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VALPROIC ACID IMPROVES NERVE INJURY IN YOUNG RATS WITH EPILEPSY BY REGULATING STXBP1

S. Guihai[1,#], W. Xiaolin[2,#], D. Yufei[3], W. Youjia[1], L. Haiying[1,*] and Z. Yuqin[1,*]

[1]Department of Pediatrics, Affiliated Hospital of Nantong University 226001, China
[2]Department of Pediatrics, Affiliated Rudong Hospital of Xinglin College, Nantong University, 226400, China.
[3]Nantong University 226001, China
#: The equal contribution in this research
[*]Correspond author's email: zhengyuqin0408@163.com; zl070619@126.com

ABSTRACT

This study aims to discuss how valproic acid improves nerve injury in young rats with epilepsy by regulating STXBP1. It also seeks to identify risk proteins for epilepsy through bioinformatics analysis. 30 young rats were divided into three groups, namely Normal, Model, and VA. Each group contained 10 rats. Epilepsy models were established in all groups except the control group. After modeling, the valproic acid group was orally administered 1 mg/kg of valproic acid. Cognitive function was assessed using the water maze experiment, while hippocampal tissue morphology was observed through Nissl staining. The neuronal apoptosis rate in hippocampal tissue was detected using the TUNEL method. Immunohistochemical staining was performed to detect the NMDARl-positive cell rate in hippocampal tissue. Meanwhile, immunoblotting was used to measure the expression levels of STXBP1 and SLC2A1p proteins in hippocampal tissue. Bioinformatics analysis identified STXBP1 as a risk protein for epilepsy. Compared to the control group, the platform search time, neuronal apoptosis rate, NMDARl-positive cell rate, number of crossing platforms, and proportion of original platform search time in the model group of young mice decreased on days 1, 2, 3, and 4 ($P \leq 0.001$). In addition, the levels of STXBP1 and SLC2A1 proteins decreased ($P \leq 0.001$). In comparison to the model group, platform search time, neuronal apoptosis rate, and NMDAR1-positive cell rate in the valproic acid group of young mice decreased on days 1, 2, 3, and 4. However, the number of crossing platforms and the proportion of original platform search time increased ($P \leq 0.001$). In addition, the levels of STXBP1 and SLC2A1 proteins significantly increased ($P \leq 0.001$). In conclusion, valproic acid can significantly improve cognitive function, reduce the expression of NMDAR1, and inhibit neuronal apoptosis in juvenile epileptic rats. The mechanism might be related to its regulation of STXBP1 expression.

Key words: Epilepsy; Valproic acid; Cognitive function; STXBP1

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INTRODUCTION

Epilepsy is a sudden, transient, and recurrent disease characterized by brain dysfunction caused by the abnormal discharge of brain neurons. It is the most common chronic neurological condition in children, with an incidence rate of up to 5% (Singh *et al*., 2020). Although the majority of children with epilepsy do not develop intellectual disabilities, some may experience temporary or permanent cognitive impairments. Clinical studies have shown that epilepsy is often complicated by attention deficit hyperactivity disorder (ADHD) in children. This comorbidity significantly impacts both their physical and mental health and remains a key concern for neurologists (Fotopoulos *et al*., 2024). Synaptic vesicles play a crucial role in neurotransmitter release and neural electrical activities. Recent studies have shown that synaptic vesicle transport is closely related to the pathogenesis of epilepsy. In addition, some epilepsy syndromes have been associated with mutations in the genes encoding synaptic vesicle proteins. The STXBP1 gene, located on chromosome 9, encodes syntaxin-binding protein-1 (STXBP1), an important protein in synaptic vesicular transport and neurotransmitter release. It also plays a significant role in the formation of integral membrane protein receptor complexes and synaptic vesicle fusion (Ma *et al*., 2015). In 2008, Saitsu *et al*. (Saitsu *et al*., 2008) first identified mutations in the STXBP1 gene in children with Ohtahara syndrome. With the widespread use of second-generation sequencing technology, an increasing number of cases of STXBP1-related disorders have been reported (Syrbe *et al*., 2015; Romaniello *et al*., 2015). In this study, proteins that interact with STXBP1 in the development of epilepsy

were initially inferred through epilepsy data analysis. It was then explored whether valproic acid (VA) imparts its therapeutic effects on epilepsy by regulating STXBP1 in animal experiments, with the aim of providing a basis for the clinical treatment of epilepsy.

MATERIALS AND METHODS

Protein-protein interaction (PPI) network analysis: Epilepsy gene analysis data were used to construct a PPI network for epilepsy-related targets. The minimum interaction score between targets was 0.4. The results were saved in TSV format and imported into Cytoscape 3.8.2 software to build the PPI network.

GO enrichment analysis: Improving core targets into the DAVID database (https://david.ncifcrf.gov) (Sherman *et al*., 2022) for GO analysis (scoring thresholds is P value is less than 0.001 and the top 30 genes) using R-4.2.3 software. GO enrichment analysis was performed and the GO enrichment chart was plotted

Experimental animals: Thirty 0-day-old Sprague-Dawley (SD) rats, weighing 20-30 g, were obtained from Hunan SJA Laboratory Animal Co., Ltd., with an animal production license number SCXK (Xiang) 2021-0010. The rats were bred in the Animal Laboratory of the Affiliated University of our hospital. The breeding environment was maintained at a humidity of 55%-60% and a temperature of 25℃ under a simulated light-dark cycle. They were fed with a sterile diet for 14 days, with 5 rats per cage. The cages were regularly cleaned and disinfected. The rats were used in relevant experiments after one week of adaptive feeding.

Reagents and instruments: VA (Hunan Xiangzhong Pharmaceutical Co., Ltd., China); lithium chloride, pilocarpine, and scopolamine (Sigma, USA); 0.9% saline and 4% tetraformaldehyde (Merck Life Science Technology (Nantong) Co., Ltd., China); phosphate buffered saline (PBS) (Condice Chemical (Hubei) Co., Ltd., China]; Nissl staining kit (Nanjing Jiancheng Bioengineering Institute, China); TUNLE kit (Abcam, China); mouse anti-human STXBP1 and SLC2A1 antibodies (Chinese Abcam, China); immunohistochemical kit, electrochemiluminescent (ECL) solution, enzyme-linked immunoassay kit, and BCA protein quantitative kit (Shanghai Enzyme-Linked Biotechnology Co., Ltd., China); Forma 900 series ultra-low freezer (Thermo Scientific, USA); centrifuge 5424R high-speed refrigerated centrifuge (Beckman, USA); and protein electrophoresis apparatus (Beijing Liuyi Instrument Factory, China).

