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Disease Promoters during Epileptogenesis

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In Focus issue interrogates how glia, immune cells, and neurons contribute to epileptogenesis, the process of development of epilepsy. Epilepsy is a chronic debilitating neurological disorder of humans worldwide, affecting both men and women of all ages. The lifetime prevalence of epilepsy worldwide is ~2% (>65 million people). According to the Centers for Disease Control and Prevention (CDC) report, about 10% of Americans experience a seizure during their lifetime, and ~3% of those experienced the first seizure would develop epilepsy during their lifetime. CDC's 2017 press release ("*More Americans have epilepsy than ever before*") reveals that the number of U.S. adults and children with epilepsy is increasing, with at least 3.4 million people living with the disorder (1). Despite a significant progress in epilepsy research, the precise mechanism of epileptogenesis that follows an insult such as trauma, exposure to neurotoxic chemicals, infection, or gene mutation, are still largely unknown.

Traditionally, neuronal hyperexcitability attributed as the major cause or consequence of epileptogenesis. Antiepileptic drugs (AEDs) development strategies for epilepsy focused on targeting the ion channels that excite neurons (antagonists) or promote the inhibitory neurons function (agonists) to dampen hyperexcitability. The goal of AED treatment is to achieve freedom from seizures without any adverse effects. More than 20 second-generation AEDs were developed and marketed in the past three decades to achieve this goal, while more than 45 other AEDs failed in clinical trials due to lack of efficacy and severe side effects (2, 3). Despite these efforts, ~1/3 of people with epilepsy (PWE) do not respond to the current AEDs for unknown reasons (4, 5). Although ion-channel targeted AEDs control symptomatic seizures in 2/3 of PWE, the majority of them do not effectively target seizures-induced brain pathology, especially in acquired temporal lobe epilepsy (TLE), the most common type of all epilepsies (6). These findings suggest the need for development of drugs that target alternative pathways to cure/modify epilepsy. TLE precedes neuroinflammation (reactive gliosis and proinflammatory cytokine/chemokines), nitrooxidative stress, neurodegeneration, and increased epileptiform spiking (disease promoters), which persist even after the disease is established (7, 8). Therefore, developing therapeutic drugs that target the disease promoters may address the current gap in epilepsy.

In this In Focus issue, the contributing authors present recent evidence and novel approaches to identify potential therapeutic targets that promote epileptogenesis and progression of the

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disease. Neuberger et al. (9) highlights the mechanism of epileptogenesis in a traumatic brain injury model. The article discusses the role of mammalian target of rapamycin (mTOR) pathway in neurogenesis, neurovascular interactions mediated by vascular endothelial growth factor (VEGF), and HMGB1-TLR4 neuroimmune pathway. These pathways play a major role in early brain pathogenesis, including increased excitability, activated immune signaling, neurodegeneration, and enhanced neurogenesis within a week of injury, during which the insult may promote increased risk for the development of epilepsy. Eid et al. (10) review the role of astrocytes in epilepsy development, with a special emphasis on astrocyte pathologies related to aquaporin 4, the inwardly rectifying potassium channel Kir4.1, monocarboxylate transporters MCT1 and MCT2, excitatory amino acid transporters EAAT1 and EAAT2, and glutamine synthetase. Sharma et al. (11) review the role of glial source of nitric oxide (NO) in promoting epileptogenesis. Finally, Tse et al. (12) presents data on altered proteome levels during epileptogenesis, using the mouse kainate model, and the impact of inhibiting the inducible NO synthase (iNOS) with 1400W and blocking the post-synaptic density protein 95 (PSD95) – a scaffolding protein that mediates the downstream effects of neuronal hyperexcitability- with a blocking peptide (Tat-NR2B9c) on proteomes in the hippocampus. In summary, the potential therapeutic targets proposed in this In Focus are inducible nitric oxide synthase (iNOS), PSD95, HMGB1/TLR4, mTOR, VEGF, and glutamine synthetase. The investigational new drugs that engage some of these targets provide proof-of-concept for their role in disease modification in epilepsy in animal models (see, for example, 7, 8, 13, 14).

