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Synaptic Amplification in Motoneurons: Computational and Mechanistic Implications

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***Abstract*—Motoneurons are known to possess the latent ability to amplify their inputs in a voltage-dependent manner. Additionally, this synaptic amplification is known to be under neuromodulatory control. This paper presents results from a computer modeling study for one possible mechanism, termed electrotonic compression, which could underlie this behavior.**

I. Introduction

MOTONEURONS have been studied for nearly five decades. As such, much of what we hold true for neurons in general arose from early motoneuron analyses [1]. However, motoneuron research as undergone a sea change in recent years as novel forms of synaptic integration have been observed [2-6]. Namely, motoneurons are now known to possess the latent ability to exhibit bistability [3] as well as to intrinsically accentuate their inputs (referred to as synaptic amplification [5]). The mechanism behind bistability has been shown to be L-type calcium-based voltage plateaus in the dendrites of these cells and to be under the control of descending neuromodulatory projections [7, 8]. The mechanism behind synaptic amplification, on the other hand, remains unresolved. What is known is that it too is under neuromodulatory control, is voltage dependent and is generally believed to have dendritic origin [5].

Synaptic amplification has the ability to massively enhance incoming synaptic commands, with amplification factors (i.e. gain) reaching 5.0 or higher [5]. Thus, under proper conditions the amplifying mechanism provides the preponderance of the current reaching the soma. Additionally, amplification is gradable with both voltage and neuromodulatory input, and both excitatory and inhibitory inputs can be amplified [9].

This paper explores one possible mechanism for synaptic amplification based on active conductances canceling dendritic resistance and capacitance, thereby reducing dendritic electrotonic length (L). We term this electrotonic compression.

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II. Methods

A. Model Generation

All model outputs were calculated using a custom-built simulation environment, and compartmental voltages were computed via numerical integration of initial values and finite differences of state variables. The model was implemented as a 10 compartment (1 somatic, 1 initial segment, 8 dendritic), parallel conductance, finite-element approximation to motoneuron morphology and function. Parameter specification was constrained by a two-pronged objective strategy: 1) estimation of differential conductance values necessary to achieve local compensation of passive, cable properties (i.e. electrotonic compression) while 2) maintaining proximity to the ion channel subtypes and kinetic properties reported in the literature for mammalian spinal motoneurons. Table I gives the location and maximal conductance values (G_{Max}) for the ion channel arrangement found to satisfy the objectives put forth above.

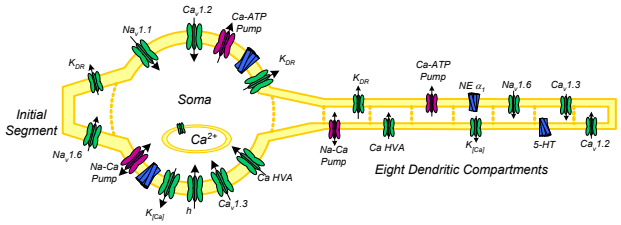

Figure 1. Illustration of the 10 compartment motoneuron model. Although a broad sampling of channel and receptor resources are pictured here, the conductance subset and spatial distribution comprising the present implementation is specified in Table I.

In order to achieve the state of reduced L, we first evaluated the ratios of K_{DR} and $Na_V1.6$ producing a "flat spot" in the local (i.e. within a single dendritic compartment) I-V relation. Since L is simply the dimensionless form of the space constant (λ), minimizing this property is accomplished by making membrane resistance approach infinity:

$$\lambda = \sqrt{\frac{aR_m}{2R_a}} \to 0 \text{ as, } R_m \to \infty \quad (1)$$

where a is the radius of a cylindrical cable, and R_m and R_a are the specific (i.e. scaled by cylindrical geometry) membrane and axial resistances, respectively. Figure 2 depicts the result of this process wherein a region of zero slope arises in the local I-V function. The slow evolution of

the voltage command (thin trace, 8 mV/s) closely approximates steady-state conditions, therefore the passive leak current and the charging of membrane capacitance are effectively compensated over the reduced slope range. Once the local I-V was established, the compartment was replicated to form the entire dendritic cylinder then coupled to the somatic compartment.

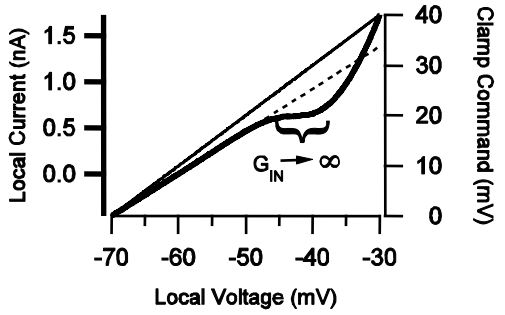

Figure 2. Single dendritic compartment (local) I-V function. The current response (bold trace) evoked by a slowly rising voltage command (thin trace) exhibits a reduced slope region in the presence of a ~ 3:5 ratio of K_{DR} to $Na_V1.6$. The stippled line denotes the input conductance (G_{IN} = 46 nS) measured near resting potential.

