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Research Article

Treatment with Taper Up- Off Protocol of Opium Tincture Could Change the Ion Channels Activity in Hippocampus of Epilepsy Rodent Model: A Brief Report

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Abstract

Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures resulting from abnormal, excessive electrical discharges in the brain. The epilepsy model was developed in rats to assess behavioral, pathological alterations, and potential molecular mechanisms. Present study is an early results of investigate of the effects of opium tincture on hippocampus of epilepsy rat model.

The epilepsy rat model were treated with taper up-off of opium tincture protocol called Dezhakam-step-time (DST) in four different dosages. The hippocampus tissues were collected, RNA extracted and cDNA synthesis were performed. The expression level of ion channel related genes have been assessed using the quantitative Real-time PCR.

All ion channels related genes were significantly altered in hippocampus tissue of epilepsy models vs. normal controls hippocampus tissue. Results showed all doses of the taper-up-off opium tincture treatment had altered the expression level of several genes. The GABA-A receptor, sodium voltage-gated channel and calcium voltage-gated channel related genes were changed after the opium tincture treatment, especially at higher dosages.

The early findings of the gene expression study regarding epilepsy models rats treated with opium tincture suggest that the ion channels pathways activity has been potentially re-regulated and approached to the normal level after the treatment. It seems that the DST method of opium tincture usage may potentially reduce the neuronal excitability and help to balance between excitation and inhibition in the brain of epileptic patients.

Keywords

Epilepsy, Opium tincture, Taper up-off, Gene expression, Ion channels.

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Introduction

Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures, which are sudden bursts of abnormal electrical activity in the brain [1]. These disruptions in neuronal communication can manifest in various ways, from brief lapses of awareness or muscle jerks to severe, prolonged convulsions, depending on where in the brain the disturbance originates and how widely it spreads [2]. The etiology of epilepsy is diverse and often multifaceted, though in many cases, the precise cause remains idiopathic [3]. Identified causes can be broadly categorized into structural, genetic, infectious, metabolic, immune, and unknown origins. Structural causes include acquired brain injuries from stroke, trauma, or tumors, as well as congenital malformations [4]. Genetic factors play a significant role, with

some epilepsies running in families or arising from spontaneous gene mutations affecting ion channels or neuronal development [5]. Infections like meningitis or encephalitis, metabolic disorders impacting brain function, and autoimmune conditions where the body's immune system attacks brain cells can also lead to epilepsy [4]. Risk factors like age, family history, and other neurological conditions like dementia can also contribute to its development [2]. Several genes associated with ion channel function, which are crucial for neuronal excitability and signal transmission, are intrinsically related to epilepsy [5,6]. It has been reported that dysfunction in these genes may disrupt normal neuronal firing patterns that in turn could lead to seizures [7]. The genes encoding gamma-aminobutyric acid (GABA) receptors, voltage-gated sodium channels, potassium channels, and calcium channels are among the most important ion channel-related genes implicated in epileptic pathophysiology [6,7].

While opium-based drugs are widely prescribed for pain management, concerns regarding their potential side effects and addictive properties mandate careful consideration. Opium tincture, known historically as Laudanum, functions as an opioid analgesic and has additionally been used to treat diarrhea, control neonatal opioid withdrawal, and act as a cough suppressant [8]. Despite its uses, the influence of opium and its constituent opiate alkaloids on gene expression and epigenetic patterns in mammals is presently unclear. Analyzing gene expression offers a promising avenue to elucidate the extensive effects of opioid compounds across the entire physiological system, including their involvement in fundamental molecular processes impacting immune responses, neural functions, and the central nervous system [9].

The present article is the report of early findings of the study aimed to evaluate the transcriptomic pattern of the epilepsy rat model treated with a protocol of taper up-off of opium tincture. In this report the results of expression level of ion channels related genes in epileptic rat models which are opium tincture-treated, untreated, and control groups have been presented.

