INVESTIGATIONAL NEW DRUGS FOR FOCAL EPILEPSY

Abstract

For more than 30 years, antiepileptic drug development has been based on specific assumptions regarding the neurobiology of epilepsy but all marketed drugs have not changed the proportion of drug refractory patients. It is, therefore, evident that new molecular targets need to be identified. Advances in neurobiology and molecular pharmacology are bringing into the epilepsy field new neurochemical functions such as those modulated by cannabinoid, serotonin, melatonin and galanin receptors. Among all different compounds, the melatonin type 3 receptor agonist beprodone and cannabidiol are those at the more advanced stage of development. Interestingly, despite the structural analogies with tetrahydrocannabinol, the anticonvulsant activity of cannabidiol is not mediated by an interaction with cannabinoid receptors. Neurosteroids represent another remarkable class of drugs and among them ganaxolone is the one at the more advanced stage of development. Furthermore, for the first time, potential disease-modifying agents and techniques are entering the epilepsy market. Rapalogues such as everolimus and the antibiotic minocycline are currently under development for specific epileptic syndromes like tuberous sclerosis or Angelman syndrome. Finally, optogenetics, though still at an early stage of development, represent a futuristic therapeutic strategy for drug-refractory epilepsies.

Key Words: epilepsy, antiepileptic drugs, cannabinoid, galanin, serotonin, melatonin, mTOR, rapamycin, everolimus, minocycline, optogenetics

1. INTRODUCTION

Antiepileptic drugs (AEDs) still remain the mainstay for the treatment of epilepsy but despite two decades in which a new compound was launched almost annually, 30% of patients still remain uncontrolled. It has been estimated that around 15 million people worldwide have drug refractory epilepsy [1] and many patients also have cognitive, psychological, psychiatric, and social impairments, as well as impaired quality of life and an increased risk of premature death [2]. It appears evident that new drugs are more than warranted but while many drugs can limit seizures, no drug can still prevent the underlying cause of epilepsy or the development of epilepsy (epileptogenesis) in patients who are at risk (e.g. following brain injury, stroke etc.). For these reasons, among all drugs currently under development, two groups are of interest: AEDs with new mechanisms of actions and **potential** disease modifying agents.

The last three generations of compounds have focused basically on the same neurobiological targets, namely voltage-dependent ion channels, direct modulation of GABAergic and glutamatergic neurotransmission. Advances in neurobiology and molecular pharmacology are bringing into the epilepsy field new neurochemical pathways such as cannabinoid, serotonin, melatonin and galanin receptors. Furthermore, for the first time, **potential** disease-modifying agents and techniques appeared in the epilepsy market. The mammalian target of rapamycin (mTOR) pathway now represents a major target in specific epilepsy syndromes as well as the antibiotic minocycline. Optogenetics may represent a new therapeutic strategy not only in genetic but also in post-stroke or post-traumatic epilepsies.

2. NEW MECHANISMS OF ACTION

2.1 Cannabinoid

For many years, it has been speculated that cannabis, or some components of the cannabis plant, may have antiepileptic properties. It is now established that tetrahydrocannabinol (THC) has some anticonvulsant properties that are mediated by CB1 receptors, which are G protein-coupled cell membrane receptors expressed ubiquitously in neurons of the central nervous system [3]. However, the two major compounds currently under investigations do not exert antiepileptic effect through this pathway. In the case of cannabidiol (CBD), the mechanism of action is not entirely clarified but some authors proposed the inhibition of adenosine uptake as the main antiepileptic mechanism [4]. For cannabidivarin (CBDV), a homolog of CBD with the side-chain shortened by two methylene bridges, the mechanism of action is completely unknown and further research is needed [4]. Data on current trials involving CBD is summarised in **Table 1**. Despite the wide compassionate use, especially in children with drug-refractory epilepsy, data on efficacy is still contradictory and properly designed, high quality, and adequately powered trials are definitely needed [5].

