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Induction and binary expression of LTP/LTD in a minimal model of the CaMKII system

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The calcium/calmodulin-dependent protein kinase II (CaMKII) plays a key role in the induction of long-term post-synaptic modifications following synaptic activation. Experiments suggest that these long-term synaptic changes are all-or none switch-like events between discrete states [1]. The biochemical network involving CaMKII and its regulating protein signaling cascade has been hypothesized to durably maintain the evoked synaptic state in the form of a bistable switch [2,3]. However, it is still unclear whether different experimental LTP/LTD protocols lead to corresponding transitions between the two states in models of such a network. Furthermore, the biochemical mechanisms and signaling cascades giving rise to the non-linearities exhibited during LTP/LTD induction remain elusive.

Starting from a detailed biochemical model, a minimal model describing the CaMKII phosphorylation (activation) level is presented which preserves the features of a comprehensive description. CaMKII autophosphorylation is governed by calcium/calmodulin binding and is a highly cooperative process. CaMKII dephosphorylation is mediated by protein phosphatase 1 whose activity is indirectly regulated by a calcium-dependent balance of kinase (protein kinase A) and phosphatase (calcineurin) activity. These two competing effects are implemented via phosphorylation- and dephosphorylation rates changing the CaMKII phosphorylation level and are realized as simple step functions activating above different calcium levels.

The model retains previous results [2,3], two stable states of CaMKII phosphorylation exist at resting intracellular calcium concentrations. With an appropriate positioning of the de-/phosphorylation thresholds, high calcium transients can switch the system from the weakly-(DOWN) to the highly-phosphorylated (UP) state of the CaMKII (similar to a LTP event) and intermediate Ca(2+) concentrations can lead to switching from the UP to the DOWN state (similar to a LTD event). As a basic principle, this can be achieved if the CaMKII dephosphorylation activates at lower Ca(2+) levels than phosphorylation. This simple approach allows us to address whether or not a read-out system using the calcium level as the sole input signal can account for the non-linearities exhibited during LTP/LTD induction. It is shown that this simple realization of the CaMKII system can qualitatively reproduce experimental plasticity results in response to spike-timing dependent plasticity (STDP) protocols (spike-pairs and -triplets), presynaptic stimulation protocols and pairing protocols. Our investigations show that a minimal model of the CaMKII protein network can account for both induction (through LTP/LTD-like transitions) and storage (due to its bistability) of synaptic changes. However, we suggest that the dynamics of the global calcium time course play a crucial role for the sign of synaptic changes alongside the cross-talk between signaling cascades that include the one considered here.

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