Firing Pattern Formation by Transient Calcium Current in Model Motoneuron

N. Svirskienė, G. Svirskis

Laboratory of Neurophysiology, Kaunas Medical University
Mickeviciaus 9, LT3000 Kaunas, Lithuania
gytis@cns.nyu.edu

Abstract

Firing properties of neurons are important in signal detection and generation in nervous system. Spinal cord motoneurons have membrane properties adapted to muscle properties. In this work we explored the relation between the first interspike interval and the amplitude of injected current. It was shown that increased sensitivity of firing frequency to the injected current at higher firing frequencies is due to the transient calcium current. Particularly, the specific density of N-type channels and the speed of their deactivation define the steepness and onset of the second range in frequency versus current relation.

Key words: neural system, motoneuron, action potential, calcium channel, modeling.

1 Introduction

Information in nervous system is transmitted by series of action potentials, which are generated in neurons and targeted to other neurons or specific organs. Although, it is not known how information is coded in these series of events, considerable efforts were applied to find out biophysical mechanisms in neurons responsible for a generation of variety of action

potential patterns observed in behaving animals. Not surprisingly, it was found that neurons possess multiple types of ionic channels with different temporal properties and sensitivity to membrane potential.

Spinal cord motoneurons have obvious function to activate muscles, and, thus, are good objects to investigate how membrane properties are tuned by the natural selection to neuronal function. Muscles by their own have properties, which are optimized for efficiency in producing movements. It is known that optimal force generation in fast muscles requires specific pattern of action potentials: if first several action potentials are fired with high frequency, a high force could be further sustained by a following low frequency firing [10].

On the other hand, intracellular recordings of membrane potential in motoneurons showed that the frequency of firing depends nonlinearly on injected current strength [7, 9]. This non-linearity manifests as two semi-linear ranges where the second range is steeper than the first. Similar relations are present for the initial firing rate and for sustained stationary firing. The later was investigated in modeling study previously [8] showing that slow calcium currents in dendrites are necessary for this phenomenon.

In this work we investigated mechanisms of frequency to current relation (f-I) for the first two spikes. Modeling results suggest that transient calcium current is responsible for the generation of the second steeper range of f-I relation. The steepness is defined by the specific conductance of the current, and the point of the appearance is defined by the decay time constant.

2   Model Definition and Realization

The model neuron consisted of a spherical soma with the diameter of 100 μm and a dendrite. Dynamics of the soma membrane potential, V, were governed by the following equation:

$$C\mathrm{d}V/\mathrm{d}t = -V/R_{\mathrm{m}} + I_{\mathrm{dendr}} + I(V)S,$$

where C=0.16 pF is soma membrane capacitance, R_{m}=32 MΩ is membrane resistance, S is soma membrane area, I_{dendr} is current flowing to the cable representing dendritic tree. The passive membrane properties of the cable were the same as in the soma, the length was 3mm, the diameter was 5 μm, and specific intracellular resistance was 660 kΩ*μm. I_{dendr} was calculated as described previously [1]. $I(V)$ is a current generated in 1 μm^2 by four potential dependent channels:

$I(V) = G_{Na}M^3H\ (V - 55) + G_{KDr}\ N^3\ (V + 85) + G_{Ca}M_N^2H_N(V - 80) + G_{KCa}(V + +85)C_{Ca}^2/\ (C_{Ca}^2 + K_{Ca})$,

where $G_{Na}=140*10^{-5}$ µS/µm^2, $G_{KDr}=80*10^{-5}$ µS/µm^2, G_{Ca}, G_{KCa} are specific conductances for sodium current, potassium delayed rectifier current, N-type calcium current, and calcium sensitive potassium current respectively. C_{Ca} is calcium concentration in µM. $K_{Ca}=0.3$ µM. Gating variables for the potential dependent currents obeyed following relations:

$M = 1./(1. + \exp[-(V + 35)/7.8])$,

$dH/dt = (1/(1 + \exp[(V + 55)/7]) - H)\ /\ (30\ /\ (\exp[(V + 50)/15] + \exp[\ -\ (V + +50)/16]))$,

$dN/dt = (1\ /\ (1 + \exp[\ -\ (V + 20)/22.5]) - N)\ /\ (2/\ (\exp[(V + 40)/40] + \exp[-\ (V + +40)/50]))$,

