Proceedings of the 4th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/70/2024.18243

Advances in Drug Treatment of Refractory Epilepsy

Xinyu Cen

Biomedical Department, Beijing City University, Beijing, 100094, China

jjkandv@163.com

Abstract. Refractory epilepsy is a nervous system disease that does not respond well to conventional anti-epileptic drugs, and has always been a difficult problem to be solved in the medical field. The purpose of this paper is to comprehensively review and analyze the current progress of drug therapy for refractory epilepsy, in order to provide reference for future clinical practice and research. In this paper, the definition, classification, pathogenesis and mechanism of refractory epilepsy were summarized. Subsequently, the application and limitations of traditional antiepileptic drugs, as well as the development and clinical application of new antiepileptic drugs, such as CBD and P2X7R, were discussed in detail. This paper looks forward to the future research direction and challenges, focusing on the trends and challenges of new drug development, as well as the application prospects of precision medicine in the treatment of refractory epilepsy. Finally, it is pointed out that the future treatment of refractory epilepsy still needs to face the technical maturity of advanced technology in practical application, and the development of new drugs and new treatments requires a lot of money and time investment, and clinical trials may fail.

Keywords: Refractory Epilepsy, Drug Treatment, New Antiepileptic Drugs, Personalized Treatment, Precision Medicine.

1. Introduction

Epilepsy is a common disease of the nervous system. There are about 70 million epilepsy patients worldwide, and the number of epilepsy patients in China is close to 10 million, second only to cerebrovascular diseases. Despite the approval of more than 20 new drugs for epilepsy treatment in the past three decades, there has been little change in the proportion of patients who remain resistant to medication[1]. The proportion of drug-resistant patients remains basically unchanged. This fact reminds us that the treatment of epilepsy still faces huge challenges. Further research and innovation are needed to improve the effectiveness and specificity of treatment and bring more hope to epilepsy patients. In terms of the treatment results of drug therapy, approximately one-third of patients achieve seizure control through a single antiseizure medication (ASM). Another one-third of patients need to combine two or more drugs to achieve seizure-free status[2]. The chance of not experiencing another episode is significantly lower in the remaining third of patients, and a considerable number will continue to endure uncontrolled episodes. As a result, researchers have been actively pursuing the development of novel medications for the treatment of drug-resistant epilepsy. This article discusses the limitations of traditional antiepileptic drugs and the development and clinical application of new antiepileptic drugs, and looks forward to future drug research and development that should focus on exploring potential therapeutic targets. At the same time, the rise of precision medicine provides new

DOI: 10.54254/2753-8818/70/2024.18243

possibilities for individualized treatment. In this process, the close integration of scientific research and clinical practice, as well as the cooperation of multidisciplinary experts, will jointly promote the progress of the treatment of refractory epilepsy, and bring better quality of life and treatment experience to patients.

2. Definition of Refractory Epilepsy

Refractory epilepsy, a term that does not merely refer to the severity of epilepsy, describes a clinical phenomenon where seizures remain inadequately controlled despite appropriate treatment with antiepileptic drugs. This condition is typically defined as the persistence of seizures in patients after attempting two or more appropriate antiepileptic drugs, which have been used at adequate doses and for a sufficient duration, without significant reduction in seizure frequency. Under this definition, refractory epilepsy does not include cases where poor treatment outcomes are due to factors such as poor patient compliance, severe adverse drug reactions, or causes that cannot be removed (e.g., tumors). The formal definition of refractory epilepsy was proposed by the International League Against Epilepsy (ILAE), and it is a clinical diagnosis that emphasizes the attempts and failures of drug treatment. According to the type of seizures, refractory epilepsy can be further subdivided into partial refractory epilepsy and generalized refractory epilepsy. Partial refractory epilepsy is usually caused by focal brain injury, with seizures originating from a specific area of the brain and potentially spreading to other regions. Generalized refractory epilepsy, on the other hand, involves abnormal discharges in both hemispheres of the brain, typically presenting as generalized tonic-clonic seizures[3]. The pathogenesis of refractory epilepsy is intricate and usually associated with numerous factors. Genetic elements hold a significant position in refractory epilepsy. Some gene mutations, like SCN1A and SCN8A, are linked to ion channel dysfunctions. This can result in heightened neuronal excitability and then trigger epileptic seizures. Drugs must cross the blood-brain barrier to be effective. In drug-resistant epilepsy patients, overexpression of multiple drug transporter proteins hinders the smooth passage of drugs through the blood-brain barrier or cerebrospinal fluid barrier to reach the brain tissue. The insufficient drug concentration around the epileptic focus impacts the treatment outcome. Additionally, the neural network hypothesis posits that due to neuronal degeneration and synaptic network remodeling, the epilepsy control system of the brain is suppressed, and the access of drugs to the target is restricted[4]. Therefore, comprehensive consideration is needed in treatment to find the most suitable personalized treatment plan.

