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Poster presentation

Role of inhibition in the suppression of α-motoneuron hyper-excitability following chronic spinal cord injury

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Introduction

The monosynaptic spinal stretch reflex consists of glutamatergic Ia muscle spindle afferents synapsing on α-motoneuron (α-MN) dendrites. Also, renshaw cells (RC) mediate a direct recurrent inhibition of α-MNs potentially via $GABA_A$ and glycinergic receptors. The RC synapses are confined to α-MN dendrites. Several studies have implicated a $GABA_B$ receptor mediated pre-synaptic inhibition of the Ia terminal during reflex generation. Supra-spinal inputs further modulate the efficacy of the synaptic inputs to the α-MN, e.g. brainstem nuclei exert a tonic monoaminergic inhibition on RCs. Following spinal cord injury (SCI), hyper-reflexia and motor spasticity occur with concomitant α-MN hyper-excitability. The hyper-excitability has largely been attributed to an enhancement of dendritic persistent inward currents (PICs), while inhibitory pathways may also play a role. However, the effect of a combination of PIC enhancement and changes in inhibitory inputs on α-MN excitability is yet unclear [1]. In this study, we use a network model for the monosynaptic stretch reflex with RC-type recurrent inhibition of the α-MN to test the hypothesis that GABAergic inputs are essential for suppressing α-MN hyper-excitability after chronic SCI.

Methods

We use conductance-based Hodgkin-Huxley formalism to represent individual neurons within the network. The α-MN is modeled using separate soma and dendritic compartments to signify the dendritic confinement of Ia and RC synapses and PIC channels. The synaptic variables for $GABA_A$, glycine and Ia afferent input are modeled as scalar equations while a constant current input represents the slower $GABA_B$ pre-synaptic Ia inhibition. The rise and decay rates of $GABA_A$ currents are ~3 times slower than the glycinergic currents. The tonic inhibition to RC is modeled as a constant current. Model simulations are performed using the XPPAUT software.

Results

The model α-MN shows hysteresis in the firing frequency-injected current (f-*I*) relationship (A) similar to experiments. Presence of RC inhibition is able to mask the *f-I* hysteresis (B). Disinhibiting RC to mimic SCI and eliminating $GABA_A$ (C), but not glycine inhibition (Fig. 1D) recovers hysteresis. An increase in RC inhibition due to disinhibition may not be sufficient to suppress *f-I* hysteresis. In the presence of Ia input, removal of $GABA_B$ inhibition of the Ia terminal alone unmasks the hysteresis. These results suggest that GABA-receptor mediated inhibition and its slower kinetics are integral for control of α-MN excitability.

Implications

Baclofen ($GABA_B$ agonist) treatment after chronic SCI alleviates pain and spasticity. Moreover, recent DNA microarray studies suggest down regulation of GABA receptor genes 7+ days post SCI [2]. Our model prediction support

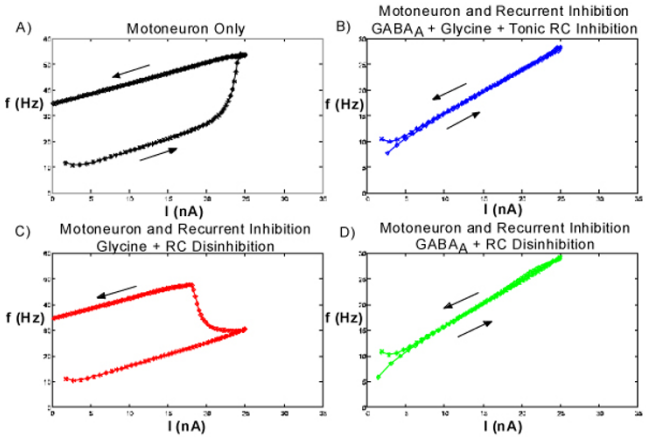

Figure 1
F-I curves; upward and downward arrows represent f-I response for increasing and decreasing currents respectively.

these experimental observations and provide directions for further studies to characterize spinal GABAergic mechanisms in the control of α-MN excitability chronically after injury.

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