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Inhibitory conductance dynamics in cortical neurons during activated states ☆

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Abstract

During activated states in vivo, neocortical neurons are subject to intense synaptic activity and high-amplitude membrane potential (V_m) fluctuations. These "high-conductance" states may strongly affect the integrative properties of cortical neurons. We investigated the responsiveness of cortical neurons during different states using a combination of computational models and in vitro experiments (dynamic-clamp) in the visual cortex of adult guinea pigs. Spike responses were monitored following stochastic conductance injection in both experiments and models. We found that cortical neurons can operate in a continuum between two different modes: during states with equal excitatory and inhibitory conductances, the firing is mostly correlated with an increase in excitatory conductance, which is a rather classic scenario. In contrast, during states dominated by inhibition, the firing is mostly related to a decrease in inhibitory conductances (dis-inhibition). This model prediction was tested experimentally using dynamic-clamp, and the same modes of firing were identified. We also found that the signature of spikes evoked by dis-inhibition is a transient drop of the total membrane conductance prior to the spike, which is typical of states with dominant inhibitory conductances. Such a drop should be identifiable from intracellular recordings in vivo, which would provide an important test for the presence of inhibition-dominated states. In conclusion, we show that in artificial activated states, not only inhibition can determine the conductance state of the membrane, but inhibitory inputs may also have a determinant influence on spiking. Future analyses and models should focus on verifying if such a determinant influence of inhibitory conductance dynamics is also present in vivo.

Keywords: Spike-triggered average; Conductance dynamics; Dynamic-clamp

1. Introduction

During activated states in vivo, neocortical neurons are subject to intense synaptic activity and high-amplitude membrane potential (V_m) fluctuations [3,6]. These "high-conductance" states may strongly affect the integrative properties of cortical neurons [2]. Models show that there is an infinite number of combinations of excitatory and inhibitory conductances that can yield V_m dynamics similar to in vivo recordings. Two extreme regimes in this continuum are low-conductance (LC) states, where excitatory and inhibitory conductances are approximately equal, or high-conductance (HC) states, in which inhibitory conductances are several-fold larger than excitatory conductances (cf. Fig. 1A). In this contribution, our goal is to compare these two states with respect to the conductance dynamics underlying spike initiation.

2. Spike-triggered averages during activated states

In order to determine the optimal pattern of conductance that triggers spikes, we first compared LC and HC states using a Hodgkin–Huxley type model. The predictions of this model were then tested using dynamic-clamp experiments in guinea pig cortical slices.

Our computational model consists of a single-compartment equipped with a passive leak conductance as well as active Hodgkin–Huxley type sodium and potassium channels. Details of the model can be found in [1]. From this model, we have calculated spike-triggered averages (STA) of the excitatory and inhibitory conductances. As shown in Fig. 1B, in LC states, excitatory conductances

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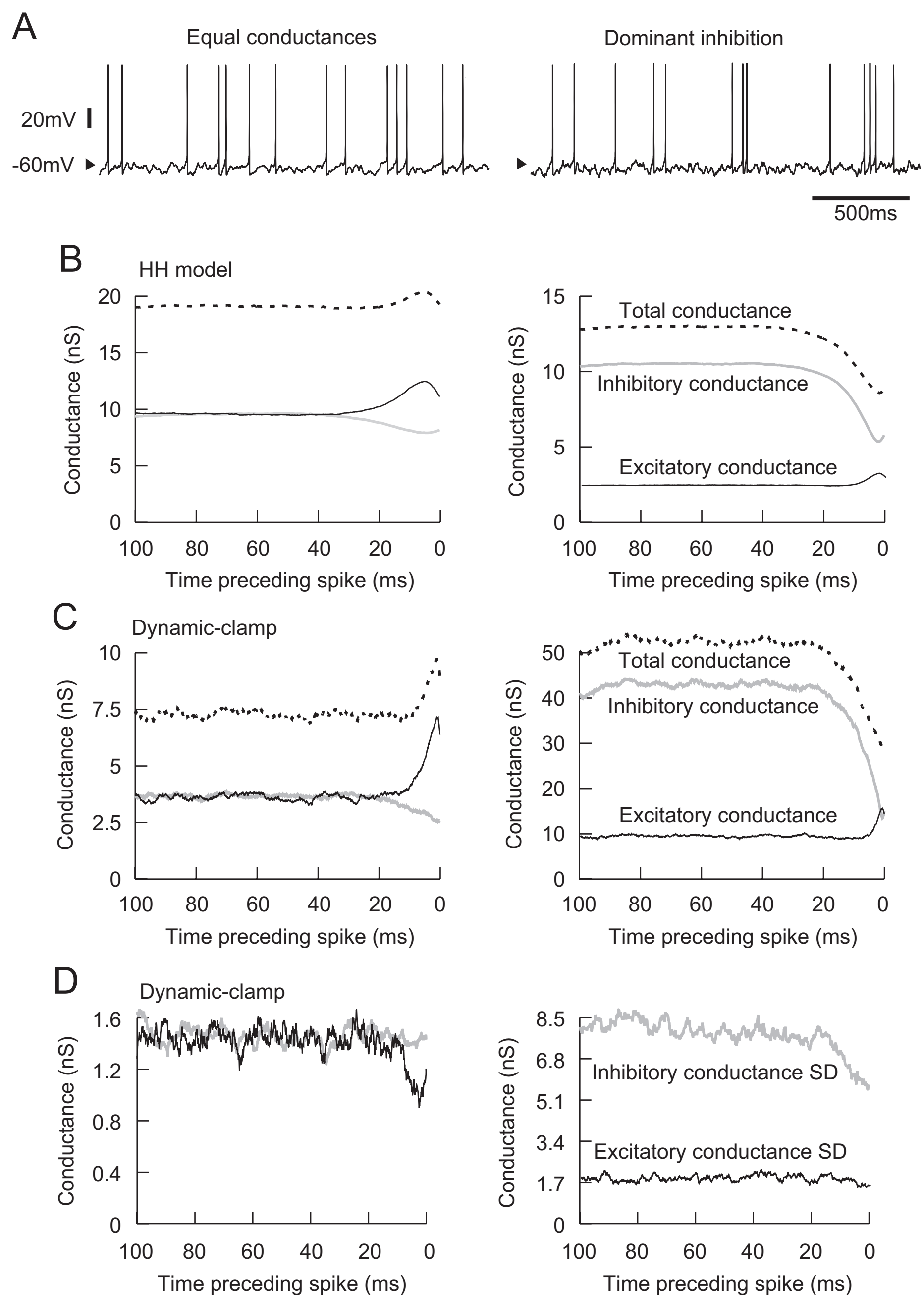

