Modelling reduced excitability in aged CA1 neurons as a calcium-dependent process

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Abstract

We use a multicompartmental model of a CA1 pyramidal cell to study changes in hippocampal excitability that result from aging induced alterations in calcium-dependent membrane mechanisms. Based on experimental predictions, the model incorporates N- and L-type calcium channels which are respectively coupled to slow and fast afterhyperpolarization potassium channels. N-type channels show calcium-dependent inactivation (CDI), while L-type channels display two opposing forms of autoregulatory feedback: calcium-dependent facilitation (CDF) and calcium-dependent inactivation (CDI). Model parameters are calibrated using *in vitro* data from physiological studies. Computer simulations reproduce the experimentally observed decreased excitability of aged CA1 cells which results from increased calcium influx, subsequently larger postburst afterhyperpolarization and enhanced spike frequency adaptation. We find that aging induced alterations in CA1 excitability can be explained by a simple coupling mechanism that links L-type calcium channels with sAHP current.

Key words: calcium-dependent modulation, aging, sIAHP, L-type Ca^{2+} channels

1 Introduction

One of the most devastating consequences of normal aging is the accompanying decline in learning and memory capacity. Despite the amount of research

work in the field, the underlying molecular mechanisms associated with these deficits remain uncertain. A number of physiological studies have shown that synaptic plasticity in hippocampal CA1 neurons is impaired with aging due to an excess of calcium influx, but the exact mechanisms and associated interactions that lead to increased internal Ca^{2+} concentration remain unclear. Experimental findings suggest that the increase in internal Ca^{2+} accumulation can be explained by a substantial increase in the functional density of single L-type Ca^{2+} channels [13]. This increase can in turn be linked to an enlargement of somatic calcium action potential width and a subsequent enhancement of Ca^{2+}-dependent afterhyperpolarization and spike frequency adaptation [12].

The voltage-gated L-type calcium channel displays two opposing feedback mechanisms: calcium-dependent facilitation (CDF) and calcium-dependent inactivation (CDI). Both mechanisms are collectively termed as delayed facilitation and seem to regulate the above physiological properties. The calcium sensor mediating both processes may be the calcium binding protein calmodulin (CaM) [1], which also regulates Ca^{2+}-dependent gating of SK potassium channels [5]. Delayed facilitation exhibits a slow rising time and decay, and is induced by a short train of action potentials or a depolarizing prepulse [3]. Its time course and activation protocol, are remarkably close to that of the slow afterhyperpolarization (AHP) in hippocampal pyramidal neurons [4]. Previous studies suggest that the AHP slow dynamics result from direct coupling of SK channels with L-type calcium channels [3], [12].

According to recent experimental findings [2], [6], [15], a similar coupling scenario might hold for N-type calcium channels and the calcium-activated large conductance potassium channels (BK channels) underlying the fast AHP. BK channels inactivate rapidly, accounting for the frequency-dependent decline of the fast AHP and the subsequent spike broadening during repetitive firing [6]. On the other hand, N-type Ca^{2+} channels display calcium-dependent inactivation [15]. Since intracellular Ca^{2+} concentration is an indicator of the electrical activity of the neuron [11], a connection between the above conductances seems reasonable.

Although experimental findings suggest a direct connection between the aforementioned calcium-potassium channel types, no modelling work has been done to investigate the effect of such a coupling on the cell's electrical activity. In this work, we modify a previously developed detailed compartmental model of a CA1 pyramidal neuron [16] to include sAHP and fAHP K^+ channels which are coupled to L-type Ca^{2+} channels and stores, and N-type Ca^{2+} channels and stores, respectively. We show that this coupling can, to a large extent, explain calcium-dependent aging induced alterations in neuronal excitability.

