyperthermia, changes in tonicity, nerve transections, and oxygen or glucose deprivation. These changes have been suggested as contributory to the epileptic phenotype; however, they are not independently responsible for seizure generation as evidenced by the inability to stop seizures by completely blocking GABA receptors (Galanopoulou, 2007). Although the implications of this receptor shift after insult remain unclear, further studies into the balance between these changes and other receptor changes may be crucial to understanding the complex reorganization associated with epileptogenesis.

Ion channels. A variety of ion channels have been identified as potential regulators or dysregulators of ion homeostasis and signal propagation in neurons. Potassium, chloride, and calcium channels all seem to play a role in epileptogenesis and dysregulation of homeostasis. Several types of Cl^- channels have been indicated in epileptogenesis. Cl^- carbonic anhydrase VII channels have been implicated in differential GABA receptor activity during development. Cl^- import is associated with cell depolarization and NKCC1 GABA receptor subtype. Export of chloride is associated with hyperpolarization and KCC2 GABA subtype (Galanopoulou, 2007). Additionally, CLC-3 voltage-gated Cl^- channels have been associated with proper inhibitory signaling. CLC-3 knockout mice have been linked to hippocampal degeneration similar to that found in MTLE. Additionally, CLC has been identified with VGAT presynaptically in

the CA1 region. This relationship is thought to contribute to appropriate vesicle acidification for inhibitory release (Riazanski et al., 2011).

The role of K^+ channels in epilepsy is also varied in relation to MTLE. Oliveria and colleagues (2010) found that Ca^{2+}-sensitive K^+ channels regulate neuronal excitability by regulating firing frequency of action potentials. The role of these channels is protective, and defects in the channels lead to epileptogenic outcomes (Oliveira et al., 2010). Potassium channels of the K_v7 family, particularly $K_v7.2$ and $K_v7.3$, seem to be major players in regulation of neuronal firing. Acting as the basis of the M-current; they create a slowly activating and deactivating K^+ current that serves to regulate membrane excitability. The therapeutic value of these receptors is being exploited with upcoming pharmaceutical options, the most promising of which is retigabine (Miceli et al., 2011). Kir4.1 potassium channels may also play a role in epileptogenesis via impaired K^+ buffering secondary to astrogliosis (Yang et al., 2010).

Blocking Na^+ channels has been shown to protect neurons and prevent seizure initiation in rat hippocampal neurons. Blockage of Na^+ channels has also been shown to protect cells by decreasing reactive oxygen species liberation and decreasing calcium influx associated with cell damage and death (Das et al., 2010). Calcium channels also appear to play a role in regulation via their association with GABA channels. GABA-mediated depolarization may activate Ca^{2+} channels (Galanopoulou, 2007). Clarification of the roles of ion channels in epilepsy and pursuit of novel therapies that address channel changes may be useful in seizure attenuation for patients whose epilepsy is resistant to current medications.

Ca^{2+} regulation and calpain. Through a plethora of previous research it has been made clear that calcium dysregulation and increases in intracellular calcium levels are associated with cell death (Stucki et al., 2004; Araujo et al., 2010). How this process is initiated and propagated, however, remains unclear. Recent research has indicated that the calcium-dependent cysteine proteases, or calpains, may play a central role in developing and sustaining increased calcium concentrations and neuron hyperexcitability that eventually leads to cell death (Stucki et al., 2004; Araujo et al., 2010; Feng et al., 2011). In KA rat models, an increase in calpain levels in brain tissue has been observed after 6–24 hr of KA-induced seizures (Stucki et al., 2004). Further studies have indicated that calcium influx that is related to the plasma membrane Ca^{2+} ATPase working in reverse is most instrumental in activating calpain. However, it is unclear why this link exists (Araujo et al., 2010). It also remains unclear whether Ca^{2+} dysregulation occurs first, followed by calpain activation in a linear fashion, or whether calpain activation by increased calcium levels leads to increased Ca^{2+} dysregulation. Further investigation into the cause-and-effect relationships of calcium and calpain changes in neuronal excitability and death is warranted in order to improve understanding of epileptogenesis and to propose new treatment options. Nonetheless, calpain inhibition has been found to be neuroprotective and beneficial in several neurodegenerative disorders (Jantas et al., 2011; Kaur et al., 2011) and CNS injuries, including TBI and spinal cord injury (McDowell et al., 2011; Mustafa et al., 2011; Ray et al., 2011).

