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Foundational dendritic processing that is independent of the cell type-specific structure in model primary neurons

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Abstract

It has long been known that primary neurons in the brain and spinal cord exhibit very distinctive dendritic structures. However, it remains unclear whether dendritic processing for signal propagation and channel activation over dendrites is a function of the cell type-specific dendritic structure. By applying an extended analysis of signal attenuation for the physiological distributions of synaptic inputs and active channels on dendritic branches, we first demonstrate that regardless of their specific structure, all anatomically reconstructed models of primary neurons display a similar pattern of directional signal attenuation and locational channel activation over their dendrites. Then, using a novel modeling approach that allows direct comparison of the anatomically reconstructed primary neurons with their reduced models that exclusively retain anatomical dendritic signaling without being associated with structural specificity, we show that the reduced model can accurately predict dendritic excitability of the anatomical model in both passive and active mode. These results indicate that the directional signaling, locational excitability and their relationship are foundational features of dendritic processing that are independent of the cell type-specific structure across primary neurons.

Keywords

primary neurons; dendritic structure; signal propagation; dendritic excitability; reduced modelling

Introduction

Almost 100 years ago, Ramón y Cajal clearly showed that primary neurons in the mammalian central nervous system possessed morphologically distinct dendritic structures [22]. Dendrites were further demonstrated to contain not only thousands of synaptic contacts

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but also a variety of voltage-gated ion channels [27]. Thus, understanding how effectively the synaptic or intrinsic signals are evoked and propagate in dendrites is a fundamental step in the understanding of neuronal function. The spatiotemporal interaction of electrical signals produced at the dendrites and soma through the branching dendritic network shapes the output firing patterns of primary neurons [10, 24]. Most efforts have focused on investigating the causal relationship between the dendritic structure and the firing output generated near the cell body [19, 29]. However, little is known about how the diversity of the dendritic structure is related to dendritic processing for signal propagation and channel activation over the dendritic arbors.

Studies on dendritic anatomy have demonstrated that a complex dendritic processing exists not only for signal attenuation between the soma and dendrites but also for channel activation over the dendritic trees. Both experimental evidence and computational analyses have emphasized that the attenuation of electrical signals in dendrites is directional with respect to the propagation direction (i.e., direction dependent signal propagation) [9, 23, 31]. That is, the signal attenuation is much more severe in the somatopetal direction than it is in the somatofugal direction at all path lengths along the dendrites. In addition, the activation of voltage gated ion channels was shown to be locational with respect to the distribution over the dendritic branches (i.e., location dependent channel activation) [17, 20, 25]. The classical view of channel activation in dendrites is that as the channel is located further from the soma, more inputs are required at the soma to activate the channel due to the signal attenuation along the dendrites. However, most previous analyses of dendritic signaling and excitability were performed for the limited conditions between the soma and a single point in the dendrites (i.e., point-to-point condition) within the same type of primary neurons. Furthermore, very few studies have investigated how dendritic signaling and excitability are associated with each other.

Here, we determine whether the directional signaling and locational excitability of the dendrites as well as their relationship are a function of the cell type-specific structure among different types of primary neurons in the brain and spinal cord. Four types of primary neurons with the most distinctive morphologies were selected from the neocortex, hippocampus, cerebellum and spinal cord [4, 5, 26, 30]. An anatomically reconstructed and its reduced model were built for each type of primary neuron and analyzed in more natural conditions between the soma and all points in the dendrites (i.e., point-to-all condition) reflecting the distribution of synaptic inputs or active channels on many dendritic branches under physiological conditions. Our analysis demonstrates that directional signal propagation, locational channel activation and their relationship in the dendrites are not dependent on the neuronal type-specific structure but the generic features of the primary neuron dendrites in the central nervous system.