1.1 Theoretical model

The compartmental model used in this work was run within the NEURON simulation environment using the variable time step method (CVode) [10]. The biophysical model, the morphology of which is shown in fig. 1A, is an extension of a previous model described in [16]. The model consists of 183 compartments and includes a variety of passive and active membrane mechanisms known to be present in CA1 pyramidal cells. These include a leak current (I_{leak}), two types of Hodgkin-Huxley-type sodium and potassium currents (somatic and axonic I^{sa}_{Na} and I^{sa}_{Kdr}, dendritic I^{d}_{Na} and I^{d}_{Kdr}), A-type and m-type potassium currents (I_A, I_m) a hyperpolarization-activated H-current (I_h), four types of voltage-dependent calcium currents, including an LVA T-type current (I_{CaT}), an N-type current (I_{CaN}), an R-type current (I_{CaR}) and an HVA L-type current (I_{CaL}), two types of calcium-dependent potassium currents (slow, and fast AHP current I_{sAHP} and I_{fAHP}), a persistent sodium current (I_{pNa}), a D-type K^+ current (I_D) and 4 types of synaptic current, namely, AMPA, NMDA, GABA_A and GABA_B. Densities and distributions of the mechanisms included in the model are based on published empirical data and are fully described in [17]. Channel equations for all new mechanisms are described in [7] while additional equations and channel densities are detailed in Appendix A. Main changes to earlier model properties affecting the present study are described in the following paragraphs.

We use a simple, exponentially decaying Ca^{2+} pool to measure internal calcium concentration. The benefit of this approach is that a single parameter, i.e. the decay time constant, needs to be defined for the entire model. We chose a small value for this parameter, so that the internal calcium concentration ($[Ca^{2+}]_i$) closely follows variations in I_{Ca}, with a minimal accumulation of Ca^{2+}. $[Ca^{2+}]_i$ is used to modulate calcium-dependent activation and inactivation of L- and N-type calcium channels.

To model the coupling between sAHP and L-type calcium channels, and fAHP with N-type channels respectively we use two additional pools of $[Ca^{2+}]_i$: 1) Ca^{2+} accumulation due to influx from L-type channels, $[L - Ca^{2+}]_i$, is used to modulate sAHP channels while 2) Ca^{2+} accumulation due to influx from N-type channels, $[N - Ca^{2+}]_i$, is used to modulate fAHP channels.

As a result of the L-type channel delayed facilitation property, the model exhibits a feedback loop where an increase in Ca^{2+} influx further increases L-type channel conductance. The sAHP current in turn follows the time course of the L-type calcium signal.

