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# The Possible Pathophysiological Alterations of Epilepsy and Its Relation With Other Neurological Disorders

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## ABSTRACT

For people with epilepsy, the primary indicator of a lower health-related quality of life is the existence of comorbidities linked to neurological, cardiovascular, or mental illnesses, aside from seizure symptoms. Compared to the general population, people with epilepsy have up to eight times higher rates of several disorders, such as depression, cognition impairment, and heart disease. The relationship between comorbidities and epilepsy can be explained by a number of processes, such as reciprocal relationships and shared risk factors. To aid in the early detection and treatment of comorbid disorders, there is an urgent need for innovative and proven screening tools and guidelines. There is preliminary evidence that certain diseases, like depression and migraine, have a negative impact on the quality of life and seizure outcome. The aims of this review, is to investigate and demonstrate the different pathophysiological alterations, including inflammatory pathways, and the relationship between epilepsy and its comorbidities (Alzheimer and depression disorders) through the latest published clinical and experimental data. Through an investigation of different research papers and the obtained data, it has been shown that epilepsy is linked to other co-morbidities through different pathological alterations. It has also been observed that neuroinflammatory/oxidative stress pathway plays a major role in pathophysiology of epilepsy and its connections with its co-morbidities.

**KEYWORDS:** Epilepsy, cognition impairment, depression, neuroinflammation.

## 1. INTRODUCTION

Epilepsy, a neurological condition, is characterized by frequent, irregular disruptions of brain activity. It is among the most prevalent chronic illnesses in the world, affecting about 50 million people of all ages. In wealthy nations, the median prevalence of epilepsy over the course of a lifetime was 5.8 per 1,000 people, whereas in developing nations it might reach 15.4 per 1,000 people [1]. Three types of epilepsy can be identified depending on the causative aetiology: idiopathic, acquired (symptomatic), and cryptogenic (presumed symptomatic). Idiopathic epilepsy, which is thought to be hereditary in nature and typically manifests in childhood, is defined as epilepsy without an underlying structural brain lesion or other neurological signs or symptoms. The term "*acquired epilepsy*" implies epileptic seizures that are caused by one or more distinct anatomical brain abnormalities. Cryptogenic epilepsy is a term used to describe epilepsy that is thought to be symptomatic but has no known aetiology [2]. About 40% of cases of epilepsy have known causes. These causes can be brain tumors, ischemic stroke, traumatic brain injury, intracerebral hemorrhage, infections of the central nervous system, multiple neurodegenerative diseases, and prolonged acute symptomatic seizures such as complex febrile seizures or status epilepticus (SE) [3].



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On the other hand, the International League against Epilepsy has differentiated between two main categories of seizures: partial (focal) seizures, which develop locally in one hemisphere of the brain, and generalized seizures, which affect both hemispheres of the brain. Partial seizures affect most epileptic sufferers [2]. Partial epilepsy most commonly occurs in the form of temporal lobe epilepsy (TLE), which is notoriously hard to treatment. Temporal lobe components, particularly the hippocampus, amygdala, and piriform cortex, may be responsible for this type of epilepsy as they are particularly vulnerable to brain insults that promote epileptogenesis. So, TLE is frequently studied to learn more about the mechanisms underlying epileptogenesis, pharmacoresistance to epilepsy, and the development of antiepileptogenic or disease-modifying therapies [4].

## 2. MATERIALS AND METHODS

The preparation of this study involved a thorough evaluation of the literature that was accessible using major scientific databases: PubMed, Scopus, and Google Scholar. Epilepsy, pathophysiology of epilepsy, epilepsy and co-morbidities are the keywords used to gather about 40 papers (published between 2004 and 2024) collected over 4 weeks. Following the compilation of published articles, the findings were analyzed then categorized according to the review's subject.

