The Effects of Gabapentin on Epileptic Seizures: A Computational Model

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ABSTRACT

Anticonvulsant sedatives are commonly used to stop epileptic seizures; however, many result in significant harmful side-effects. In this paper, we explore gabapentin, an alternative anticonvulsant, as a safer, more effective treatment for epileptic seizures. The goal of our study was to determine the conditions under which gabapentin has the greatest potential to suppress epileptic seizures through its interactions with voltage-gated Ca^{2+} channels. First, we ran an existing network model of the CA3 region of the hippocampus. Next, we rendered the model seizure prone through impaired dendritic inhibition to pyramidal cells due to the dysfunction of O-LM interneurons. Then, we implemented gabapentin into the network as a parameter that acts as a proxy for dosage and scales the Ca^{2+} channel conductance in excitatory neurons. By increasing the dosage of gabapentin, the resulting Ca^{2+} current was decreased, inhibiting the seizure. In fact, at high doses of gabapentin, we saw seizures were significantly suppressed. Our model supports the efficacy of gabapentin as a seizure medication. However, clinical trials are needed to find appropriate dosages and side effects of the drug.

Introduction

According to the Centers for Disease Control and Prevention, 3.4 million people in the United States had active epilepsy in 2015. Epilepsy is a neurological disorder in which electrical misfires caused by damaged neurons trigger recurrent seizures in patients. Neuron damage is generated by an overaccumulation of calcium ions (Ca^{2+}) in the mitochondrial membranes, which compromises the membranes and causes embedded neurons to misfire. Side effects of epileptic seizures include uncontrollable jerking movements, loss of memory, and restricted awareness. A focal seizure, illustrated in figure 1, affects only one side of the brain and body, and tends to be less severe than a generalized seizure, which affects both sides of the brain and body. Focal seizures are the most common type of seizures with epilepsy.

Anticonvulsant sedatives are commonly used to stop epileptic seizures; however, these treatments have been known to result in significant harmful side-effects. Administering gabapentin, an alternative anticonvulsant and nerve pain medication, has proven to be a safer treatment for epileptic seizures compared to anticonvulsant sedatives. Gabapentin reduces the excitability of neurons in the brain, which play a major role in seizures and the transmission of pain signals, by interacting with cortical neurons at auxiliary subunits of voltage-gated calcium channels. Gabapentin works by showing a high affinity for binding sites throughout the brain correspondent to the presence of the voltage-gated calcium channels, especially $\alpha 2\delta 1$, which seems to inhibit the release of excitatory neurotransmitters in the presynaptic area which participate in epileptogenesis.

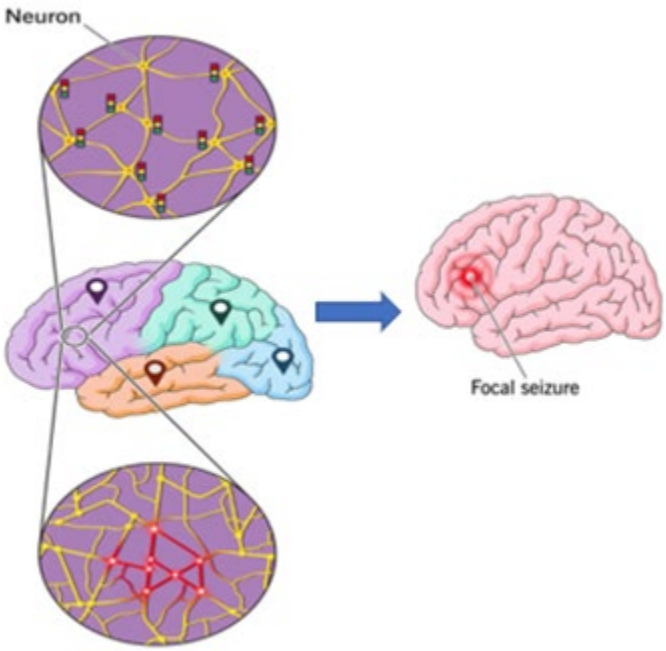


Figure 1. Focal seizure.
Adapted from https://my.clevelandclinic.org/-/scassets/images/org/health/articles/22789-seizure