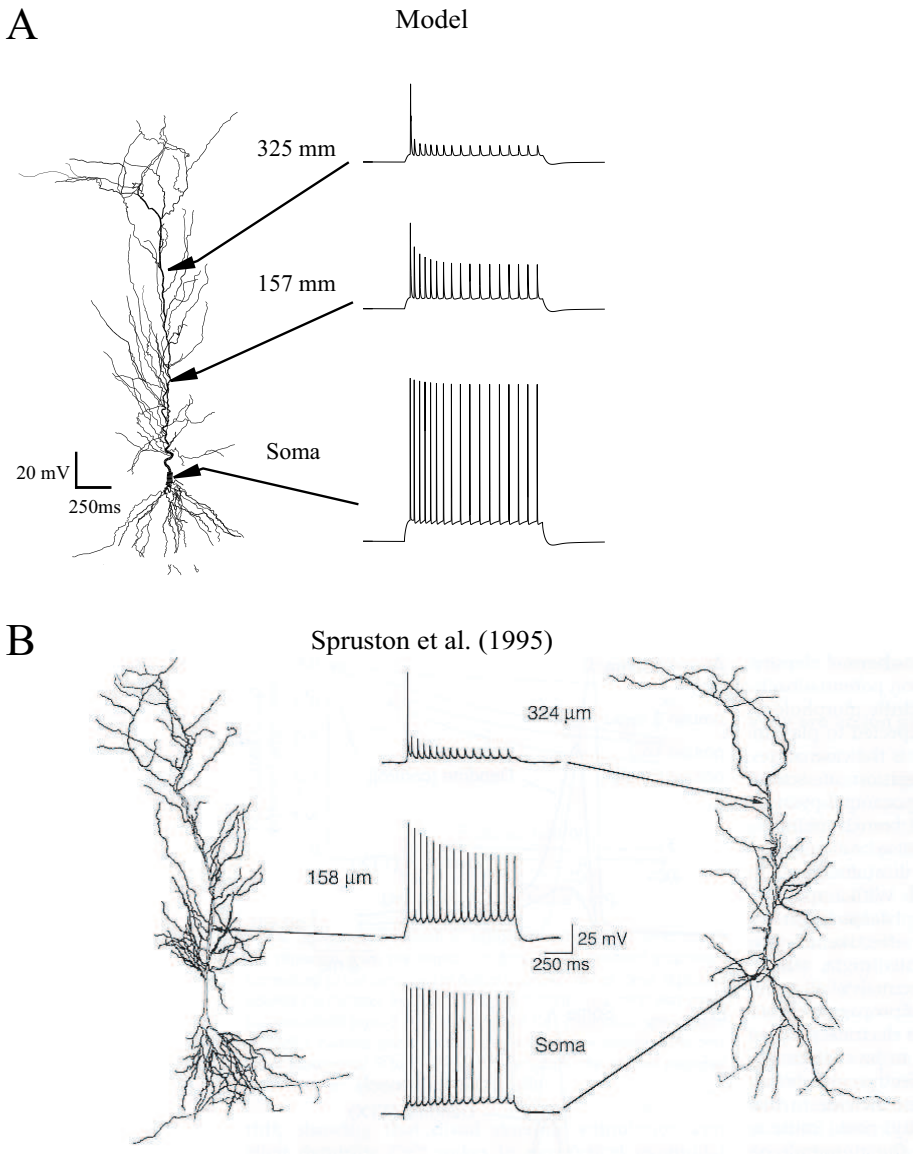

Fig. 1. A. Backpropagating action potentials evoked by somatic current injection (220 pA, 700ms) show typical pattern of distance and time-dependent attenuation of spike height; results from Spruston et al (1995) are reproduced in B for comparison.

2 Results

2.1 Model Validation

We tested our model cell using a constant depolarizing current injection at the soma while recording simultaneously at the soma and two locations in the apical trunk. We observed a pattern of distance and time-dependent attenuation of BPAPs (fig. 1A) similar to that reported by [18] (fig. 1B).

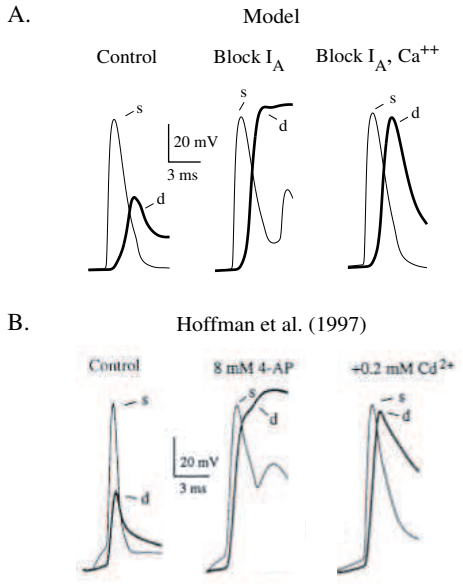

Fig. 2. Initial somatic and dendritic spikes are shown in response to somatic current injection (300 pA, 50 ms) in control conditions (left), with block of I_A (middle) and with block of Ca^{2+} currents (right). Results are comparable to those of Hoffman et al (1997).

