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MEETING REPORT

HIGHLIGHTS IN EPILEPSY RESEARCH

CURRENT TOPICS FROM THE 136TH ANNUAL MEETING OF THE AMERICAN NEUROLOGICAL ASSOCIATION, SEPTEMBER 25-27, 2011

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CONTENTS

Summary 855
Introduction 855
Targeting Trk-B in search of magic bullets to prevent epileptogenesis 856
Novel drug candidates for the treatment of epilepsy 856
JAK/STAT inhibitors in epilepsy 857
SNAREs/SNARE regulators in kindling models of epilepsy 857
Conclusion 858
References 858

SUMMARY

The 136th Annual Meeting of the American Neurological Association (ANA) was held in San Diego, California, USA, September, 25-27, 2011. During three days, there were extensive presentations, debates and discussions held in the context of recent advancements in neurological research. Neurological disorders pose a serious threat to the public worldwide. These disorders are difficult to treat, probably due to the very complex nature of the nervous system. It is often very difficult and challenging for neurologists to provide appropriate treatment regimens for these patients. This compels researchers to explore novel therapeutic strategies for such disorders. This meeting discussed some of the advancements in the area of epilepsy, stroke, neuromuscular diseases, neuro-ophthalmology, headache, neuro-oncology, dementia and aging. The major highlights of the meeting were special interest group (SIG) symposia, where both experienced and young investigators were allowed to present their research outcomes. There were opportunities for both students/fellows and junior faculty members to learn strategies for proper time/project management. The present review article discusses some of the deliberations held in the field of epilepsy at the meeting.

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INTRODUCTION

The American Neurological Association (ANA) is a premier organization of neurologists and neuroscientists with an aspiration to advance the field of neurology and provide better treatment options for patients suffering from these difficult-to-treat disorders. The society also aims to provide education and training to budding neurologists by providing them an understanding of the pathophysiological basis of these disorders and assisting them in exploring novel therapeutic regimens. The ANA holds an annual meeting for its members, fellows and students to discuss novel outcomes in the field of neurology. This year's meeting was held in San Diego in September. Some of the topics of deliberation during the meeting were cerebrovascular diseases, movement disorders, circadian rhythms, epilepsy, neuromuscular diseases, dementia, aging, and headache and pain. The present review discusses some of the deliberations in the field of epilepsy.

Neurological disorders are disorders of the central and peripheral nervous system. According to the World Health Organization (WHO), hundreds of millions of people are affected by these disorders. For example, 62 million people worldwide have cerebrovascular diseases, 50 million people are living with epilepsy, 326 million suffer from migraine and 24 million people have dementia and Alzheimer's disease. Various wonder drugs are available for the treatment of these disorders. Despite the availability of these drugs, approximately one-third of these patients continue to suffer from the consequences of their illness. Have we made any progress in treating these patients effectively? Let's take an example of epilepsy research. During an era when epilepsy was linked to hysteria and masturbation, bromides (potassium bromide, sodium bromide and ammonium bromide) were the only molecules available for seizure management. Sir Charles Locock in 1853 treated several of his epileptic patients with bromides (1). However, the use of bromides was linked to serious side effects and life-threatening adverse events. Unfortunately, approximately one-third of this patient population was resistant to bromide therapy, which compelled researchers to explore other more effective and safer drugs. In this

modern era, more than 25 drugs are currently available for the treatment of epilepsy. However, it is quite unfortunate that one-third of the epileptic population remains resistant to these modern drugs and continues to have seizures. It is a matter of debate as to "what have we achieved in these years?" Although we have not made remarkable progress in improving the percentage of the population resistant to epilepsy pharmacotherapy, we have made significant progress in providing safer antiepileptic drugs to these patients. Moreover, we have reduced the severity of seizures and the number of seizure attacks per week/month/year, and this was possible only with the advent of novel drugs for the treatment of epilepsy.

TARGETING TRK-B IN SEARCH OF MAGIC BULLETS TO PREVENT EPILEPTOGENESIS

The term epileptogenesis refers to a process whereby the normal brain suddenly becomes epileptogenic (2, 3). The process of "epileptogenesis" may get installed in the brain due to both acquired and genetic reasons. It is not yet clear how a normal brain suddenly becomes epileptogenic. Some people are more susceptible to epileptogenesis than others and genes may play a major role in the pathophysiology of epilepsy. Antiepileptic drugs are known to treat seizure expression and not the epileptogenic process in the brain.

The popular saying "seizures beget seizures" (4) can be evidenced from the kindling experiments in animal models. An insult to brain such as head trauma or CNS infections may set up an epileptogenic process in the brain that is characterized by recurrent spontaneous seizures later in life. A single episode of status epilepticus lasting 30 minutes to hours can induce temporal lobe epilepsy in some patients, which persists for a lifetime. Studies have indicated that febrile seizures during childhood can lead to the development of temporal lobe epilepsy in adults (2). Therefore, it is important to find novel therapeutic drugs and targets that could prevent the occurrence of epileptogenic processes. These drugs could be given whenever there is any serious insult to the brain and this could prevent the brain from progressing to an epileptic brain.