$dM_N/dt = (1/\ (1 + \exp[\ -\ (V + 30)/\ 5]) - M_N)\ /\ \tau_{act}$,

$dH_N/dt = (1/\ (1 + \exp[(V + 45)/\ 5]) - H_N)\ /\ 12$,

where τ_{act} is activation time constant of N-type calcium current. The changes of calcium concentration were calculated by solving equation

$dC_{Ca}\ /dt = -\ K_aI_{Ca} - K_r\ (C_{Ca} - 0.05)$,

where $K_a =250$ µM*µm^2/nA, Kr=0.015 ms^{-1}. The system of differential equations was solved numerically by using implicit Cranck-Nicholson scheme with a time step of 5 µs.

3 Results

First, we defined parameter values, which resulted in action potential and aftehyperpolarization reminiscent to that published in literature [6, 9]. Because of nonlinear relations between parameters it would be difficult to define a single set of parameters without a reasonable starting values. We took the initial values from a recent modeling study for motoneurons [3]. However, a model with such parameters did not produced two different ranges in the f-I

relation of the first two spikes. Instead, the augmentation of the frequency was less and less as the injected current value was increased.
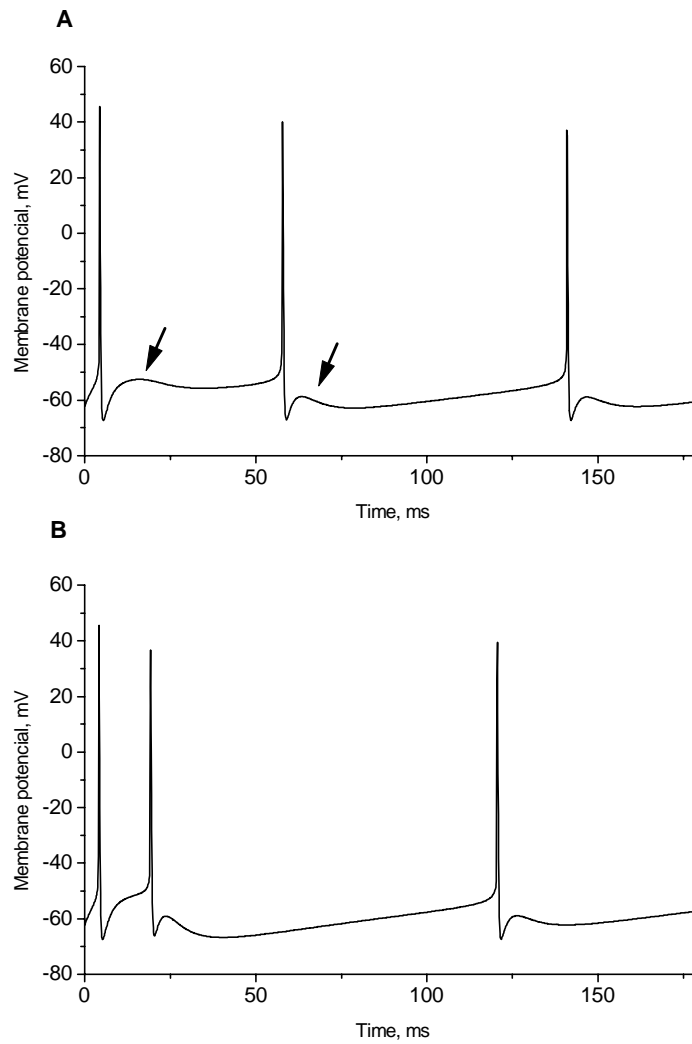
A

B

Fig. 1. Firing patterns of model motoneuron. A. Response to the 2.3 nA current injection. The specific conductance of calcium channels was $20*10^{-5}$ $\mu S/\mu m^2$. The calcium current manifests as an afterdepolarization following fast hyperpolarization (arrows). B. Response to the 2.4 nA current injection. The afterdepolarization, hump, shown in A is responsible for the fast firing of the first two action potentials

