Effects of voltage trajectory on action potential voltage threshold in simulations of cat spinal motoneurons

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Abstract

A single-cell neuronal model was used to investigate the effect of membrane trajectory on voltage threshold ($V_{th}$) for action potential generation. Previous results suggested that hyperpolarization of $V_{th}$ could be produced by a rapid membrane depolarization, but this effect is limited to the first spike in a train. This study shows rapid current injections hyperpolarize $V_{th}$ because they are more effective in activating the sodium current underlying spiking. The hyperpolarization of $V_{th}$ induced by rapid membrane depolarization becomes less effective in altering $V_{th}$ when other mechanisms of enhancing the fast sodium current underlying action potentials are activated. © 2000 Published by Elsevier Science B.V. All rights reserved.

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1. Introduction

During fictive locomotion evoked by stimulation of the midbrain locomotor region (MLR) in decerebrate cat, motoneurons receive alternating excitatory and inhibitory inputs from the central pattern generator (CPG). These inputs produce rhythmic oscillations of membrane potential termed locomotor drive potentials (LDPs, [3]). If the neuron is recruited during locomotion, it fires action potentials on the depolarized portion of the LDP. Compared to the resting condition, cat lumbar motoneurones undergo various changes in excitability during fictive locomotion. Recently, Krawitz et al. [4] showed that the voltage threshold ($V_{th}$) for action potential generation becomes hyperpolarized during fictive locomotion.

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The effects of a rapid membrane potential depolarization on $V_{th}$ were examined in our recent study [4]. Current pulses (15 nA and 500 ms) were injected into the motoneurons at rest to produce very rapid membrane depolarizations. The results showed that the $V_{th}$ for action potential generation could be hyperpolarized by a rapid membrane depolarization produced by the injection of a rapid current pulse at rest. But the $V_{th}$ hyperpolarization produced by the current pulses was restricted to the first spikes of the train and was small compared to the amount of the $V_{th}$ hyperpolarization seen during locomotion. The present study utilizes a single cell computer model to examine the mechanisms by which the membrane potential trajectory can affect $V_{th}$ as part of our larger goal of understanding how the $V_{th}$ is modulated during fictive locomotion.

2. Computer model

A single-cell model with five compartments (axon, initial segment (IS), soma, proximal dendrite and distal dendrite) was built using GENESIS software [1]. The details of building the model cell are described in another manuscript [2]. Briefly, the model included a fast sodium current ($I_{Na}$) and a delayed rectifier potassium current ($I_{K(DR)}$) in the axon, initial segment and soma compartments. Additional currents included in the soma compartment were a calcium-dependent potassium current ($I_{K(AHP)}$), a fast transient potassium current ($I_{K(A)}$), a hyperpolarization activated current ($I_{h}$) and three classes of voltage activated calcium currents (L-Type: $I_{Ca(L)}$, N-Type: $I_{Ca(N)}$, and T-type: $I_{Ca(T)}$). The proximal dendritic compartment included

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**Fig. 1.** Single-cell model and initial properties. A. A single-cell model with five compartments was built that retained morphological features of motoneurones important for the generation of anti- and orthodromic action potentials. The input resistance of the model cell $R = 2.0 \ \text{M\Omega}$; membrane time constant $t_m = 4 \ \text{ms}$; and the rheobase current $I_{rb} = 11 \ \text{nA}$. B. Repetitive firing of the model cell was evoked by injecting a triangular current (starting from $-5 \ \text{nA}$ with peak $30 \ \text{nA}$ and duration $1 \ \text{s}$, not shown) to the soma compartment. The mean value of the voltage threshold was $-35.8 \pm 0.7 \ \text{mV}$ (dark line). C. Frequency-current ($F-I$) relation produced by step current injections into the soma compartment. The slope of the primary range is $1.1 \ \text{Hz/nA}$, and the slope of the secondary range is $11 \ \text{Hz/nA}$. The frequency was calculated by dividing the number of spikes by the duration (500 ms) of each step current.
$I_{K(AHP)}$, $I_{Ca(N)}$ and $I_{Ca(L)}$. No active conductance was included in the distal dendrite compartment. The input resistance of the model cell = 2.0 MΩ; membrane time constant = 4 ms; and the rheobase current = 11 nA. Resting membrane potential = $-60$ mV. The time step for simulation was = 0.05 ms. The simulations were done on Pentium PCs running the Linux operating system.

Fig. 1A illustrates a schematic of the single-cell model. Repetitive firing of the model cell was evoked by injection of a triangular current to the soma compartment (starting from $-5$ nA with peak of 30 nA and duration of 1 s, not shown) as shown in panel B. The mean value of $V_{th}$ was $-35.8 \pm 0.7$ mV. The $F-I$ relation produced by step current injections is shown in panel C.

