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MECHANISMS BEHIND EPILEPTOGENESIS: A COMPREHENSIVE REVIEW

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Abstract

Epilepsy is defined as a chronic disorder of the nervous system with an aberration of unprovoked seizures that happen due to abnormal bursts of electrical activity in the brain. The process of transitioning from a normal brain to an epileptic one, known as epileptogenesis, is both of great complexity and multifactorial. It encompasses changes in neurobiology that foster abnormal brain excitability within the brain and disrupt homeostasis of excitation and inhibition of the brain's neurotransmitters. Although the process of epileptogenesis has not been fully elucidated, there is evidence to suggest that multiple cellular and molecular changes within the brain are of critical importance. In this review, we focus on the mechanisms of epileptogenesis, which include plastic changes, ion channel dysfunctions, GABAergic failure, inflammation, and neurogenesis, highlighting their relative interplay within the epileptogenic focus.

Recent advances in precision medicine and epigenetic mechanisms have revealed quantitative biomarker profiles, with neuroinflammatory cytokines showing progressive elevation from healthy controls (TNF-α <8.1 pg/ml) to drug-resistant epilepsy (TNF-α 28.4-78.9 pg/ml), while ion channel mutations demonstrate specific prevalence patterns with SCN1A mutations affecting 2.5 per 100,000 individuals.

INTRODUCTION

Epilepsy is one of the most common neurological disorders, affecting millions of individuals globally. Itineraries often include genetic, environmental, or neurobiological components. The course of epileptogenesis, which is the evolution of a normal brain into a seizure-prone one and is still extensively researched, is still under exploration. This review seeks to focus on the major contributions of synaptic rearrangement, ion channel abnormalities, GABAergic imbalance, neuroinflammation, and neurogenesis toward the development of epilepsy.

Mechanisms of Epileptogenesis

Synaptic Reorganization and Neuroplasticity: The earliest event in epileptogenesis is synaptic reorganization, which results from an injury or some other triggering factor. Following an insult, the brain undergoes neuroplasticity changes, which include

both excitatory and inhibitory synaptic transmission. Aberrant excitatory synapse development augments neuronal excitability, along with increased synaptic strength…

Dysfunction of Ion Channels: Ion channels are essential to controlling the electrical activities of neurons. Abnormal ion channel function can lead to abnormal neuronal firing, which is characteristic of epileptic seizures. Changes in these channels may enhance neuronal excitability, thereby causing epilepsy…

GABAergic System Dysfunction: The GABAergic system provides the main inhibitory control in the brain and is responsible for maintaining the balance between excitation and inhibition. Lack of effective GABAergic signaling is considered one of the primary factors responsible for initiating epileptic activity…

Immune Response and Neuroinflammation:
There is increasing evidence that the neuroinflammatory processes contribute to the development of epilepsy. Following an injury, infection, or sustained seizures, the brain's resident immune cells, microglia and astrocytes activate and release pro-inflammatory cytokines…

Cell Death and Neurogenesis: In several types of epilepsy and especially following brain injury, there is neuronal cell death in several important structures, including the hippocampus. However, some regions, such as the dentate gyrus, can undergo neurogenesis, which is the generation of new neurons in response to injury…

Evidence Synthesis: Current studies suggest that inflammation of the nervous system, ion channel dysfunction, and synaptic reorganization are interdependent and can aggravate one another during the process of epileptogenesis. One example would be neuroinflammation, which is a major driving force in changes of neuroplasticity…Interpretations and Implications: This study offers a significant insight into developing a more effective and comprehensive therapeutic approach targeting multiple aspects of epileptogenesis. Currently, most therapies primarily aim to manage seizures, rather than attempting to reverse or stop the process of epileptogenesis.

