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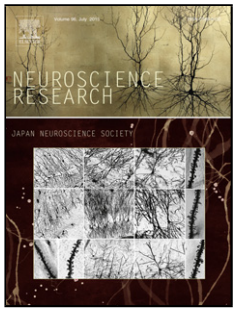

Possible role of backpropagating action potentials in corticospinal neurons in I-wave periodicity following a TMS pulse

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Update article for NSR

Possible role of backpropagating action potentials in corticospinal neurons in I-wave periodicity following a TMS pulse.

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Highlights

- Ca spike is initiated by synaptic input and backpropagation of action potentials at the dendrite.
- The Calcium spike initiates a burst of somatic action potentials causing repetitive firing of CSTN.
- The bursting of CSTNs may determine the intervals of successive I-waves in the motor cortical TMS.

Abstract

A single pulse of TMS or direct electric stimulation over M1 causes repetitive synchronized firing of corticospinal tract (CST) neurons. Two mechanisms for the repetitive firing have been proposed: a cascade of synaptic inputs to the pyramidal neurons and a single reverberating circuit of interneurons. Here, we propose another possibility in which bursting of CST neurons is produced by dendritic Ca^{2+}-spikes.

Backpropagation of the initial action potential (I1-wave) from the soma interacts with synaptic input in the dendrites to initiate a dendritic calcium spike. These Ca^{2+}-spikes produce a burst of somatic action potentials that starts about 1.5ms after the initial discharge of the neuron, which may produce the later I-waves.

Keywords: TMS, Motor cortex, I wave, dendrite, Dendric computation Backpropagation activated coupling

A single pulse of both transcranial magnetic stimulation (TMS) or direct electric stimulation over the primary motor cortex (M1) causes repetitive synchronized firing of corticospinal tract (CST) neurons that can be recorded as a sequence of descending volleys in the corticospinal tract (CST). The first of these discharges is known as the direct wave (D-wave); later waves are known as indirect waves (I-waves) that occur at intervals of about 1.5ms (Amassian et al, 1987; Di Lazzaro et al, 2012). The lowest intensity TMS pulses over the hand area of the human motor cortex preferentially recruit I-waves; a D-wave is seen only with high intensity TMS. The D-wave is caused by direct activation of corticospinal neurons at, or near to, the axon initial segment or, with higher intensities, at the point where the axons bend into the CST in the white matter (Rothwell et al, 1994). However, the TMS pulse tends to activate other neurons that trans-synaptically either activate or inhibit the corticospinal neurons. This leads to a cascade of synaptic inputs to the pyramidal neurons that traditionally accounts for the generation of the I-waves (Di Lazzaro *et al.*, 2012).

Initial concepts (Amassian & Cracco, 1987) suggested that each I-wave was triggered by arrival of a separate and synchronized volley of EPSPs from neighboring neurons thus representing an “I1-wave EPSP”, an “I2-wave EPSP” etc. One TMS pulse could then activate a first monosynaptic input to generate the “I1-wave EPSP” and a second disynaptic input to generate the “I2-wave EPSP” etc. Alternatively, a single reverberating circuit of interneurons could be responsible for the repetitive I-wave responses. It should be noted that both possibilities involve a chain of synaptic connections. If the EPSPs at each synapse lasted 10-15 ms, it seems unlikely that these circuits alone could generate sufficient synchrony to produce I-waves every 1.5 ms because of increasing temporal dispersion of EPSPs at late intervals. One possibility is that in order to sustain synchronous firing, each EPSP would have to be quickly terminated by a concomitant IPSP, which would sharpen the temporal precision of the excitatory inputs.

Another possibility is that synaptic inputs arrive approximately synchronously at proximal and distal locations of the dendritic tree. Such a model was explored by Rusu and colleagues (Rusu *et al.*, 2014). In that model, layer 3 neurons provided excitatory and inhibitory synaptic inputs to all parts of the soma and dendrites of pyramidal neurons. Each TMS pulse produced a single discharge of each layer 3 neuron, with the result that each synapse onto the layer 5 pyramidal neurons was activated only once. If the TMS intensity was above motor threshold, stimulation evoked a net excitatory input. Activity of synapses on the soma caused the initial depolarization of the spike trigger zone at the axon hillock, resulting in the I1-wave; inputs to more distal parts of the dendritic tree reached the trigger zone later, over the next few milliseconds, and resulted in a sustained depolarization of the spike trigger zone. In the model, this leads to a burst of repetitive firing which produced the I2 and later I-waves. Sodium and potassium channel properties at the spike trigger zone were adjusted so that a sustained depolarization would generate firing at around 600Hz, equal to the periodicity of the I-waves.