Background

Voltage-Gated Calcium Ion Channels

Fernández-Quintero et al. (2021) observe that communication in our body runs on electricity and explain it as follows. Between the exterior and interior of every living cell, there is a difference in electrical charge, or voltage. Rapid changes in this so-called membrane potential activate vital biological processes, ranging from muscle contraction to communication between nerve cells. Ion channels are cellular structures that maintain membrane potential and help 'excitable' cells like nerve and muscle cells produce electrical impulses. They are specialized proteins that form highly specific conduction pores in the cell surface. When open, these channels let charged particles such as calcium ions through, rapidly altering the electrical potential between the inside and outside the cell. To ensure proper control over this process, most ion channels open in response to specific stimuli, which is known as 'gating.' For example, voltage-gated calcium channels contain charge-sensing domains that change shape and allow the channel to open once the membrane potential reaches a certain threshold.

Structure and Function of Voltage-Gated Calcium Ion Channels

Rajakulendran et al. (2016) provide a detailed overview of the calcium channel structure shown in figure 2. Calcium channels are multimeric membrane complexes, and each consists of a principal α1 subunit, which defines the channel type. In figure 2A, they show the topology of the α1 subunit, which consists of four domains (I–IV), each containing six transmembrane segments (S1–S6). The S4 segment of each domain is lined with positively charged amino acids and acts as the voltage sensor. The S5–S6 interlinker lines the pore of the channel. In figure 2B, they show the schematic of the channel complex for high-voltage-activated (HVA) and low-voltage-activated calcium channels and their diverse biological roles. HVA channels consist of a principal α1 subunit, which forms the channel pore, a β subunit,

which is cytoplasmic, an extracellular α2δ subunit, which is attached to the membrane via a glycophosphatidylinositol anchor, and possibly a γ subunit.

In the nervous system, calcium channels support a host of biological processes, including gene expression, neuro-architectural development, intracellular signal propagation, membrane oscillation, and neurotransmitter release. The variety of calcium channel types required to support such diversity of function is achieved by the various combinations with which the subunits co-assemble, the result being the generation of multiple channels with each showing finely tuned biophysical properties tailored to cell- and network-specific roles. Two functions, in particular, have implications for seizure generation: their involvement in neurotransmitter release, and their role in burst firing.

