SIMULATIONS OF THE CULTURED GRANULE NEURON EXCITABILITY

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Abstract

In this study we have developed a detailed biophysical model of a cultured rat cerebellar granule neuron and simulated its excitability under different experimental conditions. The basic excitability properties of a granule neuron, such as the specific action potential waveform, the overall firing patterns induced by current stimulation, and the linear frequency-current relation are the main model constraints. Simulations show that for a one-compartmental granule neuron model, the constraints are met using six different voltage- and time-dependent ion channel types and a simplified calcium dynamics linked to BK_{Ca} channel function. Models of single cultured granule neurons form an important basis for creating larger network models of cultured neurons.

Keywords

cell culture, cerebellum, computational model, excitability, granule neuron

Summary

Cerebellum is known to be important in controlling, fine-tuning and predicting movements. To study the properties of its interesting neuronal circuitry, we used compartmental modeling techniques, Hodgkin-Huxley type reconstructions of ion channel/current behavior, and a submodel for calcium dynamics to mathematically describe the granule neuron excitability. The model neuron was

implemented using the GENESIS neuronal simulator [Wilson et al., 1989], and optimized and fine-tuned based on a semi-automatic, iterative approach, specifically created for the present model [Linne, 2001]. The cellular components of the model and the starting parameter values of the subsequent equations were selected based on data from *in vivo* and *in vitro* experiments on cerebellar granule neurons. The basic excitability properties of the granule neuron, used as the main constraints of the model, were gathered from several publications [e.g. Lin and Moran, 1990; Brickley et al., 1996; D'Angelo et al., 1998; Shibata et al., 2000], as well as from our own recordings [Jalonen et al., 1990; Linne et al., 1996]. Emphasis was put on data from neurons in culture.

Simulations show, that for a one-compartmental neuron six voltage- and time-dependent ion channel types (K_A, K_{Dr}, K_{ir}, BK_{Ca}, Na_F and Ca_{HVA}) and simple calcium dynamics reliably reproduce the experimentally recorded basic firing properties of the cultured granule neuron. This suggests that a one-compartmental representation is sufficient for reproducing the constraints for a small cultured neuron. The model neuron is able to reproduce the following basic electroresponsive properties: **(1)** fast frequent firing, up to 300 Hz, **(2)** linear frequency-current (*f-I*) relation, **(3)** realistic action potential waveform, specific for a cultured granule neuron, and **(4)** delay in firing with small current stimulations. Furthermore, simulations by eliminating particular ion channel currents from the final fine-tuned model (resembling experimental ion channel inhibition) further validated the model robustness.

Present model has the following strengths: **(i)** it consists of a realistic set of ion channels, characterized for a rat cerebellar granule neuron, **(ii)** it is able to reproduce the basic electroresponsive properties, specifically the linear *f-I* relation, under current stimulation conditions, **(iii)** it is reliable and robust to changes in key parameters, being able to mimic the behavior of real neurons under similar experimental conditions, and **(iv)** it is implemented on a GENESIS platform, which makes it more flexible to be used for further implementations at network and subcellular levels. For the future subcellular modeling a lot of biochemical kinetic and molecular data, specifically obtained from the

cultured granule neuron, is already available.

In conclusion, we have developed a biophysical model for a cultured cerebellar granule neuron, which is capable of reproducing the major electroresponsive properties of its real counterpart [see also Linne and Jalonen, 2000; Linne, 2001]. This model is an addition to earlier compartmental models for cerebellar granule neurons, which include models for a turtle [Gabbiani et al., 1994] and for a rat [D'Angelo et al., 2001]. Those two models, however, are mainly aimed at mimicking neuronal behavior in slice preparations. Single neuron models, such as the model here presented for a neuron in culture conditions, can be used for various kind of simulations of the complex interactions between ion channels and excitability. Specifically, the present model serves as an ideal template for simulating the excitability during neuronal differentiation in various culture preparations, such as the explant cultures used by Shibata et al. (2000). Single-cell culture models can be further utilized as basis for complex network models of cultured neurons, which have been recently increasingly studied by multielectrode array systems [Chang et al., 2001].

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