

A new bursting model of CA3 pyramidal cell physiology suggests multiple locations for spike initiation.

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One of the most peculiar characteristics of hippocampal CA3 pyramidal cell activity is the direct transition from quiescence to a complex train of spikes (burst) in response to somatic injection of current pulses. Experiments have partially elucidated the complex dynamics underlying CA3 electrophysiological behavior, but to date the detailed mechanisms causing the burst and its initiation are not fully understood.

Computer simulations allow the development and formulation of sophisticated hypotheses regarding the sub-cellular correlates of firing activity in neurons. A previous model of CA3 pyramidal cell physiology, with active conductances based on experimental data through 1995, and real morphologies, reproduced most experimental features of the burst, including the number and shape of spikes and $[Ca]_i$ dynamics and distribution. However, recent findings suggested different dendritic distributions of active properties, as well as additional currents that were not included in such model. These properties might be relevant for the cellular mechanisms of burst generation.

Here we present a novel computational model of CA3 pyramidal cells with updated channel distributions. The model contains seven potassium currents ($I_{K(DR)}$, $I_{K(A)}$, $I_{K(M)}$, $I_{K(C)}$, $I_{K(AHP)}$, $I_{K(D)}$, I_h), fast sodium current (I_{Na}), three calcium currents ($I_{Ca(T)}$, $I_{Ca(L)}$, $I_{Ca(N)}$), and Ca^{2+} dynamics with radial diffusion, buffering, and pumping. The kinetics and dendritic distribution of these properties reflect the current experimental knowledge and differs significantly from the previous model. For example, I_{Na} and $I_{K(DR)}$ are uniformly distributed throughout the entire neuron, $I_{K(A)}$ and I_h have a dendritic density linearly increasing with distance from the soma, $I_{K(C)}$ decreases linearly, disappearing at a distance of $150\mu m$ from the soma, and $I_{K(AHP)}$ is ten times lower in apical than in basal dendrites. The model was implemented and validated using several real morphologies from reconstructed CA3 pyramidal cells.

This updated model displays somatic bursting activity and dendritic $[Ca]_i$ dynamics similar to that obtained the previous 1995 model, and in agreement with experimental recording and imaging data. However, detailed analysis revealed that the processes underlying burst generation in the two models are different. While in the 1995 model all spikes were initiated in the soma, in the updated model the first spike of the burst is initiated in the soma, but the second somatic spike is preceded by a Na^+ spike $\sim 200\mu m$ in the dendrites, as a response to the first spike back propagation. This dendritic spike propagates both backwards and forward, and it reaches the soma just before the rise of the (second) somatic spike. The remaining somatic spikes of the burst appear to be caused by an even more complex spatial interplay between active properties of dendrites and soma.

Thus, although different dendritic distributions of active properties can lead to essentially the same somatic firing pattern, the mechanisms underlying such a pattern are different. Our model makes the experimentally testable prediction that a distribution of conductances reflecting up-to-date experimental knowledge results in a burst in which spikes may be initiated both in the soma and in the dendrites.

These results are particularly interesting in light of recent discussions concerning dendritic involvement in spike initiation. Although in bursting subicular neurons somatic spikes always precede dendritic ones, a regenerative dendritic activation preceding somatic spikes is known to occur in neocortical neurons, where it subserves specific computational properties. Thus, if experimentally confirmed in CA3 pyramidal cells, this effect could shed new light on the biophysical mechanism underlying coding in the hippocampal network.