Axon initial segment position changes CA1 pyramidal neuron excitability

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Abstract

The axon initial segment (AIS) is the portion of the neuronal membrane responsible for action potential generation in many neural cell types. Recent work by Matthew Grubb and Juan Burrone (2010) show that the AIS can shift its location in an activity-dependent manner: long-term depolarization induced by high extracellular potassium concentrations in cultures of dissociated hippocampal neurons results in a distal shift of the AIS from the soma. In a computational model of a hippocampal CA1 pyramidal neuron, we show that moving the AIS distally from the soma results in an overall decrease of the excitability of the cell. This spatial shift effectively functions as a mechanism for homeostatic plasticity.

1 Introduction

Neurons contain information in their firing rate, an output produced by the summation and integration of a barrage of synaptic inputs. As excitatory synaptic currents increase, so does firing rate, typically producing a sigmoidal relationship between inputs and output (Figure 1). However, this means that when inputs are very strong or very weak, small changes in input strength are not reflected by changes in firing rate (whereas changes of the same magnitude in the middle region of the curve produce large changes in firing rate). In order to counteract the loss of information induced by these plateaus in the input-output (I-O) relationship, neurons are capable of modulating themselves in order to move inputs back into the sensitive region of the curve. There are two principle ways of doing this. First, neurons can globally alter the strength of their synapses, thereby changing the amount of input they see given the same level of presynaptic activity. This effectively keeps the I-O within the realm of maximum sensitivity on the same I-O curve. Alternatively, neurons can shift that curve altogether. This achieves a similar effect as reducing synaptic weights, and is accomplished by modifying the excitability (the spike-generating ability) of the neuron. Together, these two mechanisms are forms of homeostatic plasticity, referring to a neuron's global tuning of its I-O curve (as opposed to more synapse-specific forms of plasticity like long-term potentiation and depression).

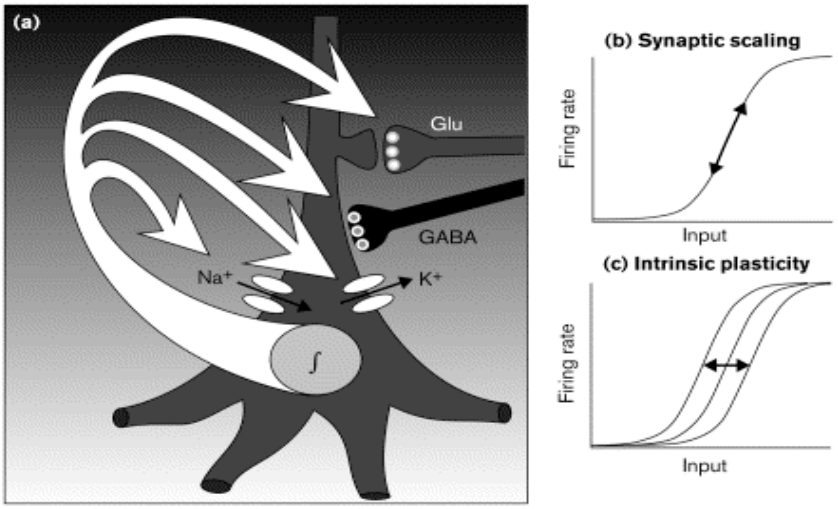

Figure 1: Homeostatic scaling (from [1]).

For our project, we used computational modeling to explore how a form of intrinsic plasticity affects neuronal excitability. Our project was inspired by the work of Grubb and Burrone (2010), who showed that intrinsic plasticity could be generated in a novel way, by the movement of the axon initial segment. In canonical pyramidal cells (the most common glutamatergic cell type in hippocampus and cortex), synaptic input travels to the soma of the neuron via arborizations of apical and basal dendrites. There, postsynaptic currents travel into the axon, first portion of which is called the axon initial segment (AIS). This region, distinguished physically by its selective aggregation of various scaffolding proteins intracellularly and a density of sodium channels in its membrane, is responsible for generating action potentials in the neurons.

As the ability of the AIS to generate a spike is dependent on how much excitatory current it receives, and given that these currents (which began in the dendrites) decrement in amplitude as they travel along the membrane, the movement of the AIS away from the soma should reduce the neuron's spiking. Grubb and Burrone [2] show in a series of experiments in dissociated hippocampal cultures that, indeed, in the presence of prolonged elevated activity such distal relocations of the AIS occur. Furthermore, they show empirically that this movement reduces the cells' excitability (Figure 2). By submitting hippocampal cell cultures to high extracellular potassium levels (15 mM) from 12 through 14 days in vitro (DIV), the authors noted a distal shift of the axon initial segment compared to neurons under control conditions observed through two-photon imaging of a fluorescently-tagged AIS scaffolding protein, ankyrin G. The length of the AIS was the same between the two groups.