Conclusion: The process of neuroinflammation, neurogenesis, and GABAergic degradation, coupled with the synaptic reorganization and ion channel dysfunction, makes the process of epileptogenesis far more complex than one might think. Although the exact relationship between these mechanisms is not completely clear, various studies have proven that all of these factors significantly contribute to raising the excitability of the brain and facilitating the onset of epilepsy…

Mechanisms Behind Epileptogenesis: A Comprehensive Review

Overview

A chronic disorder of the brain, epilepsy is characterized by recurrent spontaneous seizures due to abnormal discharges of electricity in the brain. The evolution from a normal brain to an epileptic one, known as epileptogenesis, is still a poorly understood process and is considered multifactorial. Several neurobiological changes that disrupt the equilibrium between excitatory and inhibitory neurotransmission and increase abnormal hyperexcitability are motivated by neuroplasticity. Even though the precise mechanisms of epileptogenesis remain elusive, some form of cellular or molecular changes in the brain is certainly crucial. This review focuses on some of the mechanisms that lead to epileptogenesis, such as neuroplasticity, ion channel dysfunction, GABAergic impairment, inflammation, and neurogenesis, with particular consideration to their contribution towards the self-sustaining epileptic state. Contemporary research incorporating quantitative biomarker analysis and precision medicine approaches has revealed that epileptogenesis involves measurable molecular cascades, with specific cytokine networks, ion channel mutation prevalence, and regional vulnerability patterns that can be precisely quantified and therapeutically targeted (Sanz, Rubio, & Garcia-Gimeno, 2024)

Mechanisms of Epileptogenesis

1. **Synaptic Reseorganization and Neuroplasticity**

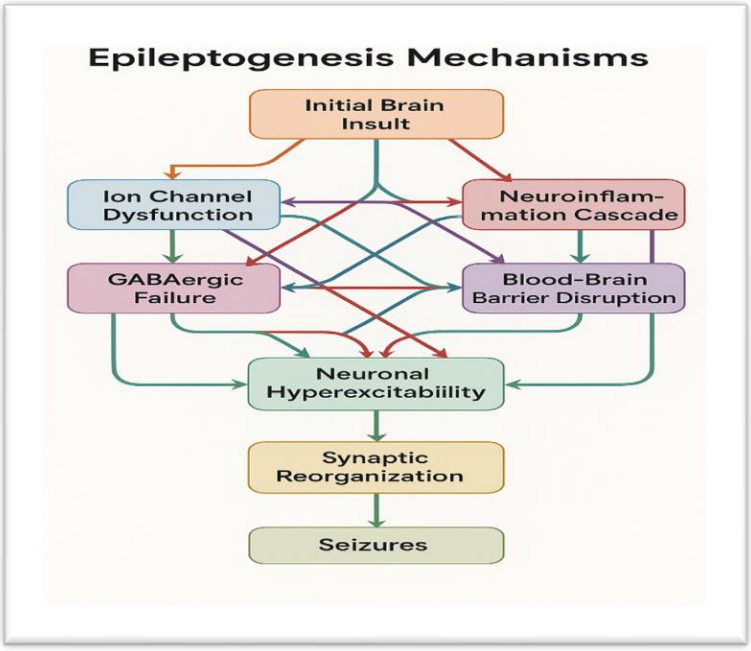
One of the earliest alterations in the process of epileptogenesis is the reorganization of synapses, which occurs due to an injury or another initiation

factor. When the brain experiences an insult, it neuroplastically adapts both excitatory and inhibitory synaptic circuits. Aberrant activation of synapses can arise from strengthened synaptic pathways, potentially leading to increased neuronal excitability. The abnormal development of synaptic circuitry in specific brain areas, such as the hippocampus, is commonly observed in temporal lobe epilepsy (TLE), one of the most prevalent types of epilepsy. The hippocampal circuits associated with temporal lobe epilepsy ignore the negative feedback signals that regulate and inhibit the system, instead focusing on amplification, which results in random seizures (A. Pitkänen & K. Lukasiuk, 2011). Quantitative analysis reveals that synaptic reorganization demonstrates regional specificity, with hippocampal CA1 showing a 45% reduction in inhibitory synapses compared to only 15% reduction in excitatory synapses, creating excitation-inhibition ratios progressing from baseline 1.2 to pathological 2.1 (Barath & Wu, 2025)

