DENDRITIC CALCIUM CURRENTS IN THALAMIC RELAY CELLS

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Techniques of *in vitro* whole-cell recording and compartmental modeling were combined to investigate dendritic structure and calcium currents in individual thalamocortical neurons. Voltage-clamp recordings of I_T obtained in intact and dissociated ventrobasal neurons were used to constrain I_T conductances and passive parameters incorporated in morphorealistic models. High dendritic I_T densities were found necessary to establish congruent model behavior. Several methodologies based on axial resistance conservation were developed to algorithmically reduce thalamocortical morphology into a behaviorally congruent low-order compartmental model. This type of simplified model is suitable for investigating the functional role played by distal T-current localization at the network level in sleep oscillations and epilepsy.

INTRODUCTION

Rhythmic bursting is one of two characteristic firing patterns observed in individual thalamocortical (TC) neurons. This firing pattern is an essential player in the induction and perpetuation of certain oscillatory modes of cortical circuits, such as sleep oscillations and epileptic hypersynchrony[1]. In the present study, we combined experimental and computational approaches in an investigation of: i) the dendritic localization of the low-threshold Ca^{2+} current (I_T) that underlies this rhythmic bursting, and ii) the role played by the dendritic morphology in producing this firing pattern.

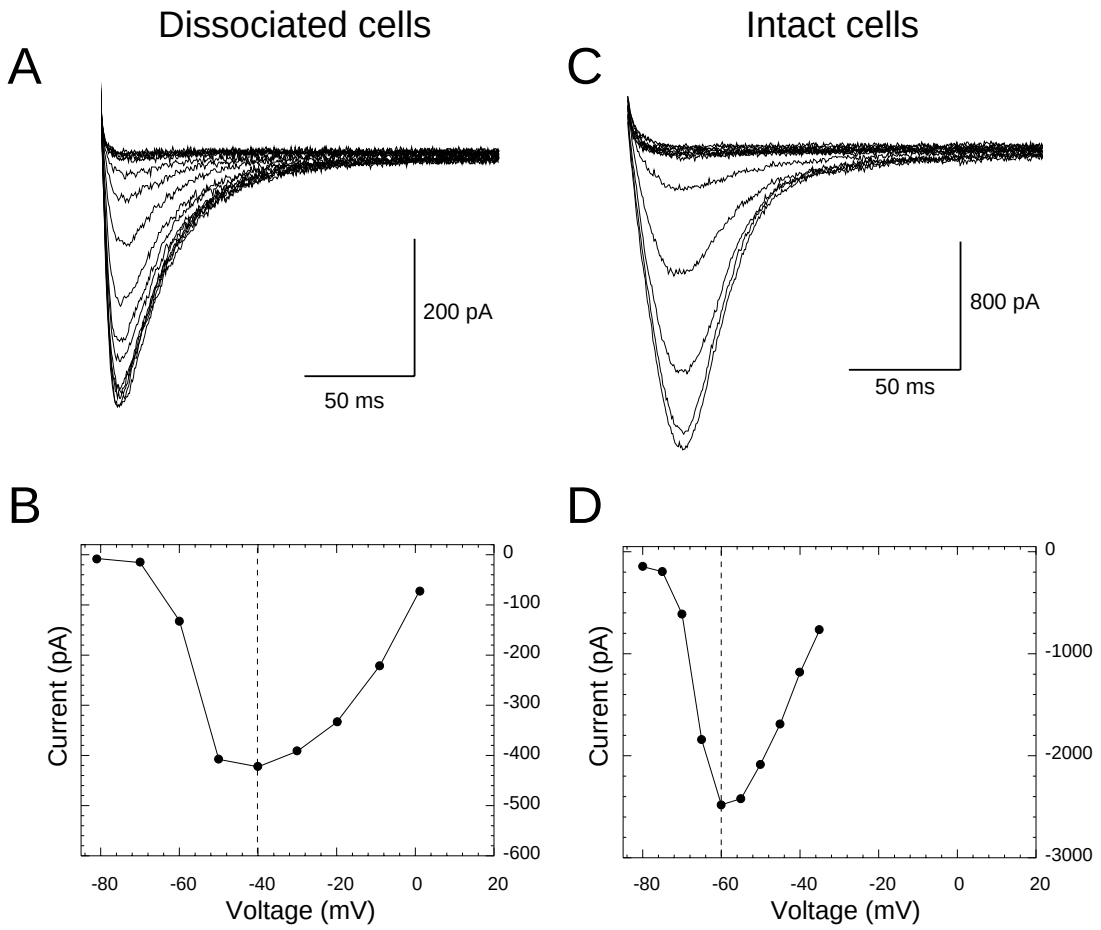

Figure 1. Voltage-clamp recordings of I_T in thalamocortical cells.
A. Inactivation protocol in a dissociated TC cell (holding voltages of V_h=-125 to -60 mV; command voltage V_c=-30 mV). B. I-V curve of I_T activation in the same cell (V_h=-100; V_c=-80 to +12 mV). C. Inactivation protocol in an intact TC cell (V_h=-105 to -40 mV; V_c=-65 mV). D. I-V curve of activation in the same cell (V_h=-100; V_c=-80 to -35 mV). Dotted lines in B-D indicate V_c used in A,C. All recordings correspond to 24 $^\circ C$. Methods described in detail in[2]. B and D were modified from a previous study[3].

