



Novel dynamics of dendritic integration in the high conductance state of cortical neurons

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Abstract

Neocortical neurons in vivo operate in a high-conductance state which may affect the dynamics of dendritic integration, but this aspect remains only barely characterized. We investigated this problem by using biophysical models of morphologically reconstructed neocortical pyramidal neurons in which isolated and paired synaptic events were studied according to their dendritic location. We show that during active states, there is an ongoing dynamics of randomly occurring forward- and back-propagating dendritic action potentials. This dynamics determinantly impacts on how individual or paired synaptic events interact, leading to a type of integrative behavior which is different from classical models of dendritic integration. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Cerebral cortex; Dendritic integration; Synaptic background activity; Dendritic spikes; Computational models

1. Introduction

Active states, such as wakefulness, are characterized by sustained and irregular activity in all types of cortical neurons [6,10]. Recent intracellular measurements in vivo indicate that this synaptic activity is responsible for inducing a high-conductance state in pyramidal neurons [1,4,8]. However, the consequences of this high-conductance state on dendritic integration in pyramidal neurons still remain to be characterized.

In the present paper, we investigated this problem using computational models of morphologically-reconstructed pyramidal neurons of cat parietal cortex. We show that

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the high conductance due to network activity, the highly fluctuating intracellular activity and active dendrites define a state where the dynamics of dendritic integration is radically different compared to that considered classically.

2. Methods

A computational model was designed based on a morphologically reconstructed layer VI neocortical pyramidal cell of cat parietal cortex, obtained from a previous study [2] (Fig. 1A). The passive parameters were estimated by matching the model to passive responses obtained intracellularly after application of TTX and synaptic blockers [4,8]. Three types of active currents (sodium current, delayed rectifier and V_m -dependent potassium currents) were simulated by inserting voltage-dependent conductances based on Hodgkin–Huxley type models with densities according to recent measurements [4].

Synaptic currents were incorporated by using two-state kinetic models [5] of AMPA and GABA_A receptors. Quantal conductances were estimated by matching the model to recordings of miniature synaptic events [4]. The densities of synapses in different

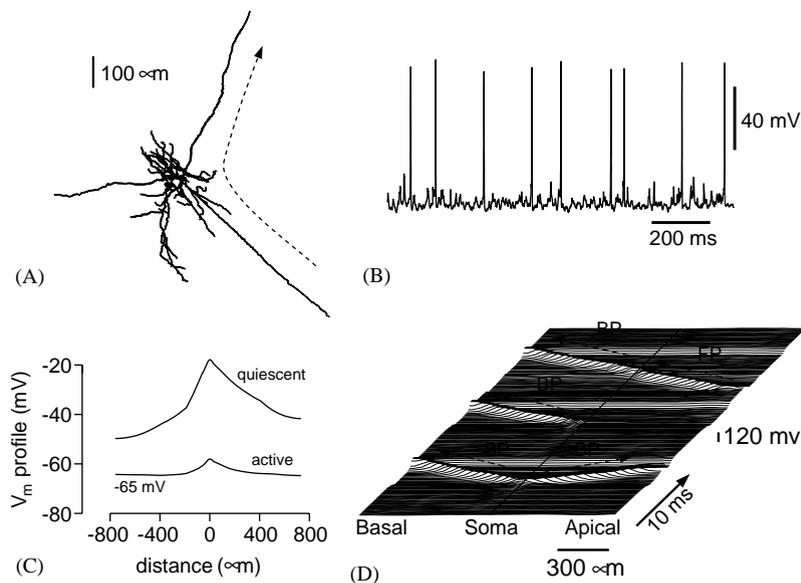


Fig. 1. (A) Morphologically reconstructed neocortical pyramidal layer VI neuron of a cat incorporated in the modeling studies. (B) Correlated Poisson-distributed synaptic background activity leads to V_m fluctuations and spontaneous tonic firing behavior. (C) Somatodendritic V_m profile along the path shown in (A) (dashed line) at steady-state following injection of current in the soma (+0.8 nA). In the absence of synaptic activity (quiescent) there was moderate attenuation, in contrast to the high attenuation of the active state (average over 1000 trials). (D) Somatodendritic V_m profile (same path as in (A)) in the presence of synaptic background activity as a function of time. Spike initiation sometimes occurred close to the soma, leading to back-propagating action potentials (BP). In other instances, spike initiation occurred distally and led to forward-propagating action potentials to the soma (FP).

regions of the cell were estimated from morphological studies in neocortical pyramidal cells [3], leading to a total of 16563 glutamatergic and 3376 GABAergic synapses.

Synaptic background activity was simulated by the firing of inhibitory and excitatory synapses according to a Poisson-like process with average rates of 5.5 Hz for GABA_A and 1.0 Hz for AMPA synapses. In addition, the statistics of the background activity was modified by introducing a redundancy (labeled by a correlation parameter c) in the Poisson-distributed random numbers assigned to the presynaptic compartments (see [4,7,9] for details).

