Effect of tetrodotoxin on neurons with different mutants of the sodium channel
Final Report

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1 Abstract

A combination of chemical and electrical processes in cells bring about a signal through neurons which is called the action potential. These processes are regulated through ion channels that open and close under certain conditions. When neurotoxins make contact with neurons they disrupt this process. We have studied this disruption through the specific neurotoxin Tetrodotoxin(TTX). We find that merely adding 'TTX-resistant' channels to a neuron may in fact make it more vulnerable to TTX.

1.1 Research question

How does the effect of tetrodotoxin on the functioning of the action potential differ for neurons with different distributions of the sodium channel types?

1.2 Hypothesis

For our hypothesis we argued that a distribution with more TTX resistance channels would be more resistant to TTX.

1.3 Model

The model has two levels. Firstly there is the change of membrane potential through time. This is described by a differential equation whose terms are constants and functions of channel states. Secondly there is the change of channel states through time. This is described by a system of differential equation whose terms are functions of membrane potentials. A channel state is determined by

the state of the gates in that channel. A channel is open if and only if all gates are open. These equations form the classic Hodgkin Huxley model (HH). We extended it by adding more channels to the model. This amounts to adding a term per type of channel to the voltage derivative and extra equations for the gating evolution. These new channels represent mutations of the sodium channels that are either TTX sensitive (TTX-S) or TTX resistent (TTX-R). The parameter fits for their distinct gating dynamics are taken from (Herzog et al, 2001). Finally we used data from (Roy and Narahashi, 1992) to model the effect of the TTX on the TTX-S channels. An injected current during was used to get an action potential started. To get an action potentials started, a current was applied for 3 ms.

1.4 Numerical method

To get our results we used several numerical methods, namely: Euler method, Gillespie method and the Runge-Kutta method.
To determine initial values, a neuron is simulated until it is in equilibrium for a while. Initial values for a neuron in equilibrium are then found by randomly selecting states of that neuron during equilibrium. To solve the HH-style system of equations we used both the Euler and Runge-Kutta method. For a more stochastic simulation, we also used the Gillespie algorithm to compute the gating dynamics. The idea is to stochastically choose a time step inversely proportional to the total amount of change in the system. Then after each time step exactly one gate transition is stochastically chosen to perform. That stochastic choice is proportional to the actual rate of change of the different gate transitions in the system (Chow and White, 1996).

1.5 Final result

We found that our hypothesis was incorrect. Counterintuitively we found that neurons with only TTX sensitive channels appear to be more resistant to TTX. Though counterintuitive, it does seem to be consistent with the observation that

2 Method and results

2.1 Method

We used Deepnote to construct a Jupyter notebook in which we had two primary objects, namely a neuron class and a model class. The neuron class contained the parameters that made up the properties of the neuron. This class also contained the properties of the different gates and how they reacted.

The model class contained the intialization of the neurons that were made with the neuron class. It also contained the run function and the code for the different numerical methods used.

The specific parameter values that were used in our project were taken from Herzog et al. (2001). See in particular the section V́oltage-dependent currents.

2.2 Results

(Herzog et al, 2001) had already observed that a neuron with just TTX-S has a lower resting potential but a higher action potential than a neuron with both TTX-S and TTX-R given no TTX in the system. We reproduced these results and additionally found out that this effect also implies that, counterintuitively, a neuron with both TTX-S and TTX-R is significantly more strongly inhibited by TTX. This leads to more latency when transmitting a signal through a chain of neurons and to a dampening of the peak of the action potential in the TTX-S and TTX-R neuron. So our hypothesis was incorrect.

2.3 Conclusion

Our model can seemingly reproduce the classic HH model and a more modern fit of mutant channels. However, more systematic validation of the model is needed. Also we've only compared one fit for the TTX-S and TTX-R mutant, while there are in fact within these categories a lot of distinct isoforms with different properties. Yet these results do seem to suggest that a neuron with both TTX-S and TTX-R may not be straightforwardly more resistant to TTX than one with just TTX-S.

References

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