PAST, PRESENT, AND FUTURE TREATMENT FOR MTLE

Past Treatment

The earliest therapies for epilepsy were generalized, and their mechanisms were unclear despite their widespread use. Bromide, given as potassium bromide, was the first effective treatment for generalized epilepsy (Sieveking, 1857); however, it can produce unpleasant and even dangerous cutaneous side effects and is not ubiquitously effective (Diener et al., 1998). Phenobarbital, a barbiturate, was the next antiseizure medication discovered and still helps patients deal with epilepsy by facilitating GABA-mediated Cl^- channel opening (Yellanki et al., 2011). Unfortunately, phenobarbital often leaves patients feeling sedated, but it and potassium bromide are still useful for SE and MTLE management. Phenytoin was introduced in 1939 as a nonsedating alternative to phenobarbital and likely acts to suppress the intrinsic Na^+ currents and thus aberrant neuronal firing in the brain (Mantegazza et al., 2010). Many other drugs, including primidone, trimethadione, and ethosuximide were also derived from modifications made to the structure of phenobarbital (this includes phenytoin), and they all work via Na^+ channel suppression (for a more thorough review see Krall et al., 1978).

Present Therapies

Current therapies abound for MTLE. If the past therapies can be considered first-generation antiepileptic drugs (AEDs), then the generalized therapies developed from the 1960s until 1990 can be considered second-generation AEDs, and the third-generation AEDs would be represented by those molecularly targeted or modified drugs derived since 1990 (Löscher and Schmidt, 2011). Most of the AEDs developed from 1960 until 1990 were derivatives of the benzodiazepines. Carbamazepine, valproate, and other benzodiazepines were the first AEDs to differ significantly in function from the barbiturates (Shorvon, 2009). Carbamazepine was better tolerated than phenobarbital, although it also works through Na^+ channel modification. Valproate and the rest of the benzodiazepines, rather than modifying ion channels, inhibit neuronal excitation by mediating GABA release; however, the sedating effect is retained (Olkkola and Ahonen, 2008).

Although characterization of drugs as second or third generation differs among reviewers (see Löscher and Schmidt, 2011, vs. Johannessen Landmark and Patsalos, 2010), it is clear that 14 new drugs have entered the market since 1990. Rather than list each of these drugs

TABLE II. Overview of Review Relevant Drugs and Therapeutic Targets

Therapeutic target	Drug/effector	Mechanism	Developmental stage	References
Adenosine kinase	5-Iodotubercidin	Enzyme inhibitor	Clinical trials	Gouder et al., 2004; Boison, 2008
Inflammatory markers				
IL-1β	IL-1ra, dexamethasone	Receptor-mediated suppression	Animal models	Marchi et al., 2009, 2011
TNFα[a]	A-438079, A-740003	TNFα receptor antagonists	Animal models	Vezzani et al., 2008; Kim et al., 2011
COX-2	Celecoxib, parecoxib, SC58236	Enzyme suppression, proteoglycan inhibition	Clinical, animal models	Holtman et al., 2009; Polascheck et al., 2010; Ravizza et al., 2011
NFκB	A-438079, A-740003	TNFα receptor antagonists	Animal models	Kim et al., 2011
Glutamate receptors				
AMPAR	GYKI 52466	Receptor antagonist	Animal models	Epsztein et al., 2005
NMDAR	*Searsia* extract	NMDA antagonist	Animal models	Marchetti et al., 2011
KAR	Glutamate, kainic acid	Modulates presynaptic glutamate release	Animal models	Ben-Ari and Dudek, 2010
GABA	Phenobarbital, primidone, valproate (secondarily)	Potentiates GABA release	Clinical	Löscher and Schmidt, 2011
Ion channels				
K^+	Retigabine, flupirtine	Controls hyperpolarization	Clinical trials	Miceli et al., 2011
Na^+	Lamotrigine, phenytoin, primidone, trimethadione, valproate	Potentiates GABA effects	Clinical	Löscher and Schmidt, 2011
Ca^{2+}	Ethosuximide	T-type Ca^{2+} channel blocker	Clinical	Löscher and Schmidt, 2011
Cl^-	Phenobarbital (secondary)	Potentiates GABA effects	Clinical	Löscher and Schmidt, 2011
AQP	AQP knockout mouse	Osmolarity regulation and $[K^+]$	Animal models	Lee et al., 2004; Eid et al., 2005; Strohschein et al., 2011
mTOR	Rapamycine	Mitosis and motility inhibitor	Preclinical	Chong et al., 2010; Carson et al., 2011; Buckmaster and Wen, 2011; Wong, 2011

