CRITICAL REVIEW

Neurodegenerative pathways as targets for acquired epilepsy therapy development

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Abstract
There is a growing body of clinical and experimental evidence that neurodegenerative diseases and epileptogenesis after an acquired brain insult may share common etiological mechanisms. Acquired epilepsy commonly develops as a comorbid condition in patients with neurodegenerative diseases such as Alzheimer's disease, although it is likely much under diagnosed in practice. Progressive neurodegeneration has also been described after traumatic brain injury, stroke, and other forms of brain insults. Moreover, recent evidence has shown that acquired epilepsy is often a progressive disorder that is associated with the development of drug resistance, cognitive decline, and worsening of other neuropsychiatric comorbidities. Therefore, new pharmacological therapies that target neurobiological pathways that underpin neurodegenerative diseases have potential to have both an anti-epileptogenic and disease-modifying effect on the seizures in patients with acquired epilepsy, and also mitigate the progressive neurocognitive and neuropsychiatric comorbidities. Here, we review the neurodegenerative pathways that are plausible targets for the development of novel therapies that could prevent the development or modify the progression of acquired epilepsy, and the supporting published experimental and clinical evidence.

KEYWORDS
AMPA, amyloid-β, glutamate, mTOR, neuroinflammation, tau

1 | INTRODUCTION

Epilepsy is one of the most common and disabling neurological disorders worldwide. The etiologies of acquired epilepsy are diverse, but a causative epileptogenic brain injury, such as stroke, status epilepticus, traumatic brain injury (TBI), or infection, can be identified in a proportion of patients.[1] There is increasing evidence that acquired epilepsy can be a progressive disorder, associated with cognitive decline and worsening of other neuropsychiatric comorbidities and the development of pharmacoresistance.[2–7] Clinical and experimental evidence has shown an association of epilepsy with different neurodegenerative pathways such as tau, amyloid-β-related, the mammalian target of rapamycin (mTOR).[8]

Neurodegeneration is a broad term defined as the progressive alterations of neuronal function, which often

involves neuronal death, and has been described in a wide variety of brain conditions such as stroke, traumatic brain injury, multiple sclerosis, Alzheimer disease, amyotrophic lateral sclerosis, Parkinson's disease, Huntington disease, and acquired epilepsy.[9–12] Observations in experimental models of acquired epilepsy in animals and in vitro are providing a better understanding of different neurodegenerative pathways that may contribute to excitotoxicity, cell death, neurogenesis, and axonal sprouting, which could provide possible pharmacological targets for the development of anti-epileptogenic or disease-modifying therapies (Figure 1). A clear etiological link between the neurodegeneration with the development of epileptic seizures has not yet been proven, and it remains possible that the neurodegeneration observed in patients and animal models with acquired epilepsy is an incidental result of the injury or a secondary effect of the repeated epileptic seizures.[12–14] Nevertheless, studies targeting neurodegenerative mechanisms have reported protective effects against epileptogenesis following an acquired brain insult and thus provide evidence linking these and promise for the future development of this approach clinically.[15–23]

This review focuses on some of the neurodegenerative mediators and pathways, such as AMPA receptors, tau, amyloid, mTOR, and neuroinflammation that represent potential targets to prevent or modify acquired epilepsy, and the published experimental literature supporting this approach.

2 | NEURODEGENERATIVE MECHANISMS RELEVANT TO ACQUIRED EPILEPSIES

The acquired epilepsies comprise a heterogeneous group in which a structural abnormality or metabolic condition secondary to a brain injury has been attributed to play a major role in the risk of developing epilepsy.[24] TLE is the most common form of acquired epilepsy that is often resistant to drug treatment, where seizures continue to occur despite anti-epileptic drug treatment.[25] Despite decades of study of TLE, and more than 15 new anti-epileptic drugs that have been introduced into clinical practice, at least 30% of the patients are resistant to medical treatment.[25,26] A variety of different brain insults can be the trigger of the acquired epileptogenic, such as status epilepticus (SE), febrile seizures, TBI, infection, prenatal or perinatal injuries, congenital abnormalities, brain tumors, autoimmune, or genetic disorders associated with brain malformations, with the chance of the development of epilepsy likely enhanced by genetic determinants.[1,26–31] Epileptogenesis is a cascade of molecular, functional, and structural processes that are triggered by a brain insult and are capable of generating spontaneous seizures. During epileptogenesis, the limbic structures

Key points

- Neurodegenerative diseases and epileptogenesis after an acquired brain insult may share common etiological mechanisms
- Targeting neurodegenerative pathways have the potential to have both anti-epileptogenic and disease-modifying effects in acquired epilepsy
- Modification of tau, amyloid-β, neuroinflammation, mTOR, and AMPA pathways are plausible targets for the development of epilepsy therapies

manifest a variety of neurodegenerative changes that may contribute to the development of acquired epilepsy. The initial insult is often followed by a latent period that comprises a cascade of molecular, morphological, functional, and structural changes.[32] This latent period is variable from months to years in humans [33] and continues to create a hyperexcitable network prone to develop spontaneous seizures.[4,34–42]

