

Updated Insights into Epilepsy Mechanism and Treatment

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Abstract. Epilepsy is the most prevalent, persistent, and deadly kind of neurological disorder. affecting 65 million individuals globally. To update the current understanding about its pathophysiological processes, diagnosis, classification criteria, and treatment targets, this review summarized the most updated advances accordingly. The pathogenesis of epilepsy can be the abnormal glial cells, glutamate metabolism, or injury of blood-brain barrier. The current epilepsy classification system was introduced in 2017 by ILEA. It has three levels of classification, starting with classification of seizure type and may be followed by further classification as an Epilepsy type with sufficient imaging evidence, and even further classified as an Epilepsy Syndrome with sufficient imaging evidence combined with the patient's background information. Classification may stop at any level depending on the resources available. All in all, this review updated the most recent advanced findings about epilepsy to promote further research works.

Keywords: Epilepsy, Glia Cells, Neurotransmitter, Epilepsy treatment.

1. Introduction

Epilepsy is an illness that affects the central nervous system (neurology) and is characterized by aberrant brain activity, which is characterized by seizures or periods of odd behavior, feelings, and even loss of consciousness. Despite the fact that epilepsy can be effectively treated in the vast majority of instances, there is a significant treatment gap, particularly in low-income and middle-income nations. This is due to the fact that antiepileptic medications are either unavailable or prohibitively costly. To improve the understanding of it, this review will discuss the pathogenesis, latest classification standard, and the advanced treatment method to epilepsy disorder respectively.

2. The pathogenesis of epilepsy disorder

Generally, pathogenesis means the mechanisms whereby a disease is produced, and the process by which an infection leads to disease. It tells us the causes of the disease and how does the disease develop. It is important for us to find the potential causes of epilepsy since it is one of the most common chronic disorders that could happen to individuals of all ages. Here are some of the theories that attract widespread attention.

2.1. Abnormal glial cells

The role of glial cells in the causation of epilepsy is crucial for scientists and researchers to pay attention to. Understanding the connection between glial cells and epilepsy disorder will help scientists find new strategies for treating epilepsy besides letting patients constantly take in anti-epileptic drugs. How glial cells and neurons interact with each other is indispensable to the brain function. If glial cells are not functioning properly, most likely it will lead to or cause epilepsy. The main role of glial cells is supporting the neurons by surrounding the nerve cells and hold them in place in order to provide nutrients and oxygen to them. Also, glial cells protect the neurons against

oxidative stress. In general, if glial cells become abnormal, neurons would fail to function properly too, which may lead to epilepsy since it is a disease that is exclusively related to neurons.

The glial cell that is most related to epilepsy disorder is astrocytes. Astrocytes are star-shaped cells that are found in the brain which are responsible for taking in and redistributing ions and water, glucose metabolism and nerve cells communication [1]. The sudden onset of epilepsy is possibly due to the disturbances of any of these functions.

The ions people talk about is specifically potassium. It is continually released from our neurons, and bind with the neurotransmitter at synapses. It causes the potassium concentration to increase in the extracellular space around the synapses. Action should be taken to remove extra potassium in order to prevent nearby neurons from depolarization, which may then lead to epileptic seizures. So, the function of astrocytes to take up potassium seems to be the most important part in causing epilepsy disease. There is a channel called Kir4.1 (potassium inwardly rectifying), which plays an important role in taking up potassium in the extracellular space [2]. The dysfunction of it increases the probability of seizures. Also, scientist did related experiment on mouse. Mouse that are Kir4.1 knock-out showed phenotype characterized by severe epilepsy and often died few weeks after giving birth to baby mouse. It came out with evidence to prove the dysfunction of Kir4.1 is highly associated with epilepsy.

