Modeling Neuroinflammatory Pathways of Astrocytes, Microglia, and Neurons

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Abstract

Recent findings suggest that astrocytes play a critical role in CNS health and influence the onset of neurodegenerative diseases such as ALS, Parkinson's Disease, and Alzheimer's Disease.[1] However, little is known about how astrocytes, which normally serve a neuroprotective role, are transformed into a cell that helps to trigger neuron death. In order to gain insight into this mechanism, we developed two models that offer insight as to how neuroinflammatory agents modulate calcium oscillations within the astrocytes. The first model we constructed, which we title "the core model", represents homeostatic oscillatory patterns of an astrocyte that can be manipulated to simulate the presence of glutamate. In addition to this, because our research findings suggest that ATP and glutamate stimulate the same isoenzyme that directs the production of IP_3,[5] we developed an "extended model" that represents an additional ATP stimulus on the astrocyte. We plan to expand our model to continuously integrate more dynamics of the chemical agents that connect the signals between neurons, microglia, and astrocytes and look for crucial patterns that could lend insight to these complex neurodegenerative diseases.

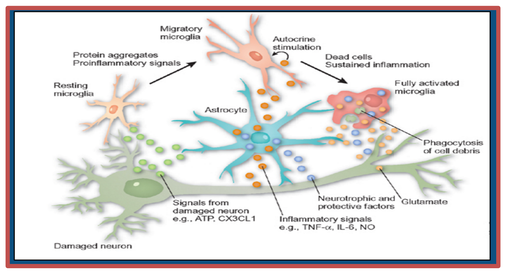

Figure 1. Graphic Illustration of simplified neuroinflammatory pathways of neurons, astrocytes, and microglia.
Illustration taken from Appel *et al.* 2009

Background

Astrocytes are a cell type often found proximal to the neuron's synaptic gap and are involved in maintaining neuronal health in the central nervous system. Recently, astrocytes have gained attention due to their contribution to neuronal homeostasis and their ability regulate a wide variety of neurotrophic factors within the neuronal environment. Experiments suggest that that astrocytes use oscillations in their cytosolic calcium concentration to relay signals from one cell to another.

Despite the importance of understanding the astrocyte's oscillatory calcium mechanism, due to the complexity of the cell it is not possible to experimentally examine the entire process as a whole. Computational models, however, allow for the construction of a virtual cell, one that contains the chemicals deemed most important to the oscillatory process. Models reduce an extremely complex system down to the features that are expected to capture physiological processes. Ideally, they can be used in conjunction with experimental data to gain insight into the mechanism, and potentially, allow for the development of pharmaceutical agents that inhibit or stop deconstructive pathways that develop, such as those postulated in neurodegenerative diseases.

Using the literature and prior work in the Hemkin lab, we constructed two new models to theorize how neuroinflammatory signals could alter intracellular calcium dynamics. The first model we developed is a hybrid of two previous models that have provided insight as to how Ca^{2+} oscillations are modulated by an intracellular protein, IP_3 .[2,4] This model can also give insight to how a glutamate stimulus alters these modulations. Our extended model expands on this core model and predicts how the chemical dynamics of IP_3 is directly affected by additional extracellular signals such as ATP (Figure 1).

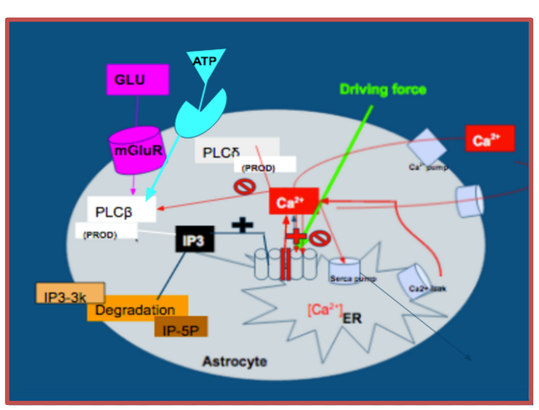

Fig. 1 Overview of model

d/dt ($Ca_{cytosol}$) = +IP3R - SERCA +Jleakext->cyt

Li Rinzel *et al.* 1994 -> sub in IP3 production and degradation term from G-CHI model (De Pitta *et al.* 2009)

d/dt ($IP3_{cytosol}$) = +PLCβ / PLCδ prod. – degradation
(De Pitta *et al.* 2009; Tewari *et al.* 2012)

d/dt (h) = Wallach *et al.* 2014 (no noise)

Experimental Design

To ensure our model simulated physiological processes, we used experimental literature to help construct a mathematical representation that offers insight to the chemical dynamics of the astrocyte.

