Drugs of the Future 2011, 36(4): 341-345

CCC: 0377-8282/2011
DOI: 10.1358/dof.2011.36.4.1626643

MEETING REPORT

ADVANCES IN EPILEPSY RESEARCH

64TH ANNUAL MEETING OF THE AMERICAN EPILEPSY SOCIETY, SAN ANTONIO, TEXAS, USA

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SUMMARY

The 64th Annual Meeting of the American Epilepsy Society (AES) was held in San Antonio, Texas, USA, on December 3-7, 2010. The meeting was attended by both basic and clinical scientists from diverse educational and ethnic backgrounds. Discussed at the meeting were some newer advances in the management of patients suffering from epilepsy disorder. The talks were divided into symposia, presidential lectures, junior investigational workshops and poster sessions. The main emphasis of the meeting was to discuss novel therapies in the management of epileptic patients who are suffering from pharmacoresistance and where polypharmacy could be advocated. Despite the availability of more than 20 antiepileptic drugs, there is still a huge population of epileptic patients who are not symptom-free. The fear of having a next seizure attack (when and where) is always a matter of concern in these patients. The present meeting also laid emphasis on treating epilepsy in neonates, one of the biggest challenges in the field of neurology. The meeting provided, among researchers and clinicians, an international forum for the exchange of recent advances in the field of epilepsy. The present review attempts to discuss some of the lectures presented at the meeting.

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INTRODUCTION

The American Epilepsy Society (AES) is one of the oldest and premier neurological organizations in America. The main aim of the AES is to advance the understanding of both basic and clinical concepts that involve interdisciplinary approaches, basic investigations to understand the pathophysiology of the disorder and the drug treatments available to manage epileptic patients. The society, in association with the Epilepsy Foundation, Grass Foundation and other funding sources, aspires to improve the quality of life (QOL) and provide better treatment outcomes in patients suffering from epilepsy. The 64th Annual Meeting of the AES was held in San Antonio, Texas, in early December 2010. The meeting was attended by more than 4,000 researchers and clinicians involved in both basic and clinical research in the field of epilepsy. The deliberations were divided into symposia, plenary lectures, special interest group meetings, investigator workshops, poster sessions, poster walking tours and exhibitions. There were some special workshops for junior members, including fellows, post-doctoral researchers, instructors and assistant professors.

Epilepsy is a common and severe neurological disorder characterized by recurrent and unprovoked seizures. Approximately 1-2% of the world's population suffers from epilepsy disorder (1, 2). One in 26 Americans will develop epilepsy at a certain point in their lifetime. Patients suffering from epilepsy often have comorbid disorders such as anxiety, depression, migraine, etc. (3). Similar to other neurological disorders, there is a huge social stigma attached to epilepsy and society needs to be educated about the diagnosis and treatment options available for its management. One way to treat epilepsy is to reduce the excitation in the brain, as there is excessive depolarization and asynchronous firing of neurons in the brain of epileptic patients. This could be possible if we either: 1) increase the levels of inhibitory neurotransmitters such as γ-aminobutyric acid (GABA) or adenosine in the brain; or 2) decrease excitatory neurotransmitters such as glutamate (4).

More than 20 antiepileptic drugs are available that can manage the symptoms of epilepsy. Unfortunately, despite the availability of these drugs, we are still not able to provide full remission in epileptic patients. More than 20-30% of epileptic patients fall in the category of pharmacoresistance in whom three or more antiepileptic

drugs are ineffective in stopping the seizures (5). There could be many causes of pharmacoresistance in epilepsy, including hippocampal sclerosis, ion channel mutations, autoimmune processes, internalization of receptors, P-glycoproteins, etc. (6). Therefore, in these patients, we definitely need to explore novel drugs that could be used either alone or in combination with other standard antiepileptic drugs for the management of epilepsy.

There has been much debate about managing comorbid disorders in epilepsy. Various antidepressant and antianxiety drugs are concomitantly prescribed with antiepileptic drugs. Prescribing these drugs could improve the QOL in patients suffering from epilepsy. There has always been anxiety regarding the next seizure attack among epilepsy patients, which could happen anywhere at social or public events. Therefore, researchers are in the process of developing seizure prediction devices (seizure prediction belts), which could alert the patient ahead of time of an impending seizure, and these devices are of great interest to patients with uncontrollable epilepsy (7). In this way, patients can take appropriate steps in time to prevent the onset of full-blown convulsions.

