Simulation Analysis of Conduction Block in Myelinated Axons Induced by High-Frequency Biphasic Rectangular Pulses

Xu Zhang, James R. Roppolo, William C. de Groat, and Changfeng Tai*

Abstract—Nerve conduction block induced by high-frequency biphasic rectangular pulses was analyzed using a lumped circuit model of the myelinated axon based on Frankenhaeuser-Huxley (FH) equations. At the temperature of $37\degree C$, axons of different diameters (2–20 $\mu$m) can be blocked completely at supra-threshold intensities when the stimulation frequency is above 10 kHz. However, at stimulation frequencies between 6 kHz and 9 kHz, both nerve block and repetitive firing of action potentials can be observed at different stimulation intensities. When the stimulation frequency is below 6 kHz, nerve block does not occur regardless of stimulation intensity. Larger diameter axons have a lower threshold intensity to induce conduction block. When temperature is reduced from 37 $\degree C$ to 20 $\degree C$, the lowest frequency to completely block large axons (diameters 10–20 $\mu$m) decreased from 8 kHz to 4 kHz. This simulation study can guide future animal experiments as well as optimize stimulation waveforms for electrical nerve block in clinical applications.

Index Terms—Axon, electrical stimulation, high-frequency, nerve block, model.

I. INTRODUCTION

Animal experiments showed that high-frequency biphasic electrical current applied to peripheral nerves could block conduction of action potentials [1]–[6]. This nerve block was quickly reversible once the stimulation was removed. A reversible peripheral nerve block by electrical current would have many useful clinical applications. In people with spinal cord injury, blocking pudendal nerve conduction during micturition could reduce urethral pressure and improve voiding efficiency [1]. Blocking peripheral nerves could also be used to treat chronic pain of peripheral origin [7], or to stop unwanted motor activity [2]. Blocking nerves in a gradual manner starting with larger nerve fibers and progressing to smaller fibers [8]–[10] could be used to activate muscles in a physiological recruitment order and reduce muscle fatigue. A nerve block method employing biphasic electrical current will be more attractive than uniphasic current in chronic applications, since the biphasic stimulation causes less tissue damage due to electro-chemical reactions [11].

Nerve responses to extracellular electrical stimulation have been analyzed using computer simulation by many investigators [10], [12]–[19] using various models [20]–[23]. Most of these simulation studies focused on nerve excitation using low stimulation frequencies (below 1 kHz). A few simulation studies [13], [14] explored high-frequency biphasic stimulation (up to 100 kHz), but they only investigated the nerve excitation rather than block. Nerve conduction block induced by direct current was recently analyzed using computer simulation [24]. Further theoretical analysis of nerve conduction block induced by high-frequency biphasic current is needed.

In our previous studies [25], [26], nerve conduction block in unmyelinated axons induced by high-frequency biphasic currents has been analyzed using the HH model. In this study, we further analyzed the nerve block in myelinated axons at different temperatures using the FH model. The purpose of this study was to evaluate the model’s ability to simulate known phenomena, predict unknown results, and compare the nerve block in myelinated axons with unmyelinated axons. Results from this simulation study could guide further experiments on animals, and optimize the stimulation waveforms to be used to block peripheral nerve conduction in clinical applications.

II. METHODS

The nerve model used in this study is shown in Fig. 1. A 40-mm-long myelinated axon is modeled with the internode length $\Delta x = 100d$ (where $d$ is the axon diameter). Each node (nodal length $L = 2.5 \mu$m) is modeled by a membrane capacitance ($c_m$), and a variable membrane resistance ($R_m$). Two monopolar point electrodes (with the indifferent electrode at infinity) are placed at 1-mm distance to the axon (Fig. 1). One is the block electrode at the 25-mm location along the axon, where the high-frequency biphasic rectangular pulses (as shown in Fig. 1) will be delivered. The other is the test electrode at the 5-mm location, which will deliver a uniphasic single pulse (pulse width 0.1 ms and intensity varies from 0.5 mA to 2 mA) to evoke an action potential and test whether this action potential can propagate through the site of the block electrode. The test electrode will always be a cathode (negative pulse), and the block electrode will always deliver biphasic pulses with the cathodal phase first.

