



REVIEW

The Intersection of Impaired Ion Channels and Depleted Mitochondria in Epileptic Seizures: A Narrative Review

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ABSTRACT: Epilepsy is sustained by a self-reinforcing triad of ion channel dysfunction, mitochondrial impairment, and oxidative stress that lowers seizure threshold and drives epileptogenesis. This review examines how genetic channelopathies and redox-dependent post-translational modifications of voltage-gated sodium, calcium, and potassium channels disrupt excitatory–inhibitory balance, and how electron transport chain dysfunction amplifies reactive oxygen species, compromises adenosine triphosphate (ATP)-dependent membrane stability, and activates mechanistic target of rapamycin complex 1. Key convergences include oxidative ion channel modification, ATP-sensitive potassium channel impairment, synaptic lipid peroxidation, and gamma-aminobutyric acid (GABA)-ergic transporter dysfunction. Temporal lobe epilepsy is characterized by focal mitochondrial pathology, whereas genetic generalized epilepsies reflect thalamocortical channelopathies, a distinction with direct therapeutic implications. Precision strategies integrating mitochondria-targeted antioxidants, ion channel modulators, antioxidant supplementation N-acetylcysteine, α -lipoic acid, and mTOR inhibitors (rapamycin, everolimus) provide a mechanistic framework for interrupting the redox–metabolic–electrical feedback loop sustaining seizures and advancing disease modification.

KEYWORDS: Epilepsy; epileptogenesis; ion channelopathies; mitochondrial dysfunction; oxidative stress; mechanistic target of rapamycin complex 1; lipid peroxidation; redox signaling

1 Introduction

Epilepsy is a chronic neurological disorder characterized by a persistent predisposition to recurrent seizures, accompanied by neurobiological, cognitive, and psychosocial consequences [1–3]. The etiology of epilepsy is multifactorial, encompassing genetic predisposition and acquired brain injuries [4,5]; however, the fundamental mechanism underlying epileptogenesis is neuronal hyperexcitability [6,7]. A comprehensive literature search was conducted using PubMed/MEDLINE, Scopus, and Google Scholar,

with priority given to studies published between 2005 and 2025, and inclusion of seminal earlier works were historically relevant. Search terms included combinations of epilepsy, epileptogenesis, mitochondrial dysfunction, oxidative stress, ion channels, channelopathies, mTOR signaling, lipid peroxidation, and GABAergic inhibition, among others. Mitochondrial dysfunction has become a pivotal pathogenic mechanism that substantially contributes to excitotoxicity and a decrease in the seizure threshold [8,9]. Mitochondria are crucial organelles that govern cellular energy production via oxidative phosphorylation, a key step for sustaining neural homeostasis [10].

The electron transport chain (ETC) comprises four protein complexes (I-IV) embedded in the inner mitochondrial membrane that sequentially transfer electrons coupled to proton pumping, ultimately driving ATP synthase to sustain cellular energy production. Dysfunction of electron transport chain complexes, particularly complexes I and III, represents an important pathophysiological mechanism in epilepsy [11–13]. These complexes are essential for adenosine triphosphate (ATP) synthesis and serve as primary sites for reactive oxygen species (ROS) formation [14,15]. Inhibition or impairment of complexes I (NADH dehydrogenase) and III (cytochrome bc1) causes electron leakage that interacts with molecular oxygen, leading to the generation of superoxide anion and other ROS [16,17]. Mitochondrial function is closely associated with its ion channels, including the mitochondrial calcium uniporter (MCU), the sodium-calcium exchanger (NCLX), the voltage-dependent anion channel (VDAC), and the mitochondrial permeability transition pore (mPTP) [18]. Dysfunction of complexes I and III may impair the regulation of these channels. Concurrently, excessive ROS generation alters MCU activity and increases mPTP sensitivity, thereby reducing calcium buffering capacity and promoting ion leakage, which compromises mitochondrial membrane potential. The resulting bioenergetic instability subsequently affects neuronal ion channels responsible for excitability (Na^+ , Ca^{2+} , and K^+), thereby heightening the likelihood of seizures [19,20]. These mechanistic details are particularly relevant because they establish the molecular basis through which mitochondrial impairment directly modulates neuronal ion channel function.

Complex I is particularly vulnerable to oxidative damage and metabolite-induced inhibition during seizures, which exacerbates ROS production and impairs neuronal ATP synthesis [21,22]. This bioenergetic dysfunction directly affects energy-dependent processes, such as maintenance of ion gradients via the Na^+/K^+ -ATPase pump. Additionally, it impairs repolarization mediated by potassium channels, including K_{ATP} channels, which normally activate under low ATP conditions as a protective mechanism against hyperexcitability [23,24]. Such dysfunction promotes partial membrane depolarization [25]. Excessive ROS initiates molecular events that contribute to a decreased seizure threshold by damaging essential components of neuronal excitability [26]. Evidence indicates that mitochondrial dysfunction is not solely a consequence of seizure-induced neuronal injury but may function as an early contributor in epileptogenesis [27,28]. This concept is corroborated by human studies: post-surgical analysis of hippocampal tissue from patients with drug-resistant TLE has revealed significant reductions in ETC complex I and III activity alongside elevated oxidative damage markers, directly linking bioenergetic failure to pharmacoresistance and poor surgical outcomes [21,29,30]. This perspective suggests that bioenergetic changes may occur prior to the electrical expression of the disease, even before electroencephalographic (EEG) discharges are documented [31].

Studies in animal models have demonstrated that respiratory chain dysfunction occurs prior to the onset of interictal or ictal EEG discharges, indicating early bioenergetic alterations in neural networks [19,32,33]. An early alteration involves disruption of mitochondrial calcium homeostasis, resulting in diminished buffering capacity and subsequent cytosolic calcium excess [34]. Calcium (Ca^{2+}) overload, resulting from aberrant mitochondrial permeability transition pore opening and reduced Ca^{2+} extrusion via the NCLX exchanger, acts as a major trigger for excitotoxicity and activation of enzymes that contribute to chronic

hyperexcitability [27,35]. Early increases in basal ROS generation have been described before detectable EEG activity in experimental models, suggesting that oxidative stress may participate in early epileptogenic processes rather than representing a byproduct of seizures [36–38]. Oxidative stress resulting from mitochondrial dysfunction can impair voltage-gated sodium (Nav) and calcium (Cav) channels through post-translational modifications, representing a relevant molecular mechanism contributing to neuronal hyperexcitability [39]. Potassium channels, including Kv and K_{ATP} channels, are also affected, as oxidative modification may reduce conductance and hinder efficient repolarization, thereby prolonging action potential duration and enhancing abnormal neural synchronization [40]. Lipid peroxidation of synaptic membranes is another fundamental contributor to cellular damage in epilepsy [41]. Synaptic membranes are particularly susceptible due to their elevated levels of polyunsaturated fatty acids (PUFAs) and their proximity to mitochondria, major sources of ROS [42,43].

The interaction of ROS with PUFAs initiates a cascade that generates reactive aldehydes, including malondialdehyde and 4-hydroxynonenal (4-HNE), which are widely used indicators of oxidative stress [44]. This damage compromises the structural integrity of the lipid bilayer, altering membrane fluidity and permeability and directly affects embedded proteins such as neurotransmitter receptors [45,46] and ion channels; consequently, lipid peroxidation may enhance excitability by modifying glutamate and GABA receptor conformation, impairing neurotransmitter uptake and disrupting transporter function, including GABA transporter GAT-1, thereby linking membrane oxidative injury to network disinhibition [47–49]. Oxidative stress may also disrupt inhibitory pathways by impairing GABA transport [50]. GABA is the principal inhibitory neurotransmitter, and its reuptake from the synaptic cleft is mediated by GABA transporters (GATs), with GAT-1 being particularly relevant in epilepsy [51]. Impaired GABA reuptake disrupts the excitatory/inhibitory balance within neural circuits and may facilitate the propagation of epileptic activity [22,52]. This mechanism is especially relevant in the hippocampus, where GABA-mediated regulation is essential for preventing hyperexcitability and epileptogenesis [50,53,54].

The relevance of these mechanisms may differ among epilepsy types. Temporal lobe epilepsy (TLE) represents a focal epilepsy frequently associated with significant oxidative stress, mitochondrial dysfunction, and altered ion channel regulation within the hippocampus [21,55,56]. In contrast, genetic generalized epilepsies (GGE), which are usually self-limited epilepsy syndromes presenting symptoms only during infancy or childhood, are characterized primarily by a thalamocortical network in which mitochondrial dysfunction-induced oxidative stress may represent either a contributing factor or a secondary phenomenon depending on the underlying genetic background, although there is not a well-established correlation between mitochondrial dysfunction and GGE among the consulted literature [57]. This distinction carries direct therapeutic implications: in TLE, adjunctive use of mitochondria-targeted antioxidants (e.g., MitoQ, CoQ10) or mTOR inhibitors (rapamycin) may address the structural bioenergetic substrate contributing to pharmacoresistance, whereas in GGE, therapeutic emphasis should remain on modulation of thalamocortical network dynamics through selective ion channel modulators (e.g., Cav3.x blockers, GABA_A receptor-positive allosteric modulators), with antioxidants playing a secondary, adjunctive role [58,59]. A comprehensive understanding of the interplay between mitochondrial dysfunction and oxidative stress is essential for identifying novel therapeutic targets capable of interrupting the cycle of bioenergetic failure and neuronal hyperexcitability in chronic epilepsy [29,60]. In summary, this section establishes a framework in which mitochondrial dysfunction, oxidative stress, and ion channel dysregulation are not independent contributors but mechanistically intertwined amplifiers of epileptogenesis. The convergence of these pathways on shared downstream targets, including mTORC1 signaling, lipid peroxidation, and GABAergic transporter impairment, not only accounts for the progressive nature of epilepsy but also identifies a set of tractable

molecular entry points for disease-modifying intervention. The sections that follow examine each of these mechanisms in depth, with emphasis on translational and clinical relevance.

2 Early Mitochondrial and Ion Channel Dysfunction in Epileptogenesis: Pre-EEG Changes

2.1 Bioenergetic Failure and Ion Channel Vulnerability

Mitochondrial dysfunction is not merely a consequence of seizure-induced neuronal damage; rather, it functions as an early biomarker and pathological contributor in epileptogenesis, manifesting before detectable EEG abnormalities. We would like to note that the supporting evidence establishes a temporal association rather than a causal relation between mitochondrial dysfunction and epileptogenesis [28,34,61]. This framework proposes that bioenergetic changes occur prior to the overt electrical manifestation of the disease, identifying mitochondria as a crucial target for prevention [60,62]. Mitochondrial ion channels, including the MCU, NCLX, and ATP-dependent potassium channels (mitoK_{ATP}), are pivotal regulators of calcium homeostasis; their dysfunction impairs calcium homeostasis, mitochondrial membrane potential, and ROS production processes closely associated with neuronal excitability [25].

The epileptogenic phase, the asymptomatic interval following an initial insult (such as trauma or infection) and preceding the onset of spontaneous seizures, is characterized by subtle yet progressive alterations in mitochondrial function [37,63]. Studies in animal models of epilepsy have demonstrated that mitochondrial oxygen consumption and respiratory chain activity may be impaired prior to the emergence of interictal or ictal EEG discharges [19,64,65]. This early alteration often manifests as a reduced capacity for ATP production, indicating bioenergetic compromise within vulnerable neural networks [27,66,67]. Such energy deficiency directly affects the ability of neurons to maintain resting membrane potential and to repolarize efficiently after activity, thereby increasing susceptibility to hyperexcitability [17,68,69]. Fig. 1 illustrates the interplay between mitochondrial dysfunction and ion channel alterations during the pre-EEG epileptogenic phase, highlighting key molecular mechanisms underlying early bioenergetic failure and calcium dysregulation. Classical neuronal ion channels, including Nav, Kv, HCN, Cav, and ionotropic glutamate receptors [α -amino-3-hydroxy-5-methyl-4-isoxazolpropionic (AMPA) and N-methyl-D-aspartate (NMDA)], contribute to this vulnerability. Their function depends on adequate energy supply and preserved ionic gradients, which are maintained by ATP-dependent processes such as the Na⁺/K⁺-ATPase and are tightly coupled to mitochondrial activity [12,13,17].

2.2 Calcium Dysregulation as an Early Epileptogenic Trigger

An early event described in experimental models is the disturbance of mitochondrial calcium homeostasis [70,71]. Even in the absence of overt electrical discharges, mitochondrial capacity to regulate cytosolic calcium may be compromised, leading to intracellular Ca²⁺ accumulation [70,72]. This phenomenon is influenced by dysregulation of channels such as the MCU, whose excessive activity can promote Ca²⁺ overload, and by impaired NCLX function, which normally facilitates mitochondrial Ca²⁺ extrusion. Cytosolic calcium overload resulting from mitochondrial dysfunction acts as a major driver of excitotoxic signaling and activation of calcium-dependent enzymes, thereby establishing conditions that favor persistent hyperexcitability [27,72,73]. Concurrently, elevated Ca²⁺ levels enhance activation of voltage-gated calcium channels (e.g., Cav2.x) and potentiate NMDA receptor opening, further increasing excitability [74,75].

2.3 Early ROS Generation and Oxidative Modification of Ion Channels

Early ROS generation has been documented prior to detectable EEG abnormalities in experimental models [19]. Although epileptic discharges further amplify ROS production, basal increases during

epileptogenesis suggest that oxidative stress may participate in early network instability rather than solely representing a downstream consequence of seizures [37]. Progressive ROS accumulation can modify neuronal macromolecules, including membrane lipids and voltage-gated ion channel proteins [40,76], potentially reducing the functional stability of channels such as Kv1.1, Kv7.2/KCNQ, Nav1.1/SCN1A, and HCN [77–79]. These alterations may lower the excitability threshold and facilitate the emergence of epileptiform activity [17].

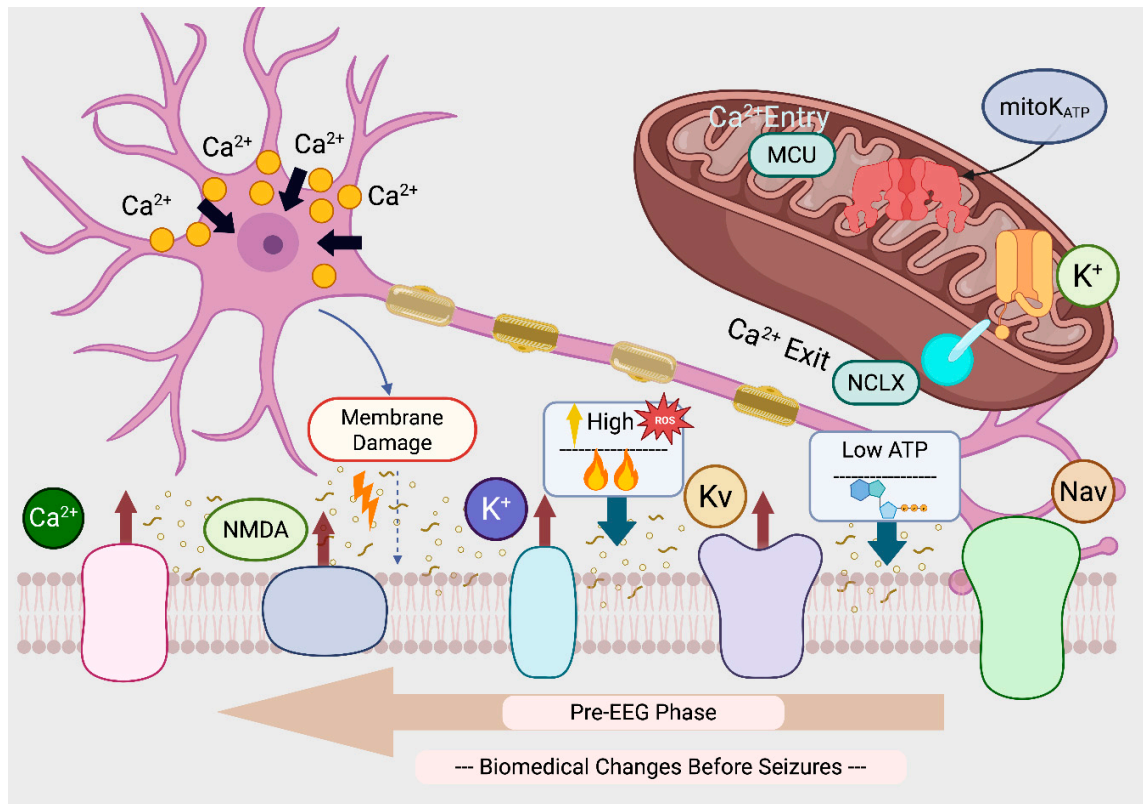


Figure 1: Mitochondrial and ion channel dysfunction during the pre-EEG epileptogenic phase. The schematic depicts molecular events occurring before detectable EEG abnormalities. Mitochondrial dysfunction, characterized by impaired Ca^{2+} handling through mitochondrial calcium uniporter (MCU) and mitochondrial sodium-calcium exchanger (NCLX) dysregulation, contributes to cytosolic Ca^{2+} accumulation in neuronal compartments. Concurrent mitochondrial ATP depletion and increased ROS production compromise the function of critical neuronal ion channels, including voltage-gated potassium channels (Kv), voltage-gated sodium channels (Nav), as well as NMDA receptors. Dysfunctional mitochondrial ATP-sensitive potassium ($\text{mitoK}_{\text{ATP}}$) channels may further destabilize membrane potential. This pre-seizure biochemical environment promotes neuronal hyperexcitability and represents a potential target for early therapeutic intervention prior to the onset of spontaneous seizures. Orange-brown arrows indicate pathological processes; the beige arrow highlights the temporal window of the pre-EEG phase preceding clinical manifestations. Created in BioRender. By Pérez-Villavicencio J. and Villa-Robledo O. under Perez Godinez, D. O., license use authorization (2026) <https://BioRender.com/zaztv8o>.