*TNFα receptor p75 agonists also show protection.

and their myriad brand names, it is more useful to note that the therapeutic functionalities of these drugs revolve around manipulation of Ca^{2+} channels, Na^+ channels, and GABA. Many excellent reviews, including those of Löscher and Schmidt, Landmark and Patsalos, and Rogawski and Löscher, clarify specific functionalities of these drugs (Table II sumarizes these findings). These medications, although they do not open any new doors on the subject of curing MTLE, reduce the risk of contraindications found in earlier drugs. This enhances the opportunity for patients and physicians to mediate side effects by developing specialized treatment paradigms. Unfortunately, the increased effectiveness of these new AEDs compared with the early successes of valproate and carbamazepine is minimal (if any), and, for MTLE patients, nearly one-third will find that no AED will adequately manage their seizures (Löscher and Schmidt, 2011). Löscher and Schmidt also discuss the cost-benefit of vagus nerve stimulators and surgical resection of sclerotic tissue; however, the mechanistic significance of bypassing or overcoming aberrant signals by vagus nerve stimulation or wholesale removal of brain tissue are somewhat outside the scope of this review. Nevertheless, these therapies are effective.

Future Therapies

To reiterate, even with the vast increase in the number of AEDs available for treatment of MTLE, the effectiveness of any AED for any patient remains arguably unchanged (Löscher and Schmidt, 2011). Contraindications are better managed today than at any time in the past, but effective seizure-eliminating therapy is not. It is therefore vital that we continue to elaborate the known mechanisms of epilepsy from gliosis and neurodegeneration to inflammation and ion channel disruption.

Intracellular and extracellular osmolarity regulation can greatly influence inflammation, ion concentrations, and even action potential firing. AQP channels have been linked to Kir4.1 in astrocytes both in human tissue and in rodent models of epilepsy (Lee et al., 2004; Eid et al., 2005) as well as gap junction coupling between astrocytes (Strohschein et al., 2011). Blocking

or inactivating AQPs significantly reduces osmotic dysfunction associated with seizures and reduces seizure severity and onset in animal models. ADK is also upregulated in astrocytes from epileptic hippocampi (Gouder et al., 2004; Aronica et al., 2011). It is no stretch to think that the energy requirements for AQP4 and Kir4.1 reorganization in astrocytes are modulated in part by ADK activity. If ADK is indeed found to modulate AQP4 and Kir4.1 activity in astrocytes, then one might hypothesize that manipulating ADK, AQP4, and/or Kir4.1 in epilepsy models might allow reversible modulation of neuronal activity by directly modifying astrocyte buffering of ions and neurotransmitters.

One drug that has already received FDA approval for cancer therapy might also be beneficial for epileptic patients. Rapamycin has recently received much attention as a potential broad-spectrum mechanistic effector of seizure suppression and irregular structural modification in the epileptic hippocampus (Chong et al., 2010). This drug targets the mammalian target of rapamycin (mTOR) protein, which is involved with growth factor production, neuronal plasticity and remodeling, glial activation, and cellular motility. As such, it would seem rapamycin has the potential to be a catch-all therapy for MTLE, not to mention epilepsy as a whole. It reduces glial swelling (Carson et al., 2011), suppresses axon sprouting in MTLE mouse models (Buckmaster and Wen, 2011), and generally suppresses seizure onset and severity in both KA and pilocarpine models of epilepsy (Wong, 2011). Unfortunately, rapamycin was originally FDA approved as a cancer chemotherapeutic because of its ability to inhibit mitosis and motility of cells, which calls into the question its safety as a long-term treatment for epilepsy. Still, the possibilities offered by such a multifaceted agent (rapamycin) and its target (mTOR) are intriguing.

