A model of mGluR-dependent calcium oscillations in lamprey spinal cord neurons

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Abstract

Slow Ca^2+ oscillations caused by release from intracellular stores have been observed in neurons in the lamprey spinal cord. It has been shown that they are triggered by activation of metabotropic glutamate receptors on the cell surface. The pathway leading from receptor activation to the IP3-mediated release of Ca^2+ from the endoplasmatic reticulum (ER) has been modelled in order to facilitate further understanding of the nature of these oscillations. The model generates Ca^2+ oscillations with a frequency range of 0.01-0.09 Hz, as compared to 0.005-0.033 in the lamprey. A prediction of the model is that the frequency will increase with a stronger extracellular glutamate signal.

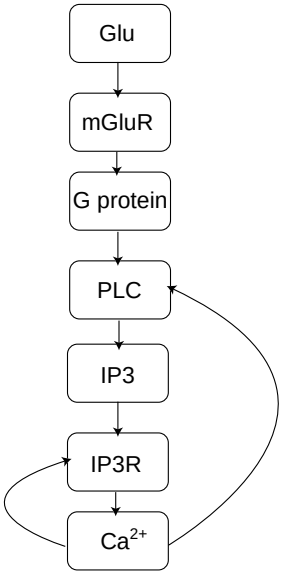

Figure 1: The main components of the pathway considered in this model.

Summary

Calcium is an important intracellular messenger molecule, both in neurons and other cells. Cells at rest have a cytoplasmic Ca^2+ level around 0.1 μM [1], but the concentration is dynamically regulated and can rise to approximately 1μM during oscillations [3]. The increase is mainly caused by release of calcium ions from intracellular stores, the most important of which is the endoplasmatic reticulum (ER). Gated channels such as the IP3 receptor (IP3R) induce the release of calcium ions from the ER, and ionic pumps work in the other direction to bring Ca^2+ into the ER.

Intracellular, IP3-mediated calcium oscillations have been observed in the lamprey. These oscillations are dependent on activation of metabotropic glutamate receptors (mGluR) on the cell surface [4]. The mGluRs, in turn, activate G proteins that initiate a biochemical cascade which ends in the binding of IP3 to the IP3R and a subsequent release of calcium from the ER. Figure 1 shows the main components in the biochemical pathway leading from mGluR activation up to IP3-induced release of calcium ions from the ER.

The pathway has been modelled with coupled differential equations based on standard biochemical kinetics. The equations were solved using the XP-

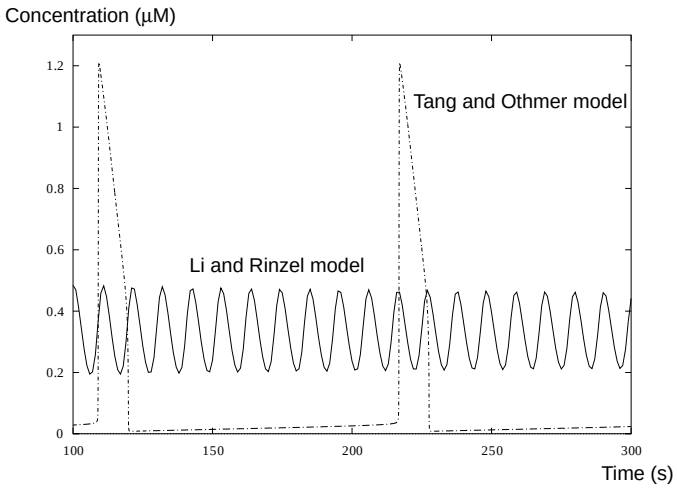

Figure 2: Calcium level oscillations produced using the two different IP3R models.

PAUT package [2]. Binding constants and other parameters were based on values found in literature, although some of them have had to be modified in order to obtain the right qualitative behaviour.

The model readily gives rise to oscillations in intracellular calcium levels across a frequency range of 0.01-0.09 Hz. This is in agreement with experimental data, where the frequency varies between 0.005 and 0.033 Hz. Two different models of the IP3 receptor, described in ([5], [6]) respectively, have been used and generate oscillations with different shapes and frequencies. Calcium concentrations plots from sample runs with the two receptor models are shown in Figure 2.

Our model generates calcium oscillations both when IP3 levels oscillate and when they do not. It is not known from experiments whether IP3 levels do in fact oscillate. One of the testable predictions of the model is that an increased extracellular glutamate signal should give rise to oscillations of a higher frequence, regardless of the IP3R model used.

It has been shown that Ca^2+ oscillations caused by mGluR activation have a distinct effect on the locomotor pattern in lamprey: they decrease its frequency. We plan to use this mathematical model to understand the reason for this. The biochemical model of the pathway will eventually be integrated into a previously existing biophysical model of a spinal lamprey neuron.

References

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