Animal grouping and modeling: 30 young rats were randomly divided into three groups, namely Normal, Model, and VA. Each group contained 10 rats. Epilepsy rat models were established in the Model and VA groups. Briefly, lithium chloride (127 mg/rat) was intraperitoneally injected in the young rats, followed by scopolamine (1 mg/kg) 20 hours later. 30 minutes after administering scopolamine, pilocarpine (30 mg/kg) was intraperitoneally injected until status epilepticus occurred. If status epilepticus did not occur within 30 minutes, another 30 mg/kg of pilocarpine was administered. Successful modeling was assessed using the Racine scale, with the appearance of grade 4 and 5 symptoms indicating success. After 90 minutes of epilepsy, 10 mg/kg of diazepam was intraperitoneally administered to terminate the status epilepticus. The rats in the VA group were orally administered VA at a dose of 1 mg/kg for 7 consecutive days.

Water maze test: The water maze consisted of a circular tank with a diameter of 1.3 meters and a height of 0.5 meters in middle of tank. The tank was made of transparent glass. The water depth was 0.3 meters, and room temperature water was used. The platform was not placed in the tank for 1 day prior to the test. This allowed the young rats to swim freely for 120 seconds and familiarize themselves with the surrounding environment for 5 days before the test began. In the place navigation experiment, the platform was placed in the tank. In addition, the young rats were immersed in the water, facing the pool wall in the northeast, northwest, southwest, and southeast directions on the first 4 days. The time taken for the rats to find the platform was recorded. If they did not find the platform within 120 seconds, the time was recorded as 120 seconds. In the space exploration experiment, the platform was removed from the tank. In addition, the young rats were immersed in the water with their heads facing the northeast pool wall. The number of platform crossovers within 120 seconds and the time spent searching for the platform were recorded.

Nissl staining: After the water maze test, 5 rats were randomly selected from each group and euthanized after being anesthetized with an intraperitoneal injection of 1% pentobarbital sodium. Fresh hippocampal tissue was collected for Nissl staining and TUNEL assay. Briefly, the hippocampal tissue was fixed in neutral formalin solution for 12 hours, dehydrated in a gradient of ethanol, embedded in paraffin, and sliced into 4 μm-thick sections. The sections were dewaxed with formaldehyde and rehydrated with water. They were then stained in Cresyl violet stain solution at 56℃ in an incubator for 60 minutes, rinsed with deionized water, and subjected to Nissl differentiation for 1-3 minutes until the background was nearly colorless. After quick dehydration and xylene clearing, the sections were mounted with neutral resin.

TUNEL assay: Sections of hippocampal tissue were sliced, embedded in paraffin, and dehydrated with

alcohol. After washing the sections with PBS 3 times, each for 5 minutes, a 20 µg/ml protease K solution was added and incubated at 23℃ for 30 minutes. The sections were washed again with PBS and incubated with a 3% H_2O_2 solution for 5 minutes. After another PBS wash, the sections were wiped and stained with 50 µl of the LTUNEL reaction mixture, followed by staining with 4',6-diamino-2-phenylpyridine (DAPI) at 37°C for 60 minutes. The sections were washed with PBS again, and the number of apoptotic cells was counted using an optical microscope.

Determination of STXBP1 protein expression in the hippocampus by immunohistochemical staining

The remaining rats in each group were sacrificed. In addition, the hippocampus was removed for immunohistochemical staining and Western blot analysis. Briefly, paraffin-embedded hippocampal tissue sections were prepared, dewaxed, dehydrated, and washed with PBS 3 times at 5-minute intervals. The sections were blocked with goat serum at 37°C for 60 minutes, followed by the addition of an anti-STXBP1 antibody (1:500), which was incubated at 4°C for 24 hours. The secondary antibody, HRP-conjugated goat anti-rabbit IgG (1:1000), was added and incubated for 30 minutes. After washing the sections with PBS, 50 µl of streptavidin-biotin complex was added, and color was developed using diaminobenzidine. The sections were then washed, the color reaction was terminated, and the slides were cleared and mounted. Cells with brown granules in the nucleus were considered positive. The integral optical density, or the average optical density of 5 fields of view (100x), was calculated using the Image-Pro Plus 6.0 image system for each section.

Western blot: The hippocampal tissue was washed with PBS and chopped. 1 mL of cell lysis buffer was added, and the mixture was then centrifuged at 1000 rpm at 4°C for 5 minutes. The supernatant was collected, and protein concentration was determined using the BCA method. Protein samples (20 µg each) were loaded into each well and separated by SDS-PAGE, then transferred to a polyvinylidene fluoride (PVDF) membrane using a pre-cooled transfer buffer, prepared and stored at 4°C. The membrane was blocked with skim milk for 1 hour and then incubated overnight at 4°C with anti-STXBP1 (1:150) and SLC2A1 (1:200) antibodies. After washing the tissue with TTBS 3 times for 10 minutes each, the secondary antibody, goat anti-rabbit IgG (1:2500), was added. Protein levels were then analyzed using the JY-Clear ECL chemiluminescence imaging system.

Statistical analysis: Data were analyzed using GraphPad Prism 8 software. The measurement data for each group followed a normal distribution and were presented as mean ± SD. Analysis of variance was used for comparisons among groups. In addition, the LSD t-test was applied for pairwise comparisons between groups. Differences with a p-value of ≤0.05 were considered statistically significant.

RESULTS

PPI network analysis: A PPI network diagram of epilepsy targets was constructed using the STRING platform, which included 63 nodes and 785 edges, as shown in Fig. 1. STXBP1 was a key node and played a crucial role in the pathogenesis of epilepsy.

GO enrichment analysis: GO enrichment analysis was conducted using the David platform. GO, which stands for Gene Ontology, was used to annotate the molecular function, biological process, and cellular component of gene products. A total of 52 GO terms were identified by screening the enrichment terms with an adjusted P-value < 0.05. The 30 pathways with the highest adjusted P-values are shown in Fig. 2. The results indicate that STXBP1 plays a significant role in the pathogenesis of epilepsy.

