

Progress of Therapy in Epilepsy

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Abstract. Nowadays, over 50 million people worldwide suffer from epilepsy, with its origins often linked to brain injuries or genetic factors. Despite advancements in medical research, the cause of epilepsy remains elusive for approximately 70% of patients, highlighting a significant gap in our understanding of the disorder. Moreover, because of problems including medication resistance and side effects from conventional Antiseizure medications (ASMs), new approaches to therapy are needed. This review summarizes different mechanisms and Available therapies for epilepsy, and point out some new and developing treatments with an emphasis on precision medicine and innovative pharmacological targets. GPCRs and neuroinflammatory pathways have the potential to be effective therapeutic targets, according to some novel literature review. By customizing medicines to each patient's unique genetic profile, these developments, when combined with precision medicine, are increasing treatment efficacy and decreasing adverse effects. This research suggests that if this emerging discovery incorporated into clinical practice in the future, it may improve patient quality of life and worldwide epilepsy care and public health policies should be strengthened.

Keywords: Epilepsy; epidemiology; treatment.

1. Introduction

Epilepsy stands as one of the most common neurological disorders globally, characterized by frequent, spontaneous seizures that impact people of all ages. There are many different varieties of epilepsy, and only 20% have known mechanisms, making epilepsy therapy extremely complex. Antiseizure medications (ASMs) have significantly improved as a result of advances in neurobiology and pharmaceutical sciences; nonetheless, a third of people with epilepsy still struggle with drug-resistant epilepsy. The ideal antiepileptic medicine would be broad-spectrum and have a minimal impact on central nervous system function and quality of life, however none of the current antiepileptic drugs fit these criteria. This has led to a renewed emphasis on discovering novel treatment targets and understanding the mechanisms causing epilepsy. Ion channels and targeting neurotransmitter systems has shown promise in recent trials, and new research on genetic and inflammatory pathways is also being explored. This review explores the progression of epilepsy treatment from conventional techniques to cutting-edge strategies like precision medicine and biopharmaceuticals, with the goal of providing a thorough picture of both persistent difficulties and encouraging developments in the search for more efficient and individualized epilepsy care.

2. Epidemiology

Epilepsy is a neurological disorder characterized by recurrent seizures, affecting more than 70 million people worldwide. Between 4 and 10 persons out of every 1000 are thought to have active epilepsy, meaning they are either still experiencing seizures or require medication. Epilepsy incidence varies greatly amongst demographic groups and geographical areas due to a variety of factors, including socioeconomic level, healthcare accessibility, genetic predisposition, and environmental impacts. Significantly, some reports point out the disparities in access to treatment and diagnostics, particularly in low and middle-income countries where a substantial treatment gap persists. The World Health Organization reports that the average incidence of epilepsy in developed nations is approximately 50 cases per 100,000 people, whereas in underdeveloped nations it is almost twice as high. Despite available effective treatments, a vast majority of those suffering from epilepsy in these regions remain untreated, leading to preventable morbidity and mortality. Furthermore, social

cognition in epilepsy is also another big topic, which is crucial for improving the quality of life and healthcare outcomes for individuals living with epilepsy. The stigma associated with epilepsy has been a significant focus in recent literature, with studies examining the risk and protective factors related to stigma among individuals with epilepsy. These can include visual seizures, a lack of public understanding and awareness of epilepsy, negative attitudes and ideas about the condition, social isolation, and discrimination in a variety of situations such as job, education, and healthcare. Thus, public health activities and research are important in improving diagnosis, treatment, and overall quality of life for persons suffering from epilepsy.

Epilepsy drug development need to escalate since the continued drug resistance in up to a third of epilepsy patients. Overcoming drug resistance remains a key focus in epilepsy research, with the development of innovative treatment options being explored [1]. Treatment development now focuses on discovery of novel mechanisms of action and syndrome-specific therapies.

2.1. Classification

The International League Against Epilepsy (ILAE) updated the definition and classification of epilepsy in 2022 [2], "A cluster of clinical and electroencephalographic features, often supported by specific etiologies" is how the International League Against Epilepsy (ILAE) describes an epilepsy syndrome. These encompass factors that are structural, genetic, metabolic, immunological, and infectious. Based on the genesis of seizures (focal or generalized), age at onset (infants, children, adults), and correlation with developmental or epileptic encephalopathies, epilepsy syndromes are categorized. The classification method divides epileptic syndromes into three categories: age-related syndromes, etiology-based syndromes and specific symptom complexes. This classification aids in determining the best course of treatment as well as forecasting the disorder's progression.

