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Advances and Challenges in Understanding and Treating Epilepsy: A Concise Review

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ABSTRACT

Epilepsy is a chronic brain disorder characterized by recurrent and unprovoked seizures. The uncontrolled, abnormal, paroxysmal discharge of neurons in the brain initiates seizures, which are clinical manifestations of epilepsy. The International League Against Epilepsy (ILAE) classified seizures into three categories: focal, generalized, and unknown-onset seizures, based on clinical characteristics and affected brain regions. Treatment for epilepsy primarily involves anti-seizure medications (ASMs) that help stabilize the electrical signals in the brain. However, 30% of patients appear to be refractory to treatment. ASMs effectively control seizures but do not influence epileptogenesis, the silent seizure-free period from brain injury to the first unprovoked seizure. The exact mechanism of epileptogenesis remains controversial. Consequently, advancements in treatment could stem from a deeper understanding of epilepsy's underlying pathophysiology. Besides, there is a critical need for new pharmaceuticals that are both safe and effective in preventing epilepsy progression and improving patients' quality of life. This article reviews epilepsy and epileptogenesis pathophysiology, the recent classification of seizure types, current treatment strategies, and animal models used to better understand epilepsy. Additionally, it discusses the emerging research directions for antiepileptogenic drugs, highlighting recent advancements aimed at addressing the limitations of current ASMs and offering new insights into epilepsy treatments.

Keywords: epilepsy; seizures; epileptogenesis; anti-seizure medications.

1. Introduction

The International League Against Epilepsy (ILAE) defines epilepsy as a brain disorder characterized by the occurrence of at least two unprovoked (reflex) seizures more than 24-hours apart, or one unprovoked seizure with a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next ten years, or receiving an epilepsy syndrome diagnosis (**Fisher et al., 2014**). Epileptogenesis refers to the period between an initial brain insult and the onset of the first unprovoked seizures, during which significant neuronal alterations take place (**León Navarro, Crespo, & Martín, 2020**)**.** A common feature in epilepsy is the disrupted balance between excitatory (glutamatergic) and inhibitory γ-aminobutyric acid ((GABA)ergic) signals at the synaptic level, which can trigger seizures. Beside this classical assumption, other new mechanisms are still arising, and the exact pathophysiology of epilepsy is still controversial, far more complex, and not fully understood (**Walker & Kozlowski, 2005**)**.** The term "epileptic seizure" was used to differentiate seizures resulting from abnormal neuronal firing from those resulting from nonepileptic events **(Shorvon, Andermann, & Guerrini, 2011)**. The ILAE classifies seizures into three categories: a) focal, b) generalized, and c) unknown-onset seizures (Table 1). The current antiseizure medications (ASMs) are the first-line drugs used for epilepsy treatment. Nevertheless, they are still insufficient and challenging (**Ghosh et al., 2023**) and not all patients respond to treatment (**Kwan & Brodie, 2000**). Hence, alternative approaches for drug-resistant epilepsy and targeting the biological mechanisms underlying epileptogenesis represent a promising strategy for epilepsy prevention. However, efforts to selectively address molecular pathways to prevent or modify the development of epilepsy have been limited, with no therapeutic intervention achieving success to date (**Shariff et al., 2024**). This review aims to comprehensively explore and critically analyze various aspects of epilepsy, including epileptogenesis, postulated mechanisms, the current classification of epileptic seizures, and the limitations of existing ASMs. Furthermore, it seeks to highlight the ongoing efforts and emerging perspectives in targeting biological pathways for the prevention and management of epilepsy.

Discussion

1. Molecular mechanisms of epileptogenesis

Epileptogenesis is a progressive pathological process (Figure 1) that transforms certain brain regions into epileptic ones that tend to cause spontaneous seizures (**León Navarro et al., 2020)**. Both acquired and hereditary variables could be to blame. Previously, epileptogenesis was only expressed as the latent period "LP," which denoted the time interval between the epileptogenic insult and the onset of unprovoked clinical seizures. Recently, researchers have taken into account the observed subconvulsive seizures that followed the first one, as well as the increase in severity and occurrence of seizures over time (**Pitkänen, Lukasiuk, Dudek, & Staley, 2015**). As a result, the new terminology of epileptogenesis comprises multistage processes, beginning with the development of epileptogenic tissues and extending to the propagation of the epilepsy condition over time. Epileptogenesis may be triggered by genetic factors or acquired ones (**Curatolo et al., 2018**). Genetic factors include genetic abnormalities in ion channels, neurotransmitter receptors, or any other related components that modify their typical functioning or disturb the equilibrium between the excitatory and inhibitory inputs (Steinlein, 2004). Acquired factors can result

from a number of brain insults and neurological diseases with wide etiological diversity sharing one common outcome of brain epileptiform activity (Zilberter, Popova, & Zilberter, 2022).

1.1. The imbalance between excitatory and inhibitory neurotransmission

Gamma-aminobutyric acid (GABA) is considered the main inhibitory neurotransmitter; while glutamate is the main excitatory neurotransmitter. An imbalance between them, either by decreased inhibition, increased excitation, or both, greatly contributes to seizure generation (**van van Hugte, Schubert, & Nadif Kasri, 2023**).

