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The Effect of Extracellular Potassium Concentration on Muscle Fiber Conduction Velocity Examined Using Model Simulation

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Abstract— **During fatiguing contractions muscle fiber conduction velocity (CV) decreases progressively. The exact cause of this is not yet fully known, although recent studies suggest that changes in extracellular potassium concentration play an important role. A model was developed to examine the effect of accumulation of extracellular potassium ions on the muscle fiber action potential and its CV. As the extracellular potassium concentration was increased, the action potential progressively broadened, reduced in peak-peak amplitude and its CV decreased. However, when the inward rectifier channels were blocked, the changing shape of the action potential and the reduction of its CV with increasing extracellular potassium were dramatically reduced. The simulation results support the hypothesis that the reduction in muscle fiber CV observed during sustained fatiguing contractions may be due in part, to increased accumulation of extracellular potassium ions and suggest that the inward rectifier currents play an important role on the relationships observed.**

I. Introduction

Muscle fatigue may be defined as a progressive decrease in the force-generating capacity of the muscle. It is an on-going process that begins at the onset of muscle contraction and incorporates a range of changes that take place, including a reduction in the muscle fiber conduction velocity (CV). During sustained fatiguing contractions, a progressive decrease in muscle fiber CV and consequently in the median frequency of the EMG power spectrum is observed. The reduction in both CV and the median frequency form the basis of commonly used indices of muscle fatigue [1]. Previously it has been proposed that the reduction in muscle fiber CV may be caused by changes in blood flow, the concentration of metabolic by-products such as lactic acid, creatine phosphate accumulation, pH changes and the simultaneous combination of increasing extracellular potassium and decreasing extracellular sodium concentrations [2].

Recent evidence, however, suggests that the reduction in muscle fiber CV may primarily be due to changes in ionic concentrations, in particular the accumulation of extracellular potassium ions [3], [4]. Experimental studies *in vitro* have shown a reduction in muscle fiber CV and a reduction in action potential amplitude with increasing extracellular potassium concentrations [3].

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Potassium ions are released during each action potential and accumulate during sustained muscle contraction, rising up to 9 mM during intense exercise [4]. This increase in extracellular potassium ion concentration tends to depolarize the transmembrane resting potential. Therefore, in order to maintain the resting membrane potential, the extracellular potassium ions are transported inward by means of the sodium-potassium pump and the inward rectifier current [4], [5].

An understanding of the physiological mechanisms responsible for the changes in CV during fatigue is important to enable observed changes in the surface EMG signal to be correctly interpreted, and ultimately to relate them to the muscle contractile mechanisms. While previous simulation studies have examined the effect of muscle fiber CV on the surface EMG signal, the underlying physiological mechanisms responsible for the decrease in CV have not been incorporated. Furthermore, the associated changes in the action potential waveform have not been considered.

The aim of this study was to examine the effect of variations in extracellular potassium concentration on the muscle fiber transmembrane action potential and CV. A model was developed in which specific parameters could be altered and ionic channels could be blocked to examine their individual contributions to changes in muscle fiber CV during fatiguing contractions. The model was used to examine the effect of increasing extracellular potassium concentration on the transmembrane action potential and muscle fiber CV.

II. Methods

The propagating muscle fiber action potential was simulated using a model based on previous models developed by Adrian and Peachey [6] and Wallinga *et al*., [5] using values for skeletal mouse muscle fibers.

The model consists of membrane capacitance, the sodium current, I_{Na}, the potassium delayed and inward rectifier currents, I_{DR} and I_{IR} respectively, including their inactivation processes, the chloride current, I_{Cl}, and the Na-K pump current, I_{NaK}, in both the surface membrane [5] and the tubular membrane [6]. The tubular membrane was adapted from the non-linear tubular membrane model presented in [6]. The inward rectifier and chloride currents were used to replace the leak current presented in the original Hodgkin-Huxley model [7] and the sodium-potassium pump was added in order to further stabilize the tubular and surface resting membrane potentials. These were simulated as

described in Wallinga *et al.* [5].

The surface membrane current, I_m, was defined as

$$I_m = \frac{r}{2R_i}\frac{\partial^2 V_m}{\partial x^2} = I_C + I_{ionic} + I_T \quad (1)$$

where R_i is the intracellular resistance, V_m is the transmembrane potential and I_C is the capacitive current across the membrane,

$$I_C = C_m \frac{\partial V_m}{\partial t} \quad (2)$$

I_{ionic} is the sum of the ionic currents,

$$I_{ionic} = I_{IR} + I_{DR} + I_{Na} + I_{Cl} + I_{NaK} \quad (3)$$

The ionic currents in the tubular system were defined similar to the sarcolemma ionic currents as in equations (1)-(3). The tubular system was divided into 16 concentric compartments as described by Adrian and Peachey [6].

