Morphological Control of $InsP_3$-Dependent Calcium Release in Spiny Dendrites

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ABSTRACT

The synaptic inputs on cerebellar Purkinje cells occur at distinct structures, called spines, that protrude from the dendrites. The spines have an approximately spherical shape with a diameter of about 1 μm and are connected to the dendrite via a narrow neck that has been shown to cause a diffusion barrier. Long term depression of synaptic strength requires inositol-1,4,5-trisphosphate ($InsP_3$)-mediated calcium release, but the Type 1 $InsP_3$ receptor in the Purkinje cell, while highly abundant, is extraordinarily insensitive to $InsP_3$. We have applied the *Virtual Cell* modeling system (described in the paper by Schaff et al.) to try to resolve this apparent paradox. Both 1D and 2D spatial models were based on experimental image data; kinetics describing $InsP_3$ production, calcium release, calcium pumping, and calcium binding to buffers were all explicitly incorporated into the model with parameters constrained by experiment. A single stimulus of a single spine produces a robust $InsP_3$ signal that is, however, insufficient to release Ca^{2+}. Multiple stimuli of a single spine, as from a train of synaptic firings, can be integrated over short timescales (100 – 500ms) to locally release Ca^{2+} within the spine, but not in the adjacent dendritic branchlet. A key origin of this spatial confinement is the buildup of $InsP_3$ in the spine due to the presence of the diffusion barrier at the spine neck. Interestingly, however, localization of the calcium signal also requires both the low sensitivity of the receptor and its high density throughout the dendrite. The low sensitivity of the receptor has the effect of widening the dynamic range of its response to $InsP_3$ assuring a minimal response in the dendritic branchlet, while the high density assures a sufficiently rapid response in the spine. (Supported by NIH grants GM35063 and RR13186)