Pharmacological Interventions in Epilepsy

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Epilepsy is a non-communicable disease of the brain that affects people of all ages. It is characterized by episodes of spontaneous and abnormal electrical activity in the brain. It is often accompanied by depression, anxiety, and substantially increased morbidity and mortality. A large number of third-generation antiepileptic drugs are available, but they have multiple side effects causing a decline in the quality of life. The inheritance and etiology of epilepsy are complex with multiple underlying genetic and epigenetic mechanisms. Different neurotransmitters play intricate functions to maintain the normal physiology of various neurons.

Keywords: anti-convulsants ; anti-epileptic drugs ; drug targets ; epileptogenesis ; non-communicable disease ; seizures ; transcriptional modifications ; pseudo-resistance

1. Introduction

Epilepsy is a group of chronic non-communicable neurological disorders categorized by spontaneous recurrent seizures [1][2]. These seizures result from episodes of abnormal electrical activity in the brain. The process by which epilepsy develops in an otherwise normal brain is called epileptogenesis. Epilepsy may result from a head injury, brain tumors, brain infections like meningitis or encephalitis, stroke, birth defects, and sometimes even altered levels of entities like blood sugar or sodium [3].

During the last 30 years, there has been a huge advancement in the treatment of many types of seizures due to the introduction of over 15 third-generation antiepileptic drugs (AEDs) [4]. Around 70–80% of patients enter remission with present AEDs who have new onset of epilepsy. Among 20–30% of patients, these medications are not able to control seizures. Besides, there is no AED that can prevent the development of the disease before the occurrence of the first seizure. Unfortunately, there is also drug-resistant epilepsy that is not controlled by or responds to AEDs. This shows the urgent need to develop appropriate therapeutic strategies to tackle the complex situation of epilepsy. Devising better treatment paradigms for epilepsy using various pharmaceutical and therapeutic approaches would need a better understanding of the different clinical and experimental strategies for the development and discovery of more efficient treatment methods that can help prevent and control the diseases [5][6][7].

2. Role of Genes, Genetics and Inheritance

The newly emerging genetic technology has played a significant role in the discovery of a variety of genes that are associated with epilepsy. The advancement of genomic techniques and gene sequencing has substantially enhanced the knowledge about the genetic variations taking place in the human genome. Studies estimate that there is an underlying genetic cause in about half of all cases of epilepsy [8]. Currently, with the emerging research of epigenetic biomarkers, MicroRNAs (miRNAs) have been assumed to play a significant role. MiRNA molecules 19-25 nucleotides long regulate gene expression as post-transcriptional modifiers [9]. Differential expression of more than 100 miRNAs has been reported in epilepsy. Among them, because of their predominant role in biological processes related to epilepsy, such as neurodegeneration, neuronal growth, and neuroinflammation, miR-132, miR-155, and miR-146a have been highlighted primarily [9]. Some cases of genetic mutations result in the core symptom of epilepsy, while changes in a few of the genes are responsible for malformations in the gross development of the brain that cause seizures. There are around 84 genes classified as epilepsy genes based on the OMIM database results. Mutation in these classified genes leads to epilepsy as a core symptom. There are approximately 73 genes that are categorized as neurodevelopment-associated epilepsy genes [8]. According to the OMIM database (https://www.ncbi.nlm.nih.gov/omim, accessed on 24 April 2021), there are about 536 genes responsible for causing associated diseases of epilepsy [8][10].

3. Epigenetics Involved in Epilepsy

Recent studies show epigenetics playing essential roles in temporal lobe epilepsy [11]. Therefore, studying the role of epigenetic changes in the development of the disease has become an emerging topic in the area of research. The knowledge of epigenetic mechanisms helps in providing the putative conceptual framework in the development of therapies that can help in the prevention of the disease. Epileptogenesis should be considered as a target point for developing therapy when there is an increment in the severity and frequency of impulsive recurrent seizures. Various processes that take place along with epileptogenesis are mossy fiber sprouting, dysfunction of adenosine together with gliosis, aberrant connectivity, neuronal cell loss, and neuroinflammation [12][13]. TCF4, MECP2, UBE3A, and CHD2 are some of the regulatory genes associated with epilepsy. Among these, the CHD2 gene is responsible for encoding a protein that remodels chromatin, and deregulation of CHD2 might have a downstream effect on other genes [14].