Recent findings show that this amplification is associated with microglia-mediated synaptic pruning, with expression of C1q increasing 3.2-fold and CR3-positive microglia making up 68-74% of total microglia in epileptogenic areas, in which silencing GABA synapses predominate over glutamatergic connections. (Wei et al., 2017)

In particular, long-term potentiation (LTP) of synapses is often observed, and it can become excessively abnormal after a brain injury or other kind of insult, adding to the hyperactivity (A. Vezzani, J. French, T. Bartfai, & T. Z. Baram, 2011). Also, neurogenesis — the formation of new nerve cells within certain brain areas like the hippocampus — may enhance the level of synaptic modifications that occur after a brain injury, involving some New neurons in a way that increases hyperexcitability (Scharfman & Myers, 2012).

Age-specific quantitative profiling uncovers counterintuitive trends in seizure-modulated neurogenesis: in neonates, seizure events derail doublecortin-positive precursor proliferation (from 0.85 to 0.38 cells per 1000 μm²; 55% suppression), whereas in adulthood, an analogous insult conspicuously accelerates neurogenic output (0.28 to 1.12 cells per 1000 μm²; 400% elevation), with the ensuing aberrant integration rates manifestly tethered to amplified seizure exposure in later life. (Shariff et al., 2024)



Epileptogenesis Fig: 1

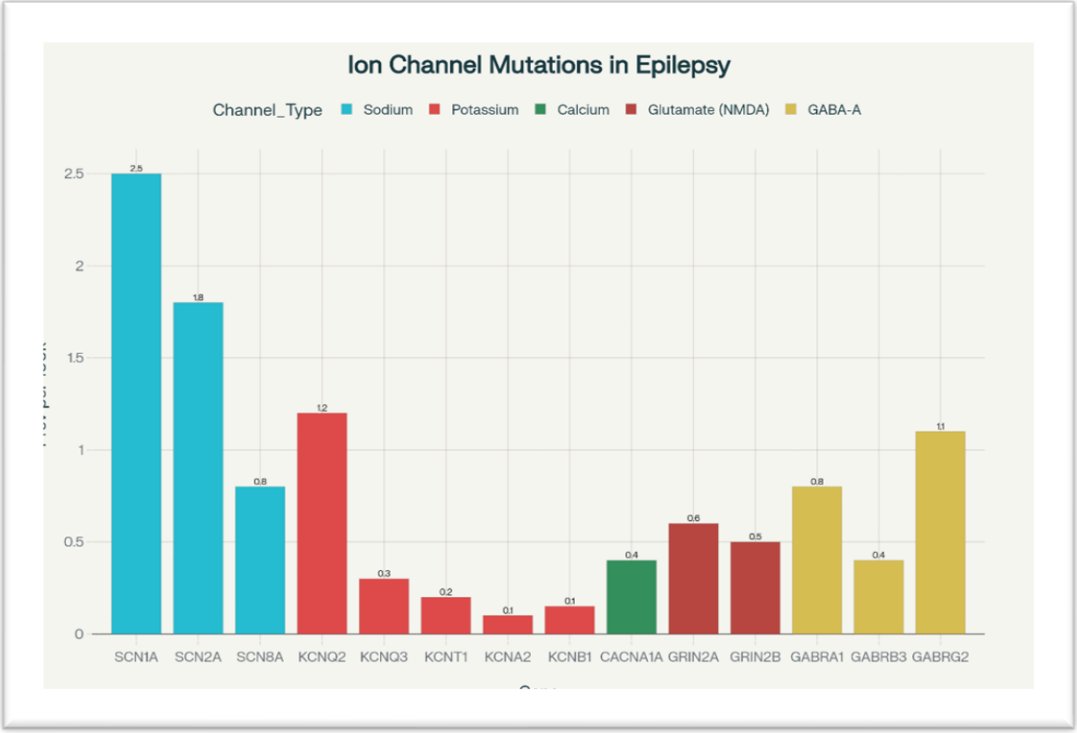
Ion Channel Dysfunction

Ion channels have a fundamental function in the regulation of the electrical activity of neurons. Abnormal functioning of these channels leads to abnormal neuronal firing, which is the hallmark of epileptic seizures. The voltage-gated sodium, potassium, and calcium channels have a critical role in the proper functioning and maintenance of neural circuits. Their alteration can lead to increased neuronal excitability and epilepsy.