2.4 Therapeutic Implications and Emerging Biomarkers

Recognition of these early biochemical and bioenergetic alterations offers a therapeutic window that is less accessible once epilepsy is established and recurrent EEG discharges are present [63]. Identification of subclinical mitochondrial dysfunction prior to paroxysmal EEG activity may enable neuroprotective

interventions aimed at attenuating or delaying epileptogenesis [27]. Strategies under investigation include agents that enhance ETC efficiency (e.g., CoQ10, currently in Phase II/III trials for mitochondrial epilepsies [60,80]), mitochondrial-targeted antioxidants, such as MitoQ (demonstrated neuroprotection in preclinical status epilepticus models [38]) and modulators of key ion channels including Kv7 stabilizers of which ezogabine demonstrated anticonvulsant efficacy in clinical trials, though it was withdrawn in 2017 due to off-target effects; next-generation Kv7 activators with improved selectivity are currently in Phase II evaluation [81]. MCU modulators and mitoK_{ATP} openers remain in early preclinical development, with feasibility for human application pending pharmacokinetic optimization and blood-brain barrier penetration studies [19,80]. These approaches may prove more effective during early stages than after chronic seizure networks are consolidated. In clinical contexts, primary mitochondrial epilepsies illustrate the pathogenic relevance of bioenergetic failure, as intrinsic mitochondrial defects can directly precipitate epileptic phenotypes, frequently associated with abnormal EEG patterns or multifocal discharges [82,83]. In these disorders, impaired energy metabolism may secondarily influence ion channel function. In acquired epilepsies, early mitochondrial dysfunction is increasingly regarded as a significant modulator of neuronal excitability and synaptic plasticity, rather than a purely secondary event [84].

Current research also focuses on the development of non-invasive biomarkers capable of detecting bioenergetic and oxidative stress alterations in cerebrospinal fluid or blood, potentially allowing identification of individuals at risk for epilepsy before overt EEG abnormalities appear [37,85]. Concrete candidates include: (i) cerebrospinal fluid (CSF) lactate/pyruvate ratio, which is elevated in mitochondrial epilepsies and correlates with seizure burden [86]; (ii) plasma malondialdehyde (MDA) and 4-HNE, validated oxidative stress markers elevated 1.5–2-fold in GGE and >3-fold in TLE [30,87]; (iii) blood mitochondrial DNA copy number, proposed as a systemic indicator of mitochondrial stress; and (iv) emerging metabolomic profiles including acylcarnitines and tricarboxylic acid cycle intermediates detectable by mass spectrometry in plasma samples from pre-symptomatic animal models [37,85]. While clinical validation in prospective human cohorts remains necessary, these analytes represent the most tractable current candidates for early biomarker development. Mitochondrial and neuronal ion channels, therefore, represent promising targets for early diagnosis and disease-modifying interventions aimed at interrupting epileptogenesis at its initial stages.

3 Mitochondrial Dysfunction and Ion Channels in Temporal Lobe Epilepsy Compared to Primary Generalized Epilepsies

Mitochondrial dysfunction and oxidative stress have been implicated across different epilepsy types; however, their extent, localization, and mechanistic relevance differ between TLE and GGE [29]. TLE, the most common focal epilepsy in adults, is characterized by a distinct epileptogenic process frequently associated with an initial precipitating injury (e.g., mesial hippocampal sclerosis) and structural abnormalities detectable by neuroimaging or histopathology [21,88]. In contrast, GGEs, including juvenile absence epilepsy, are primarily considered disorders of thalamocortical network synchronization with a strong genetic basis and typically lack overt macroscopic structural lesions [89]. This divergence in pathophysiological substrate is reflected in differential ion channel involvement. In TLE, acquired functional alterations have been described in Nav, Kv, HCN, Cav, and NMDA/AMPA receptor channels, often secondary to recurrent excitotoxic injury and network remodeling [90–92]. In GGEs, pathogenic mechanisms more commonly involve inherited mutations or functional variants in channels such as T-type calcium channels (Cav3.x), GABA_A receptors, and HCN2, which are critical for thalamocortical oscillatory dynamics [93,94]. As detailed in Table 1, epilepsy-associated ion channel genes exhibit well-established genotype-phenotype

correlations that are fundamental for understanding disease mechanisms and for developing precision-based therapeutic strategies.

Table 1: Major Ion Channel Genes Implicated in Genetic Epilepsies and Network Excitability Disorders.

Gene	Protein (Channel Type)	Mutation Type	Associated Epilepsy Syndrome	Molecular Mechanism	Key References
SCN1A	Nav1.1 (voltage-gated Na ⁺)	LOF (>1257 mutations)	Dravet syndrome; GEFS+	↓ Inhibitory interneuron excitability; impaired Na ⁺ channel inactivation	[95–99]
SCN2A	Nav1.2 (voltage-gated Na ⁺)	GOF/LOF	Neonatal seizures; EIEE	GOF: ↑ persistent Na ⁺ current (INaP); LOF: delayed onset	[100]
SCN8A	Nav1.6 (voltage-gated Na ⁺)	GOF (<i>de novo</i>)	Early-onset EIEE; poor prognosis	↑ Persistent Na ⁺ current; enhanced channel activation	[101,102]
SCN1B	β1 subunit (Na ⁺ channel)	LOF	GEFS+; idiopathic epilepsy	Altered α subunit function; impaired channel trafficking	[103]
KCNQ2	Kv7.2 (voltage-gated K ⁺)	LOF	BFNC; severe EIEE	↓ M-current → impaired repolarization; neuronal hyperexcitability	[104,105]
KCNQ3	Kv7.3 (voltage-gated K ⁺)	LOF	BFNC	↓ M-current → reduced K ⁺ efflux	[104]
KCNA1	Kv1.1 (voltage-gated K ⁺)	LOF	TLE; episodic ataxia	↓ K ⁺ conductance → prolonged action potentials	[106]
KCNT1	Slack (Na ⁺ -activated K ⁺)	GOF	Malignant migrating epilepsy of infancy	↑ Na ⁺ -activated K ⁺ current; aberrant neuronal firing	[107,108]
CACNA1A	Cav2.1 (P/Q-type Ca ²⁺)	GOF/LOF	FHM + epilepsy; EA-2	GOF: ↑ Ca ²⁺ influx; LOF: ↓ neurotransmitter release	[109–111]
CACNA1H	Cav3.2 (T-type Ca ²⁺)	GOF	Childhood absence epilepsy	↑ Low-threshold T-current → 3 Hz spike-wave discharges	[112,113]
CACNA1E	Cav2.3 (R-type Ca ²⁺)	GOF/LOF	DEE (1st year of life)	Altered Ca ²⁺ homeostasis; impaired synaptic transmission	[114]
CACNB4	β4 subunit (Ca ²⁺ channel)	Variable	IGE; modifier in Dravet syndrome	Modulates α subunit voltage dependence and trafficking	[115]
GABRG2	GABA _A receptor γ2 subunit	LOF	Febrile seizures; Dravet syndrome	↓ GABAergic inhibition; reduced receptor surface expression	[116,117]
GABRA1	GABA _A receptor α1 subunit	LOF	Dravet syndrome; EIEE; blindness	↓ GABAergic inhibition; impaired Cl [−] influx	[118]
GABRB2/B3	GABA _A receptor β2/β3 subunits	LOF	Dravet syndrome; EIEE	↓ GABAergic inhibition; altered receptor assembly	[118]
CLCN2	ClC-2 (voltage-gated Cl [−])	LOF	CAE; JAE; JME	Altered Cl [−] homeostasis; weakened GABAergic inhibition	[20,119]
CLCN4	ClC-4 (X-linked Cl [−] channel)	LOF (X-linked)	X-linked EIEE; intellectual disability	↓ Cl [−] flux; impaired neuronal inhibition	[120,121]

Table 1: *Cont.*

Gene	Protein (Channel Type)	Mutation Type	Associated Epilepsy Syndrome	Molecular Mechanism	Key References
HCN1	HCN1 (hyperpolarization-activated)	LOF	Early infantile EIEE	↓ Ih current → altered resting membrane potential	[122,123]
HCN2	HCN2 (hyperpolarization-activated)	LOF/GOF	EIEE; severe neurodevelopmental disorder	Altered Ih current → network dysfunction; thalamocortical dysregulation	[124]

Note: Summary of the major ion channel genes implicated in epilepsy, their mutation types (gain-of-function [GOF] or loss-of-function [LOF]), associated syndromes, and principal molecular mechanisms. Voltage-gated sodium channel genes (SCN family) constitute the most frequently mutated group, while potassium (KCNQ, KCNA, KCNT), calcium (CACNA), GABA_A receptor, chloride channel, and HCN genes contribute to altered membrane repolarization, inhibitory transmission, and network rhythmicity. In addition, the table primarily emphasizes genes implicated in genetic and network-level epilepsies; acquired focal epilepsies, such as TLE, more commonly involve secondary channel dysfunction rather than primary germline mutations. Upward arrows (↑) indicate increased expression, activity, or upregulation; downward arrows (↓) indicate decreased expression, activity, or downregulation. Abbreviations: GOF, gain of function; LOF, loss of function; EIEE, early infantile epileptic encephalopathy; GEFS+, generalized epilepsy with febrile seizures plus; BFNC, benign familial neonatal convulsions; TLE, temporal lobe epilepsy; FHM, familial hemiplegic migraine; EA, episodic ataxia; DEE, developmental and epileptic encephalopathy; IGE, idiopathic generalized epilepsy; CAE, childhood absence epilepsy; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; Nav, voltage-gated sodium channel; Kv, voltage-gated potassium channel; Cav, voltage-gated calcium channel; HCN, hyperpolarization-activated cyclic nucleotide-gated channel; GABAA, gamma-aminobutyric acid type A receptor; ClC, chloride channel; Ih, hyperpolarization-activated current; INaP, persistent sodium current.

3.1 Focal Mitochondrial Impairment in Temporal Lobe Epilepsy

In TLE, oxidative stress and mitochondrial dysfunction are frequently pronounced and localized, particularly within the hippocampus and adjacent limbic structures [21,125]. The focal nature of TLE implies that bioenergetic compromise and oxidative injury are often concentrated within the seizure onset zone [93]. Recurrent excitotoxic stimulation in hippocampal circuits may initiate a maladaptive cycle of calcium dysregulation and ROS overproduction, contributing to progressive mitochondrial impairment and neuronal loss [60]. Mitochondrial calcium handling proteins, including MCU and NCLX, are central to this process, as their dysregulation promotes matrix calcium overload. Similarly, mitoK_{ATP} dysfunction may impair mitochondrial membrane potential stabilization under metabolic stress, further exacerbating oxidative imbalance [126]. In surgical specimens from patients with drug-resistant TLE, reductions in electron transport chain complex activity have been reported, supporting the presence of chronic and regionally localized bioenergetic dysfunction [29].

3.2 Network-Level Dysfunction in Genetic Generalized Epilepsies

In contrast, GGEs demonstrate a more diffuse network-level disturbance in which mitochondrial dysfunction and oxidative stress may play modulatory rather than primary structural roles [29,127]. The defining feature of GGEs is abnormal thalamocortical synchronization, enabling bilateral spike-wave discharges [128,129]. This synchronization depends critically on the rhythmic interaction of specific ion channels, particularly low-threshold Cav3.1/Cav3.2 channels, HCN channels, and GABA_A receptors, whose genetic or functional alterations facilitate pathological oscillations [130–133]. Although mitochondrial dysfunction is not generally considered the initiating structural substrate in GGEs, elevated oxidative stress biomarkers have been reported in blood and cerebrospinal fluid of affected individuals, suggesting that oxidative stress may contribute to network excitability or represent a secondary systemic consequence of recurrent seizures [86].

3.3 Mechanistic Distinctions and Therapeutic Implications

The primary distinction between TLE and GGE lies in anatomical localization and mechanistic hierarchy rather than the mere presence or absence of oxidative stress [134]. In TLE, mitochondrial dysfunction and oxidative injury are increasingly recognized as integral components of the epileptogenic cascade, potentially contributing to hippocampal sclerosis and pharmacoresistance [135]. Oxidative modifications of voltage-gated ion channel proteins including Nav1.1, Kv1.1, Kv7.2, HCN1, and Cav2.x have been associated with altered channel kinetics and enhanced local hyperexcitability in experimental and human studies [81,136,137]. Markers of oxidative damage, such as malondialdehyde, are significantly elevated in resected hippocampal tissue from patients with refractory TLE compared to controls [30], supporting a structural contribution of mitochondrial impairment to chronic focal epilepsy [138].

On the other hand, generalized epileptiform discharges in GGEs reflect large-scale thalamocortical oscillatory dysfunction rather than focal structural mitochondrial failure. Oxidative stress in these conditions may contribute to associated comorbidities such as neuroinflammation or cognitive dysfunction rather than acting as a primary driver of epileptogenesis [29,139,140]. Subtle bioenergetic alterations may influence excitability by modulating channels such as HCN2, Cav3.x, and GABA_A receptors, thereby affecting generalized oscillatory dynamics [30,141]. This distinction has therapeutic implications: in TLE, mitochondrial-targeted interventions or antioxidants may be conceptualized as adjunctive strategies aimed at limiting focal neurodegeneration, whereas in GGEs, therapeutic emphasis remains primarily on modulation of thalamocortical channel dynamics and network synchronization [132,133,142]. These mechanistic distinctions have direct clinical correlates. In TLE, the progressive nature of mitochondrial damage and oxidative injury is reflected in the high rates of pharmacoresistance (up to 30–40% of patients), temporal lobe structural atrophy on MRI, and the frequency of surgical candidacy [21,88]. In contrast, GGEs generally exhibit better pharmacological responsiveness, with valproate, lamotrigine, or levetiracetam achieving seizure control in the majority of patients, consistent with the predominant role of reversible network-level channel dysfunction rather than fixed structural-metabolic pathology [89,132]. Prognostically, the presence of hippocampal sclerosis in TLE, partly attributable to cumulative oxidative and mitochondrial injury, predicts worse outcomes and heightened risk of cognitive decline, further justifying the investigation of mitochondria-targeted adjunctive therapies in this subgroup [60,135].

4 Influence of Oxidative Stress on Ion Channels and Their Role in Epileptogenesis

4.1 Oxidative Modification of Voltage-Gated Na⁺ and Ca²⁺ Channels

Oxidative stress directly contributes to neuronal hyperexcitability through ROS-mediated modification of ion channels, thereby lowering seizure threshold and increasing susceptibility to seizures triggered by stress, sleep deprivation, alcohol, or even occurring spontaneously [45,143]. Voltage-gated ion channels are central regulators of membrane excitability, and their function is highly sensitive to post-translational modifications, including oxidation of critical amino acid residues [144]. In addition to sodium and calcium channels, Kv channels, K_{ATP} channels, and GABA_A receptor-regulated chloride channels may also be functionally altered under oxidative conditions, leading to reduced inhibitory tone and enhanced excitability.

4.2 Mitochondrial Ion Channels under Oxidative Stress

Oxidative modification of Nav channels, which mediate the rapid depolarization phase of the action potential, can disrupt normal inactivation kinetics [145–147]. Under physiological conditions, these channels rapidly inactivate to limit action potential duration and prevent hyperexcitability [93]. ROS-induced

alterations may impair inactivation and promote INaP, partially depolarizing the membrane and shifting it closer to firing threshold. This persistent depolarization increases the likelihood of repetitive and sustained discharges characteristic of epileptic activity [148].

Similarly, oxidation of Cav channels, including L-type, N-type, and P/Q-type subtypes, can alter channel gating or conductance, resulting in excessive Ca^{2+} influx [149,150]. Elevated intracellular Ca^{2+} levels activate degradative enzymes, disrupt synaptic homeostasis, and promote excessive glutamate release, thereby amplifying excitotoxicity [151]. In parallel, oxidative stress affects mitochondrial ion channels that regulate bioenergetic coupling during seizure activity. Oxidative modification of VDAC may alter metabolite exchange and further enhance mitochondrial ROS production [18,25]. Dysregulation of MCU can facilitate excessive Ca^{2+} uptake, whereas impairment of the mitochondrial $\text{Na}^+/\text{Ca}^{2+}$ exchanger (NCLX) limits Ca^{2+} extrusion [25,27]. The resulting Ca^{2+} imbalance promotes pathological opening of the mPTP [71,72], leading to dissipation of membrane potential, impaired ATP synthesis, and increased neuronal vulnerability to paroxysmal discharges [25,35]. Fig. 2 illustrates how ROS-induced alterations at both plasma membrane and mitochondrial levels converge to establish the ionic basis of sustained depolarization and epileptogenesis.

4.3 Molecular Mechanisms: Cysteine Oxidation and Feed-Forward Excitability

At the molecular level, these alterations often involve oxidation of cysteine residues within ion channel subunits [71]. Reactive oxygen species such as H_2O_2 and $\cdot\text{O}^{2-}$ can covalently modify thiol groups, altering channel conformation and function [152]. Such oxidative modifications not only enhance hyperexcitability during seizures but may also contribute to long-term epileptogenesis by persistently altering intrinsic neuronal excitability [45]. ROS generation during seizures further oxidizes ion channels, creating a feed-forward cycle that sustains hyperexcitability and may contribute to status epilepticus and pharmacoresistance [39,153]. Recent studies have begun to demonstrate causality and therapeutic proof-of-concept for these oxidative mechanisms. Genetic ablation of the mitochondrial antioxidant enzyme Mn-SOD in hippocampal neurons in mice produced spontaneous seizures of cortical and hippocampal origin alongside evidence of ATP depletion and impaired neuronal excitability regulation, directly establishing mitochondrial ROS as a causal driver of epileptiform activity rather than a secondary correlate [127,154,155]. Pharmacologically, treatment with the mitochondria-targeted antioxidant MitoQ prior to pilocarpine-induced SE significantly reduced mitochondrial oxidative stress indices and attenuated chronic seizure frequency in the post-SE period [80]. Furthermore, administration of the Nrf2 activator sulforaphane, which upregulates the endogenous antioxidant defense system, reduced ROS production, restored glutathione levels, and attenuated spontaneous seizure frequency in kainate- and pilocarpine-based SE models, reinforcing the mechanistic link between redox regulation and neuronal excitability [156,157]. Beyond protein oxidation, ROS also target polyunsaturated fatty acids within neuronal membranes, initiating lipid peroxidation processes that further destabilize synaptic integrity and propagate epileptogenic signaling.