2.2. Glutamate metabolism

Glutamate is defined as a salt or ester of levorotatory glutamic acid that functions as an major excitatory neurotransmitter in our nervous system, and it can be found in food that contains high protein such as meats, dairy, eggs, and cheese, which all sounds nutritious [3]. Also, certain amount of glutamate in our CNS (central nervous system) helps us memorize different things, regulate moods, deal with our cognition, and pass chemical signals between nerve cells. Generally, it is crucial to our nervous system, especially our brain. However, too much glutamate has negative effects to your body [4]. Studies show that having too much glutamate in the brain has certain association with neurological disease such as Alzheimer's disease, stroke, epilepsy, Parkinson's disease, and Gehrig's disease. What's more, it will lead to various mental health disorder such as schizophrenia and OCD (obsessive-compulsive disorder). These are all the side-effects of having too much glutamate, which indicates the importance to efficiently remove extra glutamate in time. Similar to the potassium that is mentioned above, the release, uptake, and converse of glutamate is also controlled by astrocytes in the synapses. As a result, the disturbances in astrocyte-mediated glutamate metabolism is connected with epilepsy disorder [5].

In addition, the imbalance between glutamate concentration and GABA concentration can also be include in one of the triggers for seizure occurrence. Unlike glutamate, GABA is the predominant inhibitory neurotransmitter in our brain that works to prevent a nerve cell to send signals to another while glutamate allows the chemical messages to pass [6]. Glutamate stimulates the nerves, at the same time, GABA calms it down, and it is the way that they work to keep balance [4]. So, basically, problems would be caused if there is an increasement in glutamate concentration level in the extracellular apace or a reduction of GABA concentrations [7].

2.3. Injury of blood-brain barrier

Dysfunction of glial cells and the imbalance of glutamate and GABA levels are most frequent cause of early-onset seizures. However, there are other triggers for late epileptic seizures, one of them is the damaged blood-brain barrier. Blood-brain barrier is the barrier between plasma and cerebrospinal fluid that blocks substances from blood to enter the brain. During an ischemic stroke, our blood-brain barrier will be destroyed, which lead to the dysfunction of our neurons since blood will go through the barrier and seep into the brain tissues [8].

Despite the causes that are mentioned above, there are still others that trigger epilepsy disorders. Hopefully more in-depth understandings will be developed in the future so that more treatments would come out based on the future findings.

3. Classification of epilepsy

In 2017, the International League Against Epilepsy (ILEA) presented a revised classification system for epilepsy. The system has three levels of classification designed to allow epilepsy classification in different clinical settings with varying resources around the world [9].

3.1. The first level — Seizure Type

Epilepsy is first classified according to seizure type based on the assumption that a diagnosis of an epileptic seizure has already been made. This level classifies epileptic seizures into three categories: focal onset, generalized onset and unknown onset. These three seizures are classified depending on where they start in the brain. They can be further categorized based on the sufferer's level of awareness during the seizure and other symptoms caused by the seizures, such as movement. When there is no access to EEG and brain imaging technologies, this may be the highest level for epilepsy diagnosis [9, 10].

3.1.1. Focal onset seizures

Focal onset seizures originate in one area of the brain; it may affect a small region of the brain or a large part of one hemisphere. They can be split into two categories depending on the person's awareness during the seizure:

- 1) Focal aware seizures, during which the person is aware of the seizure and will remember the event afterwards.

- 2) Focal impaired awareness seizures, during which the person's consciousness is affected. They may appear confused.

Both focal aware and focal impaired awareness seizures can be classified as motor or non-motor onset seizures to reflect the earliest prominent symptoms. Motor onset involves motor symptoms (movement) and may be further classified into different types of motor onset seizures depending on the level of movement and the muscles involved, including automatisms, atonic, clonic, myoclonic, tonic, epileptic spasms and hyperkinetic. Non-motor onset seizures on the other hand do not involve movements but instead affects sensory perception, emotions and thinking. People who experience focal non-motor seizures are generally aware. Non-motor onset seizures can also be further classified depending on the symptoms displayed, including autonomic, behavioural arrest, cognitive, emotional and sensory. A focal onset seizure may spread to both sides of the brain, resulting in a focal to bilateral tonic-clonic seizure, during which the person is unaware of what's happening [10].

3.1.2. Generalized onset seizures

Generalized onset seizures affect both sides of the brain simultaneously and always involve loss of consciousness. Similar to focal onset seizures, generalized onset seizures can be classified either as motor or non-motor onset. Generalized motor onset seizures can be further classified as tonic-clonic, clonic, tonic, myoclonic, myoclonic-atonic, atonic and epileptic spasms. Generalized non-motor onset seizures, also known as absence seizures, often involves blanking out or staring into space. They can be further classified as typical, atypical, myoclonic and eyelid myoclonia [10].

