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A Call to Change Course for Established Epilepsy

Disease-Modifying Effects of Sodium Selenate in a Model of Drug-Resistant, Temporal Lobe Epilepsy

Casillas-Espinosa PM, Anderson A, Harutyunyan A, Li C, Lee J, Braine EL, Brady RD, Sun M, Huang C, Barlow CK, Shah AD, Schittenhelm RB, Mychasiuk R, Jones NC, Shultz SR, O'Brien, TJ. *eLife*. 2023;12: e78877. doi:10.7554/eLife.78877

There are no pharmacological disease-modifying treatments that have an enduring effect to mitigate the seizures and comorbidities associated with established chronic temporal lobe epilepsy (TLE). Sodium selenate has been reported to have anti-epileptogenic effects if given before TLE onset. However, the majority of TLE patients already have established epilepsy when they present to the clinic. This study aimed to evaluate for disease modifying effects of sodium selenate treatment in the chronically epileptic rat post-status epilepticus (SE) model of drug-resistant TLE. Wistar rats underwent kainic acid-induced SE or sham. Ten-weeks post-SE, rats were randomly assigned to receive either sodium selenate, levetiracetam, or vehicle subcutaneous infusions continuously for 4 weeks. To evaluate the effects of the treatments, one week of continuous video-EEG was acquired before, during, and 4, 8 weeks post-treatment, followed by behavioral tests. Targeted and untargeted proteomics and metabolomics were performed on post-mortem brain tissue to identify potential pathways associated with modified disease outcomes. Telomere length has emerged as a potential biomarker of chronic brain conditions was investigated as a novel surrogate marker of epilepsy disease severity in our current study. The results showed that sodium selenate treatment was associated with mitigation of measures of disease severity at 8 weeks post-treatment cessation; reducing the number of spontaneous seizures ($p < 0.05$), cognitive dysfunction ($p < 0.05$ in both novel object placement and recognition tasks), and sensorimotor deficits ($p < 0.01$). Moreover, in the brain post-mortem selenate treatment was associated with increased protein phosphatase 2A (PP2A) expression, reduced hyperphosphorylated tau, and reversed telomere length shortening ($p < 0.05$). Network medicine integration of multi-omics/ pre-clinical outcomes identified protein-metabolite modules positively correlated with the TLE phenotype. Our results provide evidence that treatment with sodium selenate results in a sustained disease-modifying effect in chronically epileptic rats in the post-KA SE model of TLE, including improved comorbid learning and memory deficits.

Commentary

Temporal lobe epilepsy (TLE) is the most common form of epilepsy with focal seizures and is frequently resistant to anti-seizure medication (ASM). Overall, the prognosis for people with drug-resistant TLE includes a higher risk for memory and mood problems, lower quality of life, and an increased risk for sudden unexpected death in epilepsy. In addition to ASM, current options for refractory epilepsy patients include neurosurgical brain resection, responsive neurostimulation, and vagal nerve stimulation.[1] Surgical resection of the epileptogenic zone provides the best chance for long-term seizure freedom and may have disease-modifying effects but is not applicable to many patients and can have significant adverse effects. The triggers for the onset of TLE are multifaceted and include traumatic brain injury and infections such as encephalitis or meningitis that result in gliosis of the hippocampus in the temporal lobe. Blood vessel malformations in the brain, stroke, brain tumors, and several genetic syndromes can also result in TLE. Since a small subset of patients with these known causative factors go on to develop TLE, targeting the "latent-period"[2] with a preventative or disease-modifying therapy would require the ability to accurately predict the most high-risk patients for TLE. However, such predictive biomarkers for TLE have not yet been established. Furthermore, the prediction for which of the TLE patients will likely become refractory is currently unknown. The clinical unmet need for TLE in general and drug-resistant TLE specifically is the lack of post-diagnosis interventions that change the course of the disease for both severity and progression. All current drugs for epilepsy help curb seizures symptomatically as ASMs rather than disease-modifying therapies.