2.2 Galanin

Galanin is one of the most inducible neuropeptides. Its biosynthesis is increased 2 to 10-fold upon axotomy in the peripheral nerve and upon seizure activity in the brain [6]. This observation suggests that agonists of galanin receptors (GalR1–3) may be useful therapeutic agents in neuroprotection. GalR2 agonists seem to have anticonvulsant and analgesic/anxiolytic properties and a specific agonist (NAX 810-2) [4] is currently under preclinical investigation (**Table 1**).

2.3 Serotonin

The involvement of serotonin (5HT) pathways in epilepsy is based on data from animal models and human positron emission tomography (PET) imaging studies showing a role for 5HT-1A receptors in the pathophysiology of epilepsy [7]. In addition, many patients with epilepsy suffer from depression and anxiety, and the modulation of serotoninergic neurotransmission is a standard treatment for those disorders [8]. Nalutozan (PRX 0023) is a selective 5HT1A agonist currently under investigation

[4]. Nalutozan has completed a clinical trial in anxiety and a randomized cross-over pilot study in 24 patients with epilepsy is on-going.

Another serotoninergic drug, not entirely new, is fenfluramine [9]. It was previously marketed for obesity as it has clear amphetamine-like effects but it is basically a serotonin reuptake inhibitor. Fenfluramine was withdrawn in 1997 after reports of heart valve disease and pulmonary hypertension, including cardiac fibrosis. On-going trials are investigating the compassionate use in Dravet syndrome.

2.4 Melatonin

Beprodone (VLB-01) is a melatonin type 3 receptor agonist under Phase IIb development in focal epilepsy [4]. It is supported by a large dataset from preclinical studies, including the maximum electroshock (MES) model, audiogenic seizures, strychnine, bicuculline and pentylenetetrazole (PTZ) model in mice and rats as well as Phase I and Phase II studies [4]. A 24-week, randomized, double-blind, placebo-controlled trial of VLB-01 (1500 mg/day) in 224 patients (age 18—65 years) with focal epilepsy showed a 60% reduction in seizure frequency after 224 days as compared to 20% reduction for placebo [4]. Further studies are on-going.

2.5 Neurosteroids

Ganaxolone, SAGE-547 (allopregnanolone) and SAGE-217 are neuroactive steroids which act as positive allosteric modulators of both synaptic and extra-synaptic GABA-A receptors [4]. GABA-A receptors are widely regarded as validated drug targets for a variety of disorders, with decades of research and multiple approved drugs targeting these receptor systems. Proof-of-concept data for ganaxolone in the treatment of refractory paediatric seizures and as monotherapy for adult refractory focal onset seizures is now available and supports further investigations in specific paediatric syndromes [10]. SAGE-547 is an intravenous agent entering Phase III clinical development as an adjunctive therapy for the treatment of super-refractory status epilepticus (SRSE), as well as an exploratory Phase IIA clinical trial for the treatment of essential tremor and as an adjunctive therapy for the treatment of severe postpartum depression [4]. SAGE-217 is still under preclinical development and showed robust efficacy in rodent models of seizures and status epilepticus [4]. In contrast to both allopregnanolone and ganaxolone, SAGE-217 possess a pharmacokinetic profile optimized for once daily oral administration but it has not been administered to human subjects to date, so no human pharmacokinetic data is available.

2.6 Others

Fenofibrate [11] is a peroxisome proliferator-activated receptor alpha agonist mimicking the metabolic changes induced by the ketogenic diet (KD). KD is a well-known treatment for epilepsy in selective cases [12], especially in paediatric syndromes, but it is burdened by a number of limitations such as being compliant with the diet, access to a specialist dietician service, difficulties in patients with swallowing problems etc. A clinical trial of fenofibrate in frontal lobe seizures is on-going.