CONCLUSIONS

Over the past few decades, many studies have sought to identify and treat key changes associated with epilepsy and spontaneous seizures. Many changes have been identified, both morphologically and biochemically, but a comprehensive understanding of the progression of epilepsy remains elusive. This review serves to give an overview of current studies examining changes associated with epilepsy. These studies are important for revealing possible mechanisms of treatment and together help to solidify the larger, and much more complicated, picture of epilepsy as a whole. The plethora of changes associated with epilepsy onset are further complicated by varying onsets of change. Much of the mystery of epilepsy is now a ''chicken and egg'' phenomenon. Novel experiments that help in the understanding of changes in the framework of time are necessary for a more comprehensive understanding of epilepsy and for more targeted therapy aimed at the affector molecules at the appropriate time in epileptogenesis.

Basic understanding of morphological changes such as mossy fiber sprouting, gliosis, and neuron death may lead to identification of specific molecules released either as a result of cellular changes or as a prequel to the changes. Further understanding of the interplay among ion channels, cellular signaling, neurotransmitter excretion and reuptake, and inflammatory factors in pre-epileptic and epileptic tissue is necessary for appropriate treatment of the disease. Future research offers many opportunities for novel molecule identification, delineation of events associated with epileptogenesis, and new therapeutic modalities.

REFERENCES

Araujo IM, Carreira BP, Carvalho CM, Carvalho AP. 2010. Calpains and delayed calcium deregulation in excitotoxicity. Neurochem Res 35:1966–1969.

Arganaraz GA, Konno AC, Perosa SR, Santiago JF, Boim MA, Vidotti DB, Varella PP, Costa LG, Canzian M, Porcionatto MA, Yacubian EM, Sakamoto AC, Carrete H Jr, Centeno RS, Amado D, Cavalheiro EA, Junior JA, Mazzacoratti Mda G. 2008. The renin-angiotensin system is upregulated in the cortex and hippocampus of patients with temporal lobe epilepsy related to mesial temporal sclerosis. Epilepsia 49:1348–1357.

Aronica E, Zurolo E, Iyer A, de Groot M, Anink J, Carbonell C, van Vliet EA, Baayen JC, Boison D, Gorter JA. 2011. Upregulation of adenosine kinase in astrocytes in experimental and human temporal lobe epilepsy. Epilepsia (in press).

Bae EK, Jung KH, Chu K, Lee ST, Kim JH, Park KI, Kim M, Chung CK, Lee SK, Roh JK. 2010. Neuropathologic and clinical features of human medial temporal lobe epilepsy. J Clin Neurol 6:73–80.

Baram TZ, Jensen FE, Brooks-Kayal A. 2011. Does acquired epileptogenesis in the immature brain require neuronal death. Epilepsy Curr 11:21–26.

Ben-Ari Y, Dudek FE. 2010. Primary and secondary mechanisms of epileptogenesis in the temporal lobe: there is a before and an after. Epilepsy Curr 10:118–125.

Boison D. 2008. The adenosine kinase hypothesis of epileptogenesis. Prog Neurobiol 84:249–262.

Buckmaster PS, Wen X. 2011. Rapamycin suppresses axon sprouting by somatostatin interneurons in a mouse model of temporal lobe epilepsy. Epilepsia (PMID 21883182).

Carson RP, Van Nielen DL, Winzenburger PA, Ess KC. 2011. Neuronal and glia abnormalities in Tsc1-deficient forebrain and partial rescue by rapamycin. Neurobiol Dis (in press).