Materials and Methods

Animal Modeling Protocol

This study utilized Sprague-Dawley rats, with twelve males and twelve females aged about nine weeks in each group. At the start of the study, male body weights ranged from 230 grams to 255 grams, and female body weights ranged from 202 grams to 218 grams. To induce epilepsy in rats, Pentylenetetrazole kindling-induced epilepsy rat models, used to reach the fully-kindled state and stable seizures. First the rats were raised at the animal house with room temperature natural light-dark cycle along with water and food ad libitum. Injection of intra-peritoneally (ip) of 35 mg/kg Pentyletetrazole (PTZ) (Sigma-Aldrich, St. Louis, USA) was used to induce kindling. Then the distilled water had been administered by oral gavage (p.o) (10 mL/kg). Two PTZ dose injections were made consecutively, at 48 h interval. Animals were placed after each injection, individually in polycarbonate cage and observed for 30 min. The onset of epilepsy was determined via the Racine seizure scale, based on previous studies [10].

Table 1: Groups' demographic data.

Group name	Description
G1	PTZ-induced epilepsy model treated with dose 1 opium tincture
G2	PTZ-induced epilepsy model treated with dose 2 opium tincture
G3	PTZ-induced epilepsy model treated with dose 3 opium tincture
G4	PTZ-induced epilepsy model treated with dose 4 opium tincture
Epilepsy rat model	PTZ-induced epilepsy model with no treatment
Normal control	Healthy rats with no treatment
Sham	Normal rats with force-feeding of water

PTZ: Pentyletetrazole

Opium Tincture Treatment Protocol

The study administered opium tincture to rats using the laboratory-developed Dezhakam-step-time (DST) method, a taper up-off protocol. This 18-day regimen involved 36 total administrations (twice daily). Initially, the lowest dose was given, increasing by 20% (0.8 coefficient) at each of the first 18 administrations (9 days). Subsequently, the dosage was decreased by the same 20% rate over the next 18 administrations (9 days), ensuring the first and final doses were identical. The study employed four distinct dosage regimens. For instance, the first regimen ranged from an initial 2.35 mg/kg to 65.58 mg/kg by the 18th dose, while the second, third, and fourth regimens commenced at 3.52 mg/kg, 4.7 mg/kg, and 5.87 mg/kg, respectively.

Euthanasia and Tissue Collection

At the end of the experiment, all animals were sacrificed with 100 mg/kg pentobarbital sodium based on previous studies. Housing and euthanasia procedures were performed based on the ARRIVE55 Guidelines checklist and previous studies [11,12]. For tissue culturing, the hippocampus tissue of rats was obtained and immediately processed for molecular analysis.

Gene Expression Examinations

Total RNA was isolated from rat hippocampus tissue samples. The100 mg hippocampus tissues, underwent homogenization in an ice bath by introducing 1 ml of TRIZOL lysis reagent. Subsequently, 300 µl of chloroform was incorporated and meticulously blended. The resultant mixture was then chilled on ice for a duration of 10 minutes, followed by centrifugation at 9,800 × g for 15 minutes at a temperature of 4°C. Upon isolation of the clear upper layer (supernatant), an equivalent volume of isopropanol was combined with it. This solution was then allowed to rest at ambient temperature for 5 minutes before being subjected to another centrifugation at 9,800 × g for 10 minutes at 4°C. The residual liquid (supernatant) was then discarded, and the pellet was rinsed with 1 ml of 75% ethanol, succeeded by a final centrifugation at 9,800 × g at 4°C. Following the removal of the washing solution, the RNA precipitate was solubilized in 50 µl of diethylpyrocarbonate (DEPC) water, thereby yielding the purified RNA. The quantity of the isolated RNA was ascertained using a Nanodrop-1000 spectrophotometer, while RNA quality was appraised via the BioRad Experion automated electrophoresis system (BioRad Laboratories Inc.). All extracted RNA specimens were preserved at -80°C until subsequent processing. Complementary DNA (cDNA) was then synthesized

utilizing the RevertAid Premium First Strand cDNA Synthesis Kit (Thermo Scientific - Fermentas, Latvia; #K1652), conforming to the provided protocol.