Epigenetic modifications are also responsible for many of the pathological changes that take place during epileptogenesis. Many changes have been shown to occur in the central nervous system cells that alter the gene expression due to DNA methylation and histone acetylation and methylation [15][16].

Various processes like histone modifications that involve either adding up or eliminating the acetyl or methyl groups are suggested to be associated with epileptogenesis. According to the hypothesis of DNA methylation implicated in epileptogenesis, seizures can induce epigenetic modifications and can exaggerate the process of epileptogenesis. DNA hypermethylation, along with the amplified activity of DNA methylating enzymes has been implicated in the development of experimental and human epilepsy [17].

Histone modification is one of the epigenetic mechanisms that have the considerable potential to alter the neuronal expression of genes by exerting their additive effects in a correlated manner [11]. The principal role of histone proteins is to support the tertiary and quaternary structure of the DNA. Disruption in these vital epigenetic machinery leads to various disorders such as epilepsy, autism, Rett syndrome, etc.

DNA methylation is dependent on several biochemical enzymatic reactions. One such reaction pathway is the S-adenosylmethionine-dependent transmethylation pathway, which is controlled by glycine and adenosine under the regulation of adenosine kinase (ADK). In chronic epilepsy, it is observed that there is an increase in the ADK and a resulting decline in adenosine, which leads to elevated DNA methylation in the brain. Thus, interference with methylation of DNA gives the new conceptual prospect to control and prevent epilepsy. Glycine modifying therapies can also be regarded as an alternative opportunity that affects the process of DNA methylation and, ultimately, the process of epileptogenesis. Therefore, understanding the epigenetics of epileptogenesis might help in the discovery and development of therapeutic interventions [12][18].

4. Neurotransmitter Release Machinery in Epilepsy

4.1. Glutamate Receptors

Glutamate is an excitatory neurotransmitter responsible for stimulating an increase in calcium and sodium conduction through ligand-gated ion channels (**Figure 1**). A wide spectrum of anti-convulsant properties is displayed by AMPA antagonists and NMDA antagonists in animal models with acute and chronic epilepsy [19]. Once seizures begin, the activity-dependent plasticity of the glutamate receptors becomes a vital feature of the epileptic brain.

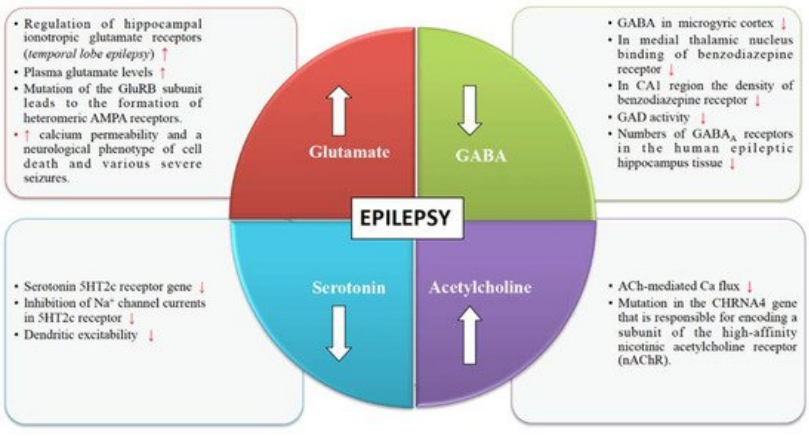

Figure 1. Neurotransmitter mediated changes in epilepsy. Different changes have been observed in the brain due to the increase in the levels of glutamate and acetylcholine and a decrease in the levels of serotonin and GABA. Such

modulations due to various physiological conditions or comorbid situations have been reported, which should be taken into account while designing any pharmacological interventions in the epileptic patients.

4.2. GABA Receptors

Various pieces of evidence from several clinical and experimental data underline the role of GABA in the mechanism and management of epilepsy (**Figure 1**). The synaptic inhibition by GABA plays an essential role in regulating neuronal excitability, which has been linked to epilepsy. GABAergic neurotransmission that is controlled by Cl^- permeable $GABA_A$ receptors can exhibit both seizure-repressing and -stimulating activity [20].

4.3. Cholinergic Receptors

The structural and functional diversity of the neuronal nicotinic acetylcholine receptors (nAChRs) perform modulatory functions throughout the mammalian brain (**Figure 1**). Nicotinic receptors are involved in various developmental mechanisms such as memory, attention, and learning. Disruptions in cholinergic mechanisms can lead to several disorders such as epilepsy, Parkinson's disease, dementia, schizophrenia, autism, Alzheimer's disease, etc. [21].