3. Advances in Drug Treatment

3.1. Application and limitations of traditional antiepileptic drugs

Once patients are diagnosed with refractory epilepsy, the first choice is to select a reasonable and standardized combination drug treatment. When discussing the advances in drug treatment for refractory epilepsy, the application and limitations of traditional antiepileptic drugs cannot be overlooked. These drugs are diverse in type and mechanism of action, primarily controlling seizures by modulating neurotransmitters and inhibiting abnormal discharges. Commonly used antiepileptic drugs include oxcarbazepine, levetiracetam, clonazepam, and phenytoin. After combined use, they can inhibit synaptic potentials, ion channels, or enhance GABA function, all of which have good effects; however, their role in neuronal repair is relatively small. Therefore, the treatment effect for refractory epilepsy tends to decline with increased usage frequency (and the development of drug resistance). In the treatment of refractory epilepsy, the effectiveness of traditional drugs is often not ideal[5]. Benzodiazepines and barbiturates are the main classes of drugs used to treat epilepsy, including both monotherapy and polytherapy targeting GABAA receptors. In particular, benzodiazepines exert their anticonvulsant effects by binding to allosteric sites between the α and γ subunits of the GABAA receptor. The interactions of these drugs at their binding pockets increase the receptor's affinity for the neurotransmitter GABA, without directly inducing Cl- influx through ion channels. Therefore,

DOI: 10.54254/2753-8818/70/2024.18243

benzodiazepines do not increase the duration of opening of the chloride channels, but rather increase the frequency, thereby enhancing the physiological hyperpolarization effect of GABA[6].

On one hand, some patients may develop drug resistance, which leads to a decrease in the effectiveness of treatment. On the other hand, traditional drugs can be accompanied by many side effects, affecting the quality of life of patients. Therefore, conducting an objective evaluation of the efficacy of traditional drug treatments for refractory epilepsy helps us gain a more comprehensive understanding of the current therapeutic landscape and provides valuable references for further research. In addition, there are issues related to drug interactions, especially interactions between topiramate, loperamide, clonazepam, phenytoin, and carbamazepine. Recently, the therapeutic use of steroids has been shown to reduce the burden of seizures in many epileptic conditions. This may be due to the improved distribution of drugs in the brain. Neurosteroids serve as positive modulators and hold a crucial role in governing neuronal excitability and neuroplasticity. Neurosteroids with anticonvulsant properties are those that increase GABAergic inhibition. Neurosteroids, as opposed to benzodiazepines, have the ability to directly open receptor chloride channels at low micromolar concentrations. Furthermore, neurosteroids have the ability to produce broad-spectrum anticonvulsant effect by acting on all subtypes of GABA-AR in the brain. This suggests that neurosteroids may be used to treat epileptic conditions. Neurosteroids exhibit broad-spectrum anticonvulsant efficacy in a variety of seizure types because they are effective GABA ergic agonists. Compared to benzodiazepines, the synthetic neurosteroid ganaxolone (GX) is more effective at suppressing status epilepticus because it operates on both extrasynaptic and synaptic GABA-ARs. In animal models of epilepsy and opna-induced RSE, GX has broad-spectrum anticonvulsant efficacy. In a phase 2 open-label dose-finding research, 17 RSE patients (8 males and 9 females) had their safety and effectiveness of adding intravenous GX to standard treatment ASMs evaluated. Patients with convulsive or non-convulsive SE who were resistant to at least one second-line ASM (aged 23 to 88 years) were included in the trial (NCT03350035). Throughout the trial, a total of 23 associated adverse events were recorded, of which 16 were mild, 5 were moderate, and 2 were severe. However, a large number of patients (53 instances in the low and medium dose groups and 1 case in the high dose group) discontinued treatment due to ineffectiveness or unfavorable sedative effects.

