HHS Public Access

Author manuscript

Neurobiol Dis. Author manuscript; available in PMC 2020 March 01.

Published in final edited form as:

Neurobiol Dis. 2019 March ; 123: 1–2. doi:10.1016/j.nbd.2018.10.003.

PREFACE: Antiepileptogenesis following traumatic brain injury

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Despite decades of research that have led to an understanding of many causes of epilepsy, and yielded over 20 new antiseizure drugs as well as several novel non-drug therapies, there remain no antiepileptogenic treatments that prevent epilepsy, nor would it be possible to effectively identify and prove such treatments. The design of clinical trials to test potential antiepileptogenic compounds that might be identified in the animal laboratory would currently be prohibitively expensive, requiring very large populations of patients to be followed for several years. Furthermore, a major obstacle to research in this area is the fact that studies from single institutions are inadequate to answer the most important questions.

Efforts are underway to facilitate the development of antiepileptogenic therapies by removing barriers and by promoting large-scale collaborative research efforts by multidisciplinary teams of basic and clinical neuroscientists with access to extensive patient populations, well-defined and rigidly standardized animal models, and cutting-edge analytic methodology. A major focus is on the development of biomarkers that can identify patients at high risk of developing epilepsy following a potential epileptogenic insult, such as traumatic brain injury (TBI), which would permit enrichment of the study population for a clinical trial. Biomarkers that reliably permit the diagnosis of post traumatic epilepsy, or its absence, could also help to shorten clinical trials by determining whether an antiepileptogenic intervention was effective after TBI without the need to wait months or years for seizures to occur. Biomarkers of antiepileptogenic processes could also permit the development of more cost-effective, rapid-throughput animal models for discovery of potential antiepileptogenic compounds. Finally, the search for biomarkers of epileptogenesis would likely reveal fundamental neuronal mechanisms that could point the way towards novel targets for antiepileptogenic interventions.

This special issue of Neurobiology of Disease highlights recent work contributing to an ultimate objective of identifying approaches to prevent epilepsy, and carrying out cost-effective clinical trials to prove their efficacy. The first review by Engel provides an overview of epileptogenesis and the utility of biomarkers in tracking epileptogenic

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processes, facilitating, and strengthening the design of clinical trials that aim to study epileptogenesis and its prevention or modification by various treatments (Engel 2018). This review also introduces the Epilepsy Bioinformatics Study for Antiepileptogenic Therapy (EpiBioS4Rx), a Center Without Walls for translational research in antiepileptogenesis, an international multidisciplinary research project recently funded by the National Institutes for Neurological Disorders and Stroke (https://epibios.loni.usc.edu). EpiBioS4rx includes both preclinical and clinical projects that are designed to identify biomarkers of post-TBI epileptogenesis, investigate new treatments for their potential to prevent post-TBI epilepsy (PTE) and modify biomarkers of post-TBI epileptogenesis. Furthermore, EpiBioS4Rx was designed to establish a network of advanced centers capable of carrying out future clinical trials of potential antiepileptogenic drugs, and incorporates a public engagement program involving the education and collaboration of consumer organizations, and professionals, to design and execute future large-scale, cost-effective, interventional clinical trials of antiepileptogenic therapies.

Animal models have held an essential role in furthering our understanding of the underlying pathogenic processes after TBI. The invited review by Brady, Casillas-Espinosa et al (Brady et al. 2018) discusses the existing animal models of TBI and PTE while Dadas and Janigro (Dadas and Janigro 2018) discuss the evidence that blood brain barrier breakdown underlies the pathogenesis of PTE. Cognitive and behavioral comorbidities are an essential component of TBI and PTE; Semple et al outline the preclinical evidence on how animal models of TBI and PTE can be used to study such comorbidities (Semple et al. 2018).