4.4. Serotonin Receptors

Serotonergic neurotransmission has been shown to have a potential role in epilepsy [22]. Serotonin receptors (5-HTRs) have been therefore considered as promising candidate targets for the development of new AEDs (**Figure 1**). Studies show 5-HT regulates a wide variety of focal and generalized seizures. Agents like 5-hydroxytryptophan and 5-HT reuptake blockers are known to increase the extracellular serotonin levels and hence inhibit focal as well as generalized seizures.

5. Drug Resistant Epilepsy

Drug-resistant epilepsy (DRE) is also known as refractory epilepsy or pharmaco-resistant epilepsy. It can be defined as a failure of two or more sufficient trials of tolerated, chosen, and appropriately used AEDs regimens, which can be administered as monotherapies or in combination to get relief from seizures. Around one out of four patients with seizures develop DRE [23]. DRE patients have increased risks of injuries, psychosocial problems, and premature death [24][25][26].

5.1. Alterations in the Drug Targets

This hypothesis states that sensitivity to the treatment is decreased due to the alterations in the cellular targets of the drugs. The α_2 subunit of the neuronal Na^+ channel, which is encoded by the SCN2A gene, has been found to be related to anti-epileptic drug resistance [23]. However, this hypothesis cannot explain the contributory role of the alterations in drug targets in causing epilepsy in patients resistant to several drugs with different modes of action [27][28].

5.2. The Inability of the Drugs to Reach Their Targets

This transporter hypothesis postulates that at the epileptic target, drug resistance may apply to the overexpression of the multidrug efflux transporters. P-glycoprotein is the most widely researched efflux transporter whose primary function is to maintain the integrity of the blood–brain barrier by decreasing the cerebral build-up of the substrate drugs [23]. Up-regulation of efflux transporters such as P-glycoprotein in capillaries and abnormal expression in neuronal and glial cells has been described in various studies on patients with DRE [29].

5.3. Real Targets Missed by the Drugs

Presently, the primary usage of the AEDs is only to prevent seizures rather than focusing on the pathogenic processes that are causing the disease. Autoantibodies to the ion channels that are associated with neuronal inhibition and excitation, including voltage-gated ion channels and NMDA and GABA receptors, have been identified in patients with seizures. Such cases have been seen predominantly in multiple circumstances of encephalitis and occult cancer. However, these patients usually are unable to respond to conventional anti-epileptic drugs [23][30][31].

6. Non-Conventional Therapeutic Strategies

6.1. Ruling Out Pseudo-Resistance

It is the phenomenon in which the seizures persevere because the fundamental disorder has not been adequately treated. So, it is imperative to rule out or correct the underlying disorder before the drug treatment can be considered to have failed. There can be several situations in which misdiagnosis of epilepsy can take place. Cardiac arrhythmia, vasovagal

syncope, and other neurological disorders such as migraine and transient ischemic attacks are some of the conditions that imitate epileptic seizures [23][32].

6.2. Combination Therapy

According to many studies and research data, the combination of drugs helps in controlling the disease. The same drugs at differential dosages have been seen to suit different patients. Various natural or herbal-based drugs like Cicuta virosa and Nux vomica have been shown to be effective in reducing seizure activity and other physiological parameters in animal models of epilepsy [7][33].

6.3. Non-Drug Treatment

Patients who are suffering from DRE have surgery as an alternative method for treatment, mainly if they have a surgically remedial disease like unilateral hippocampal sclerosis or other curable lesions. Therefore, depending on the indication, a number of surgical procedures can be performed to treat and control epilepsy after the deliberation of further trials of anti-epileptic drugs [34].

7. Modern Approaches for Treatment

7.1. MTOR Pathway

This signaling pathway is the mammalian target of rapamycin, which is responsible for regulating cell growth, cell proliferation, cell differentiation, and cell metabolism in the brain. Many studies have shown that dysregulation of mTOR is responsible for the pathogenesis of acquired forms of epilepsy, such as temporal lobe epilepsy [4]. Therefore, therapeutic intervention in this pathway can lead to the discovery of more tolerable anti-epileptic and anti-epileptogenic drugs [35][36].

