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EPILEPSY AND EPILEPTIC SYNDROME

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Abstract

Epilepsy is one of the most common neurological disorders. In most patients with epilepsy, seizures respond to available medications. However, a significant number of patients, especially in the setting of medically-intractable epilepsies, may experience different degrees of memory or cognitive impairment, behavioral abnormalities or psychiatric symptoms, which may limit their daily functioning. As a result, in many patients, epilepsy may resemble a neurodegenerative disease. Epileptic seizures and their potential impact on brain development, the progressive nature of epileptogenesis that may functionally alter brain regions involved in cognitive processing, neurodegenerative processes that relate to the underlying etiology, comorbid conditions or epigenetic factors, such as stress, medications, social factors, may all contribute to the progressive nature of epilepsy. Clinical and experimental studies have addressed the pathogenetic mechanisms underlying epileptogenesis and neurodegeneration.

We will primarily focus on the findings derived from studies on one of the most common causes of focal onset epilepsy, the temporal lobe epilepsy, which indicate that both processes are progressive and utilize common or interacting pathways. In this chapter we will discuss some of these studies, the potential candidate targets for neuroprotective therapies as well as the attempts to identify early biomarkers of progression and epileptogenesis, so as to implement therapies with early-onset disease-modifying effects.

INTRODUCTION

Epilepsy is one of the most common neurological disorders affecting 50 million people worldwide.^{1,2} It is a chronic neurological disorder characterized by a predisposition to generate recurrent unprovoked epileptic seizures.³ An epileptic seizure is a transient abnormal synchronization of neurons in the brain that disrupts normal patterns of neuronal activity (*electrographic seizure*) and may manifest with a variety of signs and symptoms (*electroclinical seizure*). These may include focal or generalized convulsive or atonic behaviors (i.e., tonic-clonic, myoclonic, tonic, atonic), paroxysmal abnormal sensory or autonomic symptoms, impaired consciousness or alertness (absence seizures, complex

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partial seizures). Epileptic syndrome, on the other hand, is used to denote “a complex of signs and symptoms that define a unique epilepsy condition”.⁴

Epilepsy is a general term encompassing a variety of “*epilepsy diseases*”, each of which is attributed to a single etiology.⁴ Epilepsy can be associated with a constellation of neurobiologic, cognitive, psychological and social sequelae, which may greatly impact on the quality of life, especially of patients who do not respond to available therapies.³ This has prompted the proposal to revisit the terminology of epilepsy and refer to it as a “disease” rather than a “disorder”, so as to raise the level of awareness and urgency to find better ways to address these issues and alleviate or cure epilepsy.⁵

The progressive course of epilepsy (e.g., increase in frequency, duration and severity of seizures) and associated neurological dysfunction (e.g., physical, cognitive and behavioral impairment) can, in certain patients, mimic neurodegenerative diseases. The underlying pathogenetic mechanisms may relate to the progressive nature of epileptogenesis and its impact on the function and physiology of brain regions involved in cognition, the cumulative effect of the seizures and their therapies, epigenetic factors such as stress, changes in life style and environment.

Epileptogenesis is the process of forming a focus capable of generating spontaneous seizures.⁶ Epileptogenesis evolves and progresses over several years in humans or months in rodents and may disrupt normal neuronal development and differentiation. In combination with the ongoing effects of seizures or epileptic discharges, epileptogenesis may result in developmental disabilities and cognitive decline in epilepsy patients. Given the chronicity and progressive nature of these processes, a key question in epilepsy research is to identify neuroprotective therapies that halt or reverse epilepsy and its sequelae. In this chapter, we will review the clinical and experimental evidence for the neurodegenerative aspects of epilepsy addressing the following questions:

1. Is epilepsy a progressive disorder with neurodegenerative features?
2. Which mechanisms underlie neurodegeneration in epilepsy?
3. Is it possible to diagnose and prevent these neurodegenerative aspects of epilepsy?

CLINICAL FEATURES OF EPILEPSY: IS EPILEPSY A NEURODEGENERATIVE DISORDER/SYNDROME?