Another challenging field in epilepsy research is the treatment of seizures in neonates (8). Drugs such as benzodiazepines that are effective in treating adult epilepsy are often ineffective in neonates. The $GABA_A$ receptors, which are commonly inhibitory in nature (benzodiazepines are allosteric modulators of $GABA_A$ receptors) in the adult brain, are found to be excitatory in neonatal brain (9). With this change in polarity, the whole concept of GABAergic treatment options available ($GABA_A$ receptor modulator drugs) changes. Therefore, in neonates, there is a need to explore other novel targets besides $GABA_A$ receptor-modulatory drugs (benzodiazepines) to stop seizures. Another area of debate these days is the occurrence of sudden unexpected death in epilepsy patients (SUDEP), and the reason behind SUDEP is still under exploration (10). Once the mechanism behind SUDEP is clear, novel drug therapies could be explored.

GABAergic NEUROTRANSMISSION IN NEONATES

Neonatal seizures are the most frequently observed category of epilepsy and may lead to motor and cognitive disabilities. Any kind of neurological insult, such as hypoxic-ischemic encephalopathy, cerebral infarction, hemorrhage or infection, could lead to an epileptogenic process in neonates (11). Benzodiazepines such as phenobarbital have been the mainstay in the treatment of neonatal seizures for many years, but these drugs are often ineffective. Phenytoin, a sodium channel blocker, is an alternative treatment for the management of neonatal seizures, but this drug is also not very effective in treating neonatal seizures (12). The mechanism behind resistance to benzodiazepine drugs in neonates is still a mystery, although it has been shown that during the neonatal stage, GABAergic neurons are excitatory in nature and undergo transition from the excitatory state to the inhibitory state during the development process (13).

The intracellular concentration of chloride ions determines the polarity of GABAergic neurotransmission. The levels of chloride ions are maintained by cation-chloride cotransporters such as solute carrier family 12 member 2 (NKCC1; an inwardly directed Na^+-K^+-$2Cl^-$ cotransporter), which leads to chloride ion entry and solute carrier family 12 member 5 (KCC2; an outwardly directed K^+-Cl^- cotransporter), which mediates the exit of chloride ions (Fig. 1). In neonatal neurons, the intracellular concentration of chloride ion is higher due to higher activity of solute carrier family 12 member 2 cotransporters, and the binding of GABA to $GABA_A$ receptors leads to efflux of chloride ion and thus depolarizing GABAergic neurons. On the other hand, in mature neurons, there is high activity of KCC2 and the expression of NKCC1 is decreased, thus leading to lower concentrations of intracellular chloride ions. Therefore, in mature neurons, when GABA binds to $GABA_A$ receptors, there will be an influx of chloride ions and thus inhibitory hyperpolarization. In other words, the high concentration of intracellular chloride ions renders barbiturates and benzodiazepines ineffective in neonatal seizures. Recent updates have suggested that bumetanide, an FDA-approved diuretic, enhances the effect of phenobarbital in a neonatal seizure model (intact hippocampal preparations in vitro) (14, 15), and could therefore be a novel treatment for neonatal seizures (16).

PERAMPANEL: A NOVEL AMPA RECEPTOR ANTAGONIST

Most of the antiepileptic drugs mainly act via four mechanisms: 1) voltage-gated sodium channels; 2) enhancing GABAergic neurotransmission; 3) presynaptic neurotransmitter release mechanism; and 4) postsynaptic glutamate receptors. Despite the availability of drugs targeting these mechanisms, we are still unable to achieve complete remission in 20-30% of epileptic patients.

Glutamate is an excitatory neurotransmitter in the brain. There has always been a delicate balance between glutamatergic excitation and GABAergic inhibition. Disturbance in this balance can lead to neurological complications, including epilepsy. Glutamate is known to act on both metabotropic and ionotropic receptors. The ionotropic receptors include kainate, AMPA (γ-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate) or quisqualate and NMDA (*N*-methyl-D-aspartate). The AMPA receptor plays an important role in plasticity, especially long-term potentiation and synaptic transmission. AMPA receptors are involved in epileptogenesis and seizure-induced brain damage. Targeting AMPA receptors may be useful for the treatment of epilepsy. These drugs could be useful as combination therapy with other antiepileptic drugs, including NMDA receptor blockers (17). However, the safety and tolerability profile of these drugs needs to be determined.