Moreover, acquired epilepsy, specifically affecting the temporal lobe, is associated with an increased incidence of neuropsychiatric disturbances, including anxiety, depression, memory, and learning disabilities.[43–47] These associated neuropsychiatric comorbidities often worsen over time, resembling in some cases a neurodegenerative condition.[12] The underlying pathogenic mechanisms may relate to the progressive nature of epilepsy and its impact on the function of the different brain regions involved in cognition and the cumulative effects of therapies and epigenetic factors. Learning, cognition, verbal, and long-term memory are often affected in acquired epilepsy, since the most common focus is located in the limbic system.[48–51] The duration of epilepsy has been correlated with the degree of hippocampal sclerosis, cortical atrophy, and reduced psychometric intelligence in some studies,[48–51] but not others.[52,53]

During epileptogenesis, a wide spectrum of potentially pro-epileptogenic neurodegenerative changes is seen in limbic structures including mossy fiber sprouting[4,34–42]; neuronal reorganization-synaptic remodeling[54–57]; neurogenesis[58]; blood-brain barrier disruption, γ-aminobutyric acid (GABA) receptor, and GABAergic neurons changes[59–63]; alterations in peptide and brain-derived neurotrophic factor (BDNF) expression[36,64,65]; neuroinflammation[23,66]; changes in ion channels[67]; alterations in axonal transport, amyloid-β peptide, tau, and PP2A pathology[15,68]; and other cellular and functional changes.[54,56,57,69–73] These neuropathological changes are not specific of epilepsy; however, they are similar to those of neurodegenerative disorders such as Alzheimer's disease,[12,74–86] even when there is no clear history of epilepsy.[12] Neurodegeneration is

3) Amyloid-β pathways

1) AMPA mechanisms

AMPAR

Aggregates of amyloid-β

2) tau based mechanisms

PP2A/PR55

GSK-3B

CDK5

4) mTOR pathway

mTOR

Apoptosis

Hyperphosphorylated tau

RNA

5) Neuroinflammation

Inflammatory mediators
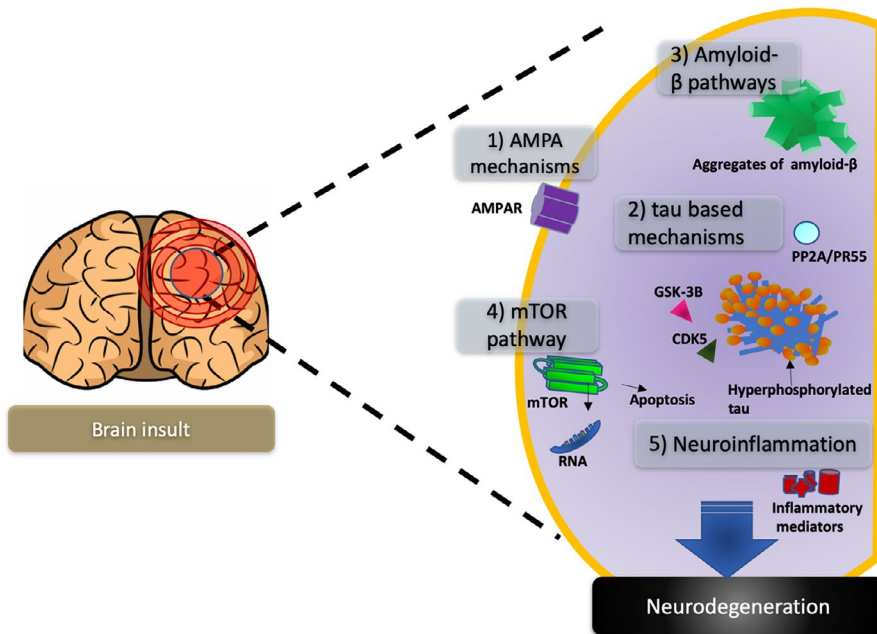
Brain insult

Neurodegeneration

FIGURE 1 Neurodegenerative pathways in acquired epilepsy. A brain insult triggers a cascade of mechanisms that may be involved in the development of acquired epilepsy, and five neurodegenerative pathways implicated in the development of acquired epilepsy, (1) AMPA mechanisms, (2) tau-based mechanisms, (3) amyloid-β pathways, (4) mTOR pathway, and (5) neuroinflammatory mediators, are reviewed in this manuscript as they represent potential targets for drug development