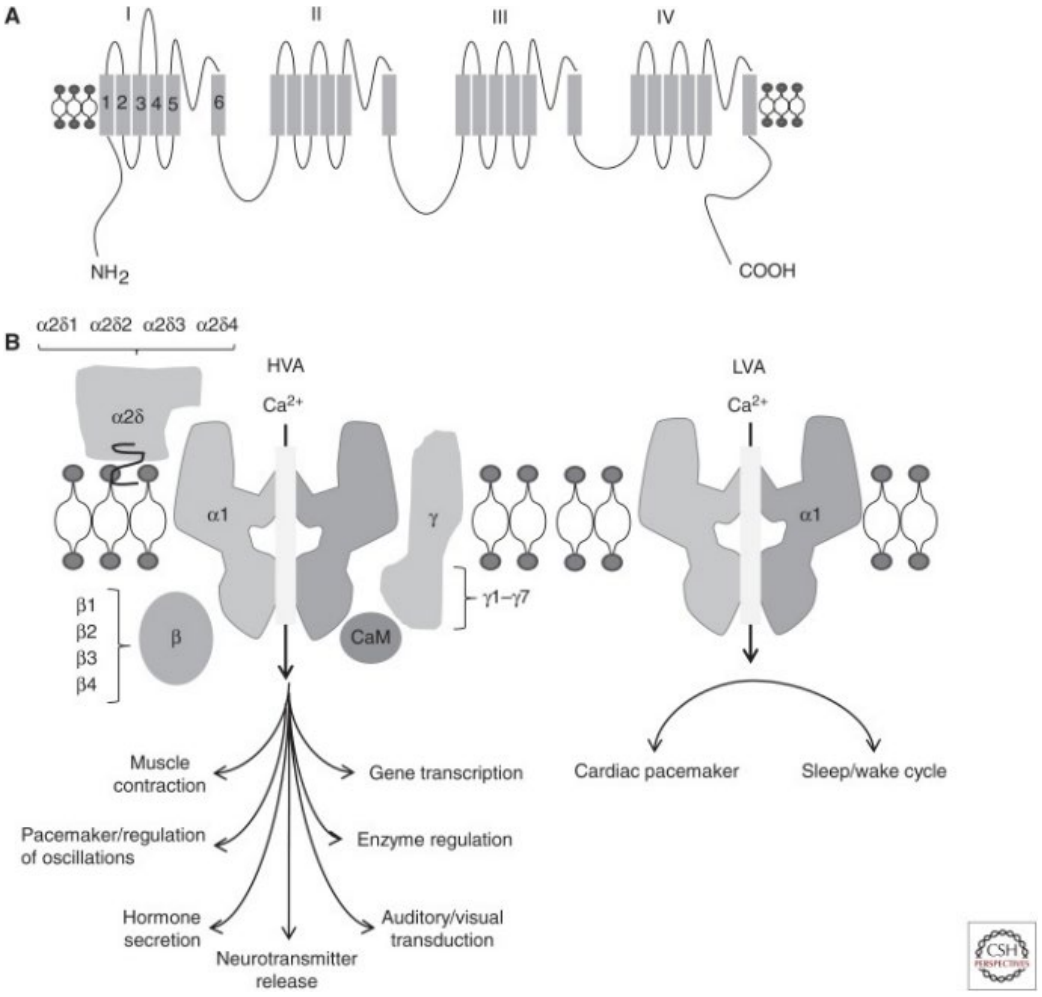


Figure 2. Structure and function of voltage-gated calcium channels.

Figure 3 shows how gabapentin interacts with cortical neurons at α2δ subunits, which control synaptic transmission in excitable neurons, and modulates certain types of Ca^{2+} current. Specifically, Gabapentin reduces the release of mono-amine neurotransmitters by binding to NMDA receptors on the postsynaptic terminal.

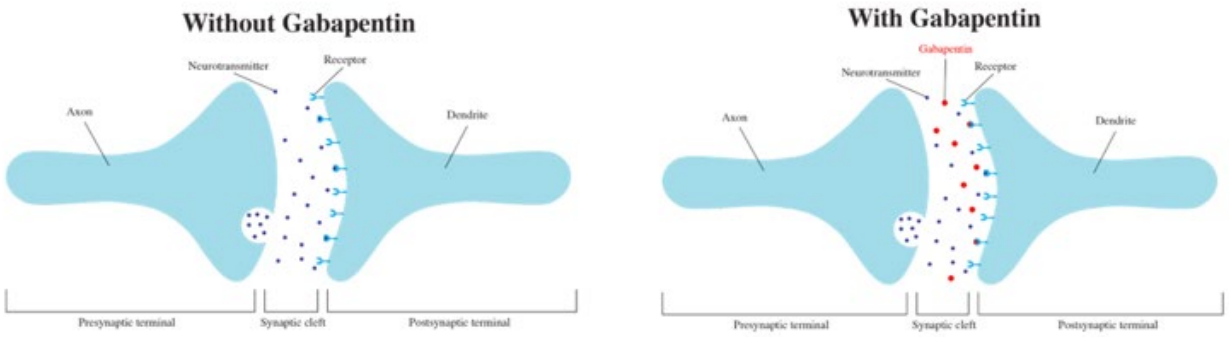


Figure 3. Gabapentin interaction with cortical neurons.