Perampanel is an investigational compound from Eisai for the treatment of epilepsy. It is a highly selective and potent, noncompetitive AMPA receptor antagonist that is under clinical development for the treatment of partial seizures. The molecule has high affinity for AMPA receptors and lower affinity for other glutamate or neurotransmitter actions (18). In a phase III clinical trial, perampanel at doses of 4 and 8 mg was found to be very effective in reducing mean seizure frequency and increasing the responder rate in epileptic patients. The molecule appears to be quite safe at therapeutic doses and the common adverse effects reported were dizziness, headache and somnolence. The molecule is also under investigation for the treatment of neuropathic pain, multiple sclerosis and migraine prevention. In one of the abstracts presented at the 18th Meeting of the European Neurological Society, perampanel was effective in animal models of seizures, such as audiogenic seizures, maximal electroshock convulsions and pentylenetetrazol-induced seizures, with

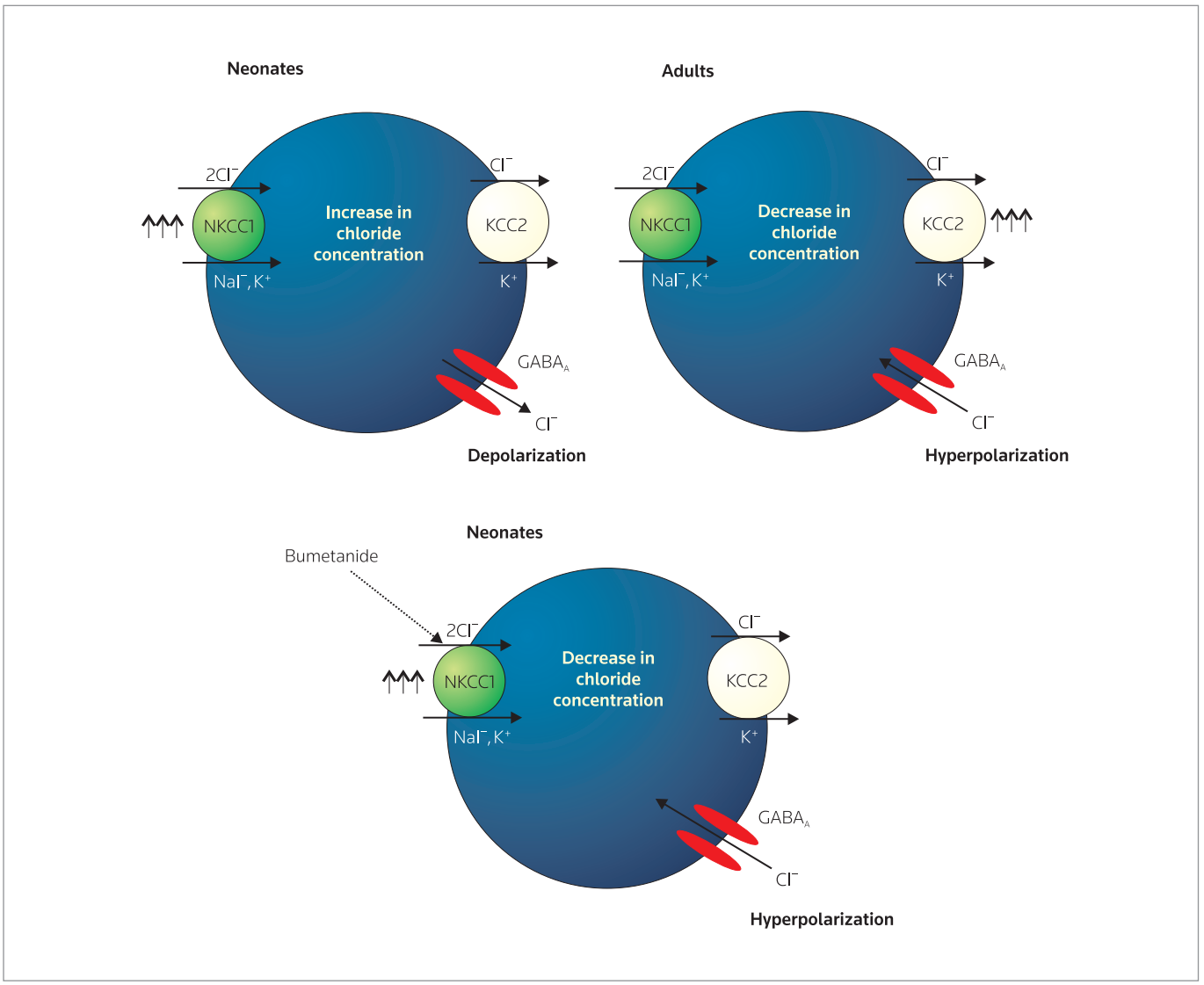
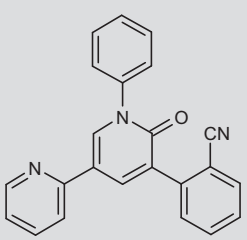


Figure 1. Nature of GABAergic neurons in neonatal and adult brain and its modification by bumetanide.