Time spent searching the platform, the number of platform crossovers, and the percentage of time spent searching the platform in each group of young rats

Time spent searching the platform was increased, while the number of platform crossovers and the percentage of time spent searching the platform were decreased on Days 1, 2, 3, and 4 in young rats of the Model group compared to those of the Normal group (all P<0.001). In addition, time spent searching the platform decreased, while the number of platform crossovers and the percentage of time spent searching the platform were increased on Days 1, 2, 3, and 4 in young rats of the VA group compared to those of the Model group (all P<0.001). These results are shown in Table 1.

Morphology of the hippocampus in each group of young rats as observed by Nissl staining: Neurons in the hippocampus of rats in the Normal group were regularly arranged with an intact structure and abundant Nissl bodies. In the Model group, neuronal structure was severely damaged, with disordered neuron morphology, a decreased number of neurons, and a disappearance of Nissl bodies. In the VA group, neuronal injury improved, and the number of neurons and Nissl bodies increased compared to the Model group (Fig. 3).

Apoptosis of nerve cells in the hippocampus by TUNEL assay: The number of apoptotic nerve cells in the hippocampus of animals in the Model group significantly increased compared to the Normal group (P≤0.001, Fig. 4). However, the number of apoptotic nerve cells in the hippocampus of rats in the VA group was significantly reduced compared to the Model group (P ≤ 0.001, Fig. 4).

NMDAR1 levels in the hippocampus by immunohistochemical staining: The IOD value of NMDAR1 in the Model group was significantly higher compared to the Normal group (P≤0.001, Fig. 5). In addition, the IOD value of STXBP1 in the VA group was significantly lower than in the Model group (P≤0.001, Fig. 5).

Expression levels of STXBP1 and SLC2A1 proteins in the hippocampus as determined by Western blot.

The levels of STXBP1 and SLC2A1 proteins in the Model group were significantly lower compared to the Normal group (P ≤ 0.001, Fig. 6). In contrast, the levels of STXBP1 and SLC2A1 proteins in the VA group were significantly higher compared to the Model group (P≤0.001, Fig. 6).

