Location-dependent differences between somatic and dendritic IPSPs

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Abstract

Recent experimental evidence suggests that inhibitory synapses are associated with different actions depending upon their location (Miles et al., Neuron 16 (1996) 815–823). We investigated that question of whether this effect is due to different subspecies of GABA\textsubscript{A} receptors giving rise to distinct responses (Pearce, Neuron 10 (1993) 189–20) or cable filtering by the dendritic tree. The effects of electrotonic filtering on GABA\textsubscript{A} receptor mediated IPSPs were studied in hippocampal pyramidal cells. We implemented two models with different morphologies where these differences could be explained by electrotonic filtering alone. Our parameter search resulted in realistic passive cell models where the dependence of electrotonic attenuation on morphological distance agreed with that seen in reconstructed cells. (\textcopyright\ 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

Inhibitory synapses are thought to be distributed throughout the dendrites and the soma of pyramidal cells in several cortical regions. Recent experimental evidence suggests that inhibitory synapses of different locations are associated with specific
actions based on their position. It has been observed that IPSP responses to GABA
have different time-courses corresponding to the different locations of receptors. This
can be explained by either the electrotonic filtering by the dendritic tree or different
subspecies of GABA_A receptors giving rise to distinct responses. Pearce [4] has found
that these differences are explained by different ratios of two pharmacologically
distinct species of GABA_A receptors in the dendrites versus the soma. In paired
recordings conducted by Miles and coworkers [3], where response properties could
be directly related to specific synapses, IPSPs could be fitted with single exponentials
which raises the possibility that the differences are due to filtering effects. This is
interesting because if different IPSPs are due to post-synaptic receptors with identical
kinetics then it is curious how the different actions attributed to these synapses arise.
In our study we systematically explore the possibility that the differences in the
time-courses of IPSPs are due to passive cable filtering.

2. Methods

We have used the standard multi-compartmental biophysical modeling technique
with the GENESIS simulator. Following usual methods applied to similar problems
[5], a passive pyramidal cell with simplified “ball & stick” (Fig. 1A) and with detailed
morphology (Fig. 2A) was simulated, both based on the model described by Traub et
al. [7]. Passive physiological parameters were set to values generally assumed in
literature [1,2,5–7]. The synapses were modeled with double exponential kinetics.

\[ G_{\text{syn}} = \frac{A.G_{\text{max}}}{\tau_1 - \tau_2} (e^{-t/\tau_2} - e^{-t/\tau_1}) \quad \text{for} \quad \tau_2 > \tau_1. \] (1)

The simulations used the Crank–Nicholson implicit integration method with a time
step of 100 ms for somatic IPSPs (single compartment phenomena) and 1 ms for
dendritic (multi-compartmental) phenomena.

We explored the parameter space to get a good fit for the somatic IPSP as measured
experimentally by Miles et al. [3]. For each run we found the values of time to peak
(ttp), amplitude (amp) and duration at half amplitude (daha) and calculated the error
based on Eq. (2).

\[ \text{Error} = \frac{|\text{simulated}_X - \text{measured}_X|}{|\text{measured}_X|}, \] (2)

where \( X \) is one of the three IPSP properties mentioned above (ttp, amp or daha).
These were then used to calculate the total error for the simulated IPSP according to
Eq. (3). Note that daha is taken into account with half weight.

\[ \text{Error}_{\text{total}} = \sqrt{\text{Error}_{\text{ttp}}^2 + \text{Error}_{\text{amp}}^2 + \frac{\text{Error}_{\text{daha}}^2}{2}}. \] (3)

To calculate relative errors, first both measured and simulated values were substituted
with their dendritic to somatic ratios as given in Eq. (4) and then errors were
calculated according to Eqs. (2) and (3). It was introduced to avoid the accumulation of errors as the original fits were already burdened with some mismatch.

\[ \text{rel}_x = \frac{X_{\text{comp}}}{X_{\text{soma}}} \times 100, \]  

(4)

where \( X_{\text{comp}} \) is the value of \( X \) (one of ttp, amp or daha) in the IPSP generated in the dendritic compartment \( \text{comp} \), \( X_{\text{soma}} \) is the value of \( X \) in the soma.

3. Results and discussion

First, we tried to reproduce the somatic IPSP measured by Miles et al. [3] by finding the optimal values for the parameters of our synaptic conductance kinetics. In
this case we modeled applying inhibition to the soma and, as throughout our whole work, recorded the changes of membrane potential in the somatic compartment (Figs. 1B and 2B). We made a detailed exploration of the parameter space and in the following simulations we used the parameters found to be best here.

Then the location of inhibition was changed, but not the parameters of the synaptic kinetics, by applying it to different dendritic compartments, each time further from the soma. With membrane potential still being recorded at the soma, we examined the change in properties of the IPSP and the total error of the fit with respect to the dendritic IPSP measured by Miles et al. [3] (Figs. 1C, 2C). We tried to match their values in terms of absolute and relative match as described in the Methods. There was an optimal electrotonic distance needed for reproducing the dendritic IPSP (Figs. 1D, 2D) that translated into an anatomical distance of 250–500 μm.
4. Conclusions

Our simulations showed that it is possible to reproduce the differences seen between somatic and dendritic IPSPs as measured at the soma previously by others, thus raising the possibility that although there are a number of known GABA\(_A\) receptors, interneuron to pyramidal cell synapses use the same one regardless of location. This is supported by that we simulated the electrotonic attenuation with morphological distances comparable to that seen in reconstructed cells. Future simulations can describe the functional effects of this electrotonic attenuation of IPSPs on the bursting behavior of pyramidal cells.

References