In our model with four potential dependent currents, two currents,

calcium and calcium sensitive potassium, could be responsible for the desired effect, since sodium current and delayed rectifier potassium current are too strong and generate all-or-nothing action potential. We also noticed that recordings of membrane potential in motoneurons show a small "hump" just after fast afterhyperpolarization [6]. To get the same shape of afterhyperpolarization following action potential, the conductance of N-type calcium channels, G_{Ca}, was increased. The stronger calcium current resulted in higher calcium concentrations and, subsequently, in deeper afterhyperpolarizations. In order to compensate for this deepening, conductance of the calcium sensitive potassium current, G_{KCa}, had to be decreased. Also, the sensitivity of calcium dependent potassium current, K_{Ca}, had to be such that the increase of calcium concentration after an action potential would not maximally activate this current. When K_{Ca} was equal to 0.3 µM the calcium dependent potassium current was activated more with each next fired action potential. For values of $G_{Ca}=20*10^{-5}$ µS/µm^2 and $G_{KCa}=5*10^{-5}$ µS/µm^2 desired shape of afterhyperpolarization with an initial hump was achieved (arrows in Fig. 1A).

Next, we calculated f-I relation in this model. At small injected current values the firing frequency increased almost linearly (Fig. 2A, dashed line), but at the current value of 2.4 nA the firing frequency of the first two spikes jumped to high values. The mechanism of the jump could be understood by comparing firing patterns just before (Fig 1A) and just after (Fig 1B) the jump. It can be seen that the second action potential moved to the "hump" resulting in the jump of the firing frequency. However, in published experimental data such jumps are absent.

In order to make the transition between different f-I ranges smooth, we reduced calcium conductance to $10*10^{-5}$ µS/µm^2 and adjusted conductance of calcium sensitive potassium conductance to $7*10^{-5}$ µS/µm^2. In this case, the afterhypepolarization decayed almost without "humps" after the first spike, but it was still non-monotonous after the second spike resembling experimentally observed shape. These adjustments eliminated the jump in f-I relation (Fig 2A, solid curve) and made the second range of firing less steep. Next we asked what parameter defines the onset of the second range. Apparently, it should be the duration of calcium current decay, since this current compensates for the outward current and change the slope of afterhyperpolarization. To check this, the activation time constant, τ_{act}, which also sets the time scale of decay of the current, was reduced from 12 ms to 8 ms. For such a model the onset of the second range in f-I relation moved to the higher frequencies as expected (Fig 2B, dashed line). Also, the onset required stronger stimulation current, because reduced activation time resulted in increased current, higher calcium concentrations and deeper afterhyperpolarizations.
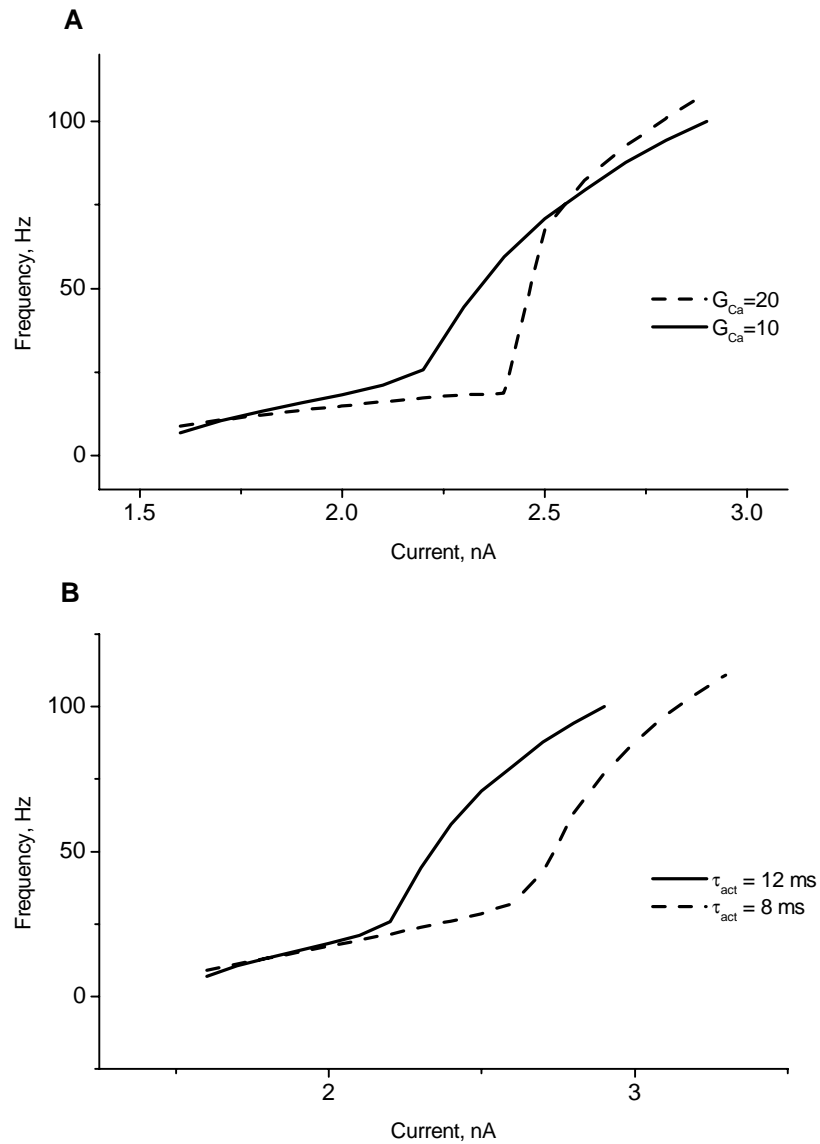
Fig. 2. Frequency-current relations for the first interspike interval. A. Comparison of relations between models with different strength of calcium current. The increase of the calcium current resulted in steeper increase of the firing frequency. The activation time constant was 12 ms. B. When time constant for deactivation of calcium channel was reduced the onset for the second range moved to higher firing frequencies. The specific conductance of calcium current was $10*10^{-5}$ $\mu S/\mu m^2$.