3. Results

High-conductance states were simulated using high-frequency release conditions at excitatory and inhibitory synapses, which were estimated from intracellular measurements in vivo [4]. The frequency of release events was matched to the input resistance and average V_m obtained in this experiments. To match the level of fluctuations and spontaneous firing of the recorded cells, it was necessary to introduce a weak correlation between random synaptic events at a level consistent with the weak correlation found between pairs of neurons in monkey cerebral cortex [11]. This models successfully reproduced electrophysiological parameters in agreement with in vivo measurements, and a spontaneous firing activity between 5 and 20 Hz (Fig. 1B).

The first consequence of the high-conductance induced by background activity is a marked enhancement of voltage attenuation (Fig. 1C). A second and more surprising result is that the initiation and propagation of spikes in dendrites is favored by the voltage fluctuation. Thus, active states are characterized by a continuous and intense local dendritic spiking activity, to which both forward- and back-propagating spikes contribute (Fig. 1D).

We next investigated the averaged impact of individual synaptic events on the soma under active conditions. Without background activity, there was an exponential decrease of somatic EPSP amplitudes with increasing path distance, as expected from passive voltage attenuation (Fig. 2A and B1). In the presence of uncorrelated background activity ($c = 0$), the high conductance and associated high attenuation led to an even stronger decrease of the EPSP amplitudes as a function of distance (Fig. 2B2), as expected from cable theory. Remarkably, the situation was radically different with correlated background activity ($c = 0.7$, Fig. 2B3). Here, the impact of individual synaptic events became approximately equivalent for all sites. This location independence of synaptic inputs can be explained by the fact that in active states the cell is dominated by the intrinsic dynamics of dendritic spikes as shown above, leading to a somatic impact of given synaptic events which is roughly independent of their location.

To investigate further dendritic integration schemes, we analyzed the somatic responses to paired subthreshold synaptic background events. Averaging all synaptic events irrespective of their location, but representing them as a function of the delay between individual events, revealed that the cell is able to temporally resolve delayed events down to about 3 ms (Fig. 3A). Whereas the somatic impact was much higher

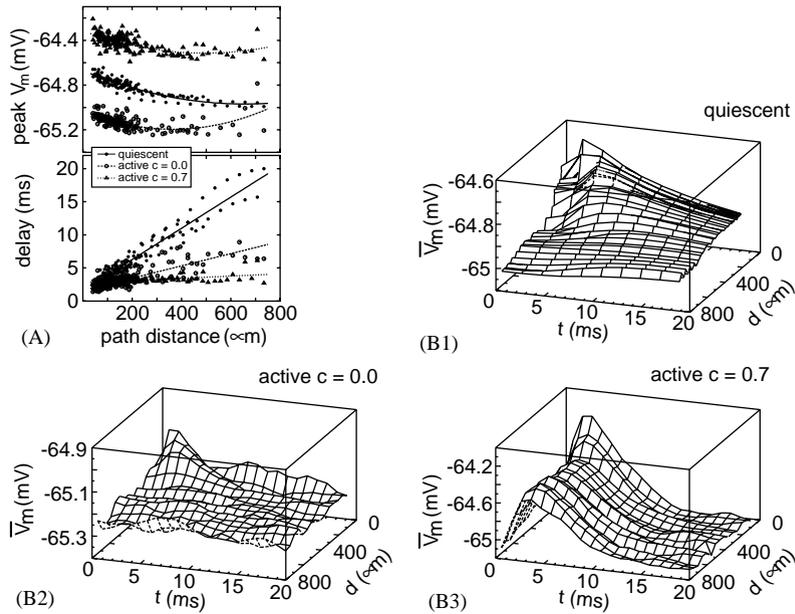


Fig. 2. (A) Somatic V_m response to subthreshold synaptic stimulation which do not initiate dendritic spikes. In quiescent conditions, the height of the EPSP peaks decreases for increasing path distances due to voltage attenuation (upper plot). Contrary, in the presence of correlated synaptic background the decrease of the EPSP peaks is smaller, suggesting that distal dendrites have a roughly equivalent impact as proximal dendrites. The lower plot shows the delay between the stimulating synaptic event and the somatic EPSP response peak, where correlated background activity also leads to a clear decrease in the delay time. (B) Average V_m response to subthreshold stimulation as a function of the time after stimulus and the path distance. Whereas in the absence of background activity (B1) there is a clear location dependence of the EPSP in response to the stimulation, the latter becomes nearly location independent when correlated background activity is present (B3).

with correlated background activity (Fig. 3A2), the time resolution of delayed events was the same with or without correlation (compare with Fig. 3A1).

Representing the peak EPSP as a function of the delay and relative distance between the two synapses $d_{\text{rel}} = |d_1 - d_2|$, where d_i denotes the path distance of event i , shows a qualitatively different spatial resolution behavior (Fig. 3B). Without correlations, the EPSP height decreases for increasing relative pair distances d_{rel} (Fig. 3B1), leading to a spatial window in which paired synaptic events show a higher somatic impact. The increase for the highest d_{rel} values can be traced back to the higher probability for evoking dendritic spikes in the outer regions of the dendritic tree. In the presence of correlated background activity (Fig. 3B2), there was no such spatial windowing, but instead a temporal window in which paired synaptic events lead to a high somatic EPSP. This can be explained by the “synchronization” of synaptic background events spread all over the dendritic tree. These results indicate that in active states the correlation of background events can be used to switch the dendritic integration behavior from temporal to spatial coincidence detection.

