Epilepsy Currents
2019, Vol. 19(1) 47-48

DOI: 10.1177/1535759718822035
journals.sagepub.com/home/epi
SAGE

From DREADD to Treatment in Temporal Lobe Epilepsy

Pharmaco-Genetic Therapeutics Targeting Parvalbumin Neurons Attenuate Temporal Lobe Epilepsy

Wang Y, Liang J, Chen L, Shen Y, Zhao J, Xu C, Wu X, Cheng H, Ying X, Guo Y, Wang S, Zhou Y, Wang Y, Chen Z. *Neurobiol Dis*. 2018;117:149-60. Epub 2018/06/13. doi:10.1016/j.nbd.2018.06.006. PubMed PMID: 29894753.

Temporal lobe epilepsy (TLE) is the most common type of epilepsy and is often medically refractory. Previous studies suggest that selective pharmaco-genetic inhibition of pyramidal neurons has therapeutic value for the treatment of epilepsy; however, there is a risk of disrupting normal physical functions. Here, we test whether pharmaco-genetic activation of parvalbumin neurons, which are transgenetically transduced with the modified muscarinic receptor hM3Dq, can attenuate TLE. We found that pharmaco-genetic activation of hippocampal parvalbumin neurons in epileptogenic zone not only significantly extends the latency to different seizure stages and attenuates seizure activities in acute seizure model but also greatly alleviates the severity of seizure onsets in 2 chronic epilepsy models. This manipulation did not affect the normal physical function evaluated in various cognitive tasks. Further, the activation of parvalbumin neurons produced an inhibition on parts of surrounding pyramidal neurons, and the direct inactivation of pyramidal neurons via the viral expression of a modified muscarinic receptor hM4Di produced a similar anti-ictogenic effect. Interestingly, pharmacogenetic inactivation of pyramidal neurons was more sensitive to impair cognitive function. Those data demonstrated that pharmaco-genetic seizure attenuation through targeting parvalbumin neurons rather than pyramidal neurons may be a novel and relatively safe approach for treating refractory TLE.

Commentary

Temporal lobe epilepsy (TLE), characterized by spontaneous seizures, behavioral abnormalities, and changes in hippocampal morphology, is one of the most common forms of refractory epilepsy in adults.[1] Resection of the seizure focus can be an effective treatment strategy; however, the procedure is invasive and patients with bilateral seizure foci or unknown seizure origination are not good surgical candidates. In addition, a substantial number of patients do not achieve adequate seizure control with currently available pharmacological treatments or experience unwanted side effects. Consequently, there is a need to identify more efficacious therapies for patients with TLE.

Experimental rodent models of TLE successfully recapitulate the key clinical features and have advanced our understanding of the molecular and cellular basis of TLE. These models also provide the opportunity to test novel therapeutic strategies. In this study, Wang and colleagues explored the therapeutic potential of using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) to either activate hippocampal parvalbumin (PV) neurons or inhibit hippocampal pyramidal neurons in an acute kainic acid (KA) model, a kindling model of TLE, and the intrahippocampal KA TLE model. DREADDs rely on the use of modified human muscarinic receptors that are responsive to otherwise inert ligands such as clozapine-N-oxide (CNO). In the current study, the engineered inhibitory Gi-coupled human muscarinic receptor hM4Di and the excitatory Gq-coupled human muscarinic receptor hM3Dq were used to either decrease or increase neuronal excitability, respectively. Cell specificity was achieved using *Cre*-inducible adeno-associated viruses expressing either hM4Di or hM3Dq in combination with *Cre* recombinase expression in either inhibitory PV neurons or excitatory pyramidal neurons. Specifically, the authors evaluated the seizure protective effect of increasing the activity of PV neurons in the mouse models by injecting a *Cre*-inducible adeno-associated virus expressing hM3Dq into the right ventral hippocampus of *Pvalb-Cre* mice. Conversely, the activity of pyramidal neurons was reduced by injection of an adeno-associated virus expressing hM4Di into the right ventral hippocampus of *CaMKII2α-Cre* mice.

First, the effects of activating hippocampal PV neurons were evaluated in an acute intrahippocampal KA model by an intraperitoneal injection of CNO 30 minutes prior to KA administration. The authors observed a dose-dependent increase in the latency to different seizure stages, reduced duration of the first generalized tonic-clonic seizure (GTCS), and reduced

mortality. Next, the same approach was used in a hippocampal-kindling model. Using fully kindled mice, activation of PV neurons was able to reduce seizure severity and duration during kindling stimulation. The authors also examined the effect of activation of hippocampal PV neurons in the intrahippocampal KA TLE model 2 months after KA administration. During the 3 days of CNO treatment (1 mg/kg), a reduction in spontaneous seizure frequency and duration was observed when compared to the 3 days prior to and after CNO treatment.