Chamberlain SE, Jane DE, Jones RS. 2011. Pre- and post-synaptic functions of kainate receptors at glutamate and GABA synapses in the rat entorhinal cortex. Hippocampus (in press).

Chong ZZ, Shang YC, Zhang L, Wang S, Maiese K. 2010. Mammalian target of rapamycin: hitting the bull's-eye for neurological disorders. Oxid Med Cell Longev 3:374–391.

Crespel A, Coubes P, Rousset MC, Brana C, Rougier A, Rondouin G, Bockaert J, Baldy-Moulinier M, Lerner-Natoli M. 2002. Inflammatory reactions in human medial temporal lobe epilepsy with hippocampal sclerosis. Brain Res 952:159–169.

Das A, McDowell M, O'Dell CM, Busch ME, Smith JA, Ray SK, Banik NL. 2010. Post-treatment with voltage-gated Na^+ channel blocker attenuates kainic acid-induced apoptosis in rat primary hippocampal neurons. Neurochem Res 35:2175–2183.

de Lanerolle NC, Kim JH, Williamson A, Spencer SS, Zaveri HP, Eid T, Spencer DD. 2003. A retrospective analysis of hippocampal pathology in human temporal lobe epilepsy: evidence for distinctive patient subcategories. Epilepsia 44:677–687.

de Moura JC, Tirapelli DP, Neder L, Saggioro FP, Sakamoto AC, Velasco TR, Panepucci RA, Leite JP, Assirati JAJ, Colli BO, Carlotti

CGJ. 2010. Amygdala gene expression of NMDA and $GABA_A$ receptors in patients with mesial temporal lobe epilepsy. Hippocampus (in press).

Diener W, Sorni M, Ruile S, Rude P, Kruse R, Becker E, Bork K, Berg PA. 1998. Panniculitis due to potassium bromide. Brain Dev 20:83–87.

Eid T, Lee TS, Thomas MJ, Amiry-Moghaddam M, Bjornsen LP, Spencer DD, Agre P, Ottersen OP, de Lanerolle NC. 2005. Loss of perivascular aquaporin 4 may underlie deficient water and K^+ homeostasis in the human epileptogenic hippocampus. Proc Natl Acad Sci U S A 102:1193–1198.

Epsztein J, Represa A, Jorquera I, Ben-Ari Y, Crepel V. 2005. Recurrent mossy fibers establish aberrant kainate receptor-operated synapses on granule cells from epileptic rats. J Neurosci 25:8229–8239.

Feng ZH, Hao J, Ye L, Dayao C, Yan N, Yan Y, Chu L, Shi FD. 2011. Overexpression of mu-calpain in the anterior temporal neocortex of patients with intractable epilepsy correlates with clinicopathological characteristics. Seizure 20:395–401.

Frasca A, Aalbers M, Frigerio F, Fiordaliso F, Salio M, Gobbi M, Cagnotto A, Gardoni F, Battaglia GS, Hoogland G, Di Luca M, Vezzani A. 2011. Misplaced NMDA receptors in epileptogenesis contribute to excitotoxicity. Neurobiol Dis 43:507–515.

Fritschy JM, Kiener T, Bouilleret V, Loup F. 1999. GABAergic neurons and $GABA_A$-receptors in temporal lobe epilepsy. Neurochem Int 34:435–445.

Galanopoulou AS. 2007. Developmental patterns in the regulation of chloride homeostasis and $GABA_A$ receptor signaling by seizures. Epilepsia 48(Suppl 5):14–18.

Gorter JA, van Vliet EA, Aronica E, Lopes da Silva FH. 2001. Progression of spontaneous seizures after status epilepticus is associated with mossy fibre sprouting and extensive bilateral loss of hilar parvalbumin and somatostatin-immunoreactive neurons. Eur J Neurosci 13:657–669.

Gorter JA, Goncalves Pereira PM, van Vliet EA, Aronica E, Lopes da Silva FH, Lucassen PJ. 2003. Neuronal cell death in a rat model for mesial temporal lobe epilepsy is induced by the initial status epilepticus and not by later repeated spontaneous seizures. Epilepsia 44:647–658.