Overview of Epilepsy and Epileptic Syndrome

Seizures are usually described as having focal (or partial) or generalized onset; however in certain cases the onset cannot be readily determined. Focal-onset seizures are generated by abnormal activity stemming from one brain region. They are further classified as simple (with intact consciousness) and complex partial seizures (with altered level of consciousness). If seizures arise or engage bilaterally distributed networks they are described as generalized, such as generalized tonic-clonic, absence, atonic or myoclonic seizures.^{4,7}

The etiologies of epilepsy and epileptic syndromes are diverse. Brain lesions, including malformation of cortical development, tuberous sclerosis complex, neoplasms and hypothalamic hamartomas are major causes of drug-resistant epilepsy and often required surgical interventions. Genetic mutations, such as in sodium channels or γ -aminobutyric acid (GABA) receptor subunits, have been linked to epileptic syndromes, like juvenile myoclonic epilepsy or Dravet syndrome.^{8–10} Other etiologies include infections of central nervous system (e.g., meningitis and encephalitis), vascular disease (e.g., cerebral infarction and hemorrhage), traumatic brain injury and other neurodegenerative disease (e.g., dementia and multiple sclerosis). When the etiology is known, epilepsy is categorized as symptomatic or of structural/metabolic etiology if it is unknown but suspected as cryptogenic. The term idiopathic has been used so far to denote epilepsies of presumed genetic etiology.^{7,11} Epileptic syndromes are also categorized by age of onset, i.e., in neonatal, infantile, juvenile, adult, or seizure type i.e., myoclonic, sensory, absence.

The course of epileptic syndromes and their response to the available therapies differ. Seizures can be controlled with appropriate drugs in approximately 70% of cases.^{12,13} However, some of them cannot discontinue their drugs as seizures may recur. The remaining 30% of patients are intractable with standard medical treatment and sometimes require surgical interventions. This medically intractable subpopulation of patients is also more likely to manifest the adverse cognitive sequelae. The choice and efficacy of available therapies differ among the various epilepsy types, as they exhibit distinct pathogenetic mechanisms. In the following sections we will focus more on the research stemming from temporal lobe epilepsy (TLE), one of the most common focal-onset epilepsies, as it has been more widely studied both clinically and experimentally and we will sporadically refer to other epileptic syndromes, as needed.

Progressive and Neurodegenerative Aspects in Temporal Lobe Epilepsy (TLE)

TLE is one of the common focal (localization-related) types of epilepsy in adult patients. Hippocampal sclerosis is the characteristic pathological finding in TLE (then called mesial temporal lobe epilepsy (MTLE)) and particularly so in the medically-refractory subpopulation of TLE patients. Characteristic semiologies of the observed seizures in TLE include aura of unusual sensations, fear, feeling of prior familiar experience (*déjà vu*), peculiar odor and abdominal sensation (epigastric aura), alteration of consciousness, motionless staring, automatism (unusual and purposeless movement) of mouth and extremities, post-ictal confusion.^{14–16} Spontaneous seizures in MTLE begin usually in childhood and adolescence between 4 and 16 years of age.¹⁷ A history of febrile convulsions or status epilepticus within the early years of life is retrospectively obtained in majority of patients.^{14,16} Once habitual seizures begin, they often initially respond to antiepileptics and may even remit for many years. However, after this “silent” period, seizures recur and may then become drug-resistant.^{14,16} Therefore, it is assumed that epileptogenesis is maintained and progressing during this period.

Cognitive performance, learning and long-term memory are often affected in TLE, since the epileptogenic focus is located in the vicinity of one of the primary brain regions involved in memory. Verbal memory deficit has been more commonly associated with language-

dominant sided TLE and nonverbal memory is affected more in nonlanguage-dominant sided TLE.^{18–20} Importantly, age at epilepsy onset and longer duration of illness also influence the cognitive impairment of TLE patients.¹⁹ Patients with childhood-onset TLE have reduced total white matter volume which is associated with poorer cognitive status.²¹ Children with seizure onset before 5 years of age have lower IQ regardless of the type of seizures.²² Development of hippocampal sclerosis and atrophy and psychometric intelligence in patients with chronic TLE have been correlated with epilepsy duration¹⁹ implying a progressive and neurodegenerative course of TLE.