3. Results

In order to examine the possible mechanisms by which a rapid change in membrane potential produces the $V_{th}$ hyperpolarization, we injected triangular currents with varying slopes into the soma compartment of the model. Fig. 2 shows these simulation results. In panels A and B the somatic membrane potentials were shown in the top panels, the net membrane currents ($I_m$) in the middle, and the injected triangular currents in the bottom.

Fig. 2A shows that a single spike was evoked by injecting a triangular current (starting at $-5$ nA with peak 15 nA and duration 125 ms) into the soma compartment. The slope of the ramp current was 0.33 nA/ms (bottom panel in A). The $V_{th}$ for this spike was $-42.0$ mV (top panel in A), and the peak membrane current ($I_m$) underlying the spike was $-126$ nA (middle panel in A). Increasing the slope of the ramp current to 0.66 nA/ms (bottom panel in B) evoked three spikes in the model cell (top panel in B). The $V_{th}$ for the first spike was $-43.4$, $\sim 1.5$ mV lower than that in panel A. The peak $I_m$ for this spike was $-140$ nA (middle panel in B), 14 nA larger than that in A. The $V_{th}$ for the remaining two spikes were $-40.2$ and $-39.9$ mV, respectively, which were relatively depolarized compared with the first spike. The $I_m$ corresponding to these two spikes were also smaller than that for the first spike. These results suggest that steeper slopes of the ramp current produce a larger peak $I_m$ and a lower $V_{th}$ for the first spike initiation. A systematic series of simulations were done and the results are summarized in Fig. 2C. These results show that increasing the slope of the ramp current results in an increase in the peak $I_m$. This increased $I_m$ would in turn cause a lowering of $V_{th}$.

In regard to spike initiation, the major component of the $I_m$ at the rising phase of the spike was mainly from the fast sodium current ($I_{Na}$). Therefore, the hyperpolarization of $V_{th}$ produced by a rapid membrane depolarization is likely due to a rapid activation of the $I_{Na}$, which was relatively limited to the first spike of the train. In contrast, slower depolarizations would cause relatively greater accommodation and be relatively less effective in activating the $I_{Na}$ underlying the action potential.

The relationship between the enhanced activation of the fast sodium current by rapid membrane depolarization and the $V_{th}$ hyperpolarization during fictive locomotion was further explored in Fig. 3. Panels A and B illustrate conditions where
Faster rates of current injection are more effective at activating action potentials. A. A triangular current (bottom panel: starting at $-5$ nA with peak 15 nA and duration 125 ms) was injected into the soma compartment. The slope of the ramp was 0.33 nA/ms. Peak membrane current ($I_m$) underlying the action potential was $-126$ nA (middle panel), and the $V_{th}$ of the spike was $-42.0$ mV (top panel). B. Doubling the slope of the ramp current to 0.66 nA/ms (bottom panel: starting at $-5$ nA with peak 35 nA and duration 125 ms) increased the peak $I_m$ for the first spike to $-140$ nA (middle panel) and hyperpolarized the $V_{th}$ of the first spike to $-43.4$ mV (top panel). $V_{th}$ for the remaining two spikes were $-40.2$ mV and $-39.0$ mV respectively. C. Upper panel: relation between the slope of the injected ramp current and the peak $I_m$. Lower panel: relation between the slope of the ramp current and the $V_{th}$ of the first spike of the spike train.

Conductances of the initial segment compartment have been modified to produce $V_{th}$ effects which we have previously postulated to be analogous to that observed during fictive locomotion [2]. In panel A the max $g_{Na}$ was increased by 100% and in panel B the delayed rectifier potassium conductance (max $g_{K(DR)}$) was decreased by 70%. Panel C shows the control response, without modification of the model’s properties. In each condition the membrane potential is shown in top the panel, current injection in the middle, and action potential $V_{th}$ in the bottom. The $V_{th}$ was plotted as dot corresponding to each spike in the top panel. The circled dot represents $V_{th}$ of the first spike in each spike train. Current pulses (middle panels: 15 nA and 500 ms) superimposed on triangular current (starting at $-10$ nA with peak 15 nA and duration 10 s) were used to produce rapid membrane depolarizations similar to a procedure used in our cat experiments [4].