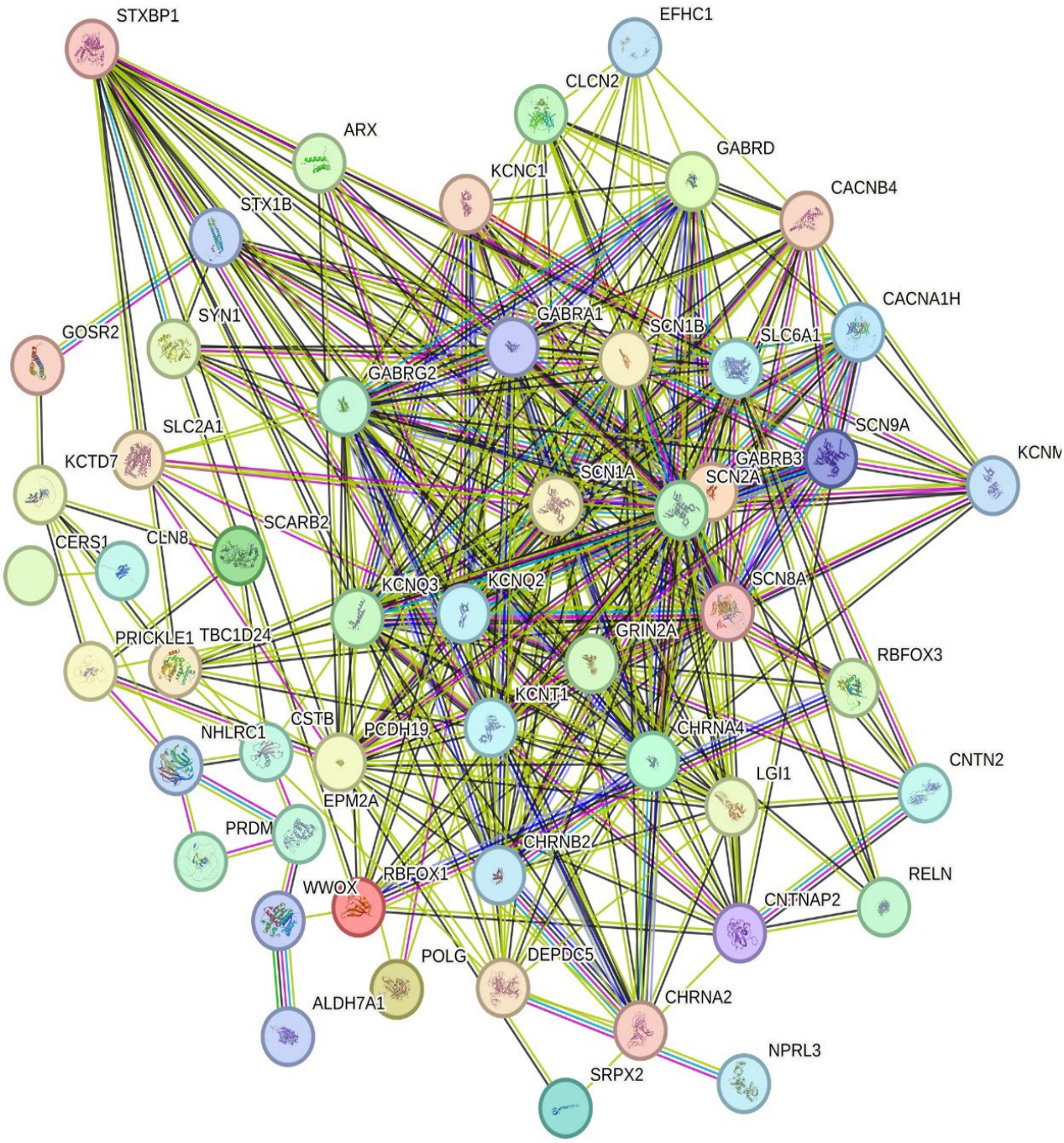


Figure 1. PPI network

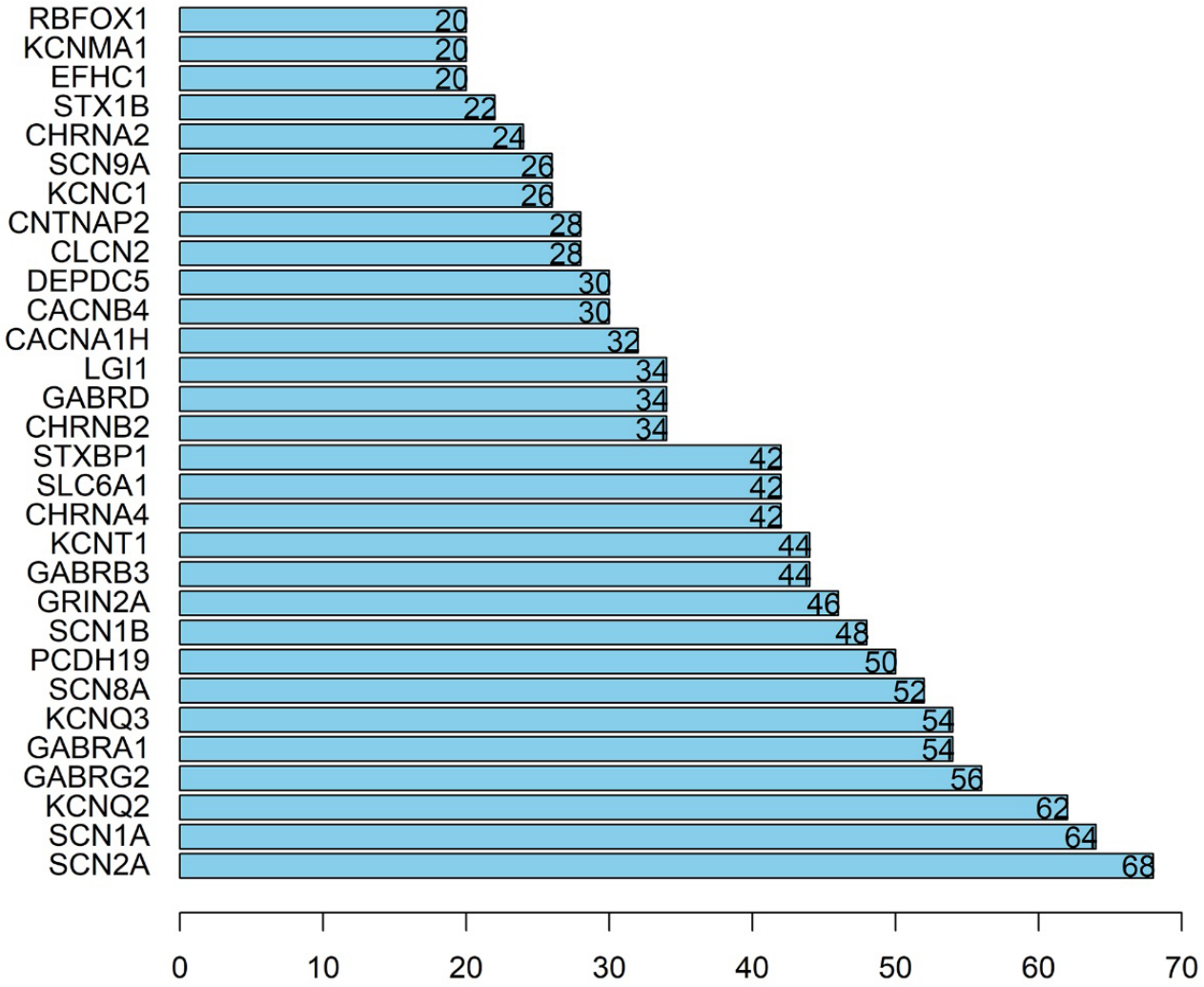


Figure 2. GO enrichment

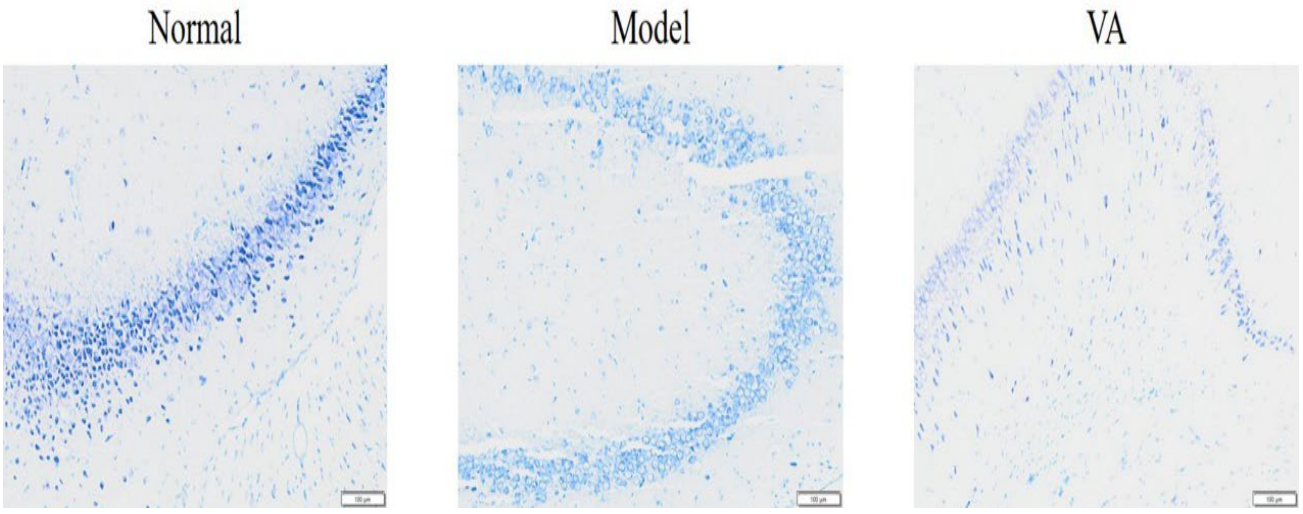
