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Original Research Article

Pharmacological Therapies for Seizures and Epilepsy

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Abstract:

Epilepsy, a chronic neurological disorder characterized by recurrent, unprovoked seizures, affects millions worldwide. Despite advances in understanding its pathophysiology, epilepsy remains a complex condition influenced by genetic, developmental, and environmental factors. This research delves into the anatomical and physiological mechanisms underlying seizure generation, focusing on inflammation, blood-brain barrier dynamics, the mTOR pathway, and cellular electrophysiology. Additionally, the study explores the classification of seizures and the specificities of Mesial Temporal Lobe Epilepsy (MTLE) and genetic epilepsy. With the growing demand for effective treatments, this work reviews current pharmacological therapies, including traditional anticonvulsants like Carbamazepine and Valproate, as well as emerging treatments like Cannabidiol and Brivaracetam. By examining the mechanisms of action and therapeutic efficacy of these drugs, the research aims to provide a comprehensive understanding of how these therapies contribute to seizure management. This work offers valuable insights for clinicians and researchers alike, aiding in the development of more targeted and effective treatment strategies for epilepsy.

Keywords: Epilepsy, Seizures, Pharmacological Therapies.

Introduction

Seizures and Epilepsy: A seizure is a transient and sudden event that results from abnormal, excessive, synchronous discharges of neurons in the brain, which can affect the behavior, movements, feelings, and consciousness of the person experiencing it [1][2].

Seizure is a clinical presentation due to the abnormal and synchronized neuronal activities which are predominantly found in the cerebral cortex [3]

Epilepsy is a long-lasting condition of the brain that leads to repeated episodes of seizures, which are sudden, intense, and coordinated electrical impulses in the

brain cells that alter the person's actions, feelings, and awareness [4][5]to diagnose epilepsy, you need to have two or more seizures that happen without a clear cause and are more than 24 hours apart. This is the standard definition of epilepsy, but the ILAE (a group of experts on epilepsy) suggested some changes to make it more accurate. They said that epilepsy is a brain disease that can be defined by any of these situations:

- You have two or more seizures that are not triggered by anything and are separated by more than 24 hours.
- You have one seizure that is not triggered by anything, and you have a high chance (at least 60%) of having more seizures in the next 10 years, like someone who had two unprovoked seizures.
- You have a specific type of epilepsy that is known as an epilepsy syndrome.[6]

Anatomical and Physiological mechanisms of seizures: At the crossroads of intricate anatomical and physiological phenomena, seizures unfold as dynamic neurological events, involving a cascade of factors such as inflammation, blood-brain barrier dynamics, mTOR pathway regulation, apoptosis, ion channel imbalances, neurogenesis, oxidative stress, and thalamocortical circuitry disruptions.

1. Inflammation and Blood-Brain Barrier Dynamics:

The interplay between inflammation and the integrity of the blood-brain barrier assumes a pivotal role in the orchestration of seizure events.

Inflammatory cascades cultivate an environment conducive to seizures by amplifying hyperexcitability. Functioning as a safeguard, the blood-brain barrier meticulously governs the influx of inflammatory mediators, influencing susceptibility to sei-

zures [7].Inflammation possesses the potential to impact the endothelial layer of cerebral vessels, disrupt connections between endothelial cells, and trigger abnormal angiogenesis. These changes culminate in heightened permeability of the blood-brain barrier and infiltration of immune cells [8].

Dysfunction in the blood-brain barrier and concurrent neuroinflammation stand out as contributors to seizure initiation. Compromised blood-brain barrier integrity facilitates the entry of pathogens, blood cells, and endo- and exogenic substances into the brain, initiating local inflammation and angiogenesis, potentially exacerbating epilepsy [8].

Activation of brain mast cells, induced by allergic, environmental, and/or stress-related triggers, can result in focal disruption of the blood-brain barrier and neuroinflammation. This intricate interplay contributes significantly to the genesis of seizures [9]

2. mTOR Pathway and Apoptosis:

The intricate mTOR pathway, a sophisticated signaling network governing the synthesis of proteins and the regulation of cellular growth, plays a pivotal role in the molecular processes of epileptogenesis – the transformation of a typical brain into an epileptic one. Perturbations in this pathway, arising from genetic mutations, environmental influences, or pharmacological agents, can incite irregular proliferation and survival of both neurons and glia. These modifications contribute to structural and functional alterations in the brain, establishing conditions favorable for the onset of seizures. Apoptosis, a programmed cellular demise mechanism eliminating damaged or unnecessary cells, is also intricately associated with epilepsy, serving as either a trigger or a consequence of excessive neuronal excitation and inflammation. A comprehensive grasp of the involvement of apoptosis and the mTOR pathway in epilepsy holds the promise of revealing innovative targets for therapeutic interventions aimed at preventing or mitigating seizure activity [10][11].