Progressive and Neurodegenerative Aspects of Pediatric Epilepsies: Evolution of Seizures and Developmental Factors

Epilepsies with onset in the early stages of life have multivariate etiologies, presentations and prognosis. Of particular interest are the early life epileptic encephalopathies, which may significantly impair cognitive development, leading to language or more global regression. If not appropriately treated, residual intellectual disabilities may persist.^{23–26} Among these catastrophic types of epilepsies, infantile spasms or West syndrome has attracted particular interest due to its characteristic presentation, modes of treatment and impact on the infant's development, should it not respond to therapy. West syndrome presents with a unique seizure type, infantile spasms, which are clusters of flexor, extensor, or mixed flexor-extensor spasms; a distinct electroencephalographic pattern called hypsarrhythmia and psychomotor delay/arrest.^{11,27} In the majority of patients (approximately 60–70% in various cohorts), a specific underlying pathology can be found, rendering them into the symptomatic or structural/metabolic group.^{27–31} Control of spasms may be obtained with some medications such as adrenocorticotropic hormone and vigabatrin, but recurrence of spasms, evolution to other type of seizure and psychomotor retardation are frequently seen. Infantile spasms sometimes develop to Lennox-Gastaut syndrome, which has also been associated with intellectual and developmental disability. However, early cessation of spasms and normalization of the electroencephalogram (EEG) with treatment as well as good neuropsychological status prior to the onset of spasms correlated with favorable prognosis.^{28,32–37} These emphasize that ongoing unremitting seizures and epileptic activity as well as the underlying pathologies may contribute to the ongoing cognitive deterioration. They also underline the feasibility of identifying new, more potent disease-modifying therapies for this condition.

NEURODEGENERATIVE CHANGES IN EPILEPSIES: CELLULAR AND MOLECULAR MECHANISMS

Cellular and Molecular Mechanisms of Epileptogenesis

As epileptogenesis develops, numerous changes at the cellular or synaptic level occur that ultimately lead to the formation of abnormal neuronal circuits with increased excitability. These include neuronal cell loss, gliosis, increased expression of immediate-early genes like c-fos and c-jun, neurogenesis, synaptogenesis, alterations in excitatory and inhibitory cell signaling, inflammatory mediators, changes in voltage-gated ion channels and autoimmune processes.³⁸

Neuronal cell loss commonly observed in human epileptic tissue obtained from resective surgeries or in animal models of status epilepticus and epilepsy. Neuronal damage can occur due to excitotoxic effects of glutamate. Glutamate is an excitatory neurotransmitter in the brain that is released during prolonged seizures or other pathological conditions generating a surfeit of neuronal activity.³⁹ Glutamate-induced excitotoxicity is mediated by intense depolarization, calcium influx leading to activation of Ca^{2+} dependent intracellular signals, oxidative stress/free radical damage and activation of apoptotic pathways such as caspase activity, P53 stress response and the proapoptotic Bcl protein.³⁹ The degree and distribution of neuronal loss in the brain is not uniform and depends upon the type or model of epilepsy, age, sex, hormonal milieu among other modifiers.^{40–44}

Gliosis is often observed in the human tissue of epileptic focus. Animal experiments using chemically-induced status epilepticus demonstrated an activation and increased presence of astrocytes and microglia.⁴⁵ These glial cells are suggested to play roles in the development of epilepsy. Through releasing cytokines, such as interleukin 1β (IL- 1β) and tumor necrosis factor- α (TNF α), glial cells cause chronic inflammatory state in the epileptic focus which may further influence neuronal excitability and survival.^{46,47} In addition, glial cells may increase extracellular K^{+} and glutamate,⁴⁸ neurogenesis and tissue remodeling⁴⁹ further promoting epileptogenesis.

