7-19-2008

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Rajanikanth Vadigepalli
Department of Pathology, Thomas Jefferson University, Philadelphia, PA 19107, USA, raj@mail.dbi.tju.edu

BMC Neuroscience

Poster presentation

Open Access

Multi-scale modeling of angiotensin II induced neuronal regulatory mechanisms in the brain

Rajanikanth Vadigepalli*, Dirk Fey and James S Schwaber

Address: Department of Pathology, Thomas Jefferson University, Philadelphia, PA 19107, USA

Email: Rajanikanth Vadigepalli* - raj@mail.dbi.tju.edu

* Corresponding author

from Seventeenth Annual Computational Neuroscience Meeting: CNS*2008
Portland, OR, USA. 19–24 July 2008

Published: 11 July 2008

BMC Neuroscience 2008, **9**(Suppl 1):P47 doi:10.1186/1471-2202-9-S1-P47

This abstract is available from: http://www.biomedcentral.com/1471-2202/9/S1/P47

Introduction

In this study, we focus on the multi-scale dynamics involved in neuronal regulatory mechanisms at two levels: signaling dynamics elicited by neuropeptide receptors and their crosstalk with the electrophysiological processes. The particular system considered is the angiotensin II (AngII) receptor type 1 (AT1R) signaling and modulation of electrical activity in the cardiorespiratory control neurons in the brainstem. AngII acting via AT1R in the brainstem influences the baroreceptor reflexes thus modulating cardiac and respiratory homeostasis. Stimulation of brainstem neurons by AngII has been shown to result in dynamic changes in excitability, a neuronal adaptation lasting several minutes, and this response is mediated by AT1R activated by AngII [1].

Methods

We have developed a multi-scale mathematical model that integrates a detailed kinetic reaction model of the AT1R mediated signaling pathway with a Hodgkin-Huxley-like model of the membrane electrophysiology. Our model includes Gq-protein-mediated activation of Ca^{2+}-dependent enzymes Protein Kinase C (PKC) and Calcium/calmodulin-dependent protein kinase II (CaMKII). The electrical model contains channels that are relevant to cardiorespiratory neurons in the brainstem [2]. The key aspects of the integrated model include: (1) change in the conductance of potassium channels upon phosphorylation by PKC and CaMKII, (2) voltage dependence of Na^{+}-Ca^{2+} exchanger, and (3) compartmentalized Ca^{2+} balance accounting for signaling-mediated and voltage-dependent mechanisms. The parameters were identified either by fitting to experimental data summarized in [3], or via sensitivity analyses searching for robust parameter ranges.

Results

In order to identify contribution of each of PKC and CaMKII, we simulated a 'blockade' of channel phosphorylation by either kinase (Figure 1). Blocking PKC-dependent modulation resulted in a faster, but delayed, increase in firing rate. However, blocking CaMKII-dependent phosphorylation had an effect on overall 'gain' but not on the pattern of neuronal excitability dynamics. Another key hypothesis of the integrated model is compartmentaliza-

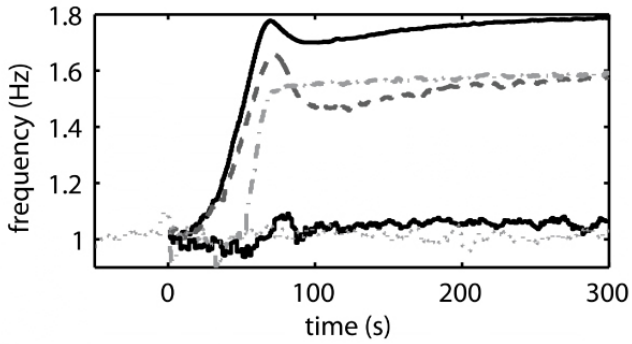

Figure 1
Response of the integrated model to 100 nM AngII stimulus. Nominal response (upper solid line), phosphorylation by CaMKII is blocked (dashed), phosphorylation by PKC is blocked (dash-dotted), phosphorylation by PKC and CaMKII are blocked (lower solid line), no AngII stimulus (dotted).

tion of Ca^{2+} levels between membrane and cytosol (with the two interacting via a buffer) without which the system cannot exhibit AngII-elicited increase in neuronal excitability. Sensitivity analysis revealed significant effects of a number of signaling reactions on the overall Ca^{2+} balance. These hypotheses form the basis for experimental validation of the key mechanisms via pharmacological modulators of kinases and channels.

Acknowledgements

Research Support: NIH/HLB R33 HL087361 to JSS

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