Modeling I_M Channels in Hippocampal CA1 Oriens/Alveus Interneurons

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Abstract

Recent experimental work suggests that a muscarinic sensitive potassium current, I_M, is a component of the sustained outward current in hippocampal oriens/alveus (O/A) interneurons. This channel plays a key role in controlling membrane excitability and can be modulated by a variety of neurotransmitters, hormones and second messengers. We use voltage clamp experimental data to characterize the kinetics of this channel and incorporate it into a single compartment model. Using multi-compartment models based on reconstructed O/A interneuron morphologies we determine what possible channel distributions of I_M in the soma and dendrites match the experimental data.

Summary

The M-current (I_M) is a non-inactivating potassium conductance composed of KCNQ channel subtypes. This channel plays a key role in regulating cell excitability. In sympathetic neurons, M-channels are thought to be composed of a heteromeric assembly of KCNQ2 and KCNQ3 subunits, but recombinant studies have shown that homomeric assemblies of KCNQ2 can also generate a potassium current which has a smaller conductance value. KCNQ2 homomers also have a greater sensitivity to TEA (tetraethylammonium) and a more depolarized activation curve than the KCNQ2/3 heteromers (Wang et al., Science vol. 282, pp 1890-1893, 1998). The M current has been described and modeled in pyramidal neurons but has not yet been characterized in interneurons. Recent experiments on CA1 hippocampal oriens/alveus (O/A) interneurons have revealed that a KCNQ2-like conductance is a component of the sustained outward current in these cells (C.J. McBain et al. *SFN abstract **799.10**, 2003*). This conductance can control the O/A interneuron excitability via cholinergic neuromodulation.

The distribution of channels in the somato-dendritic architecture can affect the biophysical characteristics measured at the soma. Voltage-clamp data from O/A interneurons reveal an I_M channel with a KCNQ2-like TEA sensitivity but with a more depolarized steady-state activation curve than that of recombinant KCNQ2 channels. This difference in activation curves could be a result of different kinetics for the interneuronal I_M channel from the KCNQ2 channel measured in oocyte studies (Jow and Wang, Molecular Brain Research, vol. 80, pp 269-278, 2000) and/or could be accounted for by different channel distributions along the somato-dendritic tree. We use

mathematical models for I_M based on pure KCNQ2 channel kinetics and average voltage-clamp data measured from hippocampal O/A interneurons to determine the possible I_M channel distribution in these cells.

Using average voltage-clamp data from O/A hippocampal interneurons, we develop a kinetic model based on Hodgkin-Huxley formalism for the muscarinic sensitive current, I_M. The current obeys the equation:

$$I_M = g_M r (V - E_K)$$

where g_M is the maximal conductance of the current, r is the probability of the activating particle to be in the permissive position, V is the voltage and E_K is the reversal potential for potassium. The transitions of the activating particle, r, were schematized as the following first-order kinetic reaction:

$$1 - r \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} r$$

from which it follows

$$dr/dt = \alpha(V)(1 - r) - \beta(V)\, r$$

which can be rewritten as

$$dr/dt = [r_\infty(V) - r] / \tau(V)$$

where

$$\tau(V) = 1 / [\alpha(V) + \beta(V)]$$

$$r_\infty(V) = \alpha(V) / [\alpha(V) + \beta(V)]$$

Functions for the rate constants, α and β, are derived from the experimental values of time constants of activation and deactivation at various voltage steps and from the r_∞ curve measured experimentally which is of the form.

$$r_{\infty}(V) = 1 / [\ 1 + exp((V-V_{1/2}) / k)\ ]$$

where V is the membrane voltage, $V_{1/2}$ = -18.1 ±1.2 mV is the voltage at half activation and k = 12.1± 1 is the slope at that voltage. The steady-state activation curve was measured experimentally using tail current analysis. The activation time constants are voltage dependent and range from 4 – 80 ms. Activation time constants increase with more hyperpolarized membrane voltage.

We develop a single compartment model using the software NEURON. This model includes passive properties taken from the average values measured experimentally in oriens/alveus interneurons. We incorporate the kinetic model we developed for the I_M channel and simulate the same voltage clamp protocols used experimentally to obtain channel densities.

We use Neurolucida to reconstruct two oriens/alveus hippocampal interneuron morphologies from 14-21 day old mice. Passive properties measured experimentally for each cell are incorporated specific to the cell. Using the biophysical characteristics obtained in the single compartment model as a starting point, we explore a variety of I_M channel distributions and densities including purely somatic, evenly distributed over the somatic-dendritic area and limited distribution in the soma and proximal dendrites. Using these different distribution profiles we simulate the voltage clamp protocols in the modeled cell and compare with experimental traces from that particular cell. In addition we compare these distribution profiles using biophysical characteristics more akin to a pure KCNQ2 kinetics model. In this way, we can determine what possible distributions and densities of the I_M channel in O/A interneurons are present.

Interneurons at the stratum oriens/alveus (O/A) border receive both cholinergic and GABAergic innervation from the septum and provide feedback inhibition to CA1 pyramidal neurons. These interneurons have been found to be active during *in vivo* theta oscillations (Klauberger et al., Nature, vol. 421, pp 844-848, 2003) which are associated with memory and learning. Muscarinic receptor activation has a direct affect on cell excitability via the I_M channel. The characterization of this channel in O/A interneurons will allow us to build on previous modeling work done on this cell type and help us understand the affect of specific neuromodulators on cell excitability and it's contribution to the network theta rhythm.