Gene expression profiling experiments have associated different classes of genes with epileptogenesis: Immediate early genes, genes involved in calcium homeostasis, intra/extracellular signaling, neuronal/synaptic transmission, morphology, cell cycle/fate, injury/survival, metabolism as well as genes of yet unknown function.⁵⁰ More than 2000 genes have been linked with TLE.⁵⁰

A classical example of synaptic remodeling and aberrant circuitry formation is the mossy fiber sprouting observed in both human and experimental models of TLE. The mossy fibers, axons of the dentate granule cells, normally terminate their synaptic terminals into the dentate hilus and CA3 subfield (stratum lucidum). After precipitating insults or repeated seizures, the mossy fibers are reorganized and sprout into the inner molecular layer of the dentate gyrus to form new synaptic terminals with dendrites of interneurons (like basket cells) and primarily spine and dendrites of granule cells.⁵¹ This synaptic reorganization may be triggered by neuronal cell loss and, at least during the early period after seizure, it may physiologically restore the inhibitory input to the granule cells, by forming excitatory connections upon the basket inhibitory interneurons.⁵¹ However, in later periods, it may result into recurrent excitation of granule cells, promoting excitability. It has been estimated that a sprouted granule cell develops about 500 newly formed synaptic contacts with granule cells and less than²⁵ contacts upon interneurons⁵² suggesting that this formation ultimately results into a primarily recurrent excitatory collateral circuit. The mossy fiber sprouting after the precipitating injury or recurrent seizures is found in not only the inner molecular layer of the dentate gyrus but also at other hippocampal regions, including dentate hilus, stratum oriens of CA3 subfield.^{53,54} Thus, this synaptic reorganization is hypothesized to render hippocampus hyperexcitable.

The balance between excitatory (i.e., glutamatergic) and inhibitory (i.e., GABAergic) neuronal functions plays a crucial role in the development of epilepsy. Repeated seizures, especially if prolonged and certain types of initial precipitating insults may lead to a loss of GABAergic inhibitory interneurons in the hippocampus.⁵¹ Functional changes may occur however even in the absence of cell loss and with seizures of lesser severity. Only a few seizure-like ictal episodes can be sufficient to cause fast and lasting enhancement in synaptic signal transmission in the hippocampal networks (long-term potentiation) through shifting the excitation/inhibition balance towards a more excitatory state.⁵⁵ This shift was attributed to both an enhancement of non-NMDA glutamatergic transmission but also a positive shift in the reversal potential of GABA to less hyperpolarizing inhibitory potentials. Similar shift to more excitatory state of neurotransmission is also found in malformations of cortical development and tuberous sclerosis complex which are common causes of medically intractable epilepsy. Specifically, a decrease in GABAergic interneurons, decrease in GABA_A receptors and their subunits, a reduction in L-glutamic acid decarboxylase isoforms (enzyme synthesizing GABA), or vesicular GABA transporter, increase in postsynaptic glutamate receptors and their subunits have been described.^{56–58} Additionally, regulation of inhibitory or excitatory receptors can be effected by transcriptional factors, neuropeptides or secreted molecules that become activated in seizures. An example is the regulation of GABA_A signaling through brain derived neurotrophic factor (BDNF), both at the level of GABA_A receptor expression as well as the regulation of cation-chloride cotransporters that control their activity.^{59,60}

Functional changes play a larger role in early life epileptogenesis, when the brain is not only more resistant to seizure-induced injury but also normally operates under a different excitation-inhibition setpoint.^{61–63} Epileptogenesis is developmentally regulated. There are “critical periods” when an insult may have more disruptive effects upon neuronal differentiation and plasticity that may ultimately lead to epileptogenesis or cognitive deficits.^{64,65} These do not always result in hyperexcitability, just as early life seizures do not always lead to subsequent epilepsy. Changes, however, in the quality of synaptic input may alter the way neurons communicate and networks operate, contributing to the observed cognitive impairment that follows early life seizures. The observed changes in inhibitory and excitatory neurotransmission following early life seizures are age, model, sex and cell-type specific but can also be modified by epigenetic factors and other stressors.^{9,66–69}

The complexity of these processes becomes more evident when one considers the dynamic changes that normally occur in the developing brain. One example is the substantia nigra, which is involved in the control of seizures but also in cognition, as it acts as Go/No Go gatekeeper in networks that determine both the function of the prefrontal cortex as well as of seizure control.⁷⁰ During development, the substantia nigra undergoes functional changes that depend upon age and sex but also experience, i.e., early life seizures or stress.^{71,72} As a result, the communication protocols that control the activity of these seizure-control and Go/NoGo decision centers may become dysfunctional, contributing to the increased susceptibility to subsequent epilepsy and cognitive deficits that are observed in patients with early life epilepsies.