a progressive process that evolves during acquired epileptogenesis[87]; however, some studies suggest that the neurodegeneration may not directly result in the epileptogenesis, but it may induce other processes that do.[88,89] Hippocampal sclerosis is the pathological landmark of chronic drug-resistant mesial TLE and is characterized by neuronal loss in the hippocampus, reactive gliosis, and reorganization of the synaptic connections. However, not all with TLE have hippocampal sclerosis.[90–92] Neuronal cell loss is commonly seen in patients with acquired epilepsy and in different animal models, including the post-traumatic and post-status epilepticus models.[15,22] Neuronal death causes a cascade of changes that includes massive release of intracellular Ca^{2+}, oxidative stress, and activation of apoptotic pathways such as caspase, P53 and Bcl,[70,71,75,78,84] and others.[93–102] In response to this, there is an activation and increased presence of astrocytes and microglia, a process known as gliosis. Glial cells and microglia release pro-inflammatory cytokines, such as interleukin 1ß (IL-1ß) and tumor necrosis factor α (TNF-α), which promote gliosis[103,104] and perpetuate a chronic inflammatory state that further influences the hyperexcitability and promotes aberrant neurogenesis and tissue remodeling, which further enhance epileptogenesis.[103,105,106]

Mossy fiber sprouting is another pathological landmark seen in the hippocampal formation of acquired chronic epilepsy patients, in particular those with mesial TLE, and in animal models that represents aberrant synaptic remodeling and hyperexcitable neuronal network formation.[105,107–109] The increase in interictal epileptiform spike frequency in the chronic epileptic phase in animal models of TLE correlates with the development of spontaneous seizures, neuronal loss, and mossy fiber sprouting.[91,110] The imbalance between inhibitory and excitatory mechanisms plays a role in the development of epilepsy, but also in the initiation and maintenance of spontaneous seizures.[71,72] N-methyl-D-aspartate (NMDA) receptor activation might play a role for inducing the trans-synaptic alterations that underlie TLE epileptogenesis.[33] In fact, repeated seizures may lead to loss of GABAergic inhibitory interneurons in the hippocampus.[111–113] In addition, regulation of inhibitory and excitatory receptors can be influenced by neuropeptides such as brain BDNF.[64,114,115] However, the mechanisms of GABA, NMDA, BDNF, and other neuropeptide-related neurodegeneration are out of the scope of this review and will not be discussed in the current manuscript.

This review will focus on the discussion of the AMPA, tau, amyloid-β, mTOR, and neuroinflammatory pathways as potential targets for drug development.

3 | AMPA RECEPTOR NEURODEGENERATIVE MECHANISMS

The majority of fast excitatory synaptic neurotransmission in the central nervous system is mediated via glutamate activation of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors.[115,116] This neurotransmitter system not only drives abnormal hyperexcitable circuitry during an epileptic seizure but also could initiate neurodegenerative processes by excessive calcium uptake and pushing the cells toward apoptotic cell death.[117]

The AMPARs primarily mediate fast neurotransmission by serving as a glutamate-gated cation channel. In addition to initiating neuronal firing, AMPARs also underlie aspects of synaptic plasticity[116] such as long-term potentiation, learning, and memory.[118] Glutamate chronic neuronal excitotoxicity is a newer concept, but has linked glutamate excitotoxicity to neurodegenerative processes in Huntington's disease, Parkinson's disease, and Alzheimer's dementia.[9]

Similarly, excessive glutamate receptor activation has been linked epilepsy.[119] In acquired epilepsy, particularly in TLE, increases in glutamate excitotoxicity have been described as an important initial mechanism for neuronal injury that leads to neuronal cell death and neurodegenerative processes that may lead to overall hyperexcitable tissue reorganization by mechanisms described earlier.[54,73] These events could in turn promote increased burst firing in reticular neurons enhancing epileptogenic circuit synchrony, promoting the development of seizures.[120–124]

The hippocampus has been identified as the seizure initiating zone in many TLE patients as well as in different animal models.[125] GABAergic neurons are found primarily in the basket cells located in deep portions of the granule cell layer in the dentate gyrus.[26,126] However, repeated seizures and excitotoxicity lead to death of these interneurons that are critical to maintain the balance between excitation and inhibition in the hippocampus.[105,113,127]

Glutamate is the major excitatory neurotransmitter in the hippocampal formation.[73] The mossy fiber pathway runs from the dentate gyrus granule cells to the pyramidal cells of the CA3; after excitotoxicity and neuronal cell death due to the initial brain insult or to repeated seizures, the mossy fibers are reorganized and sprout into the inner molecular layers of the dentate gyrus to form aberrant synaptic terminals with dendrites of GABAergic interneuron basket cells and with granule cells.[113] This abnormal reorganization renders the hippocampus hyperexcitable and prone to the development of spontaneous seizures.[107]