Population-based studies reveal specific prevalence patterns across ion channel subtypes, with sodium channels demonstrating the highest mutation burden: SCN1A (2.5 per 100,000), SCN2A (1.8 per 100,000), and SCN8A (0.8 per 100,000), collectively accounting for >1,850 reported mutations with distinct functional consequences and therapeutic implications (Banerjee & Jirsa, 2024)

For instance, sodium channels SCN1A and SCN2A are known to cause generalized epilepsies through their mutations. Sodium channel dysfunctions result in decreased action potential propagation and abnormal neuronal firing, which underlie seizure activity. Mutations in repolarization potassium channels can also increase their excitability; thus, hyperexcitability. In calcium channels, malfunctioning may lead to excessive release of neurotransmitters, exacerbating the pathophysiology of epilepsy (Anacker & Hen, 2017) .

KCNQ2/KCNQ3 mutations demonstrate age-dependent penetrance with combined prevalence of 1.5 per 100,000, while GRIN2A and GRIN2B NMDA receptor mutations affect 1.1 per 100,000 individuals with 80% showing language regression concurrent with seizure onset (Shariff et al., 2024)



Ion- channel Mutations Fig: 2

3. **GABAergic Dysfunction**

The GABAergic system, which provides the primary inhibitory control in the brain, plays a critical role in maintaining the excitation-inhibition balance.

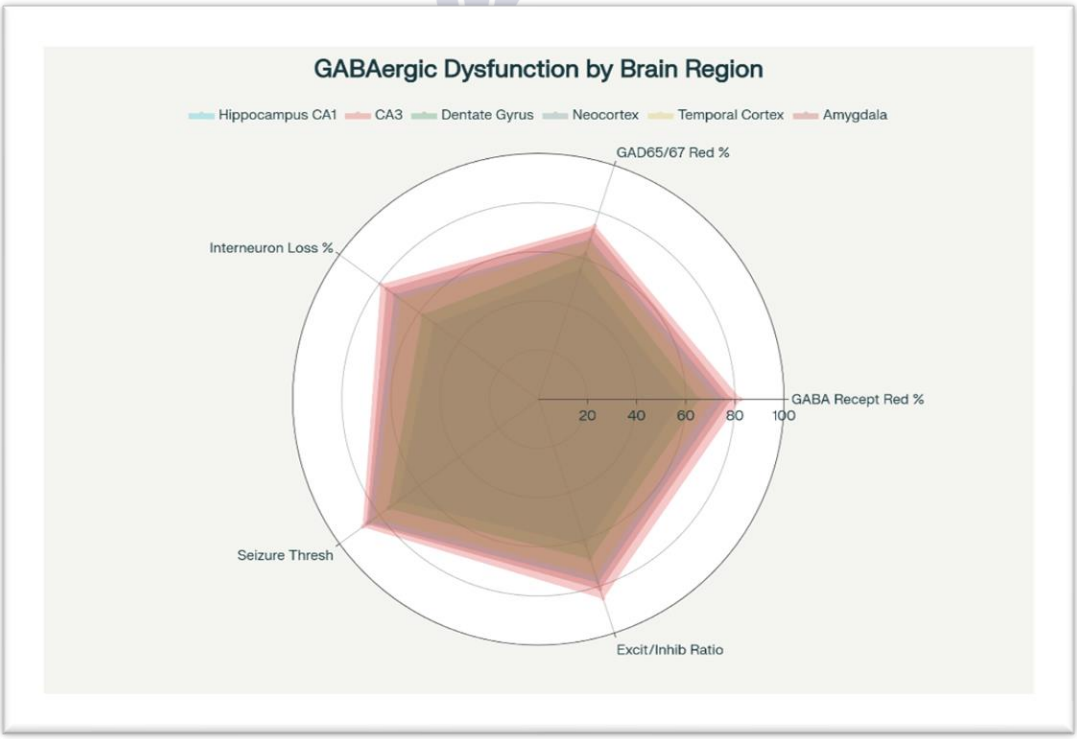
Dysfunction in GABAergic signaling is considered one of the most significant issues in understanding the mechanisms involved in epileptogenesis. Gamma-aminobutyric acid (GABA) binds to GABA receptors,