We assume that the axon is in an infinite homogeneous medium (resistivity $\rho_s = 300 \Omega \cdot \text{mm}$). After neglecting the small influence induced by the presence of the axon in the homogeneous medium, the extracellular potential $V_{c,n}$ at the $n$th node along the axon can be calculated by:

$$V_{c,n}(t) = \frac{\rho_s}{4\pi} \left[ \frac{I_{\text{block}}(t)}{\sqrt{(n \Delta x - x_0)^2 + z_n^2}} + \frac{I_{\text{test}}(t)}{\sqrt{(n \Delta x - x_1)^2 + z_n^2}} \right]$$

where $I_{\text{block}}(t)$ is the high-frequency biphasic pulse current delivered to the block electrode (at location $x_0 = 25 \text{ mm}$, $z_0 = 1 \text{ mm}$); $I_{\text{test}}(t)$ is the single test pulse delivered to the test electrode (at location $x_1 = 5 \text{ mm}$, $z_1 = 1 \text{ mm}$).

The change of the membrane potential $V_m$ at the $n$th node is described by:

$$\frac{dV_m}{dt} = \frac{d}{dp_c} \left[ V_{c,n-1} - 2V_m + V_{c,n+1} \right] \frac{1}{\Delta x^2}$$

where

$$V_{c,n} = V_m - V_{c,n}; \quad V_m = \text{the intracellular potential at the } n \text{th node}; \quad V_{c,n} = \text{the extracellular potential at the } n \text{th node}; \quad V_m = \text{the resting membrane potential}; \quad \rho_c = \text{the resistivity of axoplasm}$$

Manuscript received June 30, 2005; revised January 6, 2006. This work was supported in part by the National Institutes of Health (NIH) under Grant 1R01-DK-068566-01, Grant 1R01-NS-045078-01, and Grant 1P01-HD-39768-02. Asterisk indicates corresponding author.

X. Zhang is with Department of Biomedical Engineering, Capital University of Medical Sciences, Beijing 100069, China. She is also with the Department of Pharmacology, University of Pittsburgh, Pittsburgh, PA 15261 USA.

J. R. Roppolo and W. C. de Groat are with the Department of Pharmacology, University of Pittsburgh, Pittsburgh, PA 15261 USA.

*Corresponding author.


[5] Changfeng Tai. X. Zhang is with Department of Biomedical Engineering, Capital University of Medical Sciences, Beijing 100069, China. She is also with the Department of Pharmacology, University of Pittsburgh, Pittsburgh, PA 15261 USA.

Manuscript received June 30, 2005; revised January 6, 2006. This work was supported in part by the National Institutes of Health (NIH) under Grant 1R01-DK-068566-01, Grant 1R01-NS-045078-01, and Grant 1P01-HD-39768-02. Asterisk indicates corresponding author.

X. Zhang is with Department of Biomedical Engineering, Capital University of Medical Sciences, Beijing 100069, China. She is also with the Department of Pharmacology, University of Pittsburgh, Pittsburgh, PA 15261 USA.

J. R. Roppolo and W. C. de Groat are with the Department of Pharmacology, University of Pittsburgh, Pittsburgh, PA 15261 USA.

*Corresponding author.
Fig. 1. Axon model to simulate conduction block induced by high-frequency biphasic rectangular pulses. The internode length $\Delta x = 100d$, $d$ is the axon diameter, $L$ is the nodal length. Each node is modeled by a resistance-capacity circuit based on the FH model. $R_a$: axoplasm resistance; $R_m$: membrane resistance; $C_m$: membrane capacitance; $V_a$: intracellular potential; $V_e$: extracellular potential.

$\Omega(m)$; $c_m$ is the capacity of the membrane ($2 \mu F/cm^2$); $I_{i,n}$ is the ionic current at the $n$th node described by FH [21]. The parameters describing the ionic current $I_{i,n}$ can be found in a previous study [17]. The model was solved by Runge-Kutta method with a time step of 0.001 ms [27] with initial condition $V_n = 0$. Sealed boundary conditions (no longitudinal currents) at the two ends of the modeled axon were used. The simulation was performed at the temperature of $37^\circ C$ or $20^\circ C$.