5 Lipid Peroxidation Damages Synaptic Membranes

Lipid peroxidation is a pathological process characterized by the oxidative degradation of membrane lipids, particularly polyunsaturated fatty acids (PUFAs), which are highly abundant in neuronal membranes. It represents a major mechanism of oxidative injury in epilepsy [41,158]. Synaptic membranes are especially vulnerable due to their high PUFA content, intense metabolic activity, and proximity to mitochondria, a principal source of ROS [42,159]. The process is initiated when ROS, such as the hydroxyl radical ($\cdot\text{OH}$), attack double bonds of PUFAs, abstracting a hydrogen atom and generating a lipid radical. This radical rapidly reacts with molecular oxygen to form a lipid peroxyl radical, propagating a chain reaction

across adjacent membrane lipids. The final products of this cascade include reactive aldehydes such as malondialdehyde and 4-HNE [160], widely used as biomarkers of oxidative stress in epilepsy [161]. Structural disruption of the lipid bilayer alters membrane fluidity, permeability, and microdomain organization, directly affecting membrane-embedded proteins, including neurotransmitter receptors, transporters, and ion channels [162–164]. Changes in membrane biophysical properties can modify the conformation and function of glutamatergic (NMDA and AMPA) and GABAergic receptors, thereby disturbing the balance between excitation and inhibition [46,165]. Fig. 3 illustrates the progressive deterioration of synaptic membrane architecture induced by ROS-driven lipid peroxidation.

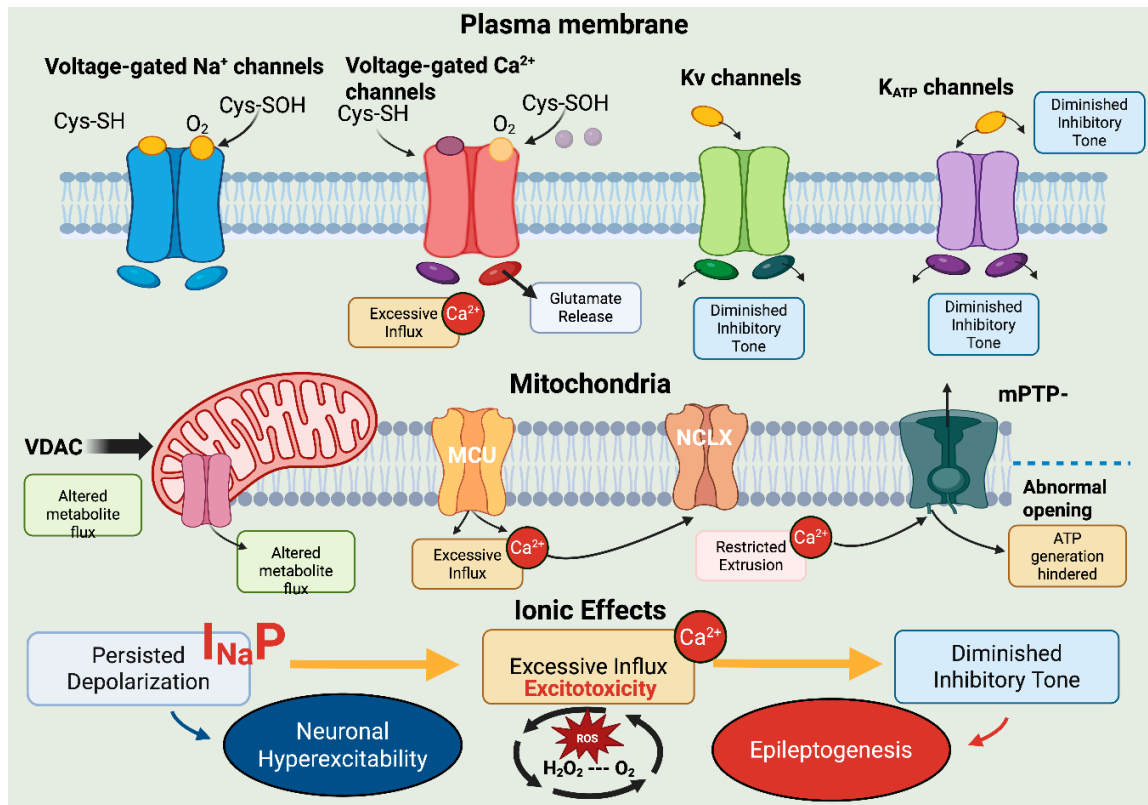


Figure 2: Oxidative stress-mediated ion channel dysfunction and its role in epileptogenesis. The diagram shows the dual-level impact of ROS on neuronal excitability. At the plasma membrane level, oxidation of cysteine residues (Cys-SH, reduced thiol group; Cys-SOH, sulfenic acid) in voltage-gated Na⁺ and Ca²⁺ channels leads to excessive cation influx and persistent depolarization (InaP, persistent sodium current), while oxidative damage to voltage-gated potassium channels (Kv) and ATP-sensitive potassium channels (K_{ATP}) results in diminished inhibitory tone and reduced membrane repolarization capacity. At the mitochondrial level, altered metabolite flux through the voltage-dependent anion channel (VDAC), excessive Ca²⁺ influx via the mitochondrial channel uniporter (MCU), restricted Ca²⁺ extrusion through the mitochondrial sodium-calcium exchanger (NCLX), and abnormal opening of the mitochondrial permeability transition pore (mPTP) collectively compromise ATP production and exacerbate ROS generation, including H₂O₂ and superoxide anion (O²⁻). These ionic effects converge to create a pathological state of neuronal hyperexcitability characterized by excessive Ca²⁺-mediated excitotoxicity and diminished inhibitory tone, ultimately driving the epileptogenic process. Orange arrows indicate pathological cascades; the feedback loop emphasizes the self-perpetuating nature of oxidative stress in epilepsy. Created in BioRender. By Pérez-Villavicencio J. and Villa-Robledo O. under Perez Godinez, D. O., license use authorization (2026) <https://BioRender.com/v5diyyvt>.

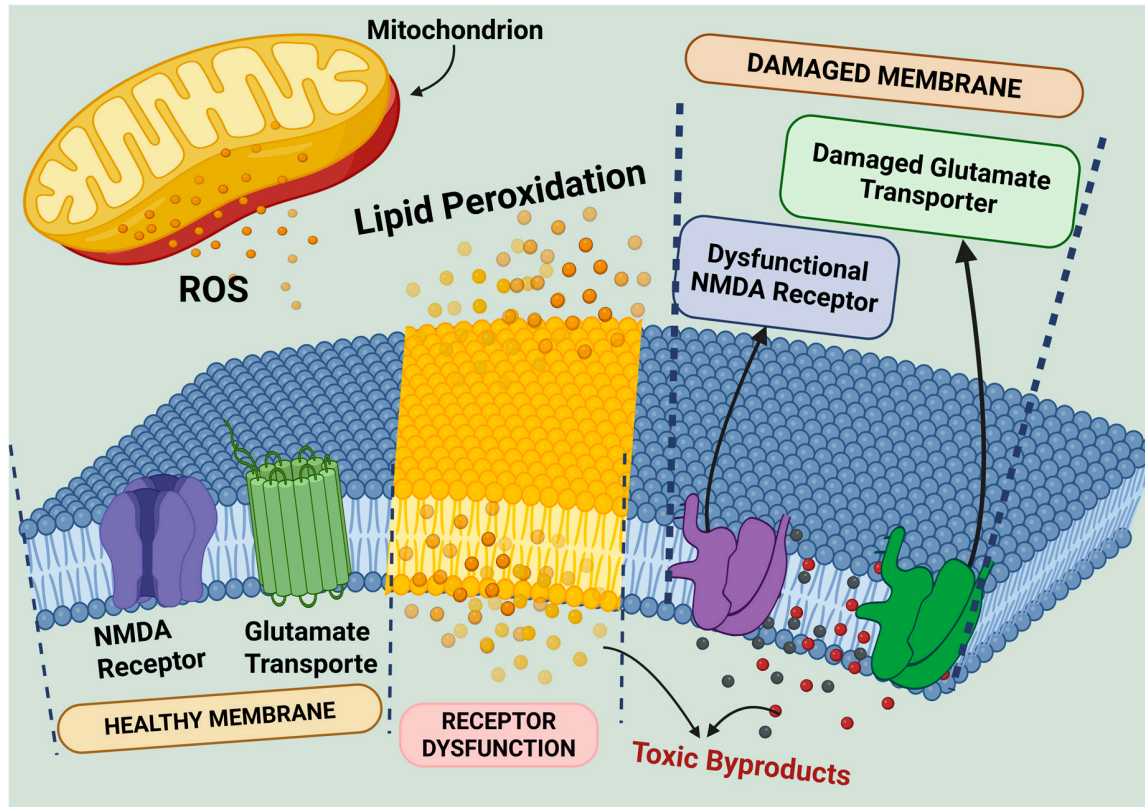


Figure 3: Lipid peroxidation-mediated synaptic membrane damage in epilepsy. The illustration contrasts a healthy synaptic membrane (left) with a membrane undergoing oxidative damage (right). In the healthy state, the lipid bilayer maintains structural integrity, supporting proper function of embedded NMDA receptors and glutamate transporters. Mitochondrial ROS initiation of lipid peroxidation, triggering a chain reaction that degrades polyunsaturated fatty acids within the membrane, resulting in compromised membrane fluidity and permeability. This structural deterioration leads to dysfunctional NMDA receptor conformation, impaired glutamate transporter function, and accumulation of toxic byproducts including reactive aldehydes (4-HNE, malondialdehyde). The damaged membrane domain exhibits disorganized lipid architecture, contributing to uncontrolled glutamate release, impaired neurotransmitter reuptake, and excitotoxicity. Yellow/orange dots represent lipid peroxidation products and ROS propagation; red dots indicate toxic aldehyde byproducts. This membrane pathology represents a critical mechanism driving synaptic dysfunction and epileptogenic hyperexcitability. Created in BioRender. By Pérez-Villavicencio J. and Villa-Robledo O. under Perez Godinez, D. O., license use authorization (2026) <https://BioRender.com/lgmtlr5>.

In epilepsy, such membrane alterations contribute to hyperexcitability through multiple mechanisms [166]. Lipid peroxidation may facilitate excessive glutamate release, impair inhibitory neurotransmitter uptake, and disrupt synaptic vesicle integrity [165,167,168]. Moreover, 4-HNE forms adducts preferentially with histidine, lysine, and cysteine residues on synaptic proteins. Documented targets include: (i) the glutamate transporter GLT-1/EAAT2, in which 4-HNE adduction at Cys373 reduces transport velocity (V_{max}) by up to 60%, thereby impairing glutamate clearance and amplifying excitotoxic cascades [167]; (ii) voltage-gated sodium channels particularly Nav1.6 where 4-HNE adduction impairs fast inactivation and enhances persistent sodium current (I_{NaP}), thereby lowering seizure threshold [147,148]; and (iii) the Na^+/K^+ -ATPase pump, whose oxidative inhibition by 4-HNE disrupts ionic gradient maintenance and promotes sustained membrane depolarization. Collectively, these protein-specific modifications provide a mechanistic substrate linking lipid peroxidation to synaptic hyperexcitability beyond non-specific mem-

brane fluidity changes. Lipid peroxidation has been consistently documented in TLE models, where its extent correlates with neurodegeneration, synaptic reorganization, and disease chronicity [87,127]. Experimental evidence further indicates that antioxidant strategies capable of limiting lipid peroxidation attenuate neuronal damage and reduce seizure frequency, supporting a contributory role of membrane oxidative injury in epileptogenesis [169,170].

Among the membrane proteins particularly vulnerable to lipid peroxidation are GABA transporters, whose oxidative impairment further destabilizes inhibitory neurotransmission and contributes to seizure propagation.

6 Inhibition of GABA Transport by Oxidative Damage

GABA is the principal inhibitory neurotransmitter in the central nervous system and plays a central role in maintaining excitatory-inhibitory balance and seizure suppression [171]. GABA reuptake from the synaptic cleft into neurons and astrocytes is mediated by GABA transporters (GATs), among which GAT-1 represents the predominant subtype implicated in epilepsy [51,172]. Oxidative stress generated during seizures or mitochondrial dysfunction directly affects the structure and function of these membrane transporters [50,52]. GAT proteins contain oxidation-sensitive residues, particularly cysteine thiol groups, that are susceptible to modification by ROS [80,173]. Oxidative modification can induce conformational changes that reduce substrate affinity or decrease maximal transport velocity (V_{max}), thereby impairing GABA reuptake efficiency [174,175]. Acute inhibition of GAT-1 may transiently elevate extracellular GABA levels; however, oxidative damage occurs in a context of widespread synaptic dysfunction, including impaired GABA_A receptor responsiveness and reduced presynaptic GABA availability [176,177]. Under these conditions, dysregulated transporter activity contributes to network instability rather than coordinated enhancement of inhibition. Moreover, GAT-mediated reuptake is essential for replenishing presynaptic GABA pools and maintaining tonic and phasic inhibitory currents [178]. Chronic oxidative impairment of GAT function may therefore compromise neurotransmitter recycling, disrupt astrocyte neuron metabolic coupling, and impair spatial buffering of GABA. This dysfunctional regulation destabilizes inhibitory control within vulnerable regions such as the hippocampus, where precise GABAergic modulation is critical for preventing hyperexcitability and seizure propagation [53,179], as illustrated in Fig. 4. Experimental evidence suggests that protecting GATs from oxidative modification may represent a therapeutic strategy [180]. Although pharmacological GAT-1 inhibition (e.g., tiagabine) can enhance synaptic GABA under controlled conditions [51], oxidative transporter dysfunction occurs alongside receptor impairment, membrane damage, and mitochondrial failure, contributing to a broader cascade of cellular injury [181]. Restoring redox homeostasis and preserving transporter integrity may therefore represent a more physiologically coherent approach to stabilizing inhibitory neurotransmission in epilepsy. Recent experimental evidence supports this translational concept. In a kainate model of TLE, treatment with N-acetylcysteine (NAC), a glutathione precursor and direct antioxidant, preserved GAT-1 surface expression and transport kinetics in hippocampal astrocytes, correlating with reduced extracellular GABA dysregulation and attenuated seizure duration [170]. Similarly, α -lipoic acid administration restored GAT-1 V_{max} in oxidatively challenged hippocampal synaptosomes, an effect dependent on its ability to regenerate reduced glutathione and prevent cysteine thiol oxidation in the transporter [60]. MitoQ, by scavenging mitochondrial ROS at the site of their generation, has been shown to indirectly protect GAT-1 function by reducing the mitochondria-derived oxidative burden in perisynaptic astrocytic processes [38]. These findings collectively indicate that antioxidant strategies preserving GAT-1 redox integrity may represent a viable adjunctive approach to enhancing GABAergic inhibition in oxidative-stress-driven epilepsies.

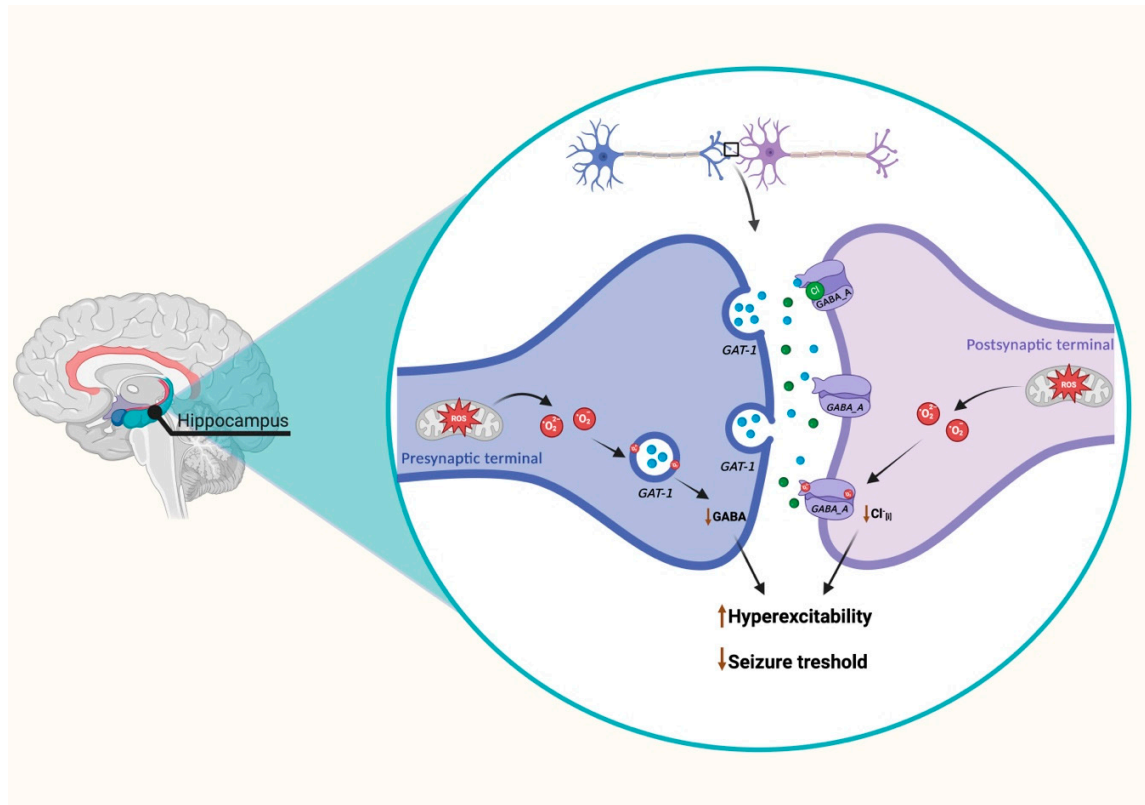


Figure 4: ROS-mediated dysfunction of GABA transport in the hippocampus. Excessive ROS generated during seizures or mitochondrial impairment oxidize redox-sensitive residues in the GABA transporter 1 (GAT-1), reducing reuptake efficiency. Although partial transporter inhibition may transiently elevate extracellular GABA, concurrent oxidative impairment of GABA_A receptors, presynaptic GABA synthesis, and mitochondrial bioenergetics results in ineffective inhibitory signaling. Disrupted GABA recycling and spatial buffering destabilize excitatory–inhibitory balance within hippocampal circuits, promoting network hyperexcitability and seizure propagation. (↑): increasing; (↓): decreasing. Created in BioRender. By Villa-Robledo O. and Pérez-Villavicencio J. under Perez Godinez, D. O., license use authorization. (2026) <https://BioRender.com/6mg6c3y>.