Gouder N, Scheurer L, Fritschy JM, Boison D. 2004. Overexpression of adenosine kinase in epileptic hippocampus contributes to epileptogenesis. J Neurosci 24:692–701.

Hayashi K, Ueshima S, Ouchida M, Mashimo T, Nishiki T, Sendo T, Serikawa T, Matsui H, Ohmori I. 2011. Therapy for hyperthermia-induced seizures in Scn1a mutant rats. Epilepsia 52:1010–1017.

Holtman L, van Vliet EA, van Schaik R, Queiroz CM, Aronica E, Gorter JA. 2009. Effects of SC58236, a selective COX-2 inhibitor, on epileptogenesis and spontaneous seizures in a rat model for temporal lobe epilepsy. Epilepsy Res 84:56–66.

Jankowsky JL, Patterson PH. 2001. The role of cytokines and growth factors in seizures and their sequelae. Prog Neurobiol 63:125–149.

Jantas D, Lorenc-Koci E, Kubera M, Lason W. 2011. Neuroprotective effects of MAPK/ERK1/2 and calpain inhibitors on lactacystin-induced cell damage in primary cortical neurons. Neurotoxicology (in press).

Jaworska-Adamu J, Dmowska M, Cybulska R, Krawczyk A, Pawlikowska-Pawlega B. 2011. Investigations of hippocampal astrocytes in lipopolysaccharide-preconditioned rats in the pilocarpine model of epilepsy. Fol Histochem Cytobiol 49:219–224.

Johannessen Landmark C, Patsalos PN. 2010. Drug interactions involving the new second- and third-generation antiepileptic drugs. Expert Rev Neurother 10:119–140.

Jung KH, Chu K, Lee ST, Kim J, Sinn DI, Kim JM, Park DK, Lee JJ, Kim SU, Kim M, Lee SK, Roh JK. 2006. Cyclooxygenase-2 inhibitor, celecoxib, inhibits the altered hippocampal neurogenesis with attenuation of spontaneous recurrent seizures following pilocarpine-induced status epilepticus. Neurobiol Dis 23:237–246.

Kaur J, Mencl S, Sahaboglu A, Farinelli P, van Veen T, Zrenner E, Ekstrom P, Paquet-Durand F, Arango-Gonzalez B. 2011. Calpain and PARP activation during photoreceptor cell death in P23H and S334ter rhodopsin mutant rats. PLoS One 6:e22181.

Kharatishvili I, Pitkanen A. 2010. Posttraumatic epilepsy. Curr Opin Neurol 23:183–188.

Kharatishvili I, Nissinen JP, McIntosh TK, Pitkanen A. 2006. A model of posttraumatic epilepsy induced by lateral fluid-percussion brain injury in rats. Neuroscience 140:685–697.

Krall RL, Penry JK, Kupferberg HJ, Swinyard EA. 1978. Antiepileptic drug development: I. History and a program for progress. Epilepsia 19:393–408.

Lee TS, Eid T, Mane S, Kim JH, Spencer DD, Ottersen OP, de Lanerolle NC. 2004. Aquaporin-4 is increased in the sclerotic hippocampus in human temporal lobe epilepsy. Acta Neuropathol 108:493–502.

Li JM, Zeng YJ, Peng F, Li L, Yang TH, Hong Z, Lei D, Chen Z, Zhou D. 2010. Aberrant glutamate receptor 5 expression in temporal lobe epilepsy lesions. Brain Res 1311:166–174.

Linard B, Ferrandon A, Koning E, Nehlig A, Raffo E. 2010. Ketogenic diet exhibits neuroprotective effects in hippocampus but fails to prevent epileptogenesis in the lithium-pilocarpine model of mesial temporal lobe epilepsy in adult rats. Epilepsia 51:1829–1836.

Löscher W, Schmidt D. 2011. Modern antiepileptic drug development has failed to deliver: ways out of the current dilemma. Epilepsia 52:657–678.

