Motoneuron Output Regulated by Ionic Channels: A Modelling Study of Motoneuron Frequency-Current Relationships during Fictive Locomotion

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Abstract: Objective: Spinal motoneuron excitability is changed during fictive locomotion. These changes include the hyperpolarization of voltage threshold for action potential generation, reduction of afterhyperpolarization and input resistance, and alteration of gain of the frequency-current (F-I) relationships. The mechanisms responsible for these dynamic changes in membrane properties of spinal motoneurons is unknown. In a previous modeling study it was predicted that the lowering of voltage threshold for action potential generation could be induced by increasing the conductance of transient sodium currents or reducing the conductance of delay-rectified potassium currents. These predictions were approved experimentally in the later pharmacological studies. However, the ionic basis responsible for the changes in the spinal motoneuron excitability during fictive locomotion remains unclear. The purpose of the present study is to explore the channel mechanisms underlying the changes in the F-I relationships with regulation of neuronal excitability. Methods: A single neuron model was built based on the membrane properties of cat lumbar motoneurons. The model contained ten active conductances, including transient sodium (gNaT), persistent sodium (gNaP), delay-rectifier potassium (gKdr), calcium-dependent potassium (gKahp), potassium A-current (gKa), L-type calcium (gCaL), N-type calcium (gCaN), T-type calcium (gCaT), H-current (gh), and leak potassium (gleak) conductance. The model was used to investigate the effects of modulating ionic channels on the F-I relationships. A sine waveform current was injected into the model cell to produce membrane potential oscillations that mimicked the step cycles or locomotor drive potentials (LDPs). Conductance of selected channels was altered to simulate the
changes in membrane properties similar to those observed in lumbar motoneurons during fictive locomotion, and then the corresponding F/I relationships were calculated with and without LDPs to figure out the changes in output of the motoneuron model comparing with the control ones. The F-I relationships with LDPs were calculated in both excitatory and inhibitory phases of the LDPs, respectively. **Results:** (1) The gain of an F-I relationship could be increased by reducing the somatic gKahp, increasing the initial segment (IS) gNaT or gNaP, negatively shifting the state variables (m and h) of IS gNaT or gNaP, reducing the IS gKdr, positively shifting the state variable (n) of IS gKdr, and increasing the somatic gCaL; (2) The gain of an F-I relationship could be also lowered by reducing the input resistance (Rin); (3) Without altering the ionic conductance, the F-I relationship could be parallel shifted to the left in the excitatory phase of the LDPs and to the right in the inhibitory phase of the LDPs, suggesting that the constant current injection produced parallel shifting of an F-I relationship. The positive current injection shifted the F-I relationship to the left while the negative current injection shifted it to the right. **Conclusion:** (1) Multi-ionic channels regulate the output of the spinal motoneurons. (2) Modulation of gKahp, gNaT, gNaP, gKdr, gCaL and Rin alters the gain of the F-I relationships similar to those observed during fictive locomotion. This study provides insight into the channel mechanisms underlying the changes in the F-I relationships during fictive locomotion.

**Keywords:** F-I relationship, ion channels, fictive locomotion, modelling.