$I^T_{ionic(j)}$ is the sum of the ionic currents in the tubular membrane in compartment j,

$$I^T_{ionic(j)} = I^T_{IR(j)} + I^T_{DR(j)} + I^T_{Na(j)} + I^T_{Cl(j)} + I^T_{NaK(j)} \quad (4)$$

and I_T is the total tubular membrane current,

$$I_T = \frac{(V_m - u_{16})}{\left(\left(\frac{1}{g_{L(16)}}\right) + R_a\right)} \quad (5)$$

where u_{16} is the voltage across the tubular membrane in the outermost compartment, and R_a is the access resistance.

Values for model parameters used in the simulation results presented are given in Table 1. The remaining values are as described in [5].

The extracellular potassium concentration was progressively increased to examine the effect on the action potential waveform and CV. Each channel was then blocked in turn, to examine its influence on the transmembrane action potential and CV at different levels of extracellular potassium concentration.

The simulations were repeated at a range of different temperatures, using a temperature scaling factor, ϕ to adjust the rate equations and the sodium and potassium conductances for the new temperature [8]. A Q_{10} value of 1.5 was used to account for the temperature dependence of the sodium and potassium conductances and a Q_{10} of 2.5 for the temperature dependence of the rate equations, as described in equation (6).

$$\phi = Q_{10}^{(T_C - 20)/10} \quad (6)$$

where T_C is the temperature (ºC).

The model was implemented in Matlab 7.0.1 (Mathworks Ltd., Cambridge, MA, USA).

TABLE I
SUMMARY OF MODEL PARAMETERS

Symbol	Unit	Description	Value
C_m	µF/cm^2	Surface membrane capacitance	0.9
g_l	mS/cm	Tubular lumen conductance	10
r	cm	Fiber radius	$20 * 10^{-4}$
Δx	cm	Length of fiber segment	$200 * 10^{-4}$
C_T	µF/cm^2	Tubular membrane capacitance	0.9
Δt	msec	Time interval	0.0001

III. RESULTS

As the extracellular potassium concentration was increased, the resting membrane potential was observed to increase as shown in Figure 1.

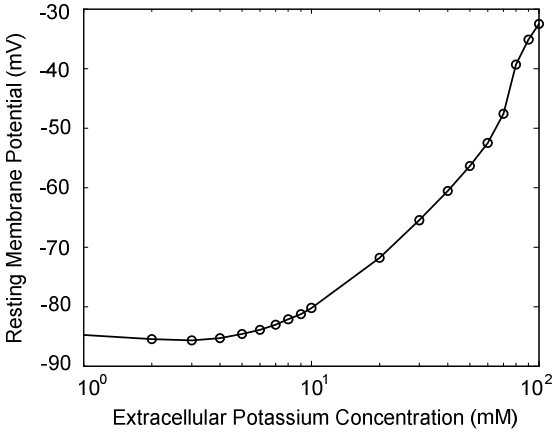

Fig. 1. The transmembrane resting potential at different levels of extracellular potassium concentration.

A progressive broadening of the transmembrane action potential and a reduction of its amplitude was also observed with increasing extracellular potassium concentration, Figure 2. For example, when the extracellular potassium concentration was increased from 5 to 10 mM, the peak-peak amplitude of the transmembrane action potential decreased from 130.08 mV to 99.92 mV at 20˚C.

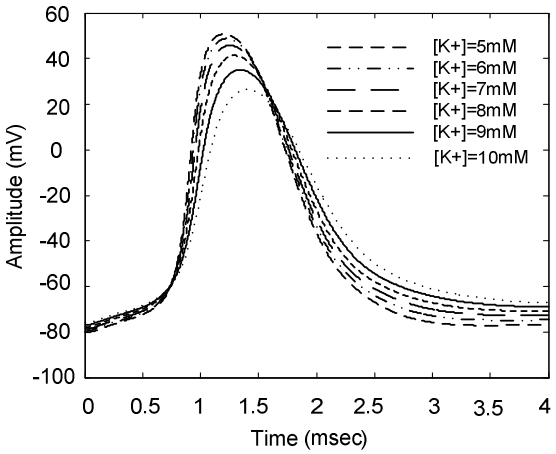

Fig. 2. Variation in the transmembrane action potential with increasing extracellular potassium concentration [K+].

Consistent with the broadening of the transmembrane potential, muscle fiber CV was observed to decrease progressively as the extracellular potassium concentration was increased, reducing from 2.64 m/s to 2.09 m/s at 20˚C as extracellular potassium concentration was increased from 5mM to 10mM, Figure 3.