7 Ion Channel Genes and Their Function in Hyperexcitability in Channelopathies

While oxidative mechanisms significantly contribute to acquired and progressive epileptogenic processes, a substantial proportion of epilepsies arises from primary genetic alterations in ion channel genes. Advances in molecular genetics have enabled the identification of pathogenic variants encoding sodium, potassium, calcium, and chloride channels, as well as associated receptor subunits, establishing channelopathies as a major category of monogenic epilepsies characterized by intrinsic neuronal hyperexcitability [182–184]. Understanding the functional consequences of these mutations is essential for the development of precision-based therapeutic strategies.

7.1 Voltage-Gated Sodium Channels (SCN Family)

Voltage-gated sodium channels (Nav) are fundamental for action potential initiation and propagation. Mutations in SCN genes represent one of the most prevalent causes of epileptic channelopathies [95]. SCN1A (Nav1.1) is the gene most frequently associated with severe epileptic syndromes, including Dravet syndrome and generalized epilepsy with febrile seizures plus (GEFS⁺) [96]. In Dravet syndrome, loss-of-

function mutations preferentially impair inhibitory interneurons, leading to network disinhibition and hyperexcitability [97,98]. Clinical severity correlates with the degree and location of channel dysfunction, with pore-region mutations generally producing more severe phenotypes than variants outside critical functional domains [99]. SCN2A (Nav1.2) exemplifies genotype-phenotype complexity, as both gain-of-function (GOF) and loss-of-function (LOF) variants produce epilepsy with distinct temporal and clinical profiles. GOF mutations are typically associated with neonatal or early-onset epileptic encephalopathies, whereas LOF variants may present later in development, underscoring the importance of functional characterization for therapeutic decision-making [100]. SCN8A (Nav1.6) is frequently affected by *de novo* GOF mutations that cause early-onset developmental and epileptic encephalopathy with poor prognosis. Additionally, SCN8A variants may act as genetic modifiers in Dravet syndrome [101,102]. Mutations in SCN1B, encoding the $\beta 1$ auxiliary subunit, further illustrate how alterations in channel regulation, not only pore-forming α subunits, can contribute to febrile seizures and idiopathic epilepsy [103].

7.2 Voltage-Gated Potassium Channels (KCNQ and KCNA Genes)

Potassium (Kv) channels are critical for membrane repolarization and stabilization of resting membrane potential, thereby constraining repetitive firing. Loss-of-function mutations reduce outward potassium currents and favor hyperexcitability [185,186]. KCNQ2 and KCNQ3 encode Kv7.2 and Kv7.3 subunits responsible for the M-current, a low-threshold potassium conductance that suppresses repetitive discharges. Variants in these genes are classically associated with benign familial neonatal seizures (BFNS); however, more severe KCNQ2 mutations can produce early-onset developmental and epileptic encephalopathy, indicating that the magnitude of channel dysfunction determines clinical severity [104,105]. KCNA1 (Kv1.1) has been associated with temporal lobe epilepsy (TLE) and episodic ataxia, whereas KCNT1, encoding sodium-activated potassium (Slack) channels, is implicated in malignant migrating focal seizures of infancy [106–108]. These examples highlight the diverse and context-dependent roles of potassium channels in regulating network excitability.

7.3 Voltage-Gated Calcium Channels (CACNA Genes)

Voltage-gated calcium channels (Cav) regulate calcium influx, thereby influencing neurotransmitter release and synaptic plasticity. Both GOF and LOF mutations may produce epileptic phenotypes. CACNA1A, encoding the P/Q-type channel Cav2.1, is a pleiotropic gene: GOF variants are linked to familial hemiplegic migraine and epilepsy, whereas LOF mutations cause episodic ataxia type 2 [109–111]. CACNA1H (Cav3.2), a T-type channel, has been strongly associated with idiopathic generalized epilepsies, particularly childhood absence epilepsy. GOF mutations enhance low-threshold T-type currents that contribute to the generation of 3 Hz spike-wave discharges characteristic of absence seizures [112,113]. CACNA1E (Cav2.3, R-type channel) is associated with developmental and epileptic encephalopathy presenting in early infancy with refractory seizures [114]. The CACNB4 gene, encoding the $\beta 4$ auxiliary subunit, has been linked to idiopathic generalized epilepsy and may function as a modifier gene in Dravet syndrome [115]. Collectively, these channelopathies demonstrate how primary alterations in ion channel structure or regulation can intrinsically destabilize neuronal networks. Notably, although these disorders originate from genetic mutations, downstream mechanisms, including oxidative stress, mitochondrial dysfunction, and synaptic membrane instability, may further amplify hyperexcitability, suggesting convergence between genetic and acquired epileptogenic pathways. In addition to voltage-gated cation channels, genetic alterations affecting inhibitory neurotransmission, particularly GABA receptors and chloride channels, represent a critical mechanism underlying epileptic hyperexcitability.

8 GABA Receptors and Chloride Channels (GABR and CLCN Genes)

Inhibitory neurotransmission in the central nervous system is primarily mediated by GABA, which activates GABA_A receptors to permit chloride (Cl⁻) influx, resulting in membrane hyperpolarization and suppression of neuronal firing [177]. Genetic mutations affecting GABA_A receptor subunits or chloride channels compromise this inhibitory mechanism and shift network balance toward hyperexcitability. GABRG2, encoding the $\gamma 2$ subunit of the GABA_A receptor, has been associated with a broad phenotypic spectrum ranging from febrile seizures to severe developmental and epileptic encephalopathies, including Dravet syndrome [116]. Most pathogenic variants result in loss-of-function, reducing receptor surface expression or channel conductance and thereby weakening inhibitory transmission [117]. Similarly, mutations in GABRA1 ($\alpha 1$ subunit) and GABRB2/GABRB3 ($\beta 2/\beta 3$ subunits) are implicated in epileptic encephalopathies, including Dravet syndrome. Structural deletions involving GABRA1 may produce epilepsy accompanied by visual impairment, highlighting the pleiotropic consequences of receptor dysfunction [118].

Beyond receptor subunits, chloride homeostasis is critically regulated by voltage-gated chloride channels. CLCN2 (CIC-2) has been associated with idiopathic generalized epilepsies such as childhood absence epilepsy, juvenile absence epilepsy, and juvenile myoclonic epilepsy, although the strength of this genetic association remains debated given inconsistencies in early family-based studies [20,187]. Loss-of-function mutations disrupt intracellular chloride balance, attenuating the hyperpolarizing effect of GABA and thereby reducing inhibitory efficacy [20,119]. CLCN4, an X-linked chloride channel gene, is linked to epileptic encephalopathy with intellectual disability affecting both sexes [120,121].

Collectively, mutations in GABR and CLCN genes illustrate how impaired inhibitory signaling, whether through receptor dysfunction or altered chloride gradients, constitutes a central mechanism in epileptic channelopathies. Importantly, the convergence between genetic and acquired mechanisms of GABAergic impairment deserves explicit elaboration. In patients carrying GABRG2 or GABRA1 loss-of-function variants, seizure activity *per se* generates a secondary oxidative environment in which ROS directly modify GABA_A receptor subunits, particularly through oxidation of redox-sensitive cysteine residues in the channel lining M2 domain, further reducing chloride conductance and compounding the genetic deficit [116,117]. Mitochondrial dysfunction in this context may further impair GABAergic inhibition through at least three non-redundant mechanisms: (i) ATP depletion compromises the chloride co-transporters KCC2 and NKCC1, which depend on the Na⁺/K⁺-ATPase to maintain the transmembrane chloride gradient necessary for hyperpolarizing GABA responses a mechanism particularly relevant in neonatal and developing networks [20,119]; (ii) mitochondria-derived ROS oxidize GAT-1, reducing presynaptic GABA recycling and depleting available inhibitory neurotransmitter pools; and (iii) elevated cytosolic calcium secondary to mPTP opening and impaired NCLX function activates calcineurin, which dephosphorylates and internalizes GABA_A receptors, reducing their surface density. This mechanistic bridge between genetic channelopathy and acquired metabolic-oxidative injury has therapeutic implications: patients with genetic GABAergic epilepsies may particularly benefit from adjunctive antioxidant or mitochondrial protective strategies that prevent the secondary oxidative amplification of their primary channel deficit.

9 Other Relevant Channels and Genes

Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels generate the I_h current, a depolarizing inward conductance activated at hyperpolarized membrane potential and modulated by cyclic nucleotides [131,137]. I_h contributes to the stabilization of resting membrane potential, dendritic integration, and rhythmic oscillatory activity, particularly within thalamic relay neurons where it acts in concert

with T-type Ca^{2+} channels to determine subthreshold oscillatory properties linked to thalamocortical rhythms [131,133,137].

Pathogenic variants in HCN1 and HCN2 disrupt this finely tuned pacemaker current, leading to enhanced neuronal synchronization and early-onset developmental and epileptic encephalopathies [122–124]. Dysfunction of HCN channels, therefore, represents a distinct mechanism of hyperexcitability, not through impaired inhibition or excessive depolarizing currents *per se*, but through altered intrinsic rhythmicity and network resonance. Beyond ion channels, dysregulation of intracellular signaling cascades also contributes to epileptogenesis. The mechanistic target of rapamycin mTOR pathway is a master regulator of cell growth, protein synthesis, synaptogenesis, and metabolic homeostasis. Mutations affecting key components of this pathway, including DEPDC5, TSC1, and TSC2, result in constitutive pathway activation (mTORopathies) and are strongly associated with drug-resistant focal epilepsies and cortical malformations [188–190]. Importantly, mTOR signaling is sensitive to metabolic and redox states. Oxidative stress and mitochondrial dysfunction can activate mTOR through redox-dependent modulation of upstream regulators, creating a bidirectional link between metabolic impairment and neuronal hyperexcitability [191,192]. The molecular specificity of this redox metabolic channel link warrants elaboration. Regarding HCN channels, oxidative stress decreases cAMP production through inhibition of adenylyl cyclase, reducing the cyclic nucleotide-dependent facilitation of HCN channel opening (I_h). This shifts neuronal resting membrane potential toward hyperpolarization but paradoxically destabilizes network oscillatory dynamics by impairing the dendritic integration function of I_h, contributing to thalamocortical dysrhythmia [122,124]. Additionally, direct ROS-mediated oxidation of HCN1/HCN2 cysteine residues alters voltage-dependent gating, reducing current amplitude and kinetics. Regarding mTOR pathway activation, mitochondrial ROS, particularly H_2O_2 , oxidize and inactivate PTEN (a phosphatase that normally restrains PI3K/Akt signaling upstream of mTOR) through oxidation of its catalytic cysteine (Cys124), thereby disinhibiting Akt and sustaining mTORC1 activation independently of growth factor signaling [191,193]. Simultaneously, ROS-mediated oxidative inactivation of TSC2 (tuberin) prevents its GAP activity toward Rheb, maintaining Rheb in the GTP-bound state that constitutively activates mTORC1 [194]. This dual redox mechanism (acting on both PTEN and TSC2) explains how metabolic impairment can produce robust and sustained mTORC1 hyperactivation even in the absence of primary genetic pathway mutations, creating an acquired mTORopathy like state in the epileptic brain. Thus, mTORopathies exemplify how genetic susceptibility and acquired oxidative stress converge on shared intracellular pathways that promote aberrant synaptic plasticity and epileptic network remodeling. Together, these diverse genetic and metabolic alterations underscore a central principle, epilepsy emerges not from isolated molecular defects, but from convergent disruptions in excitability control across ionic, synaptic, and intracellular signaling domains.

10 Oxidative Stress and the mTORC1 Pathway in Epilepsy

Oxidative stress is a potent upstream activator of the mechanistic target of rapamycin complex 1 (mTORC1), a master regulator of cellular growth, metabolism, and synaptic remodeling that is highly responsive to energy and redox status [188,195]. Aberrant mTORC1 hyperactivation represents a central pathogenic mechanism in several epilepsy syndromes, particularly those associated with cortical malformations and pharmacoresistance [196]. Mitochondrial dysfunction plays a pivotal role in this process. Excessive production of ROS secondary to excitotoxicity and impaired oxidative phosphorylation leads to redox-dependent oxidation and functional inactivation of TSC2, thereby relieving its inhibitory control over the small GTPase Rheb and sustaining mTORC1 activation [193,194]. This mechanism establishes oxidative stress not merely as a consequence of seizures, but as an active driver of epileptogenesis through

persistent metabolic signaling dysregulation. Sustained mTORC1 activation enhances cap-dependent protein synthesis, including proteins involved in synaptic plasticity and glutamatergic signaling, such as AMPA receptor subunits, thereby increasing synaptic density and excitatory transmission [197,198]. Additionally, mTORC1 influences neuronal morphology through p70S6K1-dependent actin remodeling that drives somatic hypertrophy, megaloneuron formation, and aberrant axonal sprouting establishing recurrent excitatory circuits hallmarks of focal cortical dysplasia type II and tuberous sclerosis complex [199,200]. At the ion channel level, mTORC1 hyperactivation upregulates Nav1.1 and Nav1.2 surface expression while suppressing Kv1.1 and Kv4.2, collectively lowering action potential threshold and tilting intrinsic neuronal excitability toward sustained depolarization [195,201].

Importantly, mTORC1 signaling also modulates ion channel expression and kinetics. Hyperactivation has been associated with altered regulation of voltage-gated sodium channels (Nav1.1/Nav1.2), potassium channels (Kv1.1, Kv4.2), T- and L-type calcium channels, and ROS-sensitive TRP channels, collectively increasing intrinsic excitability and lowering seizure threshold [195,201]. Recurrent seizures further exacerbate Ca^{2+} influx, intensifying mitochondrial dysfunction and reinforcing a self-perpetuating ROS mTORC1 feedback loop (Fig. 5) [202,203].

Quantitative differences in oxidative stress biomarkers and mitochondrial dysfunction parameters, TLE and primary generalized epilepsy (PGE) are summarized in Table 2. These data highlight the predominantly focal and severe mitochondrial impairment observed in TLE compared to the more diffuse and systemic alterations characteristic of PGE, with important implications for targeted therapeutic strategies.

Table 2: Oxidative Stress Biomarkers and Mitochondrial Dysfunction in Different Epilepsy Types.

Biomarker/Feature	Temporal Lobe Epilepsy (TLE)	Primary Generalized Epilepsy (PGE)	Measurement Method	Key References
Complex I activity	Highly increased, >3-fold (hippocampus, focal)	↓ (mild, systemic)	Spectrophotometry; oxygen consumption	[4,11,12,32]
Complex III activity	Moderately decreased (focal limbic structures)	No significant change/↓ (variable)	Spectrophotometry; cytochrome c reduction	[16,127]
ATP levels	Severely decreased, >50% reduction (severe depletion)	↓ (moderate reduction)	Luminometry; bioluminescence assay	[19,27,34]
Mitochondrial membrane potential ($\Delta\psi\text{m}$)	Moderately decreased (significant depolarization)	No significant change/↓ (mild or absent)	JC-1 staining; TMRM fluorescence	[25]
Basal ROS levels	Highly increased, >3-fold (hippocampus, localized)	↑ (CSF/blood, systemic)	DCF-DA; MitoSOX; EPR spectroscopy	[19,37,70]
Malondialdehyde (MDA)	Highly increased, >3-fold (tissue: 3–5× control)	↑ (plasma: 1.5–2× control)	TBARS assay; HPLC	[21,30,87]
4-HNE (lipid peroxidation)	Highly increased, >3-fold (synaptic membranes)	↑ (moderate elevation)	Immunohistochemistry; ELISA	[87,160]
Protein carbonylation	Moderately increased, 2–3 fold (oxidized proteins)	↑ (mild oxidation)	DNPH assay; Western blot; oxyblot	[30,45]
SOD activity	Moderately decreased (reduced antioxidant defense)	No significant change/↓ (preserved or mildly reduced)	Activity assay (xanthine oxidase method)	[87]
Glutathione (GSH)	Severely decreased, >50% reduction (severe depletion)	↓ (moderate reduction)	HPLC; Ellman's reagent; fluorometric assay	[30,58]

Table 2: Cont.

Biomarker/Feature	Temporal Lobe Epilepsy (TLE)	Primary Generalized Epilepsy (PGE)	Measurement Method	Key References
Catalase activity	Mildly decreased (impaired H ₂ O ₂ clearance)	No significant change (normal)	Spectrophotometric assay (H ₂ O ₂ decomposition)	[87]
[Ca ²⁺] mitochondrial	Highly increased, >3-fold (calcium overload)	↑ (elevated)	Fura-2; Rhod-2; X-Rhod-1 fluorescence	[25,34,71,72]
[Ca ²⁺] cytosolic	Moderately increased, 2–3-fold (persistent elevation)	↑ (transient elevation)	Calcium imaging (Fluo-4, GCaMP)	[70,74]
mPTP opening propensity	Highly increased, >3-fold (increased susceptibility)	↑ (moderately increased)	Calcein-cobalt quenching; Ca ²⁺ retention capacity	[25]
Tissue source availability	Surgical resection (hippocampus)	N/A (no surgery)	Biopsy; resected tissue analysis	[21,30,88]
CSF biomarkers	Elevated MDA, protein carbonyls, lactate/pyruvate ratio	Moderate MDA elevation	Biochemical assays on CSF samples	[30,86]
Blood/plasma biomarkers	Moderate elevation (systemic spillover)	Detectable elevation (primary systemic)	Serum/plasma biochemical analysis	[30,58,86]

Note: Comparison of quantitative alterations in mitochondrial bioenergetics and oxidative stress markers between focal (TLE) and generalized (PGE) epilepsies. TLE is characterized by severe, localized mitochondrial impairment, particularly in hippocampal structures with marked reductions in electron transport chain activity and ATP levels, accompanied by pronounced lipid peroxidation (MDA, 4-HNE accumulation), antioxidant depletion (SOD, GSH), Ca²⁺ overload, and increased mPTP susceptibility. In contrast, PGE exhibits milder and more diffuse alterations, predominantly detected in systemic compartments (CSF and plasma). These differences highlight distinct pathophysiological patterns, with focal bioenergetic failure in TLE versus systemic redox imbalance in PGE, carrying implications for targeted therapeutic strategies. Upward arrows (↑) indicate increased expression, activity, or upregulation; downward arrows (↓) indicate decreased expression, activity, or downregulation. Abbreviations: ROS, reactive oxygen species; MDA, malondialdehyde; 4-HNE, 4-hydroxynonenal; SOD, superoxide dismutase; GSH, glutathione; mPTP, mitochondrial permeability transition pore; CSF, cerebrospinal fluid; ATP, adenosine triphosphate; Δψ_m, mitochondrial membrane potential; TBARS, thiobarbituric acid reactive substances; HPLC, high-performance liquid chromatography; DNP, 2,4-dinitrophenylhydrazine; DCF-DA, 2',7'-dichlorodihydrofluorescein diacetate; TMRM, tetramethylrhodamine methyl ester; EPR, electron paramagnetic resonance; ELISA, enzyme-linked immunosorbent assay; N/A, not applicable.