2.1.1 Age of onset

According to the stage of onset of disease, firstly, neonatal and infantile onset syndromes, such as West Syndrome and Infantile Spasms. Secondly, childhood onset syndromes (Childhood Absence Epilepsy and Lennox-Gastaut Syndrome). And the adult-onset syndromes such as Temporal Lobe Epilepsy.

2.1.2 Epilepsy type

This classification is determined by the origin and characteristics of the seizures.

Focal Epilepsy, which are further classified according to the presence or absence of awareness and originate in a particular region of the brain.

Generalized Epilepsy, such as absence, myoclonic, and tonic-clonic seizures, impact the whole brain from the beginning.

Combination generalized and focal epilepsy affects certain patients, causing seizures that exhibit both focal and generalized features.

Unknown onset seizures used when the cause of a seizure cannot be established.

2.1.3 Etiology

This categorization is based on Classification based on underlying cause of disease. For instance, genetic one (Juvenile Myoclonic Epilepsy), structural or metabolic such as symptomatic epilepsy caused by structural brain abnormalities and infectious/ immune-mediated resulting from the sequelae of encephalitis.

This classification serves many purposes than just classification; it improves diagnostic accuracy, guides treatment decisions, forecasts the course of disease, and supports some research endeavors. Accurate categorization enables medical professionals to recognize the distinctive features of epilepsy syndromes, which is essential for choosing the best treatment options that are least likely to cause side effects and most likely to be successful. Knowing the categorization also aids in forecasting the disease's natural course and how it will affect neurological development, which is important for patient care and counseling, in keeping with the trend of precision treatment development in the future.

2.2. Mechanism

Although traumatic brain injury is a major contributor to symptomatic epilepsy, the precise process causing recurrent seizures is still unknown [3]. Trauma to the brain can interfere with regular neuronal function, causing hyperexcitability and aberrant over-firing neurons that might appear as seizures. Furthermore, imbalance of neuronal excitation or inhibition is a common cause of epilepsy in genetic illnesses and metabolic circumstances.

The occurrence of epilepsy is closely related to ion channels, neurotransmitters, synaptic connections, neurovascular units, glial cells, etc. This article reviews the research progress on the mechanism of epilepsy from the following aspects: ion channel dysfunction, abnormal neural electrical activity, neurotransmitter imbalance, inflammatory pathway and genetic factors.

Ion channel abnormalities are a key factor in the pathophysiology of epilepsy. Sodium channel blockers can help maintain membrane potential by reducing the frequency and amplitude of neuronal action potentials. Conversely, abnormal sodium channels typically result in increased neuronal excitability. The pathophysiology of epilepsy is significantly influenced by calcium channels, particularly T-type calcium channels, especially in absence seizures. Calcium channel blockers lessen the influx of calcium ions, which lowers neural excitability. Furthermore, sudden unexpected death may be associated with prolonged action potential duration and QT interval in epilepsy, possibly as a result of a greater contribution from neuronal sodium channels to cardiac late Na⁺ current [4].

Modulation of the neurotransmitter system is also pivotal in epilepsy. As a significant inhibitory neurotransmitter, GABA decreases neuronal excitability to hyperpolarizes the cell membrane by mediating chloride ion influx through GABAA receptors. Nonetheless, a decreased GABA system function results in impaired transmission of inhibitory signals in some epileptic patients. On the other hand, glutamate enhances the excitability of neurons by facilitating the entry of sodium ions via AMPA receptors. Excessive glutamate signaling activation in epilepsy can lead to neuronal synchronization and over-excitation, which in turn can produce epileptic seizures. Through the effect on AMPA receptors, which mediate excitatory synaptic signals, glutamate plays a crucial role in excitatory neurotransmission. The normal and pathological activity of neural circuits, including those implicated in epilepsy, is based on this function [5].

Inflammatory pathway, such as the overexpression of COX-2 and TNF α , contribute to neuronal injury and hyperexcitability by increasing the release of excitatory neurotransmitters. Glial cell-mediated glutamate release, dependent on P2Y1 receptor activation, further exacerbates epileptic episodes.

The overexpression of COX-2 has been linked to neuronal injury, and prostaglandin E2 (PGE₂), a byproduct of COX-2, increases the release of excitatory neurotransmitters via EP receptors, therefore contributing to the development and maintenance of epilepsy. In several animal models of epilepsy, induction of cyclooxygenase-2 (COX-2) has been demonstrated to encourage epileptogenesis and contribute to neuronal damage. In mice, kainic acid-induced seizures and mortality are exacerbated by overexpression of COX-2 [6].

TNF α is an inflammatory agent that can increase glutamate release from glial cells, which in turn can induce hyperexcitability of neural networks. Glial cell-mediated glutamate release is thought to be mostly dependent on P2Y1 receptor activation, which may have consequences for the onset of epileptic episodes. Aberrant astrocyte signaling, particularly involving TNF α -triggered glutamate release and P2Y1 receptor activation, has been implicated in driving network hyperexcitability in epilepsy [7].