For the quantification of candidate gene expression (detailed in Table 2), Real-Time PCR was utilized. Specific primers and probes were designed using the GenScript Real-time PCR (TaqMan) Primer Design software, and their specificity was corroborated through BLAST analysis against the NCBI database. Calibration curves were constructed from serial four-fold dilutions of pooled cDNA derived from randomly chosen control rat RNA samples. Quantitative Real-Time PCR was executed in triplicate using the CFX96 Touch Real-Time PCR Detection System (BIO-RAD, California, United States). Quality control criteria encompassed the lack of signal in no-template control samples and a standard curve R^2 value exceeding 0.99. PCR reaction efficacy was computed via the Lin-Reg PCR online application (Amsterdam, Netherlands). The TaqMan® PCR Starter Kit (Thermo Scientific - Fermentas, Latvia) was employed for all reactions. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) functioned as the reference gene for normalization, and relative gene expression ratios were ascertained using the Livak ($2^{\wedge-\Delta\Delta Ct}$) equation.

Statistical Assessments

Statistical evaluations were carried out utilizing SPSS software, version 25. The distribution's normality for all variables underwent scrutiny via the Kolmogorov-Smirnov test. For discerning statistical disparities among multiple group comparisons, one-way ANOVA was implemented. To mitigate potential confounding elements, ANCOVA was applied to ascertain the sustained significance of differences between groups, with RNA integrity metrics, cDNA synthesis fidelity, qPCR plate/run characteristics, and primer/probe efficacy serving as covariates. Corrections for multiple comparisons were performed using the Bonferroni method. All descriptive data are presented as the mean ± standard deviation (SD).

Results

Gene Expression Analysis

Reliable gene expression analysis was ensured by the high quality of all RNA samples, each showing an RNA quality indicator (RQI) value greater than 9.5. The study's findings, detailed in Table 3, reveal significant alterations in gene expression when comparing experimental groups to normal controls. Specifically, Group 3 (G3) exhibited the most pronounced changes relative to the epilepsy rodent model. Furthermore, the mRNA levels of any genes did not differ significantly between male and female rats in any of the tested groups.

Results of gene expression analyses showed that all fourteen candidate genes were significantly altered in epilepsy model compared with normal controls (and sham group). The genes associated to subunits of GABA receptors were all down regulated in epilepsy model. All groups treated with opium tincture showed significantly up regulation of GABRB2, GABRB3 and GABRD, while GABRA1and GABRG2 were only significantly over expressed in G3 and G4 compared with epilepsy model with no treatment. Two genes related to potassium voltage-gated channels, KCNQ2 and KCNQ3 were significantly down expressed in epilepsy

Table 2: List of studied genes.

Gene symbol	Full name of gene	Description
GABRA1	Gamma-Aminobutyric Acid Type A Receptor Subunit Alpha1	Encodes the alpha-1 subunit of the GABA-A receptor, a major inhibitory neurotransmitter receptor in the brain, often implicated in epilepsy.
GABRB2	Gamma-Aminobutyric Acid Type A Receptor Subunit Beta2	Encodes the beta-2 subunit of the GABA-A receptor, contributing to the functional diversity and pharmacology of this inhibitory ion channel.
GABRB3	Gamma-Aminobutyric Acid Type A Receptor Subunit Beta3	Encodes the beta-3 subunit of the GABA-A receptor, mutations in which are associated with various neurological disorders including epilepsy and Angelman syndrome.
GABRD	Gamma-Aminobutyric Acid Type A Receptor Subunit Delta	Encodes the delta subunit of the GABA-A receptor, which forms receptors that mediate tonic (persistent) inhibition and are highly sensitive to neurosteroids.
GABRG2	Gamma-Aminobutyric Acid Type A Receptor Subunit Gamma2	Encodes the gamma-2 subunit of the GABA-A receptor, crucial for receptor trafficking, synaptic localization, and benzodiazepine sensitivity.
CACNA1A	Calcium Voltage-Gated Channel Subunit Alpha1 A	Encodes the alpha-1A subunit of a voltage-dependent calcium channel, critical for neurotransmitter release and muscle contraction, and linked to neurological disorders like episodic ataxia and migraine.
CACNB4	Calcium Voltage-Gated Channel Subunit Beta4	Encodes the beta-4 subunit of a voltage-gated calcium channel, which modulates the properties and trafficking of alpha-1 subunits.
SCN1A	Sodium Voltage-Gated Channel Alpha Subunit 1	Encodes the alpha-1 subunit of a voltage-gated sodium channel, a key component for action potential generation, and mutations are a major cause of severe epilepsies like Dravet syndrome.
SCN2A	Sodium Voltage-Gated Channel Alpha Subunit 2	Encodes the alpha-2 subunit of a voltage-gated sodium channel, crucial for neuronal excitability and signal propagation, with mutations implicated in epilepsy and neurodevelopmental disorders.
SCN3A	Sodium Voltage-Gated Channel Alpha Subunit 3	Encodes the alpha-3 subunit of a voltage-gated sodium channel, which contributes to neuronal excitability and is implicated in some forms of epilepsy.
SCN8A	Sodium Voltage-Gated Channel Alpha Subunit 8	Encodes the alpha-8 subunit of a voltage-gated sodium channel, a key component for action potential initiation in neurons, and mutations are associated with severe early-onset epileptic encephalopathies.
SCN1B	Sodium Voltage-Gated Channel Beta Subunit 1	Encodes the beta-1 subunit of a voltage-gated sodium channel, which modulates the function and trafficking of the alpha subunits and is linked to various forms of epilepsy.
KCNQ2	Potassium Voltage-Gated Channel Subfamily Q Member 2	Encodes a subunit of a voltage-gated potassium channel that forms the M-channel, playing a critical role in regulating neuronal excitability and associated with benign familial neonatal seizures.
KCNQ3	Potassium Voltage-Gated Channel Subfamily Q Member 3	Encodes a subunit of a voltage-gated potassium channel that, along with KCNQ2, forms the M-channel, regulating neuronal firing and implicated in various forms of epilepsy.