The recognition of mTORC1 hyperactivation as a redox-sensitive driver of epileptogenesis has supported the clinical use of mTOR inhibitors such as rapamycin and everolimus, which suppress mTORC1 activity through FKBP12-dependent mechanisms [204–206]. Beyond seizure reduction, these agents indirectly attenuate oxidative stress, normalize mitochondrial function, and restore autophagic and mitophagic flux, thereby reducing the accumulation of dysfunctional mitochondria the primary intracellular source of ROS [192,207–209]. mTORC1 inhibition also interacts with antioxidant regulatory pathways, including Nrf2-mediated transcriptional control of detoxifying enzymes, further enhancing cellular resilience to oxidative damage [210]. At the electrophysiological level, normalization of mTORC1 activity stabilizes neuronal membranes, downregulates aberrant Nav and Cav channel expression, restores Kv-mediated repolarization currents, and limits pathological activation of ROS-sensitive TRP channels (TRPM2, TRPV1, TRPC5), reducing Ca²⁺-dependent excitotoxic signaling [192,211]. Clinically, everolimus reduces seizure frequency and improves cognitive outcomes in tuberous sclerosis complex (TSC), while rapamycin attenuates neuroinflammation and oxidative stress in temporal lobe epilepsy models, supporting a disease-modifying role beyond symptomatic seizure control [212,213]. Collectively, these findings position mTOR inhibitors as

metabolic modulators capable of restoring mitochondrial and ionic homeostasis, interrupting the oxidative stress mTORC1 cycle, and addressing a core pathogenic mechanism in epilepsy. The molecular interplay between oxidative stress, mTORC1 hyperactivation, and pharmacological inhibition is schematically depicted in Fig. 5. In experimental TSC models, everolimus restores potassium conductance and reduces aberrant calcium permeability, thereby limiting Ca^{2+} -dependent signaling cascades such as CaMKII and calcineurin that contribute to epileptogenic plasticity [212,214,215].

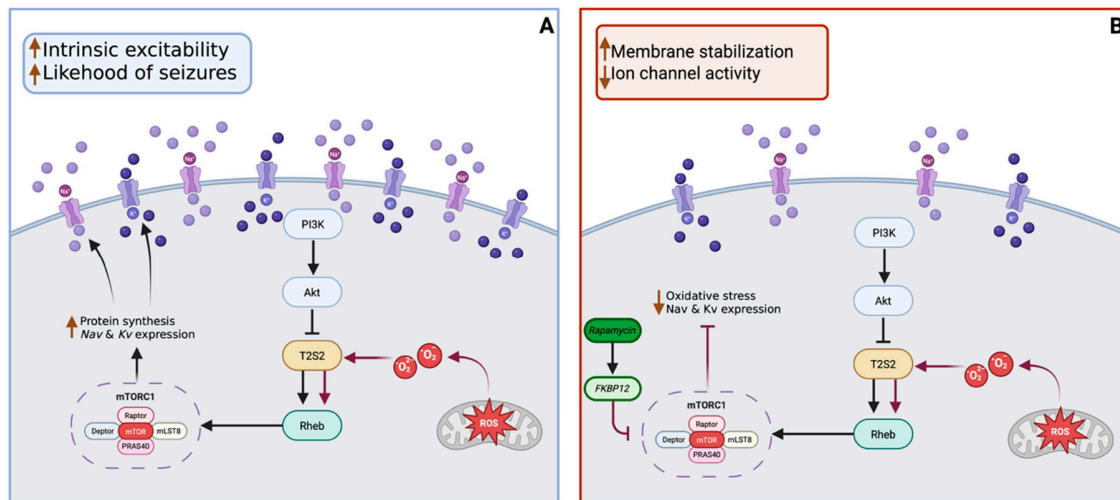


Figure 5: Rapamycin-mediated inhibition of the PI3K/Akt/mTORC1 pathway reduces neuronal excitability. (A): This panel illustrates the interaction between mitochondrial dysfunction and mTORC1 hyperactivation in epilepsy. Impaired mitochondria generate excessive ROS, which oxidize and functionally inactivate TSC2, relieving its inhibitory control over Rheb. Persistent Rheb activation sustains mTORC1 signaling, promoting increased protein synthesis, synaptic remodeling, and overexpression of excitability-related proteins, including sodium (Nav1.1/Nav1.2) and potassium (Kv1.1/Kv4.2) channels. These alterations enhance intrinsic neuronal excitability, facilitate aberrant firing synchronization, and lower the seizure threshold. Recurrent seizures further increase Ca^{2+} influx and mitochondrial stress, reinforcing a self-perpetuating ROS–mTORC1 cycle that contributes to epileptogenesis. (B): In contrast to panel A, this panel depicts the inhibitory effect of rapamycin on mTORC1. Rapamycin binds to FKBP12, forming a complex that directly inhibits mTORC1 activity. As a result, excessive protein synthesis and ion channel overexpression are reduced, mitochondrial ROS production decreases, and oxidative balance is restored. By normalizing mitochondrial function, rapamycin stabilizes neuronal membranes, regulates Nav and Kv channel activity, and limits Ca^{2+} -dependent pro-epileptogenic signaling pathways. Overall, mTOR inhibition interrupts the oxidative stress mTORC1 feedback loop, reducing neuronal hyperexcitability and seizure susceptibility. Upward arrows (↑) indicate increased expression, activity, or upregulation; downward arrows (↓) indicate decreased expression, activity, or downregulation. Created in BioRender. By Pérez-Villavicencio J. and Villa-Robledo O. under Perez Godinez, D. O., license use authorization (2026) <https://BioRender.com/pwq5tdy>.

11 Conclusions and Future Perspectives

This review highlights the intricate interplay between mitochondrial dysfunction, oxidative stress, and ion channel dysregulation as convergent mechanisms underlying epileptogenesis. Rather than acting as isolated pathological processes, these alterations form a self-reinforcing network in which impaired bioenergetics, excessive ROS production, and aberrant ion channel signaling collectively destabilize neuronal excitability. oxidative stress emerges as a central mediator linking metabolic failure to electrical dysfunction. When antioxidant defenses are overwhelmed, redox-dependent modifications of ion channels,

transporters, and signaling pathways including the mTORC1 cascade promote sustained hyperexcitability. Importantly, these mechanisms differ between epilepsy subtypes. Focal epilepsies such as temporal TLE are characterized by pronounced, region-specific mitochondrial impairment and severe oxidative damage, whereas PGE exhibit more diffuse and systemic redox alterations. These distinctions carry important implications for precision therapeutic strategies. Although mitochondrial dysfunction is unlikely to represent the sole trigger of neuronal hyperexcitability, mounting evidence supports its role as a critical amplifier of seizure susceptibility through disrupted calcium homeostasis, ATP depletion, and ROS-mediated signaling [27,35,153]. Genetic channelopathies, mTOR pathway mutations, and acquired metabolic stress converge on common downstream pathways that ultimately shift the excitatory-inhibitory balance toward pathological synchronization [166,182,189]. Therapeutic strategies targeting these interconnected mechanisms are summarized in Table 3. Current approaches include mitochondrial protectants, antioxidant compounds, ion channel modulators, and mTOR inhibitors [194]. While agents such as everolimus have demonstrated disease-modifying effects in TSC-associated epilepsy [213–215], most mitochondrial-targeted therapies remain in preclinical or early translational stages [205,206]. Challenges such as blood–brain barrier permeability, bioavailability, optimal dosing, and patient stratification continue to limit clinical translation [204].

Table 3: Therapeutic Strategies Targeting Mitochondrial Dysfunction and Ion Channels in Epilepsy: Preclinical and Clinical Evidence.

Therapeutic Strategy	Primary Target	Mechanism of Action	Development Stage	Key Evidence	Key References
Coenzyme Q10 (CoQ10)	ETC complexes I/III	Electron carrier; mitochondrial antioxidant; enhances ATP synthesis	Clinical trials (Phase II/III)	↓ Seizure frequency in refractory epilepsy; improved mitochondrial function	[60,80]
MitoQ (mitoquinone)	Mitochondrial matrix	Targeted mitochondrial antioxidant; ROS scavenger; lipophilic cation	Preclinical (animal models)	Neuroprotection in status epilepticus models; ↓ oxidative damage	[38,80]
Cyclosporin A	mPTP	Inhibits mPTP opening; prevents Ca ²⁺ -induced permeability transition	Preclinical	↓ Mitochondrial damage preserves Δψ _m ; neuroprotection	[25]
α-Lipoic acid	General antioxidant	ROS scavenger; regenerates GSH and vitamins C/E; metal chelation	Clinical trials (adjunct)	Adjunct therapy; ↓ oxidative stress markers	[60]
Vitamin E (α-tocopherol)	Lipid membranes	Lipid peroxidation inhibition; membrane stabilization	Clinical trials	Mixed results in pediatric epilepsy; antioxidant effects	[169]
N-acetylcysteine (NAC)	GSH synthesis	GSH precursor; direct ROS scavenger; anti-inflammatory	Clinical trials	↓ Oxidative stress; improved antioxidant defense	[170]
Curcumin	Nrf2 pathway	↑ Antioxidant enzyme expression (SOD, catalase, GPx); anti-inflammatory	Preclinical (<i>in vivo</i>)	Anti-epileptogenic in TLE models; ↓ neuroinflammation	[213]

Table 3: Cont.

Therapeutic Strategy	Primary Target	Mechanism of Action	Development Stage	Key Evidence	Key References
Resveratrol	SIRT1/Nrf2 pathways	Promotes mitochondrial biogenesis; activates antioxidant pathways	Preclinical	Neuroprotection; ↓ oxidative stress; anti-apoptotic	[60,143]
Retigabine (ezogabine)	Kv7.2/7.3 (KCNQ2/3)	M-current activation; neuronal hyperpolarization	FDA approved (withdrawn 2017)	Effective anticonvulsant; withdrawn due to adverse effects (retinal, skin)	[80,81]
Novel Kv7 activators	Kv7 channels	Enhanced Kv7 opening; improved selectivity and stability	Preclinical/Phase II	Promising efficacy; better safety profile than retigabine	[81]
Tiagabine	GAT-1	GABA reuptake inhibition; ↑ synaptic GABA concentration	FDA approved	Adjunct therapy in focal epilepsy; enhances GABAergic inhibition	[51,180]
Rapamycin (sirolimus)	mTORC1	FKBP12 binding; mTORC1 inhibition; ↑ autophagy/mitophagy	Preclinical + clinical (TSC)	Anti-epileptogenic; ↓ seizures in TSC; ↓ neuroinflammation	[204,213]
Everolimus	mTORC1	mTORC1 inhibition; ↑ autophagy; normalizes protein synthesis	FDA approved (TSC + SEGA)	↓ Seizure frequency in TSC; ↑ cognitive function; disease-modifying	[205,206,212, 214,215]
Rapamycin + Curcumin	mTOR + Nrf2/oxidative stress	Synergistic: anti-inflammatory + antioxidant + autophagy induction	Preclinical (TLE models)	Superior efficacy vs. monotherapy; ↓ oxidative stress + neuroinflammation	[213]
CoQ10 + Antiepileptic drugs	Mitochondria + ion channels	Dual mechanism: bioenergetic support + seizure suppression	Clinical (small trials)	↑ Efficacy vs. AED alone; adjunctive benefit	[60]
Ellagic acid + Allopurinol	Xanthine oxidase + ROS	↓ H ₂ O ₂ production; ROS scavenging; uric acid reduction	Preclinical (<i>in vivo</i>)	↓ Epileptiform activity; ↓ astrogliosis post-status epilepticus	[60]

Note: This table summarizes pharmacological approaches ranging from preclinical agents to FDA-approved therapies. Strategies are grouped into four mechanistic categories: (1) mitochondrial protectants (e.g., CoQ10, MitoQ, cyclosporin A, α -lipoic acid) that preserve electron transport chain function, prevent mPTP opening, and support ATP production; (2) antioxidants (vitamin E, NAC, curcumin, resveratrol) that reduce ROS and enhance endogenous defense pathways such as Nrf2; (3) ion channel modulators (retigabine, Kv7 activators, tiagabine) that restore excitatory–inhibitory balance; and (4) mTORC1 inhibitors (rapamycin, everolimus) that normalize protein synthesis and promote autophagy/mitophagy. Everolimus represents a clinically validated example in tuberous sclerosis complex–associated epilepsy. Combination and precision-based strategies targeting metabolic and electrophysiological dysfunction are emerging, although clinical translation remains limited by pharmacokinetic and patient-selection challenges. Upward arrows (↑) indicate increased expression, activity, or upregulation; downward arrows (↓) indicate decreased expression, activity, or downregulation. Abbreviations: ETC, electron transport chain; mPTP, mitochondrial permeability transition pore; ROS, reactive oxygen species; GSH, glutathione; Nrf2, nuclear factor erythroid 2-related factor 2; SIRT1, sirtuin 1; SOD, superoxide dismutase; GPx, glutathione peroxidase; Kv7, voltage-gated potassium channel subfamily 7; KCNQ, potassium voltage-gated channel subfamily Q; M-current, muscarinic receptor-suppressed potassium current; GAT-1, GABA transporter 1; GABA, gamma-aminobutyric acid; mTORC1, mammalian target of rapamycin complex 1; FKBP12, FK506-binding protein 12; TSC, tuberous sclerosis complex; SEGA, subependymal giant cell astrocytoma; TLE, temporal lobe epilepsy; AED, antiepileptic drug; FDA, Food and Drug Administration; $\Delta\psi_m$, mitochondrial membrane potential; ATP, adenosine triphosphate.

Future research should prioritize biomarker-guided therapeutic selection, development of multi-target combination regimens, and deeper characterization of cell-type–specific mitochondrial dynamics. Notably,

the contribution of glial mitochondrial dysfunction and redox signaling remains incompletely understood. Given the regional and cellular heterogeneity of brain metabolism, delineating neuron–glial metabolic interactions may reveal subtype-specific vulnerabilities and novel intervention points. Advancing toward a systems-level understanding of redox–metabolic–electrical coupling will be essential for transforming epilepsy treatment from symptomatic seizure control to mechanism-based disease modification.

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Abbreviations

4-HNE	4-hydroxynonenal
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ATP	Adenosine triphosphate
BDNF	Brain-derived neurotrophic factor
BFNC	Benign familial neonatal convulsions
CA1	Cornu ammonis 1
CA2	Cornu ammonis 2
CAE	Childhood absence epilepsy
CaMKII	Calcium/calmodulin-dependent protein kinase II
Cav	Voltage-gated calcium channel
ClC	Chloride channel
CNS	Central nervous system
CoQ10	Coenzyme Q10
CREB	cAMP response element-binding protein
CSF	Cerebrospinal fluid
Cys-SH	Cysteine thiol group
Cys-SOH	Cysteine sulfenic acid
DCF-DA	2',7'-dichlorodihydrofluorescein diacetate
DEE	Developmental and epileptic encephalopathy
DNPH	2,4-dinitrophenylhydrazine
EA	Episodic ataxia
EEG	Electroencephalographic/Electroencephalogram
EIEE	Early infantile epileptic encephalopathy
ELISA	Enzyme-linked immunosorbent assay
EPR	Electron paramagnetic resonance
ETC	Electron transport chain
FDA	Food and Drug Administration
FHM	Familial hemiplegic migraine
FKBP12	FK506-binding protein 12

GABA	Gamma-aminobutyric acid
GABA _A	Gamma-aminobutyric acid type A receptor
GAT	GABA transporter
GAT-1	GABA transporter 1
GEFS+	Generalized epilepsy with febrile seizures plus
GOF	Gain of function
GPx	Glutathione peroxidase
GSH	Glutathione
H ₂ O ₂	Hydrogen peroxide
HCN	Hyperpolarization-activated cyclic nucleotide-gated channel
HPLC	High-performance liquid chromatography
I _h	Hyperpolarization-activated current
IGE	Idiopathic generalized epilepsy
INaP	Persistent sodium current
JAE	Juvenile absence epilepsy
JME	Juvenile myoclonic epilepsy
K _{ATP}	ATP-sensitive potassium channel
KCNQ	Potassium voltage-gated channel subfamily Q
Kv	Voltage-gated potassium channel
LOF	Loss of function
MCU	Mitochondrial calcium uniporter
MDA	Malondialdehyde
mitoK _{ATP}	Mitochondrial ATP-dependent potassium channel
MitoQ	Mitoquinone
mPTP	Mitochondrial permeability transition pore
mTOR	Mammalian target of rapamycin
mTORC1	Mammalian target of rapamycin complex 1
NAC	N-acetylcysteine
NADH	Nicotinamide adenine dinucleotide (reduced)
Nav	Voltage-gated sodium channel
NCLX	Sodium-calcium exchanger
NMDA	N-methyl-D-aspartate
Nrf2	Nuclear factor erythroid 2-related factor 2
O ₂ [−]	Superoxide anion
•OH	Hydroxyl radical
PE	Primary epilepsy
PGE	Primary generalized epilepsy
PTZ	Pentylentetrazole
PUFAs	Polyunsaturated fatty acids
ROS	Reactive oxygen species
SCN1A	Sodium voltage-gated channel alpha subunit 1
SEGA	Subependymal giant cell astrocytoma
SIRT1	Sirtuin 1
SOD	Superoxide dismutase
TBARS	Thiobarbituric acid reactive substances
TLE	Temporal lobe epilepsy
TMRM	Tetramethylrhodamine methyl ester
TrkB	Tropomyosin receptor kinase B
TRP	Transient receptor potential
TSC	Tuberous sclerosis complex
TSC1	Tuberous sclerosis complex 1
TSC2	Tuberous sclerosis complex 2
VDAC	Voltage-dependent anion channel
Δψ _m	Mitochondrial membrane potential

