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Poster presentation

Neurogranin provides a kinetic proof reading mechanism for decoding Ca^{2+} signals that may govern the induction of synaptic plasticity

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At excitatory synapses of hippocampal CA1 pyramidal neurons, the activation of postsynaptic calcium/calmodulin-dependent protein kinase II (CaMKII) by calmodulin (CaM) during a brief high magnitude elevation of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) results in LTP induction. Conversely, the same protein, CaM, activates PP2B (calcineurin) during a prolonged modest rise of $[Ca^{2+}]_i$ that induces LTD [1,2]. We would like to understand the mechanism by which the same protein (CaM) can activate one process while suppressing the other?

One possible candidate protein with the potential to regulate CaM distribution among its targets is neurogranin (Ng or also called RC3). Ng is a 78 amino acid neuronal protein enriched in CA1 pyramidal neurons that interacts with the C-terminal lobe of CaM both in the presence and absence of Ca^{2+} [3]. Interestingly, the N-terminal lobe of CaM binds dephospho-CaMKII tighter than the C-terminal lobe and Ng accelerates the Ca^{2+} dissociation from the C-terminal lobe of CaM in the presence of CaMKII [3]. The dissociation of Ca^{2+} promotes the dissociation of CaM from its target. However, once autophosphorylated at Thr286, CaMKII becomes resistant to the action of Ng and binds CaM with much higher affinity than PP2B [3,4]. Lastly, an extended exposure of Thr286-phosphorylated CaMKII to lower Ca^{2+} concentrations leads to a slow CaM dissociation followed by an inhibitory phosphorylation at Thr305/306, which in turn prevents the rebinding of CaM to CaMKII [5]. This inhibitory phosphorylation may a mechanism to prevent (unintended) LTP induction through a stochastic and accidental autophosphorylation of CaMKII.

Here we use a simple but realistic mathematical model constructed on experimental data of Ca^{2+}-CaM-Ng-CaMKII interactions and investigate the potential kinetic proof reading mechanism underlying the induction of synaptic plasticity in CA1 pyramidal neurons [6,7]. We specifically test if the kinetic mechanism described above and the simulated pattern/dynamics of Ca^{2+} dependent PP2B/CaMKII activation is consistent with the reported induction protocols of synaptic plasticity, especially with that of the synaptic timing dependent plasticity (STDP). We also examine the role of Ng using experimental data of Ng knockout animals [8]. These simulation results support the idea that Ng serves as a kinetic barrier of CaMKII activation and proofreads Ca^{2+} transients during induction of plasticity.

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