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Steep decrease in the specific membrane resistance in the apical dendrites of hippocampal CA1 pyramidal neurons

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ABSTRACT

Specific membrane resistance (R_m), distributed non-uniformly over the dendrite, has a substantial effect on neuronal information processing, since it is a major determinant in subthreshold-synaptic integration. From experimental data of dendritic excitatory postsynaptic potential (EPSP) spread, we previously reported that non-uniform R_m distribution in hippocampal CA1 pyramidal neurons could be expressed as a step function. However, it remains unclear how steeply R_m decreases. Here, we estimated the R_m distribution using sigmoid function to evaluate the steepness of decrease in R_m. Simulations were performed to find the distribution which reproduced experimental voltage responses to extracellular electric field applied to CA1 slices, in contrast to the EPSP spread. Distribution estimated from the responses to electric field was a steep-sigmoid function, similar to that from the EPSP spread. R_m in distal dendrite was estimated to be $\lesssim 10^{3.5}\ \Omega\,\mathrm{cm}^2$ whereas that in proximal dendrite/soma was $\gtrsim 10^{4.5}\ \Omega\,\mathrm{cm}^2$. Our results not only supported previous studies, but, surprisingly, implied that R_m decreases at a location more distal, and that distal dendrite was leakier, than previous estimates by other groups. Simulations satisfactorily reproduced the responses to two distinct perturbations, suggesting that steep decrease in R_m is reliable. Our study suggests that the non-uniform R_m distribution plays an important role in information processing for spatially segregated synaptic inputs.

1. Introduction

Dendrites are spatially extended complex structures with non-uniformly distributed electrical membrane properties, resulting in an enrichment of information processing in a single neuron (Segev et al., 1995; Rall, 1999; Häusser et al., 2000; Gulledge et al., 2005; Kath, 2005). In particular, active ion channels, which are distributed non-uniformly over the dendrite, have received attention in order to understand information processing in dendrites (Stuart and Sakmann, 1994; Magee and Johnston, 1995; Johnston et al., 1996, 2000). However, the specific membrane resistance, which is distributed non-uniformly over the dendrite, also has important effects on information processing in dendrites, as it is one of the major factors determining subthreshold-synaptic integration. Theoretical studies have shown that the manner of propagation of excitatory postsynaptic potentials (EPSPs) along the dendrite is greatly influenced by passive membrane properties, such as the specific membrane resistance and specific membrane capacitance (Rall, 1959, 1960, 1964, 1967; Rall et al., 1967; Spruston et al., 1999; Williams and Stuart, 2003), suggesting that the impact of synaptic inputs applied to the dendrite on somatic firing strongly depends on the passive membrane properties over the dendrite. Furthermore, it has been suggested that the manner of spatial and temporal summation in dendrites is substantially influenced by the passive membrane properties (Spruston et al., 1999). Since axons from different regions tend to be found on spatially segregated regions of the dendrite (Shepherd, 2003), the distribution of passive membrane properties over the dendrite might play a key role in integrating information from different regions. Thus, to understand how synaptic inputs from different regions are processed, as a first step, we need to clarify the spatial non-uniform distribution of the specific membrane resistance over the dendrite.

It is possible to overcome the technical difficulties involved in the direct measurement of the specific membrane resistance in the distal dendrite by using indirect methods that are combinations

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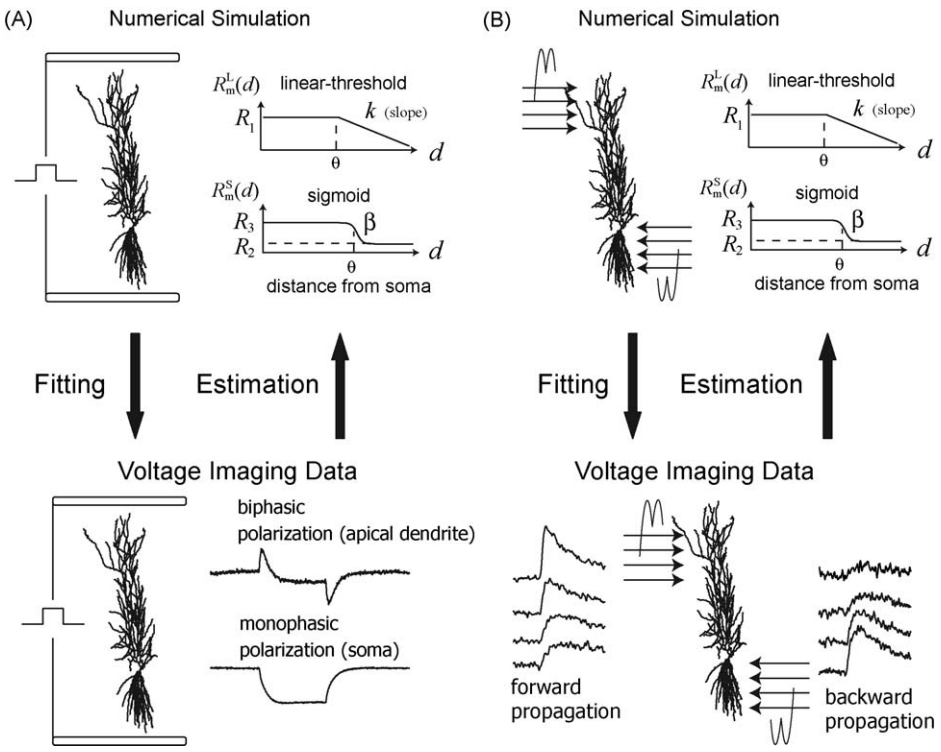