Therefore, strategies that can inhibit the AMPA receptor activity have the potential to reduce excessive excitatory responses that could to neurodegenerative changes and may be promising targets for the development of anti-epileptogenic and disease-modifying drugs.[128,129]

Perampanel is a non-competitive and highly selective AMPA receptor antagonist that has recently completed phase III of clinical trials and has been approved as an adjunctive treatment for drug-resistant partial-onset seizures.[130–133] Perampanel also decreases intracellular Ca^{2+} concentration induced by AMPA receptor activation that would have the net effect of decreasing excitability.[134,135] Perampanel has shown to reduce neuronal cell death in the hippocampus and the piriform cortex in the lithium-pilocarpine post-SE model,[136] but does not have anti-epileptogenic properties.[137]

Similar neuroprotective effects have been described with other AMPA antagonists.[138]

4 | TAU-BASED MECHANISMS IN EPILEPSY

There is building clinical and experimental evidence linking tau-based neurodegenerative mechanisms with the epilepsy development,[15,68] suggesting for a neurodegenerative basis for acquired epilepsies. Tau, a microtubule-associated protein, performs important physiological functions in neurons, including providing stabilization to microtubules as well as contributing to axonal transport. The binding of tau to microtubules and thereby its physiological functions are regulated by a balance in phosphorylated and non-phosphorylated forms of tau (as reviewed by Zheng et al[139] for details on tauopathies). A partially phosphorylated tau is needed for the physiological functioning, whereas a hyperphosphorylated tau can aggregate and lead to impairment of normal functions and cessation of cell survival mechanisms and contribute to neurodegeneration.[140,141]

Abnormalities in the expression and phosphorylation of tau have also been described in stroke,[142] epilepsy, Alzheimer's disease, frontotemporal dementia, and chronic traumatic encephalopathies.[143] In clinical situations, pathological deposition of hyperphosphorylated tau has been observed in brain samples obtained from surgical resection of epileptic tissue from patients with drug-resistant chronic TLE.[144–147] Similarly, brain tissue from other drug-resistant epileptic conditions such as focal cortical dysplasia also displays hyperphosphorylated tau.[148] Moreover, tau-based pathologies are also reported acutely after traumatic brain injury, a major component for secondary injury, and is associated with neurological symptoms and cognitive decline,[68,145] as also reported in animal models of TBI.[68,149] Elevated levels of tau and hyperphosphorylated tau have also been observed in cerebrospinal fluid from epilepsy patients with partial and convulsive seizures, as well as following status epilepticus.[150–152] Such changes were determinants of poor prognosis and higher risk to develop epilepsy.[150] These findings in human patients suggest a possible role in targeting tau pathologies as disease-modifying treatment, but also provide a possible biomarker for predicting epilepsy development after a brain insult that should be further investigated and validated.

The involvement of tau-based mechanisms in epilepsy has been further supported by neuropathological findings from both genetic[153,154] and acquired models of epilepsy.[15] Furthermore, there is evidence that genetic[155,156] or pharmacological[15,157,158] manipulations of tau phosphorylation alter seizure induction or epilepsy development after an epileptogenic brain insult. In addition to the impact of

hyperphosphorylated tau, total tau has been implicated in altering excitation/inhibition balance,[159] Roberson et al, who showed that mice with tau genetic knockout display reduced seizure severity and latency to chemoconvulsant-induced seizures.[159]

There is also building evidence that tau-based mechanisms enhance neuronal excitability. An unstable microtubule assembly at axonal segments dysregulates the resting membrane potential and thereby generations of action potentials.[160] Accordingly, not only pharmacological regulation or genetic manipulation of tau phosphorylation but also inhibiting total tau has shown protection against induced seizures.[156,157,161,162] Interestingly, tau knockout mice that underwent experimental stroke using a middle cerebral artery occlusion, developed less pentylenetetrazol evoked seizures, were protected from excitotoxic brain damage neurological deficits following stroke by site-specific inhibition of glutamate-induced and Ras/ERK-mediated toxicity.[162] Contrary to this, recent work has also suggested a role of tau phosphorylation in diminishing neuronal activity and attenuated seizure activity to 4-aminopyridine induction.[163,164]