Genetic factors are also crucial in the pathophysiology of epilepsy. For instance, certain gene variations are linked to an increased risk of epilepsy, such as the GRM4 gene's CAACG haplotype [8]. These genetic differences could impact other biochemical pathways linked to neuronal excitability, the balance of neurotransmitter systems, or ion channel function. These several elements work together to make epilepsy a complicated, multifaceted brain condition.

3. Treatments

3.1. Traditional Treatment

Although the mechanisms of epilepsy are diverse, of epilepsy treatment lies in the use of Antiseizure medications (ASMs), which often involve modulation of ion channels or enhancement of neurotransmitter inhibition and the mainstay of therapy is still oral medications. Currently, about 30 ASMs are available for epilepsy therapy.

The main actions of most ASMs on molecular targets can be divided into four broad groups:

(a) Modulation of voltage-gated ion channels: For example, Phenytoin and Carbamazepine stabilize neuronal membranes and reduce neuron firing by blocking sodium channels stabilize neuronal membranes and reduce neuron firing. Ethosuximide, blocking the voltage-gated calcium channels.

(b) Enhancement of GABA-mediated inhibition: Valproate, a broad-spectrum AED, works by increasing GABA levels and blocking sodium and calcium channels, effective against various seizure types. Tiagabine, inhibitors of GAT1 GABA transporter.

(c) Inhibition of synaptic excitation mediated by ionotropic glutamate receptors: newer agents like Perampanel target specific neurotransmitter systems serve as the antagonists of AMPA receptors.

(d) Direct modulation of synaptic release through effects on components of the release machinery, including SV2A and the $\alpha_2\delta$ subunit of voltage-gated calcium channels such as Gabapentin and Pregabalin [9].

Epilepsy is a multifaceted complex disease and so is its treatment. Additionally, a considerable number of patients exhibit drug resistance, underscoring the need for ongoing innovation in epilepsy pharmacotherapy. This highlights the dual challenges of managing epilepsy: controlling seizures and mitigating treatment side effects to enhance patient outcomes.

The exact mechanisms behind epilepsy are diverse and still unknown, which contributes to the inadequate efficacy of anti-seizure medications that mainly target membrane ion channels and neurotransmission. Epilepsy is a multifaceted complex disease and so is its treatment. Despite their benefits, these drugs come with significant side effects which can affect patient compliance and quality of life. Sleepiness, nausea, dizziness, and weight gain are some of the side effects that have been observed. There are also some possible psychological and cognitive side effects, such as mood swings and memory issues, that may be brought on by these drugs. Furthermore, these drugs may result in teratogenicity, which can result in miscarriages or disabled offspring [10].

3.2. New Treatment

Currently, ASMs are developed largely to reduce neuronal hyperexcitability, but these treatments frequently interfere with normal neural transmission, resulting in considerable adverse effects. Furthermore, standard drugs can impair central nervous system function and general quality of life, with around one-third of people developing drug resistance. There is an urgent need for new therapeutic targets and medications that can successfully prevent and treat epilepsy. By learning more about the fundamental mechanisms of epileptogenesis, it is possible to develop novel medicines that target the abnormal processes while avoiding disturbance to normal neuronal function. This shift to precision medicine in epilepsy treatment has the potential to provide more targeted and effective interventions, ultimately improving outcomes and quality of life for those living with epilepsy.

GPCRs play a role in many different neurophysiological processes, and epilepsy is one of the neuropathological conditions associated with GPCR dysfunction. Surprisingly, current ASMs do not directly target GPCRs, despite their critical roles in the central nervous system, indicating a gap in the therapeutic landscape [11]. EP1, EP2, and FP are the most thoroughly investigated prostanoid receptor subtypes in animal models of epilepsy, and they have provided significant evidence of their involvement in epileptic seizures.

There are four main family: Prostanoid receptors, Cannabinoid receptors, Adenosine receptors and Metabotropic glutamate receptors. Prostanoid receptors, in particular, have been demonstrated to play

a role in modulating neuronal excitability in epilepsy, implying that they could be novel targets for antiepileptic treatment. For example, activation of PGE2 receptors plays a dual role in neuroprotection and neurotoxicity, therefore carefully regulating both pathways could contribute in the development of new antiepileptic medicines. Furthermore, the study suggests that GPCR-mediated pathways may influence the balance of neuronal excitability and inhibition by changing cAMP and Ca²⁺ signaling, giving a theoretical foundation for creating medications targeting these signaling pathways.