## 3. RESULTS AND DISCUUSION

### 3.1. Pathogenesis of Epilepsy

#### 3.1.1. Neurotransmission Signaling Pathway

Regarding epilepsy, glutamate and γ-aminobutyric acid (GABA) are the two neurotransmitters that have been thoroughly investigated in epilepsy. The glutamatergic and GABAergic systems are both important in the occurrence of epilepsy. It has been suggested that an imbalance between glutamate-mediated excitation and GABA-mediated inhibition is the cause of neuronal hyperexcitability in epilepsy [4]. In general, glutamate receptors are divided into two categories: metabotropic (G protein-coupled) and ionotropic (ligand-gated cation channels), which include AMPA, N-methyl-D-aspartic acid (NMDA), and kainate. Glutamate receptor overexpression is one of the glutamatergic molecular pathways implicated in the development and course of epilepsy. Excessive glutamatergic activity is a major factor in hyperexcitability and epilepsy, and these pathways contribute to it. This occurrence, referred to as "paroxysmal depolarizing shift" on the electroencephalogram, is intracellularly linked to neuronal epileptic discharges. A massive excitatory synaptic potential with burst discharge characteristics can be linked to the paroxysmal depolarizing shift. This potential is dependent on the activation of AMPA receptors as the initial components and NMDA receptors as the later components [5, 6]. The mGluRs belong to the G-protein-coupled receptor superfamily. Eight mGluRs (mGluR1-8), each possessing seven structural transmembrane domains, have been identified. The majority of them present alternatively spliced isoforms. Structurally, mGluRs are characterized by a large extracellular N-terminal domain, which acts as a glutamate binding site. The eight mGluR subtypes are conventionally divided into three subgroups according to sequence homology, post-receptor signaling connections, and pharmacology. Group I members (mGluR1 and mGluR5) are typically postsynaptically localized; this position regulates neuronal excitability by stimulating the Gαq/Gα subunit to induce phosphatidylinositol 4,5-bisphosphate hydrolysis via phospholipase C activation.


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Another key feature of Group I mGluRs is their enhancing effect on glutamate NMDA receptor activation. In contrast, Group II (mGluR2 and mGluR3) and Group III (mGluR4, mGluR6, mGluR7, and mGluR8) members are both presynaptically and postsynaptically localized. Of note, Group II and III receptor activation inhibits Ca2+ channels and activates K+ channels to mediate presynaptic inhibition of neurotransmitter release. Therefore, it was demonstrated that activation of group II (mGluR2 and 3) or group III metabotropic glutamate receptors (mGluR4, 6, 7 and 8) has been established to be neuroprotective in vitro and in vivo. In contrast, group I mGluRs (mGluR1 and 5) need to be antagonized to evoke protection [7]. The process underlying epilepsy is also influenced by other neurotransmitters, including dopamine, noradrenaline, and serotonin. The monoamine neurotransmitter serotonin, sometimes referred to as 5-hydroxytryptamine, is produced from the amino acid tryptophan. The central nervous system expresses a number of serotonin receptor subtypes, including 5-HT1A, 5-HT2C, and 5-HT7. Neurons in the cortex and/or hippocampus are agreed to have receptors. Experimental evidence from human and animal models indicates that there is a key role for serotonergic neurotransmission in the pathophysiology of epilepsy: reduction in 5-HT1A receptor binding in the epileptogenic zone of TLE patients; decreased seizure thresholds in mutant animals lacking the 5-HT1A or 5-HT2C receptor subtype; depletion of brain serotonin in the genetically epilepsy-prone rat model of audiogenic seizures. The variety of serotonin receptor subtypes complicates the role of the serotonergic system in regulating neuronal excitability. In general, 5-HT1A receptors can make glutamatergic neurons hyperpolarized, 5-HT2C receptors can make GABAergic neurons depolarized, while inhibition of 5-HT3 and 5-HT7 receptors can make neurons less excitable [8].

