Compartmental Models of Dichotomous Backpropagating Action Potentials in CA1 Pyramidal Neuron Dendrites [1]

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Abstract

In hippocampal CA1 pyramidal neurons, action potentials are typically initiated in the axon and backpropagate into the dendrites, shaping the integration of synaptic activity and influencing synaptic plasticity. Here we present compartmental models which reveal that a dichotomy in action potential backpropagation can be generated in response to subtle manipulations of the distribution of either sodium or A-type potassium channels in the dendrites. Based on these findings, we hypothesize that the observed dichotomy in dendritic action potential amplitude is conferred primarily by differences in either the distribution, density, or modulatory state of voltage-gated channels along the somatodendritic axis.

Neuronal dendrites mediate the conversion of complex spatial and temporal patterns of synaptic potentials into patterns of action potential output that convey the salient features encoded in presynaptic activity. In most mammalian central neurons, action potentials are initiated near or in the axon and propagate distally ("backpropagate") into the dendritic arbor. The degree to which backpropagating action potentials invade the arbor depends critically upon the dendritic morphology of neurons, which includes parameters such as dendritic diameter and the pattern of dendritic branching, and upon the relative density of inward and outward currents activated by the backpropagating action potentials.

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The dendritic depolarization provided by backpropagating action potentials is important because it triggers calcium influx through voltage-gated calcium channels located on dendritic shafts and spines. Dendritic calcium influx arising from the coincidence of repetitive patterns of backpropagating action potentials and synaptic input has been shown to be critical for the induction of some forms of synaptic plasticity.

Simultaneous somatic and dendritic whole-cell patch recordings to measure the degree to which action potentials attenuate as they propagate along the primary apical dendrites have shown a marked dichotomy in their propagation efficacy beyond 300 μm. In roughly half of the recordings (9/20), action potentials propagated strongly, showing a 26-42% decline in amplitude. By contrast, in the other half of recordings (10/20), action potentials propagated weakly, exhibiting a 71-87% attenuation.

In an effort to explain these experimental observations, we have constructed compartmental models of morphologically reconstructed CA1 pyramidal neurons to explore potential mechanisms controlling the amplitude of backpropagating action potentials in the dendrites. These models contain voltage-gated sodium channels as well as delayed-rectifying and A-type potassium channels.

In the model, weak action potential backpropagation is exhibited with uniform distributions of sodium and delayed rectifying potassium channels, and a positive somatodendritic gradient of A-type potassium channels. The same model exhibits strong action potential backpropagation, however, when a slight positive gradient is introduced to the dendritic distribution of voltage-gated sodium channels (a gradient is used to be consistent with observations of smaller, more slowly rising somatic action potentials in strongly backpropagating neurons). In this case, action potentials propagate strongly to the distal tips of the apical dendrites and oblique branches. (Action potentials can fail to actively invade a small number of specific branches, typically those of smaller diameter.) Incremental changes in the slope of sodium channel gradients produce dichotomous profiles of action potential amplitude in the distal dendrites, where action potentials either propagate actively, or attenuate to nearly a passive level. Intermediate amplitudes of backpropagating action potentials can be produced (as observed in 1 out of 20 recordings), but only by using an extremely narrow range of slopes of the sodium channel gradient.

Continuous gradients of sodium channels are not exclusively necessary to produce a dichotomy in action potential backpropagation; a weak-propagating neuron can be converted to a strong-propagating neuron by introducing local inhomogeneities (”hotspots”) of sodium channels within an otherwise uniform distribution. A dichotomy of backpropagating action potential amplitude is also exhibited by a model in which the dendritic slope of A-type potassium channels is varied, indicating that the efficacy of action potential backpropagation is sensitive to relatively subtle changes in the ratio of sodium to potassium currents.

Compartmental models can also be used to estimate the influence of branching structure on action potential backpropagation. In the experimental data a small but consistent difference in the number of oblique branches was observed in a restricted area between 300 and 350 μm from the soma, near the dendritic region where the dichotomy in action potential backpropagation could first be distinguished (2 vs. 0 primary branches on average in weak and strong-propagating neurons, respectively). The compartmental model exhibits a similar region where backpropagation dichotomy emerges, although this region occurs somewhat more proximally than in the experimental data. It is thus possible that appropriately located oblique branches could promote weak action potential propagation by drawing current from the primary apical dendrite.

We tested this possibility by removing distal dendritic branches from neuron models that exhibit weak action potential backpropagation. Removal of small numbers of oblique branches in most of these models results in a small increase in backpropagating action potential amplitude (a few millivolts). The magnitude of this effect is proportional to the diameter and length of the removed branch as well as its distance from the soma. Removal of a small number of branches, however, can convert a weak-propagating neuron to a strong one under optimal conditions. When three branches are removed from the primary apical dendrite about 200 μm from the soma, a weak-propagating neuron can be converted to a strong one only when the distribution of sodium and potassium channels yields action potentials that propagate just below the threshold for active propagation. These results indicate that the presence or absence of large, strategically located dendritic side branches has the potential to influence the efficacy of action potential backpropagation, but only if Na and K channel densities are very tightly regulated in the dendrites.

Although the precise cellular mechanisms conferring weak versus strong backpropagation are not precisely known, the compartmental model provides insight into some of the important parameters. In the simulations, relatively subtle alterations in the somatodendritic distribution of either voltage-gated sodium channels or A-type potassium channels can interconvert modeled neurons between strong and weak action potential backpropagation. Significantly, the resultant spatial profiles of action potential amplitude exhibit a dichotomy at a discrete location in the primary apical dendrite, similar to the experimental data obtained from a population of neurons.

An important aspect of the simulations is that the variance in the densities of sodium and A-type potassium channels used falls within the variance of densities that have been reported experimentally in CA1 pyramidal neurons. Thus, while it is not known in what manner and to what extent voltage-gated channel densities vary in single neurons, the simple models demonstrate the principle that relatively minor differences in the spatial profile of channel expression can exert strong effects on action potential backpropagation.