As mentioned above, neuroinflammation plays a significant role in the onset and progression of epilepsy. Some studies discovered that the activation of the HMGB1/TLR4/RAGE signaling pathway closely associated with epilepsy pathogenesis.

In animal models of acute injury-induced epilepsy, blood levels of total HMGB1 rise prior to the onset of spontaneous episodes. According to some theories, HMGB1 may have a role in the development of epilepsy following brain damage, and blood levels of this protein may be used to identify patients who are most likely to experience spontaneous seizures soon after suffering an epileptogenic injury. Moreover, during status epilepticus, the brain releases disulfide HMGB1, which may aid in epileptogenesis and the subsequent start of spontaneous seizures. Elevated blood levels of TLR4 expression and HMGB1 inflammatory subtypes have been associated with an increased risk and severity of epilepsy, as well as a resistance to anti-seizure drugs. Therefore, modifying the HMGB1/TLR4 signaling pathway, which is active in cases of drug-resistant epilepsy, may be a feasible therapeutic strategy.

Pentoxifylline may represent a promising drug to inhibit epilepsy progression by targeting this signaling pathway in pentylenetetrazol (PTZ)-kindling rats [12]. This shows that pharmacological interventions aimed at neuroinflammation could delay epilepsy development and progression. The identification of this route as a possible target for epilepsy treatment suggests that it will be important in future therapeutics [8].

The genetic discovery of epilepsies has accelerated over the last 20 years due to developments in next-generation sequencing technology and associated data analytics. In terms of gene discovery, discovering a specific genetic cause for up to 40% of cases in the developmental and epileptic encephalopathies (DEEs) has proven to be particularly successful. Precision medicine, also known as personalized medicine, customizes disease prevention and treatments based on individual differences in genetics, environment, and lifestyle. Aims to tailor treatments to individual patients based on their genetic makeup and other factors. This approach has the potential to revolutionize epilepsy treatment by providing more targeted and effective therapies.

Enthusiasm for precision medicine currently stems largely from discoveries from genetics about the causation of some of the rare, severe, typically early-onset epilepsies, including the developmental and epileptic encephalopathies. However, precision medicine has promise, it's important to recognize that many findings are anecdotal and have limited duration. It acknowledges that more effective treatments are required and that a precision medicine approach is not always successful. Even yet, the method of figuring out what causes epilepsy and coming up with a sensible course of treatment is still appealing and could provide a fresh approach for epilepsies that had previously failed to respond to earlier treatments [13].

Potential etiology-specific drugs (“precision medicine”) that are currently used or discussed for treatment of severe pediatric-onset epilepsies. For example, mutated gene CHRNA4 (Cholinergic receptor nicotinic alpha 4 subunit) will induce Nocturnal frontal lobe epilepsy. Zonisamide, acetazolamide and nicotine patches can potentially achieve the targeted beneficial therapy [14].

4. Conclusions

The complexity of managing epilepsy has been highlighted by this review, underscoring the urgent need for novel therapeutic strategies that go beyond the constraints of the antiseizure medications (ASMs) already on the market. The investigation of novel pharmacological targets, including

neuroinflammatory pathways and G protein-coupled receptors (GPCRs), has created encouraging opportunities for the creation of more possible targets and potent treatments. These new targets have the potential to improve patient adherence and outcomes by lowering side effects and increasing therapeutic efficacy. Additionally, the connection between neuroinflammation and epilepsy offers a different therapeutic path that may lead to the development of fresh approaches to lessen the chronic symptoms of the condition. In conclusion, there will be a revolution taking place in the management of epilepsy. With the ultimate goal of improving the quality of life for those who suffer from epilepsy, new discoveries enable more specialized and focused approaches to treatment.

Going forward, the application of genetic insights to clinical practice may hold the potential to completely transform the treatment of epilepsy. It will be crucial for epilepsy research to include results from improved imaging methods and genomic investigations in order to further our understanding of the neurological basis of seizures. Such studies may open the door for the development of ASDs in the future that can completely stop seizures from occurring as opposed to only managing them. Furthermore, applying artificial intelligence and machine learning to epilepsy research may improve the accuracy of illness progression and response to treatment, potentially revolutionizing current practices.

In summary, the future holds a lot of opportunities as well as challenges. The goal of the epilepsy research community should be to promote interdisciplinary collaboration in order to expedite the translation of scientific findings into therapeutic practice. Furthermore, epilepsy must be given top priority by health policy makers as a public health concern. This will guarantee that new discoveries in the field will result in improved patient access to care and more extensive support networks for those who are impacted. Millions of people affected by this difficult condition may have more hope for an improved quality of life and epilepsy treatment in the future because to such coordinated efforts.

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