CONTRIBUTION OF INDIVIDUAL VOLTAGE-GATED IONIC CURRENTS IN CEREBELLAR PURKINJE CELL SOMATA TO PEAK SOMATIC MEMBRANE POTENTIAL

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Key words: Purkinje cell, compartment, ionic current, membrane

ABSTRACT

In this study, the effect of individual voltage-gated ionic currents in cerebellar Purkinje cell somata on peak somatic membrane potential is investigated. A somatic compartmental model of Purkinje cell is constructed, and somatic membran potentials with respect to individual voltage-gated ionic currents are calculated for several different current injection cases.

I. INTRODUCTION

Purkinje cell is one output neurone of cerebellar cortex. Many different types of voltage-gated ionic current are found in the Purkinje cell [1,2]. Voltage-gated ionic currents are of great importance in integrating the information received by the neurones [2]. It's reported in literature a number of modeling studies for Purkinje cells. Llinas and Nicholson [3], Shelton [4], and Rapp et al. [5] constructed the model using just passive electrical properties of the cell. These models didn't include voltage-dependent conductances reported recently to be present in Purkinje cells. The most comprehensive and detailed model of Purkinje cell was constructed by De Schutter and Bower [1]. The model consisted of 1600 compartments and included ten different-type voltage- and concentration-dependent ionic currents. In a recent study, it's shown that class-E Ca^{2+} channels and D-type K^+ channels are present and functioning in the Purkinje cell dendrites, and used in the constructed model in addition ten ionic channels [2].

II. MATHEMATICAL MODEL OF A VOLTAGE-GATED IONIC CURRENT

Ionic currents present in Purkinje cell obey Hodgkin-Huxley mathematical formalism. In that formalism an ionic current channel is assumed to have gates which are in one of two states, i.e. open or closed state [6]. Conductance of an ionic channel is defined with Hodgkin-Huxley as follows [7]:

$$G_X(v,t) = g_X m^p(v,t) h^q(v,t) \quad (1)$$

where m and h show voltage-dependent probability of being open state for activation and inactivation gates respectively, g_X is maximal conductance of ionic channel, p is the number of activation gates and q is the number of inactivation gates.

Transitions between open and closed states are modelled with first order differential equations as follows:

$$\frac{dm}{dt} = \alpha_m(v)(1-m) - \beta_m(v)m = \frac{m_\infty(v) - m}{\tau_m(v)} \quad (2)$$

$$\frac{dh}{dt} = \alpha_h(v)(1-h) - \beta_h(v)h = \frac{h_\infty(v) - h}{\tau_m(v)} \quad (3)$$

where $\alpha(v)$ and $\beta(v)$ are voltage-dependent rate functions which determine speed of transitions from one state to the other within the ion gates, and given by

$$\alpha(v) = \frac{a + bv}{c + e^{(d+v)/f}} \quad (4)$$

where a, b, c, d, f are constants.

$m_\infty(v)$ and $h_\infty(v)$ are steady-state activation(i.e. steady-state open gate fraction for activation) and inactivation(i.e. staedy-state open gate fraction for inactivation) respectively; $\tau_m(v)$ and $\tau_h(v)$ are voltage-dependent activation and inactivation time constants which are the times taken to reach a steady-state values respectively; and may be written as

$$m_\infty(v) = \frac{\alpha_m(v)}{\alpha_m(v) + \beta_m(v)} \; ; h_\infty(v) = \frac{\alpha_h(v)}{\alpha_h(v) + \beta_h(v)} \quad (5)$$

$$\tau_m(v) = \frac{1}{\alpha_m(v) + \beta_m(v)}; \tau_h(v) = \frac{1}{\alpha_h(v) + \beta_h(v)} \quad (6)$$

III. VOLTAGE-GATED ION CHANNELS IN PURKINJE CELL SOMATA

It's reported that fast sodium channel (NaF), persistent sodium channel (NaP), T-type calcium channel (CaT), A-type potassium channel (KA), persistent potassium channel (KM), anomalous rectifier channel (Kh), and delayed rectifier channel (Kdr) are present in the somata of Purkinje cell [1,2,8-11]. NaF, NaP and CaT currents depolarize cell membrane, and the others repolarize it. Kinetics of ionic currents used in this study is based on the model of the cerebellar Purkinje cell by De Schutter and Bower [1].