Methods

Sanjay et al. (2015) developed a computational model study of temporal lobe epilepsy (TLE), a common type of epilepsy with the hippocampus, a complex and vulnerable brain structure embedded deep into the temporal lobe, as the usual site of origin. The CA3 subfield of the hippocampus is reported to have a low epileptic threshold and initiates the disorder in patients with TLE. Their model of the CA3 subfield consisted of 800 pyramidal cells, 200 basket cells and 200 Oriens-Lacunosum Moleculare (O-LM) interneurons. The model is rendered epileptic when dendritic inhibition to pyramidal cells is impaired due to the dysfunction of O-LM interneurons. The model analyzes the activity patterns, oscillations, and brain rhythms when the network becomes epileptic.

To implement gabapentin into the model, voltage-gated calcium channels were added to the soma and dendrites of excitatory pyramidal cells. A gabapentin synaptic variable was created to assign various proxy dosages of gabapentin on a scale from 0 to 1. When the gabapentin dose is increased, the calcium channel conductance is reduced in the soma and dendrites of pyramidal cells. As outlined in table 1, three simulations were run at three gabapentin dose levels: no dose, medial dose, and maximum dose.

Table 1. Simulations at three gabapentin dose levels.

Gabapentin variable (Value/Percentage)	**Implied dosage**	**Ca^{2+} channel conductance**
0 / 0%	No dose	No change
0.5 / 50%	Medial dose	Moderate reduction
1 / 100%	Maximum dose	Maximum reduction

Effectively, at 0%, the model behaves as if there is no binding of gabapentin at any of the NMDA receptors, and at 100%, the model behaves as if gabapentin binds to all the receptors in the channel. Local Field Potential (LFP) graphs, Raster plots and Power Spectrum Density charts were generated for each simulation (no dose, medial dose, and maximum dose of gabapentin) using matplotlib. LFP graphs show electrical activity in the brain in the CA3 region of the hippocampus plotted in the form of voltage (mV) vs. time (ms).

Raster plots display both the firing of pyramidal cells, basket cells, and O-LM neurons at each timestamp as well as the index of each cell and neuron at that time. Power Spectrum Density charts use Fast Fourier Transforms to display dominant frequencies in firing activity.

Results

Tables 2, 3 and 4 show the LFP graphs, Raster plots and Power Spectrum Density charts for each simulation.

Table 2. LFP graphs at various gabapentin dose levels.

