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Exploring gap junction location and density in electrically coupled hippocampal oriens interneurons

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Abstract

Interneuronal networks, connected by chemical and electrical (gap junctions) synapses, are important for shaping population field rhythms in the hippocampus. Recently, weak electrical coupling has been found between oriens interneurons in the CA1 region of the hippocampus. Action potentials in one cell produced spikelets in the connected cell. We use a two-cell model network of oriens interneurons to determine the dendritic location and strength of gap junctions needed to match experimentally measured spikelet characteristics. The location of the gap junctions is predicted to be 150–200 μm from the soma, corresponding to electrotonic lengths of 0.17–0.23 as measured from the soma to the dendrite location and 0.71–1.04 as measured from the dendritic location to the soma, with a conductance of 500–800 pS.

Keywords: Interneurons; Hippocampus; Neural networks; Gap junctions; Spikelets

1. Introduction

Interneuronal networks are thought to play an important role in shaping the population field rhythms measured during exploration (theta rhythms) and memory consolidation (sharp waves and ripples) in the hippocampus. There is growing evidence that GABAergic interneuronal networks in the cortex and hippocampus are connected by both electrical and chemical synapses. Electrical synapses are specialized sites where gap-junctional channels bridge the membrane of adjacent cells. Gap junctions (GJs) allow direct transmission of charged particles and small molecules between cells and are thought to mediate synchronous firing in connected neurons. They are found between many neurons in the mammalian central nervous system [2].

Anatomical studies show that basket cells, an interneuron subtype, form dendritic GJs with other basket cells [3,4]. Modeling studies show that various network patterns including synchronous and phase-locked patterns occur depending on GJ location and strength [1,7,10]. Recent electrophysiological studies indicate that electrical coupling exists between oriens interneurons in the CA1 region of the hippocampus [12]. Full spikes in one cell failed to generate spikes in the connected cell, but rather generated spikelets of amplitudes ranging from 0.6 to 1.1 mV and delays ranging from 3 to 5 ms, indicating weak coupling between the cells. Oriens interneuron subtypes are known to have a high density of sodium and potassium channels on their dendrites allowing them to produce strong back-propagating action potentials [8]. Given that the experimental work of Zhang et al. [12] indicates that oriens interneurons are only weakly coupled, we aim to quantify what this might mean. We use our previously published multi-compartment model of an oriens interneuron [9] and explore the possible location and strength of GJs between two oriens interneurons. In order for the simulated spikelets to fall within the experimentally determined ranges we find that GJs

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must be located between 150–200 μm from the soma with a GJ strength of 500–800 pS.

2. Model and methods

Our model interneuron [9], created using the software NEURON [6], incorporates experimentally derived values for ion channel densities and kinetics, and can reproduce several key properties such as current–frequency relationships and action potential initiation sites. Ion channels included in the model interneuron are the traditional Hodgkin–Huxley (HH) sodium (I_{Na}) and delayed-rectifier potassium (I_K) channels, the transient potassium channel (I_A), the hyperpolarization-activated channel (I_h) and a leak channel (I_L). The spatially discrete form of the cable equation can be written as

$$C\frac{dV_k}{dt} = \gamma_{k-1,k}(V_{k-1} - V_k) + \gamma_{k+1,k}(V_{k+1} - V_k) - I_{\text{ionic,k}}, \quad (1)$$

where C is the capacitance, V is the voltage, t is time, γ is the coupling conductance between different connected compartments and k denotes the particular compartment. The ionic current in compartment k, $I_{\text{ionic,k}}$, includes I_L, I_{Na} and I_K for the axonal and dendritic compartments while the soma contains I_L, I_{Na}, I_K, I_A, I_h and an injected external input I_{ext}. Details for the kinetics and conductances of the ion channels can be found in Saraga et al. [9] (see Case 2 model). For every dendritic location, two electrotonic lengths can be defined, $V_{\text{in,EL}}$ and $V_{\text{out,EL}}$. The $V_{\text{in,EL}} = \ln(V_{\text{dendrite}}/V_{\text{soma}})$ where V_{dendrite} is the voltage at the dendritic location and V_{soma} is the voltage at the soma. The $V_{\text{out,EL}} = \ln(V_{\text{soma}}/V_{\text{dendrite}})$. For the longest dendrite in our model interneuron (326 μm) the $V_{\text{in,EL}}$ and $V_{\text{out,EL}}$ were 2.14 and 0.27, respectively, at a membrane voltage of −70 mV.

