

## Editorial

### Recent Advances in Pathophysiological Studies and Treatment of Epilepsy

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Epilepsy is a common neurological condition defined by recurrent, unprovoked seizures that affect 1–2% of the population worldwide. However, a little is known about both the cellular and network mechanisms of epilepsy. Therefore, in the present issue, we aimed to provide a comprehensive review of the literature on epilepsy in selected experts.

Firstly, miRNA studies were conducted on human and animal models to clarify the foundation for exploring research of miRNA in epilepsy. Several target genes and pathways of miRNA which related to the therapeutic methods to epilepsy [1, 2]. Dr. Ma reported that epilepsy biomarkers might be used as an identification of epileptic condition [3].

Secondly, substance P is widely distributed in the regions of the central nervous system associated with epilepsy and it contributes to the initiation and maintenance phases of epilepsy. *In vivo*, substance P binds to the neurokinin-1 receptor and modulates the biological activity of the receptor. Although NK-1 receptor antagonists have anti-epileptic properties in animal models [4, 5], the clinical efficacy of these drugs has not yet been verified. Therefore, Dr. Chi provides an overview of current understanding of the structural and functional mechanisms of the substance P involved in regulating epilepsy pathological process [6].

Thirdly, an increasing number of studies have shown that the activation of the 5-HT<sub>3</sub> receptor can inhibit epileptic seizures, while inhibition of the 5HT<sub>3</sub> receptor can promote spike waves. [7-9]. In this review, Dr. Huo discussed the relationship between the 5HT<sub>3</sub> receptor and epilepsy, It may provide a new insight into clinical application of epilepsy treatment.

In the past decades, despite the continuous development of antiepileptic drugs, there are still many patients with epilepsy progressing to drug-resistant epilepsy. Currently, surgical treatment is the only possible way to cure drug-resistant epilepsy. However, surgical treatment alone often results in postoperative recurrence of epilepsy. Antiepileptic comprehensive treatment mainly based on surgery is capable of effectively reducing the recurrence rate of epilepsy [10-12]. In this review, Dr Sheng summarized the pathogenesis of drug-resistant epilepsy and current comprehensive treatment mainly based on surgery. It may provide some insight into epilepsy treatment.

Choline alfoscerate ( $\alpha$ -GPC) and Cytidine 5'-diphosphocholine (CDP-Choline) are both acetylcholine precursors and are considered to act as pro-cholinergic nootropic agents. whether acetylcholine precursors have a similar effect on treating cognitive impairment in patients with epilepsy remains controversial. Dr Lee reported that acetylcholine precursors in seizure-experienced animals have produced variable results that are dependent on the timing of administration. Early administration of CDP-choline immediately after seizure increased neuronal death, blood-brain barrier (BBB) disruption and microglial activation in the hippocampus. However, administration of  $\alpha$ -GPC starting 3 weeks after seizure (late administration) improved cognitive function through reduced neuronal death and BBB disruption, and increased neurogenesis in the hippocampus [13, 14]. It may be attributed to both epileptogenic features and neuroprotective functions of several acetylcholine precursors.

Herbal medicine has always been traditionally a part of treatment of epilepsy. This is because herbal medicines are generally well tolerated, with fewer side effects. Many herbal remedies have been tested and proved effective in animal models of epilepsy [15]. Dr. Stephen briefly highlights some herbs that have been studied for their anticonvulsant activity in animal models.

Some vaccines cause a small increased risk of febrile seizures. Therefore, there has been some controversy is about their safety; particularly, concerns have been rising about febrile seizures [16, 17]. Today, the safety profile of vaccinations is greatly improved. Dr. Wang helped the reader to improve their understanding of the relationship between the different vaccines and febrile seizures to be able to reduce the risk of developing febrile seizures following vaccination.

Recently, increasing studies have established the beneficial effects of ketogenic diet on epileptic seizure reduction. Both basic experiments and clinical trials demonstrated that ketogenic diet significantly reduced seizure frequency with mild adverse effects [18, 19]. Dr. Zhang reviewed how ketogenic diet treatment exerts its anticonvulsant effects, which may help to understand the development of epilepsy and provide new treatment targets.

Some patients after stroke may develop post-stroke epilepsy, which has a negative effect on stroke prognosis and the quality of life [20]. In this review, Dr. Zhao describes new aspects emerging from research about post-stroke epilepsy, including definition, epidemiology, risk factors, mechanism, accessory examination and treatment strategies for post-stroke epilepsy, which will enrich our knowledge of this disorder.