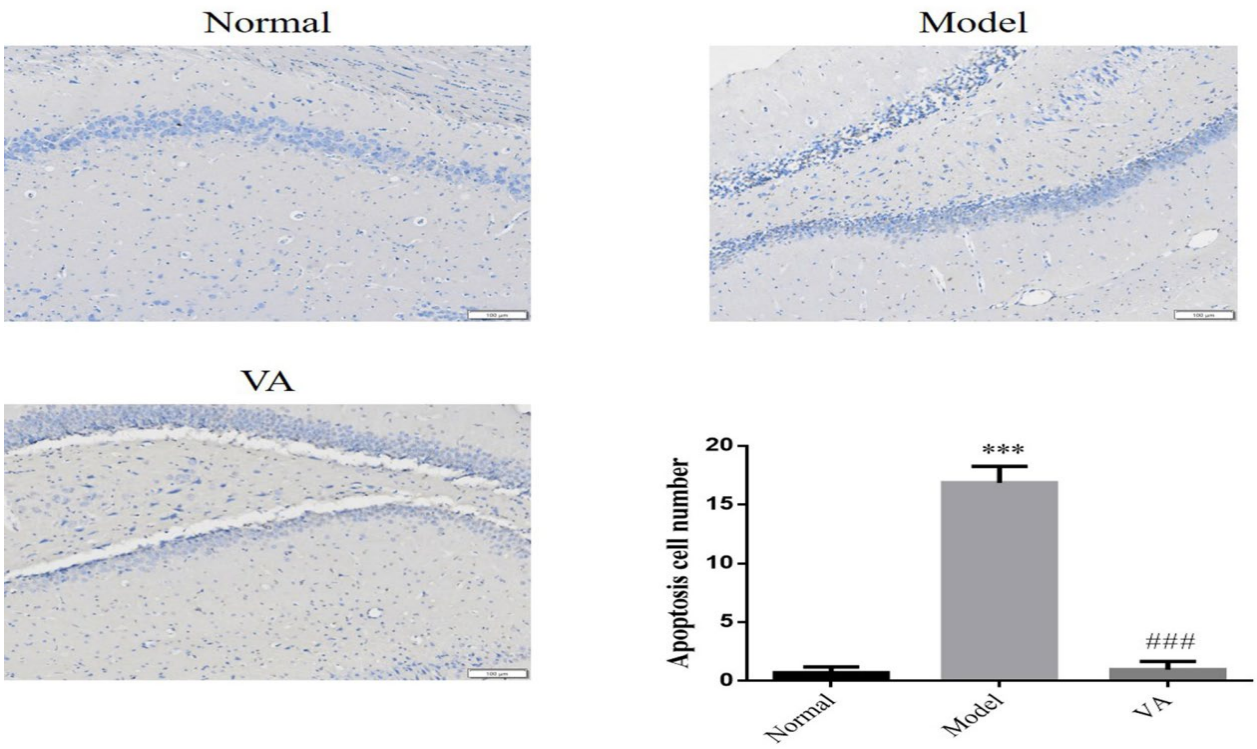
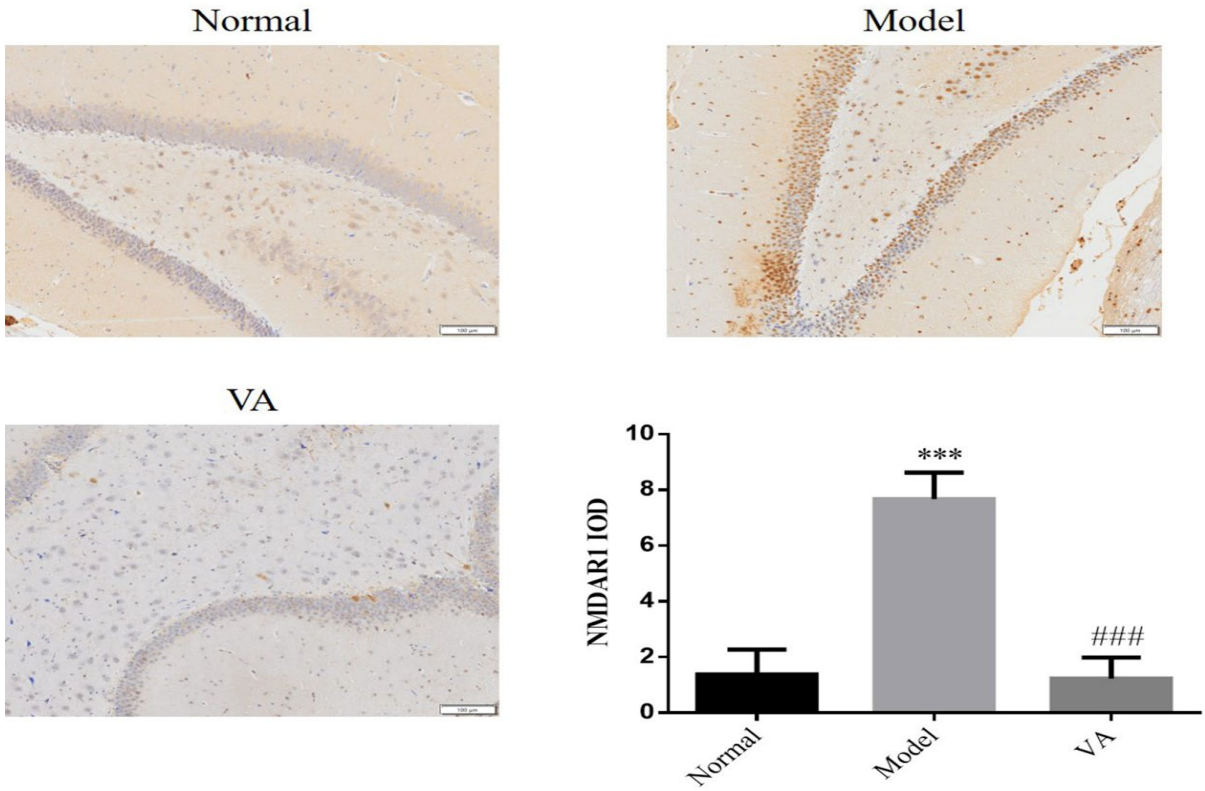


Figure 3. The morphology of the hippocampus in each group of young rats observed by Nissl staining (100×)