An important signaling pathway that controls development is the GABA_A signaling cascade. Early in life, GABA_Aergic currents are depolarizing and promote calcium entry into the cell which activates calcium-sensitive differentiating processes like cellular proliferation, migration, neuronal differentiation and synaptic integration.^{61,62} Precocious termination of these depolarizing GABA_A currents may occur after seizures or stress, in a sex, age and cell type dependent manner.⁹ This may disrupt the normal developmental processes, resulting in morphological abnormalities, such as defective arborization and dendritic spine formation of the neurons.^{73,74} Such changes can affect information reception and processing, further contributing to cognitive changes.

Structural and Functional Alterations in Hippocampal Sclerosis and MTLE

Hippocampal sclerosis is the pathological signature of MTLE. Its diagnostic pathologic features include loss of neurons at specific hippocampal regions (dentate hilus, CA1 pyramidal neurons, although CA3 and CA4 regions may also be affected), reactive gliosis in the hippocampus, reorganization of synaptic connections, including but not limited at the mossy fibers and dentate granule cell dispersion.^{75,76} Extrahippocampal lesions or atrophy may also be noted as well as dysplastic neurons.^{75–77}

A fundamental question has been whether hippocampal neuronal loss and sclerosis are the “cause” or “effect” of seizures. Clinical, neuroimaging and pathological studies favor the hypothesis that hippocampal sclerosis can be an acquired event, following prolonged seizures. Quantitative magnetic resonance imaging (MRI) have shown a consistent relationship between the degree of hippocampal sclerosis and the duration/severity of epilepsy or the total number of generalized seizures in some studies^{78–81} but not in others.^{82,83} In the study by Mathern et al⁸⁴ hippocampal sclerosis was strongly linked with initial precipitating injuries in both TLE and extra-temporal seizure patients. Early life frequent seizures were associated with abnormal postnatal granule cell development and aberrant axon sprouting, rather than with neuronal loss. However, in TLE patients, longer seizure durations were independently associated with decreased neuronal densities in all hippocampal subfields, but this occurred over several decades.⁸⁴ The hypothesis put forth was that the initial precipitating insult, during a critical period of development, may act as a “first hit”. This primes the hippocampus and when the first seizure comes, it responds with progressive neuronal loss, gliosis and reorganization, eventually leading to epilepsy.⁸⁴

Animal models of epilepsy have also provided ample evidence that hippocampal sclerosis results after prolonged seizures^{85–89} and that this effect is age, sex and experience dependent.^{40,41,43,44} However, prospective studies are needed to determine the exact temporal sequence of events and clarify whether, in some patients, pre-existing hippocampal pathologies may predispose patients to develop seizures and subsequent epilepsy.

Development of Post-Traumatic Epilepsy

Post-traumatic epilepsy is a major morbidity representing 5–6% of all epilepsy types.⁹⁰ Immediate (< 24 hours) or early (< 1 week) seizures are thought to be a nonspecific response to the injury. They may however raise the risk for subsequent epilepsy.^{90,91} Recurrent seizures may appear after a latent period of at least several months. Post-traumatic lesions

(contusions, intracerebral hematoma or subarachnoid hemorrhage) are risk factors of post-traumatic epilepsy.⁹¹ Damage by free radicals caused by iron deposition from extravasated blood as well as excitotoxicity due to accumulation of glutamate have been postulated as basic mechanisms of epileptogenesis in post-traumatic epilepsy.⁹² Indeed, intracortical injection of iron (ferric chlorides) in the rat brain has been used as a post-traumatic epilepsy model.^{93,94} Other animal models of post-traumatic epilepsy include the lateral fluid percussion and the controlled cortical impact models. These demonstrate neurodegeneration, neurogenesis, astrogliosis, microgliosis, axonal, myelin injury, axonal sprouting, vascular damage and angiogenesis in the injured cortex, perifocal area, underlying hippocampus and/or thalamus.^{95–98} Although the hippocampus is not the direct focus of injury, hippocampal hyperexcitability or disinhibition has also been reported in the lateral fluid percussion model.^{99,100} Similar to humans, epilepsy can progressively develop after an initial latent phase and may follow the physical recovery of the animals from the post-traumatic somatomotor deficits.^{96,98}

