Neurosci. Bull.
https://doi.org/10.1007/s12264-024-01215-0

www.neurosci.cn
www.springer.com/12264

EDITORIAL

Novel Mechanism, Drug Target and Therapy in Epilepsy

Cenglin Xu[1] · Yi Wang[1] · Zhong Chen[1]

Received: 27 March 2024 / Accepted: 8 April 2024

Epilepsy, which is characterized by unprovoked seizures and has a prevalence of nearly 1%, is becoming one of the leading causes of disability and death globally [1]. The exact mechanisms behind epilepsy are still unknown, which contributes to the inadequate efficacy of anti-seizure medications (ASMs) that mainly target membrane ion channels and neurotransmission [2]. Crucially, a significant fraction of patients with epilepsy (PWE) will become tolerant to ASMs, termed pharmacoresistant epilepsy [3]. For the purpose of precisely managing epilepsy, it is important to comprehend the mechanisms underlying the condition to identify new therapeutic targets. This special issue, "Novel Mechanisms, Drug Target and Therapy in Epilepsy," which includes two research articles, five reviews, and three research highlights, presents the latest advancements in epilepsy.

With its many epileptic biomarkers, electroencephalography (EEG) is a valuable tool for understanding the state of the epileptic brain. Among these, high-frequency oscillations (HFOs) are a potentially useful biomarker for identifying the epileptogenic zone and comprehending the ictogenesis-related mechanisms in epilepsy [4]. HFOs contain both physiological and pathological components. Wang and his colleagues carefully enumerate the traits, distinctions, and uses of physiological and pathological HFOs in a review paper [5]. The definition and detection techniques for pathological and physiological HFOs are covered by the writers, followed by a discussion of the distinctions between the two categories of HFOs. Notably, the clinical significance of distinguishing pathological HFOs is presented. An overview and current information regarding HFOs in epilepsy are given in this review.

The complex process that gives rise to epilepsy, called epileptogenesis, is influenced by a multitude of pathological factors. The extracellular matrix, astrocytes, microglia, neurons, vascular endothelial cells, and pericytes that comprise the neurovascular unit (NVU) are of particular interest. In this issue, Liu, Han, and their colleagues highlight the changes and molecular mechanisms of the NVU in epileptogenesis [6]. This review begins with a discussion of the NVU alterations during epileptogenesis. Next, the molecular mechanisms, potential drug targets, and biomarkers associated with NVU in epileptogenesis are presented. Crucially, the authors summarize the status of current research and provide future prospections about intervening epileptogenesis.

Thrombosponding-1 (TSP-1), a multidomain extracellular matrix protein secreted by astrocytes, is a member of the thrombospondin family [7]. Sun and colleagues have provided a summary of its function in epileptogenesis in this issue [8]. Initially, the structures and interacting molecules of TSP-1 are presented. Then, the contributions of increased TSP-1 in epileptogenesis through different mechanisms are comprehensively introduced. This review emphasizes targeting TSP-1 as a potential epilepsy treatment approach.

Neuroinflammation has been recognized as a key pathological factor in the development of epilepsy. Pro- and anti-inflammatory interleukins have been implicated in ictogenesis and epileptogenesis, according to cumulative evidences [9, 10]. An overview of the conflicting roles of interleukins in epilepsy was provided by Wang and colleagues [11]. In their review, different interleukin families are separately introduced, and their contributions to epilepsy are highlighted.

✉ Zhong Chen
chenzhong@zju.edu.cn

[1] Key Laboratory of Neuropharmacology and Translational Medicine of Zhejiang Province, School of Pharmaceutical Science, Zhejiang Chinese Medical University, Hangzhou 310053, China

Published online: 24 April 2024

Anti-tussive drug dextromethorphan has been reported to have anti-inflammatory properties with an ultra-low dose through inhibiting microglial NADPH oxidase (NOX)-mediated neuroinflammation [12]. However, whether dextromethorphan can be effective for epilepsy remains unillustrated. In a research article, Zhao, Yin, and co-authors reported that long-term administration of ultra-low dose dextromethorphan exerts long-lasting anti-seizure efficacy on kainic acid-treated epileptic mice [13]. Additionally, dextromethorphan enhances cognitive performance and lessens the loss of hippocampus neurons by blocking microglial NADPH oxidase 2. Therefore, their results highlight dextromethorphan as an alternative therapy for epilepsy.

Synaptic vesicle protein (SV) 2A is the unique acting target of first-line ASMs [2]. SV2A ligands such as levetiracetam, brivaracetam, and padsevonil are well-tolerated and effective ASMs with little drug-drug interactions. Gao, Tian, and their colleagues highlight the research and development progress of SV2A ligands for epilepsy treatment in this issue [14]. The authors began by outlining the history of SV2A's identification as an anti-epileptic target before going into great depth about the three SV2A ligands: padsevonil, brivaracetam, and levetiracetam. With strong evidence, SV2A would be a crucial target for future ASM developments.

The importance of the mammalian target of the rapamycin (mTOR) pathway has been gradually recognized in epilepsy. A previous study has reported that suppression of mTOR complex 2 (mTORC2) robustly inhibits seizures in different models [15]. The enormous potential of mTORC2 as a target for broader control of epileptic seizures is highlighted by Xu and colleagues [16]. As indicated by the authors, it is important to further develop active compounds that selectively act on mTORC2 and test their efficacy for anti-seizure purposes.

Secondary epileptogenesis, characterized by increased epileptic susceptibility and a tendency to generate epileptiform activities outside the primary focus [17], is one of the major resultants of pharmacoresistant epilepsy [3]. Low-frequency stimulation (LFS) at the subiculum has been proven as an effective strategy for epileptogenesis and pharmacoresistant epilepsy [18, 19]. In this issue, Chen, Xu, and colleagues further expand the use of LFS at the subiculum in preventing secondary epileptogenesis [20]. They report that LFS during the primary epileptogenesis process successfully prevents secondary epileptogenesis at both the contralateral and ipsilateral secondary foci. The mechanisms are associated with the inhibitory effect at the secondary focus by interfering with the enhancement of synaptic connections between the primary and secondary foci. This study provides a potential strategy for intractable secondary epileptogenesis.

Evidence suggests that the loss of inhibitory interneurons in the brain is intimately linked to reduced GABAergic activities in epileptic seizures [21]. A recent ground-breaking study assessed the GABAergic interneuron cell therapy's potential for treating epilepsy [22]. Furthermore, two research highlights that illustrate the exceptional potential of cell therapy for treating pharmacoresistant epilepsy are included in this issue [23, 24]. The authors of both literatures point out that additional study is required to clarify the GABAergic subtypes following cell therapy and to ascertain whether this therapy is helpful for different types of epilepsy and comorbidities.

To sum up, this special issue presented here will promote the understanding of the mechanisms of epilepsy, and provide substantial evidence to drive further translational studies based on these novel targets and therapies for epilepsy.

Acknowledgements This Editorial was supported by the National Natural Science Foundation of China (82330116), and the Natural Science Foundation of Zhejiang Province (D24H310001).

Conflict of interest The authors declare no competing interests.

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