BMC Neuroscience

Poster presentation

Open Access

Long term maintenance of synaptic plasticity via CPEB mediated local translation control at synapses

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from Sixteenth Annual Computational Neuroscience Meeting: CNS*2007
Toronto, Canada. 7–12 July 2007

Published: 6 July 2007

BMC Neuroscience 2007, **8**(Suppl 2):P96 doi:10.1186/1471-2202-8-S2-P96

The persistent change in synaptic efficacy, which is a basis of long term memory and learning, depends on synthesis of new proteins. The phenomenon of late long-term potentiation (L-LTP), the persistent activity dependent enhancement of synaptic efficacies, is protein synthesis dependent. The main objective of this work is to explore a possible link between activity dependent temporal and spatial regulation of gene expression and life long stability of some memories despite the rapid turnover of their molecular substrates. This work is motivated by the following three experimental observations. 1. L-LTP requires new protein synthesis but not new mRNAs [1,2]. 2. Some local mRNAs encode proteins which regulate the synaptic functions e.g., αCaMKII-mRNA encodes the αCaMKII, which has crucial role in activity induced L-LTP [3-5]. 3. Almost all the components of translational machinery are constitutively localized in dendrites [6-8]. Here, we propose a hypothesis that a molecular loop between a kinase and a translation regulation factor acts as a bistable switch to stabilize activity induced synaptic plasticity over long periods of time. We implement one possible instantiation of such a loop; an αCaMKII-CPEB molecular pair. Our proposed model of translation regulation is based on αCaMKII induced phosphorylation of CPEB at synapses which can trigger the cytoplasmic polyadenylation initiated translation of αCaMKII-mRNA at synapses in CPE dependent manner. We show that αCaMKII-CPEB loop can operate as a bistable switch. Our results imply that L-LTP should produce a significant change in the total amount of αCaMKII at potentiated synapses, but that the fraction of phosphorylated αCaMKII only moderately changes. By carrying out bifurcation analysis we identify the key parameters that determine whether the system is in a bistable region, this could indicate the key parameters that should be measured experimentally. We also demonstrate that a partial block of αCaMKII translation in the induction phase of L-LTP can block L-LTP, but a partial block of translation in the maintenance phase might not block L-LTP. Our results provide a possible explanation for why the application of protein synthesis inhibitors at the induction and maintenance phases of L-LTP can have a very different outcome. This proposed molecular switch, based on translation initiated by phosphorylation, provides the mechanistic basis both for persistency and input specificity during L-LTP.

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