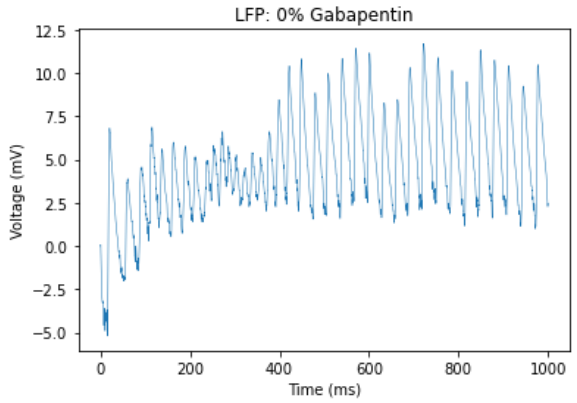
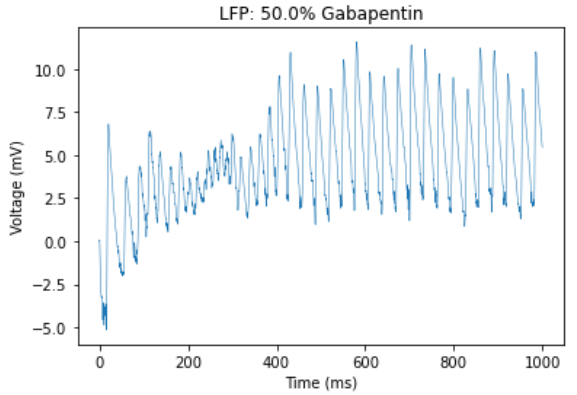
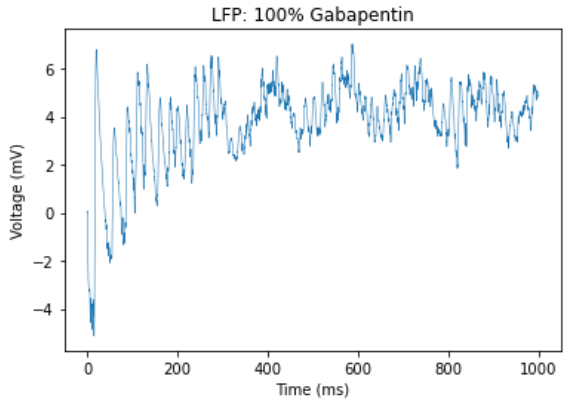
LFP graph	Observations
 **Figure 4.** LFP graph at 0% Gabapentin.	Figure 4 shows that at no dose (0% Gabapentin), the chaotic spiking activity that starts at the 400ms mark is characteristic of seizure behavior.
 **Figure 5.** LFP graph at 50% Gabapentin.	Figure 5 shows that at a medial dose (50% Gabapentin), the spiking activity still appears chaotic and seizure behavior is displayed. The medial dose did not have much of an impact on the seizure.
 **Figure 6.** LFP graph at 100% Gabapentin.	Figure 6 shows that at a full dose (100% Gabapentin), spiking activity was significantly suppressed. The potential in the brain is around 4mV, which is typical of more normal brain activity.

Table 3. Raster plots at various gabapentin dose levels.

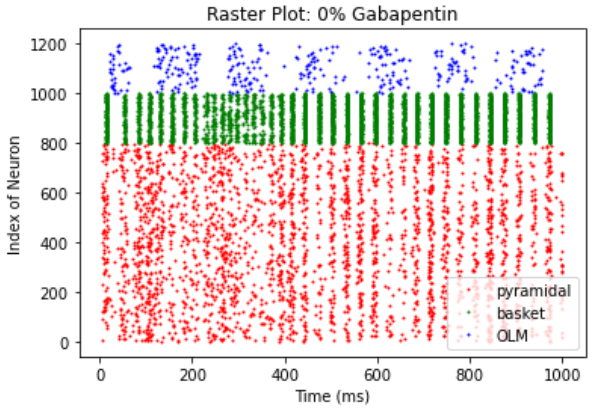
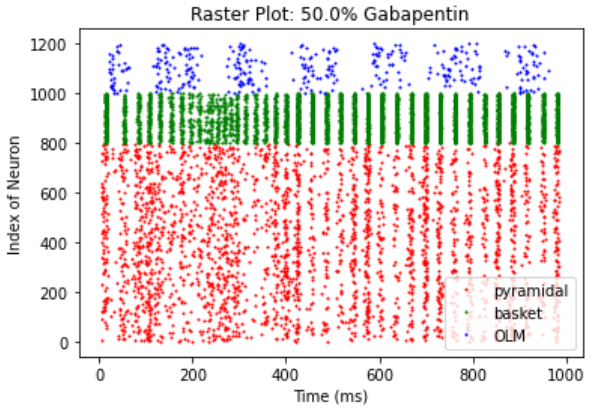
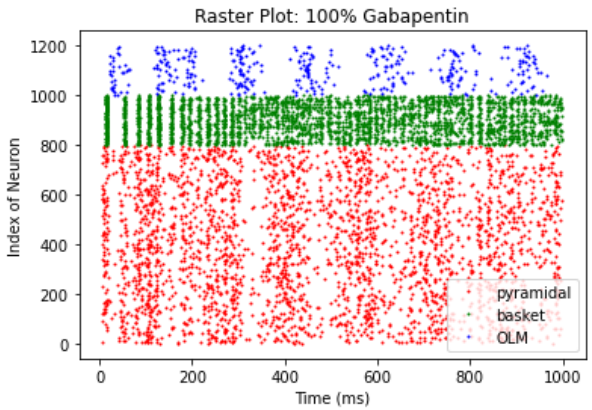
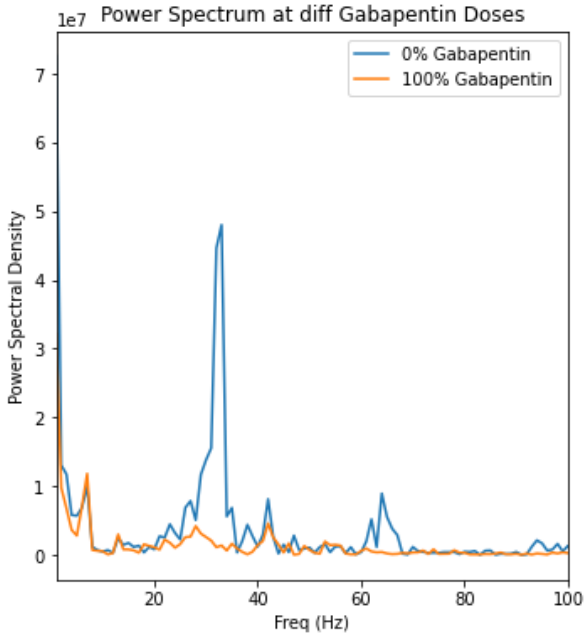
LFP graph	Observations
 **Figure 7.** Raster plot at 0% Gabapentin.	Figure 7 shows that at no dose (0% Gabapentin), the chaotic and higher frequency firing is characteristic of seizure activity.
 **Figure 8.** Raster plot at 50% Gabapentin.	Figure 8 shows that at a medial dose (50% Gabapentin), the firing appears a little less chaotic and not as frequent compared to 0% gabapentin.
 **Figure 9.** Raster plot at 100% Gabapentin.	Figure 9 shows that at a full dose (100% Gabapentin), the more rhythmic firing at lower frequency represents more normal brain activity.

