WORKSHOP REPORT

Michael Foundation Forum 2010

The Michael Foundation has been founded "to support scientific research on the most effective treatment methods as well as the causes of all illnesses associated with seizures, and to fight against the individual and social consequences of epileptic diseases." The Michael Prize (now supported by UCB) has been awarded since 1963 to stimulate epilepsy research. The list of awardees comprises 66 researchers from 13 different nations (see: http://stiftung-michael.de/e_inhalt.html). Since 1987, the Michael Forum has been established as a biennial meeting of current and past Michael prize winners to discuss recent developments in epilepsy research. The most recent meeting took place in Regensburg, Germany in September 2010, where presenters discussed the latest findings in clinical and experimental epilepsy research. The following report gives a short summary of the talks:

Heinz Beck (University of Bonn, Germany) presented new findings on integration of electrical signaling in the dendrites of hippocampal dentate granule cells.

Rüdiger Köhling (University of Rostock, Germany) reported evidence that functional small-conductance Ca^{2+}-activated K^+ channel currents (SK currents) are reduced in CA1 pyramidal neurons of chronically epileptic animals. Both the SK2 channel transcript and protein are downregulated in the epileptic CA1 region. As a consequence, the action potential after-hyperpolarization is reduced, and the remaining functional SK currents become critical for the network excitability in epileptic tissue.

Jerome Engel (University of California, Los Angeles, CA, U.S.A.) discussed the occurrence of high frequency oscillations (fast ripples) in human epileptic tissue and rodent models of epilepsy. The occurrence of fast ripples correlates with the degree of hippocampal atrophy in human tissue, with onset of spontaneous seizures, and with the development of spontaneous seizures in chronic rodent models. Therefore, high frequency oscillations might serve as a biomarker for epileptogenesis, disease progression, and ictogenesis.

Gregory L. Holmes (Dartmouth Medical School, Lebanon, NH, U.S.A.) discussed the functional consequences of interictal spikes. In a rat model, he has obtained evidence that interictal spiking in early life can result in impaired new hippocampal cell formation, a result associated with a long-lasting impairment in spatial learning. The study suggested that suppressing interictal spikes might be as important as treating seizures during brain development.

Jeffrey Noebels (Baylor College of Medicine, Houston, TX, U.S.A.) described the first viable genetic mouse model of infantile spasms syndrome. The model recapitulates critical phenotypic features of the human triplet-repeat expansion mutation in the *Arx* gene, known to be one cause of this catastrophic pediatric epilepsy syndrome. The respective Arx $(GCG)^{10+7}$ mouse mutant provides a basis for further examination of the abnormal patterns of disinhibition in affected brain regions, and for exploration of novel therapeutic strategies for reversing the interneuron migration defect underlying the neurodevelopmental disorder in this model.

Ivan Soltesz (University of California-Irvine, CA, U.S.A.) investigated the γ-aminobutyric acid (GABA) ergic control of entorhinal cortex outputs. Cannabinoid type-1 receptor expressing GABAergic basket cells selectively innervates principal cells in layer II of the medial entorhinal cortex that project outside the hippocampus, but avoid the neighboring cells that give rise to the perforant pathway. These new results revealed that the organization of both GABAergic microcircuits reflects the long-distance axonal targets of principal neurons. The findings have significant implications for basic epilepsy research and future treatment strategies aiming to modulate GABAergic targets.

Charles E. Ribak (University of California-Irvine, CA, U.S.A.) focused on a new type of neuronal death involving microglia in the adult dentate gyrus of normal and epileptic rats. Dying granule cells were found in close contact with Iba1-immunolabeled microglial cell bodies and their processes, both at the hilar and the molecular layer borders. Thorough electron microscopic analyses suggest that granule cells are dying by a novel micoglia-associated mechanism involving lysis of their plasma membranes followed by neuronal edema and nuclear phagocytosis.

Jozsef Janzsky (University of Pecs, Hungary) examined the reorganization of brain function in epilepsy and neurologic injuries by functional magnetic resonance imaging (fMRI). Independent of the lesion, a reorganization of language and memory representation can be observed in the epileptic brain. Complex alterations in language representation can also occur in other central nervous system (CNS) diseases such as Parkinson's disease as well as in peripheral nerve injury.

