Energy efficient modulation of dendritic processing functions

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Abstract

The voltage dependent ionic conductances and the passive properties of the neural membrane determine how external inputs are processed by the dendritic tree, and define the computational characteristics of neurons. However, what controls these characteristics and how they are implemented at the single neuron level, in such a way that an external input results in the coding of the appropriate output, is essentially unknown. We show here that a slow inactivation of the Na+ channel, involved in the attenuation and/or failure of APs in the dendrites, acts as an active and energy efficient filter of synaptic input, and results in an activity-dependent control of the properties of individual neurons. Thus, the activation or expression of this mechanisms could be an efficient way to selectively modulate the input/output processing properties of dendrites, and could be needed to limit or suppress the onset of a number of pathological brain disorders. © 1998 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Simultaneous somatic and dendritic recordings in hippocampal CA1 pyramidal neurons from in vitro preparations (Spruston et al., 1995), have shown that current injections into the soma or dendrites elicited a train of action potentials (AP) in the axon at first, from where they actively backpropagate into the soma and the dendritic tree. The amplitude of the backpropagated APs decreased during the train and along the major apical dendritic tree (Spruston et al., 1995; Callaway and Ross, 1995), and often a sudden decrease (a failure) was observed after a major branch point. The amount and duration of these effects were dependent on the level and duration of the current injection. The backpropagation of APs could greatly affect virtually all neuronal functions, from synaptic plasticity to the integrative and computational properties of a given neuron (Magee and Johnston, 1997; Markram et al., 1997), and the experimentally observed modifications in their amplitude cannot be explained only by the passive properties of the membrane. The reason why a train of APs should be effectively
and dynamically clipped in the dendritic tree by an active mechanism is unknown. It has been shown theoretically (Migliore, 1996) and experimentally, in the hippocampal CA1 pyramidal neurons in vitro (Colbert et al., 1997; Jung et al., 1997), that a slow sodium channel inactivation is one of the possible mechanisms that could be involved in these effects. If they will be confirmed in vivo too, the elucidation of their functional consequences on the processing properties of a neuron could be an important step to understand how a synaptic input is processed and the result relayed to the rest of the network. In this work we were interested to study how they could affect the Input/Output (I/O) characteristics of a neuron.

2. Methods

The program NEURON (Hines, 1993) was used for all simulations with a time step of 20 µs. A reduced compartmental model was used to simulate the most relevant firing properties of a CA1 hippocampal neuron, and we used only those conductances strictly needed to model a regularly spiking cell. The channel kinetics are reported in the Appendix A and the neuron model files are available from one of the authors (MM). The morphology and the passive properties of the model, as well as the channel kinetics and distribution, were the same as those used in a previous work (Migliore, 1996). Briefly, to model the attenuation and failures as observed in the experiments, an additional gating variable to implement a slow Na⁺ inactivation was included in the expression for the Na⁺ conductance in the apical dendrites, and one of the parameters, bi (see the Appendix A) was used to modulate the maximum amount of slow inactivation (bi = 1 no inactivation, bi = 0 complete inactivation). To model the coincident activation of an ensemble of synapses converging in the same dendritic area, an a-function g_{syn} = g_{syn} e^{-t/\tau} was used as excitatory synaptic conductance, with a reversal potential V_{rev} = 0 mV, g_{syn} = 6 nS and T = 3 ms. The g_{syn} value was chosen in such a way that, without a slow Na⁺ inactivation, a single synaptic stimulation of a distal dendrite was sufficient to elicit an action potential at the soma. Unless otherwise noted, this value was used in all simulations. The detailed computational features of a hippocampal CA1 neuron in vivo are not known. Beyond the trivial case in which a synaptic input is low-pass filtered by the passive properties of the membrane, the most simple processing function that could be expected to be performed is the active filtering of inputs targeting different dendritic locations. The frequency content of an input signal can affect several fundamental processes in a neuron, from synaptic plasticity to the output firing characteristics. For this reason, we used a periodic synaptic stimulation, delivered for 2 s at different frequencies, on a compartment at 150 and/or at 390 µm from the soma, and the somatic spike frequency was compared with the input synaptic frequency with or without a dendritic slow Na⁺ inactivation.