IV. COMPARTMENTAL MODEL OF PURKINJE CELL SOMATA

Purkinje cell somata model is constructed using compartmental modeling approach. Compartmental modeling in which a neuron is divided into small parts called as compartment is derived from linear cable theory [12]. Equivalent electric circuit for constructed soma compartment is shown in Figure 1. Maximal conductances and reversal potentials of ionic channels are given in Table 1. Soma compartment is modeled spherically, and radius of sphere is taken 29.8 μm. Specific membrane capacitance, CM is taken as 0.0164 F/m^2, specific membrane resistance, RM as 1 Ωm^2, resting potential as –68 mv, and reversal potential of leak current as –80 mv.

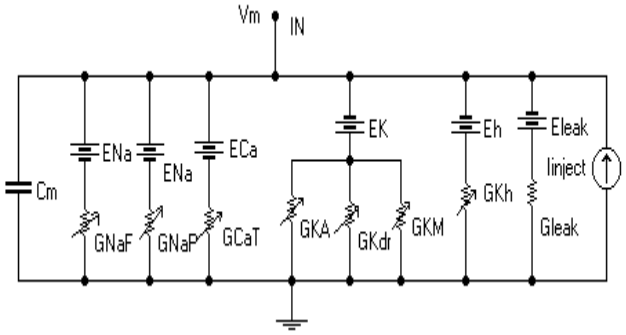

Figure 1. Equivalent electric circuit for constructed soma compartment

In Figure 1, current equation is obtained as

$$C_m \frac{dV_m}{dt} + I_{ion} = I_{inject} \quad (7)$$

where C_m , V_m , I_{ion} , I_{inject} represent membrane capacitance, membrane potential, sum of ionic currents, and injected current respectively. Sum of the ionic currents is given by

$$I_{ion} = \sum G_k(V_m - E_k) = I_{NaF} + I_{NaP} + I_{CaT} + I_{KA} + I_{Kdr} + I_{Kh} + I_{KM} + I_{leak} \quad (8)$$

So the change in membrane potential is expressed as follows:

$$\frac{dV_m}{dt} = \frac{1}{C_m}\left[I_{inject} - I_{ion}\right] = \frac{I}{C_m} \quad (9)$$

Table 1. Ionic channel parameters

Ionic channels	Maximal conductance (S/m^2)	Reversal Potential (mv)
NaF	75000	45
NaP	10	45
CaT	5	135
Kh	3	-30
Kdr	6000	-85
KM	0.4	-85
KA	150	-85

V. INTEGRATION METHOD

It's necessary to compute *m* and *h* values at each time step before calculating of membrane potential. Eq. (2) and Eq. (3) have a general form as

$$\frac{dy}{dt} = A - By \quad (10)$$

where A=α , B=α+β. We use Exponential Euler method to obtain the values of *m* and *h* for each time step. Solution of Eq. (10) for time increment Δt is given as follows :

$$y(t + \Delta t) = y(t)e^{-\Delta Tb} + \frac{A}{B}(1 - e^{-\Delta Tb}) \quad (11)$$

Substituting A=α , B=α+β into Eq. (11) gives

$$\begin{aligned} y(t+\Delta t) &= y(t)e^{-(\alpha+\beta)\Delta t} + \frac{\alpha}{\alpha+\beta}(1 - e^{-(\alpha+\beta)\Delta t}) \\ &= y(t)e^{-\Delta t/\tau} + y_\infty(1 - e^{-\Delta t/\tau}) \\ &= y_\infty + (y(t) - y_\infty)e^{-\Delta t/\tau} \end{aligned} \quad (12)$$

where y_∞ represents steady-state activation or inactivation value at present step voltage; *y(t)* represents activation or inactivation value calculated at the last step according to Eq. (12). τ represents time constant of activation or inactivation at present step voltage.