Finally, sleep and epilepsy are mutually related in a complex, bidirectional manner. However, understanding of this relationship remains unclear. In this paper, Dr. Wang addressed the issues involved in these phenomena and also discuss as the various therapies used to modify them [21, 22]. Furthermore, many drugs that regulate the sleep-wake cycle can also serve as potential antileisure agents.

In conclusion, this special issue focused on recent advances in epilepsy, particularly the effects of sleep, herbal medicine, ketogenic diet and vaccine on epilepsy. It may be helpful in both understanding how different pathophysiological processes affect seizure and identifying new therapies.

## REFERENCES

- [1] Xiang, L.; Ren, Y.; Cai, H.; Zhao, W.; Song, Y. MicroRNA-132 aggravates epileptiform discharges via suppression of BDNF/TrkB signaling in cultured hippocampal neurons. *Brain Res.*, **2015**, *1622*, 484-495. [http://dx.doi.org/ 10.1016/j.brainres.2015.06.046] [PMID:26168887]
- [2] Schouten, M.; Fratantoni, S.A.; Hubens, C.J.; Piersma, S.R.; Pham, T.V.; Bielefeld, P.; Voskuyl, R.A.; Lucassen, P.J.; Jimenez, C.R.; Fitzsimons, C.P. MicroRNA-124 and -137 cooperativity controls caspase-3 activity through BCL2L13 in hippocampal neural stem cells. *Sci. Reports*, **2015**, *5*, 12448. [http://dx.doi.org/10.1038/srep12448] [PMID: 26207921]
- [3] Liu, X.; Wu, Y.; Huang, Q.; Zou, D.; Qin, W.; Chen, Z. Grouping Pentylentetrazol-Induced epileptic rats according to memory impairment and MicroRNA expression profiles in the hippocampus. *PLoS One*, **2015**, *10*(5), e0126123. [http://dx.doi.org/10.1371/journal.pone.0126123] [PMID: 25962166]
- [4] de Lanerolle, N.C.; Kim, J.H.; Williamson, A.; Spencer, S.S.; Zaveri, H.P.; Eid, T.; Spencer, D.D. A retrospective analysis of hippocampal pathology in human temporal lobe epilepsy: evidence for distinctive patient subcategories. *Epilepsia*, **2003**, *44*(5), 677-687. [PMID: 12752467]
- [5] Baraban, S.C.; Tallent, M.K. Interneuron diversity series: Interneuronal neuropeptides--endogenous regulators of neuronal excitability. *Trends Neurosci.*, **2004**, *27*(3), 135-142. [http://dx.doi.org/10.1016/j.tins.2004.01.008] [PMID: 15036878]
- [6] Qian, F.; Tang, F.R. Metabotropic glutamate receptors and interacting proteins in epileptogenesis. *Curr. Neuropharmacol.*, **2016**, *14*(5), 551-562. [PMID: 27030135]
- [7] Li, B.; Wang, L.; Sun, Z.; Zhou, Y.; Shao, D.; Zhao, J.; Song, Y.; Lv, J.; Dong, X.; Liu, C.; Wang, P.; Zhang, X.; Cui, R. The anticonvulsant effects of SR 57227 on pentylentetrazole-induced seizure in mice. *PLoS One*, **2014**, *9*(4), e93158. [http://dx.doi.org/10.1371/journal.pone.0093158] [PMID: 24690630]
- [8] Blass, B. Sulfonamide derivatives and pharmaceutical applications thereof. *ACS Med. Chem. Lett.*, **2015**, *7*(1), 12-14. [http://dx.doi.org/10.1021/acsmchemlett.5b00466] [PMID: 26819658]
- [9] Gholipour, T.; Ghasemi, M.; Riazi, K.; Ghaffarpour, M.; Dehpour, A. R. Seizure susceptibility alteration through 5-HT 3 receptor: Modulation by nitric oxide. *Seizure*, **2010**, *19*(1), 17-22. [http://dx.doi.org/10.1016/j.seizure.2009.10.006] [PMID: 19942458]
- [10] Englot, D.J.; Birk, H.; Chang, E.F. Seizure outcomes in nonresective epilepsy surgery: an update. *Neurosurg Rev.*, **2017**, *40*(2), 181-194. [http://dx.doi.org/ 10.1007/s10143-016-0725-8] [PMID: 27206422]
- [11] Lewis, E.C.; Weil, A.G.; Duchowny, M.; Bhatia, S.; Ragheb, J. Miller I MR-guided laser interstitial thermal therapy for pediatric drug-resistant lesional epilepsy. *Epilepsia*, **2015**, *56*(10), 1590-1598. [http://dx.doi.org/10.1111/epi.13106] [PMID:26249524]
