WORKSHOP REPORT

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Eleonora Aronica,

[1]Department of (Neuro)Pathology, Academic Medical Centre and Swammerdam Institute for Life Sciences, Center for Neuroscience, University of Amsterdam; SEIN – Stichting Epilepsie Instellingen Nederland, Heemstede, The Netherlands.

e.aronica@amc.uva.nl

From October 9th to 11th 2014, Bonn hosted the 12th edition of the Michael Forum. Since 1963, the Michael Foundation (http://www.stiftung-michael.de) awards the Michael Prize for contributions to basic and clinical scientific research in epileptology every two years and organizes a meeting for the Michael Price laureates, the *Michael Forum meeting*. The Michael Forum 2014 brought together 22 Michael Price laureates and 4 members of the Board of Trustees of the Michael Foundation.

The first session of the Forum focused on Epileptogenesis and mechanisms of epileptogenicity and seizure propagation. **Pete J. Engel** started the session defining the biomarkers of epileptogenesis as objectively measured characteristic of a normal or pathologic biological process. Potential biomarkers include hippocampal changes on MRI, interictal EEG spike features including BOLD patterns on fMRI, pathological high-frequency oscillations, excitability as measured by transcranial magnetic stimulation, AMT-PET imaging, and gene expression profiles. Identification of reliable epilepsy biomarkers is a high priority area of current research. **Massimo Avoli** addressed the role of interictal spikes and particularly high-frequency oscillations (HFOs, 80-500 Hz), recorded from patients with mesial temporal lobe epilepsy (MTLE) and in animal models mimicking this disorder as markers of abnormal neural network activity. The findings

demonstrate that the transition from latent to chronic phase is paralleled by dynamic changes in interictal spike and HFO expression in EC and CA3. These changes may represent biomarkers of epileptogenicity in MTLE. **Christophe Bernard** discussed the notion of seizure threshold. Seizures belong to the repertoire of normal brain activities, i.e. they are hardwired in neuronal networks. The multiplicity of thresholds explains why seizures may appear under very different condition in a given patient. Christophe Bernard also presented evidence that the thresholds may also vary during the night/day cycle, possibly as a result of a dynamic reconfiguration of the molecular architecture of neuronal circuits. **Marco de Curtis** discussed the identification of the epileptogenic zone by computer-assisted analysis of intracranial signals during pre-surgical monitoring of patients with focal drug-resistant epilepsy. He reported about a recently developed computer-driven intracranial EEG analysis in the domains of time, frequency, and space to improve and facilitate EZ location by identifying biomarkers of the EZ (of ictogenesis). **Heinz Beck** addressed the information processing in hippocampal neurons. Using multiphoton glutamate uncaging techniques that allow the stimulation of individual synaptic sites, he described how synaptic inputs at neuronal dendrites are integrated. The first part of the presentation consisted of a demonstration that different dendritic subsegments can exhibit fundamentally different integration via dendritic spikes. In the second part of the presentation, how these forms of integration are affected by inhibition was explored. **Uwe Heinemann** in joint interaction with **Alon Friedman** discussed effects of opening of the blood brain barrier and consequent albumin dependent activation of astrocytes on homosynapstic and heterosynaptic plasticity. The data show that albumin induced changed in astrocyte function affects synaptic plasticity such that input from different regions into the hippocampus are no longer compensated by heterosynaptic plasticity.

During the second session of the Forum, different clinical studies were presented. **Dieter Janz** reported about long term follow-up in awakening epilepsy (grand mal on awakening, EGMA). Patients with a follow-up of at least 20 years were assessed retrospectively regarding 5-year terminal seizure remission. Forty-two patients were included. EGMA has a favorable long-term prognosis. With increasing age and treatment duration, antiepileptic drug withdrawal may be justified.

Matthias Koepp presented imaging data in three different populations who are all "at-risk", either of (i) developing epilepsy, (ii) suffering from recurrence of seizures, or (iii) dying from seizures. Whilst all three populations show imaging abnormalities specific to their condition and risk, they all show additional increases in grey matter in right mesio-temporal structures, which could serve as biomarker for stratification of at-risk populations. **Gregory L. Holmes** addressed the MRI biomarker for cognitive impairment following prolonged febrile seizures. He presented data from his research group showing that MRI T2 measures are predictive of performance on an active avoidance spatial task.