Table 3: Relative mRNA level and statistical comparisons of gene expression evaluations of all groups compared with normal control rats.

Gene	Epilepsy rat model	Sham	G1	G2	G3	G4
GABRA1	Ratio: 0.54 P value:0.003*	Ratio: 1.02 P value:0.2	Ratio: 0.58 P value:0.002*	Ratio: 0.64 P value:0.003*	Ratio: 0.91 P value:0.4	Ratio: 0.84 P value:0.04
GABRB2	Ratio: 0.45 P value:0.001*	Ratio: 0.95 P value:0.56	Ratio: 0.77 P value:0.03	Ratio: 0.79 P value:0.03	Ratio: 0.82 P value:0.06	Ratio: 0.87 P value:0.09
GABRB3	Ratio: 0.45 P value:0.0005*	Ratio: 0.96 P value:0.1	Ratio: 0.77 P value:0.05	Ratio: 0.88 P value:0.06	Ratio: 0.85 P value:0.11	Ratio: 0.89 P value:0.06
GABRD	Ratio: 0.67 P value:0.01	Ratio: 0.93 P value:0.32	Ratio: 0.66 P value:0.01	Ratio: 0.73 P value:0.01	Ratio: 0.78 P value:0.02	Ratio: 0.76 P value:0.02
GABRG2	Ratio: 0.44 P value:0.002*	Ratio: 1.1 P value:0.26	Ratio:0.62 P value:0.003*	Ratio:0.88 P value:0.07	Ratio:0.87 P value:0.09	Ratio: 0.91 P value:0.2
CACNA1A	Ratio: 1.43 P value:0.005*	Ratio: 1.09 P value:0.29	Ratio:1.25 P value:0.007*	Ratio:1.37 P value:0.005*	Ratio:0.96 P value:0.3	Ratio: 1.15 P value:0.08
CACNB4	Ratio: 1.63 P value:0.002*	Ratio: 0.98 P value:0.3	Ratio: 1.52 P value:0.008*	Ratio: 1.55 P value:0.006*	Ratio: 1.1 P value:0.17	Ratio:1.49 P value:0.007*
SCN1A	Ratio:1.68 P value:0.003*	Ratio: 1.04 P value:0.66	Ratio: 1.65 P value:0.003*	Ratio: 1.56 P value:0.008*	Ratio: 1.23 P value:0.05	Ratio:1.2 P value:0.06
SCN2A	Ratio: 1.55 P value:0.007*	Ratio: 1.12 P value:0.17	Ratio: 1.56 P value:0.008*	Ratio: 1.49 P value:0.005*	Ratio: 1.1 P value:0.12	Ratio: 1.2 P value:0.16
SCN3A	Ratio: 1.72 P value:0.001*	Ratio: 0.99 P value:0.4	Ratio: 1.18 P value:0.12	Ratio: 1.09 P value:0.66	Ratio: 1.05 P value:0.64	Ratio: 0.94 P value:0.7
SCN8A	Ratio: 1.68 P value:0.006*	Ratio: 1.07 P value:0.26	Ratio: 1.15 P value:0.03	Ratio: 1.1 P value:0.03	Ratio: 1.12 P value:0.08	Ratio: 1.2 P value:0.1
SCN1B	Ratio: 2.1 P value:0.001*	Ratio: 1.06 P value:0.5	Ratio: 2.06 P value:0.002*	Ratio: 1.7 P value:0.008*	Ratio: 1.07 P value:0.06	Ratio: 1.11 P value:0.07
KCNQ2	Ratio: 0.59 P value:0.008*	Ratio: 0.95 P value:0.19	Ratio: 0.62 P value:0.006*	Ratio: 0.64 P value:0.005*	Ratio: 0.61 P value:0.003*	Ratio: 0.64 P value:0.004*
KCNQ3	Ratio: 0.5 P value:0.002*	Ratio: 1.08 P value:0.13	Ratio: 0.53 P value:0.005*	Ratio: 0.59 P value:0.009*	Ratio: 0.62 P value:0.006*	Ratio: 0.66 P value:0.005*