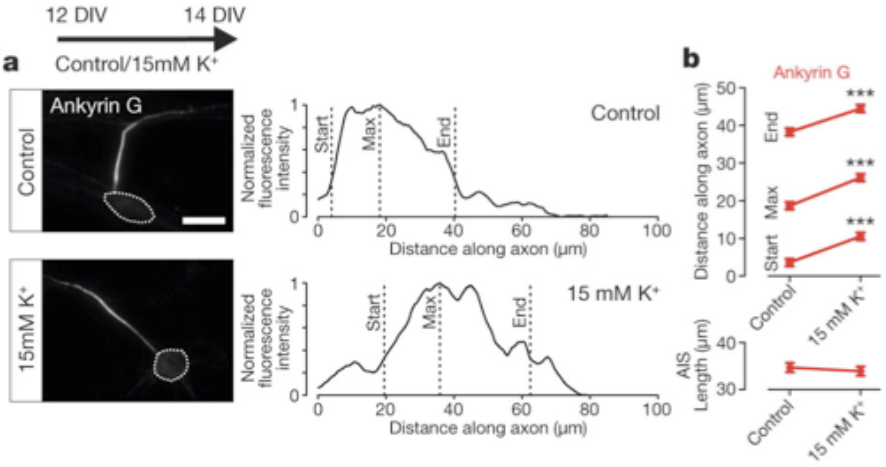

Figure 2: Activity-dependent changes in AIS position (from [2]).

2 Methods

To corroborate the work of Grubb and Burrone (2010) work, we looked at how changes in the AIS position affect neuronal excitability. We did this by running simulations of neuronal activity in a previously generated model of a hippocampal CA1 pyramidal neuron [3]. While shifting the AIS (which has passive conductances only) between one and 100 µm distally along the axon, we determined the neuron's excitability using two simple measures: the rheobase and the chronaxie. The rheobase is the minimal amount of current necessary for an infinitely long current pulse (in our case, 300 ms) to generate a single action potential in the neuron. By definition, the chronaxie is the minimal duration current delivered at twice the amplitude of the rheobase necessary for the neuron to generate a single action potential. For comparison, we also determined the constant current chronaxie at various AIS locations: the minimum time a current of 0.42 nA needs to be applied to generate an action potential in a neuron.

3 Results

3.1 Rheobase

As expected, when the AIS is basically adjacent to the soma (1 µm away from the soma), the cell requires the least amount of "infinite" (300 ms) current to generate an action potential (0.32 nA). As the AIS is artificially moved distally from the soma, it requires (in a linear fashion), more initial current to generate an action potential because of its decay (the current must travel longer down the axon). At an AIS position 100 µm from the soma, the neuron requires 0.415 nA to generate a single spike (Figure 3).

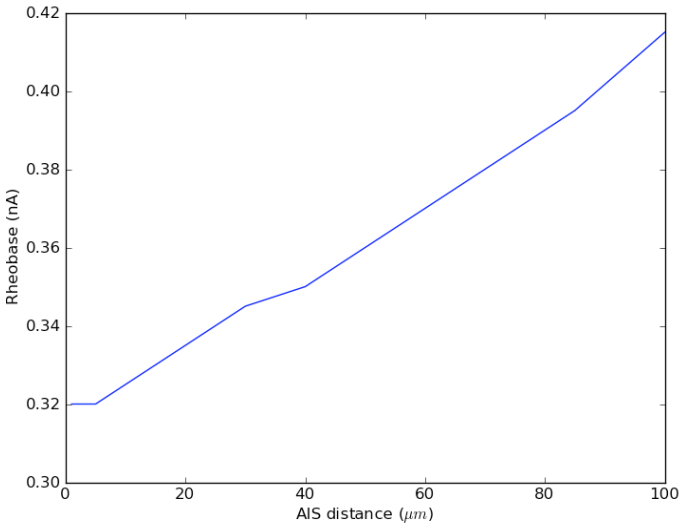

Figure 3: Rheobase

3.2 Constant current chronaxie

Next, we chose to apply the same amplitude current to our neuron while changing its AIS location. We chose 0.42 nA because it was sufficient to generate an action potential even at our furthest AIS distance of 100 µm. Again as expected, the AIS closest to the soma took the shortest duration current (25 ms) while the AIS farthest from the soma required the longest duration current (60 ms) to generate a single spike (Figure 4).

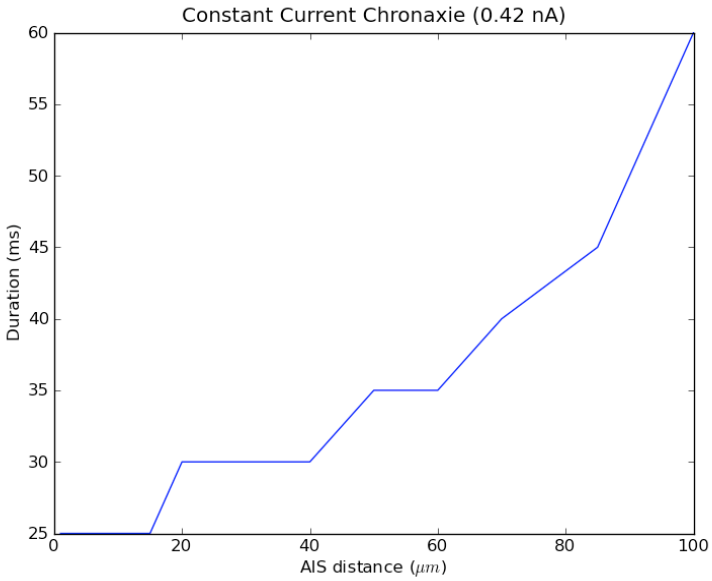

Figure 4: Constant current chronaxie (0.42 nA)