The studies on candidate biomarkers of epileptogenesis are discussed in a series of reviews. Pitkänen et al provide an extensive review of clinical and preclinical studies aiming to identify and validate epilepsy biomarkers (Pitkanen et al. 2018). The proteomic and epigenomic markers that have been investigated as potential biomarkers of PTE are outlined by Agoston and Kamnaksh (Agoston and Kamnaksh 2018), while the candidate electrophysiological biomarkers of PTE, as studied in preclinical and clinical studies, are detailed by Perucca et al (Perucca et al. 2018). Immonen et al review the imaging studies that investigated various imaging modalities as putative PTE biomarkers (Immonen et al. 2018).

Treatments are addressed in the two subsequent reviews. Saletti et al provide a critical review of preclinical and clinical studies that investigated various treatments for their ability to modify TBI and PTE (Saletti et al. 2018) while Ali et al focus on the studies targeting neurodegeneration pathways (Ali et al. 2018).

Shifting to the clinical field, Vespa et al provide the premise and design of the clinical project of EpiBioS4Rx that aims to identify biomarkers of PTE (Vespa et al. 2018). Tubi et al report their clinical data supporting that temporal lobe lesions in a clinical cohort of individuals with moderate-severe TBI increase the risk for early seizures and PTE (Tubi et al. 2018). Utilizing a different setting, Hunter et al present the evidence from soccer or collision sports players on the neurobiological effects of repetitive head impacts as well as the genetic and biological factors that may modify them (Hunter et al. 2018).

Bioinformatics is an essential tool to allow rigorous analyses and validation of big data. Duncan et al describe the infrastructure available at EpiBioS4Rx for a centralized data repository to support importing heterogeneous multi-modal data, automatically and manually linking data across modalities and sites, and searching content (Duncan et al. 2018). Finally, Correa et al outline the collaborative model for knowledge translation and participatory action research development in TBI and PTE, emphasizing the necessary steps for early involvement of all stakeholders in the study of a disease that may take months to emerge after a brain injury (Correa et al. 2018).

With this collection of expert reviews we hope to provide an essential primer of the progress done in the TBI and PTE research arena for both epilepsy and non-epilepsy experts. As emphasized in many of these reviews, paradigm-shifting progress in diagnosing, prognosticating, managing, and treating individuals with TBI and PTE can only be made through collaboration of experts from diverse areas of expertise. We hope that these reviews will provide an impetus for more research and collaborations leading to better tools to prevent TBI consequences and PTE.

Acknowledgements

ASG acknowledges grant support by NINDS RO1 NS091170, the NINDS Center without Walls U54 NS100064 (EpiBioS4Rx), the United States Department of Defense (W81XWH-13-1-0180), research funding from the Heffer Family, the Segal Family Foundations and the Abbe Goldstein/Joshua Lurie and Laurie Marsh/Dan Levitz families. ASG has received royalties for publications from Elsevier and a one-time honorarium for participation at a scientific advisory board for Mallinckrodt and is a co-Editor-in-Chief at Epilepsia Open but has no conflicts in regards to this article.

JE acknowledges research funding from the National Institutes of Health grant numbers NS-002808, NS-015654, NS-033310, NS-042372, and NINDS Center without Walls, U54 NS100064 (EpiBioS4Rx).

SLM is the Charles Frost Chair in Neurosurgery and Neurology and partially funded by grants from NIHU54 NS100064 and NS43209, US Department of Defense (W81XWH-13-1-0180), and the Heffer Family and the Segal Family Foundations and the Abbe Goldstein/Joshua Lurie and Laurie Marsh/Dan Levitz families. S.L.M. has no conflicts of interest in regards to this article. He is serving as Associate Editor of Neurobiology of Disease and is on the editorial board of Brain and Development, Pediatric Neurology and Physiological Research. He receives from Elsevier an annual compensation for his work as Associate Editor in Neurobiology of Disease and royalties from 2 books he co-edited. He received a consultant fee from UCB for participation in a DSMB. He has also received honorarium for participation in an advisory board meeting of Mallinckrodt, but there is no conflict of interest in regards to the contents of this manuscript.

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