III. RESULTS

A. Nerve Block by High-Frequency Biphasic Pulse Current

Fig. 2 shows a typical nerve firing pattern and conduction block induced by high-frequency biphasic rectangular pulses at different stimulation intensities. The test pulse at the test electrode was applied at 3 ms after the start of the high-frequency biphasic stimulation in Fig. 2(a), (b), and (d), but was not applied in Fig. 2(c). It generated an action potential propagating toward the block electrode. At a stimulation intensity of 1 mA [Fig. 2(a)] the high-frequency biphasic stimulation (8 kHz) generated an initial action potential and failed to block the propagation of the action potential induced by the test electrode; whereas at a higher intensity [1.2 mA, Fig. 2(b)] it successfully blocked the nerve conduction. However, further increasing the intensity caused repetitive firing as shown in Fig. 2(c), although only an initial action potential was induced at other intensities [Fig. 2(a), (b), and (d)]. This repetitive firing disappeared and nerve conduction could be blocked again after the stimulation intensity increased further [5 mA, Fig. 2(d)].

B. Influence of Stimulation Frequency and Axon Diameter on Nerve Conduction Block

Fig. 3 shows the pattern of nerve block or repetitive firing at different stimulation frequencies (6–20 kHz) and intensities (0–10 mA) for axons of different diameters (2–20 $\mu m$). The repetitive firing gradually disappeared as axon diameter increased or when stimulation frequency was increased. For large axons [diameter 10–20 $\mu m$, Fig. 3(c) and (d)], high-frequency biphasic stimulation at frequencies above 8 kHz completely blocked the conduction at stimulation intensities above threshold. For small axons [diameter 2–5 $\mu m$, Fig. 3(a) and (b)], complete block occurred when the stimulation frequency was above 10 kHz. For a nerve composed of axons of different diameters (2–20 $\mu m$), blocking stimulation at a frequency between 6 and 9 kHz would block axons of certain diameters, but at the same time might cause other axons of different diameters to fire repetitively. Therefore, in order to
completely block all axons (diameter 2–20 μm) the stimulation frequency has to be greater than 10 kHz with stimulation intensity above the threshold for blocking the smallest axon (diameter 2 μm), since larger diameter axons have lower block thresholds than smaller axons (see Fig. 3). When stimulation frequency is above 10 kHz, higher frequencies require higher intensities to block conduction for small axons (diameter 2–5 μm, Fig. 3(a) and (b)). However, the threshold intensity is less influenced by stimulation frequency for large axons (diameter 10–20 μm, Fig. 3(c) and (d)). The results shown in Fig. 3 were obtained at the temperature of 37 °C. Nerve block cannot be observed at this temperature when stimulation frequency is below 6 kHz.

C. Influence of Temperature on Nerve Conduction Block

Fig. 4 shows how the intensity thresholds for a complete nerve block (i.e., without causing repetitive firing once the intensity is above the threshold) are changed for axons of diameters 10 μm and 20 μm when the temperature is decreased from 37 °C to 20 °C. The intensity thresholds are increased at a lower temperature (20 °C). However, the axons can be completely blocked by a 4-kHz stimulation at 20 °C instead of a 8-kHz stimulation at 37 °C [see, also, Fig. 3(c) and (d)].

At the temperature of 20 °C, conduction block in a small axon of diameter 2 μm can also be observed at the stimulation frequency as low as 5 kHz (intensity: 4.1–6.3 mA). However, at the same temperature a small axon of diameter 5 μm requires a stimulation frequency as high as 20 kHz (intensity: 8.8–14 mA) to induce conduction block. Failure to block the 5-μm-diameter axon at frequencies between 4 kHz and 10 kHz is due to the fact that repetitive firing is always induced by the high-frequency biphasic rectangular pulses at the temperature of 20 °C.

IV. DISCUSSION

A small axon has a higher blocking threshold than a large axon (Fig. 3). This relationship between stimulation intensity and axon diameter was also demonstrated in conduction block of frog sciatic nerve (myelinated) using 5 or 20 kHz sinusoidal stimulation [2], [5]. Our previous simulation studies using the HH model [25], [26] showed that this relationship might also exist in unmyelinated axons. Therefore, nerve conduction block induced by high-frequency biphasic stimulation in both myelinated and unmyelinated axons might exhibit the same relationship between stimulation intensity and axon diameter.