We construct two-cell homogeneous networks of model cells coupled by GJs. The dendritic tree of the oriens interneuron model extends to ~300 μm from the soma. Therefore, we select four different dendritic gap junctional locations including proximal-100 μm, middle-150 μm, 200 μm, and distal-300 μm from the soma. The gap junctional current, $I_{\text{gap},k}$ between the kth dendritic compartments of cells 1 and 2 obeys the following equations:

$$I^1_{\text{gap},k} = g_{\text{gap}}(V^1_k - V^2_k) \quad \text{or} \quad I^2_{\text{gap},k} = g_{\text{gap}}(V^2_k - V^1_k), \quad (2)$$

which would be added to $I_{\text{ionic},k}$ for cell 1 or 2, respectively, g_{gap} is the GJ conductance and $V_k{}^1$, $V_k{}^2$ are the dendritic voltages at the gap junctional location for cells 1 and 2, respectively. We insert electrical connections ranging from g_{gap} = 10–3000 pS at the different dendritic sites. These values are based on a unitary conductance of 10–300 pS and 1–10 GJs per electrical connection [5–11].

3. Results

Using the isolated juvenile (7–14 days) mouse whole hippocampus preparation, Zhang et al. [12] performed dual whole cell recordings from stratum oriens interneurons under infrared microscopy. With one cell hyperpolarized to −65 mV to minimize spontaneous firing, the other cell was allowed to spontaneously fire or was injected with current to evoke action potentials. Of the total paired recordings, ~12–18% (depending on the orientation of the electrodes to the hippocampus) were found to be electrically coupled. Spontaneous or evoked spikes in one cell resulted in spikelets in the hyperpolarized cell. These spikelets persisted when cells were exposed to 50 μM AP5, 10 μM CNQX and 10 μM bicuculline which collectively block glutamatergic and $GABA_A$ receptor mediated synaptic transmission. Spikelets were abolished, however, with application of carbenoxolone, a GJ blocker suggesting that spikelets are mediated by electrical coupling.

Our oriens interneuron model spontaneously fires at a frequency of ~10 Hz. Therefore, to explore how full spikes in cell 1 can generate spikelets in the connected cell 2, a tonic hyperpolarizing current of 50 pA is injected into cell 2 to suppress spontaneous firing, similar to experiments [12]. We then explore how spontaneous firing in cell 1 generates spikelets in cell 2 depending on the GJ location and strength. Fig. 1 shows a schematic of the two cell network coupled by a dendritic GJ, represented here as a resistor. The bottom of Fig. 1 shows an action potential in cell 1 with the spikelet it generates in cell 2 superimposed at a larger voltage scale. The GJ between the two cells is located 200 μm from the soma along the dendrite and has a strength of 800 pS.

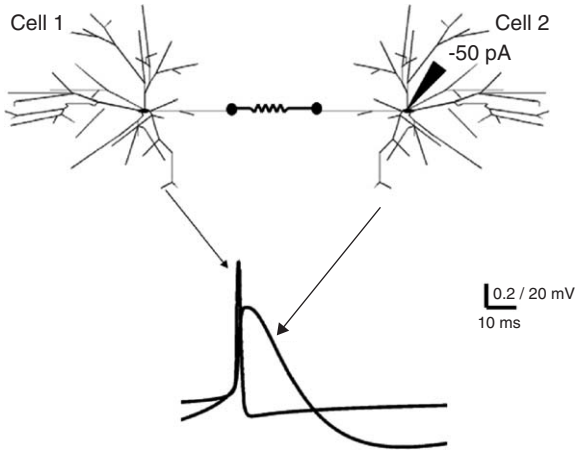

Fig. 1. Top: A schematic of the two cell homogeneous model network of O–LM interneurons connected by a dendritic gap junction, represented here by a resistor. Bottom: An example of an action potential in cell 1 and the corresponding spikelet it generates in cell 2. For each two cell network, cell 1 is allowed to spontaneously fire action potentials and cell 2 is hyperpolarized with −50 pA of current to suppress spontaneous firing. The gap junction between the two cells is located 200 μm from the soma along the dendrite and has a strength of 800 pS.