Compound 350: A New Hope for Individuals with Drug-resistant Epilepsy

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Background

According to the conceptual definition of epilepsy established by the International League Against Epilepsy (ILAE), epilepsy is a brain disorder characterised by a propensity to cause epileptic seizures and their psychosocial consequences. The practical application of this definition is typically understood to mean at least two unprovoked seizures that occurred more than 24 h apart, but a 2014 refinement defines epilepsy as a brain disease with either: (a) at least two unprovoked seizures that occurred more than 24 h apart; (b) one unprovoked seizure and a likelihood of similar seizure recurrence to the general risk after two unprovoked seizures or (c) a diagnosis of an epilepsy syndrome.[1] As it affects 50 million people worldwide and accounts for a sizable portion of the disease burden, epilepsy is a significant global health issue. Between 4 and 10 per 1,000, people are thought to have active epilepsy at any given time, which is defined as having on-going seizures or needing treatment. Worldwide, epilepsy affects about 5 million people each year. The annual diagnosis rate is roughly 49 per 100,000 in high-income countries, while it can reach 139 per 100,000 in low- and middle-income countries. Differences in healthcare infrastructure, access to healthcare prevention programs and treatment, higher incidence rates of endemic diseases such as neurocysticercosis and malaria, traffic accidents and birth injuries probably cause this discrepancy in diagnosis rates.[2]

Drug-resistant Epilepsy

Despite the on-going advancement of antiepileptic medications, over 30% of epileptic patients develop drug-resistant epilepsy, sharply increasing morbidity and mortality. Drug-resistant epilepsy, according to the ILAE, is when two well-tolerated, properly selected and used antiepileptic drug (AED) schedules, either alone or in combination, fail to produce sustained seizure freedom after adequate trials. Due to the complex aetiology and unclear pathogenesis of the condition, surgical treatment alone is frequently insufficient to treat drug-resistant epilepsy, so an antiepileptic comprehensive treatment approach based on surgery must be combined with other treatment modalities.[3]

Pathophysiology of Drug-resistant Epilepsy

The complex pathogenesis of epilepsy is thought to result from an imbalance between the excitatory and inhibitory functions of the central nervous system. The target and transporter hypotheses are two current theories for drug-resistant epilepsy. According to the transporter hypothesis, increased multidrug transporters such as P-glycoprotein, MRP and BCRP could reduce intracellular drug concentration and render antiepileptic medications ineffective. The target hypothesis states that uncontrollable epilepsy attacks are primarily reflected by abnormal ion channel function, such as voltage-gated sodium channels (VGSCs), and result from changes to the structure or function of the predetermined targets of AED. A mutation in the sodium channel-coding SCN1A gene is thought to be the primary cause of severe myoclonic epilepsy in infants. As a result, neuronal excitability rises, inhibitory loop function decreases and epileptic seizures occur. SCN1A mutations are more common in patients with drug-resistant epilepsy.[4]

Current Treatment Options

The main treatment for drug-resistant epilepsy, especially mesial temporal lobe epilepsy, is resective surgery. Two other surgical options are as follows: selective amygdalohippocampectomy, which is appropriate for patients

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with hippocampal sclerosis, and anterior temporal lobectomy, which is appropriate in cases where one side of the temporal lobe has epileptogenic zones. Epilepsy in the lateral temporal lobe has been successfully treated surgically and is safe. Hemiconvulsions, hemiplegia, epilepsy, perinatal injury, unilateral hemispheric cerebral malformations, diffuse cortical dysplasia, Rasmussen syndrome and Sturge-Weber syndrome can all be treated with hemispherectomy. Depending on the type of surgery and the type of epilepsy, different surgical treatments have different success rates. However, a multi-centre clinical trial is required to create precise, evidence-based guidelines for surgical treatment[4]. Vagus nerve stimulation (VNS) and corpus callosotomy are additional surgical methods for treating epilepsy. To stop epileptic seizures from transferring between the hemispheres, a corpus callosotomy is performed. Due to a lower risk of complications, partial callosotomy and colostomies performed using a stereotactic laser are preferred to complete callosotomy. Other seizure types may also benefit from callosotomy, which is most beneficial for drop attacks and generalised tonic–clonic seizures. To stimulate the vagus nerve and lessen seizure frequency and severity, VNS involves implanting a device in the chest. Although its mechanism of action is not completely known, VNS is effective for focal and generalised seizures. Infection/vocal cord paralysis and sensory disconnection syndrome are complications of these procedures. Patients should carefully discuss the advantages and disadvantages with their healthcare provider[5]. The available therapies for drug-resistant epilepsy come with several drawbacks and restrictions. First, surgical procedures such as resective surgery, corpus callosotomy and hemispherectomy can result in side effects such as bleeding, infection, stroke and cognitive deficits. Patients may experience long-lasting effects from these complications. Second, not every patient is a candidate for surgery, and surgical success rates vary depending on the type of epilepsy and surgery. This may reduce these treatments' efficacy for some patients. Additionally, some patients may not be able to access surgical treatments because they can be expensive and may not be covered by health insurance. The evidence for the effectiveness of these treatments is weak, and more investigation is required to ascertain their long-term advantages and risks. Further investigation is required to determine the best surgical approaches and selection standards for various epilepsy types.