3. Results

In Fig. 1 we show the membrane potential at the soma and at a distal (390 µm) compartment when a low (Fig. 1A) or high (Fig. 1B) frequency synaptic stimulation was delivered in a proximal (150 µm) dendrite (Fig. 1, arrow). The simulations showed that without a slow Na⁺ inactivation (Fig. 1A,B; left traces), a dendritic suprathreshold periodic synaptic input elicited a train of APs at the soma with a spike rate that was dependent on the input synaptic frequency. The inclusion in the model of the slow inactivation (Fig. 1A,B; right traces), resulted in a progressive reduction in the amplitude of the APs and in the consequent reduced activation of the K⁺ conductance in the dendrites, with significant effects on the firing properties at high frequency. In fact, when the slow Na⁺ inactivation was not included in the model (Fig. 1B; left traces), several synaptic pulses at 50 Hz failed to elicit an AP at the soma, because of the strong activation of the K⁺ conductance. This effect was dependent on the degree of Na⁺ inactivation (data not shown), suggesting that a synaptic input at a given frequency could be transformed in somatic APs elicited at different rates, according to the maximum degree of slow
Na\textsuperscript{+} inactivation that can be expressed on the membrane. By using several different values for the \( b_i \) parameter, we tested the effects of different upper bounds to the slow inactivation of the Na\textsuperscript{+} channel. The somatic I/O characteristics as a function of the input synaptic frequency are summarized in Fig. 2 for the limit cases of \( b_i = 0 \) (no slow inactivation, solid lines) and \( b_i = 1 \) (the channel was allowed to undergo complete inactivation, dotted lines). A systematic change in the filtering properties of the neuron was obtained over the entire frequency range tested, for both a proximal (150 \( \mu \text{m} \), Fig. 2A, open symbols, compare solid and dotted lines) or a distal (Fig. 2A, closed symbols) synaptic input.

It has been estimated that most of the energy consumption of the brain is required by the pumping mechanisms (and, in particular, by the Na\textsuperscript{+}, K\textsuperscript{+}-pump) to maintain the resting ionic concentration gradient across the membrane (Albers et al., 1989; Sokoloff, 1989) and that the firing rate could be determined by the need to use the minimum amount of energy to code the maximum amount of information (Barlow, 1969; Levy and Baxter, 1996). The energy for the work done by these pumps is provided by the hydrolysis of ATP, and depends essentially on the internal cation concentrations (Albers et al., 1989). We assumed that the number of cations crossing the membrane, during an AP, was a reasonable measure of the perturbation to the resting ionic concentrations and, thus, of the metabolic energy required by the pumps to restore the initial conditions after each AP. We calculated it directly during the simulations as \( \int_0^\tau (I_{\text{Na}} + I_{\text{K}})dt \), where \( I_{\text{Na}} \) and \( I_{\text{K}} \) are the transmembrane sodium and potassium currents. The average number of Na\textsuperscript{+} or K\textsuperscript{+} ions crossing the membrane per action potential was thus calculated as

\[
\langle \text{Na}\textsuperscript{+} + \text{K}\textsuperscript{+} \rangle_{\text{AP}} = \frac{1}{N_{\text{AP}}} \int_0^\tau (I_{\text{Na}} + I_{\text{K}})dt
\]

where \( N_{\text{AP}} \) was the number of APs elicited during a simulation. The simulations findings, shown in Fig. 2B, suggested a substantial reduction in the mean energy required to fire an AP at the soma over the entire frequency range for both a proximal (open symbols) or a distal (closed symbols) synaptic stimulation, especially at higher stimulation frequencies.

As already known (König et al., 1996) a neuron could act as coincidence detector or as temporal integrator according to its membrane properties and to the stimulation frequency. In order to test the functional consequences of a slow Na\textsuperscript{+} inactivation when two inputs at different locations were

![Fig. 1](image_url)
activated, two periodic synchronized or desynchronized subthreshold ($g_{syn} = 3$ nS) synaptic stimulations were delivered at 150 and 390 μm from the soma. In Fig. 3 we plot the I/O characteristics (Fig. 3A) and the energy requirements (Fig. 3B) when both locations were stimulated at $f_{in}$ Hz with a train of synaptic pulses delivered at the same time (synchronized, open symbols), or time shifted by $1/(2f_{in})$ s (desynchronized, closed symbols). No qualitative differences were observed with or without the slow Na$^+$ inactivation for low frequencies of stimulation. In this range the neuron behaves as a coincidence detector, as suggested by the big difference in the I/O characteristics between the synchronized or desynchronized stimulations (Fig. 3, compare the open and closed symbols in the 0–25 Hz range). On the other hand, the essential overlap of the curves for synchronized and desynchronized stimulations for higher frequencies suggests that the neuron acts as a temporal integrator in this range. In this case, a substantial change in the filtering properties was obtained when a slow Na$^+$ inactivation was included (compare the solid and dotted lines in Fig. 3A in the 25–200 Hz range). Furthermore, and in analogy with the stimulation of a single location (see Fig. 2), a ~30% reduction in the energy requirements was observed over the entire frequency range (Fig. 3B).

4. Discussion

In general, a synaptic stimulation of a given neuron is transformed in a train of somatic APs whose characteristics (such as rate and timing) are determined by the specific properties of that neuron and by the network to which it belongs.