At times, febrile status epilepticus may evolve to permanent epileptic syndrome. A major question is under what circumstances febrile status epilepticus can induce a permanent injury and epilepsy. **Solomon Moshe** discussed the febrile status epilepticus, presenting EEG and imaging data obtained within the FEBSTAT study. The FEBSTAT study (S. Shinnar, PI) is designed to address the relationship between MR imaging, serial EEG, and clinical follow-up in a cohort of children followed from the time of presentation with febrile status epilepticus. These studies are the initial step for the development of biomarkers and eventually preventive treatments when deemed necessary. **George Kostopoulos** discussed the experience of FP7-ICT project ARMOR (2011-2014), concerning the long term multimodal monitoring of epileptic patients at home. The project ARMOR combined clinical and basic neuroscience research with advanced

Information and Communication Technology (ICT tools) for developing novel ambulatory, diagnostic and long-term monitoring services. **Jeff Noebels** discussed the aim of the new NIH funded Center for Sudden Unexpected Death in Epilepsy (SUDEP). Research is designed to develop validated evidence to enable this individualized approach. The Center is a biomedical and molecular genetic research partnership linking established SUDEP investigators in an interdisciplinary collaboration that will focus on accelerating the ability of physicians to identify individuals at high risk and explore preventative interventions. **Michael Segal** discussed the utility of an automated genome-phenome analysis for seizure disorders. The genome-phenome analysis is hypothesis-independent as to the mode of inheritance, number of genes involved, and which clinical findings are most relevant. Research and application of findings in epilepsy genetics in rural areas of China are hampered by lack of validated clinical assessment tools for phenotyping at the primary care level, agreed investigation protocols, established logistics and network, and trained personnel. **Ding Ding** discussed the results of a study that aims to overcome these barriers with emphasis on building research infrastructure and capacity. An infrastructure system to conduct epilepsy genetics research in rural China has been successfully established through this project. The model developed has the potential to be applied in other low- and middle-income settings where the majority of the world's people with epilepsy live.

The last session focused on understanding pathophysiology of epilepsy and to develop new therapeutic strategies. Therapeutic management of epilepsies fails to control seizures in a relevant subgroup of patients. Thus, prevention of epilepsy development (= epileptogenesis) is preferable in patients at risk to develop epilepsy following a brain insult or induced by a genetic predisposition. Omics-based approaches can significantly enhance our understanding of epileptogenesis. **Heidrun Potschka** presented information

regarding proteome alterations occurring at different time points during epileptogenesis in the hippocampus and parahippocampal cortex in a chronic rat epilepsy model. The analysis of these comprehensive data sets guides the selection of future target candidates and of molecular biomarkers for imaging approaches. **Eleonora Aronica** discussed the alteration of miRNA expression and miRNA regulation of key signalling pathways during temporal lobe epileptogenesis. The temporal profile of miRNA expression was analyzed in three brain regions (CA1; dentate gyrus, DG; parahippocampal cortex, PHC) associated with epileptogenesis in a rat model for temporal lobe epilepsy. This study identified several signaling pathways possibly involved in temporal lobe epileptogenesis. The potent loop diuretic bumetanide is increasingly being used for experimental treatment of brain disorders. **Wolfgang Löscher** discussed different strategies to enhance brain penetration of bumetanide: (1) development of lipophilic, noncharged prodrugs that enter the brain and are cleaved to bumetanide; (2) co-administration of a compound (piperonyl butoxide) that inhibits the rapid metabolism of bumetanide; (3) co-administration of a compound (probenecid) that inhibits active efflux from the brain; (4) development of novel bumetanide derivatives with enhanced brain penetration; and (5) development of a novel brain-permeable NKCC1-selective bumetanide derivative which is devoid of the diuretic action (mediated by NKCC2). **Ivan Soltesz** addressed the development of strategies that would act only on an as-needed basis without disrupting normal interictal behaviors. As a result of recent advances, optogenetics, when combined with seizure detection, can now be used in an on-demand fashion in experimental animals to modulate neuronal activity with 1) spatial specificity, 2) cell-type specificity, 3) direction of modulation specificity, and 4) temporal specificity. The slow after hyperpolarizing potential (sAHP) following prolonged depolarizations is a major intrinsic mechanism of neuronal inhibition. Whether an altered sAHP function might be

underlying hyperexcitability in chronic epilepsy has been discussed by **Rüdiger Köhling**. He investigated the role of casein kinase 2 (CK2), a known modulator of sAHP, on sAHP in control and chronically epileptic tissue, in the pilocarpine model of chronic temporal lobe epilepsy.

At the end of the meeting new programs and possibilities of interaction between Michael Forum members and the Michael Foundation have been discussed, including the recently introduced *focused fellowship program*, which will offer to young researchers from European countries the opportunity to visit German epilepsy centres and participate in epilepsy research projects.

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. UCB supported the Forum with an unrestricted educational grant, but did not have any influence on the program of the meeting or the contents of this report. I 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.