After calculating of *m* and *h* values, it's easy to calculate an ionic current with Eq. (1) and Eq. (8). Next step at the integration is to calculate the membrane potential according to Eq. (9). The expression on the right side of Eq. (9) was calculated, so have a constant value. Therefore the integration of membrane potential is done with Forward Euler method :

$$V_m(t+\Delta t) = V_m(t) + \Delta t \frac{I}{C_m} \quad (13)$$

VI. SIMULATION RESULTS AND DISCUSSION

Initial control simulations were run with different time increments to determine which time increment produced numerically accurate results. Then fixed time increment of 10 μs was selected. Investigation consists of two steps. In the first step, voltage-gated ionic currents that depolarize the membrane are taken into consideration. Different magnitude currents are injected into the compartment which have just leak current, and peak somatic membrane potentials are calculated over 50 ms simulation duration. Then fast sodium channel (NaF), persistent sodium channel (NaP), and T-type calcium channel (CaT) are added individually to the compartment, and peak somatic membrane potentials are calculated for the same magnitude currents. The results are shown in Figure 2. As seen in Figure 2, peak membrane potentials are the least for persistent sodium channels. A fast sodium current causes higher peak membrane potential than T-type calcium current. And T-type calcium current causes peak membrane potentials as nearly same as by leak current.

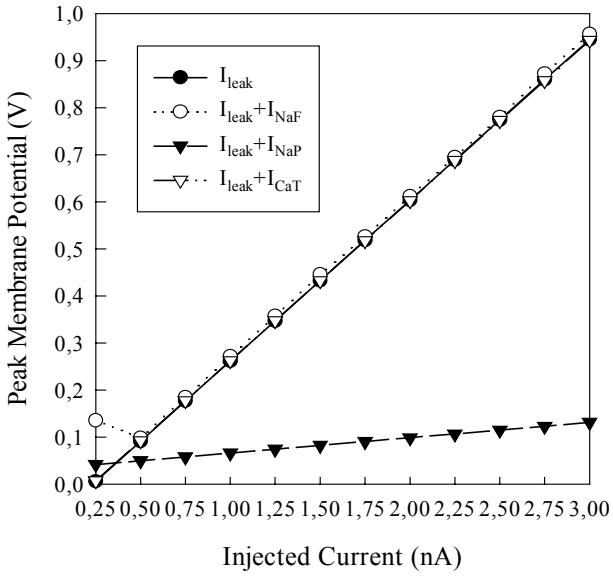

Figure 2. Effects of voltage-gated currents that depolarize membrane on the peak membrane potential

In the second step, voltage-gated ionic currents that repolarize the membrane are taken into consideration. Different magnitude currents are injected into the compartment which have just leak current, and peak somatic membrane potentials are calculated over 50 ms simulation duration. Then A-type potassium channel (KA), persistent potassium channel (KM), anomalous rectifier channel (Kh), and delayed rectifier channel (Kdr) are added individually to the compartment, and peak somatic membrane potentials are calculated for the same magnitude currents. The results are shown in Figure 3. As seen in Figure 3, delayed rectifier current causes the most repolarization. The next large repolarization occurs for the case in which persistent potassium is included. Anomalous rectifier and A-type potassium currents show less repolarization effects.

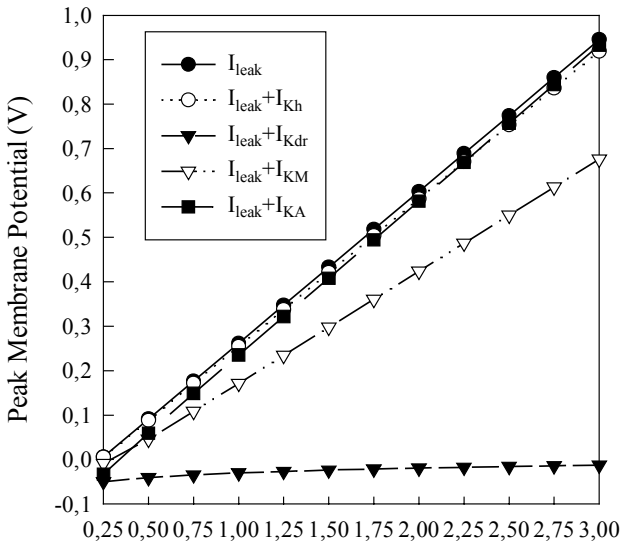

Figure 3. Effects of voltage-gated currents that repolarize membrane on peak membrane potential

VII. CONCLUSION

In this study, effects of individual voltage-gated ionic currents in cerebellar Purkinje cell somata on peak somatic membrane potential are examined. A somatic compartmental model of Purkinje cell is constructed for that purpose, and peak somatic membran potentials with respect to individual voltage-gated ionic currents are calculated for several different current injection cases. Results show that a fast sodium current causes the most depolarization effect, and delayed rectifier current causes the most repolarization effect.

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