3.1.3. Unknown onset seizures

Seizures that cannot be typed as either generalised or focal are classified as unknown onset. These seizures may occur in sleep, or no one was there to witness the seizure, or the witness is unable to describe the seizure. Unknown onset seizures can be classified as motor onset and further typed as tonic-clonic or epileptic spasms, or non-motor and further typed as behavioural arrest. When a seizure cannot be placed in any category due to insufficient information, it is typed as unclassified [10].

Seizure classification is not hierarchical, meaning classification can stop at any level and levels can be skipped. For example, a seizure can be classified as simply generalised onset without specifying whether it is motor or non-motor [10].

3.2. The second level — epilepsy type

The next level classifies the type of epilepsy based on the assumption that a diagnosis of epilepsy has already been made. Epilepsy can be classified as focal, generalised, combined generalised & focal, and unknown. Diagnosis of focal, generalised and combined generalised & focal must be supported by electroencephalogram (EEG) tests, which records the brain's electrical activity [9].

Those with generalised epilepsy may experience a number of generalised seizure types, and their EEG may show spike-wave discharges. Similarly, those with focal epilepsy may experience a number of focal seizure types which can be unifocal or multifocal but confined to one hemisphere; their EEG may show focal epileptiform discharges. Those with combined generalised & focal epilepsy may experience a range of focal and generalised seizure types, and their EEG may show spike-wave as well as focal epileptiform discharges; however, epileptiform discharges are not required for combined generalised & focal epilepsy diagnosis. Epilepsies are classified as unknown when the clinician is certain that the patient has epilepsy but there is insufficient evidence to determine whether the epilepsy is generalised, focal or combined generalised & focal. Diagnosis may also stop at this level of classification if there is insufficient evidence for further diagnosis [9].

3.3. The third level – epilepsy syndrome

A variety of information is combined to make an epilepsy syndrome diagnosis, including seizure types, epilepsy types, EEG and brain imaging tests, age of onset, family history and causes of epilepsy etc [3, 9].

Generalised epilepsies with no known causes can be classified as Idiopathic Generalised Epilepsies. These include epilepsy syndromes such as Childhood Absence Epilepsy, Juvenile Absence Epilepsy, Juvenile Myoclonic Epilepsy and epilepsies with tonic-clonic seizures alone. The cause of these epilepsy syndromes is therefore believed to be genetic [3, 9].

Epilepsy syndromes that start under the age of 2 can be divided into 3 categories:

1) self-limited Syndromes, including Self-limited Neonatal Epilepsy, Self-limited Infantile Epilepsy, Self-limited Familial Neonatal-Infantile Epilepsy, Genetic Epilepsy with febrile seizures plus, and Myoclonic Epilepsy in Infancy. Babies and infants with these syndromes usually stop having seizures after a period of time. 2) Developmental and Epileptic Encephalopathies, including Early Infantile Developmental and Epileptic Encephalopathy, Epilepsy of Infancy with migrating focal seizures, Infantile Epileptic Spasms Syndrome and Dravet Syndrome. These syndromes cause problems with development. 3) Cause-specific Syndromes, like the name suggests, have specific causes [3].

Epilepsy syndromes that start between the age of 2 and 12 can also be divided into 3 categories:

1) Self-limited focal epilepsies, including Self-limited epilepsy with centrotemporal spikes, Self-limited epilepsy with autonomic seizures, Childhood Occipital Visual Epilepsy and Photosensitive Occipital Lobe Epilepsy. Children with these syndromes experience focal seizures. 2) Genetic generalised epilepsy syndromes, including Childhood Absence Epilepsy, Epilepsy with Eyelid Myoclonia and Epilepsy with Myoclonic Absence. 3) Developmental and Epileptic Encephalopathies, including Doose Syndrome, Lennox-Gastaut Syndrome, Febrile Infection-related Epilepsy Syndrome and Hemiconvulsion-Hemiplegia-Epilepsy Syndrome. These syndromes cause problems with development [3].

There are also epilepsy syndromes that can start at any age, including Rasmussen Syndrome, Familial Mesial temporal lobe Epilepsy and Progressive Myoclonus Epilepsies [3].