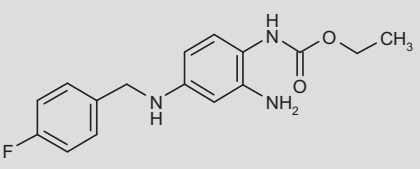
Brain-derived neurotrophic factor (BDNF) belongs to the family of compounds known as neurotrophins and plays an important role in the normal development of the central nervous system (CNS) (5). BDNF produces its action by acting on its receptor, known as BDNF/NT-3 growth factors receptor (Trk-B). This receptor belongs to a family of tyrosine kinases. When an agonist (e.g., BDNF) binds to these receptors, dimerization of the receptor occurs, leading to autophosphorylation of intracellular tyrosine residues. Activation of these receptors leads to phosphorylation of Y515, leading to Shc binding and phosphorylation of Y816, leading to activation of 1-phosphatidylinositol-4,5-bisphosphate phosphodiesterase gamma-1 (PLC-γ-1). This process further leads to the activation of Ras-RAF-ERK1/2 (MAPK), PI3K/Akt and IP_3/Ca^{2+} cascades. The IP_3/Ca^{2+} cascade and possibly the PI3K/Akt cascade, but not the Ras-RAF-ERK1/2 (MAPK) cascade, are involved in the formation of long-term potentiation (LTP) and thus the potentiation of excitatory synapses. Excessive activation of this pathway can lead to the epileptogenic process. Moreover, excessive activation of Trk-B could lead to reduced expression of the solute carrier family 12 member 5 (KCC2) channel, resulting in enhanced internalization of $GABA_A$ receptors and thus decreasing the function of GABA-mediated synaptic inhibition. This could be one of the reasons it can promote epileptogeneis (6). In summary, it is hypothesized that BDNF, by activating Trk-B receptors, could lead to an epileptogenic process. This was further demonstrated by He et al. in 2004, where genetic deletion of Trk-B receptors was shown to block the development of limbic epileptogenesis (7). Moreover, Croll et al. have shown that overexpression of BDNF enhances the limbic epilepsy process in animal models (8). Also, He et al. in 2010 showed that after a brief course of status epilepticus in animals, Trk-B activation could be seen in 1 hour, peaking at 6-24 hours and returning to normal in 3 days (9).

NOVEL DRUG CANDIDATES FOR THE TREATMENT OF EPILEPSY

In a talk held at the ANA meeting, Dr. Jacqueline A. French highlighted the need for the development of novel drug candidates for the treatment of epilepsy. Dr. French emphasized the concept of both evolutionary and revolutionary drug discovery approaches (10). Evolutionary drugs are those that are synthesized by tailoring the structures of already existing drugs, while revolutionary drugs are a totally new type of drug. Some of the examples of evolutionary drugs are brivaracetam and eslicarbazepine. These evolutionary drugs are supposed to have greater efficacy and a better safety profile compared to existing drugs. In contrast, revolutionary drugs are totally new, with unique mechanisms of action. These drugs can be administered to patients with drug-resistant epilepsy. Some of the revolutionary drugs that are in clinical trials or near completion are retigabine/ezogabine, perampanel and VX-765.

Retigabine/ezogabine

Retigabine, or ezogabine (in the U.S.), is a novel neuronal potassium channel opener approved by the U.S. Food and Drug Administration (FDA) for adjunctive treatment of partial-onset seizures in adults. Activation of neuronal potassium channels leads to hyperpolarization of membrane potential and decrease in excitability. At the molecular level, retigabine activates KCNQ2/3 (K_V7.2/7.3) voltage-gated potassium channels by binding to the activation gate of the channel in the open position (11). This can help stabilize potassium channels. These voltage-gated neuronal potassium channels are involved in mediating the M-current involved in slow activation and deactivation near the resting membrane potential, thus causing a decrease in repetitive firing of neurons under excitatory conditions. Besides acting on potassium channels, retigabine has some activity on $GABA_A$ receptors. The most common adverse events with the use of retigabine/ezogabine are dizziness and somnolence, and there is a rare but unique side effect consisting of urological symptoms, particularly urinary retention, with the chronic use of ezogabine, and this should be considered before prescribing the drug to patients.



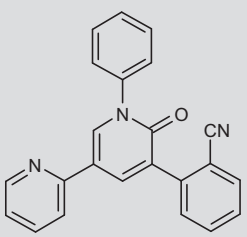
Retigabine

Perampanel

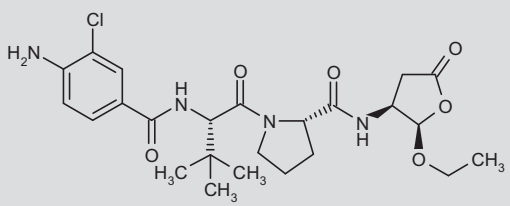
Perampanel is a novel noncompetitive AMPA receptor antagonist that is awaiting approval by the FDA for use in partial epilepsy. AMPA receptors are ionotropic non-NMDA glutamate receptors that are known to play a role in seizure initiation and maintenance. Perampanel is active in various animal models of convulsions (12). Furthermore, it blocked AMPA-induced increases in $[Ca^{2+}]_i$ with an IC_{50} of 93 nM in rat cortical neurons. Perampanel at 4 and 8 mg was effective in partial-onset seizures. There were no serious adverse events noted with perampanel in clinical studies. Some of the common adverse events include somnolence, dizziness and headache. All clinical studies with perampanel have concluded and the results have been submitted to the FDA for their review and approval.