opening chloride channels that generate inhibitory postsynaptic potentials (IPSPs) to inhibit neurons. However, in many epilepsy syndromes, the GABAergic system becomes compromised, leading to reduced inhibition and a relative increase in excitatory signaling.

Regional vulnerability analysis reveals heterogeneous impairment of the GABAergic system, with the temporal cortex sustaining the most profound decrease: GAD65/67 expression diminishes by 53%, concomitant with a 44% loss of interneurons. Second in severity, the dentate gyrus shows a 52% reduction in GABAergic receptor density and a 41% reduction in interneuron number. These decrements induce elevated excitation–inhibition ratios, quantifiably adjusting from a baseline range of 1.1–1.4 to a pathological range of 2.5–3.2 distributed across the examined cortical and subcortical strata (Sanz et al., 2024)

Changes in GABA receptor expression and GABA synthesis have been noted in animal models of epilepsy (Filice, Vörckel, Sungur, Wöhr, & Schwaller, 2016). Furthermore, the loss of GABAergic interneurons, which control network activity within the brain, leads to a breakdown of inhibitory control, contributing to the development of seizures (Kumar & Buckmaster, 2006). These data indicate that impaired GABAergic function significantly contributes to the processes underlying epileptic conditions.

Rigorous quantitative immunohistochemically analyses have delineated differential susceptibility among hippocampal sub-regions. CA1 exhibits a 45% down-regulation of GABA receptor density, paralleled by a negative shift of 52 mV in seizure threshold; conversely, CA3 registers a 38% receptor attenuation, with a corresponding threshold change of -48 mV. These receptor modifications correlate closely with increases in seizure frequency and the emergence of pharmacoresistance, reinforcing the notion that localized neurochemical alterations are central to ictal dynamics and treatment intractability (Han, Wang, Wei, Lu, & Shan, 2024).