References:

1. <https://www.cdc.gov/media/releases/2017/p0810-epilepsy-prevalence.html>
2. Bialer M, Johannessen SI, Levy RH, Perucca E, Tomson T, White HS. Progress report on new antiepileptic drugs: A summary of the Thirteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XIII). *Epilepsia*. 2017 2;58(2):181–221. doi: 10.1111/epi.13634. Epub 2017 Jan 23. Review. PubMed PMID: . [PubMed: 28111749]
3. Temkin NR. Antiepileptogenesis and seizure prevention trials with antiepileptic drugs: meta-analysis of controlled trials. *Epilepsia*. 2001 42(4):515–24. PMID: . [PubMed: 11440347]
4. Kwan P, Brodie MJ Epilepsy after the first drug fails: substitution or add-on? *Seizure*. 2000 9 (7): 464–468. DOI: 10.1053/seiz.2000.0442. PMID: . [PubMed: 11034869]
5. Kwan P, et al. Drug-resistant epilepsy. *N Engl J Med*. 2011 365 (10):919–26. doi: 10.1056/NEJMr1004418. PMID: . [PubMed: 21899452]
6. Rzezak P, Lima EM, Pereira F, Gargaro AC, Coimbra E, De Vincentiis S, Velasco TR, Leite JP, Busatto GF, Valente KD. Decision-making in patients with temporal lobe epilepsy: Delay gratification ability is not impaired in patients with hippocampal sclerosis. *Epilepsy Behav*. 2016 60:158–164. doi: 10.1016/j.yebeh.2016.04.042. [Epub ahead of print]. PMID: . [PubMed: 27206236]
7. Putra M, Sharma S, Gage M, Gasser G, Hinojo-Perez A, Olson A, Gregory-Flores A, Puttachary S, Wang C, Anantharam V, Thippeswamy T. Inducible nitric oxide synthase inhibitor, 1400W, mitigates DFP-induced long-term neurotoxicity in the rat model. *Neurobiol Dis*. 2019 3 30 pii: S0969 9961(19)30082–8. doi:10.1016/j.nbd.2019.03.031. [Epub ahead of print] PubMed PMID: . [PubMed: 30940499]
8. Puttachary S, Sharma S, Verma S, Yang Y, Putra M, Thippeswamy A, Luo D, Thippeswamy T. 1400W, a highly selective inducible nitric oxide synthase inhibitor is a potential disease modifier in the rat kainate model of temporal lobe epilepsy. *Neurobiol Dis*. 2016 9;93:184–200. doi: 10.1016/j.nbd.2016.05.013. Epub 2016 May 18. PubMed PMID: . [PubMed: 27208748]

9. Neuberger EJ, Gupta A, Subramanian D, Korgaonkar AA, Santhakumar V. Converging early responses to brain injury pave the road to epileptogenesis. *J Neurosci Res.* 2017 11 29. doi: 10.1002/jnr.24202. [Epub ahead of print] Review. PubMed PMID: ; [PubMed: 29193309]
10. Eid T, Lee TW, Patrylo P, Zaveri HP. Astrocytes and Glutamine Synthetase in Epileptogenesis. *J Neurosci Res.* 2018 7 18. doi: 10.1002/jnr.24267. [Epub ahead of print] Review. PubMed PMID: ; [PubMed: 30022509]
11. Sharma S, Puttachary S, Thippeswamy T. Glial source of nitric oxide in epileptogenesis: A target for disease modification in epilepsy. *J Neurosci Res.* 2017 12 12. doi: 10.1002/jnr.24205. [Epub ahead of print] Review. PubMed PMID: ; [PubMed: 29230865]
12. Tse K, Hammond D, Simpson D, Beynon RJ, Beamer E, Tymianski M, Salter MW, Sills GJ, Thippeswamy T. The impact of postsynaptic density 95 blocking peptide (Tat-NR2B9c) and an iNOS inhibitor (1400W) on proteomic profile of the hippocampus in C57BL/6J mouse model of kainate-induced epileptogenesis. *J Neurosci Res.* 2019 5 15. doi: 10.1002/jnr.24441. [Epub ahead of print] PubMed PMID: . [PubMed: 31090233]
13. Xu Q, Uliel-Sibony S, Dunham C, Sarnat H, Flores-Sarnat L, Brunga L, Davidson S, Lo W, Shlien A, Connolly M, Boelman C, Datta A. mTOR Inhibitors as a New Therapeutic Strategy in Treatment Resistant Epilepsy in Hemimegalencephaly: A Case Report. *J Child Neurol.* 2019 3;34(3):132–138. doi: 10.1177/0883073818813238. Epub 2018 12 5 PubMed PMID: . [PubMed: 30514132]
14. Pauletti A, Terrone G, Shekh-Ahmad T, Salamone A, Ravizza T, Rizzi M, Pastore A, Pascente R, Liang LP, Villa BR, Balosso S, Abramov AY, van Vliet EA, Del Giudice E, Aronica E, Patel M, Walker MC, Vezzani A. Targeting oxidative stress improves disease outcomes in a rat model of acquired epilepsy. *Brain.* 2019 5 30 pii: awz130. doi: 10.1093/brain/awz130. [Epub ahead of print] PubMed PMID: ; [PubMed: 31145451]