Table 4. Power Spectrum Density charts at various gabapentin dose levels.

Power Spectrum	Observations
 **Figure 10.** Power Spectrum Density chart at 0% and 100% Gabapentin.	Figure 10 shows the Power Spectrum Density chart at no dose (0% Gabapentin), and at a full dose (100% Gabapentin). The 0% Gabapentin power spectrum density chart displays beta oscillations with high density at 32 Hz and gamma oscillations at 63 Hz. Beta oscillations result in twitching activity seen in seizures, and gamma oscillations result in memory loss. The 100% Gabapentin power spectrum density chat shows significantly reduced beta and gamma oscillations.

Conclusion

Based on our analysis, a maximum dosage of gabapentin was optimal in suppressing the seizure. However, a small dosage had a minimal effect on the seizures. Our results support the current hypothesis that gabapentin is a viable anticonvulsant to treat epileptic seizures if it is supplied in appropriate doses. Our model has the potential to assist future studies of epileptic seizures by finding dosages of gabapentin that will result in the greatest decrease of uncontrollable epileptic brain activity. Future clinical trials are necessary to determine the adequate dosage and legitimacy of the drug in epilepsy patients.

References

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Rajakulendran, S., and Hanna, Michael G. (2016). The Role of Calcium Channels in Epilepsy, Cold Spring Harb Perspect Med. 2016 Jan 4;6(1):a022723. https://doi.org/10.1101/cshperspect.a022723

Sanjay, M., Neymotin, S. A., & Krothapalli, S. B. (2015). Impaired dendritic inhibition leads to epileptic activity in a computer model of CA3. Hippocampus, 25(11), 1336–1350. https://senselab.med.yale.edu/ModelDB/ShowModel?model=186768#tabs-1