1.2. The implication of neuroplasticity in epileptogenesis

Neuroplasticity is a broad term that describes the ability of the brain to adapt and respond to external insults, including injury and diseases (**Steers & Klausner, 2008**). The process by which the brain develops epilepsy is regarded as the prototypical example of plasticity (**Scharfman, 2002**). In addition, epileptic seizures are associated with complex patterns of both acute and long-term neuroplastic changes. For example, the expression of immediate early genes (IEGs), which are important for neuroplastic processes and the treatment of neurological disorders like epilepsy, is considered one of the earliest neuroplastic alterations (**Jarero-Basulto et al., 2018**). Another example of structural plasticity is neuronal loss and neurogenesis, which result in the remodeling of cell membrane matrixes and the sprouting of mossy fibers in granule cells and the hippocampal CA3 region **(Sasa, 2006**). Consequently, plasticity may be adaptive or maladaptive. Furthermore, it may be directly related to seizures or indirectly, where seizures induce cell damage that acts as the real stimulus (**Scharfman, 2002**). Further studies are needed to understand the exact implication of neuroplasticity in epileptogenesis in order to enhance the desired plasticity changes and prevent the undesired ones.

2. Epileptic seizures

2.1. Focal seizures

Focal seizures are restricted to one side of each of the two cerebral hemispheres or a particular area of the brain (**Kumar, Maini, Arya, & Sharma, 2023**). They are further subdivided into two categories: intact and impaired awareness seizures, and motor and non-motor seizures, based on the level of consciousness and the type of onset, respectively. Focal seizures may be known as simple (aware) partial seizures (**Foldvary-Schaefer & Wyllie, 2007**) or complex (impaired awareness) partial seizures (**Patel & De Jesus, 2023**). **Focal to bilateral**, previously known as secondary generalized seizures, start as focal seizures that further affect both hemispheres. It is usually preceded by auras that may vary from sensory symptoms to motor ones, e.g., convulsions that may be clonic, tonic, or both (**Martz & Bertram, 2010**).

2.2. Generalized seizures

Generalized seizures may be further subclassified into tonic-clonic, atonic, myoclonic, or absence seizures. They are primary generalized seizures that start simultaneously over both sides of the brain and are associated with loss of consciousness (**Sarmast, Abdullahi, & Jahan, 2020**).

2.2.1. Tonic-clonic seizures (Grand mal seizures)

Seizures involve tonic muscle stiffening that affects both upper and lower extremities, including the tongue, where patients may bite their tongues. Tonic seizures are followed by clonic phases with repeated jerking and muscle contractions lasting up to sixty seconds (Sontheimer, 2021). Auras, or warning signs, such as mood changes, confusion, headaches, or hallucinations, typically occur before the attacks. After the attacks, it could take the patient hours to fully recover (Scully, 2014).

2.2.2. Atonic seizures

The mneck, limb, and trunk muscles suddenly lose their tone. Unfortunately, these seizures occur without warning, so patients are prone to falls and injuries (**Kelley, 2011**).

2.2.3. Myoclonic seizures

Seizures present as jerks that may throw the patient to the floor. The brevity of the seizures prevents the determination of consciousness impairment. Furthermore, these seizures may be part of absence seizures or occur at the onset of generalized tonic clonic attacks (**Holmes, 1997**).

2.2.4. Absence seizures (Petit mal seizures)

Children between the ages of 4 and 18 are frequently observed to have brief, generalized, non-convulsive seizures (**Albuja & Khan, 2023**). Seizures are characterized by states of staring, impaired attention, and unresponsiveness. Some patients may report simple or complex visual and auditory hallucinations. Although some patients remain awake during seizures, they may show decline in their cognitive functions or memory loss, which are considered traits of impaired consciousness (**Barone, van Putten, & Visser, 2020**).

2.3. Seizures of unknown onset

This term is used to describe the seizure that occurs when the patient is alone or if it can't be described by others who witness the seizure, so due to the insufficient information, it can't be classified specifically (**Sarmast et al., 2020**).

3. Animal models in studying epilepsy

Epilepsy models may be chemical, electrical, or genetic models to mimic the epileptic seizure state (**Ates, 2021**). Moreover, as previously stated, epileptogenesis is a complex process that occurs in multiple stages. Therefore, various models have been constructed to encompass each individual stage. For instance, the early stage can be represented using the acute models of epilepsy. On the other hand, the kindling, semi-chronic and chronic models, replicates the stage of the development of the epileptic condition. Ultimately, the chronic phase, which is distinguished by the occurrence of seizures, could be indicated through the initiation of spontaneous recurrent seizures (**A. S. Galanopoulou & Moshé, 2010**).

3.1. Acute models of epilepsy

The acute models are not thought to be true models of epilepsy. Since epilepsy is defined by frequent, spontaneous seizures, they typically cause seizures rather than epilepsy (**Wolfgang Löscher, 2011**). Acute models can be

chemically induced by using chemoconvulsant agents such as pentylenetetrazole (PTZ) (**McCandless & Finesmith, 2008**). It can also be electrically stimulated, such as in the maximal electroshock (MES) model, in which alternating current is applied to the head, cornea, or ears to induce electroshock seizures, loss of posture, and tonic convulsions (**Bambal, 2011**).

