Single neuron electrophysiology of transcranial magnetic stimulation. I. Passive response.

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Introduction

Transcranial magnetic stimulation (TMS) is a widely used noninvasive stimulation technique that induces action potentials in neurons via a rapidly changing magnetic field directed through the skull. However, the interaction between neural tissue and TMS stimulation is not well understood. Kamitani et al. [1] and Miyawaki et al. [2] have investigated the afterhyperpolarization that follows TMS evoked discharge in a single cortical neuron model. They described only the neuronal response and silent period evoked by a single TMS stimulus without details as to the orientation of the stimulating E-field. We have previously reported that spiking is evoked only when the primary electric (E) field is oriented from the soma toward the apical dendrite (antidromic stimulus). An E-field oriented in the opposite direction from the apical dendrite toward the soma (orthodromic stimulus) evokes an excitatory potential (EP) considerably larger than that of an excitatory postsynaptic potential (EPSP) [4]. However, this EPSP is not sufficient to induce cell firing [4]. To better understand the behavior, we explored the passive membrane response of the model system to different stimulus magnitudes.

Methods

We employed NEURON modeling software and the same TMS modeling system including the stimulus as [1]. The channel kinetics were based on those of a multicompartment Layer 5 pyramidal neuron from cat visual cortex [3]. The cell morphology was from [1] and is illustrated in Figure 1.

A TMS stimulus equivalent to either 350 or 400 V/m was sufficient to evoke one or three spikes, respectively, in this model cell. Three spikes was the maximum number that could be evoked by the stimulus. Stronger stimulus intensities only increased the duration of the silent period following the initial burst. We primarily used the smaller 350 V/m stimulus in this study to explore the effect of a minimal strenght stimulus on passive membrane.

TMS evoked discharge in this cell in the presence of background Poisson distributed EPSPs is determined by the orientation and strength of the stimulus associated E-field. Stimulation in the antidromic direction evoked 1-3 spikes depending upon stimulus strength, whereas, stimulation in the orthodromic direction generated a single EP (~3 mV) that was considerably larger than a single EPSP (~0.75 mV) generated at rest (-70 mV) in the soma (Fig. 2).

To explore the orientation selectivity of neuronal response, the full model was reduced by removing active membrane channels and recording the passive membrane response along a piece-wise continuous axis spanning the length of the neuron. Recording points were separated by approximately 50 um.

Frequently, the passive membrane response was preceded by an obvious TMS transient (Fig. 3a). In this case the magnitude of the response was taken to be the peak membrane depolarization or hyperpolarization following the transient (Fig. 3b, maximum depolarization indicated).

Results

The temporal response of the membrane was often clearly composed of a stimulus transient followed by the membrane response and could be complex (Fig 3).

An orthodromically oriented E-field induced a depolarizing potential in the basal dendrites and soma (Fig. 4a, b-red, black; Fig. 5c-red dash) and in the full model a large EP, while a hyperpolarizing response was recorded from the distal apical dendrite (Figs 4c-red, black; 5c-red dash). It evoked a bimodal depolarization in the basal dendrites (peak: proximal 26 mV, distal 18 mV) that peaked within 0.5 ms of stimulus onset. In the apical dendrites, the same stimulus induced a small depolarization (2-3 mV) proximal to the soma. Depolarization converted to hyperpolarization within 250 um of the soma and increased to become larger than 30 mV at the distal dendritic tip (Fig. 5c-red dash, 1000 um). This distal hyperpolarization lasted less than 0.5 s.

Reversing the orientation of the stimulus inverted the response of the membrane to the single TMS pulse (Figs 4a, b, c-green, blue; 5c-green). However, the temporal profile of the membrane response was determined by the recording location and and was independent of E-field orientation (Fig. 5B).

Conclusion

In response to either an ortho- or antidromically directed E-field, the basal dendrites act as a current sink for both depolarizing and hyperpolarizing currents which dissipate rapidly in this highly branched structure as they do also in the distal apical dendrites. However, an antidromically directed E-filed drives current towards the soma along the apical dendrite and generates sufficient depolarization at the soma to evoke a spike in the full model. Alternatively, under an orthodromically directed E-field, the current sink provided by the basal dendrites would prevent cell spiking. This behavior is likely controlled in part by the resistence of the single primary apical dendrite which extends for the initial 500 um from the soma.

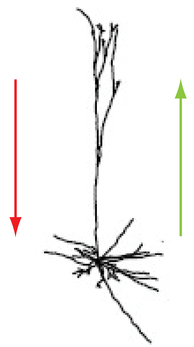

Figure 1: Vertical arrows indicate the orientation of the TMS induced primary E-field. Red: orthodromic or somatopetal stimulation, Green: antidromic or somatofugal stimulation. Only an antidromically oriented E-field induces cell firing in the full model. E-field vectors are also scale bars indicating a length of 600 μm.

