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Modeling of CREB Pathway Induced Gene Induction: From Stimulation to Repression

Authors : K. Julia Rose Mary, Victor Arokia Doss

Abstract : Electrical and chemical stimulations up-regulate phosphorylaion of CREB, a transcriptional factor that induces its target gene production for memory consolidation and Late Long-Term Potentiation (L-LTP) in CA1 region of the hippocampus. L-LTP requires complex interactions among second-messenger signaling cascade molecules such as cAMP, CAMKII, CAMKIV, MAPK, RSK, PKA, all of which converge to phosphorylate CREB which along with CBP induces the transcription of target genes involved in memory consolidation. A differential equation based model for L-LTP representing stimulus-mediated activation of downstream mediators which confirms the steep, supralinear stimulus-response effects of activation and inhibition was used. The same was extended to accommodate the inhibitory effect of the Inducible cAMP Early Repressor (ICER). ICER is the natural inducible CREB antagonist represses CRE-Mediated gene transcription involved in long-term plasticity for learning and memory. After verifying the sensitivity and robustness of the model, we had simulated it with various empirical levels of repressor concentration to analyse their effect on the gene induction. The model appears to predict the regulatory dynamics of repression on the L-LTP and agrees with the experimental values. The flux data obtained in the simulations demonstrate various aspects of equilibrium between the gene induction and repression.

Keywords : CREB, L-LTP, mathematical modeling, simulation
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