A catecholamine called noradrenaline is made from dopamine and is released by noradrenergic neurons in the central and sympathetic nervous systems, or as a hormone from the adrenal medulla. Numerous research studies illustrate the anticonvulsant function of endogenous noradrenaline in epilepsy. These include greater vulnerability to seizure induction due to noradrenaline depletion and higher neuronal injury in different limbic areas of rats following seizure induction due to noradrenaline loss. A ketogenic diet that boosts noradrenaline can have anticonvulsant effects in rodents, although boosting noradrenaline is not necessarily considered this diet's anticonvulsant mechanism of action. A series of pioneering studies in dopamine beta-hydroxylase knockout mice (that lack noradrenaline) and alpha2a receptor knockout mice support an anticonvulsant role for noradrenaline in these animal models. Knockout of the noradrenaline transporter in mice, which results in elevated levels of synaptic noradrenaline, has an anticonvulsant effect. It has also been argued that use of antidepressants that boost noradrenaline levels (and serotonin levels) is anticonvulsant, not proconvulsant. Whereas noradrenaline boosting tricyclic antidepressants may be proconvulsant at overdose levels, they may be anticonvulsant at low doses [9]. Dopamine, another catecholamine neurotransmitter, has a complicated and unclear mechanism in the aetiology of epilepsy. Researchers have discovered that the pathophysiology of two idiopathic epilepsies; juvenile myoclonic epilepsy (which has a decrease in binding potential to the dopamine transporter) and autosomal dominant nocturnal frontal lobe epilepsy (which significantly reduces dopamine D1 receptor binding) is associated with the dopaminergic pathway. This supports the theory that hyperexcitability and epilepsy are predisposed to a decline in inhibitory dopaminergic function. D1 and D2 dopamine receptor activation, on the other hand, may have distinct effects on neuronal excitability; D1 receptor has a proconvulsant impact, and D2 receptor has an anticonvulsant impact. According to recent studies, dopamine receptor binding


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in the epileptogenic zone of TLE patients reduced. For instance, a glutamate–dopamine interaction has been proposed to explain individual susceptibility to epilepsy in limbic areas. According to this hypothesis, paroxysmal activity of the cerebral cortex in the epileptic brain would increase the tonic excitation of dopamine neurons by glutamate. This would then induce phasic release of dopamine, possibly leading to downregulation or desensitization of dopamine receptors and subsequently decreased phasic responses. Indeed, dopamine exerts a marked inhibitory effect on hippocampal excitability through activation of dopamine D2 receptors (D2Rs). Anti-psychotics (i.e., dopaminergic D2-like antagonists) lower seizure thresholds in epileptic patients and promote seizures in patients with no previous history of the disease. Conversely, seizure inhibition occurs in patients administered anti-parkinsonian drugs such as pergolide and bromocriptine (which both act by stimulating D2Rs). Further observations supported the anti-convulsant effect of a low dose treatment with bromocriptine. A low dose of a D2R agonist would act through stimulation of presynaptic D2 auto receptors, leading to decreased dopamine release and preventing the downregulation of postsynaptic D2R.

According to our results using mice lacking D2R (D2R-/- mice), we postulated that D2R activation might exert a neuroprotective action on hippocampal and dopaminergic neurons against excitotoxicity. Conversely, activation of dopamine D1 receptors (D1Rs) has a proconvulsant effect, lowering the seizure threshold. The opposite action of D2R and D1R signaling might also be explained by the glutamate–dopamine interaction hypothesis for limbic epileptogenesis. Indeed, the activation of D1R in cortical tissue samples obtained from children undergoing epilepsy surgery has been shown to induce glutamate receptor-mediated neuronal hyperexcitability. More recent studies performed in animal models during seizures support these results that show a D1R-mediated activation of glutamatergic [10].

### 3.1.2. Genes, Ion Channels and Receptors

Recent developments in molecular biology and genetics have shown that the mutations in genes encoding ion channel proteins (which cause neurons to become hyperexcitable) are responsible for multiple epilepsy disorders [11]. Ion charges are used by ion channels to produce electric currents. Anion channels, on the other hand, are involved in the inhibitory mechanism for the neural excitatory process, whereas cation channels are primarily responsible for generating action potentials and contributing to neuronal excitability [12].


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**Table 1. Channelopathies associated with pathophysiology of some types of epilepsy.**

| Epilepsy Type | Sodium channel | Potassium channel | Chloride channel | Calcium channel | GABA | Acetylcholine |
|---|---|---|---|---|---|---|
| Autosomal dominant nocturnal frontal lobe epilepsy | | | | | | CHRNA4, CHRNB2 |
| Benign familial neonatal seizures | SCN2A | | | | | |
| Childhood absence epilepsy | | | CLCN2 | CACNA1H | GABRG2 | |
| Epilepsy with grand mal seizures | | | CLCN2 | | | |
| Febrile seizures | | | | | GABRG2 | |
| Infantile spasms | SCN1A | | | | | |
| generalized tonic-clonic seizures | SCN1A | | | | | |
| Juvenile absence epilepsy | | | CLCN2 | | | |
| Juvenile myoclonic epilepsy | | | CLCN2 | | | |
| Generalized epilepsy with paroxysmal dyskinesia | | KCNMA1 | | | | |