These findings support a role for tauopathies in neuronal excitability, which may be dependent on the stage of the disease and may determine a compensatory mechanism to combat disease progression. Nevertheless, tau phosphorylation is evidenced to affect neuronal excitability and may alter excitation/inhibition balance providing conditions for epileptic seizures to occur. Whether these effects are relevant during the early phases of epileptogenesis after an epileptogenic insult is an important question. The activity of protein phosphatase 2A (PP2A), the main dephosphorylating enzyme, is increased, and glycogen synthase kinase-3B (GSK-3B) and cyclin-dependent kinase 5 (CDK5), the primary phosphorylating enzymes, decreased, within few hours after the kainic acid-induced status epilepticus[165] as well as following a traumatic brain injury.[68] This tips the balance between tau phosphorylation and dephosphorylation in favor of the former, resulting in an accumulation in the brain of hyperphosphorylated tau. This is prevented by the treatment of rats following a variety of epileptogenic brain insults with the oxidized selenium salt and sodium selenate, which specifically increases the activity and expression of the specific PP2A subunit, PR55, that is responsible for dephosphorylating hyperphosphorylated tau.[15,166,167] Although the exact mechanism of how increased phosphorylation induces epileptogenesis is yet to be identified, it provides for an exciting target for the development of disease-modifying therapies in established epilepsies as well as anti-epileptogenesis treatment for inhibiting epilepsy after an epileptogenic insult.[15,21,167]

In the amygdala kindling, post-SE and post-TBI rat models of acquired epilepsy, treatment with sodium selenate inhibited the development of limbic epileptogenesis as well as cognitive and sensorimotor impairments.[68] Moreover,

sodium selenate treatment given acutely after the epileptogenic insult in these models prevented the decrease in PP2A activity and PR55 levels seen following these brain insults, as well as reducing the accumulation of hyperphosphorylated tau, mitigating neurodegenerative changes in the brain, and reducing the number of spontaneous seizures in these animal models.[15,68] Sodium selenate is currently being evaluated in human clinical trials for adult patients with prostate cancer and Alzheimer's disease.[168,169] Given all this pre-clinical evidence, it seems plausible that targeting the tau neurodegenerative pathways with sodium selenate could be an anti-epileptogenic therapy in human TLE.

5 | AMYLOID-B PATHWAY IN ACQUIRED EPILEPSY

The deleterious effects of overexpression and reduced clearance of the amyloid precursor protein (APP) and its proteolytic product, the amyloid-β peptide, in Alzheimer's disease have been widely documented in the literature.[170–172] Amyloid-β can be found in different aggregates forms in the brain, as soluble monomers, oligomers, or protofibrils before aggregating into insoluble fibrils.[173,174] The amyloid-β plaques are usually formed outside the cell and exert neurodegenerative effects influence by different pathological mechanisms.[171] Patients with Alzheimer's disease have an 8- to 10-fold risk of developing spontaneous seizures than the general population.[175–179] Recently, attention has shifted to the importance of these two proteins and the mechanisms in the development of epilepsy.[180]

Dysregulation of APP after brain injury has been demonstrated in a number of human and animal studies; however, the effects of this APP regulation are still under debate.[8]

Numerous lines of evidence in both humans and in pre-clinical transgenic models that express APP have demonstrated that an epileptogenic brain injury triggers overexpression of APP.[8,180–185] An increase in APP immunoreactivity has been shown in neurons and astrocytes in the weight drop model of TBI.[186,187] APP protein expression is increased post-fluid percussion injury in the cortex and hippocampus acutely 1-h injury.[184,185] Similar results have been reported in the kainic acid-induced post-SE model of acquired epilepsy.[188] Similarly, in patients APP can readily be detected within hours up to 2.5 years after TBI.[181–183]

Evidence shows that increased amyloid production and deposition contribute to the development of acquired epilepsy,[189] and Tg2576 mice that overexpress human APP has been shown to be susceptible to the development of seizures in the amygdala kindling model of acquired epilepsy.[190] Expression levels of APP and amyloid-β protein significantly increased in cortex and the hippocampus of the patients with temporal lobe epilepsy refractory to

medical treatment.[191] Furthermore, amyloid-β deposits start to accumulate around 10 years before the onset of clinical signs and symptoms of dementia.[192] Amyloid-β deposits have shown to increase neuronal excitability and induce hippocampal network reorganization and hyperactivation processes that have been described as epileptogenic.[193,194] Interestingly, in Alzheimer's patients, hippocampal hyperactivation only occurs in the initial stages of the disease. However, epileptiform activity and seizures can occur throughout the whole course of disease.[192,193,195,196]