The 2017 ILAE classification system introduced new terminologies to replace old ones. This was a huge improvement as the new terminologies describe the patient's symptoms, which makes the classification system more accessible to the general population. For example, simple partial seizure, which doesn't tell you the state of the patient during the seizure, was replaced with focal aware seizure, which clearly suggests that the patient is aware during the seizure. The new system is also well organised and detailed, with seizures classified into types with unique characteristics, which would really help the clinician as well as the patient in identifying the problem and choosing the appropriate

treatment. However, there are parts of the system that may cause confusion, for example both focal cognitive and focal sensory seizures may involve visual and auditory hallucinations. Although hallucinations during focal cognitive seizures are more complex, it may be difficult to distinguish between the two.

4. Medications for epilepsy

Because the pathogenesis of epilepsy is diverse and the causes of epilepsy are numerous, the target cells of drugs are also different, mainly including voltage-gated ion channels, neural synapses, and so on. There are many controversies about the pathogenesis of epilepsy in humans, and there are many fields that have not yet been discovered. Although anti-epileptic drugs have been developed for nearly a hundred years, the only thing that can be done at this stage is limit, which can only be controlled but cannot be eradicated. Medical methods that also have control effects include surgical removal of lesions, implantation of microelectronic devices, and non-drug treatments such as ketogenic diets, but this article does not mention them.

4.1. A voltage-gated ion channel as a target cell drug

4.1.1. Targeting sodium ion channels

Commonly used sodium channel blockers include phenytoin, carbamazepine, lamotrigine (LTG), oxcarbazepine, zonisamide, riluzole, sodium valproate, naphthalene, etc [11]. Their mechanisms are all anti-epileptic by inhibiting Na⁺ influx to control action potentials. New and better-blocking agents such as Cenobamate and capsaicin are still under study[12]. In addition, there is the drug lacosamide [11], although it also acts on sodium ion channels, it preferentially affects the inactivation process, biasing the sodium ion channel toward the inhibitory state, while enhancing the channel opening degree in the slowly inactivated state

4.1.2. Targeting calcium channels

Due to the difference in calcium ion channels, it is usually possible to precisely locate the target cells for treatment. For example, ethosuximide is a blocker for T-type calcium ion channels, and this molecule has high nucleophilicity for inactivated potassium ion channels. In addition, inside and valproic acids can also regulate T-type ion channels and play an anti-epileptic effect.

4.1.3. Targeting potassium cells

Different from the above two ion channels, in the course of treatment, such drugs usually activate this channel to fight epilepsy, and its target is usually Kv7. Problems with the activation of potassium channels by large conductance calcium ions also often lead to epilepsy, so BKC is also widely regarded as a potential target [11]. In addition, haloperidol and retigabine, retigabine (causing drug-induced liver injury) act on Kv2 or Kv3, haloperidol, and retigabine (causing drug-induced liver injury) [11].

4.2. Target cells at synapses

4.2.1. Regulates the GABAergic system

Two drugs, benzodiazepine, and barbiturate bind and activate GABA A receptors, hyperpolarizing the neuronal membrane potential, causing it to enter an inhibitory state. Tiagabine can reduce the absorption of GABA in nerves and keratinocytes, and Vigabatrin inhibits GABA-transaminase and is usually used together with it to increase the concentration of GABA to achieve the anti-epileptic effect [11]. Vicatalin, the GABA analog EF1502, and thiophenol alcohol also increase GABA transport through different pathways[11]. Cyrobamate is designed to activate GABA receptors and enhance the inhibitory properties of the hippocampal nerve[12]. neurosteroids, ganaxolone[13], and Ganaxolone can increase the inhibitory effect of GABA by combining.

4.2.2. Drugs that target glutamate receptors

AMPA receptors mediate fast excitatory synaptic transmission, so blocking AMPA can become an idea for the treatment of epilepsy. Both perampanel and NBQX are AMPA receptor antagonists, while the former belongs to the non-competitive sex, which is competitive. The drugs targeting NMDA receptors, topiramate (TPM), and zonisamide can only partially eliminate the symptoms, and the effect is not stable, it is best to be combined with other drugs. In addition, with mGluRs Although the targeted drug is still in the research stage, it can greatly reduce the side effects and has received widespread attention[11].

