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Modeling Analysis of Negative Effects of High Frequency Electrical Stimulation on Axonal Behaviors*

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Abstract— **High frequency biphasic (HFB) electrical stimulation were commonly used in nerve block. This study constructed a double layer amphibian axonal model to explore the negative effects possibly caused by HFB electrical stimulation. The model was based on Frankenhaeuser-Huxley (FH) equations and McIntyre-Richardson-Grill (MRG) model geometry parameters. Sodium pump and ionic diffusion mechanisms for sodium, potassium, and chloride ions were included. HFB electrical stimulation of 10 kHz at 5 mA was applied for 5 s at half the axonal length. The action potentials recorded at node three fourth of axonal length exhibited larger delays, smaller amplitudes and more positive pre-occurring resting potentials than normal ones. Changes of intracellular ionic concentrations were observed and considered as one main mechanism underlying the axonal behavior changes induced by HFB electrical stimulation. This study provides useful information about mechanism of nerve injury caused by HFB electrical blocking stimulation.**

I. INTRODUCTION

High frequency (kHz) electrical currents have been shown to be able to locally block nerve conductions in both experimental [1] and computer simulation studies [2], [3], [4], [5], [6], [7], [8], [9]. Recently, researchers have been drawn to study the possibilities of utilizing this nerve blocking method to solve neural disorder related clinical problems, such as stopping unwanted muscle movements (muscle spasms and spasticity) [10] and improving voiding efficiencies [4], [11], [12], [13], [14], [15], [16], [17], [18], etc. However, although high frequency biphasic (HFB) electrical currents are commonly used in nerve conduction blocking studies due to zero net charges introduced, the safety margin of it has not been evaluated neither in experimental nor by simulation studies.

It has been shown that long time low frequency ($<$1 kHz) electrical stimulation induced both intracellular and extracellular changes of sodium and potassium ion concentrations [19]. Since HFB electrical currents used for nerve conduction block resulted in neuronal activities of higher frequencies and magnitudes, they might be very likely to be able to cause ionic changes during their application, thus introducing negative effects to axonal functions. Clear demonstration of this possibly occurring phenomenon would enhance our understanding of nerve conduction block by high frequency electrical currents and provide useful clues for designs of more efficient and safe nerve blocking methods.

The method of modeling simulation is usually adopted in nerve conduction blocking studies and has the advantages of getting data easily for a single node of Ranvier and avoiding influences of noises in contrast to in vitro or in vivo experimental studies. In this study, one double cable axonal model based on Frankenhaeuser-Huxley (FH) equations [20] and McIntyre-Richardson-Grill (MRG) model geometry parameters [21] was constructed and used for the analyses of negative effects possibly introduced by HFB electrical stimulation.

II. METHODS

An axon (with diameter of 15 μm) model of 21 nodes with internodal compartments in between was constructed based on double cable theory. The internodal compartments consisted of explicit representations of 2 paranodal myelin attachment segments (MYSA), 2 paranodal main segments (FLUT), and 6 internodal segments (STIN), in which axolemma was modeled as conductance in parallel with capacitance and axoplasm as longitudinal conductance. Myelin sheaths around the internal compartments were aslo included and modeled as parallel combinations of resistance and capacitance. Detailed values regarding geometries of various segments and the corresponding electric equivalents of the modeled axon were the same as those used by MRG model (please see Table 1 and 2 in [21]). Membrane dynamics at nodes of Ranvier was modeled as capacitance in parallel with varialbe conductance which was described with FH equations [20]. Two single point cathodal electrodes were placed at quarter and half positions along the axon to deliver pulse train and HFB electrical current stimulus respectively. The pulse train was comprised of cathodal pulses of 0.2 ms width at 50 Hz. The HFB electrical current had symmetrical cathodal and anodal phases and started with a cathodal phase.

