Mechanisms of bistability in spinal motoneurons and its regulation

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Introduction

Spinal motoneurons represent output elements of spinal circuitry that activate skeletal muscles to produce motor behaviors. Firing behavior of many motoneurons is characterized by bistability allowing them to maintain a self-sustained spiking activity initiated by a brief excitation and stopped by a brief inhibition. Serotonin can induce or amplify bistability, influencing motor behaviors. Biophysical mechanisms of bistability involve nonlinear interactions of specific ionic currents. Experimental studies identified ionic currents linked to bistability [1,2]. Using computational modeling, we simulate motoneuronal bistability and analyze the roles of key ionic currents in its generation and regulation.

Methods
We have developed a conductance-based mathematical model of spinal motoneuron to explore and analyze the role of different ionic currents and their interactions in generation and control of motoneuronal bistability under different conditions. The one-compartmental model includes main spike-generating currents, fast sodium (*I*NaF) and potassium rectifier (*I*Kdr), as well as persistent sodium (*I*NaP), slowly inactivating potassium (*I*Kv1.2aka potassium A,*I*KA), high-voltage activated calcium (*I*CaL), Ca^{2+}-activated cation non-specific (*I*CAN), and Ca^{2+}-dependent potassium (*I*KCa, associated with SK channels) currents. Additionally, the model incorporates the intracellular Ca^{2+}dynamics including calcium-induced calcium release mechanism (CICR).
Results
Our simulations show that bistability in motoneurons relies on*I*CAN, activated by intracellular Ca^{2+}accumulated by*I*CaLand the CICR mechanism. Two other currents play modulatory roles with*I*NaPaugmenting bistability and*I*KCaattenuating or abolishing it. The interplay between*I*CANand*IKCa*shapes the membrane potential dynamics, producing post activation afterdepolarization (ADP) or afterhyperpolarization (AHP), with*I*Kv1.2modulating the membrane potential dynamics. Under certain conditions (such as an elevated extracellular K^+concentration),*INaP*can sustain bistability independently of*I*CAN.
Discussion
Our findings clarify the ionic basis of motoneuron bistability, underscoring its reliance on current interactions and external conditions, and offer insights into motor function and potential therapeutic strategies for motor disorders. Our results suggest that serotonin can induce or increase motoneuron bistability by amplifying*I*CAN(e.g., via increased intracellular Ca^{2+}concentration due to an increased*I*CaLor via 5-HT3 receptors), activation of*I*NaPor suppression of*I*KCa(both through 5-HT2 receptors).

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No
References
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