Materials and Methods

Preparation of neuronal anatomy and assignment of passive membrane properties

The data for the representative morphology of a rat neocortical L5 pyramidal cell (p21 in Dendritica, [26]), a rat hippocampal CA3 pyramidal cell (2189201 in Claiborne's lab, [4]), a rat cerebellum Purkinje cell (p19 in Dendritica, [30]), and a cat spinal α -motoneuron

(Vemoto6 in Burke's lab, [5]) were downloaded from <http://NeuroMorpho.Org> [1] and translated into the NEURON simulation environment v 6.1.1 using the Import3D tool [12]. To isolate the effect of the dendritic structure, the same values of cable parameters that were experimentally identified from the spinal motoneuron were assigned to all anatomically reconstructed primary neurons ($R_{m, \text{soma}}=225 \Omega \cdot \text{cm}^2$, $R_{m, \text{dendrite}}=1100 \Omega \cdot \text{cm}^2$, $C_m=1 \mu\text{F}/\text{cm}^2$, and $R_a=70 \Omega \cdot \text{cm}$, [8]). The selection of cable parameter values from the spinal motoneuron was made such that the models for primary neurons in the brain maintained the lowest input resistance (R_N) at their somata. R_N was $32 \text{ M}\Omega$ for the neocortical pyramidal neuron (NN), $11.7 \text{ M}\Omega$ for the hippocampal pyramidal neuron (HN), $14.5 \text{ M}\Omega$ for the cerebellum Purkinje neuron (CN), and $1.29 \text{ M}\Omega$ for the spinal motoneuron (SN). The membrane time constant (τ_m) was 7.54 ms for the NN, 8 ms for the HN, 5.83 ms for the CN, and 7.2 ms for the SN.

Generation of voltage attenuation data

For the analysis of dendritic signal propagation in the anatomically reconstructed primary neurons, a voltage attenuation (VA) factor was defined as the ratio of the voltage at the measurement site to the voltage at the stimulation site [21, 31] and calculated using the Impedance class tools built in the NEURON software. The VA_{SD} data from the soma to the dendrites were calculated as a ratio of the membrane potential at individual points on the dendrites to the membrane potential at the soma in response to a direct current (DC) input to the soma. To calculate the VA_{DS} data from the dendrites to the soma under the point-to-all condition, an electrode was placed at all individual points over the dendrites that were separated from the soma by the similar distance. The intensity of DC input via the electrode was adjusted at each dendritic point so that the DC input was normalized to the cross-sectional area of the dendritic segment at the site of stimulation. This adjustment of input intensity was made to reflect the proportional production of synaptic or intrinsic current to the surface area for the dendritic site of generation. During the simultaneous injection of the normalized DC inputs over the dendrites, the VA_{DS} factor was calculated for each dendritic point by dividing the voltage response at the soma by the voltage response at the dendritic point of stimulation. In addition, the VA_{SD}^{AC} data were calculated in response to a 250 Hz alternating current (AC) input to the soma for the purpose of constructing the reduced model of anatomically reconstructed primary neuron (see Fig. 1 in [14]). The fitting equations were identified for individual VA data and used to calculate the values for the cable parameters of the reduced models as a function of the path length from the soma (see Fig. 1 and Fig. 1 in [14] for details of the fitting equations).

Reduced modelling of primary neurons without structural specificity

The relationship between directional signal propagation and locational channel activation and its dependency on the type-specific structure in primary neurons were explicitly evaluated using a recently developed two-compartment modelling approach (see Fig. 2 in [16]). The new reduced modeling approach allowed for construction of reduced primary neuron models free of morphological characteristics (i.e., branching pattern and surface area) of their anatomical models by collapsing the dendritic tree-like topology of the anatomical model into a sphere-like compartment in its reduced model and by assigning the parameter p (the ratio of axo-somatic to total surface area) the same value (0.5) in all

reduced models. Another feature of the new reduced modeling approach is that all five cable parameters (two conductances ($G_{m,S}$ and $G_{m,D}$) for the soma and the dendrite, two capacitances ($C_{m,S}$ and $C_{m,D}$) for the soma and the dendrite and one coupling conductance (G_C) between the soma and the dendrite) of the reduced model are analytically determined from the five system properties (R_N , τ_m , VA_{SD} , VA_{DS} and VA_{SD}^{AC}) using the inverse equations [16]. Consequently, the reduced model could be built without structural specificity for each type of primary neuron while retaining directional signal propagation of the anatomical model between the axo-somatic and dendritic compartment as a function of path length from the soma. The anatomically reconstructed primary neurons were directly compared with their reduced models regarding the input resistance and the channel activation over the dendrites.

