The excitatory effect of temperature on the Hodgkin-Huxley model

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Neurostimulation has emerged as an effective means of treating a wide range of neurological disorders. Recent work has shown that precise delivery of infrared stimulation can modulate neural activity in a reversible manner. A possible mechanism underlying the excitatory effect of infrared stimulation is a localized elevation of temperature. To gain insight into how small elevations in temperature could potentially modulate neural activity, we explored the temperature sensitivity of the well-established Hodgkin-Huxley computational model of the squid giant axon. We relied on experimentally-derived temperature coefficients, or Q10 values, associated with gating kinetics for all the underlying currents and the maximum conductances, as well as the inherent temperature dependence of the equilibrium potentials of the ion conductances. While temperature elevations alone failed to induce action potentials in the computational model, small increases in temperature modulated the firing rate during constant current injection where greater than 30% increase in spike rate was observed with 2°C elevation in temperature. Furthermore, we observed that the rise in spike rate was largely due to the predicted temperature sensitivity of rate constants that form the basis of the gating parameters of the Hodgkin-Huxley computational model. Our findings suggest that the known biophysics of ion conductances may account, at least in part, for the excitatory effects of thermal elevations induced by exposure to infrared stimulation.

Abbreviations: HH – Hodgkin-Huxley; Q10 – temperature sensitivity

Keywords: Action Potentials, Infrared, Neurostimulation

Introduction

For a wide range of neurological disorders, neurostimulation provides a means of therapy and/or restoration of neural function. Typically, neurostimulation is produced by controlled delivery of electrical current through electrodes in close proximity to neurons (Testerman et al., 2006). As an alternative to electrical stimulation, recent work has shown that low intensity infrared light can alter electrical excitability of neurons, an effect that may be based on spatiotemporal elevations in temperature (Cayce et al., 2010). This is due to the fact that infrared light at sufficiently high wavelengths is well-absorbed by water-containing tissue to produce a photo-thermal effect. While a temperature sensitive ionic conductance, i.e., a pore-based pathway for ions to flow across the membrane, may be the basis of this effect, electrically excitable cells have a number of biophysical features that either have explicit temperature sensitivity or can be modeled as chemical reactions that also have temperature sensitivity. These biophysical processes include the ion channel gating kinetics, maximum conductance related to each ion channel, and the equilibrium potentials. Our overall hypothesis is that temperature sensitive biophysical processes that underlie excitation contribute to the observed elevation in neural activity. Our aims were
to: 1) explore temperature sensitivity of action potential generation using the Hodgkin-Huxley (HH) model (Hodgkin and Huxley, 1952B); 2) to identify which biophysical process is the major contributor to the temperature-induced changes in action potential generation with the model. The HH model is a computational model that describes how action potentials are initiated and propagated in neurons. It is based on physiologically relevant parameters where action potentials are the results of transient and voltage dependent changes from Na\(^+\) and K\(^+\) ion channels coupled with a passive Cl\(^-\) channel and the capacitive behavior of the cell membrane. The fundamental assumptions of the model are that 1) these channels have ionic specificity, 2) act in parallel and independently, 3) the Na\(^+\) and K\(^+\) channels contain voltage sensitive gates that follow first order kinetics consistent with a simple chemical reaction, and 4) the ionic currents through the channels are carried by ions that move across the membrane according to their respective electrochemical gradients. Utilizing the HH computational model of action potential generation, we studied how the temperature sensitive biophysical properties contributed to the membrane excitability when an increase in temperature was applied. To incorporate temperature sensitivity into the HH computational model, we made use of experimentally derived values of temperature sensitivity, or Q10, which is a measure of the rate of change of a chemical reaction or process resulting from a 10°C temperature elevation. The total membrane current, I, is the sum of the capacitive current and the ion currents. Specifically:

\[
Q10 = \left(\frac{X_1}{X_2}\right)^{10/(T_1-T_2)}
\]

where \(X_1\) and \(X_2\) are biophysical parameters at temperatures \(T_1\) and \(T_2\), respectively.

Materials and Methods

We used the HH computational model to explore the temperature sensitivity of action potential generation and firing by incorporating temperature dependence to the associated equations. First, the HH model was implemented in MATLAB and shown to demonstrate action potential waveforms consistent with prior work. Second, temperature elevations were incorporated into the model where temperature was either an explicit feature of a contributing equation within the model, or temperature sensitivity based on experimentally derived Q10 values was used. Third, with the observation of changes in action potential firing rate with temperature elevations, we examined the contribution of each biophysical process separately to identify the major contributor of the overall effect. The data presented constitute findings from original experimental runs of the model.

The HH model allows simulation of the time dependence of the axonal membrane potential, V. Several features of the model are inherently temperature dependent, permitting modeling of the effects of temperature transitions. To examine the effects of temperature on the HH model we considered the temperature-dependent features of the model. These features are rate constants, equilibrium potentials, and maximum conductance values. For features of the model where the corresponding equations do not have temperature as a parameter, we used the Q10 to describe the temperature sensitivity:
\[ I = C_m \frac{dV}{dt} + I_K + I_{Na} + I_{Cl} \]

where \( C_m \) is the membrane capacitance in units \( \mu F/cm^2 \), \( I_K \) and \( I_{Na} \) are the time- and voltage-dependent currents for \( K^+ \), \( Na^+ \), respectively, and \( I_{Cl} \) is Cl\(^-\) leak current in units of current in \( \mu A/cm^2 \) (Hodgkin and Huxley, 1952B).