3.2. Chronic models of epilepsy

Chronic models are regarded as appropriate models for investigating the enduring alterations in neurons, synapses, and receptors (**Johns, 2014**). During the chronic model of epilepsy, the hippocampus undergoes significant changes from the initial phase of epileptogenesis until the first spontaneous seizure occurs. These changes continue to occur during the chronic phase of epilepsy due to the repeated induction of seizures in animals. This process, known as "reactive plasticity," is dynamic and affects the measured parameters, which may vary depending on the time of assessment (**Bernard, 2006**).

3.2.1. Kindling model

The term "kindling" is a metaphor that refers to the amplification of a response to minor stimuli, analogous to generating a significant fire by burning small twigs. The kindling model, initially described by Goddard *et al.*, is regarded as a chronic model of epilepsy and the most representative model of epileptogenesis in humans. In this model, sub-convulsive doses of a chemical agent or electrical stimuli are repeatedly administered to induce generalized seizures in rodents. These seizures progressively intensify over time, mimicking the epileptogenesis process observed in humans (**McNamara, 1984**); (**Leung, 2017**).

4. Antiseizure medications (ASMs)

Antiseizures, often known as "antiepileptic drugs (AEDs)," are a class of drugs used to treat seizures. However, the name "antiseizures" is considered more accurate because they only treat symptoms and do not affect the course of epilepsy. In addition, they have replaced "anticonvulsants," as they inhibit both convulsive and nonconvulsive seizures (**Wolfgang Löscher & Klein, 2021**). They act through various mechanisms. They may enhance GABA by targeting GABAA receptors (e.g., benzodiazepines, barbiturates) or inhibiting GABA transporter type 1 (e.g., tiagabine) and GABA transaminase (e.g., vigabatrin). Also, they may reduce excitatory glutamate by blocking sodium channels (e.g., phenytoin) or T-type calcium channels (e.g., ethosuximide) and auxiliary calcium channels (e.g., gabapentin) or inhibiting NMDA (N-methyl-D-aspartate) receptors (e.g., felbamate) **(Rogawski & Löscher, 2004**). Recent studies suggested that they may also affect neuroplasticity, as they may provide some morphological, biochemical, and functional changes that enhance or decrease neuroplasticity in different regions of the brain (**de Souza et al., 2023**).

5. Antiepileptogenesis

Antiepileptogenesis drugs are novel drugs that interfere with the epileptogenesis process to achieve either complete neuroprotection through the prevention of the development of epilepsy and seizures (seizure cure) or partial prevention through the reduction of the severity and frequency of seizures and the associated behavioral and

cognitive impairments (seizure modification) (**W. Löscher, 2012**); **(A. Galanopoulou et al., 2021)**. The main strategies of antiepileptogenics include preventing neuronal cell death, inhibiting neuroinflammation, blocking glutamate signaling, targeting neurotrophin pathways, and modifying epigenetic processes **(Shariff et al., 2024**). Unfortunately, the current available drugs control only seizures without disease-modifying or antiepileptogenic effects (**French et al., 2021**). Different animal models demonstrated that several ASMs may show antiepileptogenic effects, such as phenobarbital, valproate, and levetiracetam; however, the clinical trials' results were disappointing (**Temkin, Jarell, & Anderson, 2001**). Therefore, the ongoing studies are increasingly directed towards targeting epileptogenesis as a novel trend in research.

Conclusion

Despite the progress in understanding epilepsy and advancing treatments, significant challenges persist. Thus, a comprehensive grasp of the mechanisms driving epilepsy is essential for the development of novel drugs. On the other hand, animal models can provide valuable insights into potential drug candidates during different phases to further understand epileptogenesis. Research and innovative strategies that not only manage seizures but also prevent their onset and progression through targeting epileptogenesis are vital for enhancing the quality of life for individuals with epilepsy.

Disclosure

The author reports no conflicts of interest in this work.

Origin of seizures in the brain	**According to:**				
	Degree of awareness		**Level of body movement**		
Focal Seizures Originate from one side of the cerebral hemisphere	**Intact Awareness (Formerly: Simple Partial** awareness is preserved	**Impaired Awareness (Formerly: Complex Partial)** awareness is impaired	**Motor Seizures** observable body movements, such as jerks	**Non-Motor Seizures** include sensory, emotional, or cognitive experiences	***May progress to: Focal to bilateral tonic-clonic** originate from one side of the cerebral hemisphere, which can progress to the other side.
Generalized Seizures project to both hemispheres simultaneously.			**Motor Seizures** Tonic-Clonic Seizures Atonic Seizures	**Non-Motor Seizures** Absence Seizures	
Unknown onset seizures			**Motor Seizures**	**Non-Motor Seizures**	**Unclassified**

ILAE:International League Against Epilepsy


1) Initial Epileptogenic Injury
2) Latent Period
Few months or years .....
Neuronal alterations
3) Emergence of Chronic Epilepsy

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