References

1. Lin K, Stafstrom CE. Cognition, behavior, and psychosocial effects of seizures in the developing brain. In: *Psychiatric and behavioral aspects of epilepsy*. Berlin/Heidelberg, Germany: Springer; 2020. p. 3–15. [\[CrossRef\]](#).
2. Khalife MR, Scott RC, Hernan AE. Mechanisms for cognitive impairment in epilepsy: Moving beyond seizures. *Front Neurol*. 2022;13:878991. [\[CrossRef\]](#).
3. Löscher W, Stafstrom CE. Epilepsy and its neurobehavioral comorbidities: Insights gained from animal models. *Epilepsia*. 2023;64(1):54–91. [\[CrossRef\]](#).
4. Kunz WS, Kudin AP, Vielhaber S, Blümcke I, Züschratter W, Schramm J, et al. Mitochondrial complex I deficiency in the epileptic focus of patients with temporal lobe epilepsy. *Ann Neurol*. 2000;48(5):766–73.
5. Folbergrová J, Kunz WS. Mitochondrial dysfunction in epilepsy. *Mitochondrion*. 2012;12(1):35–40. [\[CrossRef\]](#).
6. Sakakura K, Fujimoto A, Arai Y, Ichikawa N, Sato K, Baba S, et al. Posttraumatic epilepsy may be a state in which underlying epileptogenicity involves focal cortical dysplasia. *Epilepsy Behav*. 2021;114(Pt A):107352. [\[CrossRef\]](#).
7. Hinojosa-Figueroa MS, Cruz-Caraguay M, Torres Pasquel A, Puga Rosero V, Eguiguren Chavez CB, Rodas JA, et al. Etiologies of multidrug-resistant epilepsy in Latin America: A comprehensive review of structural, genetic, metabolic, inflammatory, and infectious origins: A systematic review. *Biomolecules*. 2025;15(4):576. [\[CrossRef\]](#).
8. Zhou Z, Austin GL, Young LEA, Johnson LA, Sun R. Mitochondrial metabolism in major neurological diseases. *Cells*. 2018;7(12):229. [\[CrossRef\]](#).
9. Xie W, Koppula S, Kale MB, Ali LS, Wankhede NL, Umare MD, et al. Unraveling the nexus of age, epilepsy, and mitochondria: Exploring the dynamics of cellular energy and excitability. *Front Pharmacol*. 2024;15:1469053. [\[CrossRef\]](#).
10. Ye L, Fu X, Li Q. Mitochondrial quality control in health and disease. *MedComm*. 2025;6(8):e70319. [\[CrossRef\]](#).
11. Rahman S. Pathophysiology of mitochondrial disease causing epilepsy and status epilepticus. *Epilepsy Behav*. 2015;49:71–5. [\[CrossRef\]](#).
12. Zsurka G, Kunz WS. Mitochondrial dysfunction and seizures: The neuronal energy crisis. *Lancet Neurol*. 2015;14(9):956–66. [\[CrossRef\]](#).
13. Liotta A, Loroach S, Wallach I, Klewe K, Marcus K, Berndt N. Metabolic adaptation in epilepsy: From acute response to chronic impairment. *Int J Mol Sci*. 2024;25(17):9640. [\[CrossRef\]](#).
14. Kühlbrandt W. Structure and mechanisms of F-type ATP synthases. *Annu Rev Biochem*. 2019;88:515–49. [\[CrossRef\]](#).
15. Fosslien E. Mitochondrial medicine—Molecular pathology of defective oxidative phosphorylation. *Ann Clin Lab Sci*. 2001;31(1):25–67.
16. Malinska D, Kulawiak B, Kudin AP, Kovacs R, Huchzermeyer C, Kann O, et al. Complex III-dependent superoxide production of brain mitochondria contributes to seizure-related ROS formation. *Biochim Biophys Acta*. 2010;1797(6–7):1163–70. [\[CrossRef\]](#).
17. Waldbaum S, Patel M. Mitochondrial dysfunction and oxidative stress: A contributing link to acquired epilepsy? *J Bioenerg Biomembr*. 2010;42(6):449–55. [\[CrossRef\]](#).
18. Nicholls DG, Vesce S, Kirk L, Chalmers S. Interactions between mitochondrial bioenergetics and cytoplasmic calcium in cultured cerebellar granule cells. *Cell Calcium*. 2003;34(4–5):407–24. [\[CrossRef\]](#).
19. Rowley S, Liang LP, Fulton R, Shimizu T, Day B, Patel M. Mitochondrial respiration deficits driven by reactive oxygen species in experimental temporal lobe epilepsy. *Neurobiol Dis*. 2015;75:151–8. [\[CrossRef\]](#).
20. Ni MM, Sun JY, Li ZQ, Qiu JC, Wu CF. Role of voltage-gated chloride channels in epilepsy: Current insights and future directions. *Front Pharmacol*. 2025;16:1560392. [\[CrossRef\]](#).
21. Puttachary S, Sharma S, Stark S, Thippeswamy T. Seizure-induced oxidative stress in temporal lobe epilepsy. *BioMed Res Int*. 2015;2015(1):745613. [\[CrossRef\]](#).
22. Rodríguez-Ramírez R, Pérez-González C, Yescas-Gómez P, Méndez Armenta M. Estrés oxidativo, Nrf2 y su papel en la epilepsia. *Arch Neurocién*. 2020;25(4):32–44. [\[CrossRef\]](#).
23. Petrushanko I, Bogdanov N, Bulygina E, Grenacher B, Leinssoo T, Boldyrev A, et al. Na-K-ATPase in rat cerebellar granule cells is redox sensitive. *Am J Physiol Regul Integr Comp Physiol*. 2006;290(4):R916–25. [\[CrossRef\]](#).
24. Fernández-Moncada I, Barros LF. Non-preferential fuelling of the Na⁺/K⁺-ATPase pump. *Biochem J*. 2014;460(3):353–61. [\[CrossRef\]](#).

25. Garbincius JF, Elrod JW. Mitochondrial calcium exchange in physiology and disease. *Physiol Rev.* 2022;102(2):893–992. [[CrossRef](#)].
26. Biswas K, Alexander K, Francis MM. Reactive oxygen species: Angels and demons in the life of a neuron. *Neurosci.* 2022;3(1):130–45. [[CrossRef](#)].
27. Chang SJ, Yu BC. Mitochondrial matters of the brain: Mitochondrial dysfunction and oxidative status in epilepsy. *J Bioenerg Biomembr.* 2010;42(6):457–9. [[CrossRef](#)].
28. Liang LP, Jarrett SG, Patel M. Chelation of mitochondrial iron prevents seizure-induced mitochondrial dysfunction and neuronal injury. *J Neurosci.* 2008;28(45):11550–6. [[CrossRef](#)].
29. Zhang X, Wu Z, Zhou X, Tao H. Mitochondrial dysfunction in epilepsy: Mechanistic insights and clinical strategies. *Mol Biol Rep.* 2025;52(1):470. [[CrossRef](#)].
30. de Araújo Filho GM, Martins DP, Lopes AM, de Jesus Brait B, Furlan AER, Oliveira CIF, et al. Oxidative stress in patients with refractory temporal lobe epilepsy and mesial temporal sclerosis: Possible association with major depressive disorder? *Epilepsy Behav.* 2018;80:191–6. [[CrossRef](#)].
31. Furukawa K, Ikoma Y, Niino Y, Hiraoka Y, Tanaka K, Miyawaki A, et al. Dynamics of neuronal and astrocytic energy molecules in epilepsy. *J Neurochem.* 2025;169(3):e70044. [[CrossRef](#)].
32. Simeone KA, Matthews SA, Samson KK, Simeone TA. Targeting deficiencies in mitochondrial respiratory complex I and functional uncoupling exerts anti-seizure effects in a genetic model of temporal lobe epilepsy and in a model of acute temporal lobe seizures. *Exp Neurol.* 2014;251:84–90. [[CrossRef](#)].
33. Zhang Y, Zhang M, Zhu W, Yu J, Wang Q, Zhang J, et al. Succinate accumulation induces mitochondrial reactive oxygen species generation and promotes status epilepticus in the kainic acid rat model. *Redox Biol.* 2020;28:101365. [[CrossRef](#)].
34. Singh S, Singh TG, Rehni AK, Sharma V, Singh M, Kaur R. Reviving mitochondrial bioenergetics: A relevant approach in epilepsy. *Mitochondrion.* 2021;58:213–26. [[CrossRef](#)].
35. Kunz WS. The role of mitochondria in epileptogenesis. *Curr Opin Neurol.* 2002;15(2):179–84. [[CrossRef](#)].
36. Rowles J, Olsen M. Perspectives on the development of antioxidant antiepileptogenic agents. *Mini Rev Med Chem.* 2012;12(10):1015–27. [[CrossRef](#)].
37. Pearson-Smith JN, Patel M. Metabolic dysfunction and oxidative stress in epilepsy. *Int J Mol Sci.* 2017;18(11):2365. [[CrossRef](#)].
38. Shekh-Ahmad T, Lieb A, Kovac S, Gola L, Christian Wigley W, Abramov AY, et al. Combination antioxidant therapy prevents epileptogenesis and modifies chronic epilepsy. *Redox Biol.* 2019;26:101278. [[CrossRef](#)].
39. Kawasaki K, Suzuki Y, Yamamura H, Imaizumi Y. Rapid Na⁺ accumulation by a sustained action potential impairs mitochondria function and induces apoptosis in HEK293 cells expressing non-inactivating Na⁺ channels. *Biochem Biophys Res Commun.* 2019;513(1):269–74. [[CrossRef](#)].
40. Alam KA, Svalastoga P, Martinez A, Glennon JC, Haavik J. Potassium channels in behavioral brain disorders. Molecular mechanisms and therapeutic potential: A narrative review. *Neurosci Biobehav Rev.* 2023;152:105301. [[CrossRef](#)].
41. Shin EJ, Jeong JH, Chung YH, Kim WK, Ko KH, Bach JH, et al. Role of oxidative stress in epileptic seizures. *Neurochem Int.* 2011;59(2):122–37. [[CrossRef](#)].
42. Pereno G, Beltramino C. Understanding the pathophysiology of epilepsy in an animal model: Pentylene-tetrazole induces activation but not death of neurons of the medial extended amygdala. *Neurologia.* 2010;25(3):148–55. [[CrossRef](#)].
43. Kakizawa S. Involvement of ROS signal in aging and regulation of brain functions. *J Physiol Sci.* 2025;75(1):100003. [[CrossRef](#)].
44. Hassan W, Noreen H, Rehman S, Kamal MA, da Rocha JBT. Association of oxidative stress with neurological disorders. *Curr Neuroparmacol.* 2022;20(6):1046–72. [[CrossRef](#)].
45. Borowicz-Reutt KK, Czuczwar SJ. Role of oxidative stress in epileptogenesis and potential implications for therapy. *Pharmacol Rep.* 2020;72(5):1218–26. [[CrossRef](#)].
46. Incontro S, Musella ML, Sammari M, di Scala C, Fantini J, Debanne D. Lipids shape brain function through ion channel and receptor modulations: Physiological mechanisms and clinical perspectives. *Physiol Rev.* 2025;105(1):137–207. [[CrossRef](#)].

47. Freitas RM, Sousa FCF, Vasconcelos SMM, Viana GSB, Fonteles MMF. Pilocarpine-induced status epilepticus in rats: Lipid peroxidation level, nitrite formation, GABAergic and glutamatergic receptor alterations in the hippocampus, striatum and frontal cortex. *Pharmacol Biochem Behav.* 2004;78(2):327–32. [\[CrossRef\]](#).
48. Elblehi SS, Abd El-Maksoud EM, Aldhahrani A, Alotaibi SS, Ghamry HI, Elgendy SA, et al. Quercetin abrogates oxidative neurotoxicity induced by silver nanoparticles in wistar rats. *Life.* 2022;12(4):578. [\[CrossRef\]](#).
49. Magdaleno Roman JY, Chapa González C. Glutamate and excitotoxicity in central nervous system disorders: Ionotropic glutamate receptors as a target for neuroprotection. *Neuroprotection.* 2024;2(2):137–50. [\[CrossRef\]](#).
50. Parsons ALM, Bucknor EMV, Castroflorio E, Soares TR, Oliver PL, Rial D. The interconnected mechanisms of oxidative stress and neuroinflammation in epilepsy. *Antioxidants.* 2022;11(1):157. [\[CrossRef\]](#).
51. Benarroch E. What is the role of GABA transporters in seizures? *Neurology.* 2021;97(12):580–4. [\[CrossRef\]](#).
52. Sears SM, Hewett SJ. Influence of glutamate and GABA transport on brain excitatory/inhibitory balance. *Exp Biol Med.* 2021;246(9):1069–83. [\[CrossRef\]](#).
53. Navidhamidi M, Ghasemi M, Mehranfarid N. Epilepsy-associated alterations in hippocampal excitability. *Rev Neurosci.* 2017;28(3):307–34. [\[CrossRef\]](#).
54. Lepeu G, van Maren E, Slabeva K, Friedrichs-Maeder C, Fuchs M, Z'Graggen WJ, et al. The critical dynamics of hippocampal seizures. *Nat Commun.* 2024;15(1):6945. [\[CrossRef\]](#).
55. Shen KF, Yang XL, Liu GL, Zhu G, Wang ZK, Shi XJ, et al. The role of voltage-gated chloride channels in the epileptogenesis of temporal lobe epilepsy. *EBioMedicine.* 2021;70:103537. [\[CrossRef\]](#).
56. Sumadewi KT, Harkitasari S, Tjandra DC. Biomolecular mechanisms of epileptic seizures and epilepsy: A review. *Acta Epileptol.* 2023;5(1):28. [\[CrossRef\]](#).
57. Ponomareva D, Ivanov A, Bregestovski P. Analysis of the effects of pentose phosphate pathway inhibition on the generation of reactive oxygen species and epileptiform activity in hippocampal slices. *Int J Mol Sci.* 2024;25(3):1934. [\[CrossRef\]](#).
58. Lorigados Pedre L, Gallardo JM, Morales Chacón LM, Vega García A, Flores-Mendoza M, Neri-Gómez T, et al. Oxidative stress in patients with drug resistant partial complex seizure. *Behav Sci.* 2018;8(6):59. [\[CrossRef\]](#).
59. Łukawski K, Czuczwar SJ. Understanding mechanisms of drug resistance in epilepsy and strategies for overcoming it. *Expert Opin Drug Metab Toxicol.* 2021;17(9):1075–90. [\[CrossRef\]](#).
60. Pardo-Peña K, Yáñez-Hernández A, Medina-Ceja L, Morales-Villagrán A. Ellagic acid and allopurinol decrease H₂O₂ concentrations, epileptiform activity and astrogliosis after status epilepticus in the hippocampus of adult rats. *Exp Brain Res.* 2022;240(4):1191–203. [\[CrossRef\]](#).
61. Lopriore P, Gomes F, Montano V, Siciliano G, Mancuso M. Mitochondrial epilepsy, a challenge for neurologists. *Int J Mol Sci.* 2022;23(21):13216. [\[CrossRef\]](#).
62. Duchen MR. Mitochondria in health and disease: Perspectives on a new mitochondrial biology. *Mol Aspects Med.* 2004;25(4):365–451. [\[CrossRef\]](#).
63. Rho JM, Boison D. The metabolic basis of epilepsy. *Nat Rev Neurol.* 2022;18(6):333–47. [\[CrossRef\]](#).
64. Kundap UP, Paudel YN, Shaikh MF. Animal models of metabolic epilepsy and epilepsy associated metabolic dysfunction: A systematic review. *Pharmaceuticals.* 2020;13(6):106. [\[CrossRef\]](#).
65. Kaur A, Goel RK. Modelling epilepsy associated Alzheimer's disease through mitochondrial complex-I inhibition: Neurochemical and therapeutic perspectives. *Neurochem Res.* 2025;50(3):163. [\[CrossRef\]](#).
66. Zanfardino P, Doccini S, Santorelli FM, Petruzzella V. Tackling dysfunction of mitochondrial bioenergetics in the brain. *Int J Mol Sci.* 2021;22(15):8325. [\[CrossRef\]](#).
67. Nicholls DG. Oxidative stress and energy crises in neuronal dysfunction. *Ann N Y Acad Sci.* 2008;1147:53–60. [\[CrossRef\]](#).
68. De La Rossa A, Laporte MH, Astori S, Marissal T, Montessuit S, Sheshadri P, et al. Paradoxical neuronal hyperexcitability in a mouse model of mitochondrial pyruvate import deficiency. *eLife.* 2022;11:e72595. [\[CrossRef\]](#).
69. Bierhansl L, Gola L, Narayanan V, Dik A, Meuth SG, Wiendl H, et al. Neuronal mitochondrial calcium uniporter (MCU) deficiency is neuroprotective in hyperexcitability by modulation of metabolic pathways and ROS balance. *Mol Neurobiol.* 2024;61(11):9529–38. [\[CrossRef\]](#).