Other mechanisms incorporating ionic diffusion and sodium pump were introduced into the model as those in [22]. Chloride ion was also introduced as a major carrier of leakage current to balance trans-membrane ionic currents during resting state. All ion types (sodium, potassium, and chloride) were considered to have the same diffusion process which could be described with the Fick's law of dissusion: $J = D * A * (dC/dx)$, where D is the diffusion coefficient of ions, A is the cross sectional area through which diffusion

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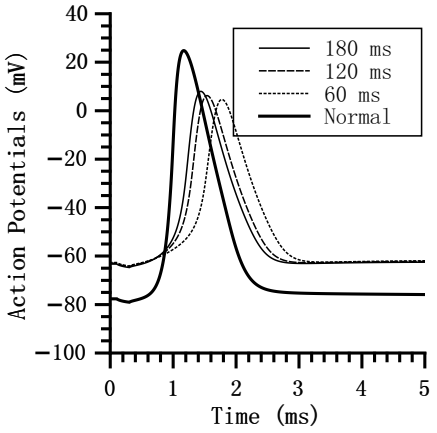

Fig. 1. Action potentials under normal condition and following cessation of 5s HFB electrical stimulation.

occurrs, dC is ionic concentration difference, and dx is the distance along ionic concentration gradients. The resting potential was set at -83 mV, at which 1) the amount of influx ions equaled the amount of efflux ions; 2) inward sodium and outward potassium currents through ionic channels equaled, respectively, the outward sodium and inward potassium currents contributed by sodium pump. At rest, both membrane potential and intra- and extra-cellular ionic concentrations kept constant.

During simulation, HFB electrical current of 10 kHz was delivered for 5 s at the amplitude of 5 mA. The activities of the modeled axon (membrane potential and ionic concentrations, etc) were recorded from two nodes at the positions right under stimulating electrode and three fourth of the axon length for further analyses.

III. RESULTS

Action potentials at node three fourth of the axonal length were plotted in Fig. 1. In contrast to the normal action potential, those obtained following cessation of 5s HFB electrical stimulation exhibited quite different shapes which varied along time. The changed action potentials were characterized by small amplitudes and larger delays to appear. These phenomena were similar to our previous experiment results on isolated frog's sciatic nerves [23]. One thing needs to be noted here is that the resting potential measured just before generation of action potentials also changed towards depolarization direction more than ten millivolts compared with the normal ones.

Detailed changes of action potentials in delay, amplitude, and pre-generation resting potential along time were further plotted in Fig. 2. The differential delay between changed and normal action potentials reached maximal positive value just after HFB electrical stimulation cessation, and became gradually smaller until to a maximal negative value, after which an approximately monotonically increasing trend of it was observed. Both amplitudes and pre-generation resting potentials of changed action potentials tended to recover to the normal values (Fig. 2b and c).

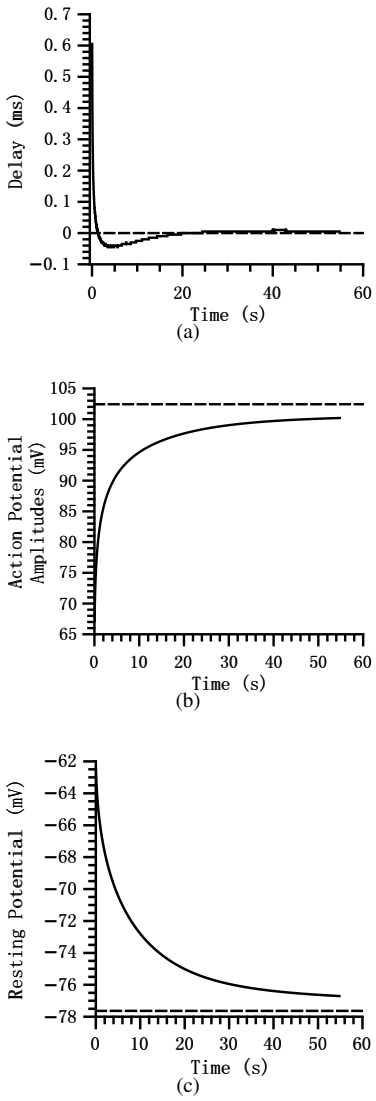

Fig. 2. Differential delay values between changed and normal action potentials (a), action potential amplitudes (b), and resting membrane potentials (c) along time following cesstion of HFB electrical stimulation. The dashed lines indicate normal values.