Matthias Koepp (National Hospital for Neurology and Neurosurgery, London, U.K.) investigated the cortical

activation patterns and connectivity of the motor cortex and its modulation through cognitive interaction in patients with juvenile myoclonic epilepsy (JME) and healthy controls. An increased coactivation of the motor system was found in JME patients during cognitive tasks monitored via functional magnetic resonance imaging (fMRI). The effect appeared only during the more demanding tasks, and was more pronounced in patients with more recent seizures.

Ortrud K. Steinlein (University of Munich, Germany) reviewed the current knowledge on mutations in nicotinic acetylcholine receptors (nAChRs) as a cause of familial nocturnal frontal lobe epilepsy (ADNFLE). Based on recent research, it has become obvious that carriers of some ADNFLE mutations are more likely than others to be affected by additional neurologic features, including cognitive deficits and schizophrenia-like symptoms. Expression experiments in *Xenopus* oocytes demonstrated that the clinical phenotypes can be matched to biopharmacologic profiles specific for each mutation.

Thomas Sander (University of Cologne, Germany) studied genetic factors predisposing to idiopathic generalized epilepsies. Genome-wide linkage and association studies on idiopathic generalized epilepsy (IGE) syndromes performed within an EU-funded research initiative resulted in intriguing insights into the respective complex genetic traits. Rare recurrent microdeletions collectively account for a significant fraction of the genetic etiology of common IGE syndromes.

Brian Meldrum (King's College, London, U.K.) critically discussed various experimental approaches used to study antiepileptogenic effects in rodent models. He emphasized the fact that there is a lack of appropriate and/or practicable animal models reflecting development of seizures due to different clinical conditions, including perinatal hypoxia/ischemia and developmental brain disorders. Novel antiepileptogenic strategies were discussed, such as targeting neurotrophins or their intracellular signaling cascades.

Wolfgang Löscher (TiHo, Hannover, Germany) gave an overview on studies testing disease-modifying and/or antiepileptogenic effects in rodent models. Several experimental investigations explored the efficacy of antiepileptic drugs resulting in clinical testing of selected compounds in preventive approaches; additional experimental studies have targeted neurodegeneration, inflammation, immune responses, and neuronal hyperexcitability. Recent data obtained with a neuromodulation strategy, using bumetanide as an inhibitor of the Na^+-K^+-$2Cl^-$ co-transporter NKCC1, were presented.

Alon Friedman (Ben-Gurion University, Beersheva, Israel) focused on blood–brain barrier (BBB) dysfunction as a target for antiepileptogenesis. Human and experimental data substantiating the critical role of loss of BBB integrity during epileptogenesis were presented. Targeting TGFβ signaling, which contributes to the consequences of BBB dysfunction, counteracted epileptogenesis in a rodent model. Analysis of BBB permeability was suggested as a valuable biomarker for epileptogenesis in patients at risk.

Heidrun Potschka (University of Munich, Germany) reported on peptide mimetics as a novel strategy for disease modification. Neural cell adhesion molecule-(NCAM−) and erythropoietin-derived peptides showed promising effects on the cellular consequences of a status epilepticus in rodent models. Moreover, an erythropoietin-derived peptide attenuated spatial learning deficits in a post status epilepticus model.

Acknowledgments

The attendees of the Forum are grateful to the Michael Foundation for the opportunity to meet every 2 years, providing a unique platform to discuss the latest findings in epilepsy research. Sabine Reith is acknowledged for the excellent organization of the meeting.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Heidrun Potschka
potschka@pharmtox.vetmed.uni-muenchen.de
Institute of Pharmacology, Toxicology, and Pharmacy, Ludwig-Maximilians-University, Munich, Germany

Commentary

Considering economic reality in calculating the financial burden of epilepsy in China

Epilepsy is the most serious common neurologic disorder, affecting people of all ages and socioeconomic classes worldwide. It imposes a considerable burden on the society and on families. Developing countries carry 90% of the financial burden of epilepsy, as 85% of the world's 50 million people with epilepsy live in developing countries (de Boer, 2002). However, the economic burden caused by epilepsy has not been adequately examined in these countries. In those studies that do exist, cost of illness is traditionally estimated under direct costs (cost of medical treatment, other nonmedical expenditures such as travel to hospital, and so on), indirect costs (due to lost productivity), and intangible costs (related to the emotional and social impact of illness on the economy). We can conclude from such studies that the burden on the families of