70. Kovac S, Domijan AM, Walker MC, Abramov AY. Seizure activity results in calcium- and mitochondria-independent ROS production via NADPH and xanthine oxidase activation. *Cell Death Dis.* 2014;5(10):e1442. [[CrossRef](#)].
71. Matuz-Mares D, González-Andrade M, Araiza-Villanueva MG, Vilchis-Landereros MM, Vázquez-Meza H. Mitochondrial calcium: Effects of its imbalance in disease. *Antioxidants.* 2022;11(5):801. [[CrossRef](#)].
72. Walkon LL, Strubbe-Rivera JO, Bazil JN. Calcium overload and mitochondrial metabolism. *Biomolecules.* 2022;12(12):1891. [[CrossRef](#)].
73. Jiang C, Shen J, Wang C, Huang Y, Wang L, Yang Y, et al. Mechanism of aconitine mediated neuronal apoptosis induced by mitochondrial calcium overload caused by MCU. *Toxicol Lett.* 2023;384:86–95. [[CrossRef](#)].
74. Dietrich D, Kirschstein T, Kukley M, Pereverzev A, von der Brélie C, Schneider T, et al. Functional specialization of presynaptic Cav2.3 Ca^{2+} channels. *Neuron.* 2003;39(3):483–96. [[CrossRef](#)].
75. Blackburn JK, Silva JP, Petitto E, Cholewa D, Fasler-Kan E, Volynski KE, et al. The mechanism of LTX^{N4C} -induced Ca^{2+} influx involves latrophilin-mediated activation of $\text{Ca}_v2.x$ channels. *Int J Mol Sci.* 2025;26(22):11200. [[CrossRef](#)].
76. Gao L, Li Y, Schultz HD, Wang WZ, Wang W, Finch M, et al. Downregulated Kv4.3 expression in the RVLM as a potential mechanism for sympathoexcitation in rats with chronic heart failure. *Am J Physiol Heart Circ Physiol.* 2010;298(3):H945–55. [[CrossRef](#)].
77. Kirichok YV, Nikolaev AV, Krishtal OA. K^{+} out accelerates inactivation of Shal-channels responsible for A-current in rat CA1 neurons. *Neuroreport.* 1998;9(4):625–9. [[CrossRef](#)].
78. Wu X, Hernandez-Enriquez B, Banas M, Xu R, Sesti F. Molecular mechanisms underlying the apoptotic effect of KCNB1 K^{+} channel oxidation. *J Biol Chem.* 2013;288(6):4128–34. [[CrossRef](#)].
79. Spinelli S, Remigante A, Liuni R, Mantegna G, Legname G, Marino A, et al. Oxidative stress-related cellular aging causes dysfunction of the Kv3.1/KCNC1 channel reverted by melatonin. *Aging Cell.* 2024;23(8):e14185. [[CrossRef](#)].
80. Ji D, Mylvaganam S, Ravi Chander P, Tarnopolsky M, Murphy K, Carlen P. Mitochondria and oxidative stress in epilepsy: Advances in antioxidant therapy. *Front Pharmacol.* 2025;15:1505867. [[CrossRef](#)].
81. Musella S, Carotenuto L, Iraci N, Baroli G, Ciaglia T, Nappi P, et al. Beyond retigabine: Design, synthesis, and pharmacological characterization of a potent and chemically stable neuronal Kv7 channel activator with anticonvulsant activity. *J Med Chem.* 2022;65(16):11340–64. [[CrossRef](#)].
82. Canafoglia L, Franceschetti S, Antozzi C, Carrara F, Farina L, Granata T, et al. Epileptic phenotypes associated with mitochondrial disorders. *Neurology.* 2001;56(10):1340–6. [[CrossRef](#)].
83. Lee S, Na JH, Lee YM. Epilepsy in leigh syndrome with mitochondrial DNA mutations. *Front Neurol.* 2019;10:496. [[CrossRef](#)].
84. Fine AL, Liebo G, Gavrilova RH, Britton JW. Seizure semiology, EEG, and imaging findings in epilepsy secondary to mitochondrial disease. *Front Neurol.* 2021;12:779052. [[CrossRef](#)].
85. Pandey R, Ngaju P, Janghorban M, Abuelazm H, Malaeb K, Aryal KP. Noninvasive biomarkers for disease diagnosis and health monitoring. In: Mahato K, Chandra P, editors. *Biosensors for personalized healthcare.* Singapore: Springer; 2024. p. 27–47. [[CrossRef](#)].
86. Hanin A, Lambrecq V, Denis JA, Imbert-Bismut F, Rucheton B, Lamari F, et al. Cerebrospinal fluid and blood biomarkers of status epilepticus. *Epilepsia.* 2020;61(1):6–18. [[CrossRef](#)].
87. Maes M, Supasitthumrong T, Limotai C, Michelin AP, Matsumoto AK, de Oliveira Semão L, et al. Increased oxidative stress toxicity and lowered antioxidant defenses in temporal lobe epilepsy and mesial temporal sclerosis: Associations with psychiatric comorbidities. *Mol Neurobiol.* 2020;57(8):3334–48. [[CrossRef](#)].
88. Ogren JA, Wilson CL, Bragin A, Lin JJ, Salamon N, Dutton RA, et al. Three-dimensional surface maps link local atrophy and fast ripples in human epileptic hippocampus. *Ann Neurol.* 2009;66(6):783–91. [[CrossRef](#)].
89. Vorderwülbecke BJ, Wandschneider B, Weber Y, Holtkamp M. Genetic generalized epilepsies in adults—Challenging assumptions and dogmas. *Nat Rev Neurol.* 2022;18(2):71–83. [[CrossRef](#)].
90. Beck H, Yaari Y. Plasticity of intrinsic neuronal properties in CNS disorders. *Nat Rev Neurosci.* 2008;9(5):357–69. [[CrossRef](#)].
91. Goldberg EM, Coulter DA. Mechanisms of epileptogenesis: A convergence on neural circuit dysfunction. *Nat Rev Neurosci.* 2013;14(5):337–49. [[CrossRef](#)].

92. Ghasemi M, Schachter SC. The NMDA receptor complex as a therapeutic target in epilepsy: A review. *Epilepsy Behav.* 2011;22(4):617–40. [[CrossRef](#)].
93. Armijo JA, Shushtarman M, Valdizan EM, Cuadrado A, de las Cuevas I, Adin J. Ion channels and epilepsy. *Curr Pharm Des.* 2005;11(15):1975–2003. [[CrossRef](#)].
94. Tao H, Chen Z, Wu J, Chen J, Chen Y, Fu J, et al. DNA methylation signature of epileptic encephalopathy-related pathogenic genes encoding ion channels in temporal lobe epilepsy. *Front Neurol.* 2021;12:692412. [[CrossRef](#)].
95. Catterall WA, Kalume F, Oakley JC. Nav1.1 channels and epilepsy. *J Physiol.* 2010;588(Pt 11):1849–59. [[CrossRef](#)].
96. Audenaert D, Van Broeckhoven C, De Jonghe P. Genes and loci involved in febrile seizures and related epilepsy syndromes. *Hum Mutat.* 2006;27(5):391–401. [[CrossRef](#)].
97. Al Hosani S, Varghese S. Dravet syndrome: A rare form of epilepsy. *Case Rep Med.* 2024;2024(1):6710512. [[CrossRef](#)].
98. Rosch RE, Goldberg EM. SCN1A and dravet syndrome. In: Baram TZ, Shinnar S, Stafstrom CE, editors. *Febrile seizures: New concepts and consequences*. Cambridge, MA, USA: Academic Press; 2022. p. 43–63. [[CrossRef](#)].
99. Brunklaus A, Brünger T, Feng T, Fons C, Lehtikainen A, Panagiotakaki E, et al. The gain of function SCN1A disorder spectrum: Novel epilepsy phenotypes and therapeutic implications. *Brain.* 2022;145(11):3816–31. [[CrossRef](#)].
100. Wolff M, Johannesen KM, Hedrich UBS, Masnada S, Rubboli G, Gardella E, et al. Genetic and phenotypic heterogeneity suggest therapeutic implications in SCN2A-related disorders. *Brain.* 2017;140(5):1316–36. [[CrossRef](#)].
101. Estacion M, O'Brien JE, Conravery A, Hammer MF, Waxman SG, Dib-Hajj SD, et al. A novel *de novo* mutation of SCN8A (Nav1.6) with enhanced channel activation in a child with epileptic encephalopathy. *Neurobiol Dis.* 2014;69:117–23. [[CrossRef](#)].
102. Talwar D, Hammer MF. SCN8A epilepsy, developmental encephalopathy, and related disorders. *Pediatr Neurol.* 2021;122:76–83. [[CrossRef](#)].
103. Aebly A, Sculier C, Bouza AA, Askar B, Lederer D, Schoonjans AS, et al. SCN1B-linked early infantile developmental and epileptic encephalopathy. *Ann Clin Transl Neurol.* 2019;6(12):2354–67. [[CrossRef](#)].
104. Rogawski MA. KCNQ2/KCNQ3 K⁺ channels and the molecular pathogenesis of epilepsy: Implications for therapy. *Trends Neurosci.* 2000;23(9):393–8. [[CrossRef](#)].
105. Legros L, Adle-Biasette H, Dozières-Puyravel B, Khung S, Elmaleh-Bergès M, Lesca G, et al. Neuropathology findings in KCNQ2 neonatal epileptic encephalopathy. *Seizure.* 2022;99:36–9. [[CrossRef](#)].
106. Villa C, Combi R. Potassium channels and human epileptic phenotypes: An updated overview. *Front Cell Neurosci.* 2016;10:81. [[CrossRef](#)].
107. Khan R, Chaturvedi P, Sahu P, Ludhiadch A, Singh P, Singh G, et al. Role of potassium ion channels in epilepsy: Focus on current therapeutic strategies. *CNS Neurol Disord Drug Targets.* 2024;23(1):67–87. [[CrossRef](#)].
108. Hammer MF. Transgenic mouse models of sodium and potassium channelopathies in epilepsy: Insights into disease mechanisms and therapeutics. *Biosci Rep.* 2025;45(10):567–95. [[CrossRef](#)].
109. Lauerer RJ, Lerche H. Voltage-gated calcium channels in genetic epilepsies. *J Neurochem.* 2024;168(12):3853–71. [[CrossRef](#)].
110. Pietrobon D. Function and dysfunction of synaptic calcium channels: Insights from mouse models. *Curr Opin Neurobiol.* 2005;15(3):257–65. [[CrossRef](#)].
111. Garg D, Mohammad S, Shukla A, Sharma S. Genetic links to episodic movement disorders: Current insights. *Appl Clin Genet.* 2023;16:11–30. [[CrossRef](#)].
112. Chen Y, Parker WD, Wang K. The role of T-type calcium channel genes in absence seizures. *Front Neurol.* 2014;5:45. [[CrossRef](#)].
113. Matsumoto A, Kasuya G, Tumurbaatar S, Masuda T, Wakabayashi K, Kawada M, et al. Compound heterozygous variants of CACNA1H change channel properties and contribute to intractable epilepsy with myoclonic-atonic seizures. *J Hum Genet.* 2026;71(5):255–63. [[CrossRef](#)].
114. Schneider T, Neumaier F, Hescheler J, Alpdogan S. Cav2.3 R-type calcium channels: From its discovery to pathogenic *de novo* CACNA1E variants: A historical perspective. *Pflugers Arch.* 2020;472(7):811–6. [[CrossRef](#)].
115. Ohmori I, Ouchida M, Miki T, Mimaki N, Kiyonaka S, Nishiki T, et al. A CACNB4 mutation shows that altered Ca_v2.1 function may be a genetic modifier of severe myoclonic epilepsy in infancy. *Neurobiol Dis.* 2008;32(3):349–54. [[CrossRef](#)].

116. Li X, Guo S, Sun Y, Ding J, Chen C, Wu Y, et al. GABRG2 mutations in genetic epilepsy with febrile seizures plus: Structure, roles, and molecular genetics. *J Transl Med.* 2024;22(1):767. [[CrossRef](#)].
117. Kang JQ, Macdonald RL. Molecular pathogenic basis for *GABRG2* mutations associated with a spectrum of epilepsy syndromes, from generalized absence epilepsy to dravet syndrome. *JAMA Neurol.* 2016;73(8):1009–16. [[CrossRef](#)].
118. Hernandez CC, Shen Y, Hu N, Shen W, Narayanan V, Ramsey K, et al. *GABRG2* variants associated with febrile seizures. *Biomolecules.* 2023;13(3):414. [[CrossRef](#)].
119. Bi M, Hong S, Zhou H, Wang H, Wang L, Zheng Y. Chloride channelopathies of ClC-2. *Int J Mol Sci.* 2014;15(1):218–49. [[CrossRef](#)].
120. Palmer EE, Stuhlmann T, Weinert S, Haan E, Van Esch H, Holvoet M, et al. *De novo* and inherited mutations in the X-linked gene *CLCN4* are associated with syndromic intellectual disability and behavior and seizure disorders in males and females. *Mol Psychiatry.* 2018;23(2):222–30. [[CrossRef](#)].
121. Sahly AN, Sierra-Marquez J, Bungert-Plümke S, Franzen A, Mougharbel L, Berrahmoune S, et al. Genotype-phenotype correlation in *CLCN4*-related developmental and epileptic encephalopathy. *Hum Genet.* 2024;143(5):667–81. [[CrossRef](#)].
122. Novella Romanelli M, Sartiani L, Masi A, Mannaioni G, Manetti D, Mugelli A, et al. HCN channels modulators: The need for selectivity. *Curr Top Med Chem.* 2016;16(16):1764–91. [[CrossRef](#)].
123. Mujahid, Waqas A, Almazni IA, Zaman G, Alam Q, Eid TM, et al. A novel loss of function variant in *HCN1* gene underlies early infantile epileptic encephalopathy 24 [EIEE24]. *Mol Syndromol.* 2025;16(2):152–64. [[CrossRef](#)].
124. Houdayer C, Phillips AM, Chabbert M, Bourreau J, Maroofian R, Houlden H, et al. Mono and biallelic variants in *HCN2* cause severe neurodevelopmental disorders. *medRxiv.* 2024. [[CrossRef](#)].
125. Hussein MAM, Kiwan NA, Aly YR, Badawy AA, Hussein AM. Role of hippocampus in epileptogenesis: New insights in the cross-talks between the underlying mechanisms. *Acta Neurol Belg.* 2025. [[CrossRef](#)].
126. Di Marco G, Gherardi G, de Mario A, Piazza I, Baraldo M, Mattarei A, et al. The mitochondrial ATP-dependent potassium channel (mitoK_{ATP}) controls skeletal muscle structure and function. *Cell Death Dis.* 2024;15(1):58. [[CrossRef](#)].
127. Rowley S, Patel M. Mitochondrial involvement and oxidative stress in temporal lobe epilepsy. *Free Radic Biol Med.* 2013;62:121–31. [[CrossRef](#)].
128. Zandi AS, Javidan M, Dumont GA, Tafreshi R. Automated real-time epileptic seizure detection in scalp EEG recordings using an algorithm based on wavelet packet transform. *IEEE Trans Biomed Eng.* 2010;57(7):1639–51. [[CrossRef](#)].
129. Vidyaratne LS, Iftikharuddin KM. Real-time epileptic seizure detection using EEG. *IEEE Trans Neural Syst Rehabil Eng.* 2017;25(11):2146–56. [[CrossRef](#)].
130. Lory P, Nicole S, Monteil A. Neuronal Cav3 channelopathies: Recent progress and perspectives. *Pflügers Arch Eur J Physiol.* 2020;472(7):831–44. [[CrossRef](#)].
131. Rivolta I, Binda A, Masi A, DiFrancesco JC. Cardiac and neuronal HCN channelopathies. *Pflügers Arch Eur J Physiol.* 2020;472(7):931–51. [[CrossRef](#)].
132. Seo S, Leitch B. Altered thalamic GABAA-receptor subunit expression in the stargazer mouse model of absence epilepsy. *Epilepsia.* 2014;55(2):224–32. [[CrossRef](#)].
133. So TW, Choi HY, Xu H, Zhu J, Shi L, Ip JPK. Hippocampal dorsal CA1: Functional connectivity and role in HCN channelopathies in affective diseases and epilepsy. *IBRO Neurosci Rep.* 2025;18:644–56. [[CrossRef](#)].
134. Balestrini S, Arzimanoglou A, Blümcke I, Scheffer IE, Wiebe S, Zelano J, et al. The aetiologies of epilepsy. *Epileptic Disord.* 2021;23(1):1–16. [[CrossRef](#)].
135. Yuen AW, Sander JW. Impaired mitochondrial energy production: The basis of pharmacoresistance in epilepsy. *Med Hypotheses.* 2011;77(4):536–40. [[CrossRef](#)].
136. Rusina E, Simonti M, Duprat F, Cestèle S, Mantegazza M. Voltage-gated sodium channels in genetic epilepsy: Up and down of excitability. *J Neurochem.* 2024;168(12):3872–90. [[CrossRef](#)].
137. Kodirov SA. Roles of funny HCN. *Comp Biochem Physiol Part C Toxicol Pharmacol.* 2025;295:110205. [[CrossRef](#)].
138. Yang H, Yin F, Gan S, Pan Z, Xiao T, Kessi M, et al. The study of genetic susceptibility and mitochondrial dysfunction in mesial temporal lobe epilepsy. *Mol Neurobiol.* 2020;57(9):3920–30. [[CrossRef](#)].