Therefore, it is proposed that either anion or cation channels can cause epileptogenesis when there is an imbalance of ion charges brought on by channelopathies. Channelopathies play a major role in the pathophysiology of epilepsy in humans, especially idiopathic epilepsy. Idiopathic epilepsy has been linked to mutations in genes that express potassium, sodium, chloride, calcium, and cholinergic and GABA receptors. Furthermore, channelopathies may possibly contribute to the pathophysiology of acquired epilepsy by causing secondary alterations in ion channels through posttranslational and transcriptional pathways [13] (Table 1). However, new research indicates that hyperpolarization activated cyclic nucleotide gated (HCN) channels are involved in channelopathy, which may be linked to absence seizures and TLE. Neurons' resting membrane potential is regulated by the hyperpolarization-activated cationic current (Ih), which is conducted via voltage-gated HCN channels. Membrane hyperpolarization causes HCN channels to open; this inhibits Ih's impact on neuronal excitability. Researches using experimental animal models have demonstrated that loss of channel expression and downregulation of HCN channels lead to a decrease in Ih density and, then, causes neuronal hyperexcitability [14].

### 3.1.3. Inflammatory Pathways

Cytokines have been linked to inflammatory responses and immune system activation. Recent research using animal models has demonstrated the role of inflammatory cytokines in the aetiology of epilepsy. It has been demonstrated that brain areas implicated in the generation and propagation of epileptic activity have overexpressed and upregulated levels of inflammatory cytokines, such as interleukin-1β (IL-1β) and tumor necrosis factor-α. (TNF-α) [15]. The non-neuronal cell components of the central nervous system, glial cells, in particular microglia and astrocytes, are recognized to be the source of the inflammatory cytokines in epilepsy. Thus, during epileptogenesis, glial cells are involved in immune or inflammatory


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response regulation [16]. Microglia and astrocytes that have released inflammatory cytokines typically trigger a series of downstream inflammatory events that can draw in neurons and stimulate the adaptive immune system. It has been discovered that these inflammatory cytokines negatively impact neurons by changing their excitability, releasing harmful mediators, and making the blood-brain barrier (BBB) more permeable [17, 18]. Furthermore, inflammatory responses can change the permeability of the BBB. By binding to the transforming growth factor-β receptor on astrocytes, serum albumin is taken up, leading to subsequent events that contribute to neural hyperexcitability and ultimately epileptiform activity. This is one way that the breakdown of the BBB might generate epileptogenesis [19].

Furthermore, it was demonstrated by Fabene and his colleagues that the pathophysiology of seizures involves inflammatory cell adhesion. They demonstrated that after a seizure generated by pilocarpine, there is an increase in the production of vascular cell adhesion molecules and an enhancement in leukocyte adherence to endothelial cells in cerebral blood vessels. This adhesion is mediated by leukocyte integrins and leukocyte mucin P-selectin glycoprotein ligand-1. As a result, there is an increase in leukocyte extravasation, brain inflammation, blood-brain barrier leakage, enhanced neuronal excitatory transmission, and eventually epileptogenesis [20].

### 3.1.4. Apoptotic Pathway

Apoptosis is a process of programmed cell death that multicellular organisms go through during normal growth and development to preserve cell homeostasis. Apoptotic pathways may play a role in neuronal cell loss following brain traumas, among other mechanisms like excitatory glutamate-mediated toxicity, as demonstrated by experimental and clinical studies [21]. In mammals, two main gene families regulate the apoptosis pathway: the Bcl-2 family proteins and the caspases. The caspase family of cysteine proteases primarily serves as an apoptotic initiator (caspases 2, 8, 9, 10, and 11) or an executioner (caspases 3, 6, and 7). Important regulators of the apoptotic process in cellular life and death decisions are proteins belonging to the Bcl-2 family. Its pro- and anti-apoptotic members (such as Bax, Bak, Bad, Bid, and other BH-3 only proteins) and anti-apoptotic members (such as Bcl-2, Bcl-XL, Bcl-W, and Mcl-1) are thought to be responsible for this property [22]. In addition to caspases and Bcl-2, other proteins involve in controlling cell death pathways include p53, Fas ligand, and nuclear factor kappa B [23].

