Decreased Calcium Concentrations Lead to Hyperexcitability in Computational Network Model of the Dentate Gyrus

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Introduction

- Epilepsy, one of the most common neurological disorders, is characterized by recurrent seizures.
- Studies have shown that hypocalcemia, or low calcium concentration in the blood, is associated with seizure activity[1].
  - However, this correlation is counterintuitive (e.g. Ca^{2+} is necessary for neurotransmitter release).
- We test two mechanisms: reduced $[Ca^{2+}]_o$ can result in increased neuron firing by driving voltage-gated[2] (VGSC) and leak[3] (NALCN) sodium channel activity in the cell.

Significance

- The goal of this study is to explain the relationship between hypocalcemia and seizures by testing mechanisms influenced by decreased $[Ca^{2+}]_o$.

Methods

- Adapted a computational network model of the dentate gyrus[4].
  - 527-cell model → excitatory & inhibitory cells.
- Added code to simulate the effect of $[Ca^{2+}]_o$ on NALCN and VGSC channel activity:
  - VGSC: every 10-fold change in $[Ca^{2+}]_o$ → 20mV shift in VSGC voltage sensitivity.[3]
  - NALCN: added new leak conductance ($g_{leak,na}$) to represent NALCN; lowered $[Ca^{2+}]_o$ modulates conductance as follows: new $g_{leak,na}$ = base $g_{leak,na}$ *11.94/[1 + 6.04*e^(1.98*log($[Ca^{2+}]_o$))].[2]
- Ran both separately with $[Ca^{2+}]_o$ at every 0.1 step between 2.0 and 0.1 mM (inclusive) for 300 ms.

Results

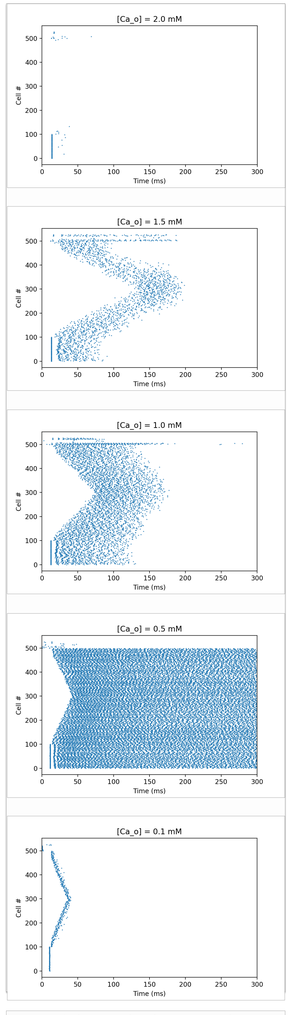

Figure 1: Spike raster plots demonstrating the impact of decreasing $[Ca^{2+}]_o$ influencing VGSCs in the dentate gyrus. Each dot represents a neuron firing at the specified time.

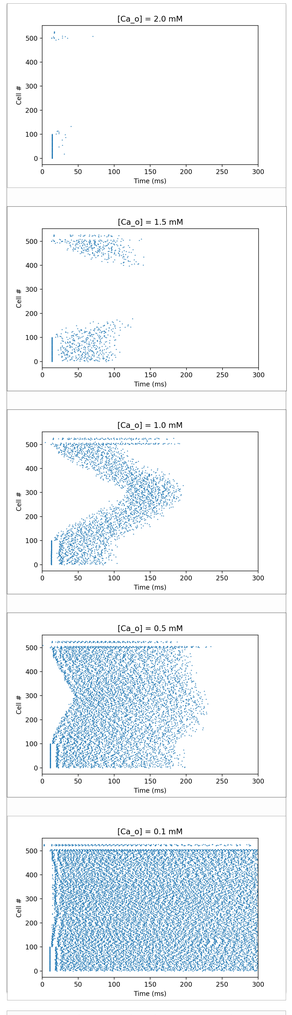

Figure 2: Spike raster plots demonstrating the impact of decreasing $[Ca^{2+}]_o$ influencing NALCN in the dentate gyrus. Each dot represents a neuron firing at the specified time.

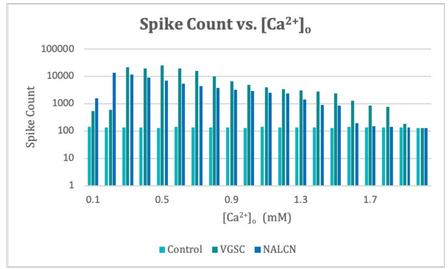

Figure 2: Spike counts at different $[Ca^{2+}]_o$ concentrations for VGSC, NALCN, and control channels.

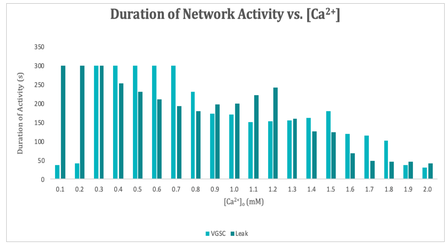

Figure 3: A bar graph comparing the durations of network activity between the VGSC and NALCN channels at different $[Ca^{2+}]_o$. Note: durations are capped at 300 ms due to simulation time.

Trends

- For VGSCs, activity increases as $[Ca^{2+}]_o$ decreases from 2 mM to ~0.3 mM.
- After ~0.3 mM, lowered $[Ca^{2+}]_o$ no longer has effect on excitability in the VGSC model.
  - This may be due to inhibitory effects of low $[Ca^{2+}]_o$ (such as inactivated Ca^{2+}-gated potassium channels) overpowering the VGSC effect.
- NALCN is initially slow to increase but continues to increase to lower $[Ca^{2+}]_o$ ranges while VGSC activity is suppressed.
  - This could explain the observation by Lu et al. (2010) that cells without NALCN don't show the same increased excitability; mid-range $[Ca^{2+}]_o$ between 0.1 mM and 2.0 mM was not emphasized in their study.

Conclusions

- Decreased $[Ca^{2+}]_o$ leads to increased excitability in our model.
- Confirms role of VGSCs and NALCN in hypocalcemic hyperexcitability.
- Limitations of this study:
  - Only observed two out of many neuronal mechanisms influenced by $[Ca^{2+}]_o$.
  - VGSC code used values from amphibian neurons.
  - NALCN code used approximated values.
- First step in using computational modeling to simulate correlation between hypocalcemia and seizures.
- Future studies can build on our approach to further study mechanisms for hypocalcemia-induced seizures.

Literature Cited

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