The time- and voltage-dependent currents can be written as the product of maximum conductance levels \( g_{\text{max},K} \), \( g_{\text{max},Na} \), and \( g_{\text{max},Cl} \) for \( K^+ \), \( Na^+ \), and \( Cl^- \), respectively, the electrochemical driving force, which is the difference between the membrane voltage and the equilibrium potentials, and time- and voltage-dependent gating variables \( n \), \( m \), and \( h \), which vary between 0 and 1, for \( K^+ \) and \( Na^+ \) such that:

\[
I = C_m \frac{dV}{dt} + g_{\text{max},K} n^4 (V - E_K) + g_{\text{max},Na} m^3 h (V - E_{Na}) + g_{\text{max},Cl} (V - E_{Cl})
\]

where \( E_K, E_{Na}, \) and \( E_{Cl} \) are the equilibrium potentials for \( K^+ \), \( Na^+ \), and \( Cl^- \), respectively, in units of mV (Hodgkin and Huxley, 1952B). For baseline conditions at 6 °C, \( g_{\text{max},K}, g_{\text{max},Na}, \) and \( g_{\text{max},Cl} \) were set at 120, 36, and 0.3 mS/cm\(^2\), respectively. Temperature sensitivity was incorporated for the maximum membrane conductance levels and the equilibrium potentials. A Q10 value of 0.446 was used for the maximum conductance values (Fitzhugh and Cole, 1964). The equilibrium potentials for the sodium, potassium and chloride ions were determined using the Nernst equation in units of mV where it is explicitly a function of temperature:

\[
E_{ion} = \frac{RT}{F} \ln \frac{[ion]}{[ion]_o}
\]

where \( R \) is the universal gas constant in Joules per Kelvin per mole, \( T \) is the absolute temperature in Kelvin, \( F \) is Faraday’s constant in Coulombs per mole, and \([ion]_o\) and \([ion]\) are the intracellular and extracellular concentrations of a specific ion, respectively (Hodgkin and Huxley, 1952A).

The gating variables essentially dynamically modulate the amount of total conductance of the simulated membrane for a specific ion. The variables, \( m \), \( n \), and \( h \) are voltage and time dependent, obey first order kinetics consistent with a chemical transition from closed to open, and range from 0 to 1. For example, the \( n \) gate representing \( K^+ \) channel activation transitions from being closed \((1-n)\) to open \((n)\) according to rate constants \( \alpha_n \) and \( \beta_n \). For example:

\[
\frac{dn}{dt} = \frac{\alpha_n(1 - n) - \beta_n n}{\beta_n - \alpha_n}
\]

The rate of change of each of the gating variables is a function of the rate constants that define a transition between gating variable states of open and closed. Specifically:

\[
\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n
\]

\[
\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m
\]

\[
\frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h
\]

The rate constants, in units of ms\(^{-1}\), are functions of membrane voltage and were defined based on the original Hodgkin-Huxley model:

\[
\alpha_n = \frac{0.01(10 - V)}{\exp(\frac{10 - V}{10}) - 1}
\]

\[
\beta_n = 0.125 \exp(\frac{V}{80})
\]
\[ \alpha_m = \frac{0.1(25 - V)}{\exp\left(\frac{25 - V}{10}\right) - 1} \]

\[ \beta_m = 4.0 \exp\left(-\frac{V}{18}\right) \]

\[ \alpha_h = 0.07 \exp\left(-\frac{V}{20}\right) \]

\[ \beta_h = \frac{1}{\exp\left(\frac{30 - V}{10}\right) + 1} \]

These values fit data derived from experimental voltage clamp work performed on the squid giant axon at 6 °C. To perform simulations, the values of \( n, m, \) and \( h \) were continuously updated by integration for each time increment based on the voltage and the respective rate constants. To incorporate temperature sensitivity for the gating variables \( n, m, \) and \( h \), the rate constants were adjusted using the Q10 relationship and applying it to all \( \alpha \) and \( \beta \) values. For rate constants, we chose a Q10 value of 3 (Hodgkin et al., 1952; Li et al., 2013).

To initialize the computer simulations, the initial membrane voltage value, \( V_0 \), was calculated using the Goldman-Hodgkin-Katz equation:

\[ V_0 = \frac{RT}{F} \ln \left( \frac{P_K[K^+] + P_{Na}[Na^+] + P_{Cl}[Cl^-]}{P_K[K^+] + P_{Na}[Na^+] + P_{Cl}[Cl^-]} \right) \]

a special case of the Nernst equation in which \( P_K, P_{Na}, \) and \( P_{Cl} \) represent the resting membrane permeability of \( K^+ \), \( Na^+ \), and \( Cl^- \) ions.