EXPERIMENTAL OBSERVATIONS

Voltage-clamp recordings were first obtained in dissociated ventrobasal TC neurons. The dissociation procedure removes most of the dendritic tree and leaves behind a soma with several trunks of proximal dendrite[2]. In these dissociated neurons, I_T showed a bell-shaped I-V curve with peak current amplitude of about 400 pA at around -40 mV (Fig. 1A-B).

Voltage-clamp recordings of I_T were then obtained in intact TC cells in ventrobasal thalamic slices. In this case, by contrast to dissociated cells, the maximal T-current amplitude was found to be much larger, from 2 to 8.3 nA (of which one example is shown in Fig. 1C), and there was a marked shift in the I-V curve, with the peak now occurring at -70 to -60 mV (Fig. 1D).

COMPUTATIONAL MODELS

Of the group of intact TC neurons that were recorded and filled with biocytin, one was reconstructed using a tracing system and incorporated into the NEURON simulator (Fig. 2, intact-cell model). Passive responses recorded in this neuron were used to constrain the fitting of the model's passive parameters by running successive iterations of a simplex algorithm. The iterations were repeated until the model converged to this experimental recording (Fig. 2B). This procedure yielded optimized parameters that were found to be consistent with typical values for TC neurons. I_T was simulated using Goldman-Hodgkin-Katz equations[4], with activation and inactivation kinetic parameters based on voltage-clamp experiments on dissociated TC cells[2], which were described in detail in a previous paper[3].

Next, a dissociated-cell model was constructed by removing most of the dendritic tree of the intact-cell model. The soma and two proximal segments were retained so as to match the morphology and the input capacitance of dissociated TC neurons. Using this geometry and a uniform perisomatic distribution of T-channels, simulated voltage-clamp protocols established that I_T must have a permeability of 0.17 μm/s to yield an I-V curve with a maximum current amplitude around 400 pA and peak occurring around -40 mV (Fig. 2D). This T-current density was used in the proximal region of the cell ("perisomatic density") for all subsequent simulations.

In voltage-clamp simulations run on the intact-cell model, this perisomatic T-current density could not reproduce the peak I_T amplitude of intact neurons. More importantly, the perisomatic density, when extended to the whole neuron, was insufficient to produce bursts of action potentials in current-clamp simulations[3]. On the other hand, the range of peak T-current in intact neurons (2 to 8.3 nA) and the range of I-V curve shifts could be resolved by inserting T-channels in the outlying dendrites, with a permeability of 0.25 μm/s (Fig. 2E). The range of peak T-current amplitudes observed in different intact TC cells could be resolved with this model using dendritic T-current densities between 0.17 and 0.65 μm/s, which are about 1.5 to 4 times greater than the perisomatic density. Even a high but non-physiologic T-channel density, distributed strictly perisomatically, could not account for both the peak amplitude and the I-V curve shift simultaneously.

Next, the Bush-Sejnowski theme of axial resistance conservation[5] was used in developing several algorithms for reduction of the dendritic arbors of thalamocortical neurons. These algorithms were applied to the geometry of the intact-cell model in order to obtain length, diameter and axial resistance constraints for several low-order compartmental models (Fig. 3A).

The remaining model parameters were then optimized against experimental voltage-clamp recordings. Optimization against input resistance data and against recordings of passive responses to voltage-clamp protocols yielded virtually identical ratios of leak conductance density for the intact-cell and reduced models. Further, these ratios differed by less than one percent from the corresponding dendritic surface area ratios.

To determine the distribution of T-channels appropriate for the reduced models, permeability values from the intact-cell model were adopted after being scaled with the leak conductance ratio. With this somatodendritic distribution, the reduced models performed in accord with the intact-cell model (Fig. 3B-C). On the other hand, a strictly perisomatic distribution of T-current (1.05 μm/s) was not able to reproduce both the peak current and the I-V curve shift at the same time (Fig. 3D-E).