Consistently with the aforementioned evidence, different mice models that overexpress APP also show hyperexcitation in individual neurons, interictal spikes, and spontaneous seizures in cortical and hippocampal networks.[83,197–207] One of them, the APdE9 transgenic mouse model, generated by crossing transgenic mice expressing the APP human protein and the human PS1-dE9 (deletion of exon 9),[208] has been reported to have spontaneous seizures and increased neuronal excitability.[204–207] Similarly, another study analyzed four different lines of transgenic mice expressing familial mutant or wild-type human APP and reported aberrant synchronous activity in cortical and hippocampal networks, as well as spontaneous seizures in the mutant mice.[63] Moreover, these transgenic mice were more susceptible to develop seizures after pentylenetetrazol, pilocarpine, or kainic acid administration.[63] It has been hypothesized that this aberrant excitatory neuronal activity induced by human APP and increased Amyloid-β production could trigger compensatory inhibitory mechanisms constraining the capacity for synaptic plasticity and contributing to network dysfunction.[63,205] Other mechanisms of epileptogenicity described for amyloid-β deposits have been related to the excessive dopamine release and activation of the dopamine 1 receptor.[209–211] Excessive activation of dopamine 1 receptors disrupts the GABAergic inhibitory input by reducing GABA release from fast-spiking interneurons.[210] This leads to an excitatory/inhibitory imbalance and consequently hyperexcitability of pyramidal cells. The hyperexcitability of pyramidal cells further increases the amyloid-β deposits creating a vicious cycle.[212,213] Furthermore, amyloid-ß accumulation induces microglia activation and release of pro-inflammatory mediators, which can promote the development of seizures and epilepsy.[8]

On the other hand, some authors have hypothesized that injured neuronal cells upregulate APP production as an attempt to repair the damage caused by injury.[8,214–216] Severe experimental TBI has shown to increase the expression of genes encoding proteins involved in amyloid-β clearance and reduced amyloid-β plaques in the mouse APP/PS1 model, which overexpresses APP.[217] Similarly, in the PDAPP mice model, which exhibits high human APP expression, amyloid-β deposits were reduced even 8 months after TBI, while sham animals displayed increasing amyloid burden.[218,219] Interestingly, mice lacking APP (APP-KO) showed increased vulnerability

to mild TBI compared with the wild-type controls (WT) after a mild CCI.[220] In addition, intracerebroventricular administration of recombinant secreted fragment APPα (sAPPα) in APP-KO mice reduced the functional deficits observed after moderate TBI.[221] This neuroprotective aspect of APP upregulation is based on the hypothesis that the sAPPα may be neuroprotective and the secreted fragment APP ß (sAPPß) is not.[222,223] However, the exact mechanism by which APP and amyloid-β can be epileptogenic needs to be elucidated.

Nevertheless, the current evidence in the pre-clinical models and in patients suggests that the modulation of APP and amyloid-β production, the prevention of amyloid-β aggregation, or promotion of its clearance could be potential therapeutic targets to prevent the development of epilepsy.[224] The modulation of APP secretases, proteins that cleaves and prevents APP aggregation, has been explored as a therapeutic approach with conflicting evidence. Loane and colleagues show that pharmacological inhibition of γ-secretase decreased APP and amyloid-β production and reduced neurodegeneration and improved motor and cognitive recovery after controlled cortical impact-induced TBI.[225] In contrast, γ-secretase inhibition failed to hypersynchronous oscillatory activity and spontaneous seizures in a APP transgenic mice model of Alzheimer's disease.[212] Intracerebroventricular administration of APP96-110, a peptide that interacts with the D1 heparin binding site, following controlled cortical impact in mice showed promising neuroprotective effects.[226,227] Furthermore, APP96-110 administration in Sprague Dawley rats after a diffuse TBI improved cognitive outcomes and reduced axonal injury.[227]

Reduction of inhibition of the c-Jun N-terminal kinase (JNK) pathway is another potential therapeutic strategy to prevent the development of epilepsy.[228] Aberrant activation of JNK intracellular signaling cascade has been reported in Alzheimer's disease patients and in mouse models, suggesting that it might be involved in a number of neurodegenerative mechanisms associated with the disease.[228–230] SP600125, a specific JNK inhibitor, has been described to reduce APP expression levels and amyloid-ß production, inhibition of inflammatory responses, and apoptotic neurodegeneration among other pathological features of after TBI. Remarkably, treatment with SP600125 also seems to redirect APP processing from the amyloidogenic to the non-amyloidogenic pathway, without affecting amyloid-ß clearance but suppressing its production.[228]

Valproic acid, one of the most commonly prescribed antiseizure drugs, has shown to affect the production of amyloid[231] and to reduced epileptiform activity in mice models that overproduce amyloid-ß; however, the effects are not sustained after treatment discontinuation.[232] Similar effects have been shown with lamotrigine[233] and bexarotene.[234] Huperzine A, an acetylcholinesterase inhibitor, has shown promising anticonvulsant,[235] reducing amyloid accumulations and synaptic

deficits.[236,237] Levetiracetam reduces abnormal spike-wave activity, and in chronic use (12 days), reverses hippocampal remodeling and cognitive deficits in mice model that overexpresses human APP.[238]

Although these approaches have been widely explored in the TBI and Alzheimer's disease research field, the findings can promote insights and bolster the rationale for developing an APP and amyloid target therapy as disease-modifying or anti-epileptogenic therapy in acquired epilepsy.[8]