A rapid membrane depolarization produced hyperpolarization of the $V_{th}$ when comparing the first spikes to subsequent spikes in the train. The difference was 1.7 mV.
Fig. 3. Effects of rapid membrane depolarizations on voltage threshold ($V_{th}$). The membrane potential is shown in the top panel, current injection in the middle, and voltage threshold in the bottom. In all three panels current pulses (15 nA, 500 ms) were superimposed on triangular current (starting at $-10$ nA with peak 15 nA and duration 10 s) and injected into the soma compartment to produce rapid membrane depolarizations. The fictive locomotion state was simulated by increasing initial segment (IS) sodium conductance ($\max g_{Na}$) by 100% (panel A) or by reducing the IS delayed rectified ($\max g_{K(DR)}$) by 70% (panel B). Each dot shown in the bottom panels represents the $V_{th}$ for each spike shown in the top panels, respectively. The circled dots represent the $V_{th}$ of the first spikes in the spike trains. Dashed lines represent the mean values of $V_{th}$ for the first spikes in the spike train while the dark lines represent the mean values of the $V_{th}$ for the subsequent spikes. A. The fictive locomotion state was simulated by increasing IS $\max g_{Na}$ by 100%. The mean value of the $V_{th}$ for all spikes was $-43.5 \pm 1.4$ mV. The mean values of the $V_{th}$ for the first and subsequent spikes were $-44.7 \pm 0.8$ (dashed line) and $-43.0 \pm 0.7$ mV (dark line), respectively. B. The fictive locomotion state could be also simulated by reducing the IS $\max g_{K(DR)}$ by 70%. The mean value of $V_{th}$ for all spikes was $-41.4 \pm 1.2$ mV while the mean values of the $V_{th}$ for the first and subsequent spikes were $-42.6 \pm 0.7$ (dashed line) and $-41.1 \pm 0.4$ mV (dark line) respectively. C. Repetitive firing was evoked by the same current injection as used in A and B. Conductances of the model cell were not modified. The mean values of $V_{th}$ were $-37.6 \pm 3.0$ mV for all spikes, $-41.4 \pm 1.6$ mV for the first spikes (dashed line), and $-36.2 \pm 0.6$ mV for the subsequent spikes (dark line).

in panel A, 1.5 mV in panel B, and 5.2 mV in panel C while the mean values of $V_{th}$ for the first spikes (dashed lines) were $-44.7$, $-42.6$, and $-41.4$ mV and those for the subsequent spikes (dark lines) were $-43.0$, $-41.1$ and $-36.2$ mV, respectively. These results indicated that the effect of rapid membrane depolarizations on $V_{th}$ was smaller in simulated fictive locomotion (A and B) than that in control (C). The hyperpolarization of the $V_{th}$ produced by the rapid depolarization was restricted to the first spike in the spike train.

On the other hand, the mean value of $V_{th}$ for all spikes was hyperpolarized by 7.7 mV in panel A (mean $-43.5$ mV), 5.6 mV in panel B (mean $-41.4$ mV), and
1.8 mV in panel C (mean −37.6 mV) compared to the mean value of the $V_{th}$ (−35.8 mV) measured under triangular current injection in control (Fig. 1B). The amount of $V_{th}$ hyperpolarization produced by the rapid membrane depolarization in control (panel C) was smaller than the amount of $V_{th}$ hyperpolarization produced by a modulation of IS $g_{Na}$ (panel A) or IS $g_{K(DR)}$ (panel B). This result suggests that the hyperpolarization of $V_{th}$ seen during fictive locomotion is not dependent on the rapid membrane depolarization.

The above results suggest that the hyperpolarization of $V_{th}$ induced by rapid membrane depolarization (as illustrated in Fig. 2) is less effective in altering $V_{th}$ during fictive locomotion when other mechanisms of enhancing the sodium conductance underlying action potentials (either directly through modification of the sodium conductance, or indirectly by modification of the delayed rectifier conductance) are activated. The fact that the two mechanisms of altering $V_{th}$: (1) rapid membrane depolarization and (2) modulation of conductance properties seem to not be additive provides further evidence that neuronal $V_{th}$ is likely more affected by modulation of neuronal conductances rather than being determined by the trajectory of the membrane potential.

4. Conclusion

These simulation results compliment experimental observations that the $V_{th}$ for action potential generation can be hyperpolarized by a rapid membrane depolarization. However, $V_{th}$ hyperpolarization produced in this way was limited to only the first spike in the spike train, and the amount of the $V_{th}$ hyperpolarization was small. These limitations are likely due to the kinetics of the fast sodium channel. The hyperpolarization of $V_{th}$ induced by rapid membrane depolarization seems less effective in altering $V_{th}$ when other mechanisms of enhancing the fast sodium current underlying action potentials are activated.

References

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Kelvin Jones received a Ph.D. in Neuroscience from Simon Fraser University in 1996. It was during this time that he developed a love affair with motoneurones and wrote his first haiku in their honor. Since that time he has pursued a wide range of activities, scientific and otherwise, in hopes of impressing his grade nine Language Arts teacher who lamented the decline of the Renaissance.

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