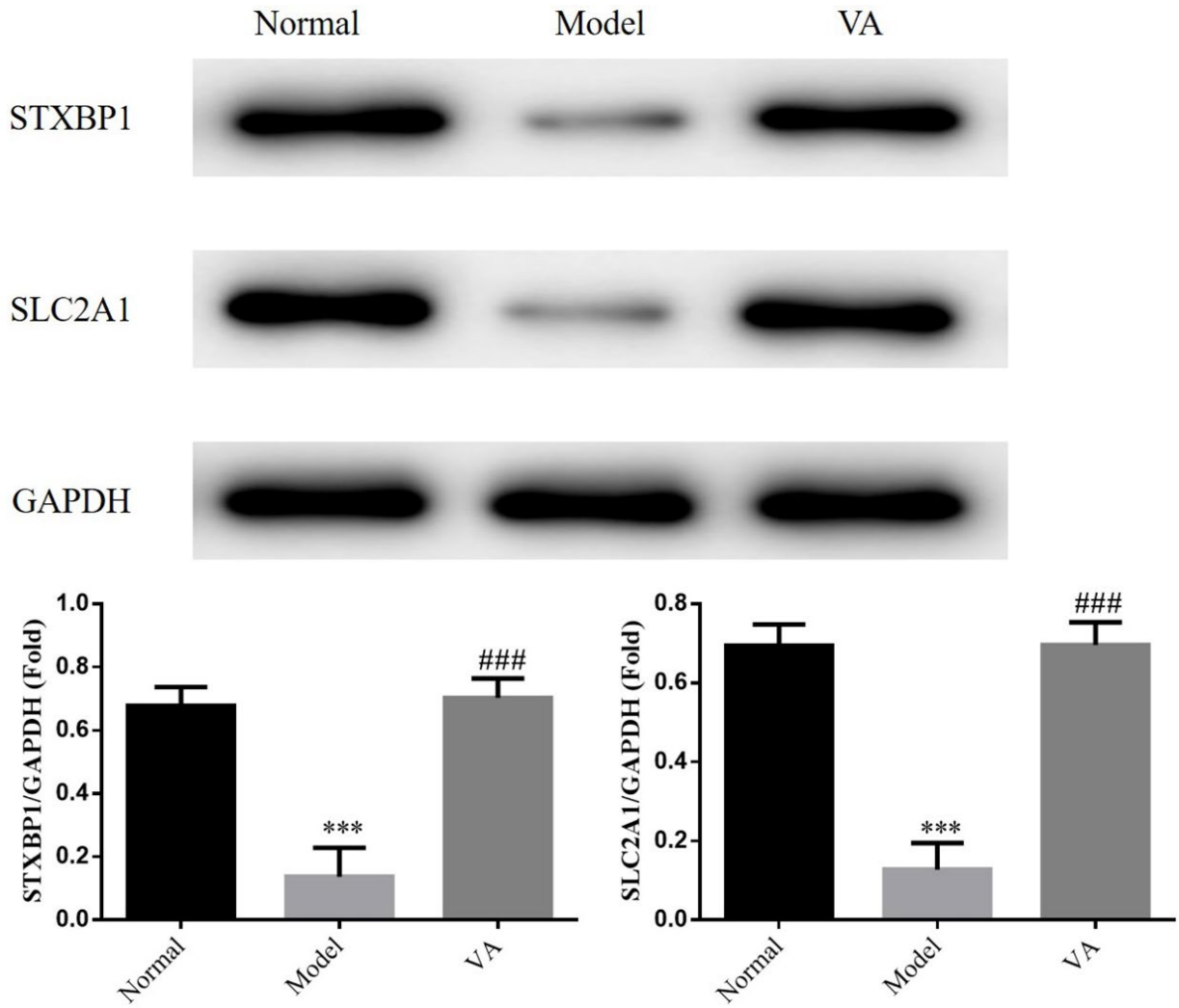
***: P＜0.001, vs. Normal group; ###: P＜0.001, vs. Model group

Figure 4. Apoptosis of nerve cells in the hippocampus by TUNEL assay (100×)



***: P＜0.001, vs. Normal group; ###: P＜0.001, vs. Model group

Figure 5. Expression of NMDAR1 in the hippocampus by immunohistochemical staining (100×)



***: P＜0.001, vs. Normal group; ###: P＜0.001, vs. Model group

Figure 6. Expression levels of STXBP1 and SLC2A1 proteins in the hippocampus determined by Western blot

Table 1. The search platform time, number of times the mice cross the platform, and the proportion of search time on the original platform for each group of young mice (Mean±SD).

Group	n	Search platform time (s)				Crossing platforms times	The proportion of search time on the original platform (%)
		1d	2d	3d	4d		
Normal	9	27.21±3.59	17.43±3.56	11.19±2.96	7.04±1.35	15.64±3.84	58.68±6.70
Model	9	48.51±5.19***	42.74±5.49***	36.46±4.95***	22.53±4.16***	6.35±1.21***	23.06±2.12***
VA	9	36.75±4.66###	32.19±4.44###	30.15±3.59###	16.54±3.05###	10.54±1.65###	37.49±5.06###

***: P＜0.001, compared with Normal; ###: P＜0.001, compared with Model group

DISCUSSION

Epilepsy is a sudden and recurrent brain dysfunction caused by the abnormal discharge of brain neurons. It is a chronic neurological disorder with a high incidence rate in children. This condition leads to serious damage to cognitive function and severely impacts both the physical and mental health of children. Epileptic patients often experience varying degrees of cognitive dysfunction, with clinical symptoms mainly manifesting as impaired concentration, language difficulties, and reaction time disorders. These issues can seriously affect

their social life and, in some cases, may lead to suicide or self-harm behaviors (Steriade *et al*., 2021). Drug therapy is currently the main treatment for epilepsy. VA is a first-line drug commonly used in clinical practice due to its favorable safety profile and lack of adverse effects on consciousness.

In this study, an animal model of epilepsy was established through intraperitoneal injection of lithium chloride and pilocarpine. This model was characterized by spontaneous recurrent seizure attacks with clinical and pathological features similar to those of human epilepsy (Wang *et al*., 2024). Seizures can cause damage to cognitive function to varying degrees. The main mechanisms involve increased glial cell proliferation after epileptic attacks, the kindling effect induced by repeated firing of brain neurons, and imbalanced neurotransmitter levels in the brain after neurosynaptic reorganization. This imbalance results in high levels of γ-aminobutyric acid and other neurotransmitters, which induce oxidative stress response, leading to neuronal degeneration, necrosis, and ultimately cognitive impairment (MacLean *et al*., 2024). The results of this study indicate that the time spent searching for the platform was reduced, while the number of platform crossovers and the percentage of time spent searching for the platform were increased in young rats of the VA group compared to those of the Model group. These findings indicate that VA can improve spatial exploration, learning, memory, and cognitive function. VA is highly effective in the treatment of epilepsy by enhancing the function of inhibitory neurotransmitters, which helps reduce the abnormal discharge of brain neurons. In addition, reduced levels of neurotransmitters can block the transportation of potassium and sodium ions, decreasing cellular excitability. As a result, VA not only fights off epilepsy but also enhances cognitive function (Rostami *et al*., 2024). Studies have shown that VA significantly improves the cognitive function of epileptic patients with minimal adverse effects (Ancora *et al*., 2024). Animal studies further support these findings, showing that epileptic rats in the VA treatment group exhibited shorter escape latencies and increased platform-crossing frequency. These findings suggest that VA significantly enhances the cognitive function of epileptic rats (Xie *et al*., 2023).