139. Madireddy S, Madireddy S. Therapeutic strategies to ameliorate neuronal damage in epilepsy by regulating oxidative stress, mitochondrial dysfunction, and neuroinflammation. *Brain Sci.* 2023;13(5):784. [\[CrossRef\]](#).
140. Łukawski K, Czuczwar SJ. Oxidative stress and neurodegeneration in animal models of seizures and epilepsy. *Antioxidants.* 2023;12(5):1049. [\[CrossRef\]](#).
141. Pan JW, Williamson A, Cavus I, Hetherington HP, Zaveri H, Petroff OA, et al. Neurometabolism in human epilepsy. *Epilepsia.* 2008;49(3):31–41. [\[CrossRef\]](#).
142. Galashin AS, Konakov MV, Dynnik VV. Evolution of ideas about the mechanisms of neuronal network hyperactivation and burst firing in epilepsy. Contribution of potassium-induced activation of potassium-conducting channels to network hyperactivation. *Biophysics.* 2024;69(4):639–48. [\[CrossRef\]](#).
143. Quincozes-Santos A, Bobermin LD, Tramontina AC, Wartchow KM, Tagliari B, Souza DO, et al. Oxidative stress mediated by NMDA, AMPA/KA channels in acute hippocampal slices: Neuroprotective effect of resveratrol. *Toxicol In Vitro.* 2014;28(4):544–51. [\[CrossRef\]](#).
144. Adegoke VA, Dongol Y, Gonzalez T, Song A, Clark RJ, Lewis RJ, et al. Proline hydroxylation and C-terminal amidation in μ -conotoxins increase structural stability and potency at sodium channels. *Aust J Chem.* 2025;78(9):CH25071. [\[CrossRef\]](#).
145. Jones F, Gamper N, Gao H. Kv7 channels and excitability disorders. In: *Pharmacology of potassium channels.* Berlin/Heidelberg, Germany: Springer; 2021. p. 185–230. [\[CrossRef\]](#).
146. Soboleva EB, Amakhin DV, Sinyak DS, Zaitsev AV. Modulation of seizure-like events by the small conductance and ATP-sensitive potassium ion channels. *Biochem Biophys Res Commun.* 2022;623:74–80. [\[CrossRef\]](#).
147. Yarotsky V, Contois L, Hahn YK, Nass SR, Knapp PE, Hauser KF. Novel voltage-dependent Cl^- channels in striatal medium spiny neurons are unrelated to ClC-1 or other known Ca^{2+} -induced Cl^- channel/transporter types. *Neurosci Lett.* 2025;844:138032. [\[CrossRef\]](#).
148. Fouda MA, Ghovanloo MR, Ruben PC. Late sodium current: Incomplete inactivation triggers seizures, myotonias, arrhythmias, and pain syndromes. *J Physiol.* 2022;600(12):2835–51. [\[CrossRef\]](#).
149. Pikor D, Hurla M, Słowikowski B, Szymanowicz O, Poszwa J, Banaszek N, et al. Calcium ions in the physiology and pathology of the central nervous system. *Int J Mol Sci.* 2024;25(23):13133. [\[CrossRef\]](#).
150. Laryushkin DP, Maiorov SA, Zinchenko VP, Gaidin SG, Kosenkov AM. Role of L-type voltage-gated calcium channels in epileptiform activity of neurons. *Int J Mol Sci.* 2021;22(19):10342. [\[CrossRef\]](#).
151. Binignat O, Olloquequi J. Excitotoxicity as a target against neurodegenerative processes. *Curr Pharm Des.* 2020;26(12):1251–62. [\[CrossRef\]](#).
152. Netto LES, Machado LESF. Preferential redox regulation of cysteine-based protein tyrosine phosphatases: Structural and biochemical diversity. *FEBS J.* 2022;289(18):5480–504. [\[CrossRef\]](#).
153. Sun H, Li X, Guo Q, Liu S. Research progress on oxidative stress regulating different types of neuronal death caused by epileptic seizures. *Neurol Sci.* 2022;43(11):6279–98. [\[CrossRef\]](#).
154. Liang LP, Waldbaum S, Rowley S, Huang TT, Day BJ, Patel M. Mitochondrial oxidative stress and epilepsy in SOD2 deficient mice: Attenuation by a lipophilic metalloporphyrin. *Neurobiol Dis.* 2012;45(3):1068–76. [\[CrossRef\]](#).
155. Fulton RE, Pearson-Smith JN, Huynh CQ, Fabisiak T, Liang LP, Aivazidis S, et al. Neuron-specific mitochondrial oxidative stress results in epilepsy, glucose dysregulation and a striking astrocyte response. *Neurobiol Dis.* 2021;158:105470. [\[CrossRef\]](#).
156. Sandouka S, Shekh-Ahmad T. Induction of the Nrf2 pathway by sulforaphane is neuroprotective in a rat temporal lobe epilepsy model. *Antioxidants.* 2021;10(11):1702. [\[CrossRef\]](#).
157. Folbergrová J, Ješina P, Otáhal J. Protective effect of sulforaphane on oxidative stress and mitochondrial dysfunction associated with status epilepticus in immature rats. *Mol Neurobiol.* 2023;60(4):2024–35. [\[CrossRef\]](#).
158. Petrovic S, Arsic A, Ristic-Medic D, Cvetkovic Z, Vucic V. Lipid peroxidation and antioxidant supplementation in neurodegenerative diseases: A review of human studies. *Antioxidants.* 2020;9(11):1128. [\[CrossRef\]](#).
159. Bourre JM. Roles of unsaturated fatty acids (especially omega-3 fatty acids) in the brain at various ages and during ageing. *J Nutr Health Aging.* 2004;8(3):163–74.
160. Valgimigli L. Lipid peroxidation and antioxidant protection. *Biomolecules.* 2023;13(9):1291. [\[CrossRef\]](#).
161. Li H, Zhang Y, Zhang Y, Li Y, Wang H. Inhibition of oxidative stress and the Neuropilin-2-induced neuroinflammatory pathway by EMO ameliorates epileptic seizures in the preclinical model of epilepsy. *Redox Rep.* 2025;30(1):2547405. [\[CrossRef\]](#).

162. Hajieva P, Abrosimov R, Kunath S, Moosmann B. Antioxidant and prooxidant modulation of lipid peroxidation by integral membrane proteins. *Free Radic Res.* 2023;57(2):105–14. [[CrossRef](#)].
163. Barrantes FJ. Modulation of a rapid neurotransmitter receptor-ion channel by membrane lipids. *Front Cell Dev Biol.* 2024;11:1328875. [[CrossRef](#)].
164. Kalinichenko LS, Kornhuber J, Sinning S, Haase J, Müller CP. Serotonin signaling through lipid membranes. *ACS Chem Neurosci.* 2024;15(7):1298–320. [[CrossRef](#)].
165. Scimemi A. Structure, function, and plasticity of GABA transporters. *Front Cell Neurosci.* 2014;8:161. [[CrossRef](#)].
166. Stöber TM, Batulin D, Triesch J, Narayanan R, Jedlicka P. Degeneracy in epilepsy: Multiple routes to hyperexcitable brain circuits and their repair. *Commun Biol.* 2023;6:479. [[CrossRef](#)].
167. Keller JN, Mark RJ, Bruce AJ, Blanc E, Rothstein JD, Uchida K, et al. 4-Hydroxynonenal, an aldehydic product of membrane lipid peroxidation, impairs glutamate transport and mitochondrial function in synaptosomes. *Neuroscience.* 1997;80(3):685–96. [[CrossRef](#)].
168. Li N, Wang H, Xin S, Min R, Zhang Y, Deng Y. Confinement induces oxidative damage and synaptic dysfunction in mice. *Front Physiol.* 2022;13:999574. [[CrossRef](#)].
169. Tawfik KM, Moustafa YM, El-Azab MF. Neuroprotective mechanisms of sildenafil and selenium in PTZ-kindling model: Implications in epilepsy. *Eur J Pharmacol.* 2018;833:131–44. [[CrossRef](#)].
170. Syed RU, Banu H, Khojali WMA, Osman ME, Alrashidi AM, Nasser L, et al. *In vivo, in silico* effects of sakuranetin as a multi-target nutraceutical against PTZ-induced seizures via GABA restoration and BDNF/TrkB activation. *Sci Rep.* 2025;15:45691. [[CrossRef](#)].
171. Perucca E, Bialer M, White HS. New GABA-targeting therapies for the treatment of seizures and epilepsy: I. Role of GABA as a modulator of seizure activity and recently approved medications acting on the GABA system. *CNS Drugs.* 2023;37(9):755–79. [[CrossRef](#)].
172. Fischer FP, Kasture AS, Hummel T, Sucic S. Molecular and clinical repercussions of GABA transporter 1 variants gone amiss: Links to epilepsy and developmental spectrum disorders. *Front Mol Biosci.* 2022;9:834498. [[CrossRef](#)].
173. Hilwi M, Dayan O, Kanner BI. Conformationally sensitive proximity of extracellular loops 2 and 4 of the γ -aminobutyric acid (GABA) transporter GAT-1 inferred from paired cysteine mutagenesis. *J Biol Chem.* 2014;289(49):34258–66. [[CrossRef](#)].
174. Joseph D, Nayak SR, Penmatsa A. Structural insights into GABA transport inhibition using an engineered neurotransmitter transporter. *EMBO J.* 2022;41(15):e110735. [[CrossRef](#)].
175. Bryson A, Reid C, Petrou S. Fundamental Neurochemistry Review: GABA_A receptor neurotransmission and epilepsy: Principles, disease mechanisms and pharmacotherapy. *J Neurochem.* 2023;165(1):6–28. [[CrossRef](#)].
176. Koh W, Kwak H, Cheong E, Lee CJ. GABA tone regulation and its cognitive functions in the brain. *Nat Rev Neurosci.* 2023;24(9):523–39. [[CrossRef](#)].
177. Kaur S, Singh S, Arora A, Ram P, Kumar S, Kumar P, et al. Pharmacology of GABA and its receptors. In: Kumar P, Deb PK, editors. *Frontiers in pharmacology of neurotransmitters*. Singapore: Springer; 2020. p. 241–92. [[CrossRef](#)].
178. Bhatt M, Gauthier-Manuel L, Lazzarin E, Zerlotti R, Ziegler C, Bazzone A, et al. A comparative review on the well-studied GAT1 and the understudied BGT-1 in the brain. *Front Physiol.* 2023;14:1145973. [[CrossRef](#)].
179. Shuman T. Et tu, CA2: CA2 is hyperexcitable and controls seizures in a mouse model of temporal lobe epilepsy. *Epilepsy Curr.* 2023;23(2):121–3. [[CrossRef](#)].
180. Ali I, Jupp B, Hudson MR, Major B, Silva J, Yamakawa GR, et al. *In vivo* biomarkers of GABAergic function in epileptic rats treated with the GAT-1 inhibitor E2730. *Epilepsia.* 2024;65(11):3376–90. [[CrossRef](#)].
181. Sies H, Belousov VV, Chandel NS, Davies MJ, Jones DP, Mann GE, et al. Defining roles of specific reactive oxygen species (ROS) in cell biology and physiology. *Nat Rev Mol Cell Biol.* 2022;23(7):499–515. [[CrossRef](#)].
182. Mulley JC, Scheffer IE, Petrou S, Berkovic SF. Channelopathies as a genetic cause of epilepsy. *Curr Opin Neurol.* 2003;16(2):171–6. [[CrossRef](#)].
183. D'Adamo MC, Catacuzzeno L, Di Giovanni G, Franciolini F, Pessia M. K⁺ channelepsy: Progress in the neurobiology of potassium channels and epilepsy. *Front Cell Neurosci.* 2013;7:134. [[CrossRef](#)].
184. Guerri G, Castori M, D'Agruma L, Petracca A, Kurti D, Bertelli M. Genetic analysis of genes associated with epilepsy. *Acta Biomed.* 2020;91(Suppl 13):e2020005. [[CrossRef](#)].

185. Köhling R, Wolfart J. Potassium channels in epilepsy. *Cold Spring Harb Perspect Med.* 2016;6(5):a022871. [[CrossRef](#)].
186. Zheng Y, Chen J. Voltage-gated potassium channels and genetic epilepsy. *Front Neurol.* 2024;15:1466075. [[CrossRef](#)].
187. Niemeyer MI, Yusef YR, Cornejo I, Flores CA, Sepúlveda FV, Cid LP. Functional evaluation of human ClC-2 chloride channel mutations associated with idiopathic generalized epilepsies. *Physiol Genomics.* 2004;19(1):74–83. [[CrossRef](#)].
188. Bockaert J, Marin P. mTOR in brain physiology and pathologies. *Physiol Rev.* 2015;95(4):1157–87. [[CrossRef](#)].
189. Moloney PB, Cavalleri GL, Delanty N. Epilepsy in the mTORopathies: Opportunities for precision medicine. *Brain Commun.* 2021;3(4):fcab222. [[CrossRef](#)].
190. Auvin S, Baulac S. mTOR-therapy and targeted treatment opportunities in mTOR-related epilepsies associated with cortical malformations. *Rev Neurol.* 2023;179(4):337–44. [[CrossRef](#)].
191. Lasarge CL, Danzer SC. Mechanisms regulating neuronal excitability and seizure development following mTOR pathway hyperactivation. *Front Mol Neurosci.* 2014;7:18. [[CrossRef](#)].
192. Limanaqi F, Biagioni F, Busceti CL, Fabrizi C, Frati A, Fornai F. mTOR-related cell-clearing systems in epileptic seizures, an update. *Int J Mol Sci.* 2020;21(5):1642. [[CrossRef](#)].
193. Cho CH. Frontier of epilepsy research—MTOR signaling pathway. *Exp Mol Med.* 2011;43(5):231–74. [[CrossRef](#)].
194. Hodges SL, Lugo JN. Therapeutic role of targeting mTOR signaling and neuroinflammation in epilepsy. *Epilepsy Res.* 2020;161:106282. [[CrossRef](#)].
195. Querfurth H, Lee HK. Mammalian/mechanistic target of rapamycin (mTOR) complexes in neurodegeneration. *Mol Neurodegener.* 2021;16(1):44. [[CrossRef](#)].
196. Crino PB. mTOR signaling in epilepsy: Insights from malformations of cortical development. *Cold Spring Harb Perspect Med.* 2015;5(4):a022442. [[CrossRef](#)].
197. Russo E, Citraro R, Constanti A, De Sarro G. The mTOR signaling pathway in the brain: Focus on epilepsy and epileptogenesis. *Mol Neurobiol.* 2012;46(3):662–81. [[CrossRef](#)].
198. Cao YY, Wu LL, Li XN, Yuan YL, Zhao WW, Qi JX, et al. Molecular mechanisms of AMPA receptor trafficking in the nervous system. *Int J Mol Sci.* 2023;25(1):111. [[CrossRef](#)].
199. Gerasimenko A, Baldassari S, Baulac S. mTOR pathway: Insights into an established pathway for brain mosaicism in epilepsy. *Neurobiol Dis.* 2023;182:106144. [[CrossRef](#)].
200. Ribierre T, Bacq A, Donneger F, Doladilhe M, Maletic M, Roussel D, et al. Targeting pathological cells with senolytic drugs reduces seizures in neurodevelopmental mTOR-related epilepsy. *Nat Neurosci.* 2024;27(6):1125–36. [[CrossRef](#)].
201. Chen TS, Lai MC, Huang HI, Wu SN, Huang CW. Immunity, ion channels and epilepsy. *Int J Mol Sci.* 2022;23(12):6446. [[CrossRef](#)].
202. Singh S, Singh TG, Rehni AK. An insight into molecular mechanisms and novel therapeutic approaches in epileptogenesis. *CNS Neurol Disord-Drug Targets.* 2020;19(10):750–79. [[CrossRef](#)].
203. Gao Y, Liu N, Chen J, Zheng P, Niu J, Tang S, et al. Neuropharmacological insight into preventive intervention in posttraumatic epilepsy based on regulating glutamate homeostasis. *CNS Neurosci Ther.* 2023;29(9):2430–44. [[CrossRef](#)].
204. Zhao W, Xie C, Zhang X, Liu J, Liu J, Xia Z. Advances in the mTOR signaling pathway and its inhibitor rapamycin in epilepsy. *Brain Behav.* 2023;13(6):e2995. [[CrossRef](#)].
205. Moloney PB, Delanty N. An overview of the value of mTOR inhibitors to the treatment of epilepsy: The evidence to date. *Expert Rev Neurother.* 2025;25(3):281–97. [[CrossRef](#)].
206. Griffith JL, Wong M. The mTOR pathway in treatment of epilepsy: A clinical update. *Future Neurol.* 2018;13(2):49–58. [[CrossRef](#)].
207. Yui K, Sato A, Imataka G. Mitochondrial dysfunction and its relationship with mTOR signaling and oxidative damage in autism spectrum disorders. *Mini Rev Med Chem.* 2015;15(5):373–89. [[CrossRef](#)].
208. Bondy SC, Wu M. The critical role of autophagy and phagocytosis in the aging brain. *Int J Mol Sci.* 2025;26(1):57. [[CrossRef](#)].

209. Kataura T, Wilson N, Ma G, Korolchuk VI. Mitophagy as a guardian against cellular aging. *Autophagy*. 2025;21(1):249–51. [[CrossRef](#)].
210. Perpiñán E, Sanchez-Fueyo A, Safinia N. Immunoregulation: The interplay between metabolism and redox homeostasis. *Front Transplant*. 2023;2:1283275. [[CrossRef](#)].
211. LaSarge CL, Pun RYK, Gu Z, Riccetti MR, Namboodiri DV, Tiwari D, et al. mTOR-driven neural circuit changes initiate an epileptogenic cascade. *Prog Neurobiol*. 2021;200:101974. [[CrossRef](#)].
212. Krueger DA, Care MM, Agricola K, Tudor C, Mays M, Franz DN. Everolimus long-term safety and efficacy in subependymal giant cell astrocytoma. *Neurology*. 2013;80(6):574–80. [[CrossRef](#)].
213. Drion CM, van Scheppingen J, Arena A, Geijtenbeek KW, Kooijman L, van Vliet EA, et al. Effects of rapamycin and curcumin on inflammation and oxidative stress *in vitro* and *in vivo*—In search of potential anti-epileptogenic strategies for temporal lobe epilepsy. *J Neuroinflamm*. 2018;15(1):212. [[CrossRef](#)].
214. Perek-Polnik M, Józwiak S, Jurkiewicz E, Perek D, Kotulska K. Effective everolimus treatment of inoperable, life-threatening subependymal giant cell astrocytoma and intractable epilepsy in a patient with tuberous sclerosis complex. *Eur J Paediatr Neurol*. 2012;16(1):83–5. [[CrossRef](#)].
215. Cockerell I, Christensen J, Hoei-Hansen CE, Holst L, Grenaa Frederiksen M, Issa-Epe AI, et al. Effectiveness and safety of everolimus treatment in patients with tuberous sclerosis complex in real-world clinical practice. *Orphanet J Rare Dis*. 2023;18(1):377. [[CrossRef](#)].