A Model Integrating the Cerebellar Granule Neuron Excitability and Calcium Signaling Pathways

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Abstract

Cerebellar granule cells are small glutamatergic excitatory neurons mediating information transfer between mossy fibers and Purkinje cells in the cerebellar cortex neuronal circuitry. We have developed a computational model for the cultured cerebellar granule neuron excitability using minimum number of compartments and parameters. The model is capable of reproducing the major electroresponsive properties of its real counterpart under current stimulation conditions. To computationally address the issue of intracellular modulation of excitability we have integrated kinetic biochemical models of intracellular calcium signaling pathways in the existing in vitro granule neuron model. The aim of the work is to explore the participation of intracellular calcium signaling in the information processing of a single granule neuron.

Summary

Granule cells are small relay neurons in the cerebellar cortex circuitry which receive input from mossy fibers and transfer information through parallel fibers to Purkinje cells. We have previously developed a computational model for the cultured cerebellar granule neuron (CGN) excitability using minimum number of compartments and parameters [3, 4]. The CGN model is capable of reproducing the major electroresponsive properties of its real counterpart under current stimulation conditions: fast frequent firing up to 300 Hz and linear *f-I* relation (9 Hz/pA). Furthermore, we have tested the basic effects of individual ion channel currents or combinations of them on excitability, by reducing or completely eliminating their respective channel density parameter values from the model, similarly to the idea of pharmacological blocking of ion channel activities by inhibitors [see e.g. 2]. As an example, the numerical elimination of Na_F channels prevents firing completely, and the reduction or complete elimination of K_{Dr}, Ca_{HVA} or BK_{Ca} channels induce reduction in hyperpolarization.

The electrical excitability in neurons is known to lead to changes at the molecular and genetic levels, introducing a potential mechanism for short-term and long-term memory storage. Shibata et al. (2000) have shown by experimental means that the ion channel activity and electrical excitability is essential for the proper gene expression during development and for formation of synapses in the differentiating granule neurons. For example, the increase of Na_F and K_A channel types is shown to be accompanied by a change in the type of membrane excitability from nonspiking to repetitive firing. Therefore, we have now expanded our studies on the granule neuron excitability and development by systematically varying the ion channel current combinations and densities to reproduce the current-clamp recordings of Sibata et al. (2000). Furthermore, we are studying the cascades of biochemical reactions specifically related to intracellular calcium ions. This makes it possible to study the impact of intracellular signaling pathways (ISPs) in the context of the whole neuron action potential (AP) using our previously developed compartmental model for granule neuron. The approach provides a system biological tool to study and predict the roles of signaling molecules and separate pathways for possible short-term memory storage mechanisms in a neuron.

In short, the compartmental model for CGN was implemented using the GENESIS neuronal simulator with special emphasis on model parameter and constraint selection, as well as model optimization for which we have developed a semi-automatic procedure [3, 4]. Based on experimental evidence the neuron was assumed to be one-compartmental sphere and contain six different voltage-dependent ion channel/current types (Na_F, K_{Dr}, K_A, K_{ir}, Ca_{HVA} and BK_{Ca}), for which we presented Hodgkin-Huxley type reconstructions. The active participation of calcium ions was assumed to take place in a very narrow volume close to cell membrane, possibly also involving membrane-bound calcium stores.

This paper expands the membrane-level model to incorporate intracellular signaling pathways to study the dynamic interactions of ISPs with ion channels and excitability in single cells. Specifically, we have integrated the protein kinase A and C –coupled pathways using basic chemical and Michaelis-Menten reaction kinetics and the modified parameter values presented in Bhalla and Iyengar (1999) for a hippocampal neuron. All numerical computations were done using the kinetics library, which is an extension to GENESIS simulation software [1]. The dynamically changing Ca^{2+} signal from the above simulated current-clamp experiments was used as an input signal to the modeled ISP. The studied ISPs were added one by one; after each new pathway addition there is a need for re-defining the parameter space. The effect of the intensity of the external stimuli (current stimuli) on the activation of any specific ISP was first assessed. Furthermore, the behavior of the individual ISPs was simulated to explore the possibility of inducing sustained ISP network activity after

the termination of current injection and Ca^{2+} inflow. This makes it possible to explore the properties of signaling pathways similarly to Bhalla and Iyengar (1999). The sustained activation of an ISP may serve as a candidate for molecular memory mechanism in the granule neuron.

In the future, our goal is to model the modulation of Ca_{HVA}, BK_{Ca} and K_A channels by intracellular signaling pathways and to simulate the effect of ISPs on action potential waveform and overall firing patterns. Calcium-imaging experiments combined with the current-clamp data will be used to constrain the modulatory effects of ISPs. The use of such simulation models may allow us to predict the effects of various specific intracellular signaling pathways capable of modulating neuronal excitability. In general, this work emphasizes the importance of taking into account the cell-structural, physiological and molecular-genetic aspects of the highly complex networks in a single cell. The ultimate goal of this work is to understand the information processing capabilities of single cells by utilizing the experimental information at present available from biochemical, molecular biological and array-based studies.

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