B. Synaptic Input

For analysis of dendritic amplification, synaptic excitation and inhibition were implemented as conductance sources with time-courses determined by user-defined waveforms and uniformly distributed across the dendrites. While excitatory input took the form of pulse train conductance changes (22 nS/compartment magnitude, 3 ms duration, at 10 Hz), inhibitory input was a simple conductance step (11 nS/compartment). The reversal potentials for these inputs were assumed to be close to that of the leak current (0 mV for excitatory) or the chloride Nernst potential (-80.5 mV for inhibitory).

TABLE I
DISTRIBUTION OF ION TRANSPORTERS

Channel Type & G_{Max} (μS)	***Model Compartments***									
	Soma & Axon		*(proximal)*		*Dendrite*					*(distal)*
	IS	*S*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*
$Ca_V1.2$			0.86							
$Ca_V1.3$			0.03							
h			0.2							
SK			1	0.15						
K_{DR}	1	4	0.905							
$Na_V1.2$		6								
$Na_V1.6$	5		1.53							
Pumps & I_{Max} (nA)										
Ca^{++}ATPase			1.5							
NCX			14.5							

Measurement of amplification was obtained by comparing the synaptic current reaching the soma (I_{SYN}) at a hyperpolarized holding potential with the peak I_{SYN} evoked by any single PSP; the resulting *amplification factor* is in terms of the latter divided by the former.

III. Results

Figure 3 illustrates the effects of electrotonic compression on the synaptic integration of excitatory and mixed, excitatory and inhibitory, inputs. Over the ~10 mV voltage range (-50 to -40 mV) in which the local I-V function exhibits a reduced slope, there is an apparent 3.5-fold amplification of dendritic EPSCs; see Figure 3A. When this synaptic input is supplemented with a steady inhibitory input (with half the magnitude of the excitatory input) the degree of amplification is reduced by about 40%. Thus the excitatory amplification is reduced to a factor of 2.2 and the inhibitory amplification factor is approximately 1.6; (Figure 3B).

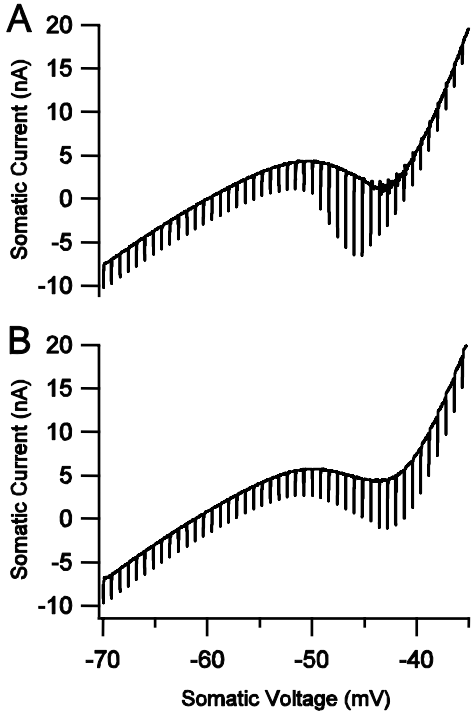

Figure 3. Amplification of excitatory and mixed synaptic inputs. *A:* Dendritic volley of EPSCs during a slow, voltage ramp undergoes local reduction of passive attenuation. This results in an apparent amplification of synaptic current (amplification factor of 3.5) as seen from the soma. *B:* The same protocol with the addition of an overlapping distribution of background inhibitory synaptic input. Although amplification of individual EPSCs still occurs it is with diminished scale (amplification factor of 2.2). Note that the negative slope region in both traces is mainly due to the subpopulation of non-inactivating $Na_V1.6$ in the initial segment.

IV. Conclusions and Discussion

Based on the model presented here, electrotonic

compression appears to be a viable means to achieve synaptic amplification. This approach is capable of amplification of both excitatory as well as inhibitory synaptic inputs even at the fastest time scales. In contrast, theories of amplification based purely on dendritic plateau potentials have been difficult to grade/control and do not amplify fast input dynamics.

It is worth noting that amplification via electrotonic compression is more accurately described as a reduction in the attenuation that a purely passive dendrite would perform. As such, it can be controlled in unique ways. Amplification can be controlled not only be increasing or decreasing the sodium and potassium channels themselves, but also by skewing the voltage distribution across the dendrite. This opens the possibility for non-linear interaction between inputs wherein, for example, proximal inhibitory inputs prevent amplification of excitatory inputs.

V. References

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