3. POTENTIAL DISEASE-MODIFYING AGENTS

Rapamycin and derivative compounds (rapalogues) like everolimus, temsirolimus, deforolimus and ridaforolimusm target a group of serine/threonine protein kinase (mTOR) that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, autophagy, and transcription. This class of drugs is already in use to prevent transplant rejection but some compounds are under investigations for autism, Alzheimer's disease and cancer. Everolimus is a selective inhibitor of mTORC1 currently under Phase II development in patients with Tuberous Sclerosis Complex (TSC) [4]. TSC is a multisystem disease in which the hyper-activation of mTOR plays a key role in determining the characteristic pathologic lesions as well as the neurologic phenotype, including epilepsy. Everolimus was initially developed as an antitumoral agent and

subsequently investigated in TSC. The effects of mTOR inhibition in mouse models of TSC were considered to be extremely important as they are more consistent with an antiepileptogenic effect rather than being only seizure suppressant [13]. However, it is important to note that everolimus failed to show any protective effect in the 6-Hz or PTZ seizure test [4].

Minocycline is a tetracycline-class antibiotic which is known to inhibit microglial activation and proinflammatory cytokine release in animal models and experimental data shows that these immune processes may play a role in epileptogenesis [14]. In fact, preclinical studies have shown dose-dependent effects in abolishing focal seizures in the 6-Hz seizure test and in reducing after discharge duration in amygdala kindled rats [4]. At the moment there is a Phase I dose escalation study to explore safety and efficacy in moderate and severe traumatic brain injury in humans and other studies in amyotrophic lateral sclerosis and schizophrenia. An open label study in children with Angelman syndrome is ongoing.

Finally, it is important to mention the role of optogenetics in the treatment of epilepsy [15]. Optogenetics is a combination of optical and genetic methods used to control the activity of specific populations of excitable cells using light with high temporal and spatial resolution. Derived from microbial organisms, 'opsin' genes encode light-activated ion channels and pumps. Opsins can be genetically targeted to well-defined neuronal populations in mammalian brains using viral vectors. Although invasive due to the need to inject a viral vector into the brain and implant a device to deliver light to opsin-transduced neurons, this approach has the potential to be effective in suppressing spontaneous seizures and may represent a new therapeutic strategy in both genetic and structural epilepsies (e.g. post-stroke or post traumatic brain injury epilepsy). However, this technique is still at an early stage of development and long-term safety and efficacy data are required in order to ensure the stability of opsin-expression for efficacy and to avoid toxicity that might result from foreign protein expression.

4. CONCLUSION

A wide variety of new molecular targets have been identified and compounds currently under development will undoubtedly cause a major change in treatment strategies for focal epilepsies. In addition, for the first time, potential disease-modifying agents and technologies are entering the epilepsy. **Obviously, other agents, not listed in this editorial, are also under development. They mainly modulate usual targets such as AMPA receptors (BGG-492) or sodium channels (YKA-3089). In other cases (FV-082) the mechanism of action is entirely unknown. A detailed and comprehensive overview of the subject is available elsewhere [4, 10].**

5. EXPERT OPINION

The current research scenario about investigational drugs for epilepsy is quite exciting although most of the compounds mentioned in this editorial are still at an early stage of development with some of them just at a preclinical stage. It is now evident that drugs with entirely new mechanisms of action are the only way to increase the number of seizure free patients as more than 20 antiepileptic drugs marketed so far have never changed the proportion of responders. This is obviously due to current animal models used to test anticonvulsant effect that probably screen for the usual mechanisms of action. New neurobiological models are urgently needed.

Among new molecular targets, melatonin and galanin receptors are definitely interesting with promising data not only for epilepsy but also for pain, anxiety and depression. This is of great interest as epilepsy is now recognized as a disorder of the brain characterized not only by an enduring predisposition to generate epileptic seizures, but explicitly also by the neurobiological,

cognitive, psychological, and social consequences of this condition. Psychiatric disorders are relatively frequent comorbidities in epilepsy, with a lifetime history identified in one out of three patients, and have a deleterious impact on quality of life, morbidity and mortality. New drugs addressing not only seizures but also potential comorbidities will allow tailored treatment strategies in selected populations.