6 | MECHANISTIC TARGET OF MAMMALIAN RAPAMYCIN PATHWAY

The mammalian target of rapamycin (mTOR) is another pathway that can contribute to neurodegeneration in epilepsy as well established to be involved in neurodegenerative conditions such as Alzheimer's and Parkinsonism.[239] mTOR is an intracellular signaling protein that belongs to the phosphatidylinositol 3-kinase (PI3K)-related kinase family, whose activity is mediated through a serine-threonine protein kinase and has been recognized as one of the pivotal cellular signal pathway to control cell survival and proliferation.[240] mTOR exists in two multiprotein complexes, namely mTORC1 that is rapamycin-sensitive and mTORC2 that is rapamycin insensitive. mTOR signaling is regulated by signals from growth factors and nutrients that bind to receptors at the membrane to activate intracellular signaling mechanisms such as PI3K, and generates PIP3 to activate mTOR, which induces protein kinase B (Akt) signaling. This inhibits negative regulators of mTOR such as tuberous sclerosis complex (TSC1/2) and induces mTOR signaling to lead protein translation of key proteins involved in synaptic plasticity, learning, and memory apart from the proteins involved in cell growth mechanisms. In the brain, mTORC1 regulates neuronal excitability, memory formation, and learning, and on the other hand, mTORC2 is found to be involved in cytoskeletal integrity and cell migration.[241] For a detailed review of mTOR signaling, readers are referred to Perluigi et al[239]

With regard to the role of mTOR pathway in neurodegeneration, a major focus of research attention has been mechanisms related to autophagy,[242,243] a self-consuming mechanism that plays a key role in cell survival by removing toxic proteins and defunct organelles.[244] Similarly, mitochondria-mediated mechanisms of inducing apoptosis are also associated with this pathway.[245] Accumulation or aggregation of pathological proteins is a common mechanism among neurodegenerative conditions and is negatively regulated by autophagy.[246] mTOR pathway–mediated regulation of autophagy has been increasingly investigated and rapamycin led inhibition of this pathway has exhibited strong effects in inhibiting aggregation of the pathological misfolded proteins.[247,248] Indeed, rapamycin-mediated inhibition of mTOR against neurodegeneration has been described to be neuroprotective in Parkinson's, Alzheimer's, and Huntington diseases.[248–250]

Considering neurodegenerative pathology in epilepsy, it is indeed relevant that mTOR pathway is involved in epileptogenesis and seizure-inducing mechanisms.[241] Abnormal mTOR activation has been reported in both genetic and acquired epilepsies. Mutations and genetic polymorphisms of TSC1 or TSC2 proteins that are intrinsic inhibitors of mTOR pathway leading to its over-activation have been associated with the development of epilepsy in humans.[251,252] Similar outcomes have also been reported in transgenic TSC1 and 2 mouse models, with rapamycin showing antiseizure and anti-epileptogenesis effects.[253–255] Accordingly, other intracellular signaling mechanisms of mTOR such as phosphatase and tensin homolog deleted on chromosome ten (PTEN), Akt, and DEPDC5 have all been associated with the development of epilepsy.[256–259] Similarly, dysregulation of the mTOR signaling has also been observed in acquired epilepsies, including increased expression of phosphor-mTOR patients with mesial temporal lobe epilepsy.[260,261] Further, the mTOR pathway is reported to be dysregulated after experimental epileptogenic insults in animal models, including SE and traumatic brain injury.[262,263] Inhibiting mTOR signaling by rapamycin has been reported to provide anti-epileptogenesis effects in animal models following an epileptogenic insult,[264,265] as well as in animal models following the establishment of pharmacoresistant epileptic seizures.[261]

While considering the mechanisms by which mTOR pathway contributes to epilepsy, it is important to recognize the myriad of the cellular process involved and how a dysregulation of those could affect neuronal excitability and contribute to neuronal circuit reorganization to promote epileptic seizures. Apart from neurodegeneration, mTOR pathways are involved in neurogenesis, newborn cell survival and migration, axonal sprouting, neuronal plasticity, and altered expression of ion channels and receptors, all of these mechanisms have been considered to be characteristic of epileptogenesis and may contribute to an excitable brain network.[266]

Rapamycin inhibits mTORC1 and has been shown to have antiseizure effects.[17,267] Treatment with rapamycin during or after the initial epileptogenic injury has shown to reduce the percentage of mice that developed post-traumatic epilepsy and the frequency of spontaneous seizures, as well as neuronal degeneration.[268,269] Similar results have also been shown in the post-SE[18,20] and neonatal hypoxia models of acquired epilepsy.[19,270] However, these results have not been replicated in the amygdala kindling[271] and in the pilocarpine-induced post-SE mice model of TLE[16] where rapamycin treatment was unable to reduce the occurrence of spontaneous seizures. Similarly, rapamycin did not persistently prevent mossy fiber sprouting

and was unable to reduce granule cell proliferation, hilar neuron loss, or generation of ectopic granule cells.[16,17,19,268,272]

