506f Determination and Analysis of the Dynamic Mechanisms That Precede Long-Term Depression in Cerebellar Purkinje Cells

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Introduction

One cellular basis for learning is the phenomenon of synaptic plasticity that has been observed experimentally in neurons. An important form of synaptic plasticity related to motor-learning tasks such as the vestibular-ocular reflex, eye-blink conditioning, and motor coordination is observed in cerebellar Purkinje cells [1]. This particular form of synaptic plasticity, known as long-term depression (LTD), is a lasting decrease in the activity of the synapses between spines on the Purkinje cell dendrites and axons of neighboring granule cells, often referred to as parallel fibers (PF).

It has been shown experimentally that LTD is induced by the repeated association of the PF and climbing fiber (CF) inputs [2]. Activation of either the PF or CF results in signaling events involving ionic calcium (Ca^{2+}). In the case of the CF, the resulting depolarization of the Purkinje cell opens voltage-sensitive calcium channels (VSCC) allowing for delocalized Ca^{2+} entry into the cytosol from the extracellular space. Activation of the PF results in release of glutamate across the synapse that is then detected by metabotropic glutamate receptors (mGluR) on the neighboring Purkinje spine. A signaling pathway is then activated resulting in the release of Ca^{2+} from the endoplasmic reticulum (ER) mediated by the inositol-1,4,5-trisphosphate receptors (IP_3R). This pathway includes a strong, nonlinear feedback mechanism in which Ca^{2+} release stimulates further Ca^{2+} release (known as calcium-induced calcium release (CICR)) up to a threshold Ca^{2+} concentration at which the mechanism begins to inhibit further Ca^{2+} release [3]. This implies that the CICR mechanism is able to switch from predominately positive feedback to predominately negative feedback as a function of the system conditions. A unique feature of Purkinje cells, as compared to other neuronal cells, is that the IP_3R are present in a much higher abundance and are much less sensitive to IP_3 *in vivo*.

Ca^{2+} elevation has been shown to be required for LTD induction in Purkinje cells (e.g., Refs. #2 and 4). It has been found experimentally that coincident activation of the PF and CF inputs results in a supralinear increase in $[Ca^{2+}]$. In other words, the change in $[Ca^{2+}]$ that is observed is significantly more than the sum of the Ca^{2+} responses obtained by exciting the PF and CF separately [5]. It is hypothesized that this strongly nonlinear response is the mechanism by which the cell detects the coincident activation of the PF and CF and is the first step in the mechanism leading to LTD. Under normal coincident activation conditions, these supralinear spikes are confined to single spines. Given the importance of Ca^{2+} signaling to the induction of the mechanisms leading to LTD, the objective of this work is to use mathematical models of a Purkinje cell that focus on the relevant Ca^{2+} signaling networks to investigate the significance of certain unique characteristics of the Purkinje cell in terms of LTD induction. The results of this work will aid in identifying those features of the cell that are most critical to the onset of LTD, including consideration of both biochemical and geometrical effects, and will provide an appreciation of the degree of robustness of the LTD-induction system. The wide availability of experimental data on Ca^{2+} dynamics in Purkinje cells makes such a modeling study feasible.

Modeling

The model developed in this work is based on a Ca^{2+} dynamics model identified in a study of neuroblastoma cells [6]. Initial modeling and simulation were performed using the Virtual Cell (http://vcell.org) biological modeling framework [7]. The model analyzed here is a compartmental (i.e., ODE) representation of a Purkinje spine that accounts for binding of Ca^{2+} to buffers (parvalbumin and calbindin), Ca^{2+} entry into the cytosol due to CF activation, diffusion of all species through the spine

neck into the dendritic shaft, extrusion of Ca^{2+} into the extracellular space, pumping of Ca^{2+} into the ER, and release of Ca^{2+} from the ER stores through the IP_3R. The IP_3R model used here is the widely-accepted, low-order model of Li and Rinzel [8]. Parameters for the model were taken from various literature sources. The parameters in the IP_3R model that determine the abundance and sensitivity of the IP_3R were adjusted to correspond to the higher abundance and reduced sensitivity of the IP_3R. Model outputs were compared with existing experimental data when available.

Results

The results demonstrate that the model is able to reproduce the supralinear Ca^{2+} spike observed during coincident PF and CF activation. The magnitude of the spike is approximately 10 times that of the linear sum of the Ca^{2+} transients observed during independent PF and CF activation, consistent with what is observed experimentally [4]. The CICR phenomenon and its switching between positive and negative feedback at the IP_3R is found to be a key component of the mechanism underlying the supralinear Ca^{2+} response. Elimination of the CICR feedback mechanism from the model prohibits the formation of the supralinear Ca^{2+} spike. The nominal parameter set allows the system to demonstrate a bifurcation between Ca^{2+} steady-states which is driven by $[IP_3]$, thus resulting in the strong supralinear change in $[Ca^{2+}]$ during coincident activation given CICR. When a parameter set corresponding to the abundance and sensitivity of IP_3R in other neuronal cells is used, the bifurcation behavior is not observed. In addition, the low sensitivity of the IP_3R is necessary to localize the Ca^{2+} spike to the intended spine and to prohibit Ca^{2+} spikes from forming in the dendritic shaft.

The results show that a second component of the mechanism underlying the supralinear behavior is the role of the Ca^{2+} buffers. Under nominal conditions, the buffers bind more than 99% of the cytosolic Ca^{2+}. During the supralinear spike, the ratio of free Ca^{2+} to bound Ca^{2+} in the cytosol increases by more than an order of magnitude. This result implies that a disproportionate amount of Ca^{2+} is not being bound to the buffers, likely due to buffer saturation. While the bound form of the buffers are free to diffuse from the spine to the proximal region of the dendritic shaft and be replaced by unbound buffers, timescale decomposition indicates that the rate of diffusion through the spine neck is relatively slow as compared to the rate of formation of the Ca^{2+} spike. Simulations in which the radius of the spine neck is increased to ease diffusion through the neck demonstrate a lack of the supralinear behavior. The rate of Ca^{2+} binding to the buffers is found to be relatively negligible in all instances.

The results show that the unique abundance and sensitivity of the IP_3R are necessary for the induction of the supralinear Ca^{2+} behavior. In addition, the rates of diffusion of the species through the spine neck and the capacity of the Ca^{2+} buffers are also critical. The system shows a very low degree of robustness to these features as relatively small changes in any of the corresponding model parameters results in a loss of the supralinear Ca^{2+} behavior and, therefore, a loss of LTD.

References

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