This study found that the pathological morphology of hippocampal tissue improved. In addition, the apoptosis rate of nerve cells decreased in the VA group compared to the Model group. This indicates that VA can protect the brains of young epileptic rats. Nissl staining revealed loss, degeneration, and necrosis of hippocampal neurons, with fewer Nissl bodies in young rats of the Model group. These changes could not support neural activity, leading to a significant decrease in neuronal survival. However, the degree of neuronal necrosis in the hippocampal tissue improved after oral administration of VA. This suggests that VA can significantly reduce neuronal death and protect hippocampal neurons. VA can inhibit neuronal apoptosis by activating multiple signaling pathways. It mainly promotes neuronal survival by reducing the expression levels of key factors in the apoptosis cascade reaction, such as Bax and caspase-3. The findings of this study show that NMDARl protein levels were high in the Model group of young rats. However, these levels decreased after oral administration of VA, suggesting that VA inhibited the expression of NMDARl. Glutamate is an important excitatory neurotransmitter in the central nervous system (CNS). Its ionotropic receptor, NMDAR, which is mostly abundant in the hippocampus, is closely related to the pathogenesis of epilepsy. Among the NMDAR subtypes, NMDAR1 plays a primary role. It is also believed that increased expression of NMDAR1 in brain tissue can accelerate excitatory neurotoxicity, leading to neuronal damage. This is a key mechanism in the pathogenesis of epilepsy (Li *et al*., 2021; de Bartolomeis *et al*., 2019). Studies have confirmed that the inhibitory effect of antiepilepserine on the excitatory neurotoxicity of glutamate in neurons of epileptic rats is related to the inhibited expression of NMDAR1 (Li *et al*., 2022). However, the inhibitory effect of VA on NMDAR1 remains unclear, necessitating future studies.

This study found that STXBP1 and SLC2A1 levels were significantly reduced in the Model group. After VA intervention, the levels of STXBP1 and SLC2A1 in the VA group significantly increased compared to the Model group. Current treatments for STXBP1 gene-related epilepsy mainly rely on anti-epileptic drugs to control the onset of the disease. However, it is expected that precise treatments targeting the underlying pathogenesis of the disease will be available in the future (Howden *et al*., 2023). Epileptic seizures can be fully controlled in approximately half of epileptic children treated with anti-epileptic drugs. However, more than half of the affected children require three types of anti-epileptic drugs. Studies have reported that treatments such as VA, levetiracetam, glucocorticoids, and ketogenic diets may be effective in managing epilepsy (Stamberger *et al*., 2017). Levetiracetam regulates synaptic vesicle release by binding to the synaptic vesicle protein SV2A. This binding inhibits calcium channels and intracellular calcium release, which may counteract the epileptogenic effect of STXBP1 mutations. Therefore, levetiracetam is considered a potential preferred drug for STXBP1 gene-related epilepsy (Liu *et al*., 2018; Stepien *et al*., 2021). PPI network analysis in this study indicates that SLC2A1 may be a downstream gene of STXBP1. Related studies have shown that SLC2A1 plays a crucial role in biological activities such as cell proliferation (Park *et al*., 2024; Zhang *et al*., 2024). This study indicates that the STXBP1/SLC2A1 signaling pathway was significantly

inhibited in the Model group, leading to neuronal apoptosis. After treatment with VA, the STXBP1/SLC2A1 signaling pathway was activated to protect brain neurons. However, our present study also had a limit, we just inferred that the correlation between VA administration and NMDAR1 expression has been unclear. In our future research, we will clearly explain this point.

In conclusion, VA can significantly enhance cognitive function, reduce the expression level of NMDAR1, and prevent neuronal apoptosis in young rat models of epilepsy. The underlying mechanism may involve the regulation of STXBP1 expression.

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REFERENCES

Ancora, C., J.D. Ortigoza-Escobar, M.A. Valletti, F. Furia, J.E.K. Nielsen, R.S. Møller and E. Gardella (2024). Emergence of lingual dystonia and strabismus in early-onset SCN8A self-limiting familial infantile epilepsy. Epileptic Disord. 26(2):219-224. doi: 10.1002/epd2.20203.

de Bartolomeis, A., C. Avagliano, L. Vellucci, L. D'Ambrosio, M. Manchia, G. D'Urso , E.F. Buonaguro and F. Iasevoli (2019). Translating preclinical findings in clinically relevant new antipsychotic targets: focus on the glutamatergic postsynaptic density. Implications for treatment resistant schizophrenia. Neurosci. Biobehav. Rev. 107:795-827. doi: 10.1016/j.neubiorev.2019.08.019.

Fotopoulos, N.H., B. Chaumette, G.A. Devenyi, S. Karama, M. Chakravarty, A. Labbe, N. Grizenko, N. Schmitz, W. Fageera and R. Joober (2024). Maternal smoking during pregnancy and cortical structure in children with attention-deficit/hyperactivity disorder. Psychiatry Res. 334:115791. doi: 10.1016/j.psychres.2024.115791.

Howden, C.W., E.E. Cook, E. Swallow, K. Yang, H. Guo, C. Pelletier, R. Jacob and K. Sugano (2023). Real-world outcomes associated with vonoprazan-based versus proton pump inhibitor-based therapy for Helicobacter pylori infection in Japan. Therap Adv Gastroenterol. 16:17562848231168714. doi: 10.1177/17562848231168714.

Liu, S., L. Wang, X.T. Cai, H. Zhou, D. Yu and Z. Wang (2018). Therapeutic benefits of ACTH and levetiracetam in STXBP1 encephalopathy with a de novo mutation: a case report and literature review. Medicine (Baltimore). 97(18): e0663. doi: 10.1097/MD.0000000000010663.

Li, X., Y. Liu, S. Wang, Y. Jiang, A.M. Algradi, Y. Zhou, J. Pan, W. Guan, H. Kuang and B. Yang (2022). The aerial parts of Bupleurum Chinense DC. aromatic oil attenuate kainic acid-induced epilepsy-like behavior and its potential mechanisms. Biomed. Res. Int. 2022 Apr 11; 2022:1234612. doi: 10.1155/2022/1234612.