3. Cellular Electrophysiology

Cellular electrophysiology, explained in depth in a specific chapter, reveals the fundamental processes of epilepsy. Phenomena such as "abrupt ‘paroxysmal’ depolarization shifts (PDSs) that occur synchronously in the majority of neurons in the local area"[12], "hypersynchronous neuronal activity during seizures", and "feedback inhibition of excitatory neurons by inhibitory interneurons"[13] are essential for understanding how seizures start and spreading.

4. **Excitation, inhibition and hyperexcitability**

The anatomic and physiological mechanisms of seizures are influenced by the dynamic balance between excitation and inhibition in the brain, which is regulated by various factors such as neurotransmitters, ion channels, glia, and blood-brain barrier. When this balance is disrupted, neuronal hyperexcitability and network hyperactivity can emerge, leading to abnormal electrical activity and seizure generation. The alterations in the expression and function of neurotransmitter receptors and ion channels, such as GABA, glutamate, and HCN channels modulating the excitation-to-inhibition (E/I) ratio and the threshold for neuronal firing. The involvement of glial cells, such as astrocytes and microglia, in regulating synaptic transmission and inflammation, which can affect the integrity of the blood-brain barrier and the permeability of immune cells and molecules.

Furthermore, it impacts the hyperexcitability and hyperactivity on synaptic plasticity, neurogenesis, oxidative stress, and thalamocortical circuitry, which can contribute to the cognitive and behavioral impairments associated with seizure, epilepsy and other Neurological disorders.[14][15]

5. Genetic, Developmental, and Metabolic Factors for the development of Seizures.

Seizures can occur due to various factors that affect the brain’s normal functioning such as inherited or spontaneous mutations in genes that regulate neuronal activity, ion channels, neurotransmitters, or metabolic pathways [16][17]. Some are developmental, such as problems in the early formation of the fetal brain, brain malformations, or genetic syndromes that involve epilepsy as a symptom [18].

Some are metabolic, such as very low blood levels of glucose, sodium, calcium, or magnesium, or inherited metabolic conditions that increase the likelihood of seizures [19]. These factors can interact with each other and with environmental triggers to cause seizures and epilepsy.

Pathophysiology

Seizures are abnormal and excessive neuronal discharges that result from various factors that disrupt the normal balance between excitation and inhibition in the brain. The pathophysiology involves multiple levels of analysis, from molecular to network, and is influenced by genetic, environmental &metabolic factors.

- **Molecular mechanisms**: Several molecules that constitute the inflammatory milieu in the epileptogenic area activate intracellular signaling pathways in neurons, glia, and cellular components of the blood-brain barrier, resulting in pathologic modifications of cell function. These molecular entities ultimately lead to alterations in synaptic transmission and plasticity, ion channel function, neurotransmitter metabolism & gene expression [20][21].
- **Synaptic mechanisms**: Synaptic dysfunction

is a hallmark of seizure pathophysiology, as it affects the communication and integration of neuronal signals. Epileptic activity causes numerous modifications in synapse function, such as changes in the probability of neurotransmitter release, the subunit composition of postsynaptic receptors, the expression of synaptic proteins, and the morphology and activity of glial cells. These changes can either enhance or reduce synaptic efficacy, depending on the type, location, and timing of the synapse [22][23].

- **Cellular mechanisms**: At the cellular level, seizure pathophysiology involves the intricate dynamics of membrane potential, intracellular calcium, and metabolic state of neurons and glia. Abnormalities in ion channels, neuronal excitability, and synaptic connectivity can precipitate seizure activity, while changes in calcium homeostasis, energy metabolism, and oxidative stress can modulate seizure susceptibility and severity. Moreover, cell death, neurogenesis, and gliosis can alter the structure and function of the epileptic network [24][25].
- **Network mechanisms**: Seizure pathophysiology also depends on the organization and interaction of neuronal circuits and networks. Seizures can originate from specific brain regions, such as the hippocampus or the neocortex, and propagate to other areas through specific pathways, such as the commissural or the thalamocortical connections. The network properties that influence seizure dynamics include the topology, connectivity, synchrony, and plasticity of the neuronal populations, as well as the modulation by neuromodulators, hormones, and systemic factors [26][27]

Classification of seizures:

In accordance with the 2017 revised classification, seizures are categorized based on distinct criteria:

- The specific region within the brain where they originate.
- The individual's level of consciousness or awareness (during the seizure episode)
- Other distinctive features exhibited during the seizure event [28].