To determine whether seizure protection in the intrahippocampal KA TLE model could similarly be achieved via DREADD-mediated inhibition of hippocampal pyramidal neuron activity, the authors also treated *CaMKII2α::hM4Di* mice with CNO for 3 days. Similar to activation of the PV neurons, the inhibition of pyramidal neurons reduced spontaneous seizure frequency. However, due to the experimental design, a direct comparison of the relative efficacy of targeting PV neurons versus pyramidal neurons was not possible since it was not clear if the genetic backgrounds of the 2 *Cre* transgenic lines were the same, which is important given that genetic background is known to influence seizure susceptibility.[2]

Despite successful amelioration of seizure phenotypes, neither the activation of PV neurons nor inhibition of pyramidal neurons was able to significantly reduce observed deficits in learning and memory in the intrahippocampal KA TLE model. This suggests that broader modulation of neuronal activity might be necessary to mitigate behavioral abnormalities. It is also possible that other features of this model, such as neuronal loss and neuroinflammation, contribute to the development of some behavioral abnormalities, which might not be ameliorated by modulating neuronal excitability. A more thorough characterization of behavioral phenotypes would also be informative since only learning and memory were examined. Other behavioral abnormalities, such as increased anxiety[3] and hyperactivity,[4,5] have been previously reported in this model. It is noteworthy that the authors examined the effect of DREADD-mediated neuromodulation on seizure and behavioral phenotypes 2 months after KA administration. It is possible that more robust effects might have been achieved with earlier intervention.

Like DREADDs, optogenetics is another recently developed technique that has been used to modulate neuronal activity in a cell-specific manner. By pairing with "on-demand" technology, Krook-Magnuson and colleagues used an optogenetic approach to detect and terminate spontaneous seizures in the intrahippocampal KA TLE model.[6] Similar to the findings of the current study, optogenetic inhibition of hippocampal pyramidal neurons or activation of PV neurons effectively suppressed spontaneous seizures. Seizure suppression in the intrahippocampal KA TLE model was also achieved with optogenetic modulation of cerebellar PV neurons,[7] suggesting that neurons in other brain regions may also provide viable targets. Accordingly, the authors of the current study found that DREADD activation of PV neurons in the motor cortex was also sufficient to increase the latency to status epilepticus and reduce the duration of the first GTCS in the acute intrahippocampal KA model.

Both DREADDs and optogenetics have proven to be powerful research tools and have led to the identification of specific cell types and brain regions that can be modulated to achieve increased seizure resistance. However, both approaches currently require the coadministration of viral vectors or additional genetic manipulations, thus posing challenges to clinical use. As such, the direct therapeutic potential of these techniques is unclear, and further advances will be necessary to facilitate clinical applications.

By Jennifer C. Wong and Andrew Escayg

References

1. Falconer MA, Serafetinides EA, Corsellis JA. Etiology and pathogenesis of temporal lobe epilepsy. *Arch Neurol*. 1964;10:233-248.
2. McKhann GM II, Wenzel HJ, Robbins CA, Sosunov AA, Schwartzkroin PA. Mouse strain differences in kainic acid sensitivity, seizure behavior, mortality, and hippocampal pathology. *Neuroscience*. 2003;122(2):551-561.
3. O'Loughlin EK, Pakan JM, McDermott KW, Yilmazer-Hanke D. Expression of neuropeptide Y1 receptors in the amygdala and hippocampus and anxiety-like behavior associated with Ammon's horn sclerosis following intrahippocampal kainate injection in C57BL/6 J mice. *Epilepsy Behav*. 2014;37:175-183.
4. Wong JC, Makinson CD, Lamar T, et al. Selective targeting of Scn8a prevents seizure development in a mouse model of mesial temporal lobe epilepsy. *Sci Rep*. 2018;8(1):126.
5. Groticke I, Hoffmann K, Loscher W. Behavioral alterations in a mouse model of temporal lobe epilepsy induced by intrahippocampal injection of kainate. *Exp Neurol*. 2008;213(1):71-83.
6. Krook-Magnuson E, Armstrong C, Oijala M, Soltesz I. On-demand optogenetic control of spontaneous seizures in temporal lobe epilepsy. *Nat Commun*. 2013;4:1376.
7. Krook-Magnuson E, Szabo GG, Armstrong C, Oijala M, Soltesz I. Cerebellar directed optogenetic intervention inhibits spontaneous hippocampal seizures in a mouse model of temporal lobe epilepsy. *eNeuro*. 2014;1(1).