Li Rinzel *et al.* 1994 developed a conventional two-variable system that models Ca^{2+} oscillations modulated by the IP_3 receptor located in the membrane of the endoplasmic reticulum.[4] De Pitta *et al.* 2009 enhanced the model to a three variable system that accounts for the production and degradation of IP_3. IP_3 production is dependent on the stimulation of two isoenzymes, PLCβ and PLCδ. While PLCδ is activated by raised cytosolic calcium levels, PLCβ is activated via external stimuli.[2] More specifically, De Pitta *et al.* 2009 proposed a model in which a glutamate stimulus factor could alter intracellular Ca^{2+} oscillations. Tewari *et al.* 2012 created a specific glutamate variable that could be altered to better simulate physiological conditions.[6]

Our goal was to predict how chemical concentrations in the astrocyte would change over time when presented with a stimulus such as ATP or glutamate. To accomplish this, our model was expressed with differential equations and the behavior of the system through time was projected using the numerical integration software of Berkeley Madonna.

Results

Core model

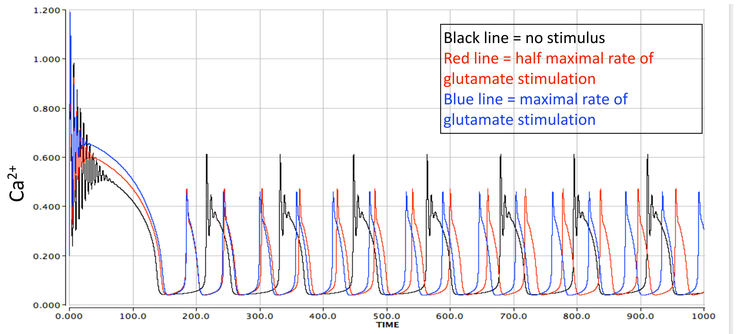

Figure 2. Changes in intracellular Ca^{2+} levels with respect to time with glutamate stimulation. In our core model, we analyzed how glutamate affects intracellular levels by manipulation of the variable vB, which represents the maximal rate of IP_3 production by PLCβ. In theory, because glutamate directly stimulates the production of PLCβ (De Pitta *et al.* 2009), we propose that manipulating vB offers insight to how glutamate has direct effect on cytosolic calcium lev els. (see model details)

Extended model

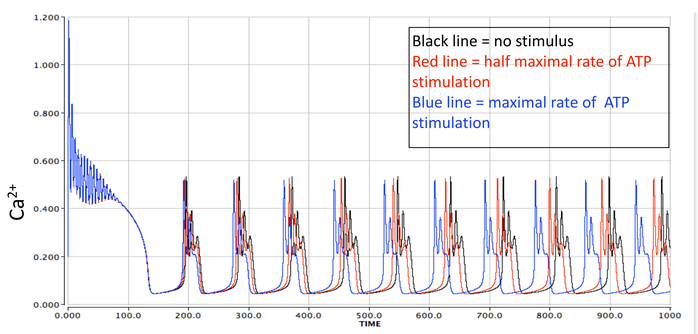

Figure 3. Changes in intracellular Ca^{2+} levels with respect to time with glutamate and ATP stimulation. In our extended model, we added a term to represent how ATP affects IP_3 production via the same pathway as glutamate, thus an added term to represent ATP stimulation can take the same form of the term that represents glutamate. In this model, we held vB at a constant value (0.5) and altered the amount of stimulation from ATP by manipulating the variable va, which we set to represent another term that reflects IP_3 production by PLCβ.