3.3 Chronaxie

In our test of the true chronaxie, we doubled the amplitude of the rheobase found at each AIS location and determined the minimum duration sufficient to generate a single spike. There is a negative linear correlation between chronaxie duration and AIS distance from the soma. The rheobase for an AIS distance of 1 µm from the soma is 0.32 nA so to determine the chronaxie we find the shortest duration pulse needed for the cell to spike from a current injection of 0.64 nA. Here, the chronaxie is 7.3 ms. The rheobase for an AIS distance of 100 µm is 0.415 nA; its chronaxie is 3.8 ms for a current injection of 0.82 nA.

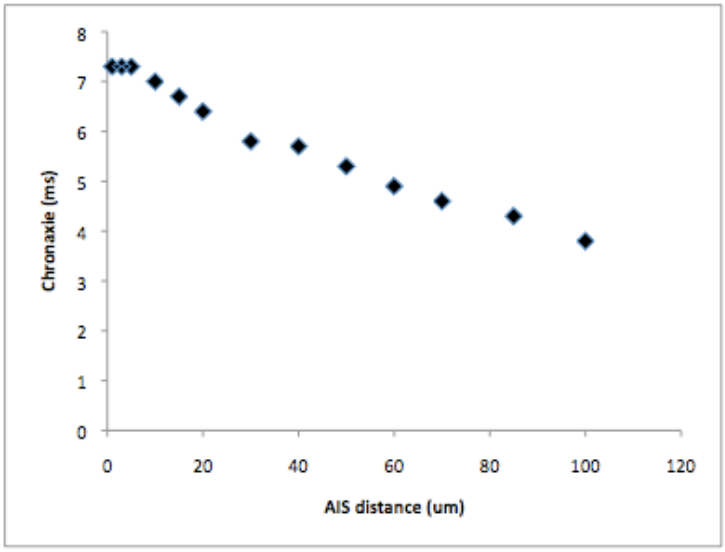

Figure 5: Chronaxie

4 Conclusions

With the use of computational modelling, our project extended the largely experimental findings of Grubb and Burrone (2010) by examining how specific parameters of neuronal excitability are affected by AIS position. We found that the rheobase of our model CA1 pyramidal cell increased linearly with increased distance of the AIS from the soma (Figure 3). The cell also required longer current pulses at a fixed current amplitude to generate a spike as the AIS moved distally (Figure 4). Finally, the chronaxie of the cell decreased linearly as AIS distance increased, although this decrease was due to the increase in current amplitude at each distance, rather than the change in distance itself (Figure 5). Altogether, our results provide additional examples of how AIS position influences neuronal excitability.

Our computational experiments lend themselves well to future experimental validation. For instance, patch clamp electrode recordings in the soma of neurons with various AIS positions can be used to both pass current and record the back-propagating spike generated at the AIS (a traditionally inaccessible region electrophysiologically). Using this setup, it should be possible to experimentally determine the rheobase and chronaxie for various AIS positions (see also Figure 4 from [2]).

Repositioning the AIS distally certainly shifts the I-O curve of the neuron to the left, making this mechanism potentially useful in regulating homeostatic plasticity. However, our results and the work of Grubb and Burrone (2010) do not fully address whether this happens in a physiological setting. In their experiments, AIS movement was induced by global excitation of the neuron in the soma and all over the dendrites by depolarization induced by increased extracellular potassium concentration or the stimulation of channelrhodopsin expressed throughout the cells membrane.

Therefore, their results may represent an extreme case not necessarily relevant to actual brain function. To more accurately simulate the type of environment where homeostatic plasticity would occur *in vivo*, it is necessary to only provide inputs at synapses in the dendrites. In our modelling environment this could be accomplished by passing synaptic currents in the dendritic arbour, rather than one large current pulse at the soma.

Finally, it is worth considering what the relative contribution of AIS movement is in the regulation of homeostatic plasticity. How does this type of change in intrinsic plasticity interact with global synaptic scaling? A computational model like the one described above, in which input currents are generated among the dendritic arbour would allow researchers to probe the possible synergy between these two forms of homeostatic plasticity.

References

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[2] Grubb, M. and Burrone, J. (2010) Activity-dependent relocation of the axon initial segment fine-tunes neuronal excitability. *Nature*. 465:1070-1076.

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