Robust safety data of these upcoming new compounds represents another key issue. In fact, although seizure freedom is an important predictor for quality of life, if it is at the expense of unacceptable side effects, adherence and quality of life may be poor. That many of the newer antiepileptic drugs have benefits in tolerability despite comparable efficacy almost certainly accounts for why some are now amongst first line options. Phase III studies will allow preliminary safety data although, as it happens in the majority of cases, phase IV post-marketing studies are the main source of information.

Finally, for the first time, potential disease-modifying agents are entering the epilepsy market. This is a rather new concept in epilepsy research and it is still at an early stage of development. In terms of biological targets, it is important to distinguish between epileptic effectors (i.e. proteins that modulate seizure threshold) and epileptogenic mediators (i.e. proteins that control the expression or the functional state of the effectors). Everolimus represents a new class of drugs targeting the epileptogenic mediator rather than the epileptic effector. Data about safety are still preliminary and will represent a key issue as subjects with tuberous sclerosis represent a fragile subgroup of patients. Optogenetics is probably the most futuristic approach to the treatment of epilepsy. The ultimate challenge in epilepsy research still is to understand mechanisms whereby a healthy brain becomes epileptic. Optogenetics offers a solution to the problem until the final question will receive a definitive answer. However, a practical problem is how to design clinical trials for potential disease modifying agents. Epilepsy prevention trials are more complex, lengthy and costly than standard anti-seizure treatment trials for many reasons such as selection of suitable participants, consent for participation, duration of treatment, length of follow-up, and the identification of an appropriate end point. Key parameters of feasible clinical trial designs will need to be adapted to the specific intervention. Most previous anti-epileptogenesis trials with standard anti-seizure drugs that were aimed at preventing epilepsy following traumatic brain injury or stroke have been unsuccessful. Future trials should be focused on subgroups of populations with the highest risk of developing epilepsy (e.g. genetically predisposed individuals, patients with traumatic brain injury, stroke, central nervous system infections or de novo status epilepticus). In addition, data on risks as a function of time after insult in the different patient populations at risk may be helpful in determining whether therapeutic windows exist to optimize the design of prevention trials. Despite a century of clinical research in epilepsy, the majority of questions are still unresolved but it is time to move from empirical treatments to targeted and disease-modifying treatments.

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Table 1. Summary of currently active studies identified in *ClinicalTrials.gov* and *Ema.Europa.eu*.

Drug	Phase	CT number	Syndrome
Allopregnanolone (SAGE-547)	III	NCT02477618	Super-refractory status epilepticus (SRSE)
Beprodone (VLB-01)	II	NCT01179854	Adults drug-refractory focal epilepsy
Cannabidiol	I II II III III III	NCT02286986 NCT02324673 NCT02332655 NCT02224560 NCT02224690 NCT02224703	Pediatric (2 - 19 years) drug-refractory epilepsy Pediatric (1-17 years) drug-refractory epilepsy Drug-refractory Sturge-Weber syndrome Lennox-Gastaut Syndrome Lennox-Gastaut Syndrome Dravet syndrome
Everolimus	II II	NCT01997255 NCT01713946	Drug-refractory Sturge-Weber Syndrome Tuberous Sclerosis Complex drug-refractory seizures
Fenofibrate	II	2011-005433-39	Adults with nocturnal frontal lobe epilepsy
Ganaxolone	II III	NCT02358538 NCT01963208	PCDH19 (Female Pediatric Epilepsy) Adult drug-refractory focal epilepsy
Minocycline	I II	NCT01058395 NCT02056665	Traumatic brain injury Angelman syndrome
Nalutozan (PRX-0023)	II	NCT01281956	Adults drug-refractory focal epilepsy
NAX 810-2			Preclinical evidence only. Due to start Phase I