Further examination of membrane behaviors at the node right under HFB electrical stimulating electrode revealed that intracellular ionic (sodium, potassium and chloride) concentrations were changed dramatically from their normal values during HFB electrical stimulation as shown in Fig. 3. Although ionic currents and gating variables had quickly changing trends towards their balanced values, the intracellular ionic concentrations recovered slowly after cessation of HFB electrical stimulation (Fig. 3) and had similar time constants as changes of resting potentials (Fig. 2c) and action potential amplitudes (Fig. 2b).

IV. DISCUSSION AND CONCLUSION

In this study, a simulation model for analysis of possible negative effects introduced by HFB electrical blocking stimulation was constructed. Simulation results with this model indicated that 5 s HFB electrical stimulation caused changes

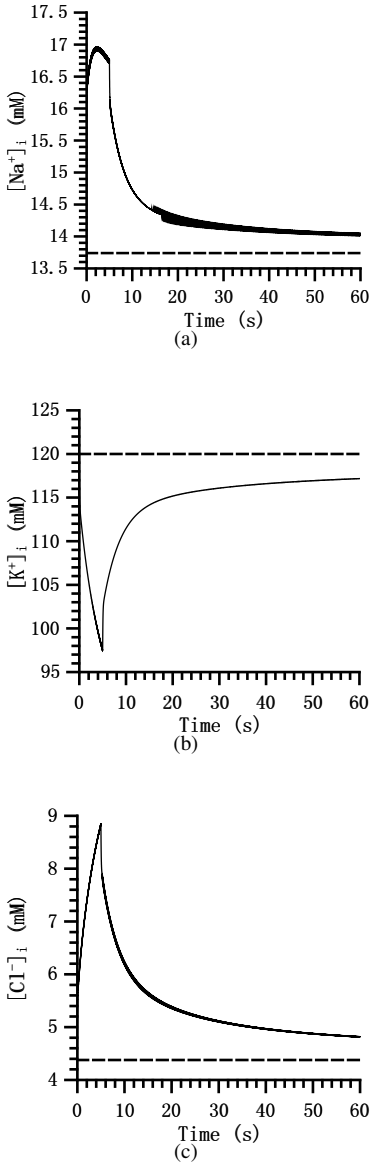

Fig. 3. Intracellular sodium (a), potassium (b), and chloride (c) concentrations at the node under electrode during and following HFB electrical stimulation. The dashed lines indicate normal values. The HFB electrical stimulation was only applied during the first 5 s.

in axonal post-stimulus behaviors. The action potentials recorded at node three fourth of axonal length exhibited larger delays, smaller amplitudes and more positive pre-occurring resting potentials. The latter two phenomena may be able to be explained by the changes of intracellular ionic concentrations induced by HFB electrical stimulation.

The results in this simulation study were similar to that in our previous experiments on isolated frog's sciatic nerves that axonal conductibility at the stimulating position following HFB electrical stimulation was decreased apparently [23]. This consistency revealed, to some extents, the possible role of intracellular ionic concentration changes in axonal injury caused by HFB electrical stimulation.

Intracellular ionic concentration changes have been demonstrated having close relations to nerve injury and may be one important problem needing to be concerned during HFB electrical stimulation. It has been shown that electrical stimulation could cause both intracellular and extracellular ionic concentration changes [19], which were usually concomitant with long lasing nerve injury such as axonal degeneration [24]. HFB electrical stimulation protocols with greater safe margins may be characterized by causing less ionic concentration changes. The model employed in this study can be used to design relatively optimized electrical nerve blocking protocols according to that principle.

Among the several changes in axonal activities induced by HFB electrical stimulation as demonstrated in this study, delays of generation of action potentials recovered most quickly in contrast to changes of resting membrane potentials and magnitudes of action potentials, and exhibited relatively complex changes, making that use of axonal excitability and conductibility as output measurements may underestimate the negative influences induce by HFB stimulation. On the other hand, recording action potentials and resting membrane potentials at nodes far from HFB electrical stimulating position, which may remain same as normal ones, may also underestimate the influences caused by HFB electrical stimulation. So, in experiments, checking intracellular ionic concentration changes may be of necessity in evaluating axonal condition.

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