### 3.1.5. Other Protein Regulation Pathways

Numerous investigations have shown that brain injuries cause changes in gene expression, and they have suggested that transcription factors may play a role in this regulation [24]. The pathophysiology of seizures is thought to be influenced by cellular immediate early genes or inducible transcription factors, such as those belonging to the Fos family (c-fos, fosB, and fos-related antigens, fra-1 and fra-2), and the Jun family (c-jun, junB, junD). The transcription factors c-fos and c-jun, which make up most of the transcription factor activator protein-1, are encoded by both gene families. Hippocampal neurons have been shown to have early up-regulation and expression of c-fos and c-jun mRNA during experimental seizures [10]. In the central nervous system, transcription factors belonging to the Jun and Fos families are primarily responsible for gene transcription as well as cell division, proliferation, and death. The molecular cascade that causes neurons to undergo apoptosis may be partially derived from


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the expression of immediate early genes [25]. Epileptogenesis is influenced by the inducible cyclic adenosine monophosphate (cAMP) early repressor (ICER), which is another transcription factor. The cAMP responsive element modulator (CREM) gene and ICER messenger RNAs, which are generated by the CREM's internal promoter, combine to form the ICER protein family. ICER functions as an endogenous repressor of transcription regulated by the cAMP-responsive element (CRE) [26]. With this property, ICER represses CRE-mediated gene transcription and antagonizes the activity of the transcription factor cAMP-responsive element binding protein (CREB), which in turn regulates neuronal plasticity and death in the nervous system. For neuronal survival, CREB is an activator of CRE transcription. After excitotoxic stimuli, ICER expression is upregulated in neurons, and overexpression of ICER in neurons has demonstrated an apoptotic effect [27].

Galanin, a different neuropeptide, has also been shown to play a role in controlling seizure activity. Galanin is engaged in many different brain activities and is broadly distributed throughout the central nervous system. It is well known for being a universal neurotransmitter inhibitor because it prevents the release of noradrenaline, glutamate, and acetylcholine, among other neurotransmitters. Put differently, it acts as a seizure modulator by activating the galanin receptors GalR1 and GalR2, which in turn restores the balance between glutamatergic stimulation and galaninergic inhibition in the dentate gyrus of the hippocampal region [28]. Following exposure to seizure stimuli, there has been a reported depletion of stored galanin in the dentate hilus. Interestingly, a few hours after the stimulation, the expression of galanin resurfaced and even increased. Furthermore, research on galanin overexpression in animal models has demonstrated that galanin significantly reduced the propensity to seizures during seizure induction. The information at hand confirmed that epileptogenesis is influenced by the control of genes and proteins [29].

### 3.2. Epilepsy and Alzheimer Disease

There may be similarities in the mechanisms behind the impairments in excitability found in both epilepsy and Alzheimer disease (AD) according to a number of studies conducted in transgenic mouse models of AD [30]. The mechanistic data indicates that certain abnormalities in the molecular pathways that control excitability are shared by AD and TLE, rather than extensive brain damage that is the common factor or the source of seizures. Even though the molecular faults in both epilepsy and AD are identical, there may be subtle variations that make seizures worse in epilepsy. For instance, a mutation in an ion channel that results in a whole loss of function is probably going to produce more of a disruption than one that only results in a partial loss of function [27].

It appears likely that aberrant amyloid precursor protein (APP) metabolism, rather than degenerating neurons, is the cause of increased excitability in AD, especially in the early stages of the illness. Stated differently, the cause of the seizures is "peptidopathy." The APP's peptide products affect a number of elements of neuronal activity and lead to increased excitability. However, it is not thought that aberrant APP metabolism in epilepsy is connected to the underlying processes that cause seizures [31]. The peptides produced by APP cleavage may have a complex effect on excitability in AD. For instance, A raises long-term potentiation and glutamatergic synaptic transmission in the hippocampus at slightly above normal levels, whereas an excess of the same peptide lowers excitability.