4 Conclusions

In this work we studied the mechanisms which are responsible for the shape of f-I relation for the first spikes in response to current injection in motoneurons. We found that the second steeper range of f-I relation requires strong N-type calcium current in soma membrane. The beginning of this range is defined by the decay time constant of this current. These findings are in agreement with experimental observations. In cat motoneurons which have similar f-I relations and show stationary bistability [5, 4] the firing starts in doublets of spikes [2] similar to that in Fig 1B. Thus, transient calcium current shape firing pattern in spinal motoneurons and enable them to effectively activate their output targets, muscles.

References

1. A. Baginskas, A. Gutman, G. Svirskis, *Bi-stable dendrite in constant electric field: a model analysis. Neuroscience* 53, p.595-603, 1993.

2. D. J. Bennett, H. Hultborn, B. Fedirchuk, M. Gorassini, *Short-term plasticity in hindlimb motoneurons of decerebrate cats. J.Neurophysiol.* 80, p.2038-2045, 1998.

3. V. Booth, J. Rinzel, O. Kiehn, *Compartmental model of vertebrate motoneurons for Ca2+-dependent spiking and plateau potentials under pharmacological treatment. J.Neurophysiol.* 78, p.3371-3385, 1997.

4. C. J. Heckman, R. H. Lee, *The role of voltage-sensitive dendritic conductances in generating bistable firing patterns in motoneurons. J Physiol Paris* 93, p. 97-100, 1999.

5. J. Hounsgaard, H. Hultborn, B. Jespersen, O. Kiehn, *Bistability of a-motoneurones in the decerebrate cat and in the acute spinal cat after intravenous 5-hydroxytryptophan. J.Physiol.(Lond)* 405, p. 345-367, 1988.

6. J. Hounsgaard, O. Kiehn, I. Mintz, *Response properties of motoneurones in a slice preparation of the turtle spinal cord. J.Physiol.(Lond)* 398, p. 575-589, 1988.

7. D. Kernell, R. Bakels, J. C. V. M. Copray, *Discharge properties of motoneurones: How are they matched to the properties and use of their muscle units? Journal Of Physiology-Paris* 93, p. 87-96, 1999.

8. R. K. D. B. Powers, *A variable-threshold motoneuron model that incorporates time- and voltage-dependent potassium and calcium conductances. J.Neurophysiol.* 70, p. 246-262, 1993.

9. P. C. Schwindt, W. E. Crill, *Factors influencing motoneuron rhytnmic firing: results from a voltage-clamp study. J.Neurophysiol.* 48, p. 875-890, 1982.

10. C. K. Thomas, R. S. Johansson, B. Bigland-Ritchie, *Pattern of pulses that maximize force output from single human thenar motor units. J. Neurophysiol.* 82, p. 3188-3195, 1999.