The anti-epileptic response of patients who completed the trial was independent of dosage despite elevated plasma levels. Intravenous injection of GX was also tested in two pediatric patients with refractory status epilepticus (7 years old and 17 years old). GX was first injected intravenously into these individuals, and then they had a maintenance infusion for a maximum of 4.5 days. Intravenous injections were administered sporadically as needed, with a gradual reduction in dosage initiated on the fifth day. Patients were then transferred to oral GX suspension therapy. In two patients, adjuvant GX successfully stopped SRSE, allowing for a safe decrease in intravenous anesthesia. Seizures were under control when switching to enteral GX[7].

3.2. Development and clinical application of novel antiepileptic drugs

In the realm of drug treatment for refractory epilepsy, the development and clinical application of new antiepileptic drugs are extremely crucial. These novel drugs come in a diverse variety of types and possess unique action characteristics, bringing more possibilities for treatment. Specifically, they regulate the balance of neurotransmitters in the brain through different mechanisms, reducing excessive neuronal excitation and thereby achieving the goal of controlling seizures. In practical applications, these new drugs have shown their potential in the treatment of refractory epilepsy. For instance, recently, there is growing interest in using products rich in cannabidiol (CBD) to treat drug-resistant epilepsy. Although there has been much speculation about the therapeutic value of cannabis products as an antiepileptic treatment, only in the past two years has there been level 1 evidence for pure CBD based on placebo-controlled RCTs in patients with Lenox-Gastaut syndrome and Dravet syndrome. The best-known report is about Charlotte, a "five-year-old American girl" diagnosed with SCN1A-confirmed Dravet syndrome in 2013 who had up to 50 generalized tonic-clonic seizures per day. After three months of treatment with cannabis extract of the high CBD

DOI: 10.54254/2753-8818/70/2024.18243

strain, it was reported that her seizures decreased by more than 90%[8]. Cannabidiol (CBD) has demonstrated good tolerance and possesses anticonvulsant and anti-inflammatory qualities. However, its mechanism of action remains not fully understood. Some medications based on CBD (such as Epidiolex, Realm Oil, etc.) have been regarded as potential treatments for refractory epilepsy. Nevertheless, CBD treatment is accompanied by side effects, with drowsiness, reduced appetite, and diarrhea being the most prevalent ones[9]. Some drugs have demonstrated remarkable effectiveness in treating specific types of refractory epilepsy, like drug-resistant epilepsy (DRE) and Lennox-Gastaut syndrome. These successful instances not only confirm the efficacy of new drugs but also offer valuable experience for future research and treatment. Research in the past few decades has provided substantial evidence that clearly shows that P2X7R plays a pathogenic role in the occurrence of seizures (the onset of epilepsy) and the development of epilepsy. A recent study by a group indicated that during SE induced by ika, mice with overexpressed P2X7Rs in microglia showed reduced responsiveness to several anticonvulsants, including lorazepam, midazolam, phenytoin, and carbamazepine, providing a theoretical basis for blocking microglial P2X7R function as an adjunctive treatment for drug-resistant epilepsy[10].