Seizures classification based on the specific region within the brain where they originate:

- **Focal seizures:** previously termed partial seizures, arise from a localized area or network of cells on one hemisphere of the brain**.**
- **Generalized seizures:** formerly known as primary generalized seizures, initiate simultaneously in networks spanning both hemispheres of the brain**.**
- **Seizures with an unknown onset:** are categorized as such if the precise commencement of the seizure is indeterminate; however, their classification may be reassessed if the onset becomes noticeable over time.
- **Focal to bilateral seizures:** Previously referred to as secondary generalized seizures, commence in one specific region or hemisphere of the brain before spreading to involve both hemispheres. The revised terminology distinguishes generalized seizures solely by their onset, with the term "focal to bilateral seizure" now replacing the previous designation of "secondary generalized seizure."

Seizures classification based on the individual's level of consciousness or Awareness.

- **Focal aware seizures:** occur when consciousness remains intact, even if the individual experiences an inability to communicate or respond during the seizure episode. This terminology replaces the previous classification of "simple partial" seizures**.**
- **Focal impaired awareness:** characterized by a disruption or impairment of consciousness at any point during the seizure event, even if the individual retains a vague understanding of the situation. This terminology replaces the former designation of "complex partial" seizures.
- **Awareness unknown:** Seizures where it is impossible to ascertain the individual's level of awareness, such as when they live alone or experience seizures exclusively during nighttime, the term "awareness unknown" may be employed, or the awareness aspect may not be specified at all.
- **Generalized seizures**: presumed to impact an individual's awareness or consciousness to some extent; therefore, no specific terminology relating to awareness is necessary for their classification**.**

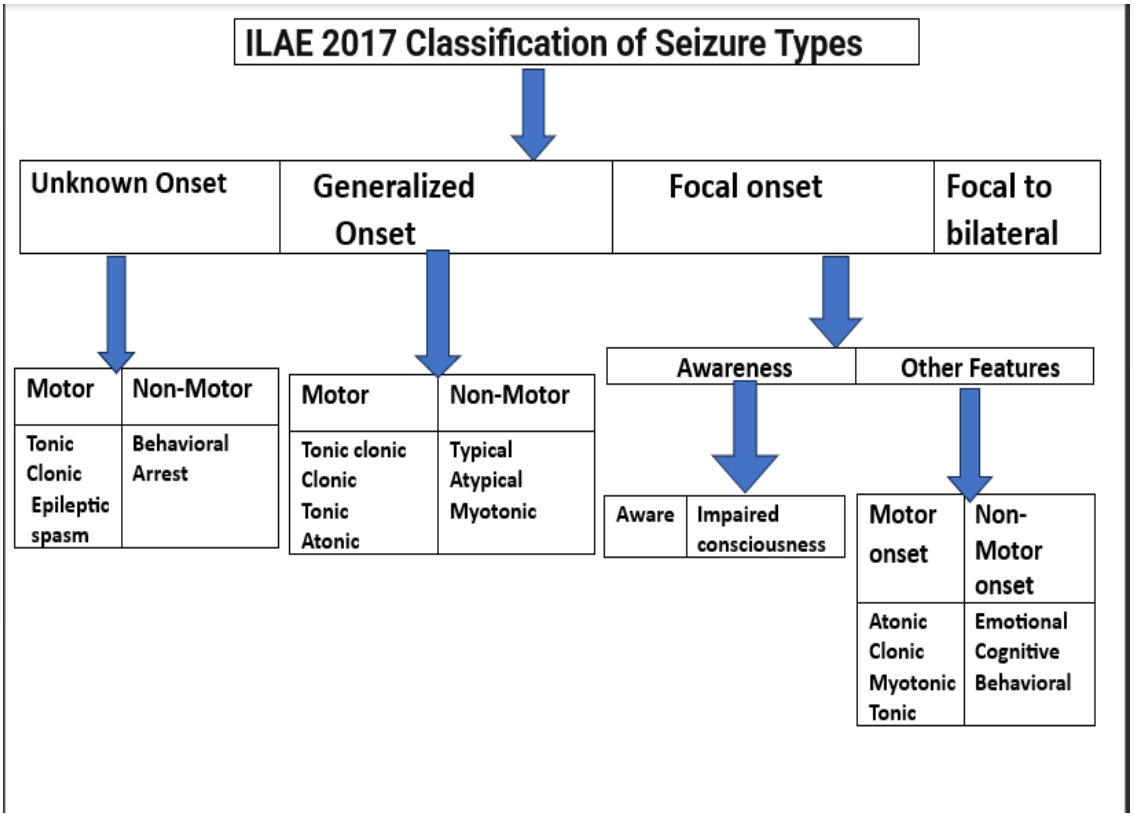

Figure 1: Classification of seizures

Mesial Temporal Lobe Epilepsy

Mesial Temporal Lobe Epilepsy (MTLE) presents as a specific form of focal epilepsy targeting the inner regions of the temporal lobe, notably impacting structures like the hippocampus, Para hippocampal gyrus, and amygdala. It stands as the predominant variant of temporal lobe seizures, constituting approximately 80% of such cases.[29]. Individuals grappling with MTLE encounter varied seizure manifestations, including focal aware seizures (commonly known as auras) and focal impaired awareness seizures (referred to as complex partial seizures). These episodes exhibit diverse symptoms, such as sensations of déjà vu, fear, epigastric sensations, olfactory or gustatory hallucinations, automatisms, and compromised language function.[30]