Assignment of dendritic excitability

The voltage-gated L-type Ca channel was placed at all points of the dendrites over the narrow band of the path length with the standard deviation of $4\ \mu\text{m}$ in the anatomical model (see Fig. 2A in [16]). The current from the active dendritic channel was calculated using the same Hodgkin-Huxley style equation and parameter values used in the previous study [16]. The maximum conductance (G_{CaL}) of the L-type Ca channel in the anatomical models varied as a function of path length such that the peak of the active current (I_{PIC}) reaching the soma is held constant in the individual primary neuron models (see Fig. 3 for details). The peak of I_{PIC} was appropriately set for the NN, HN, CN and SN such that the activation timing of the active dendritic current is similar at the distal region of the dendrites in all primary neuron models. The reduced models used for the analysis of passive dendritic excitability (i.e., input resistance) were equipped with the same type-specificity and active channel kinetics as the anatomical model. The G_{CaL} in the reduced case was determined to match the peak of I_{PIC} in the anatomical case while applying the same triangular voltage clamp at the soma (see Fig. 3 for the values of G_{CaL}).

Simulations

The analysis of the anatomically reconstructed primary neurons was performed with a fixed time step (0.025 ms) using the CNEXP integration method in the NEURON software environment (version 6.1.1). The reduced primary neuron models were built and simulated with a fixed time step (0.05 ms) using the Gear integration method in the XPPAUT software [7].

Results

All anatomical models with the same cable properties showed a similar pattern of the voltage attenuations over their dendritic trees (Fig. 1). The voltage attenuation was almost equal for both the somatopetal and somatofugal directions over dendritic regions proximal to the soma. The direction-independent voltage attenuation over these dendritic regions was attributed to the increase in the VA_{DS} , which reflected the effect of the summation of multiple inputs originating from separate dendritic branches on signal transduction to the soma. This summation effect of the dendrites on the VA_{DS} was prominent at all path lengths compared with the effect observed under the point-to-point condition with DC input to only

one point in the dendrites (see the dotted purple lines in Fig. 1). Then, the asymmetry in signal propagation between the soma and dendrites developed and persisted to the end of the path length. The voltage attenuated more for the dendrites-to-soma direction than for the opposite direction. Taken together, these results indicate that the signal propagation in the dendrites is significantly different between the point-to-point and point-to-all cases and that the directional signal propagation in the point-to-all condition is not neuronal type-specific, but rather a generic property that is caused by the dendritic branching architecture.

The excitability of dendrites was suggested to be related to the signal transduction property between the soma and dendrites [15, 21]. The passive excitability of dendrites was first compared between the full and reduced models by calculating the input resistance at all single points along the dendritic branches, against the total current injected to the dendrites under the same protocol for V_{ADs} . All fully reconstructed primary neuron models exhibited a similar locational excitability: a flat profile of input resistance in the dendritic area proximal to the soma and then an exponential increase with increasing path length. The reduced models with physiological values for the VA factors without structural specificity faithfully predicted the average value of the input resistance at all path lengths in each type of anatomical model (Fig. 2). The discrepancy in the input resistance at the distal dendritic area between the anatomical and reduced model is attributed to the error of fitting curves for voltage attenuation data at the distal dendritic area in Fig. 1. This result indicates that directional signal propagation is directly associated with passive dendritic excitability, regardless of the type-specific structure.