4. Future Research Directions and Challenges

4.1. Trends and challenges in new drug development

Future research directions mainly center on the trends in new drug development and the challenges it confronts. In the case of refractory epilepsy, new drug development is aiming at greater efficacy and safety. In recent years, the application of artificial intelligence technology and machine learning algorithms in various diseases, including epilepsy, has notably increased[11]. A computational clinical decision support system was created using a deep learning model based on patient history to suggest efficacious antiepileptic medications for children with epilepsy. A computerized clinical decision support system was developed by researchers based on 7,507 medical records from 1,000 pediatric epilepsy patients to aid in the selection of antiepileptic medications (AEDs). The system employs three multi-channel convolutional neural network (CNN) models customized for three specific AEDs (Vigabatrin, Prednisone, and Clobazam). Each CNN model can predict with high accuracy whether its corresponding AED is effective for a given patient, thus reducing unnecessary drug treatment in pediatric patients[12]. However, in the face of computer-aided drug development, there are numerous technical challenges in this process. We need to consider factors such as drug bioavailability, blood-brain barrier permeability, and drug side effects. To deal with these issues, researchers are exploring novel drug delivery systems to increase drug concentration in the brain while reducing systemic toxicity. Additionally, the utilization of gene editing technologies and nanotechnology has offered new possibilities for the treatment of refractory epilepsy. Regarding epilepsy, people with focal epilepsy may initially find that gene therapy offers a special potential. In fact, patients who choose surgical resection and have drug-resistant focal epilepsy may be the first to receive it. By injecting gene therapy vectors directly into epileptogenic foci, the possibility of influencing healthy brain tissue is eliminated or diminished, which lowers the possibility of unanticipated adverse effects.

If the treatment proves ineffective or is not well tolerated, the patient can proceed to the originally planned resection surgery. In the event that it works, the patient can forego surgery. Such evidence of effectiveness would increase the application of therapy to some focal epileptic patients who are not candidates for surgery in the larger context of future gene therapy for epilepsy[13]. A randomized, blinded, preclinical investigation served as the foundation for the first gene therapy experiment that was approved. In this work, potassium channels (EKC) in excitatory neurons were delivered using a nonintegrating lentiviral vector. Both focal neocortical and temporal lobe epilepsy models benefit from this EKC gene therapy, offering compelling evidence in favor of clinical development.

Indeed, a phase I/IIa, single-site, open-label, first-in-human experiment (ClinicalTrials.gov Identifier: NCT04601974) that was approved in 2023 is about to begin enrolling patients who meet the criteria for surgical resection but have intractable neocortical epilepsy. Through intracerebral infusion

DOI: 10.54254/2753-8818/70/2024.18243

into the intended resection area, a single dosage of LV gene therapy will be administered to a selected group of patients. The main findings of this study were related to treatment feasibility, safety, and tolerability, including surgery[14]. Among the various types of nanosystems currently being evaluated, MnPs have been proven to be one of the optimal strategies for different biomedical applications, including MRI contrast agents, cell therapy, tissue repair, thermotherapeutic ablation, drug delivery, and carrier systems. Apart from their simple and economical synthesis process, MnPs have particular advantages such as their small size (less than 100 nm), enabling penetration of cell membranes. Their biodegradability is achieved through lysosomal destruction of the iron oxide core, resulting in the incorporation of iron ions back into the hemoglobin pool. Considering the magnetic properties of MnPs, the release of special devices in the brain can be controlled by magnetic fields. Several reports have indicated that MnPs are highly biocompatible and administration does not cause toxic effects. Based on this information, MnPs may be an excellent approach to deliver Aeds to the brain parenchyma of patients with drug-resistant epilepsy. In fact, a previous study showed that intraperitoneal injection of MnPs for four weeks did not produce "significant" toxicity, histopathological changes, or adverse effects on physical development and behavior. However, it is relevant to note that MnPs are also reactive in biological environments and may induce chemical interactions and toxicological effects. Regarding this issue, it has been reported that MnPs can overproduce reactive oxygen species, a situation that may lead to oxidative stress, neuronal damage, proinflammatory effects, and altered blood-brain barrier permeability. Therefore, it is essential to determine whether adverse effects occur after long-term administration of MnPs under different physiological conditions. The loading of Aeds in nanosystems may be a promising therapy for drug-resistant epilepsy. Some of these nanosystems are so straightforward to prepare that they are already routinely used to treat different brain disorders. This advantage, combined with the diversity of modern technologies available, the availability of appropriate experimental models for anti-AED epilepsy, and the coordinated efforts of basic science, bioengineering, and clinicians will certainly facilitate the development of new and more effective nanotherapies for the treatment of anti-drug epilepsy in the coming years[15]. However, these advanced technologies still face numerous challenges in practical application, such as technological maturity, safety, and ethical issues, requiring continuous efforts and exploration from researchers.