4.2.3. Targeting synaptic vesicle glycoproteins

Levetiracetam binds to the SV2A binding site of SV2, which can promote neurotransmitter release from vesicles, and modulates this dependent neurotransmitter release[11], thereby inhibiting epilepsy. Another drug, Seletiracetam [13], which is similar in function to levetiracetam but can be 10-25 times more effective, has also entered people's field of vision over the years

Brivaracetam (BRV) as a selective high-affinity SV2A ligand can also play a good antiepileptic effect [13]. Padsevonil, which is under investigation, acts not only on presynaptic SV2 but also on postsynaptic GABA receptor targets, thus providing strong neuronal protection

4.3. Drugs that act on other targets

4.3.1. Carbonic anhydrase (CA) inhibitors

CA inhibitors can increase the influx of negative HCO_3^- ions to depolarize the contacted GABA receptors and initiate and sustain discharge. Acetazolamide can shorten the attack time but the side effects are extremely obvious. Zonisamide is used in the adjunctive treatment of partial epilepsy in adults. Both indolesulfonamides and TPM can also act on CA[11].

4.3.2. Adenosine kinase inhibitor

Mediated by adenosine A1 receptors expressed by neurons and glial cells, combined with adenosine A1 receptors, affects neuronal excitability by regulating the release of neurotransmitters, inhibits the release of presynaptic excitatory neurotransmitters, and blocks the release of neurotransmitters. Interrupts post-synaptic membrane adenosine sensory transmission and causes membrane potential hyperpolarization. Astrocyte proliferation in epilepsy is associated with overexpression of adenosine kinase, the adenosine kinase inhibitor GP-3269[11].

4.3.3. Inhibitors of mammalian target of rapamycin (mTOR)

After TSC gene mutation, the over-activation of mTOR, which controls cell growth, will change the shape of neuron cells, resulting in abnormal neurotransmitter release or abnormal excitation. mTOR inhibitors include sirolimus and everolimus[11].

4.3.4. Anti-inflammatory drugs

This drug mainly targets neuroinflammatory pathways in glial cells. Typical drugs include the following IL-1 receptor antagonists that can inhibit relapse. Anakinra and celecoxib are stimuli that can cause convulsions. increased strength selective COX-2 inhibitors, non-selective COX-1, and COX-2 inhibitors can delay the onset of disease by reducing mossy sprouting in lesions and protecting neuronal cells[14]. Indomethacin decreased medially situated subventricular zone cells and enhanced proliferation in the lateral subventricular zone and hippocampal subgranular zone [9]. Drugs found in recent years that can also reduce the frequency of epilepsy include adalimumab, tocilizumab, natalizumab, and interleukin, which target TNF, IL-6, lymphocytes, and IL-1, respectively. [14, 15]

4.3.5. Simultaneous action on multiple targets

Sodium valproate is nitrogen-free. First, it can act on neurotransmitters, inhibit adenylate cyclase in the body, and block ion channels. Topiramate has functions such as blocking T-type calcium channels, antagonizing glutamate receptors, mildly inhibiting carbonic anhydrase, and enhancing

GABA activity. Cannabidiol, extracted from cannabis species, has a sedative effect on the GABA neurotransmitter in the human brain, inhibits the excitability of the brain center, and acts as a non-selective channel blocker to maintain the misfire of sodium channels[14].

5. Conclusion

In summary, although the pathogenesis of epilepsy in humans has not yet been fully elucidated, the existing research and hypotheses on theories such as abnormal glial cells, abnormal glutamate metabolism, and damage to the blood-brain barrier have also been used in the future. The exploration has laid a solid foundation for the continuous exploration of epilepsy in recent centuries, but its general classification has gradually become clear, and there are also AEDs corresponding to the corresponding target cells for epilepsy of different causes, and AEDs are in these Explosive growths, and these new drugs are mainly based on the improvement and continuation of traditional drugs. However, due to the individual differences of patients, AEDs are sometimes ineffective, and some drugs may even have adverse effects. Therefore, the development of non-anti-epileptic drugs has gradually come to people's attention. In addition, the treatment of epilepsy will be more personalized in the future. At present, gene therapy technology is a very potent means of anti-epilepsy, but it is still in the early stage, and it is worth looking forward to.

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