The New Possible Treatment Option

According to the research, the pathophysiology of epilepsy is influenced by deficits in KCC2 activity. Chloride transporter KCC2 is essential for preserving the brain's inhibitory state of GABAergic signalling. The authors discovered a family of small molecules that stimulate KCC2 and dampen excitability in neurons. To find the KCC2 activators, the study employed a FLIPR assay and a proprietary library of 1.3 million unique chemical structures. The authors found activators from a larger library of compounds because of the assay's higher throughput compared with other screens.[6,7] Compared with other indirect potentiators of this transporter, the substances discovered in this study act in direct KCC2 activation. These additional potentiators have been demonstrated to boost KCC2 expression or alter its phosphorylation.[8] Without affecting the stability of KCC2's plasma membrane or the phosphorylation of crucial regulatory sites expressed in HEK-293 cells, the authors discovered that substance 350 significantly increased KCC2 activity. Other KCC2 phosphorylation sites' significance still needs to be understood. In acute brain slices with 0-Mg exposure, the study discovered that 350 decreased Cl accumulation in neurons and the emergence of late recurrent discharges (LRDs). It quickly distributed to the brain and prevented pentylenetetrazole (PTZ)-induced motor seizures without having any obvious reaction to mouse behaviour.[9]

According to the research, 350 pre-treatments of mice resisted the development of benzodiazepine-resistant status epilepticus (BDZ-RSE), which is caused by kainic acid (KA). In the brain, the concentration of 350 was adequate to enhance the activity of KCC2. The study additionally demonstrated that 350 successfully halted on-going BDZ-RSE and restored the efficacy of BDZs. Inadequacy in the activity of KCC2 may be essential to the pathophysiology of this condition, given 350's capacity to repeatedly stop and restart BDZ-RSE. In addition, mice with 350/BDZ treatment had markedly lower death rates of neurons in the hippocampus than controls treated with only BDZ. The authors speculate that this effect may result from 350's ability to regulate hyperexcitability[9].

As a result of the study, a class of small molecules that activate KCC2 and reduce neuronal excitability have been identified. These molecules may be used in the treatment of refractory epilepsies in people and lessen the damage to the brain. The research establishes that inhibition of BDZ-RSE and associated neuronal damage can be prevented by activating KCC2. The study identified several limitations that require further investigation. These include determining the optimal dosage of a drug to suppress seizures while avoiding any adverse side effects, evaluating the effectiveness of KCC2 activators in treating BDZ-RSE caused by other entities and examining the long-term impact of activation of KCC2 on the onset of unconstrained and recurrent seizures. The study's findings also revealed that activators of KCC2 can restore or enhance the anticonvulsant effectiveness of BDZs. However, whether the sedative effects, amnesic, anxiolytic, hypnotic and BDZs exhibit a similar synergistic effect remains uncertain[9].

Conclusion

Although surgical treatment for drug-resistant epilepsy has been successful, it frequently has drawbacks because of its complicated aetiology and unclear pathogenesis. Additionally, a thorough antiepileptic treatment approach that includes

surgery must be combined with additional treatment modalities because surgery alone is usually insufficient. A new treatment option for epilepsy compound 350 has been identified as a direct activator of KCC2, which lowers neuronal excitability and inhibits epileptic seizures. A promising alternative to surgery, compound 350, has been demonstrated to decrease the accumulation of Cl in neurons and the emergence of LRDs in acute brain slices. On a personal level, this might lessen the need for risky, invasive surgical procedures and improve one's quality of life. Locally, this might lower healthcare costs related to surgical care and make treatment more accessible to people unsuitable for surgery.

Abbreviations

ILAE, International League Against Epilepsy; AED, antiepileptic drugs, VGSCs, voltage-gated sodium channels; VNS, vagus nerve stimulation; LRDs, late recurrent discharges; BDZ-RSE, benzodiazepine-resistant status epilepticus.

Authors' Contributions

The conceptualisation of the study and editing and supervision were performed by HR and HF. The literature and drafting of the manuscript were conducted by HR, HF, BR, MM, SA and FR. All authors have read and agreed to the final version of the manuscript.

Declaration of Conflicting Interests

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