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Apart from the peptides arising from the aberrant metabolism of APP, mutations in other proteins may also cause abnormalities in excitability. A case in point is presenilin-1. Patients who have PS1 mutations or deletions are more excitable, have a lower seizure threshold, and are more likely to experience seizures [31]. Epilepsy and AD may share pathways of aberrant excitability that are not dependent on Aβ. For instance, it has been proposed that a reduction in the expression of the voltage-gated sodium channel subunit Nav1.1 in the GABAergic interneurons of hAPP mice results in a loss of inhibition [32]. The rate-limiting enzyme beta-site amyloid precursor protein cleaving enzyme 1 (BACE1), which cleaves APP to create amyloid beta protein (Aβ), may also be responsible for hyperexcitability through modulating voltage-gated sodium channel subunits. The β2 subunit of voltage-gated sodium channels, an auxiliary component in charge of the appropriate membrane localization of pore-forming α subunits, is another substrate of BACE1. When BACE1 cleaves the β2 subunit, a C-terminal fragment is released, and is then cleaved by γ-secretase to liberate the intracellular domain (ICD) [33]. The β2-ICD transfers to the nucleus and initiates Nav1.1 expression, which is partly transported to the cell surface via binding to β2. Strong expression of the Na v1.1 channel is found in the GABAergic interneuron subtype that strongly inhibits main cells. Deletion of functioning Nav1.1 subunits in these interneurons could therefore be a factor in cortical network disinhibition. Disinhibition may also result from β2 subunit cleavage and decreased quantities of functioning Nav1.1 subunits in neuronal populations that regulate the activity of other brain areas [34]. Therefore, controlling Nav1.1 expression could have a significant impact on network activity. In fact, there is a tendency towards seizures in mouse models with ablated or mutant β subunits of voltage-gated sodium channels.

It is noteworthy that both levels and the degree of this increase are connected with higher β2 subunit cleavage in AD patients' brains. Although more research is needed, these findings imply that the AD-related rise in main cell activity may be facilitated by BACE1-mediated cleavage of the β2 subunit. Different research avenues indicate that BACE1 has a variety of roles in controlling sodium channel activity and seizures [34]. For instance, BACE1 ablation can cause opposite alterations in sodium channels while still raising the risk of seizures. The mitochondrial cascade hypothesis posits that similar physiological mechanisms underlie AD and brain aging and that mitochondrial dysfunction in AD is not merely a consequence of neurodegeneration. It further suggests that mitochondrial dysfunction drives amyloidosis, Tau phosphorylation, and re-entry into the cell cycle. There is a connection between mitochondrial function and amyloidosis, as mitochondrial electron transport chain (ETC) dysfunction increases free radical production. Additionally, APP, Aβ, and the entire γ-secretase complex are found in mitochondria or mitochondrial membranes. Neuronal apoptosis in neurodegenerative diseases like AD is known to be linked to oxidative stress. Based on this hypothesis, the production of ROS is increased within mitochondria under certain stress conditions, including aging. In the absence of an effective antioxidant system, this augmented ROS production increases the likelihood of developing AD. Abnormal accumulation of amyloid β has been shown to promote ROS formation through the activation of NMDA receptors, and ROS can increase Aβ production, aggregation, tau phosphorylation, and polymerization. Increased ROS levels constitute a self-perpetuating process that contributes to the development of AD and ultimately leads to cell death through caspase activation and apoptosis [33].


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### 3.3. Epilepsy and Depression

While some antiseizure drugs have been shown to be helpful in treating mood disorders, others have been shown to worsen the symptoms of psychosis or depression [35]. The availability of transgenic animals offers benefits beyond what is practical in clinical settings when it comes to investigating processes.

#### 3.3.1. Alterations of the HPA Axis

The hypothalamic-pituitary-adrenal axis (HPA) is a key system for preserving homeostasis, and as such, it is influenced by stress and plays a role in causing symptoms and promoting plasticity [36]. Stress can cause the system to go from an adaptable range to a maladaptive one. Typically, this is indicated by abnormally high glucocorticoid levels (cortisol in humans, corticosterone in rats). The measurement of HPA axis hyperactivity in mice exposed to experimental chronic stress, such as extended physical confinement, cold stress, sleep deprivation, and mother separation, can be achieved by measuring the high plasma corticosterone (CORT) level and/or positive dexamethasone (DEX) or DEX/corticotropin releasing hormone (CRH) tests [37].

Kainic acid was stereotactically injected into the rat dorsal hippocampal area CA1 which resulted in seizures and a selective lesion in the CA3, as well as an indirect stimulation of the HPA axis that markedly increased the amount of CORT that circulated [38]. Rats treated with lithium-pilocarpine for chronic epilepsy display hyperactive HPA axis function, as demonstrated by an increased CORT response to a systemic injection of CRH and a failure to respond to a DEX challenge with depression; the degree of behavioural abnormalities was correlated with the degree of HPA axis dysfunction [39].