In fig.2A we blocked I_A by 90% throughout the cell, and found that the initial BPAP which under control conditions was severely attenuated at the dendritic recording electrode, reached full height as was also observed by [19]. Given the cell is much more excitable in this condition than normal, the dendritic response in both data and model shows a failure to repolarize, as if the voltage were dominated by an unopposed dendritic Ca^{2+} current. When calcium currents were 75% blocked to mimick bath application of 200 mM Cd^{++}, the dendritic spike, though broader than in control conditions, was more fully repolarized.

2.2 Effect of aging induced increase in Ca^{2+} influx on electrical activity

In order to study the effects of aging induced increased Ca^{2+} influx on the cell's electrical activity, we contrast simulation experiments with electrophysiological recordings from young and aged CA1 pyramidal cells. Figures 3A and 3B show experimental traces from CA1 cells grouped to equate resting membrane potentials [12]. In fig. 3A, AHP measurements were made after a burst of action potentials elicited by a 100-ms depolarizing pulse, with current adjusted to a minimal level that reliably evoked a burst of four action potentials. In figure 3B spike frequency adaptation was studied, with the use of an 800-ms duration depolarizing current injection of the same current intensity and the number of action potentials was recorded.

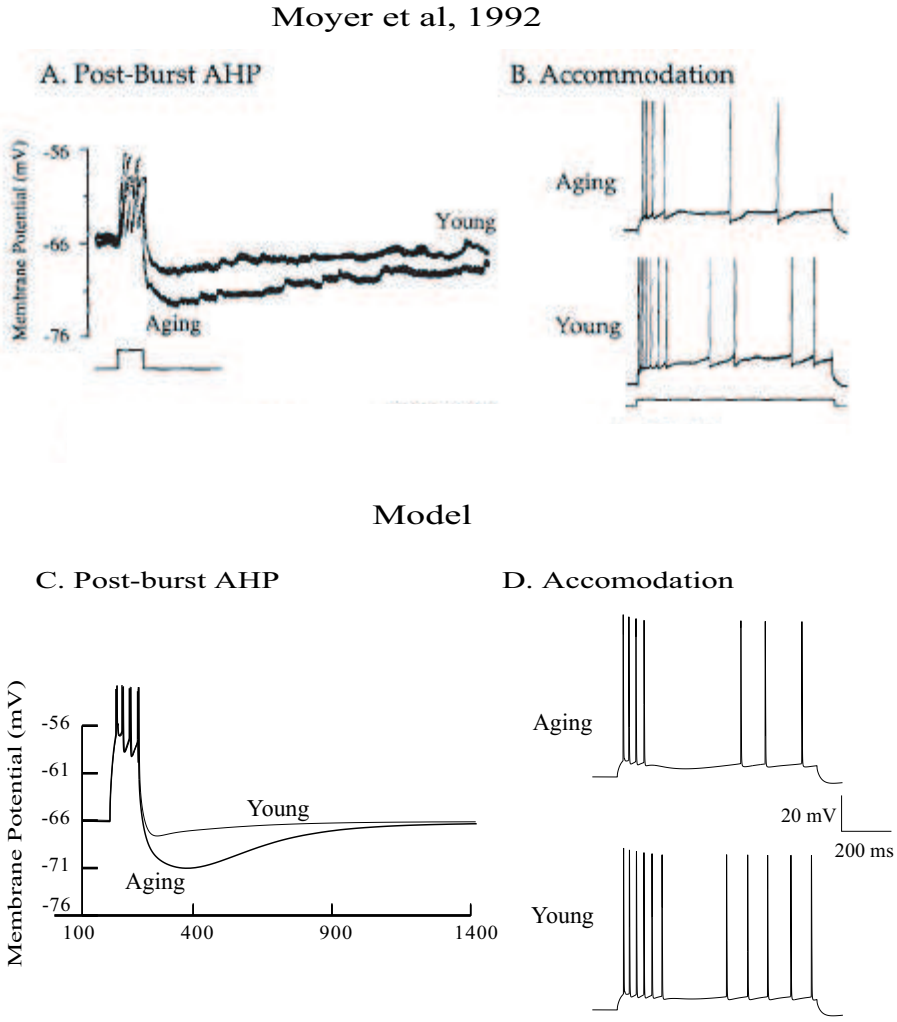

Fig. 3.