4.2. The application of precision medicine in the treatment of refractory epilepsy in the future.

Precision medicine is gradually showing its application prospects in the treatment of refractory epilepsy. As an emerging medical model, precision medicine emphasizes formulating targeted treatment plans according to individual patient differences. In the field of epilepsy, especially for refractory epilepsy, the potential advantages of precision medicine are obvious. The mutation mechanisms of epilepsy genes include not only ion channel dysfunction and neurotransmitter regulation but also multiple mechanisms such as structural genes and cellular signaling transcription[16]. Drug resistance is a major challenge in antiepileptic drug treatment. Research shows that in some patients with refractory epilepsy, the overexpression of efflux transporters like P-glycoprotein (P-gp) may reduce drug concentrations in epileptogenic tissues, resulting in limited efficacy. Additionally, structural or functional changes in voltage-gated sodium channels (VGSC), such as mutations in the SCN1A and SCN8A genes, may increase neuronal excitability and reduce the effects of antiepileptic drugs. The occurrence of this drug resistance complicates drug selection and dosage adjustments, requiring more refined personalized treatment strategies[17]. By conducting in-depth analysis of patient genotype, phenotype and other data, precision medicine is anticipated to offer more effective treatment strategies for complex cases like drug-resistant epilepsy. Nevertheless, this model also confronts numerous challenges including the completeness of data collection, the accuracy of analysis methods, and the feasibility of treatment plans. In the future, with the continuous advancement of technology and in-depth research, precision medicine is expected to play an even greater role in the treatment of refractory epilepsy.

DOI: 10.54254/2753-8818/70/2024.18243

5. Conclusion

Although current drug treatment approaches have somewhat improved the situation of patients with refractory epilepsy, they still encounter numerous challenges. Future research should concentrate on creating new drugs and potential therapeutic targets. Meanwhile, the emergence of precision medicine offers new prospects for personalized treatment. This article mainly reviews the research progress in drug treatment for refractory epilepsy but lacks specific experimental research data. In subsequent studies, adding some clinical experiments or case analyses can more strongly demonstrate the effectiveness and safety of drugs. Future research needs to explore more effective and safer antiepileptic drugs and utilize gene editing technology and nanotechnology to develop new drug delivery systems to increase drug concentration in the brain and reduce systemic toxicity. Further study the mutation mechanism of epilepsy genes, including multiple mechanisms such as ion channel dysfunction, neurotransmitter regulation, structural genes, and cell signal transcription, in order to formulate more accurate individualized treatment plans. Further explore the drug resistance mechanism of patients with refractory epilepsy, such as the role of efflux transporters and voltage-gated sodium channels, and find ways to address drug resistance. Use artificial intelligence technology and machine learning algorithms to more accurately predict drug efficacy and provide personalized treatment suggestions for patients. The treatment of refractory epilepsy requires multidisciplinary cooperation, including neuroscience, pharmacology, genetics, and so on. Future research should strengthen interdisciplinary cooperation to jointly overcome problems.

Acknowledgment

First of all, I would like to express my special thanks to my thesis supervisor for their meticulous guidance, providing me with substantial help and direction during the writing and design process of my thesis, clarifying my design ideas and operational methods, and offering effective improvement suggestions for my research topic. I have learned many lifelong lessons from them. Once again, I sincerely thank my teacher.

References

[1] Klein P, Tyrlikova I. No prevention or cure of epilepsy as yet. Neuropharmacology. 2020 May 15;168:107762. doi: 10.1016/j.neuropharm.2019.107762. Epub 2019 Sep 6. PMID: 31499048.

[2] Elkommos S, Mula M. Current and future pharmacotherapy options for drug-resistant epilepsy. Expert Opin Pharmacother. 2022 Dec;23(18):2023-2034.

[3] Chan HW, Pressler R, Uff C, Gunny R, St Piers K, Cross H, Bamber J, Dorward N, Harkness W, Chakraborty A. A novel technique of detecting MRI-negative lesion in focal symptomatic epilepsy: intraoperative ShearWave elastography. Epilepsia. 2014 Apr;55(4):e30-3.