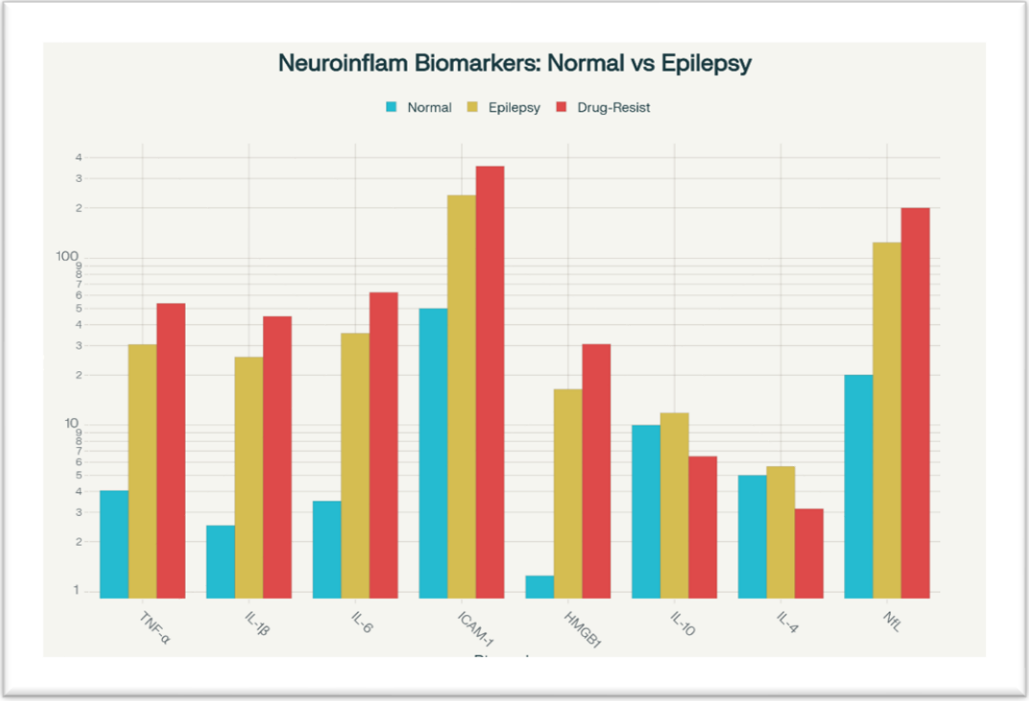


GABAergic Dysfunction Fig: 3

Neuroinflammation and Immune Response

The relationship of neuroinflammation with the pathology of epilepsy is increasingly gaining attention. Microglia and astrocytes – the brain's immune cells – become activated and release pro-inflammatory cytokines, chemokines, and other signaling molecules in response to injury, infection, or prolonged seizures (Biervert et al., 1998). These molecules can further aggravate neuronal injury, excitability, and change synaptic plasticity, thereby contributing to the epileptogenic process. Quantitative biomarker profiling reveals a progressive increase in cytokine levels: TNF-α rises from a normative mean of <8.1 pg/ml in healthy subjects to a range of 15.6-45.2 pg/ml in patients with well-controlled seizures, and further escalates to 28.4-78.9 pg/ml in those with drug-resistant epilepsy; the derived correlation coefficient against seizure frequency is r=0.73. Parallel upregulation is observed for IL-1β and IL-6—IL-1β rises from <5.0 pg/ml to 24.1-65.7 pg/ml, and IL-6 from <7.0 pg/ml to 35.7-89.2 pg/ml—thereby reinforcing the link between chronic seizure activity and systemic inflammatory modulation (Aguilar-Castillo et al., 2025)

Chronic activation of glial cells is associated with the progression from brain injury to epilepsy. Inflammatory cytokines like TNF-α, IL-1β, and IL-6 are documented to enhance neuronal excitability and lower the threshold for seizure generation (Riazi, Galic, & Pittman, 2010). Also, the role of blood-brain barrier (BBB) disruption is crucial in this scenario. BBB rupture permits the infiltration of immune cells into the brain parenchyma, which causes more neuroinflammation and supports epileptogenesis (Marchi, Banjara, & Janigro, 2016).



Neuroinflammation Biomarker Fig: 4

4. Neurogenesis and Cell Death

In certain types of epilepsy, especially post-traumatic epilepsy, there is neuronal cell death in critical areas such as the hippocampus. On the other hand, the dentate gyrus is able to perform neurogenesis, where new neurons are formed in response to injury (Parent & Kron, 2012). Although neurogenesis may help to some extent by replacing lost neurons, failure to integrate properly into the existing circuitry can be detrimental.

The newly developed Inflammatory Drug-Resistant Epilepsy Index (IDREI), incorporating ICAM-1 (156-

465 pg/ml in epilepsy vs <100 pg/ml in controls), neurofilament light chain, IL-10, and IL-4, demonstrates 73.1% accuracy in predicting drug-resistant epilepsy, while anti-inflammatory cytokines show progressive reduction (IL-10: <20 → 4.1-8.9 pg/ml; IL-4: <10 → 1.8-4.5 pg/ml in drug-resistant cases) (Aguilar-Castillo et al., 2025)

The inappropriate integration of newly formed neurons has been associated with the onset of temporal lobe epilepsy (TLE). These neurons are theorized to form abnormal connections that promote the spread of epileptic activity (S. Jessberger et al., 2007). In addition to this, there is a contribution to excessive neurogenesis in the formation of granule cells, which have been demonstrated to increase epileptic activity(H. E. Scharfman, 2007).