7.2. Inflammatory Pathways

Various studies and researches have shown shreds of evidence, which states that inflammatory mediators that are released by cells of the brain and peripheral immune cells are implicated in the foundation of seizures and the process of epileptogenesis [4]. Data and facts have emerged that changes in the inflammatory and immune pathways might be the consequences as well as the origin of the different types of epilepsy [37].

7.3. Breakdown of Blood-Brain Barrier

Irrespective of their etiology, dysfunction of the blood-brain barrier is a characteristic of epileptogenic injuries of the brain. Any harm to the blood-brain barrier microvasculature during the brain injury leads to the leakage of the serum albumin into the micro-environment of the cerebral cortex, which induces a signaling cascade in astrocytes, which results in local inflammation by activating the transforming growth factor β receptor (TGFβR) [38]. Dysfunction of the astrocytes leads to the impairment in the homeostasis of the extracellular brain environment, which further results in the increased excitability of the neurons. TGFβR is a remarkable novel target that interferes with the process of epileptogenesis. This is because of the obstruction of TGFβ signaling in the albumin is responsible for reversing the inflammation and transcriptional modifications linked with activated glia and thus prevents the progression of epileptogenesis [4][39]. Various approaches that are being employed in the therapeutics associated with epilepsy have been summarized in **Table 1**.

Table 1. Different approaches used for the treatment of epilepsy.

S. No.	Treatment Approaches	Interventions Used	Action Mechanism	Main Uses	References
A.	PHARMACEUTICAL APPROACHES (Anti-epileptic drugs)	Gabapentin	Ca^{2+} blockage	Used for generalised and focal seizures.	[40][41]
		Carbamazepine	Na^{+} channel blockage	Decrease nerve impulses that are responsible for causing seizures.	[40]
		Lamotrigine	Na^{+} channel blockage	Used as a first- line drug for generalized and focal seizures.	[42][41]
		Tiagabine	GABA potentiation	Used for partial seizures in adjunctive therapy.	[40]

S. No.	Treatment Approaches	Interventions Used	Action Mechanism	Main Uses	References
		Zonisamide	Na^+ channel blockage	Used for generalized and focal seizures.	[40][41]
		Vigabatrin	GABA potentiation	Used for infantile spasms and for focal onset of seizures.	[40]
		Perampanel	Glutamate (AMPA) antagonist	Used for partial seizures with focal onset.	[40][41]
B.	THERAPEUTIC APPROACHES	Progressive muscle relaxation	Tense a group of muscles while breathing in and relaxes them while breathing out.	Improves sleep and overall well-being. Enhances control over epilepsy by the patients.	[43]
		Yoga	Release tension in key joints through combination of body postures.	Decrease in automatic dysfunction during onset of seizures.	[43][44]
		Cognitive behavioural therapy	Restructuring of maladaptive thought patterns.	Improvement in anxiety and depression and enhanced psychosocial functioning.	[43][45]
		Vagus nerve stimulation	Used to generate impulse through electric current in vagus nerve.	Used as an adjunctive therapy for partial onset of seizures.	[46]
C.	NATURAL APPROACHES	Ketogenic diet	Neurotransmitter modulation in brain by ketone bodies.	Successful in reducing seizures and enhancing motor function.	[47][48][49]
		Vitamin D3	Increase Ca^{2+} uptake and decrease neuronal excitability.	Produces anti-convulsant effect and prevent seizures.	[50][51]
		Herbal treatments	Found to be involved in potentiation of GABAergic activity in brain.	Herbal medications control epileptic seizures and reduce side effects and increase cognitive effects of AEDs.	[52][53]

8. Conclusions

Several applicable models are available to study and understand the process of epileptogenesis [54]. However, there are still many challenges in dealing with epileptogenesis. There are so many emerging approaches that are under consideration for the treatment of DRE. Various researchers are working on pharmacotherapy and many other therapeutic approaches that can aid in the treatment of epilepsy. Complementary alternative medicines like Cicuta virosa [33] and Nux vomica [7] could be used in combination with lower doses of effective drugs for better results. Such newer combinations of drugs need more research to be done to find their efficacy. Many capable pathways including epigenomic maintenance through dietary intervention [55] and potential drug targets have been identified by many researchers that provide the approach for the treatment. The discovery of a wide variety of anti-epileptic drugs has provided great advancement in treating different types of seizures [54]. Further, understanding the role of different neurotransmitters and their effect on epileptogenesis can help in the emergence of novel treatment strategies for epilepsy in near future.

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