Model simulations are shown in figures 3C and 3D. A rather small increase in the "young" model's L-type calcium channel conductance (about 10%) was enough to replicate experimental traces for the "aged" cell. Both AHP traces and spike frequency adaptation traces were induced using similar to the experimental somatic current injections. Model traces appear similar between young and aged physiological and model neurons. Deviations in AHP time course and repolarization potential as well as adaptation traces between model and experimental data could be reduced with further refinement of L-type Ca^{2+} kinetics which drive slow AHP.

We also found that the above experimental observations could be reproduced by reducing the decay rate of the total $[Ca^{2+}]_i$ pool model (results not shown). Even a small increase in the decay time constant - e.g. from 2ms to 2.2 ms - had a marked effect in calcium influx from L-type Ca^{2+} channels, presumably because of their positive feedback mechanism (CDF), which could in turn induce an analogous increase in sAHP current and spike frequency adaptation.

Fine-tuning of N-type calcium channels and associated fast AHP conductances were not the purpose of this study as these mechanisms are not found to be greatly affected by aging. However, these channels are also regulated by calcium influx alterations and their role will be investigated in future work.

3 Conclusions

Using a realistic compartmental model of a CA1 pyramidal neuron, we show that a simple coupling mechanism which links L-type calcium channels to SK potassium channels could account for aging induced alterations in the cell's electrical activity. The cumulative increase of Ca^{2+}-influx observed in aged CA1 cells could result from (a) a simple -and relatively small- increase in L-type channel conductance or (b) a small decrease in the decay rate of the intracellular calcium concentration. Both mechanisms result in reduced excitability due to enlarged postburst afterhyperpolarization and enhanced spike-frequency adaptation. Findings suggest a possible explanation for the underlying molecular mechanisms that induce learning and memory deficits in old age.

A A. Model equations

Equations for L-type calcium channels are shown below. The time course of delayed facilitation of L-type Ca channels is identical to the time-course of sAHP.

$$I_L = g_L * \left(m^2 * h_i([Ca^{2+}]_i) + s_f^2\right) * (v - eca) \tag{A.1}$$

$$h_i([Ca^{2+}]_i) = \frac{k_i}{[Ca^{2+}]_i + k_i} \tag{A.2}$$

$$s_{f_{inf}} = \frac{[Ca^{2+}]_i^2}{[Ca^{2+}]_i^2 + b^2} \tag{A.3}$$

$$t_f = t_o + \frac{1}{[Ca^{2+}]_i^2 + b^2} \tag{A.4}$$

$t_o = 100ms$, $k_i = 0.025mM$, $b = 0.01mM$

Somatic L-type calcium conductance is: $g_L = 0.3mS/cm^2$

The state variable m is described in [7].

Equations for N-type channels are given by:

$$I_N = g_N * m^2 * h * h_i([Ca^{2+}]_i) * (v - eca) \tag{A.5}$$

$$h_i([Ca^{2+}]i) = \frac{k_i}{[Ca^{2+}]_i + k_i} \tag{A.6}$$

$k_i = 0.025mM$

Somatic N-type calcium conductance is: $g_N = 0.2mS/cm^2$

The state variables m and h are described in [7]

Equations for sAHP channel are given by:

$$I_{SK} = g_{SK} * m^2 * (v - ek) \tag{A.7}$$

$$m_{inf} = \frac{[L - Ca^{2+}]_i}{[L - Ca^{2+}]_i + b} \tag{A.8}$$

$$t_{inf} = t_o + \frac{1}{[L - Ca^{2+}]_i + b} \tag{A.9}$$

$t_o = 100ms$, $b = 0.005mM$

Somatic SK-type calcium conductance is: $g_{SK} = 0.025S/cm^2$

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