- [12] Kang, J.Y.; Wu, C.; Tracy, J.; Lorenzo, M.; Evans, J.; Nei, M.; Skidmore, C.; Mintzer, S.; Sharan, A.D.; Sperling, M.R. Laser interstitial thermal therapy for medically intractable mesial temporal lobe epilepsy. *Epilepsia*, **2016**, *57*(2), 325-334. [http://dx.doi.org/10.1111/epi.13284] [PMID: 26697969]
- [13] Kim, J.H.; Lee, D.W.; Choi, B.Y.; Sohn, M.; Lee, S.H.; Choi, H.C.; Song, H.K.; Suh, S.W. Cytidine 5'-diphosphocholine (CDP-choline) adversely effects on pilocarpine seizure-induced hippocampal neuronal death. *Brain Res.*, **2015**, *1595*, 156-165. [http://dx.doi.org/10.1016/j.brainres.2014.11.011] [PMID: 25446447]
- [14] Lee, S.H.; Choi, B.Y.; Kim, J.H.; Kho, A.R.; Sohn, M.; Song, H.K.; Choi, H.C.; Suh, S.W. Late treatment with choline alfoscerate (l-alpha glycerylphosphorylcholine, alpha-GPC) increases hippocampal neurogenesis and provides protection against seizure-induced neuronal death and cognitive impairment. *Brain Res.*, **2017**, *1654*(Pt A), 66-76. [http://dx.doi.org/10.1016/j.brainres.2016.10.011] [PMID: 27765578]
- [15] Xiao, F.; Yan, B.; Chen, L.; Zhou, D. Review of the use of botanicals for epilepsy in complementary medical systems — Traditional chinese medicine. *Epilepsy Behav.*, **2015**, *52*(Pt B), 281-289. [http://dx.doi.org/10.1016/j.yebeh.2015.04.050] [PMID: 26052078]
- [16] Pruna, D.; Balestri, P.; Zamponi, N.; Grosso, S.; Gobbi, G.; Romeo, A.; Franzoni, E.; Osti, M.; Capovilla, G.; Longhi, R.; Verrotti, A. Epilepsy and vaccinations: Italian guidelines. *Epilepsia*, **2013**, *54* Suppl 7, 13-22. [http://dx.doi.org/ 10.1111/epi.12306] [PMID: 24099052]
- [17] Yun, W.; Zhang, F.; Hu, C.; Luo, X.; Xue, P.; Wang, J.; Ge, Y.; Meng, H.; Guo, Y. Effects of ephx1, scn1a and cyp3a4 genetic polymorphisms on plasma carbamazepine concentrations and pharmacoresistance in chinese patients with epilepsy. *Epilepsy Res.*, **2013**, *107*, 231-237. [http://dx.doi.org/ 10.1016/j.eplepsyres.2013.09.011] [PMID: 24125961]
- [18] Rho, J.M.; Anderson, G.D.; Donevan, S.D.; White, H.S. Acetoacetate, acetone, and dibenzylamine (a contaminant in l-(+)-beta-hydroxybutyrate) exhibit direct anticonvulsant actions *in vivo*. *Epilepsia*, **2002**, *43*(4), 358-361. [PMID: 11952765]
- [19] Likhodii, S.S.; Serbanescu, I.; Cortez, M.A.; Murphy, P.; Snead, O.C., 3rd.; Burnham, W.M. Anticonvulsant properties of acetone, a brain ketone elevated by the ketogenic diet. *Ann. Neurol.*, **2003**, *54*(2), 219-226. [http://dx.doi.org/10.1002/ana.10634] [PMID: 12891674]
- [20] Liu, J.; Schmitt, K.L.; Kharlamov, E.A.; Stolarski, C.J.; Grayson, D.R.; Kelly, K.M. Quantitative reverse transcription-polymerase chain reaction of GABA(A) alpha1, beta1 and gamma2S subunits in epileptic rats following photothrombotic infarction of neocortex. *Epilepsy Res.*, **2002**, *52*(2), 85-95. [PMID: 12458025]
- [21] Urade, Y.; Eguchi, N.; Qu, W.M.; Sakata, M.; Huang, Z.L.; Chen, J.F.; Schwarzschild, M.A.; Fink, J.S.; Hayaishi, O. Sleep regulation in adenosine A2A receptor-deficient mice. *Neurology*, **2003**, *61*(11 Suppl 6), S94-96. [PMID: 14663019]
- [22] Hayaishi, O.; Urade, Y.; Eguchi, N.; Huang, Z.L. Genes for prostaglandin d synthase and receptor as well as adenosine A2A receptor are involved in the homeostatic regulation of nrem sleep. *Arch. Ital. Biol.*, **2004**, *142*(4), 533-539. [PMID: 15493554]

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