Perampanel

ED_{50} values of 0.47, 1.6 and 0.94 mg/kg p.o., respectively. Perampanel at 5 and 10 mg/kg was also effective in the amygdala-induced kindling model, reducing the afterdischarge duration and seizure severity as compared to control animals (19, 20). Therefore, this molecule could be a novel antiepileptic drug in the near future.

CYCLOOXYGENASE AND EPILEPSY

Neuroinflammation is known to play a major role in the pathophysiology of almost all neurological disorders of the body. Glial cells have a very important role in central nervous system (CNS) functions and diseases. Gliosis is a very common term used in stroke and multiple sclerosis that represents a stage in response to any neurological insult leading to proliferation of astrocytes and scar formation. Recently, glial cells have been speculated to play an important role in various neurological disorders. There have been various forms of

bidirectional communication between neurons and glial cells, and therefore this interaction may play an important role in the pathophysiology of epilepsy (21). Glial cells could be responsible for the generation of inflammatory mediators in the CNS. For example, the prostaglandins formed through the action of cyclooxygenase (COX) enzymes are produced by activated microglia and reactive astrocytes (22).

Both proinflammatory and antiinflammatory prostaglandins are known to date. Studies have shown that COX, particularly the COX-2 subtype, is upregulated following seizure activity. In some of our studies, we have shown that COX inhibitors are effective anticonvulsants when tested in animal models of seizures. Moreover, we have shown that rofecoxib, a selective COX-2 inhibitor, enhanced the anticonvulsant action of diazepam and muscimol (both $GABA_A$ receptor agonists). In one study presented at the 64th Annual Meeting of the AES, NS-398 was evaluated alone and in combination with diazepam, an allosteric modulator of $GABA_A$ receptors, in a lithium–pilocarpine-induced model of status epilepticus in rats. It was demonstrated that NS-398 combined with diazepam provided significant neuroprotection in CA3 and hilus of the dentate gyrus region compared to the group treated with diazepam alone. However, there was no protection in the electrographic data for the vehicle-, diazepam- and diazepam + NS-398-treated groups. Therefore, in conclusion, a COX-2 inhibitor when combined with diazepam provides more significant neuroprotection in the hippocampal region of the rat brain as compared to the effect of these molecules alone (23). There have been numerous studies depicting the anticonvulsant property of various COX inhibitors in animal models of epilepsy; however, clinical trials should be commenced to explore the efficacy and safety parameters of this class of drugs for the treatment of epilepsy.

SOLUBLE EPOXIDE HYDROLASE INHIBITORS AND EPILEPSY

Soluble epoxide hydrolase (SEH) is an enzyme involved in the metabolic conversion of epoxyeicosatrienoic acid (EET), a fatty acid signaling molecule, to dihydroxyeicosatrienoic acid (DHET) (Fig. 2).

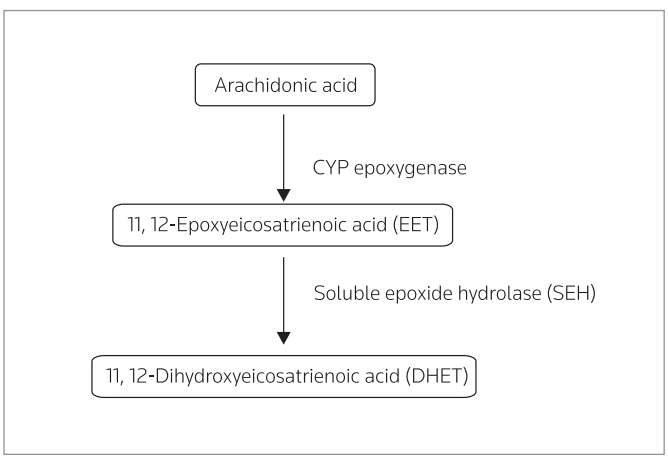
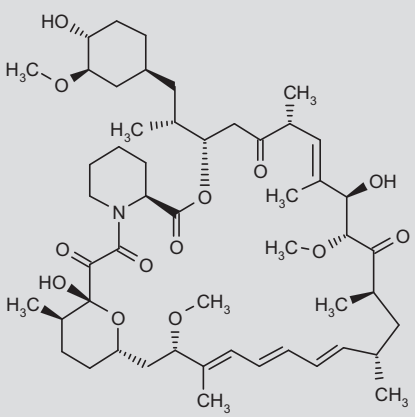