Li, Y.L., F. Liu, Y.Y. Zhang, J. Lin, C.L. Huang, M. Fu, C. Zhou, C.J. Li and J.F. Shen (2021). NMDAR1-Src-Pannexin1 signal pathway in the trigeminal ganglion contributed to orofacial ectopic pain following inferior alveolar nerve transection. Neuroscience. 466:77-86. doi: 10.1016/j.neuroscience.2021.04.032.

Ma, L., A.A. Rebane, G. Yang, Z. Xi, Y. Kang, Y. Gao and Y. Zhang (2015). Munc18-1-regulated stage-wise SNARE assembly underlying synaptic exocytosis. Elife. 4: e09580. doi: 10.7554/eLife.09580.

MacLean, A., A.S. Chappell, J. Kranzler, A. Evrard, H. Monchal and C. Roucard (20240. BAER-101, a selective potentiator of alpha2- and alpha3-containing GABA(A) receptors, fully suppresses spontaneous cortical spike-wave discharges in Genetic Absence Epilepsy Rats from Strasbourg (GAERS). Drug Dev Res. 85(2):e22160. doi: 10.1002/ddr.22160.

Park, Y., H.J. Lee, D.Y. Sim, J.E. Park, C.H. Ahn, S.Y. Park, Y.C. Lee, B.S. Shim, B. Kim and S.H. Kim (2024). Inhibition of glycolysis and SIRT1/GLUT1 signaling ameliorates the apoptotic effect of Leptosidin in prostate cancer cells. Phytother Res. 38(3):1235-1244. doi: 10.1002/ptr.8115.

Romaniello, R., F. Saettini, E. Panzeri, F. Arrigoni, M.T. Bassi and R. Borgatti (2015). A de-novo STXBP1 gene mutation in a patient showing the Rett syndrome phenotype. Neuroreport.26(5):254-7. doi: 10.1097/WNR.0000000000000337.

Rostami, F., A. Jaafari Suha, M. Janahmadi and N. Hosseinmardi (20240. Aquaporin-4 inhibition attenuates Pentylenetetrazole-induced behavioral seizures and cognitive impairments in kindled rats. Physiol Behav. 278:114521. doi: 10.1016/j.physbeh.2024.114521.

Saitsu, H., M. Kato, T. Mizuguchi, K. Hamada, H. Osaka, J. Tohyama, K. Uruno, S. Kumada, K.

Nishiyama , A. Nishimura, I. Okada, Y. Yoshimura, S. Hirai, T. Kumada, K. Hayasaka, A. Fukuda, K. Ogata and N. Matsumoto (2008). De novo mutations in the gene encoding STXBP1 (MUNC18-1) cause early infantile epileptic encephalopathy. Nat Genet. 40(6):782-8. doi: 10.1038/ng.150.

Sherman, B.T., M. Hao, J. Qiu, X. Jiao, M.W. Baseler, H.C. Lane, T. Imamichi and W. Chang (2022). DAVID: a web server for functional enrichment analysis and functional annotation of gene lists (2021 update). Nucleic Acids Res. 50(W1): W216-W221. doi: 10.1093/nar/gkac194.

Singh, G. and J.W. Sander (2020). The global burden of epilepsy report: implications for low- and middle-income countries. Epilepsy Behav. 105:106949. doi: 10.1016/j.yebeh.2020.106949.

Stamberger, H., S. Weckhuysen and P. De Jonghe (2017). STXBP1 as a therapeutic target for epileptic encephalopathy. Expert Opin Ther Targets. 21(11):1027-1036. doi: 10.1080/14728222.2017.1386175.

Stepien, K.P. and J. Rizo (2021). Synaptotagmin-1-, Munc18-1-, and Munc13-1-dependent liposome fusion with a few neuronal SNAREs. Proc. Natl. Acad. Sci. U S A. 118(4): e2019314118. doi: 10.1073/pnas.2019314118.

Steriade, C., M.J. Titulaer, A. Vezzani, J.W. Sander and R.D. Thijs (2021). The association between systemic autoimmune disorders and epilepsy and its clinical implications. Brain. 144(2):372-390. doi: 10.1093/brain/awaa362.

Syrbe, S., U.B.S. Hedrich, E. Riesch, T. Djémié, S. Müller, R.S. Møller, B. Maher, L. Hernandez-Hernandez, M. Synofzik, H.S. Caglayan, M. Arslan, J.M. Serratosa, M. Nothnagel, P. May, R. Krause, H. Löffler, K. Detert, T. Dorn, H. Vogt, G. Krämer, L. Schöls, P.E. Mullis, T. Linnankivi, A.E. Lehesjoki, K. Sterbova, D.C. Craiu, D. Hoffman-Zacharska, C.M. Korff, Y.G. Weber, M. Steinlin, S. Gallati, A. Bertsche, M.K. Bernhard, A. Merkenschlager, W. Kiess;; M. Gonzalez, S. Züchner, A. Palotie, A. Suls, P. De Jonghe, I. Helbig, S. Biskup, M. Wolff, S. Maljevic, R. Schüle, S.M. Sisodiya, S. Weckhuysen, H. Lerche and J.R. Lemke (2015). De novo loss- or gain-of-function mutations in KCNA2 cause epileptic encephalopathy. Nat. Genet. 47(4):393-399. doi: 10.1093/brain/awaa362.

Wang, H., Y. Zhao, D. Zhang, J. Li, K. Yang, J. Yang and B. Li (2024). Neuroprotective effects of quinpirole on lithium chloride pilocarpine-induced epilepsy in rats and its underlying mechanisms. Eur. J. Med. Res. 29(1):121. doi: 10.1186/s40001-024-01694-x.

Xie, P., S. Zhu, H. Zhou, R. Fang, J. Zhuang, J. Wen, M. Yang and J. He (2023). Rapamycin plays an anti-epileptic role by restoring blood-brain barrier dysfunction, balancing T cell subsets and inhibiting neuronal apoptosis. Discov Med. 35(179):1043-1051. doi: 10.24976/Discov.Med.202335179.100.

Zhang, Y.H., X.S. Liu, Y. Gao, L.L. Yuan, Huang, Y. Zhang, Z.Y. Liu, Y. Yang, X.Y. Liu, C.B. Ke, Z.J. Pei ZJ. 2024. SFXN1 as a potential diagnostic and prognostic biomarker of LUAD is associated with (18)F-FDG metabolic parameters. Lung Cancer. 188:107449. doi: 10.1016/j.lungcan.2023.107449.