[4] Sisodiya S.M. Mechanisms of antiepileptic drug resistance. Curr. Opin. Neurol. 2003;16:197–201.

[5] Huang Shicun, Xu Min. New advances in the treatment of refractory epilepsy [J]. Clinical Review, 2013, 28(11): 1315-1318.

[6] Naimo GD, Guarnaccia M, Sprovieri T, Ungaro C, Conforti FL, Andò S, Cavallaro S. A Systems Biology Approach for Personalized Medicine in Refractory Epilepsy. Int J Mol Sci. 2019 Jul 30;20(15):3717. doi: 10.3390/ijms20153717.

[7] Reddy DS. Neurosteroids as Novel Anticonvulsants for Refractory Status Epilepticus and Medical Countermeasures for Nerve Agents: A 15-Year Journey to Bring Ganaxolone from Bench to Clinic. J Pharmacol Exp Ther. 2024 Jan 17;388(2):273-300.

[8] Arzimanoglou A, Brandl U, Cross JH, Gil-Nagel A, Lagae L, Landmark CJ, Specchio N, Nabbout R, Thiele EA, Gubbay O, The Cannabinoids International Experts Panel; Collaborators. Epilepsy and cannabidiol: a guide to treatment. Epileptic Disord. 2020 Feb 1;22(1):1-14.

[9] Golub V, Reddy DS. Cannabidiol Therapy for Refractory Epilepsy and Seizure Disorders. Adv Exp Med Biol. 2021;1264:93-110. doi: 10.1007/978-3-030-57369-0_7. PMID: 33332006.

[10] Thakku Sivakumar D, Jain K, Alfehaid N, Wang Y, Teng X, Fischer W, Engel T. The Purinergic P2X7 Receptor as a Target for Adjunctive Treatment for Drug-Refractory Epilepsy. Int J Mol Sci. 2024 Jun 23;25(13):6894.

[11] Torres-Gaona G, Aledo-Serrano Á, García-Morales I, Toledano R, Valls J, Cosculluela B, Munsó L, Raurich X, Trejo A, Blanquez D, Gil-Nagel A. Artificial intelligence system, based on mjn-SERAS algorithm, for the early detection of seizures in patients with refractory focal epilepsy: A cross-sectional pilot study. Epilepsy Behav Rep. 2023 Apr 5;22: 100600.

[12] ho D, Yu MS, Shin J, Lee J, Kim Y, Kang HC, Kim SH, Na D. A computational clinical decision-supporting system to suggest effective anti-epileptic drugs for pediatric epilepsy patients based on deep learning models using patient's medical history. BMC Med Inform Decis Mak. 2024 May 31;24(1):149.

[13] Bettegazzi B, Cattaneo S, Simonato M, Zucchini S, Soukupova M. Viral Vector-Based Gene Therapy for Epilepsy: What Does the Future Hold? Mol Diagn Ther. 2024 Jan;28(1):5-13.

[14] Snowball A, Chabrol E, Wykes RC, Shekh-Ahmad T, Cornford JH, Lieb A, et al. Epilepsy gene therapy using an engineered potassium channel. J Neurosci. 2019;39:3159–69.

[15] Rosillo-de la Torre A, Luna-Bárcenas G, Orozco-Suárez S, Salgado-Ceballos H, García P, Lazarowski A, Rocha L. Pharmacoresistant epilepsy and nanotechnology. Front Biosci (Elite Ed). 2014 Jun 1;6(2):329-40.

[16] Hu Xiaoyue, Tang Jihong, Hua Ying. The current status of precision medicine in refractory epilepsy [J]. Epilepsy Journal, 2019, 5(03): 192-195.

[17] Liu J, He Y, Zhang J, Li J, Yu X, Cao Z, Meng F, Zhao Y, Wu X, Shen T, Hong Z. Functionalized nanocarrier combined seizure-specific vector with P-glycoprotein modulation property for antiepileptic drug delivery. Biomaterials. 2016 Jan;74:64-76. doi: 10.1016/j. biomaterials.2015.09.041. Epub 2015 Sep 30.