#### 3.3.2. Inflammation Role in Epilepsy and Depression

Mice administered either IL-1β or lipopolysaccharide, a bacterial endotoxin, spent longer in immobility in the tail suspension test and the foot shock test. In addition to raising plasma CORT levels, central delivery of IL-1β has been demonstrated to inhibit raphe serotonergic neuron activity in vitro [40]. In a model of experimental status epilepticus, neuroprotection was achieved through pharmacological inhibition of either IL-1β directly by the peptide antagonist anakinra or the inhibition of caspase-1, however, epileptogenesis was not sufficiently mitigated due to the administration of those agents well into the course of SE [15]. Given the circumstances, inflammation, particularly IL-1β, also appears to be a part of a positive feedback loop. Therefore, depression that is resistant to treatment may be influenced by increased IL-1β signaling.

Peripheral inflammatory pathways can also reach the central nervous system through several mechanisms, including the gut-microbiota-brain axis, which plays an important role in psychiatric disorders, including depression. Recent studies have evaluated the correlation between altered gut microbiota and depression. Indeed, it is often hypothesized that normalizing gut microbiota can improve depressive symptoms. Importantly, inflammation resulting from alterations of the gut-microbiota-brain axis has a significant adverse impact on neurotrophic levels, which are critical in overcoming depressive symptoms by maintaining synaptic plasticity. Also, the dysregulation of the HPA axis found in depression is commonly influenced by neuroinflammation, which is often caused by an imbalance in the gut-microbiota-brain axis. Importantly, many studies have also demonstrated that changes in the gut microbiota


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trigger inflammatory cytokines, such as IL-6, and IL-1β. These cytokines can reach the brain through neuroanatomical and neuroendocrine pathways, thus affecting mental health and behavior [40].

During activation of TLRs, a pro-inflammatory signaling cascade is initiated. For example, once activated by LPS, the TLR4 receptor associates with the adaptor protein myeloid differentiation factor 88 (MyD88) and induces the autophosphorylation of interleukin-1 receptor-associated kinase (IRAK). Phosphorylated IRAK1 and IRAK4 subsequently dissociate from MyD88, allowing it to interact with tumor necrosis factor receptor-associated factor 6 (TRAF6). This factor activates the transforming growth factor-β-activated kinase-1 (TAK1) complex, which promotes two inflammatory pathways involving mitogen-activated protein kinases (MAPK) and nuclear factor kappa-B (NF-κB) signaling. In the NF-κB pathway, activated TAK1 complex induces the phosphorylation of the protein inhibitor of nuclear factor kappa B (IkB), which is then polyubiquitinated and degraded. This event allows NF-κB p50/p65 to move to the nucleus. On the other hand, the activation of MAPK via TAK1 results in the phosphorylation and activation of the transcription factor activator protein-1 (AP-1). Both transcription factors bind to promoter regions that express pro-inflammatory genes such as TNF-α, inducible nitric oxide synthase (iNOS), cyclooxygenase-2, prostaglandin E2, IL-6, pro-IL-1β and components of the NLR family pyrin domain containing 3 (NLRP3) inflammasome. In particular, the NLRP3 inflammasome as well as iNOS have been explored as potential therapeutic targets for the management of depression [15].

### Future Perspectives

Inflammatory/apoptotic pathways play a major role in the pathophysiology of epilepsy. They also contribute, along with other pathophysiological mechanisms, to the linkage of pathophysiology between epilepsy and other co-morbidities, including Alzheimer and depression. This contribution paves the way for more pre-clinical and clinical studies demonstrating the accurate role and the possible therapeutic protective interventions against epilepsy and its co-morbidities.

## 4. CONCLUSION

This review outlines the various pathogenic mechanisms of epilepsy as well as the way other comorbidities interact with one another and with the pathological pathways. The development and course of epilepsy, as well as its comorbidities, are significantly influenced by these processes. These findings, especially when looked at in light of on another, highlight the urgent need for additional research to fully comprehend the connections between co-occurring mental and cognitive illnesses and epilepsy, as well as the most effective strategies to treat them.

## CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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