Development of Epilepsy in Neurodegenerative Disorders

Dementia is a risk factor for seizures and epilepsy. At least 10–22% of patients diagnosed with Alzheimer's disease may have one unprovoked seizure during the course of their disease.^{101,102} The incidence of epilepsy in Alzheimer's disease varies between 3.6–7%.¹⁰² Accumulation of β -amyloid may increase excitability and cause seizures.¹⁰³ Palop et al recently demonstrated epileptic phenotype in an animal model of Alzheimer's disease.¹⁰⁴ These provide further proof of principle that the pathways primarily responsible for neurodegeneration and epileptogenesis interact or converge.

CURRENT STATE OF DIAGNOSIS AND TREATMENT OF NEURODEGENERATION IN EPILEPSY

Clinical Biomarkers of Epileptogenesis: Can We Clinically Detect Neurodegenerative Changes?

To cure epilepsy, both epileptogenesis and the associated neurodegeneration have to be stopped and if possible reversed. This will require early detection through biomarkers that can reliably predict progression to each of these two processes. Increasing interest has been placed upon the utilization of neuroimaging abnormalities as biomarkers of progression. In the lithium-pilocarpine model of status epilepticus, abnormal T2-weighted signal in the hippocampus correlated with the ongoing edema and injury during the early phase of epileptogenesis, prior to the appearance of spontaneous seizures. Furthermore, the same authors also showed a good predictive value for the increased T2 relaxation time in the piriform and entorhinal cortices.^{105,106} In humans, early detection of MRI findings suggestive of hippocampal sclerosis have been sporadically reported after prolonged seizures and prior to the onset of spontaneous seizures.^{107–109} Prospective randomized studies are needed to investigate the temporal relationship of first appearance of hippocampal sclerosis versus the onset of epilepsy. The availability of more advanced and potentially more sensitive neuroimaging methods, such as MR spectroscopy,^{110–115} diffusion tensor imaging^{105,110,116–121} or functional neuroimaging such as positron emission

tomography^{122–125} may enhance our ability to detect epilepsy-relevant pathology in MRI-negative epileptogenic foci.

The role of the EEG as a biomarker has been long investigated. Although EEG abnormalities that increase the risk for subsequent epilepsy after an initial precipitating event have been identified,^{126–130} they do not yet carry the diagnostic sensitivity needed to initiate therapeutic or neuroprotective interventions. To identify and further investigate the validity of candidate biomarkers in predicting progression and outcome, a multi-center prospective study is ongoing, in which children with febrile status epilepticus are being followed up (FEBSTAT study).¹³¹

Do Current Treatments Improve Neurodegenerative Consequence in Epilepsy?

At present the existing antiepileptic therapies aim to stop seizures, as there are no documented pure neuroprotective therapies. Given the substantial evidence that cognitive impairment correlates with seizure severity, it is hoped that seizure control will also improve or halt the progression of cognitive decline.¹³² Indeed, the clinical experience with the medical treatment of epileptic syndromes, even of the more devastating pediatric ones, shows that early cessation of spasms and seizures with appropriate drugs also improves neurodevelopmental outcome.^{23–26,28,32–37} This may also be partially due to the fact that antiepileptic drugs directly inhibit signaling pathways that promote neurodegeneration, such as the glutamatergic pathway. Seizure control can therefore be an indirect neuroprotective therapy.¹³³

Even in patients with medically-intractable forms of epilepsy who undergo surgical resection procedures to control their seizures, surgery may improve cognitive functions. This has been reported in both adults and children after temporal lobectomies^{20 134–136} or even functional hemispherectomy for more dramatic forms of epilepsy, like Rasmussen's encephalitis.^{137–138}

However, many of these patients may still be faced with residual deficits. In others, especially the very young patients, the benefit of stopping seizures may need to be weighted against the potentially adverse effects of certain antiepileptic therapies on brain development.¹³⁹ It is therefore urgent to identify new and safer neuroprotective therapies. These may involve benign lifestyle modifications, such as environmental enrichment,¹⁴⁰ or more specialized therapies targeting the signaling pathways and metabolic processes implicated in neurodegeneration and cognitive dysfunction.