(Bernander et al., 1991). In fact, the passive properties of the membrane act as a low pass filter of input signals, in such a way that the continuous background excitatory synaptic activity does not result in an unphysiologically high firing rate, with potentially pathological consequences. However, they act globally and statically, affecting in a time-independent fashion the propagation of any signal throughout the neuron, and cannot account for the observed behavior. On the other hand, it is experimentally known that a fast Na⁺ conductance in the dendrites can change the filtering properties of neurons (Haag and Borst, 1996). In agreement with these results, our model pointed out that a voltage-dependent process, such as a slow Na⁺ inactivation, can act at the dendrites level to dynamically modulate the activity of a cell, showing what could be the possible functional consequences of the expression of this mechanism on the membrane. Also, since several activity-dependent processes, such as protein phosphorylation, may modulate the kinetic characteristics of several ionic channels, including Na⁺ (Ismailov and Benos, 1995) and its slow inactivation (Colbert and Johnston, 1998), it could be hypothesized that the input activity of a cell can determine how future inputs will be processed by the dendrites in the most efficient way. Furthermore, all the simulations consistently suggested that the expression of a slow Na⁺ inactivation on the dendritic membrane could result in a substantial reduction in the average energy required to elicit an AP in the soma, especially at higher frequencies, and this may be the most simple explanation of why this, and not another, mechanism could be used to modulate the I/O processing properties of a neuron.

It should be stressed that the results that we have obtained, for the modulation of the filtering properties of a neuron, depend only on a specific

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**Fig. 3.** Input/Output characteristics of the model neuron under a synchronized (open symbols) or desynchronized (closed symbols) periodic subthreshold synaptic stimulation with (dashed lines) or without (solid lines) a slow Na⁺ inactivation. (A) The ratio between the output spike frequency ($f_{out}$) and the frequency of synaptic stimulation ($f_{in}$) is plotted as a function of $f_{in}$. (B) The average number of Na⁺ and K⁺ ions crossing the membrane during each action potential as a function of $f_{in}$. 
property of the Na\(^+\) conductance, for which there is ample experimental support (Colbert et al., 1997; Jung et al., 1997). None of the plethora of ionic channels, that are known to be expressed on the membrane of hippocampal neurons, has the appropriate kinetic characteristics needed to influence the main results of our model.

The backpropagation of APs into the dendrites could be a process needed to generate an associative signal leading to hebbian synaptic modifications (Magee and Johnston, 1997; Markram et al., 1997). The local modulation of the slow Na\(^+\) inactivation would allow a neuron to effectively include (eliminate) from the associative process selected branches or entire distal trees that are the targets of useful (deleterious) external inputs. In any case, the average energy required to fire an AP could be reduced as much as \(\approx 30\%\).

The model predictions, on the functional consequences of a slow Na\(^+\) inactivation, could be experimentally verified in neurons where it is not expressed or has been pharmacologically blocked. A direct experimental evidence could be obtained by testing for alteration in the filtering properties. A lack of synaptic specificity in long-term potentiation, or an increased glucose consumption could also be additional experimental tests of the model suggestions. More generally, limited flexibility in the processing of synaptic inputs, an excessive energy consumption, or the disruption of the associative signal to the appropriate synapses, all with potentially pathological consequences, could be anticipated if this mechanism is not (or cannot be) activated or expressed on the membrane at the appropriate time and location.

Appendix A

Channel kinetics: Unless otherwise noted, \(x_n = 1/(1 + \alpha_n)\) and \(\tau_v = \beta_n/(1 + \alpha_n)\), where \(v\) is a gating variable, \(v\) is in mV, \(W = 10^{-3} \text{ F/RT}\), and the currents are in \(\mu\text{A/cm}^2\).

\[
I_{\text{Na}} = 20 \cdot n \cdot l \cdot i \cdot (v - 50)
\]
\[
x_i = \exp(-4 \cdot (v + 30)W)
\]
\[
\beta_i = 0.36 \exp(-3.6 \cdot (v + 30)W)
\]
\[
\beta_{i} = 3.3 \cdot 10^3 \exp(2.4(v + 60)W)
\]
\[
I_v = -I_{\text{Na}} \cdot r
\]
\[
r_\alpha = 1/(1 + \exp(20(v + 50))W)
\]
If \(\tau_n < 0.02\) then \(\tau_n = 0.02 \text{ ms}\).
If \(\tau_i < 1\) then \(\tau_i = 1 \text{ ms}\).
If \(\tau_i < 3\) then \(\tau_i = 3 \text{ ms}\).

\[
I_{K_{\text{M}}} = 0.5 \cdot m \cdot (V + 91)
\]
\[
x_m = \exp(-7 \cdot (V + 55) \cdot W)
\]
\[
\beta_m = 1.4 \cdot 10^8 \exp(-5.6 \cdot (V + 55) \cdot W)
\]
If \(\tau_m < 10\) then \(\tau_m = 10 \text{ ms}\).
\[
I_{\text{g}} = 1 \cdot q \cdot (v + 55)
\]
\[
x_q = \exp(5 \cdot (v + 93)W)
\]
\[
\beta_q = 3.6 \cdot 10^5 \exp(0.4 \cdot 5 \cdot (v + 93)W)
\]
\[
I_{K_{\text{D}}} = 4 \cdot n^{-3} \cdot \ell \cdot (v + 91)
\]
\[
x_n = \exp(-5 (v + 40)W)
\]
\[
\beta_n = 33.3 \exp(-3.5 \cdot (v + 40)W)
\]
\[
x_i = \exp(2 \cdot (v + 60)W)
\]
\[
\beta_i = 10^3 \beta_i
\]
If \(\tau_i < 0.3\) then \(\tau_i = 0.3 \text{ ms}\).

References


