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Modeling $[Ca^{2+}]_o$- and $[K^+]_o$-dependent oscillations in spinal Hb9 interneurons

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The spinal interneurons in newborn rodents, when synaptically isolated by removing the extracellular calcium ($[Ca^{2+}]_o$), demonstrate intrinsic rhythmic bursting activity that can be suppressed by riluzole, a blocker of the persistent sodium current (I_{NaP}) [2]. This finding led to the suggestion that lowering of $[Ca^{2+}]_o$ may enhance I_{NaP} by shifting its activation threshold toward more negative voltages, and raised the question of functional relevance of this finding to generation of locomotor rhythm. To assess this issue, a series of experiments was performed *in vitro* using the isolated spinal cord preparation from the neonatal rat with measurements of $[Ca^{2+}]_o$ and extracellular potassium concentration ($[K^+]_o$) during pharmacologically induced fictive locomotion. We demonstrated that with the onset of fictive locomotion, $[Ca^{2+}]_o$ reduced from 1.2 up to 0.9 mM whereas $[K^+]_o$ increased from 4 up to 6 mM. At the same time, a special study performed on the isolated genetically identified Hb9 excitatory interneurons showed that, at $[Ca^{2+}]_o$= 1 mM and $[K^+]_o$=5 mM, 12% of Hb9 cells expressed intrinsic I_{NaP}-dependent bursting, and at the concentrations typical for fictive locomotion ($[Ca^{2+}]_o$=

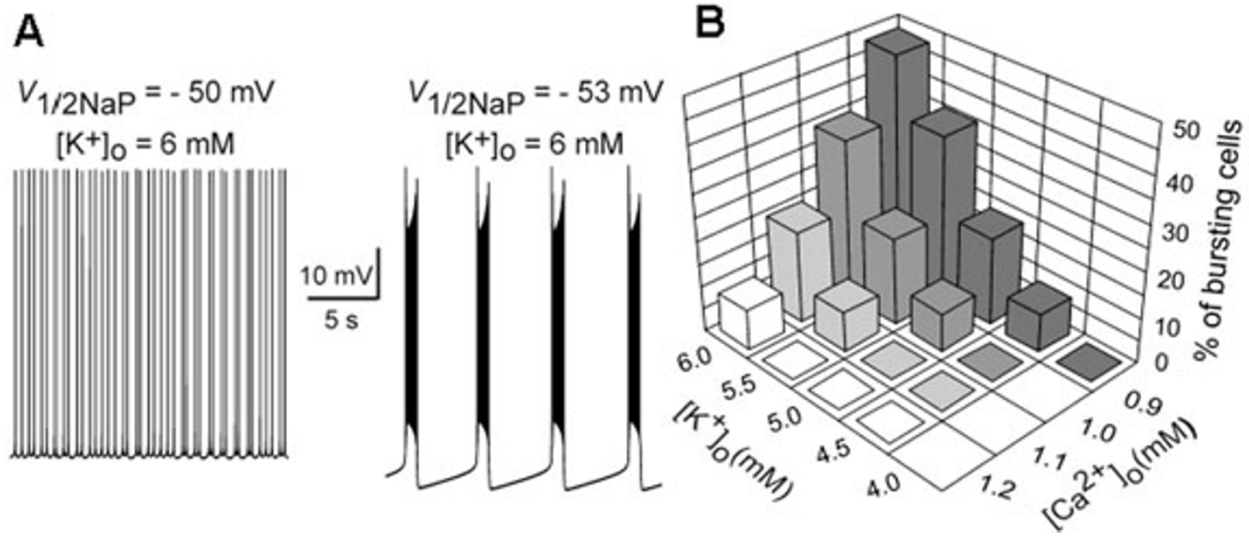

Figure 1 A. Switching from tonic to bursting activity in the modeled neuron by shifting $V_{1/2NaP}$ to more negative value. **B**. *The synergistic effect of* $[Ca^{2+}]_o$ and $[K^+]_o$*changes on emergence of bursting activity* in the modeled population of 50 uncoupled cells.

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0.9 mM and $[K^+]_o$=6 mM), as many as 50% of identified Hb9 interneurons expressed I_{NaP}-dependent bursting. Importantly, the threshold of $[Ca^{2+}]_o$ to generate bursting decreased as $[K^+]_o$ increased. The analysis of Hb9 neuron behavior during slow ramp increase of voltage revealed that lowering $[Ca^{2+}]_o$ from 1.2 to 0.9 mM induced a negative shift (~ -3 mV) in the I_{NaP} half-activation voltage ($V_{1/2NaP}$). In contrast, $V_{1/2NaP}$ was not changed when $[K^+]_o$ increased from 4 to 6 mM.

To theoretically investigate the effect of changing $[Ca^{2+}]_o$ and $[K^+]_o$ on the Hb9's pacemaker properties and firing behavior, we developed a single-compartment computational model of Hb9 neuron. In this model, we explicitly simulated a negative shift of $V_{1/2NaP}$ occurring with the reduction of $[Ca^{2+}]_o$. At $[K^+]_o$=6 mM, our model exhibited tonic activity at $V_{1/2NaP}$ = −50 mV (Fig. 1A, *left*). The rhythmic bursting emerged at $V_{1/2NaP}$ = −51 mV, and further shifting $V_{1/2NaP}$ to the left produced stable bursting (Fig. 1A, *right*). In turn, an increase in $[K^+]_o$ reduced the potassium reversal potential and hence all voltage-gated potassium currents (I_K), which provided an additional augmentation of I_{NaP}-dependent bursting [1]. To study *a synergistic effect of* $[Ca^{2+}]_o$ and $[K^+]_o$*on the emergence of bursting activity, we modeled* a population of 50 uncoupled neurons with randomly distributed parameters (see Fig. 1B). Our simulations have shown that shifting $V_{1/2NaP}$ towards more negative values induced by reducing $[Ca^{2+}]_o$ may play a major role in emergence of bursting activity in the population of spinal interneurons. We have also demonstrated that accumulation of $[K^+]_o$*can* facilitate the emergence of I_{NaP}-dependent bursting via the reduction of I_K.

In summary we suggest that co-regulation of I_{NaP} and I_K by the corresponding changes in $[Ca^{2+}]_o$ and $[K^+]_o$ may convert activity of spinal interneurons from asynchronous/tonic to the synchronized bursting. This activity-dependent switching in firing behavior may represent a fundamental mechanism for locomotor rhythm generation in the spinal cord.

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