VX-765

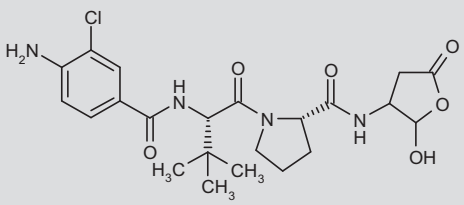
VX-765 is a prodrug that is converted to its active metabolite, VRT-43198, which in turn binds to the catalytic site and competitively inhibits caspase-1 (13). The molecule, if successful, will be unique for the treatment of epilepsy as it targets inflammatory responses in the CNS. VX-765 is being developed by Vertex Pharmaceuticals. In a phase IIa clinical trial, VX-765 was found to have a similar safety profile compared to placebo treatment. The molecule is undergoing a phase IIb clinical trial for determining efficacy in patients suffering from treatment-resistant epilepsy (10).



Perampanel



VX-765



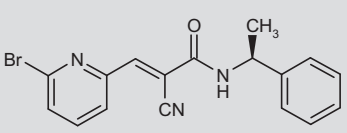
VRT-43198

JAK/STAT INHIBITORS IN EPILEPSY

The Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway is the signaling pathway involved in transducing different signals required for development and homeostasis in animals (14). It has been shown that seizures induce a decrease in $GABA_A$ receptor α1 subunit expression. GABA is a major inhibitory neurotransmitter in the brain and a decrease in brain levels of GABA may induce seizures. Furthermore, it is been shown that this decrease in the expression of the $GABA_A$ receptor α1 subunit in epilepsy is mediated by activation of the JAK/STAT pathway. In a preclinical study presented at the ANA meeting, it was shown that WP-1066, a novel inhibitor of STAT3 activation, reduced the severity and duration of status epilepticus without affecting the latency to onset of first seizures (15). Furthermore, the compound inhibited the progression of the occurrence of spontaneous seizures after status epilepticus compared to the vehicle control group. WP-1066 when administered at 50 mg/kg i.p. to rats at the onset and 1 hour after lithium/pilocarpine-induced status epilepticus resulted in a reduction of STAT3 phosphorylation in the dentate gyrus region of the hippocampus by 45%. This study implies that the JAK/STAT pathway is important in the epileptogenic process and that inhibitors of this pathway may be disease-modifying.

SNARES/SNARE REGULATORS IN KINDLING MODELS OF EPILEPSY

Neurotransmitters are released into the synapse and act on both pre- and postsynaptic membranes to produce biological actions. Neurotransmitters are stored in the synaptic vesicles and their release is calcium-dependent. Whenever there is an influx of calcium, these synaptic vesicles fuse with the presynaptic membrane and release the neurotransmitter into the synapse. This is a specialized exocytic process that is responsible for the relay of messages between different neurons to maintain the homeostatic functions of the body. The fusion of vesicles with plasma membranes is highly specialized and initiated by the formation of a ternary complex of SNAREs (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors) (16). This complex is made up of vesicle-associated membrane protein 2 (VAMP-2, synaptobrevin-2) from the synaptic vesicle and syntaxin-1 and synaptosomal-associated protein 25 (SNAP-25) from the neuronal active zone of the plasma membrane. These proteins are required for the fusion of the synaptic vesicles



WP-1066

and the release of neurotransmitter agents. The factors, including vesicle-fusing ATPase (*N*-ethylmaleimide-sensitive fusion protein; *NSF*) and synaptosomal-associated protein (SNAP) are required for SNARE complex formation. It has been hypothesized that this neurosecretory mechanism might play a role in kindling epileptogenesis and epilepsy (17). In one of the studies presented at the meeting, it was shown that mice deficient in neurosecretory proteins VAMP-$2^{+/-}$ require a 150% afterdischarge stimulus and > 2.5 as many stimuli compared to wild-type control animals. In these animals, reduction in VAMP-2 was associated with reduced glutamate release in the CA3 region of the hippocampus. Other authors have shown that tomosyn$^{-/-}$ mice required half as many stimuli and two-thirds the afterdischarge current to fully kindle as compared to wild-type controls. Tomosyn is a synaptic binding protein and acts as a placeholder for v-SNARE, and the authors of the present study speculated that tomosyn may be a negative regulator of neurotransmitter release. In conclusion, regulators of SNARE or SNAREs may play an important role in the epileptogenic process.

CONCLUSION

The 136th ANA meeting provided an important platform to disseminate recent advances in the field of epilepsy and other neurological disorders. Various novel drug candidates are undergoing clinical trials or already approved by the FDA for the treatment of these disorders. The day is not far when we will be able to achieve success in providing drug treatments to patients suffering from pharmcoresistance.

DISCLOSURES

The author states no conflicts of interest.

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