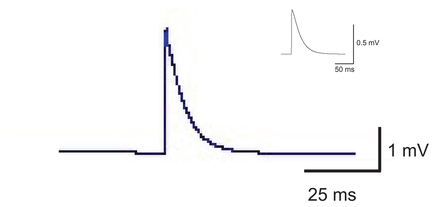

Figure 2: A large somatic evoked potential induced by TMS pulse oriented to apply an antidromic stimulus. For comparison, the inset shows an evoked somatic EPSP.

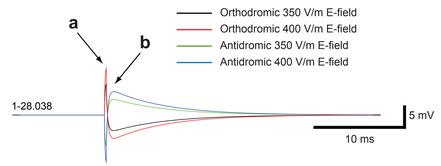

Figure 3: Temporal response of passive membrane to single TMS stimulus. a: TMS transient. b: Passive membrane response, arrow indicates time to peak and magnitude recorded for Figure 6C.

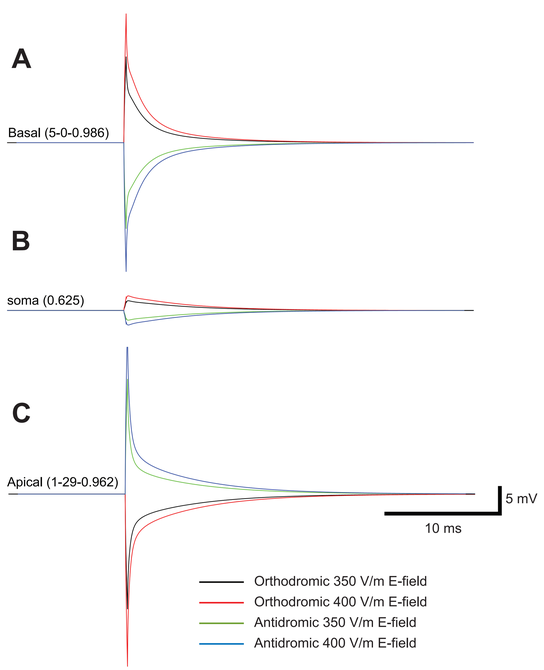

Figure 4: Temporal profiles of response of passive membrane to either a 350 or 400 V/m E-field stimulus. **A**. Tip of longest basal dendrite, **B**. Soma, **C**. Tip of longest apical dendrite.

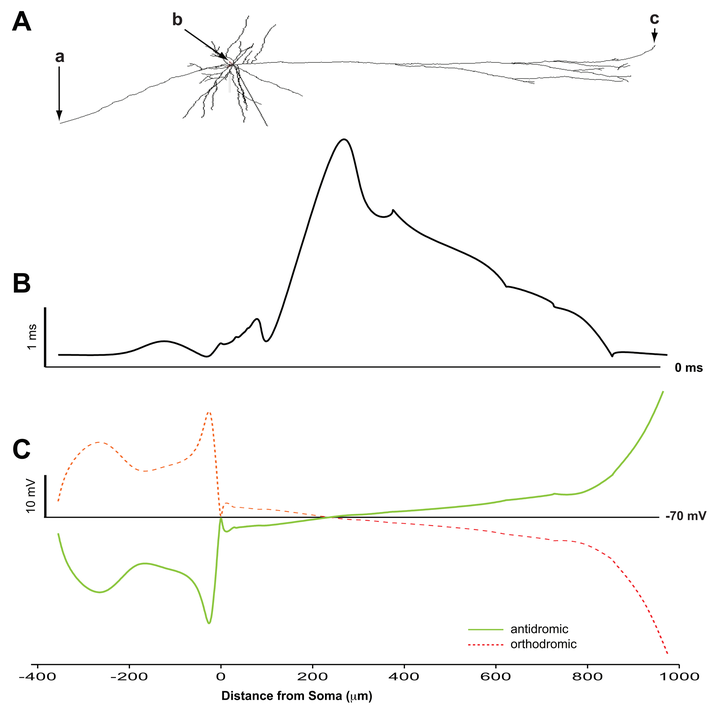

Figure 5: Spatio-temporal response of passive membrane to a single 350 V/m TMS stimulus. **A**. Cell morphology. Recording points at a, b, and c indicate locations from which the temporal profiles illustrated in Figure 4 were obtained. **B**. Time to peak of passive membrane response. **C**. Response of passive membrane to 500 us 350 V/m E-field.

References

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