The model has to be adjusted quite carefully in order for there to be sufficient numbers of active synapses on the most distal dendrites to sustain depolarization of the spike trigger zone for a sufficient length of time to generate up to five I-waves. If the dendrites are too short, the depolarization will not last long enough; if there are too few dendrites, the depolarization is too small to generate action potentials. Although the assumptions of the Rusu model are not unreasonable, we wondered whether it would be more robust if another feature of cortical pyramidal neurons were added. In addition to the Na^+ and K^+ voltage-sensitive channels that generate the action potential, there are also voltage-sensitive Ca^{2+} channels in proximal and distal dendrites that can generate Ca^{2+}-spikes that boost the effect of distal synaptic inputs, enabling them to depolarize the cell body and generate action potentials (e.g. BUZSA´ KI et al, 1998: Larkum et al, 1999; Harnett et al, 2013). Rusu et al (2014) briefly acknowledge this and note that in their simulations it produced comparable results to the simple model. The purpose of the present note is to explore how these Ca^{2+}-spikes might contribute to I-wave generation.

Usually, activation of dendritic Ca^{2+} channels requires a substantial depolarization by distal inputs, but this can be greatly facilitated if the inputs are paired with a backpropagating Na^+ spike from the cell body (Larkum, 1999, 2001; Yi et al, 2018). We speculate that the following may occur: the TMS pulse activates excitatory synaptic input to cell body and dendrites (Figure). The input to the cell body is the first to depolarize the spike trigger zone and produces the I1-wave. This action potential backpropagates to the

dendrites. Alone, this backpropagating current is insufficient to trigger the Ca^{2+}-spike in proximal dendrites, but in the presence of additional depolarization from synaptic inputs activated by TMS on the distal or proximal dendrites this generates a Ca^{2+}-spike. Although the spike does not usually propagate into the soma, the depolarization can spread electrotonically to depolarize the action potential initiation zone in the axon hillock and produce an action potential (Larkum et al, 1999, 2001, Yi et al, 2018). It would take about 1.5ms for backpropagation to/from the proximal dendrite (Larkum et al, 1999, 2001, Yi et al, 2018), which is suitably timed to contribute to an I2-wave.

Calcium action potentials have a long duration (> 10 ms) and generate burst firing of the spike trigger zone of pyramidal neurons and potentially contribute to I3 and later waves. Such later activity may also be boosted by later arriving excitatory inputs in more slowly conducting fibers activated by the TMS pulse. Or it could be that the initial backpropagating action potential (from the I1-wave) has to reach the distal dendrites before triggering a Ca^{2+}-spike. This would take about 3 ms (Larkum et al, 199, 2001; Yi et al, 2018) and potentially contribute to an I3 wave. Effectively in this model, the frequency of later I-waves reflects the responses of the spike trigger zone to a sustained calcium action potential in the dendrites, whereas the interval between I1 and I2 waves relates to the conduction time of the backpropagating I1-wave action potential into the dendrites where it initiates the calcium action potential. The amount of depolarization may decline over time, thus reducing the probability of generating I-waves, limiting the number that are produced (Watanabe et al, 2006, Shor et al, 2017).

Such a distinction between I-wave mechanisms may explain why the interval between I1 and I2 waves can differ from that between I2 and I3 waves. Recordings made with the technique of short interval intracortical facilitation (SICF) suggest that the I1- I2 interval is shorter than that between I2 and I3 (Ziemann et al, 1996). In addition, it may help explain why the I3 and later I-waves are particularly affected by short-interval intracortical inhibition (SICI) (Hanajima et al, 1998).

We envisage that this mechanism does not exclude other additional synaptic mechanisms such as monosynaptic input arriving from neighboring neurons with synapses on the cell body/proximal dendrites, explaining e.g. the breakdown of later I-waves under activation (Ziemann *et al.*, 1998) tentatively caused by “leaky membranes” (Paulus & Rothwell, 2016). In any case the key suggestion here is that backpropagating action potentials reinforce depolarization of the spike trigger zone and lead to repetitive firing of the neuron.

Finally, we note that our discussion sheds no light on a second unsolved mystery of TMS stimulation: the effect of induced current direction. In the hand area of motor cortex, stimulation with a posterior-anterior (PA) induced current flow evokes the lowest threshold and shortest latency responses, whereas the opposite, anterior-posterior (AP) direction has a higher threshold and evokes responses that occur 2-3 ms later (Sakai et al, 1997). The explanation for this most likely lies in differences in stimulation sites and has no connection to dendritic calcium channels in the membranes of pyramidal neurons.

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Figure legend

Motor cortical intrinsic oscillation mechanism

A. The 3 columns show the sequence of events for stimulation readily activating the pyramidal neurons directly such PA pulses. The left diagram (at 0 ms) illustrates initial excitation of several populations of interneurons that have synapses on the cell body and dendrites. The initial monosynaptic excitation this produces, particularly in synapses near the cell body, discharges the cell and evokes an I1-wave. The middle column shows how this I1 activity backpropagates to the dendrites where it can summate approximately 0.8ms later with continuing synaptic input to the proximal dendrites. This generates a Ca action potential that is sufficiently large (see right panel at 1.5 ms) to discharge the corticospinal for a second time and generate an I2-wave. The diagram also shows that this depolarization may also summate with later arriving synaptic inputs to the cell body.