In preclinical models, several potential disease-modifying treatments have been shown to have preventative effects when initiated prior to the onset of epilepsy. For example, sodium selenate, a protein phosphatase 2A (PP2A) activator, prevents epileptogenesis when initiated before the onset of epilepsy in chronic acquired epilepsy models.[3] Protein phosphatase 2A activity is downregulated in these models. However, the majority of TLE patients already have established epilepsy when they present to the clinic and have no known preexisting risk factors, thus limiting the utility of a preventative approach. Furthermore, drugs that reduce seizures in established epilepsy are effective only during the period of drug administration, but lose effect after withdrawal of the drug. In this study,[4] the authors evaluated sodium selenate chronic dosing as a disease-modifying treatment for established epilepsy both during and post-withdrawal of treatment. They quantified its ability to mitigate refractory seizures and the associated comorbidities using a rodent model of drug-resistant TLE with established epilepsy. This work was an extension of previous studies done by the same group[3] investigating sodium selenate's role in reducing tau's hyperphosphorylation in animal models of kindling, post-status epilepticus, and post-traumatic epilepsy. The pathogenic role of tau protein in the development of TLE in the kainic acid (KA) models with chronic spontaneous seizures and neuronal loss that mirrors the neuropathology of human mesial TLE (mTLE) supports its role in human mTLE pathogenesis.[5] Here, sodium selenate treatment was administered continuously for 4 weeks in the chronically epileptic or sham control rats randomly assigned to receive either sodium selenate, levetiracetam, or vehicle subcutaneous infusions. One week of continuous video-EEG was acquired before, during, and 4, 8 weeks post-treatment. Targeted and untargeted proteomics and metabolomics, and telomere length as a potential biomarker of chronic brain conditions, were investigated as surrogate markers of epilepsy disease severity on postmortem brain tissue. Sodium selenate treatment was associated with mitigation of measures of disease severity at 8 weeks post-treatment cessation; reducing the number of spontaneous seizures, cognitive dysfunction assessed in both novel object placement and recognition tasks, and sensorimotor deficits. The persistence of beneficial effects 8 weeks after treatment withdrawal is consistent with a disease-modifying effect, which is a novel finding compared with previous preclinical studies of drugs in epilepsy models. Sodium selenate treatment was also associated with increased PP2A expression, reduced hyperphosphorylated tau, and reversed telomere length shortening indicating a reversal of surrogate markers of disease severity. However, as these biochemical markers were only correlative, a limitation of this study was the lack of evidence for a causative disease-modifying mechanism of sodium selenate. Nevertheless, the excitement around sodium selenate for drug-resistant epilepsy is bolstered by the recent funding for clinical trials for the same[6] and reports of safety and tolerability with chronic treatment in patients with Alzheimer's disease (AD)[7] who showed a slowing of disease progression for cognitive measures though the study was not well controlled.

Interesting insights are to be had from the current study. Like levetiracetam, sodium selenate was unable to alleviate TLE seizures over the 4-week period when the continuous treatment was ongoing. By default and necessity, current interventional clinical trials for drug-resistant epilepsy have inclusion criteria that recruit patients who have not achieved seizure control previously from at least 3 ASMs in single or combination therapy. ASMs are categorized as failed medication if the patient has been on it for at least 3 months and is still refractory.[8] This means any novel therapeutic is added on in each such patient without withdrawal of the ongoing combinatorial therapy even if they are still refractory when recruited into new interventional clinical trials. This real-life caveat for clinical trials is currently unavoidable for successful recruitment into trials for drug-resistant epilepsy. Therefore, a fourth treatment group with TLE rats with a combination therapy of levetiracetam and sodium selenate would have been a desirable control and translationally relevant paradigm. Another interesting insight from the study is that the significant effects of sodium selenate were reported during the 8-week wash-out period during which the vehicle-treated group seems to have had a further progression/aggravation of their ongoing epilepsy. Therefore, the behavioral studies conducted at that same 8-week period have the added caveat that the performance on these tests would represent differences in seizing versus nonseizing groups of rats and the associated postictal effects of frequent Racine grade 4 to 5 seizures still occurring in the vehicle-treated group. A correlation between total seizure burdens at 8 weeks post-treatment and associated behavioral outcomes for all rats in the study irrespective of treatment group would help discern the effects of ongoing seizure events versus biochemical pathogenic surrogate markers of disease progression on improved performance in the sodium selenate-treated group of rats. This additionally is of great translational value since sodium selenate efficacy on seizure burdens was driven by a reduction in the frequency and duration of seizure events, not their severity as assessed by the Racine scale at 8 weeks post-treatment.

The stage of early epileptogenesis, when spontaneous recurrent seizures are not yet evident in patients, is an attractive but elusive window for interventional treatments when the goal is preventing or significantly subduing epilepsy before it occurs. Many epilepsy experts have debated this topic on multiple forums allowing researchers insights into targeting 2 possible therapeutic windows.[9] An acute but brief window for which time of insult leading to epilepsy must be known and a second, delayed process of secondary epileptogenesis that results both in the progression and emergence of refractoriness in epilepsy patients. The secondary epileptogenesis window does not require either the knowledge of the insult that resulted in epilepsy or the challenging task of estimating which patients are at the highest risk of developing epilepsy and opens a longer window for intervention after the onset of epilepsy. Plenty of evidence exists through preclinical modeling that interfering with some common processes underlying multiple etiologies like trkB/PLCγ1 inhibitor, mTOR1 pathways, JAK-STAT3,

IL-1R/TLR4, and other inflammatory pathways could be the targets of a combinatorial strategy in changing the course of or curing epilepsy.[10] The call to change the disease progression in epilepsy patients such that therapeutics not only subdue ongoing seizures but also "cure" epilepsy is stronger than ever before. However, a clinically effective epilepsy cure remains elusive. Results from the clinical trial being initiated by the authors of the current preclinical study will be eagerly awaited and provide hope[11] to the epilepsy research community not only for drug-resistant epilepsy but also other chronic neurological disorders associated with seizures.

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Declaration of Conflicting Interests

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