Fig. 1. Optimal patterns of conductance related to spikes in cortical neurons. Comparison of low-conductance (left) and high-conductance states (right). A spike is evoked at $t = 0$ ms. (A) The voltage traces in the two states obtained in models are similar in terms of V_m mean and variance (model). (B) Spike-triggered average of inhibitory, excitatory and total conductance in the model. In the LC state, the spike is preceded by a peak in excitatory and total conductance, whereas in the HC state there is a marked drop of inhibitory and total conductance just before the spike. (C) Same as (B) for guinea pig cortical neurons under dynamic-clamp. (D) Conductance standard deviations (SD) from the same experiment as in (C): in the LC state, only excitatory SD drops before the spike, whereas in the HC state inhibitory SD shows the more pronounced decrease.

always increase before the spike, while inhibitory conductances decrease. This is paralleled by an increase in total membrane conductance just before the spike, suggesting that spikes are preferentially evoked by an increase of excitatory conductance. In HC states, however, the total conductance decreases before the spike, which is necessarily caused by a decrease in inhibitory conductance. Thus, in this case, spikes are preferentially evoked by a drop of inhibition. Examination of single-trial conductance traces confirmed this analysis (not shown).

This prediction was tested in real cortical neurons using dynamic-clamp. LC and HC states were recreated by injecting fluctuating conductances similar to the model. The recordings were conducted at a temperature of 35 °C using sharp electrodes (see [5] for further details). The STAs showed the same behavior as in the model, also suggesting that spikes are evoked by a drop of inhibitory conductance in HC states (cf. Fig. 1C). The spike-triggered variances showed that in LC states, spikes were correlated with a decrease of variance of excitatory conductance, but not of inhibitory conductance (Fig. 1D, left panel). In contrast, in HC states only the variance of inhibitory conductance decreased shortly before spikes (cf. Fig. 1D, right panel), suggesting that the dynamics of inhibition has a determinant influence on spiking in HC states.

3. Discussion

We have examined two extreme cases taken from a continuum of noisy states, which evoke similar in vivo-like V_m dynamics. With respect to the optimal conductance pattern triggering spikes, we found that these patterns are very different in these two states. In LC states, spikes are preferentially evoked by an increase of excitation, associated with an increase of the total membrane conductance, which is a rather classic mode of firing. In HC states, however, spikes are preferentially evoked by a decrease of inhibitory conductance, which is associated to a decrease of the total membrane conductance. We predict that this mode of firing should be found in vivo, in high-conductance states where conductance measurements show dominant inhibitory conductances [2]. Note that the present study was limited to conductance standard deviations (SDs) that are proportional to the respective mean conductances. Further investigations are needed to explore the effect of independently varying conductance SDs on the firing mode.

In order to identify this mode of firing from intracellular recordings in vivo, we need to design specific methods to extract spike-triggered patterns of conductances from V_m activity. This task is not trivial, because of the presence of dominant intrinsic voltage-dependent currents in proximity to spikes, and also because conductances are related to the V_m through the cable equation, which is in general not solvable analytically. So, in order to extract the conductance traces prior to the spike from V_m activity, one needs to use a series of approximations. We are presently considering different approximations to yield this information with the goal to characterize the role of inhibitory conductance dynamics in modulating firing activity during active states in vivo. Preliminary results from analyzing intracellular data from cat parietal cortex in vivo indeed suggest a drop of conductance prior to the spike [4].

References

[1] A. Destexhe, D. Paré, Impact of network activity on the integrative properties of neocortical pyramidal neurons in vivo, J. Neurophysiol. 81 (1999) 1531–1547.

[2] A. Destexhe, M. Rudolph, D. Paré, The high-conductance state of neocortical neurons in vivo, Nat. Rev. Neurosci. 4 (2003) 739–751.

[3] 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.

[4] M. Pospischil, M. Rudolph, D. Shulz, I. Timofeev, A. Destexhe, Are we inhibited when we are awake? A combined intracellular and computational analysis of membrane potential dynamics in cortical neurons of awake and naturally sleeping animals, Soc. Neurosci. Abstracts 31 (2005) 276.15.

[5] Y. Shu, A. Hasenstaub, M. Badoual, T. Bal, D. McCormick, Barrages of synaptic activity control the gain and sensitivity of cortical neurons, J. Neurosci. 23 (32) (2003) 10388–10401.

[6] M. Steriade, I. Timofeev, F. Grenier, Natural waking and sleep states: a view from inside neocortical neurons, J. Neurophysiol. 85 (2001) 1969–1985.