**Results**

As shown in Figure 1, depending on the magnitude and direction of the current injection, membrane hyperpolarization or depolarization resulted. At sufficiently high depolarizing current levels, action potentials resulted. From the baseline temperature of 6°C, temperature elevations in the absence of current injection failed to evoke activity. In addition, applying a temperature elevation as high as 20°C to the HH model under conditions of constant current up to 8 \( \mu \)A/cm\(^2\) failed to evoke an action potential. However, under conditions where constant current was injected to trigger repetitive firing (e.g., >8 \( \mu \)A/cm\(^2\)), temperature sensitivity emerged. Figure 2 shows the voltage response of the model under a constant current of 10 \( \mu \)A/cm\(^2\) with 100 ms duration temperature transitions. Elevations in temperature produced marked changes in spike frequency during repetitive firing. For example, the frequency increased from 70 Hz to 170 Hz over the span of 10°C for an effective Q10 for spike rate of 2.4 (Figure 3). For temperature transitions exceeding at 5 °C and higher, the peak amplitudes of the spikes decreased.

We then investigated which of the individual biophysical mechanisms that are temperature dependent in the HH model are responsible for the changes observed with temperature transitions.
The HH model consists of three temperature sensitive components: equilibrium potential, maximum membrane conductance levels, and the rate constants. Temperature transitions were applied to the model under conditions where only separate components were permitted to vary with temperature. For example, to examine the contribution of gating kinetics, the maximum conductance and equilibrium potentials were held constant during the temperature elevation. As shown in Figure 4, the 100 ms temperature change, acting only on the equilibrium potential, showed barely any alteration to the frequency and magnitude of the resulting action potentials under repetitive firing. Likewise, when only the maximum ion conductance levels were allowed to vary with temperature, little or no change in the spike behavior was observed. However, when only the rate constants were allowed to vary with temperature, marked changes in spike behavior were observed, suggesting that the temperature dependence of the HH model is largely due to the temperature sensitivity of the rate constants.

**Discussion**

In the present study, we observed that under conditions of repetitive firing, the HH model exhibits marked sensitivity to temperature elevations. Temperature elevations alone do not appear to evoke action potentials. The temperature sensitivity emerges under repetitive firing evoked by constant current injection. With a temperature elevation of only 2°C, the firing rate increased by more than 30%. By
simulating the temperature sensitivity of individual biophysical processes, the elevation in action potential rate can be attributed largely to the temperature sensitivity of the rate constants that underlie ion channel gating in the HH model. For temperature transitions above 5 °C, there was a decrease in action potential amplitude, indicating that resting membrane conductances began to dominate membrane potential behavior. These findings are significant for understanding the potential impact of infrared stimulation of neural tissue. Our simulations indicate that temperature-dependent alterations in channel gating of endogenous ion conductance pathways may be sufficient to explain elevations in membrane excitability under repetitive firing. It is noteworthy that our simulated temperature transitions are not inconsistent with presumed thermal elevations evoked by infrared stimulation. Infrared stimulation, which has been shown to modulate excitability in rat sciatic nerve (Wells, et al., 2005), gerbil auditory neurons (Richter et al., 2008), and rat cortical tissue (Cayce et al., 2011), appears to be associated with temperature elevations on the order of 14 °C (Liang et al., 2008).

Previous studies have examined temperature sensitivity of action potential dynamics through computational models, but have not recognized the ability of temperature elevations to increase action potential frequency under repetitive firing conditions. Modeling only temperature sensitivity of the rate constants, Kuang et al. (2009) reported that the threshold for spike initiation in HH model exhibits a global minimum at the baseline temperature. Under conditions of constant current injection, Yuan and colleagues (2009) applied a sinusoidal varying temperature transition peaking from +18 to -18 °C from baseline and reported increased spiking over a limited temperature range with concomitant changes in the action potential waveform. Using the NEURON simulation environment, Georgiev and colleagues (2014) simulated single action potentials and reported that raising the temperature speeds channel kinetics such that action potentials have a faster rise time, although temperature excursions exceeding 16°C failed to elicit full sized spikes. While the present paper was under preparation, Shapiro et al. (2013), who were exploring thermal mechanisms of millimeter wave stimulation of excitable cells, described alterations in repetitive firing of HH simulated oocytes with thermal elevations consistent with our findings.

There are two major limitations of the present computational study. The first is that the majority of experimental infrared stimulation studies were performed with mammalian tissue with a baseline temperature of 37°C, rather than squid axon at 6°C. Computational models of mammalian tissue incorporate a larger array of ion channel currents and multiple compartments (e.g., Jones and Bawa, 1997; Pospischil et al., 2008) that would provide a more comprehensive framework for examining the effect of transient thermal elevations. Some neurons express the transient receptor potential family of channels that are known to be sensitive to temperature (Baez et al., 2014). The second limitation is that we did not consider changes in membrane capacitance. The Q10 for membrane capacitance is on the order of 0.1 (Adams, 1989), however there may be direct effects of infrared stimulation on membrane capacitance (Liang et al., 2008).

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