Fig. 1. A proposed method to estimate the spatial distribution of the specific membrane resistance. The distribution is estimated by an indirect method that is a combination of optical recordings and simulations. First, the time-courses of membrane potentials in the apical dendrites and soma were recorded in two different experiments: (i) membrane polarizations in response to a DC extracellular electric field and (ii) EPSPs propagating from the distal dendrite to the soma (forward propagation), and from the soma to the distal dendrite (backward propagation) induced by synaptic inputs, shown in the bottom right panel of, respectively, (A) and (B). Next, simulations were performed to reproduce these experimental data (top panels). Two candidate distribution functions of the specific membrane resistance, a linear threshold function and a sigmoid function, were considered (top right panel). To find the parameter values of each candidate distribution giving the smallest discrepancy between the simulated data and the experimental results, we performed the experiments repeatedly using different values of parameters in the candidate functions ($\{R_1, k, \theta\}$ in the linear threshold function, $\{R_2, R_3, \beta, \theta\}$ in the sigmoid function), and evaluated the dependence of the reproduction error on the parameter values by comparing the experimental data with the simulation results. Comparing the minimum errors for the two-candidate function, we selected the best function and determined the parameter ranges that could reproduce both types of experimental voltage imaging data.

of simulations and experimental data (Fig. 1). If simulation using a single neuron model can reproduce experimental data obtained from slices, the spatial profile of the specific membrane resistance assumed in the model can be regarded as an appropriate distribution. Using double whole-cell patch clamping and simulations, an estimate of the spatial non-uniform distribution of the dendritic membrane resistance has been obtained, and the distal dendrite was found to be more leaky than the proximal dendrite in both cortical layer V pyramidal neurons (Stuart and Spruston, 1998) and hippocampal CA1 pyramidal neurons (Golding et al., 2005). While the whole cell recordings give less noisy data of time trace of membrane potential, it is difficult to record membrane potentials in the multiple positions of a neuron simultaneously in the whole cell recording. On the other hand, the optical recordings with voltage-sensitive dyes (VSD) give spatial distribution of time traces of membrane potentials over the dendrite. Even though the observed responses recorded using the VSD are rather noisy and the absolute value of membrane potential can not be recorded directly using the VSD recording, the spatiotemporal distribution of membrane potentials recorded using the VSD is essential information in order to reveal the spatial distribution of electrical membrane property in the dendrite. Using experimental voltage responses to electrical stimulation of presynaptic fibers recorded using the VSD and simulation with a uniform distribution of the specific membrane resistance, it has also been suggested that non-uniformity of the specific membrane resistance exists in dendrites of hippocampal CA1 pyramidal neurons (Inoue et al., 2001), since the uniform distribution model could not consistently reproduce the experimental data for both the forward propagation (distal dendrite to the soma) and the backward propagation (soma to the distal dendrite) of subthreshold EPSPs through the dendrite of a CA1 pyramidal neuron (Inoue et al., 2001). Using simulations with a compartment model with a non-uniform specific membrane resistance, it was shown that both the forward and backward propagations of the EPSPs (Inoue et al., 2001) could be consistently reproduced using a step distribution of the specific membrane resistance (Omori et al., 2005, 2006a,b). This might imply that the specific membrane resistance shows a steep decrease in the dendrite. However, it remains unclear how the specific membrane resistance decreases in the dendrite, e.g. at what distance from the soma and with what slope. In order to determine how synaptic inputs are integrated and processed in the dendrite, we need to clarify in which part of the dendrite the decrease in the specific membrane resistance occurs, how steep the decrease is, and the absolute value of the specific membrane resistance in the distal dendrite. To clarify these properties of the non-uniform specific membrane resistance, we should also consider a sigmoid function as one of the candidates; only a step function and a linear threshold function were considered in our previous study (Omori et al., 2005, 2006a,b), neither of which include the condition of a gradual change in an arbitrary part of the dendrite.

Membrane polarizations in response to an extracellular electric field applied to hippocampal CA1 slices have been previously investigated by intracellular recording (Andreasen and Nedergaard, 1996; Fernandez et al., 2002) and by voltage imaging with a voltage-sensitive dye (Bikson et al., 2004). All three studies showed a unique distribution of membrane polarizations of CA1 pyramidal neurons. The application of a weak extracellular DC electric field to