Potential Treatments Suppressing Neurodegeneration and Epileptogenesis

A shift in the focus of experimental studies has been made, redirecting efforts to identify new neuroprotective and anti-epileptogenic therapies rather than simply antiepileptic ones. The current approaches target the known cellular and molecular mechanisms of epileptogenesis and/or neurodegeneration and are listed below.^{6,141}

1. Among the antiepileptic drugs, compounds with potential as anti-epileptogenic therapies include phenobarbital,¹⁴² valproic acid,¹⁴³ levetiracetam,¹⁴⁴ and ethosuximide.¹⁴⁵ However, some of these observations are model-specific.

Ketogenic diet also has shown neuroprotective properties.¹⁴⁶ Documentation of anti-epileptogenic and disease-modifying effect in these treatments needs more confirmation with clinical trials.

2. Drugs with antioxidant properties or actions as free radical scavengers include lipoic acid,¹⁴⁷ adenosine,¹⁴⁸ melatonin,¹⁴⁹ edaravone,^{150,151} the antiepileptic drug zonisamide,¹⁵² and vitamins C and E.¹⁵³
3. Strategies targeting molecular pathways involved in neurodegeneration¹⁴¹ include: (a) stabilization of mitochondrial membrane with neuro-immunophilins (like FK506)¹⁵⁴ and NMDA receptor antagonists,¹⁵⁵ (b) exogenous administration of neurotrophic factors such as fibroblast growth factor 2, brain derived neurotrophic factor¹⁵⁶ and neuropeptide Y;¹⁵⁷ (c) molecular manipulation of glutamate receptors (blockade of group I and activation of group II and/or III metabotropic glutamate receptor subunit);¹⁵⁸ (d) anti-apoptotic drugs: e.g., corticotrophin releasing hormone.¹⁵⁹
4. Anti-inflammatory drugs, such as inhibitors of cyclooxygenase-2, reduce the activation of prostanoid pathways (prostaglandin E2 production), microglial activation, leukocyte infiltration, cytokine release, oxidative stress and neurodegeneration.⁶
5. Inhibition of the mTOR pathway with rapamycin has an antiepileptogenic potential.⁶ Rapamycin inhibits the serine threonine protein kinase *mammalian target of rapamycin* (mTOR).⁶ Under normal conditions, mTOR activity is inhibited by hamartin (TSC1) and tuberlin (TSC2).⁶ In tuberous sclerosis complex, a loss of function mutation in either TSC1 or TSC2 results in increased mTOR activity and, therefore, activation of its downstream pathways, which ultimately leads to increased cell growth and tumor formation.¹⁶⁰ Epilepsy occurs in 80–90% of TSC patients and seizures often originate within or around hamartomatous lesions or tubers, but the specific mechanisms of ictogenesis are unknown.^{161,162} In the previous experiments with mice models of tuberous sclerosis, in which the mTOR pathway is activated, rapamycin can suppress epileptogenesis and improve the underlying pathology.^{163,164}
6. Transplantation of neuronal precursor cells, embryonic stem cells, induced pluripotent stem cells and mesenchymal stem cells are under investigation in experimental models of epilepsy due to their potential to replenish neuronal populations that have been lost in the epileptic focus.¹⁶⁵

CONCLUSION

Epilepsy can be associated with progressive cognitive decline, resembling, at times, a neurodegenerative disease. Factors that predispose to such bad outcome include early age of onset and long duration of epilepsy, underlying etiology and the type of epilepsy. Significant progress has been done in promoting our understanding of the pathophysiology of epileptogenesis and epilepsy-related neurodegeneration, especially from clinical studies and experimental models of temporal lobe epilepsy. Interventions that may potentially increase

the ability of the brain to withstand seizure-induced injury (neuroprotective treatments) have been identified. However more effective and safer neuroprotective and disease-modifying therapies are needed. The model-specific and syndrome-specific differences in etiology, pathogenesis, course and treatment of the various epileptic syndromes will require however more intense research and validation in appropriate animal models. Early predictors of epileptogenesis and neurodegeneration are warranted so as to initiate early treatment to cure epilepsy and its sequelae.

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