BMC Neuroscience

Poster presentation

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The regulatory role of NO-PKG in the cerebellar long-term depression

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from Eighteenth Annual Computational Neuroscience Meeting: CNS*2009
Berlin, Germany. 18–23 July 2009

Published: 13 July 2009

BMC Neuroscience 2009, **10**(Suppl 1):P198 doi:10.1186/1471-2202-10-S1-P198

This abstract is available from: http://www.biomedcentral.com/1471-2202/10/S1/P198

Introduction

Long-term depression (LTD) is a persistent decrease in the efficacy of synaptic transmission that results from the removal of AMPA receptors (AMPARs) from the postsynaptic cellular membrane [1]. In Purkinje cells, LTD can be induced by increasing the postsynaptic calcium concentration ($[Ca^{2+}]$) using flash photolysis of caged Ca^{2+} [2], which indicates that other second messengers are not fundamental to the occurrence of LTD. However, recent experimental data pointed out that nitric oxide (NO)-cGMP-dependent protein kinase (PKG) pathway can act upstream of Ca^{2+}-signals to regulate Ca^{2+}-induced LTD To gain insights on the biochemical mechanisms involved in this process, we built a computational model to simulate the cerebellar LTD.

Methods

The model consists of a biochemical network composed by the principal pathways involved in the LTD (NO-PKG, conventional protein kinase C (PKC) pathway, and mitogen-activated protein kinase (MAPK) pathway). NO-PKG pathway has two targets in our model: inositol 1,4,5-trisphosphate receptor (IP_3R) and G substrate. PKG phosphorylates IP_3R causing an increase in its affinity for IP_3 [3]. Furthermore, PKG phosphorylates G substrate promoting its binding to protein phosphatase 2A (PP2A), which inhibits its activity. All those biochemical reactions were adapted from previous theoretical works [2,4,5] or were constructed according to experimental data. The model was implemented with the program STEPS.

Results and discussion

As an initial stage of our work, we simulated LTD induced by flash photolysis of caged Ca^{2+} and our results show a correlation between the magnitude of LTD and the amplitude of the postsynaptic $[Ca^{2+}]$, as has been demonstrated previously [1]. To verify the role of NO-PKG pathway in this situation, we simulated the presence of a NO donor (spermine NONOate) while uncaging Ca^{2+}, and our results indicate that NO-PKG pathway decrease the half-maximum $[Ca^{2+}]$ required to induce LTD. We simulated the inhibition of PKG under the same condition, and, during this situation, the alteration in the half-maximum $[Ca^{2+}]$ concentration was not observed. Additionally, we were able to inhibit systematically the catalytic action of PKG on IP_3R and G substrate, and our results indicate that both phosphorylations are important to the regulatory role of NO-PKG pathway in the cerebellar LTD. We have similar results to LTD induced by synaptic activity. As a conclusion, our results pointed out that although cerebellar LTD can be induced only by increasing postsynaptic $[Ca^{2+}]$, NO-PKG pathway modulates this process through its action on IP_3R and PP2A activity.

Acknowledgements

We thank Keiko Tanaka and George Augustine for sharing their data.

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