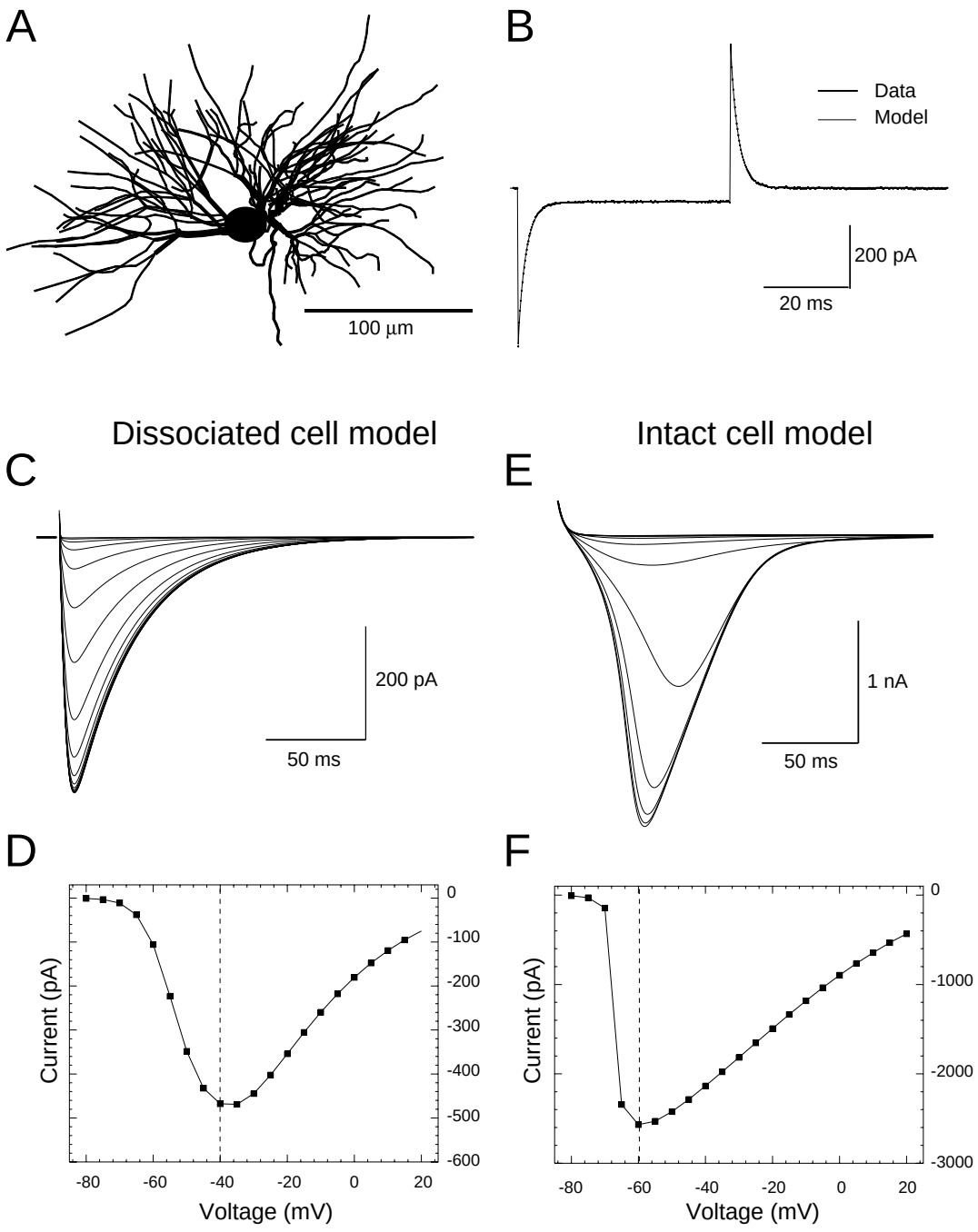

Figure 2. Multicompartmental modeling of the T-current in thalamocortical cells.
A. Reconstructed TC cell from rat ventrobasal nucleus. The cell was stained with biocytin during recording in a slice preparation[2], reconstructed using a tracing system (EUTECTIC) and incorporated into the NEURON simulator. Models with 200 compartments were used. B. Simplex fitting of the multicompartment model to passive responses in the same cell. Dots: 5 mV voltage-clamp steps during 50 ms from a holding potential of -80 mV (average of 20 traces). Continuous line: best simulation obtained after 260 iterations of the simplex procedure. C,D: Simulated voltage-clamp protocol of inactivation (C) and activation I-V curve of I_T (D) in dissociated cells (same protocols as Fig. 1A-B). E,F show the same protocols and I-V curves as in Fig 1C-D, simulated using the intact TC cell model with dendritic T-current. All simulations correspond to 24 $°C$. A-C were modified from a previous study[3].