Figure 2. Synthesis of 11,12-epoxyeicosatrienoic acid (EET) and 11,12-dihydroxyeicosatrienoic acid (DHET).

DHET is considered the inactive form, as it has no actions on EETs (24). These EETs have been found to be cardioprotective and possess vasorelaxant and antiinflammatory actions. It is hypothesized that inhibiting SEH and thus increasing the levels of EETs could be helpful in treating a variety of neurodegenerative and neuropsychiatric disorders, such as cerebral ischemia and epilepsy. In one of the studies presented at the AES meeting, it was shown that SEH was involved in status epilepticus-induced neuroinflammation in a pilocarpine-induced status epilepticus animal model. It was demonstrated that the immunoreactivity of SEH was increased in astrocytes in the molecular layer of CA1, CA3 and dentate hilus in status epilepticus in mice; the maximum effect was observed after 7 days of status epilepticus as compared to control animals. Moreover, there was an increased expression of inflammatory cytokines, such as interleukin-1 (IL-1) and IL-6 in status epilepticus animals. The SEH inhibitor AUDA (20 mg/kg i.p.) resulted in a marked decrease in the expression of these cytokines in status epilepticus mice (25). Therefore, it was concluded that SEH inhibitors may be a novel class of drugs for the treatment of epilepsy and neuroinflammation.

mTOR PATHWAY IN EPILEPSY: NEW ADVANCES IN UNDERSTANDING ITS IMPLICATIONS

The mammalian target of rapamycin (mTOR) is a serine/threonine kinase that has been shown to play an important role in the epileptogenic process. The mTOR pathway is activated by phosphatidylinositol 3-kinase (PI3K)/Akt signaling in the presence of nutrients and growth factors. In addition, mTOR is involved in protein synthesis related to cell synthesis and angiogenesis, as well as in the regulation of neuronal development. Rapamycin binds to mTOR complex 1 (mTORC1) and is an approved immunosuppressive drug used for organ transplant. The drug was found to be useful in the treatment of tuberous sclerosis complex, an inherited disorder in which tumors are formed in different organs, primarily in the brain, eyes, heart, kidney, skin and lungs. The patient may have neurological symptoms such as epilepsy, development delays and behavioral problems. In one of the studies presented at the AES meeting, it was demonstrated that rapamycin attenuated neuronal excitability and seizure sus-


Rapamycin

ceptibility in neonatal rats. It was found that mTORC1 activity was higher in both the hippocampus and cortex regions of neonate brains relative to the adult brain, and therefore that mTORC1 could be a target for preventing epileptogensis in neonates (26).

In another study presented at the meeting, it was demonstrated that a ketogenic diet is an inhibitor of mTOR (27). The ketogenic diet is a high-fat/low-carbohydrate diet and is an effective treatment for pediatric epilepsy. The mechanism of action of the ketogenic diet in epilepsy is not well understood.

It was demonstrated using Sprague–Dawley rats that a ketogenic diet reduced mTOR activity in the hippocampus and liver of normal rats; however, there was no effect of a ketogenic diet on the mTOR-hyperactivated pathway in rats with tuberous sclerosis complex. In contrast, a ketogenic diet reversed the kainic acid-induced mTOR activation. These studies suggested that a ketogenic diet might exert antiepileptic activity by inhibiting the mTOR pathway (27).

CONCLUSION

The AES continues to be an exciting platform for disseminating research and discussing novel treatment outcomes for epileptic patients. The 64th Annual Meeting of the AES discussed some of the novel approaches that are under basic and clinical investigation for the management of epilepsy. It is hoped that by discovering novel therapies, we may be able to treat the remaining 20-30% of epilepsy patients who are still struggling with pharmacoresistance and where the concept of polypharmacy has failed to provide better treatment outcomes.

DISCLOSURES

The author states no conflicts of interest.

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