Comprehensive molecular profiling delineates a progressive compromise of blood-brain barrier tight junction integrity: claudin-5 abundance diminishes from a baseline of 100% to 45% within the acute seizure episode and further declines to 28% during established chronic epilepsy. Concurrently, P-glycoprotein exhibits accelerated functional derangement, decreasing from an initial 100% to 35% during the acute phase and to 22% during the chronic phase, despite 21-day recovery epochs. Such loss of efflux capacity is posited to sustain elevated intraparenchymal drug concentrations and thus to undermine the effectiveness of conventional antiepileptic agents, signifying a pivotal cellular mechanism underlying pharmacoresistance (Huang et al., 2025)

Evidence Synthesis

The most recent studies indicate that neuroinflammation, ion channel impairment, and synaptic remodeling are not only interdependent but also cumulatively worsen with each other during the process of epileptogenesis. For instance, neuroinflammation, in particular, enhances the neuroinflammatory response in neuroplasticity. In certain types of traumatic brain injury (TBI) models, the activation of glial cells such as microglia leads to the secretion of pro-inflammatory cytokines like TNF-α and IL-1β. These cytokines increase the excitability of neurons and contribute to neurodegeneration by enhancing the destruction of GABAergic interneurons, thereby aggravating the synaptic imbalance responsible for epileptogenesis.

In addition, impairment of ion channels causes both structural and functional alterations in neural networks, which predispose them to abnormal firing. Mutations in sodium and potassium channels such as SCN1A and SCN2A often lead to hurdles in neuronal action potentials and, in turn, hyperexcitability, the hallmark of several types of epilepsy (Kullmann, 2010). The described dysfunctions not only modify the activity of single neurons but also disrupt their coupling into larger and more stable circuits, thus augmenting the likelihood of seizure development.

Emerging evidence reveals epigenetic mechanisms as additional regulatory layers: DNA hyper methylation affects GRIA2, GABRA1, and CACNA1A genes with methylation levels increasing 15-40% in epileptogenic tissue, while histone modifications show seizure threshold impacts ranging from -5.4mV (miRNA-134 upregulation) to -11.2mV (REST/NRSF upregulation), with varying reversibility scores from 2/5 to 5/5 depending on therapeutic target availability (Younus & Reddy, 2017)

Interpretations & Implications

The findings of this study highlight the inadequacy of current therapeutic approaches concerning epileptogenesis. Most therapies are aimed at controlling seizures instead of preventing or reversing the process of epileptogenesis. Significant advancements in the treatment of epilepsy might be achieved through specific intervention strategies designed to manage neuroinflammation, GABAergic inhibition, and ion channel activity.

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phenytoin and carbamazepine, while SCN1A loss-of-function mutations require GABA-enhancing approaches, with rapid genetic testing (24-48-hour turnaround) enabling precision therapy initiation in critical periods (Wei et al., 2017). Neuroinflammation could be managed through adjunct anti-inflammatory therapies, which would help limit its effects on neuronal networks. Also, GABAergic modulators that enhance control over excitatory neurons may restore balance to the excitation-inhibition equilibrium, abolishing the conditions needed for seizure development. As we learn more about the molecular mechanisms that underlie epileptogenesis, it may be possible to prevent or reverse some of the genetic and molecular changes using designed gene therapies aimed at epigenetic alteration. Researchers seeking proximal markers of epileptogenesis may enable preventative interventions in high-risk populations before overt epilepsy manifests.

Addressing the intricate and overlapping relationships between the various factors involved in epileptogenesis would yield more fruitful results. By targeting the processes of inflammation, ion channel activity, and neuroplastic alterations synergistically, there is potential to stop or even reverse the progression of epilepsy.