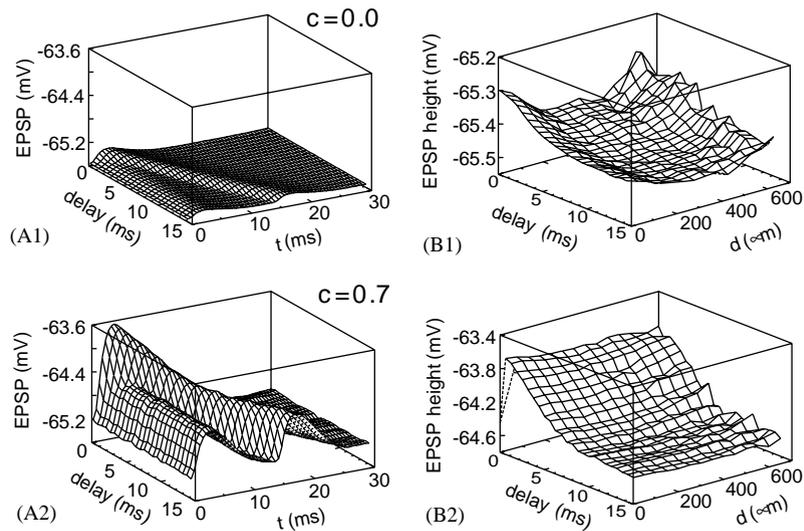


Fig. 3. (A) Average EPSPs caused by paired synaptic background events as a function of time after the first stimulus t and the delay between both events. Whereas the level of background correlation impacts the height of the somatic EPSPs, the temporal resolution remains nearly unaffected, and was found to be about 3 ms in both cases. (B) An additional spatial distinction of paired background events quantified by the relative distance d reveals in the zero correlation case (B1) a spatial window in which paired events show a much higher impact on the soma. Contrary, in the presence of background correlation (B2), the EPSP is sensitive to the delay between events, but not to their relative distance. This indicates that correlations may be used to modulate the spatial and temporal resolution of dendritic integration.

4. Conclusions

We found that during high-conductance states, neocortical neurons have an enhanced dendritic attenuation, and that the initiation and propagation of action potentials in dendrites are favored. As a consequence, there is a tremendous spontaneous dendritic spiking activity during active states, resulting in a roughly equivalent somatic impact of synaptic events irrespective their location in the dendritic tree. This predicted dendritic activity and location independence provide a number of functional advantages and can be tested experimentally.

This research supported by CNRS and the NIH (R01-NS37711).

References

- [1] L. Borg-Graham, C. Monier, Y. Frégnac, Visual input evokes transient and strong shunting inhibition in visual cortical neurons, *Nature* 393 (1998) 369–373.
- [2] D. Contreras, A. Destexhe, M. Steriade, Intracellular and computational characterization of the intracortical inhibitory control of synchronized thalamic inputs in vivo, *J. Neurophysiol.* 78 (1997) 335–350.

- [3] J. DeFelipe, I. Fariñas, The pyramidal neuron of the cerebral cortex: morphological and chemical characteristics of the synaptic inputs, *Prog. Neurobiol.* 39 (1992) 563–607.
- [4] A. Destexhe, D. Paré, Impact of network activity on the integrative properties of neocortical pyramidal neurons in vivo, *J. Neurophysiol.* 81 (1999) 1531–1547.
- [5] A. Destexhe, Z.F. Mainen, T.J. Sejnowski, in: C. Koch, I. Segev (Eds.), *Methods in Neuronal Modeling*, 2nd Edition, MIT Press, Cambridge, MA, 1998, pp. 1–26.
- [6] E.V. Evarts, Temporal patterns of discharge of pyramidal tract neurons during sleep and waking in the monkey, *J. Neurophysiol.* 27 (1964) 152–171.
- [7] N. Hô, A. Destexhe, Synaptic background activity enhances the responsiveness of neocortical pyramidal neurons, *J. Neurophysiol.* 84 (2000) 1488–1496.
- [8] D. Paré, E. Shink, H. Gaudreau, A. Destexhe, E.J. Lang, Impact of spontaneous synaptic activity on the resting properties of cat neocortical neurons in vivo, *J. Neurophysiol.* 79 (1998) 1450–1460.
- [9] M. Rudolph, A. Destexhe, Do neocortical pyramidal neurons display stochastic resonance? *J. Comput. Neurosci.* 11 (2001) 19–42.
- [10] M. Steriade, Corticothalamic resonance, states of vigilance and mentation, *Neuroscience* 101 (2000) 243–276.
- [11] E. Zohary, M. Shadlen, W. Newsome, Correlated neuronal discharge rate and its implications for psychophysical performance, *Nature* 370 (1994) 140–143.