model and opium tincture treatment made no significant change in their mRNA level and were significantly down regulated in all four treatment group compared to normal controls. Unlike the GABA receptors and potassium voltage-gated channels, genes of calcium and sodium voltage-gated channels were significantly upregulated in epilepsy models. Both Calcium Voltage-Gated Channel genes, CACNA1A (P-value =0.004) and CACNB4 (P-value =0.004) were significantly decreased in G3 group compared with epilepsy model group. Sodium voltage-gated channels genes were all over expressed in epilepsy model compared to normal. The SCN3A and SCN8A genes were significantly upregulated after the treatment with opium tincture in all four treatment groups. In addition SCN1A, SCN1B and SCN1B were significantly overexpressed in G3 and G4 in comparison with epilepsy model.

Discussion

The present study aimed to elucidate the molecular effects of a novel taper up-off opium tincture protocol, Dezhakam-step-time (DST), on the ion channel gene expression in the hippocampus of an epilepsy rat model. Findings of PTZ kindling epilepsy model confirm that the epileptic state profoundly alters the mRNA level of critical ion channel genes including down regulation of subunits of GABA receptors (GABRA1, GABRB2, GABRB3, GABRD, GABRG2), potassium voltage-gated channels (KCNQ2 and KCNQ3) along with increase of mRNA level of genes related to calcium and sodium voltage-gated channels in hippocampus tissue. On the other hand the DST opium tincture oral consumption protocol in four different dosage can modulate these expression levels, potentially guiding neuronal excitability pathways towards a more balanced physiological state. The DST method caused

the increase of GABA receptors and potassium voltage-gated channels genes and decrease of sodium voltage-gated channels genes compared with epilepsy models. No changes in calcium voltage-gated channels genes detected related to opium tincture consumption.

Epilepsy is a complex neurological disorder with a significant genetic and epigenetic component. While hundreds of genes have been associated with various forms of epilepsy, some are recognized as particularly important due to their frequent involvement in severe or well-defined epilepsy syndromes. The genetic bases of epilepsy are mostly highly complex and polygenic, along with complex interactions with environmental factors. Previous studies on human subjects showed the genetic architecture of epilepsy could be affected by phenotypic pleiotropy, locus heterogeneity and incomplete penetrance.

The PTZ kindling is a well-characterized model that recapitulates many features of human temporal lobe epilepsy, such as progressive neuronal hyperexcitability and lasting molecular and gene expression alterations in limbic structures specially the hippocampus [13]. The dysregulation of ion channels, or channelopathy which are fundamental to neuronal excitability and signal transmission, is a hallmark of epilepsy [14,15]. The pattern of downregulation of GABA receptor subunits and potassium voltage-gated channels (KCNQ2, KCNQ3) alongside the upregulation of sodium (and calcium voltage-gated channels clearly underlies the hyperexcitable state in the PTZ model, aligning with previous reports on ion channel dysregulation in acquired epilepsies [10].