For comparison of the active dendritic excitability, the voltage-gated L-type calcium channels generating persistent inward currents in the dendrites of all primary neurons in both the brain and the spinal cord [11, 28] were added to the dendrites as a function of the path length from the soma in the anatomical and reduced models (i.e., proximal, middle and distal dendritic regions). The activation and deactivation dynamics of the active dendritic currents were characterized at both the soma and the dendrites during a slowly ascending and descending voltage (Fig. 3) and a current clamp (Fig. 4) at the soma [3, 11]. All of the anatomical primary neuron models exhibited a similar landscape of locational excitability over their dendrites. The active channels in the distal dendritic area were activated faster than those channels in the proximal dendritic region during the ascending phase of triangular voltage or current stimulation. In contrast, the deactivation of active currents in the distal region occurred more slowly than for those in the proximal dendritic region during the descending phase of triangular voltage or current stimulation. The modest variation in the active current dynamics between different types of primary neurons can be attributed to variation in the input resistance of the dendrites. These results indicate that the locational dendritic excitability is not dependent on the type-specific structure. The reduced models with physiological VA factors and without structural specificity could accurately predict the activation and deactivation dynamics of the active channels along the dendrites in all anatomical models. The accurate prediction of the locational dendritic excitability by the reduced model also indicate that directional signal propagation is associated with the active dendritic excitability, regardless of the type-specific structure in the primary neurons.

Discussion

Our analysis of primary neuron dendrites suggests that cell type-specific structure may not play a key role in determining the signal attenuation, channel activation and their relationship over the dendrites in primary neurons. This finding implies that the type-specificity for dendritic signaling and excitability may be attributed primarily to variation in the dendritic cable properties (i.e., specific membrane resistivity, capacitance and axial resistivity) across primary neurons, not to the dendritic structure. On top of the foundational dendritic processing specified by cable properties, the diverse types and distributions of active channels in the dendrites may further endow individual primary neurons with type-specific dendritic signal and information processing for functional specialization [18].

A majority of experimental and computational studies have investigated the dendrite-to-soma signal propagation (i.e., V_{ADs}) and dendritic excitability under the point-to-point condition [13, 25]. The difference in the V_{ADs} between the point-to-point and point-to-all condition was noticeable at all path lengths for all types of primary neurons (Fig. 1). This finding suggests that the electrical structure of the dendrites must be evaluated for not only the signal types (i.e., DC or AC) but also the distribution of synaptic inputs or active channels in the dendritic trees. Under the point-to-all condition, the input resistance of the dendrites did not change noticeably over the dendritic regions proximal to the soma followed by the exponential increase only over the distal dendritic regions (Fig. 2). This result confirms that prediction of equal input resistances along the dendrites by the ideal cable model of the dendrites is valid only for the proximal dendritic regions in the fully reconstructed primary neurons and may provide a guideline for building biologically accurate reduced models of the dendrites. Moreover, the direct relationship between signal propagation and input resistance in the dendrites under the point-to-point condition [15] was also maintained under the point-to-all condition for all types of primary neurons.

The activation properties of active channels in the dendrites were interpreted based on the space-clamp phenomenon: by exponentially decreasing the voltage attenuation along the dendrites during a current or voltage stimulation to the soma [2, 6]. In contrast to the estimation of locational dendritic excitability by this concept, our simulation results showed that a higher voltage or current stimulation to the soma was needed to activate the closer active channels along the dendrites in the anatomically reconstructed primary neurons (Figs. 3 and 4). Our data emphasize the importance of considering the voltage attenuation properties for both directions in appreciating the activation properties of the voltage-gated ion channels in the primary neuron dendrites.

The present study has several limitations worth being pointed out. Firstly, only one representative dendritic structure was investigated for each type of primary neurons assuming the similarity in morphological characteristic of the dendrites within the same type of primary neurons. Secondly, the values of cable parameters identified from the spinal motoneuron were applied to all of the models for primary neurons in the brain ensuring the lowest input resistance at their somata. Thirdly, for the purpose of comparison in this study only one type of active channel (i.e., L-type Ca channel) that has been known to be expressed in almost all types of primary neurons was considered for the analysis of dendritic

excitability. Lastly, our analysis of dendritic signalling and excitability was performed under steady state conditions. Fundamental limitations associated with the reduced modeling approach used in the present study have been fully addressed in the previous study [16].

In conclusion, we identified the directional signaling, locational excitability and their tight relationship in the dendrites as the foundational characteristics of dendritic processing that primary neurons in the central nervous system may share independently of their specific structures. The foundational dendritic processing identified in this study may provide fundamental insights into the generic features of dendritic processing for signal propagation and channel activation in primary neurons.