Mantegazza M, Curia G, Biagini G, Ragsdale DS, Avoli M. 2010. Voltage-gated sodium channels as therapeutic targets in epilepsy and other neurological disorders. Lancet Neurol 9:413–424.

Marchetti C, Gavazzo P, Stafford GI, Van Staden J. 2011. South African plants used in traditional medicine to treat epilepsy have an antagonistic effect on NMDA receptor currents. J Ethnopharmacol (in press).

Marchi N, Fan Q, Ghosh C, Fazio V, Bertolini F, Betto G, Batra A, Carlton E, Najm I, Granata T, Janigro D. 2009. Antagonism of peripheral inflammation reduces the severity of status epilepticus. Neurobiol Dis 33:171–181.

Marchi N, Granata T, Freri E, Ciusani E, Ragona F, Puvenna V, Teng Q, Alexopolous A, Janigro D. 2011. Efficacy of anti-inflammatory therapy in a model of acute seizures and in a population of pediatric drug resistant epileptics. PLoS One 6:e18200.

Matute C. 2010. Therapeutic potential of kainate receptors. CNS Neurosci Ther (in press).

McDowell ML, Das A, Smith JA, Varma AK, Ray SK, Banik NL. 2011. Neuroprotective effects of genistein in VSC4.1 motoneurons exposed to activated microglial cytokines. Neurochem Int 59:175–184.

Miceli F, Soldovieri MV, Iannotti FA, Barrese V, Ambrosino P, Martire M, Cilio MR, Taglialatela M. 2011. The voltage-sensing domain of $K_v7.2$ channels as a molecular target for epilepsy-causing mutations and anticonvulsants. Front Pharmacol 2:2.

Mustafa AG, Wang JA, Carrico KM, Hall ED. 2011. Pharmacological inhibition of lipid peroxidation attenuates calpain-mediated cytoskeletal degradation after traumatic brain injury. J Neurochem 117:579–588.

Oliveira MS, Skinner F, Arshadmansab MF, Garcia I, Mello CF, Knaus HG, Ermolinsky BS, Otalora LF, Garrido-Sanabria ER. 2010. Altered expression and function of small-conductance (SK) Ca^{2+}-activated K^+ channels in pilocarpine-treated epileptic rats. Brain Res 1348:187–199.

Olkkola KT, Ahonen J. 2008. Midazolam and other benzodiazepines. Hdbk Exp Pharmacol 182:335–360.

Paradiso B, Zucchini S, Su T, Bovolenta R, Berto E, Marconi P, Marzola A, Navarro Mora G, Fabene PF, Simonato M. 2011. Localized overexpression of FGF-2 and BDNF in hippocampus reduces mossy fiber sprouting and spontaneous seizures up to 4 weeks after pilocarpine-induced status epilepticus. Epilepsia 52:572–578.

Pitkanen A, Sutula TP. 2002. Is epilepsy a progressive disorder? Prospects for new therapeutic approaches in temporal-lobe epilepsy. Lancet Neurol 1:173–181.

Pitkanen A, Immonen RJ, Grohn OH, Kharatishvili I. 2009. From traumatic brain injury to posttraumatic epilepsy: what animal models tell us about the process and treatment options. Epilepsia 50(Suppl 2):21–29.

Polascheck N, Bankstahl M, Löscher W. 2010. The COX-2 inhibitor parecoxib is neuroprotective but not antiepileptogenic in the pilocarpine model of temporal lobe epilepsy. Exp Neurol 224:219–233.

Ravizza T, Balosso S, Vezzani A. 2011. Inflammation and prevention of epileptogenesis. Neurosci Lett 497:223–230.

Ray SK, Samantaray S, Smith JA, Matzelle DD, Das A, Banik NL. 2011. Inhibition of cysteine proteases in acute and chronic spinal cord injury. Neurotherapeutics 8:180–186.

Riazanski V, Deriy LV, Shevchenko PD, Le B, Gomez EA, Nelson DJ. 2011. Presynaptic CLC-3 determines quantal size of inhibitory transmission in the hippocampus. Nat Neurosci 14:487–494.