The etiology of MTLE remains incompletely elucidated; however, several risk factors have been identified, encompassing brain injury, infection, stroke, tumors, or genetic predispositions that inflict damage or scarring on the temporal lobe. A prevalent observation in MRI scans of MTLE patients is hippocampal sclerosis, characterized by neuronal loss and hippocampal shrinkage. This pathology can detrimentally impact memory, learning capabilities, emotional well-being, and psychiatric stability. Despite therapeutic interventions, MTLE often exhibits resistance to anticonvulsant medications, necessitating alternative approaches like surgical intervention, particularly if seizures originate from the non-dominant hemisphere, typically the right hemisphere for most individuals. Nonetheless, surgical procedures entail potential risks and complications, such as cognitive decline, memory impairment, or alterations in personality, underscoring the imperative for meticulous evaluation of surgical benefits versus drawbacks.[31]

MTLE constitutes a chronic and formidable condition exerting profound ramifications across various domains of life, including physical health, mental well-being, social interactions, educational pursuits, and vocational engagements.

Hence, seeking professional assistance and comprehensive support from a multidisciplinary healthcare team comprising doctors, nurses, neurologists, psychologists, psychiatrists, social workers, and other pertinent specialists is paramount for effective management. Additionally, engagement with support groups or online communities tailored for individuals with epilepsy can furnish invaluable resources for navigating the emotional and practical challenges associated with MTLE.

Genetic Epilepsy

Genetic epilepsy refers to a category of epilepsies resulting from mutations in specific genes. These mutations can either be inherited or occur spontaneously during embryonic development, disrupting various aspects of brain function such as neuronal excitability, synaptic transmission, ion channel activity, and metabolic pathways. The manifestations

of genetic epilepsy are contingent upon the type and location of the gene mutation, giving rise to diverse seizure types, syndromes, and clinical features [32].

Here are a few examples:

- Pyridoxal 5-phosphate dependent epilepsy: This uncommon form of epilepsy arises due to an enzyme deficiency hindering the conversion of vitamin B6 into its active form. Consequently, neurotransmitter synthesis is compromised, leading to heightened neuronal excitability. Seizures typically initiate in infancy and show resistance to most anticonvulsant drugs.

However, therapeutic relief can be attained through elevated doses of vitamin B 6[33]

- **Benign Familial Infantile Epilepsy**

Distinguished by mutations in genes regulating sodium or potassium channels, this mild epilepsy variant prompts brief seizures occurring between 3 and 12 months of age, often resolving by age 2. Individuals with this condition commonly reach normal developmental milestones and intelligence, negating the necessity for long-term treatment.

- **Dravet syndrome:**

An aggressive epilepsy form stemming from mutations in the SCN1A gene, responsible for encoding a sodium channel subunit crucial for generating and propagating neuronal action potentials. Seizures, frequently triggered by fever, infections, or vaccinations, commence within the first year of life.

They are accompanied by developmental delays, cognitive impairment, behavioral issues, and an increased risk of sudden unexpected death in epilepsy (SUDEP).[34]

Genetic testing emerges as an indispensable diagnostic tool for identifying genetic epilepsy and shaping treatment strategies. It imparts insights into inheritance patterns and the familial recurrence risk. Nevertheless, the accessibility and conclusiveness of genetic testing vary, and some genetic epilepsies remain shrouded in limited understanding.

Consequently, seeking counsel from a neurologist and a genetic counselor, both prior to and after genetic testing, remains imperative.

Pharmacologic Therapy

Table 1: commonly used drugs for seizures [35]

Drugs	Mechanism of Action	Seizure Type
Carbamazepine	Blocks sodium channels and reduces glutamate release	Focal, generalized tonic-clonic, and mixed seizures
Valproate	Increases GABA levels and blocks sodium and calcium channels	Focal, generalized, and absence seizures
Lamotrigine	Blocks sodium and calcium channels and inhibits glutamate release	Focal, generalized, and absence seizures
Diazepam	Enhances GABA activity and produces sedation	All types of seizures, especially status epilepticus
Cannabidiol	Modulates multiple neurotransmitter systems and reduces inflammation	Severe or hard-to-treat seizures, such as Lennox-Gastaut syndrome and Dravet syndrome
Brivaracetam	Binds to synaptic vesicle protein 2A and inhibits neurotransmitter release	Focal onset seizures
Cenobamate	Blocks sodium channels and modulates GABA receptors	Focal onset seizures

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