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Highlights

- Primary neurons in CNS exhibit very distinctive structures of the dendrites.
- Dependency of dendritic signalling and excitability and their relationship on cell specific structure is investigated among different types of primary neurons.
- All anatomically reconstructed primary neurons show similar directional signalling, locational excitability and their relationship over the dendrites.
- This study identifies foundational features of dendritic processing shared across primary neurons.

Figure 1. Signal propagation in the dendrites in model primary neurons

Morphologies of spinal motoneuron (SN in **A**), hippocampal pyramidal neuron (HN in **B**), neocortical pyramidal neuron (NN in **C**) and cerebellar Purkinje neuron (CN in **D**) in the left column and voltage attenuation (VA) data calculated at all path lengths (D_{path}) from the soma in the right column. The VA_{DS} data were fit to an inverse sigmoid curve ($1/[1-\exp(-\alpha_1/\alpha_2)+\exp((D_{\text{path}}-\alpha_1)/\alpha_2)]$; solid purple line) rather than the single exponential curve ($\exp(-D_{\text{path}}/\lambda)$; dashed purple line) previously fit to VA_{DS} when this parameter was computed under the point-to-point condition. The VA_{SD} data were fit by the single exponential curve (solid black line) with the exception of the NN model, which was fit with an inverse sigmoid curve (solid black line). For VA_{SD} , $\lambda=2145.8$ for SN, 1730.4 for HN and 1060.5 for CN. For VA_{DS} , α_1 and $\alpha_2=861.9$ and 268.26, respectively, for SN, 496 and 143.35, respectively, for HN and 246.18 and 73.71, respectively, for CN. For the VA data in

the NN, α_1 and $\alpha_2=811.76$ and 523.18 , respectively, for VA_{SD} and 452.12 and 344.78 , respectively, for VA_{DS} . For the purple dotted lines in (A)–(D), $\lambda=193.7$, 176.2 , 223.1 and 153.1 , respectively.

Figure 2. Comparison of passive dendritic excitability

Each grey point indicates the input resistance at a single point on the anatomically reconstructed dendrites against the total current injected at all points at an equal path length (D_{path}) from the soma. The solid black lines display the input resistance predicted at the dendritic compartment by the reduced model. The values for the cable parameters in the reduced models were analytically determined for the VA factors calculated with the fitting equations (Fig. 1) as a function of D_{path} .

Figure 3. Comparison of active dendritic excitability during voltage clamping at the soma
 The persistent inward current (I_{PIC}) generated from voltage gated L-type Ca channels in the dendrite was characterized in the anatomical and the reduced model by subtracting the current (I_{leak}) generated by voltage clamp at the soma for the passive dendrites from that (I_{total}) for the active dendrites to follow the slowly ascending and descending voltage command at the soma (V_s). Insets show the distribution of the active channels (red dots) at proximal, middle and distal distance (D_{path}) in individual primary neuron models. For each type of primary neurons, the maximum conductance (G_{CaL}) of the active dendritic channel was adjusted to hold the peak of I_{PIC} constant at the soma. The value of G_{CaL} [mS/cm^2] was {0.77, 0.89, 3.71, 0.64, 0.73, 2.94, 0.207, 1.48, 3.07, 1.86, 0.98, 3.2} for the anatomical models and {0.074, 0.085, 0.121, 0.092, 0.102, 0.14, 0.034, 0.042, 0.098, 0.216, 0.222, 0.236} for the reduced models in order from (A) to (L).

Figure 4. Comparison of active dendritic excitability during current clamping at the soma
 The same anatomical and reduced models used for Fig. 3 were simulated for the time course of the membrane potential (V_m) at the soma (solid lines) and the dendrites (dotted lines) with voltage-gated L-type Ca channels while applying slowly ascending and descending current stimulation (I_{soma}) to the soma. Insets show the distribution of the active channels (red dots) in individual primary neuron models at proximal, middle and distal dendritic regions as in Fig. 3. Note that the peak amplitude of current stimulation to the soma was adjusted for each primary neuron type to normalize the differences in the input resistance at the soma between the primary neuron types.