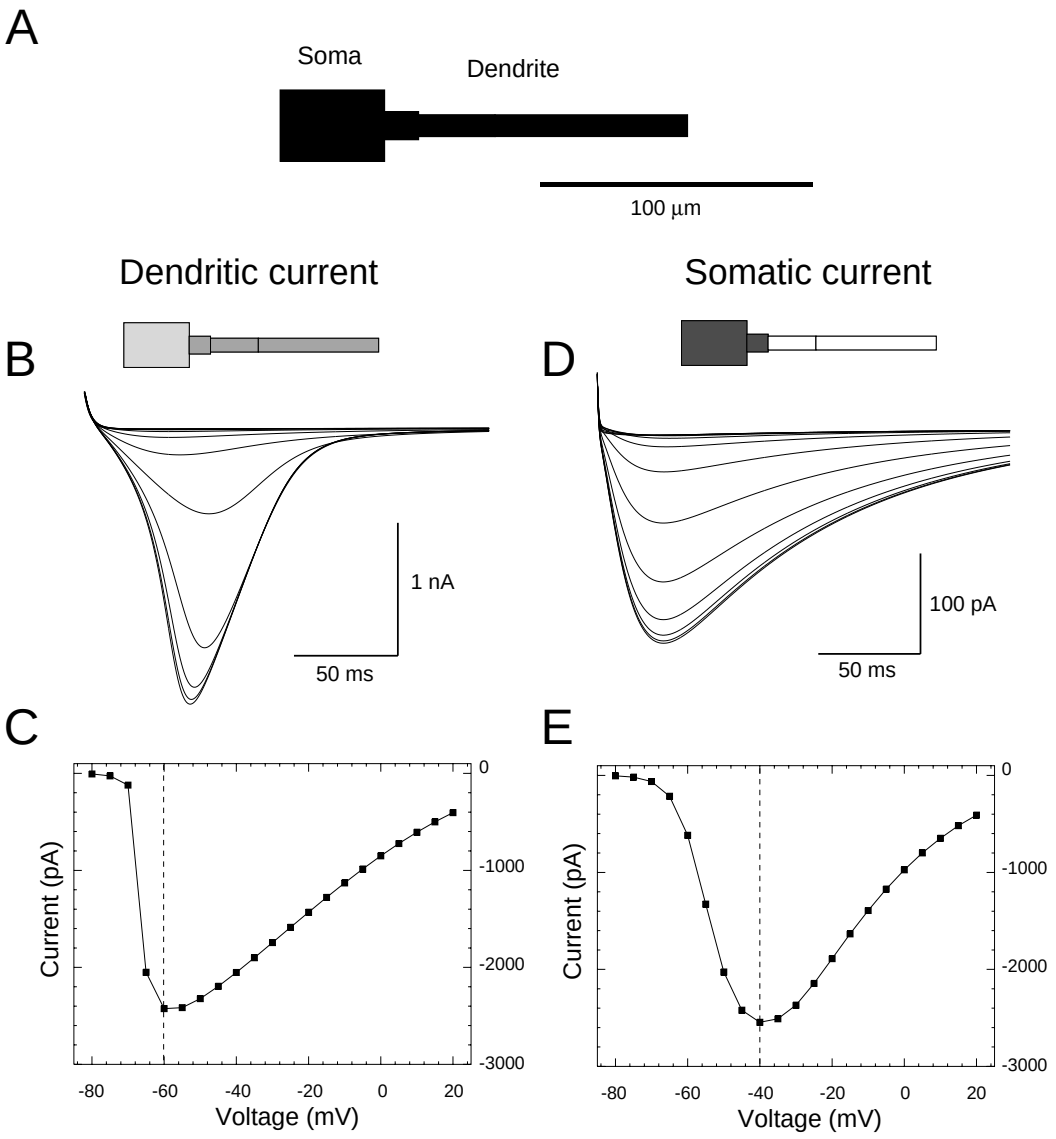

Figure 3. Low-order compartmental modeling of thalamocortical cells.
A. Simplified dendritic morphology obtained from a reduction algorithm based on the conservation of axial resistance. B,C: simulation runs of the reduced model with dendritic T-current, using the same voltage-clamp protocols as in Fig. 1C,D. D,E: same protocols run with T-current limited exclusively to the perisomatic region.

CONCLUDING REMARKS

In conclusion, morphorealistic modeling and precise matching of model parameters to voltage-clamp recordings provides strong evidence that the major portion of the T-current is localized in the dendrites of TC cells, as is similar to thalamic reticular (RE) cells[6]. Our evidence is also consistent with recent optical imaging data gathered from TC cell's dendrites 50 μm from the soma, showing significant T-current in these dendritic regions[7]. Investigations using the reduced models in TC-RE and thalamocortical networks should yield insight into the network-level role played by these extra-perisomatic portions of I_T in the induction and perpetuation of sleep oscillations and epilepsy[8].

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