Sandoval R, Gonzalez A, Caviedes A, Pancetti F, Smalla KH, Kaehne T, Michea L, Gundelfinger ED, Wyneken U. 2011. Homeostatic NMDA receptor down-regulation via brain derived neurotrophic factor and nitric oxide-dependent signalling in cortical but not in hippocampal neurons. J Neurochem (in press).

Sayyah M, Beheshti S, Shokrgozar MA, Eslami-far A, Deljoo Z, Khabiri AR, Haeri Rohani A. 2005. Antiepileptogenic and anticonvulsant activity of interleukin-1 beta in amygdala-kindled rats. Exp Neurol 191:145–153.

Sharma AK, Reams RY, Jordan WH, Miller MA, Thacker HL, Snyder PW. 2007. Mesial temporal lobe epilepsy: pathogenesis, induced rodent models and lesions. Toxicol Pathol 35:984–999.

Shinnar S, Hesdorffer DC, Nordli DR Jr, Pellock JM, O'Dell C, Lewis DV, Frank LM, Moshe SL, Epstein LG, Marmarou A, Bagiella E. 2008. Phenomenology of prolonged febrile seizures: results of the FEBSTAT study. Neurology 71:170–176.

Shorvon SD. 2009. Drug treatment of epilepsy in the century of the ILAE: the second 50 years, 1959–2009. Epilepsia 50(Suppl 3):93–130.

Sieveking EH. 1857. Analysis of fifty-two cases of epilepsy observed by the author. Med Chir Trans 40:157–166.

Sloviter RS. 1996. Hippocampal pathology and pathophysiology in temporal lobe epilepsy. Neurologia 11 Suppl 4:29–32.

Strohschein S, Huttmann K, Gabriel S, Binder DK, Heinemann U, Steinhauser C. 2011. Impact of aquaporin-4 channels on K^+ buffering and gap junction coupling in the hippocampus. Glia 59:973–980.

Stucki BL MD, Bolognani F, Perrone-Bizzozero NI, Banik NL, Griesemer DA, Ray SK. 2004. Upregulation of calpain in neuronal apoptosis in kainic acid induced seizures in rats. J Neurochem 90(Suppl 1):8.

Takahashi DK, Vargas JR, Wilcox KS. 2010. Increased coupling and altered glutamate transport currents in astrocytes following kainic-acid-induced status epilepticus. Neurobiol Dis 40:573–585.

Tian GF, Azmi H, Takano T, Xu Q, Peng W, Lin J, Oberheim N, Lou N, Wang X, Zielke HR, Kang J, Nedergaard M. 2005. An astrocytic basis of epilepsy. Nat Med 11:973–981.

Vezzani A, Granata T. 2005. Brain inflammation in epilepsy: experimental and clinical evidence. Epilepsia 46:1724–1743.

Vezzani A, Balosso S, Ravizza T. 2008. The role of cytokines in the pathophysiology of epilepsy. Brain Behav Immun 22:797–803.

Wieser HG. 2004. ILAE Commission Report. Mesial temporal lobe epilepsy with hippocampal sclerosis. Epilepsia 45:695–714.

Wong M. 2011. Rapamycin for treatment of epilepsy: antiseizure, antiepileptogenic, both, or neither? Epilepsy Curr 11:66–68.

Yang T, Zhou D, Stefan H. 2010. Why mesial temporal lobe epilepsy with hippocampal sclerosis is progressive: uncontrolled inflammation drives disease progression? J Neurol Sci 296:1–6.

Yellanki S, Jagtap S, Masareddy R. 2011. Dissofilm: a novel approach for delivery of phenobarbital; design and characterization. J Young Pharm 3:181–188.

Zhang J, Yan H, Wu YP, Li C, Zhang GY. 2011. Activation of GluR6-containing kainate receptors induces ubiquitin-dependent Bcl-2 degradation via denitrosylation in the rat hippocampus after kainate treatment. J Biol Chem 286:7669–7680.

Zheng XY, Zhang HL, Luo Q, Zhu J. 2011. Kainic acid-induced neurodegenerative model: potentials and limitations. J Biomed Biotechnol 2011:457079.