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Nonlinear behavior of kinetics of calmodulin-calcium complexes

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Experimental data obtained in last decade indicate that calcium concentration in postsynaptic intracellular solution can trigger long-term plasticity [1]. According to the "calcium control hypothesis", the low concentration of intracellular calcium $[Ca^{2+}]_i$ does not change synaptic conductivity, whereas middle and high concentrations induce LTD and LTP respectively. Such dependence requires the sensitivity of synaptic modification to be nonlinearly related to peak calcium concentration [2]. However, the calcium ions penetrated into cell are mostly bound by calmodulin (CaM), a small (16.8 kDa) ubiquitous Ca^{2+} binding protein. A CaM molecule can bind four calcium ions by two sites in C-lobe and N-lobe [3,4]. Stopped flow fluorescence studies [5,6] showed that these two sites are quasi independent and have different association/dissociation reaction constants [3,4]. Here, the minimalistic single compartment model of chemical kinetics of eight calmodulin-calcium complexes is presented.

The model is based on assumption that only double and single component reactions are going in system. The full graph of chemical reactions contains 24 association/dissociation reactions and is converted into system of nine ordinary differential equations (ODE). Free calcium concentration is presented as ODE for open system including first order, not zero intracellular calcium extrusion, square pulse calcium influx and all association and dissociation reactions with calmodulin. All simulations are performed using the interactive differential equation simulation package XPP [7]. The differential equations were integrated by fourth-order Runge-Kutta method with adaptive step built into XPP.

The simulation results show that each complex has unique dynamics. The amplitudes and moments of maximum concentrations and decay time constants vary for different complexes, and the curve of peak complex concentration to calcium injection obeyed the Michaelis-Menten-Henri law with different power coefficients. The time courses of complexes concentrations allow to separate complexes into five groups according to moment of maximal amplitude and decay time constant: early maximum moment and fast or middle decaying groups, belated maximum and fast or middle decaying groups and farther-slow group. This division and nonlinearity of peak concentrations show that different calmodulin-calcium complexes may be used as basic components for reconstruction of dependency curves of synaptic weight from free calcium concentration [2].

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