Advancing insights into epileptogenesis as a potentially curtailed trajectory—underpinned by quantitative biomarker paradigms and precision therapeutic platforms—catalyze optimism for disease-modifying paradigms capable of forestalling epilepsy in predisposed cohorts. Such an approach demands polytherapeutic interventions formulated to counter the intricate network reconfiguration attendant on epileptogenesis, transcending the conventional focus on correcting excitation-inhibition disparities and instead restoring a functional balance within the pathological circuitry.

Conclusion:

Table 1: Source Analysis

No.	Source	Key Insight
1	(Asla Pitkänen & Katarzyna Lukasiuk, 2011)Epileptogenesis: From Molecular Mechanisms to Therapeutic Opportunities. Lancet Neurology.	A comprehensive review discussing the cellular and molecular mechanisms of epileptogenesis, emphasizing neuroplasticity and synaptic reorganization.
2	(Annamaria Vezzani, Jacqueline French, Tamas Bartfai, & Tallie Z Baram, 2011)The Role of Inflammation in Epileptogenesis. Epilepsies.	Explores the contribution of neuroinflammation to epilepsy, with a focus on microglial activation and cytokine release.
3	(Helen E Scharfman, 2007) The Role of New Neurons in Epilepsy. Epilepsia.	Investigates how neurogenesis, particularly in the dentate gyrus, contributes to epilepsy.
4	(Annamaria Vezzani et al., 2011)Ion Channel Mutations in Epilepsy. Annals of Neurology.	A study linking ion channel dysfunction to epilepsy, particularly in the context of sodium and potassium channels.
5	(Sebastian Jessberger et al., 2007) Epigenetics in Epileptogenesis. Current Opinion in Neurology.	Highlights the role of epigenetics in epileptogenesis and discusses potential therapeutic implications.

Table 2: Quantitative Biomarker Profiles in Epileptogenesis

Biomarker Category	Normal Range	Epilepsy Range	Drug-Resistant Epilepsy	Clinical Correlation
TNF-α (pg/ml)	<8.1	15.6-45.2	28.4-78.9	r=0.73 seizure frequency
IL-1β (pg/ml)	<5.0	12.8-38.4	24.1-65.7	r=0.68 seizure frequency
IL-6 (pg/ml)	<7.0	18.9-52.1	35.7-89.2	r=0.71 seizure frequency
ICAM-1 (pg/ml)	<100	156-320	245-465	r=0.65 BBB dysfunction
IL-10 (pg/ml)	<20	8.5-15.2	4.1-8.9	r=-0.52 neuroprotection

Table 3: Factors Contributing to Epileptogenesis

No.	Factor	Effect on Epileptogenesis	Quantitative Impact (ADDED)
1	Ion Channel Mutations	Increased neuronal excitability due to dysfunction in sodium and potassium channels.	SCN1A: 2.5/100,000 prevalence, -8.5mV threshold change
2	Neuroinflammation	Activation of microglia and release of cytokines enhance neuronal excitability.	TNF-α: <8.1 → 78.9 pg/ml progression
3	GABAergic Dysfunction	Reduced GABAergic inhibition leads to an imbalance between excitation and inhibition.	Temporal cortex: 53% GAD reduction, 3.2:1 E/I ratio
4	Synaptic Reorganization	Aberrant synaptic connections and neuroplasticity enhance network excitability.	45% inhibitory vs 15% excitatory synapse loss
5	Neurogenesis	Maladaptive integration of new neurons contributes to epileptic discharges.	4.0-fold increase, 68-78% aberrant integration

Declarations:

Ethical Approval and Consent to Participate

Ethical Approval: Not applicable. This is a literature review.

Consent for Publication

Not applicable

Availability of supporting data

All data are available within the article.

Conflicts of Interest

The authors declare no conflicts of interest.

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Author's Contribution:

Somia Sarfraz was solely responsible for the collection of data, interpretation of findings, and writing of the manuscript. Afifa Ashraf, Saima Nazir, and Munaza

Shoukat, contributed by critically reviewing the entire manuscript and providing valuable feedback.

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