The major finding of present study is that DST protocol, administered in four distinct dosage regimens, significantly altered the expression levels of several of these dysregulated genes. These changes suggests a potential re-regulation of ion channel pathway activity towards normal levels, a crucial step in counteracting the fundamental imbalance between excitation and inhibition characteristic of epilepsy. Results may particularly noteworthy given the complex and contradictory reports about the relationship between opium and opioid based compounds. While acute usage of opioids, especially in high doses can be proconvulsant [16], and opioid withdrawal is known to precipitate seizures [17], our results indicate a distinct outcome under the controlled, tapered administration via the DST protocol. It may suggests that the specific administration regimen based on taper up and off of usage, might induce a unique neuroadaptation and long-term cellular adaptations that mitigates proconvulsant effects, instead promoting a re-establishment of neuronal balance [9].

The downregulation of GABA-A receptor subunits as inhibitory receptors and a common neuroadaptation in epilepsy, contributing to hyperexcitability [18]. Interestingly, the DST opium tincture treatment generally led to an upregulation of these subunits especially at higher dosage groups (G3 and G4). This could support the hypothesis that a restoration or even enhancement of GABAergic inhibition occurred after the period of taper up and off of opium tincture consumption. Although opioids typically inhibit GABAergic interneurons, leading to disinhibition [19], our results imply a different, compensatory long-term effect on GABA-A receptor expression. The upregulation of the GABRD subunit, which mediates tonic inhibition and is implicated in addiction [20], could be particularly impactful in rebalancing neuronal excitability. It may suggest a complex interaction where the specific tapered administration protocol might promote beneficial neuroplasticity, potentially via indirect pathways or modulation of the brain's homeostatic mechanisms, leading to increased inhibitory tone.

Potassium voltage-gated channels form the M-current, which is crucial for stabilizing neuronal membrane potential and reducing excitability [21]. The KCNQ2 and KCNQ3 which were downregulated in epileptic rats, showed persistent downregulation after opium tincture treatment which indicates that the DST protocol did not restore this specific inhibitory mechanism.

Sodium and calcium voltage-gated channel genes, which were significantly upregulated in epilepsy model, showed a distinct response to the DST protocol. The upregulation of sodium channels contributes to increased neuronal excitability by facilitating action potential initiation and propagation [22]. In addition, increased calcium channel expression can enhance neurotransmitter release and neuronal firing [23]. While the higher dosage groups (G3 and G4) showed significant overexpression for SCN1A, SCN1B, and SCN2A compared to the epilepsy model, it may suggests a complex response where some sodium channel subunits remained elevated. However, both CACNA1A and CACNB4 were significantly *decreased* in Group 3 compared to the epilepsy model. This reduction in calcium channel expression is particularly promising, as it directly counters the pro-epileptic upregulation observed in the untreated model. Calcium channel potentially inhibiting aberrant calcium influx that in turn may stabilizing synaptic transmission [24]. The differential response across various sodium and calcium channel subunits and various opium dosages highlights the intricate and often subunit-specific neuroadaptations occurring during both epileptogenesis and in response to the opium tincture oral consumption.

Unlike studies focusing on acute opioid administration or prolonged, unmanaged abuse, present study evaluate the "taper up-off" methodology called Dezhakam-step-time (DST) protocol that is pivotal to potential neuroadaptive changes which may lead to circumventing the proconvulsant risks associated with high or abrupt opioid exposure. This controlled tapering might allow the brain to gradually adjust, promoting beneficial long-term plasticity in ion channel expression that supports a re-balance of excitation and inhibition, rather than merely inducing further dysfunction. Future studies investigating the human neurons cell lines may shed more light on effects of taper up – off of opium tincture on gene expression pattern of human brain. Furthermore, a direct comparison of the DST protocol's efficacy and molecular effects against established antiepileptic drugs would provide invaluable context regarding its therapeutic potential.

Limitations

While these early findings from gene expression analysis revealed several interesting preliminary molecular insights, further studies are essential to validate these mRNA level changes with corresponding protein expression level analysis. Moreover, these molecular findings must be correlated with clinical observations such as electrophysiological recordings to directly confirm reduced neuronal excitability, seizure frequency and severity in the epilepsy model.

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