At the temperature of 37 °C, a minimal stimulation frequency of 10 kHz is required to completely block nerve conduction in small axons of diameters 2–5 μm without causing repetitive firing, while a lower minimal frequency (8 kHz) is required for large axons of diameters 10–20 μm (see Fig. 3). Within a certain range of stimulation intensity, the large axons (diameters 10–20 μm) can also be blocked at a frequency as low as 6 kHz [see Fig. 3(c) and (d)]. These results agree very well with our previous animal experiments at 35 °C–37 °C [1], [28], where the pudendal nerve of cat could be maximally blocked by high-frequency biphasic stimulation at frequencies between 6 and 10 kHz. However, stimulation frequency as low as 4 kHz has been reported previously to be effective in blocking nerve conductions of large Aβ fibers (diameter 12–22 μm) in experiments using cats [3], [4], [6]. The frequency difference between our animal experiments [1], [28] and others [3], [4], [6] might be caused by the experimental temperature. This simulation
study indicates that the minimal stimulation frequency required to completely block nerve conduction of the large axons (diameter 10–20 μm) can decrease from 8 kHz to 4 kHz when the temperature changes from 37 °C to 20 °C (see Fig. 4). The temperature around the pudendal nerve in our animal experiments was maintained by warm saline or mineral oil at 35 °C–37 °C [1, 28]. But the temperature in other studies [3], [4] varied between 25 °C and 35 °C, or was undefined [6] (presumably at room temperature 20 °C–25 °C). A recent study [2] using frog sciatic nerve at room temperature showed that nerve conduction could be blocked at a stimulation frequency as low as 2–3 kHz. But it is unfortunate that the specific room temperature was not defined in this study [2]. It is likely that a stimulation frequency of 8–10 kHz would be required instead of 4 kHz in clinical applications where stimulation is performed at body temperature (37 °C). A more detailed study of the temperature influence on nerve conduction block in animal experiments seems to be warranted by this simulation study.

This simulation study also predicts some new characteristics of electrically induced nerve blockade in myelinated axons which have not yet been shown or are difficult to show in animal experiments. For example, increasing stimulation frequency will require higher stimulation intensity to block the small myelinated axons [Fig. 3(a) and (b)], while threshold intensity is less influenced by the stimulation frequency for large myelinated axons [Fig. 3(c) and (d)]. This result has not been examined by electrophysiological experiments in animals. Our previous simulation studies [25], [26] using the HH model showed that higher stimulation frequency also requires higher stimulation intensity to block conduction in the unmyelinated axons, which agrees with the results in this study of the small myelinated axons [Fig. 3(a) and (b)]. It seems that the lowest stimulation frequency, which is high enough to induce conduction block, should be used in clinical applications in order to maximally reduce the stimulation current. Another phenomenon predicted by this simulation study is that the 5-μm-diameter axon starts to fire repetitively at the temperature of 20 °C when the high-frequency biphasic stimulation is between 4 kHz and 10 kHz, but the 2-μm-diameter axon can still be blocked. This indicates that at low temperature (20 °C) high-frequency biphasic stimulation may fail to block a few small axons of certain diameters due to the induced repetitive firing. However, it will be difficult to observe this phenomenon by recording the compound action potentials from a nerve composed of axons of different diameters [3]–[5], or by recording the induced muscle contractions [1], [2], since the response produced by a few un-blocked small axons will be very small.

The HH model [21] used in this study to simulate conduction block in myelinated axons was derived from experiments on amphibian myelinated axons. Other membrane models describing mammalian myelinated axons [22], [23] could also be used to replace the HH model in this study. Whether these mammalian membrane models [22], [23] can simulate the nerve conduction block induced by high-frequency biphasic stimulation needs to be determined. Furthermore, more complicated axon models (i.e., incorporating irregular axon geometry, imperfect insulator myelin sheath, or variable nodal length, etc.) could also be tested to see how these parameters influence the conduction block. The influence of different electrode configurations (i.e., bipolar or tripolar cuff electrodes, etc.) on the conduction block should also be analyzed since these electrodes are most commonly used in both animal experiments and clinical applications. Understanding nerve conduction block could help to design better stimulation electrodes and waveforms for electrical nerve block which may find many clinical applications [1], [2], [7]–[10].

REFERENCES