7 | NEUROINFLAMMATION

Neuroinflammation plays a substantial role in promoting neurodegenerative changes in acquired epilepsies.[273,274] On the other hand, neuroinflammation could be promoted by cells undergoing death by the release of damage-associated molecular patterns (DAMPs) such as high-mobility group box 1 proteins, purine metabolites, or proteins released from damaged extracellular matrix due to the dying of neurons.[275] These events lead to a cycle of pathways that lead to enhanced neuroinflammation and promoting further cell loss. Such events could contribute both to the pathological and functional outcomes of an epileptogenic insult. A detailed discussion of the inflammatory molecules involved in human and experimental acquired epilepsies and how such molecules may be involved in promoting seizures and epileptogenesis is discussed in another review in this special issue.[276] Pharmacological target of neuroinflammation, particularly modulating interleukins, cyclooxygenase-2, prostanoid pathways, and several chemokines are promising anti-epileptogenic and disease-modifying targets.[277,278] Of particular interest has been the involvement of interleukin-1β (IL-1β) in the pathogenesis of acquired epilepsies, with consistent reports of either its receptor blockers or inhibitors of biosynthesis providing neuroprotective, anticonvulsant, or anti-epileptic effects as well as disease-modifying effects in epilepsy models.[279–283] Interestingly, an increased inflammation has also been reported in models of genetic epilepsies,[284,285] with inhibition of IL-1β synthesis providing a seizure-suppressant effect.[285] Furthermore, blockage of purinergic receptor P_2X_7 receptor involved in the release of pro-inflammatory cytokines has been reported to reduce epileptic seizures or overall frequency of spontaneous recurrent seizures.[286,287]

High-mobility group box 1 protein (HMGB-1) is another molecule that has been increasingly investigated recently, in terms of anti-epileptic effects as well as promising findings of it providing a potential biomarker of epilepsy.[288] HMGB-1 is a DAMP and is secreted by neurons and glial cells following the formation of inflammasome and leads to the release of pro-inflammatory cytokines after activation of its receptors—Toll-like receptor 4 (TLR-4) and receptor for advanced glycation end products (RAGE).[275] Along with the potential of HMGB-1 in suppressing seizures[289,290] along with reported disease-modifying effects,[291] the pathologic disulfide isoforms of HMGB-1 have been reported to be a prospective biomarker for experimental acquired epilepsies[292] as well as in human childhood and adult epilepsies.[288,292] Notably, it has also been associated with a decline in the cognitive functions,[293] a major neuropsychiatric comorbidity associated with acquired epilepsies.

In addition to the cytokines, chemokines are other molecules contributing to the inflammatory response by mobilizing the immune cells to the site of injury. Chemokines and its receptor systems such as fractalkine/CX3CR1 and CCL2/CCR5 systems have been reported to be involved in neurodegenerative mechanisms following an epileptogenic insult.[273,294–296] Despite reports of inhibiting the signaling of these chemokines displaying neuroprotective and antiseizure effects, a disease-modifying or anti-epileptic effects of them are yet to be established.

Finally, the role of promoting anti-inflammatory cytokines to induce neuroinflammation toward an M2 phenotype has been increasingly investigated in epilepsy models.[274] This is important considering the fact that inflammation is a fairly heterogeneous process and is also involved in repair of damaged tissue. A disturbed balance in pro- and anti-inflammatory response has been shown in models of acquired and genetic epilepsies.[297,298] Though, directly attempting to release anti-inflammatory cytokines at the epileptogenic focus did not provide protective effects against epileptogenesis or neuroprotection.[299] Overall, future studies are warranted to investigate the potential of other strategies modulating neuroinflammation in this manner.

8 | CONCLUSIONS

There are significant neuropathological and neurobiological parallels between neurodegenerative diseases and acquired epileptogenesis, and both are commonly comorbid in patients and chronic animal models. All current therapies just systematically suppress seizures, but have no sustained effect to prevent the development of epilepsy, and do not mitigate its progression, or to reverse once it is established. Novel therapies targeting neurodegenerative pathways, such as tau, amyloid-β, mTOR, and neuroinflammation, have potentially to be anti-epileptogenic and/or disease-modifying therapies for patients with acquired epilepsy. These therapies may not only have beneficial effects on the epilepsy itself, but also on the associated neurocognitive and neuropsychiatric comorbidities. There is promising evidence from animal models of acquired epilepsy that compounds targeting these neurodegenerative pathways may have such anti-epileptogenic effects. However, further research is needed to validate these findings before proceeding into clinical trials.

DISCLOSURES

Neither of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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