Model Specifics

Core Model:

$$\frac{d[Ca^{2+}]cyt}{dt} = \left(v1 * \left(\frac{IP_3}{IP_3+dip3}\right)^3 * \left(\frac{Ca^{2+}}{Ca^{2+}+dact}\right)^3 * h^3 + v2\right) * (c0 - (1+c1) * Ca^{2+}) - v3 * \left(\frac{Ca^{2+}}{Ker + Ca^{2+}}\right)^2$$

$$\frac{d[IP_3]}{dt} = vB * Hg * (Odelt * \left(\frac{Kdelt}{Kdelt+IP_3}\right) * \left(\frac{Ca^{2+}}{Ca^{2+}+bigK}\right)^2) - (v3k * Hkd * Hk3) - (r5IP_3 * IP_3)$$

$$\frac{d[h]}{dt} = ohm * (hinf * h)$$

$$\frac{d[g]}{dt} = nv * gv * E - gc * g$$

$$\frac{d[R]}{dt} = \frac{I}{trec} - R$$

$$\frac{d[E]}{dt} = -\frac{E}{inac} + R$$

$$\frac{d[c0]}{dt} = Ea * jin - v4 * \left(\frac{Ca^{2+}}{Ca^{2+}+kpl}\right)^2$$

Where:

$$Hkd = \left(\frac{Ca^{2+}}{Ca^{2+}+KD}\right)^4$$

$$Hk3 = \frac{IP_3}{IP_3+K3}$$

$$Hg = \frac{g}{g + (1 + \left(\frac{KP}{KR}\right) * \left(\frac{Ca^{2+}}{Ca^{2+}+Ktt}\right))}^{0.7}$$

$$ohmh = \frac{(O2*d2*(IP_3+d1)+O2*(IP_3+d3))}{IP_3+d3}$$

$$hinf = d2 * \frac{IP_3+d1}{d2*(IP_3+d1)+(IP_3+d3)*Ca^{2+}}$$

Extended model:

$$\frac{d[IP_3]}{dt} = (vB * Hg) + (va * Hatp) * (Odelt * \left(\frac{Kdelt}{Kdelt+IP_3}\right) * \left(\frac{Ca^{2+}}{Ca^{2+}+bigK}\right)^2) - (v3k * Hkd * Hk3) - (r5IP_3 * IP_3)$$

Where:

$$Hatp = \frac{atp}{atp + (1 + \left(\frac{KP}{Katp}\right) * \left(\frac{Ca^{2+}}{Ca^{2+}+Ktt}\right))}^{0.7}$$

Parameters:

c1 = 0.185
v1 = 40 sec^{-1}
dIP_3 = 0.2 µM
dact = 0.4 µM
v2 = 0.02 sec^{-1}
v3 = 0.6 µM sec^{-1}
Ker = 0.18 µM
Ea = 0.01
Jin = 0.8 µM
v4 = 1.8 µM
K3 = 1 µM
trec = 0.8 sec
tinac = 0.003 sec
nv = 2
gv = 0.6 µM
gc = 0.1 sec^{-1}
O2 = 0.62 $\mu M^{-1} sec^{-1}$
d2 = 1.049
d1 = 0.13 µM
d3 = 0.9434 µM
kpl = 0.1 µM
vB = 0.5 µM sec^{-1}
KR = 1.3 µM
KP = 10 µM
Ktt = 0.6 µM
v3k = 0.5 µM sec^{-1}
KD = 0.7 µM
Odelt = 0.4641 µM sec^{-1}
Kdelt = 1.5 µM
bigk = 0.1 µM
va = 0.5 µM sec^{-1}
Katp = 0.0002

Conclusions

Our model successfully represents literature findings that altering glutamate (Figure 2) and ATP (Figure 3) dynamics can directly modulate calcium oscillations via IP_3, including changes in the frequency and amplitude of the behavior. To test the validity of our results, the next step of our project is to construct a phase diagram to see how the oscillations in our model change under simulation of various physiological conditions. By comparing these results to experiment, we can adjust our model to more accurately mimic actual Ca2+ oscillations, and this should allow us to gain insight to mechanism functioning in the biological system.

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Acknowledgments

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