This relationship between extracellular potassium and muscle fiber CV was maintained as the tubular system, the sodium-potassium pump and the delayed rectifier current were each blocked. However, when the inward rectifier channel was removed, the CV remained approximately constant as the extracellular potassium was altered, Figure 3. Similarly, the broadening of the action potential and the decrease in amplitude and CV were substantially less with increasing extracellular potassium concentration when the inward rectifier channel was blocked.

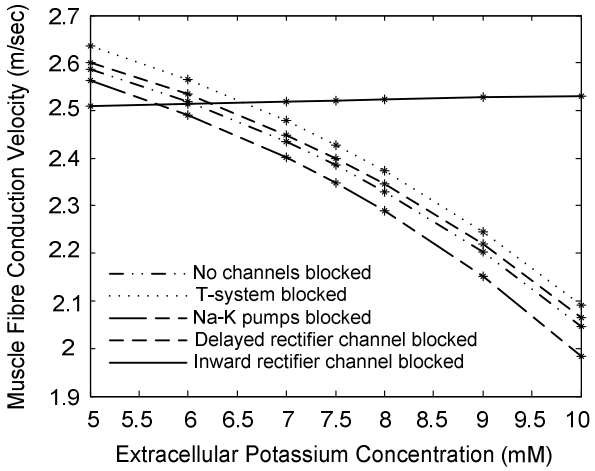

Fig. 3. The effect of increasing extracellular potassium concentration on muscle fiber CV as different channels in the model are blocked.

The sodium and delayed rectifier currents were delayed, broadened and reduced in amplitude when the extracellular potassium concentration was increased, Figure 4, as was the action potential. However, these effects were greatly reduced when the inward rectifier channel was blocked, Figure 4.

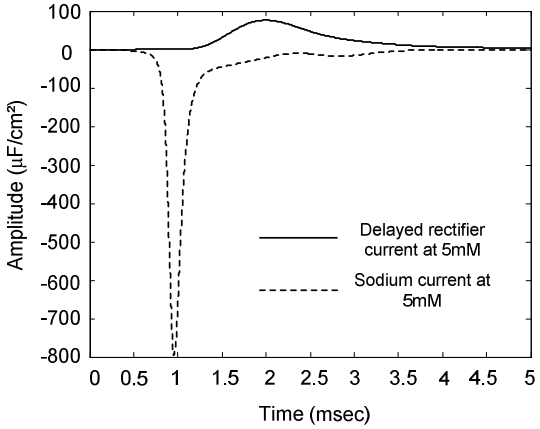

Fig. 4. (a) Simulated sodium and delayed rectifier currents for K^+ = 5 mM

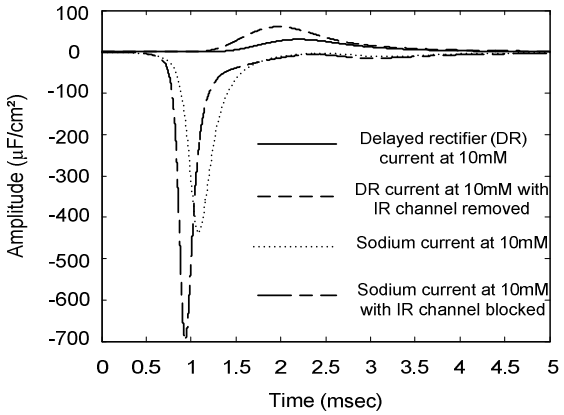

Fig. 4. (b) Simulated sodium and delayed rectifier currents for K^+ = 10 mM

A non-linear increase in muscle fiber CV was observed with increasing temperature. The dependency of CV on extracellular potassium and CV remained similar at 20ºC, 30ºC and 37ºC, Figure 5.

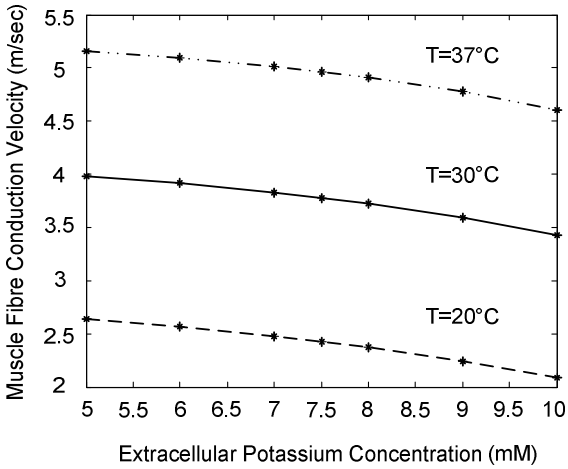

Fig. 5. The effect of increasing extracellular potassium concentration on muscle fiber CV at a range of temperatures (T).

IV. Discussion

A series of simulation studies has been presented to examine the effect of increasing extracellular potassium concentration on the transmembrane action potential and muscle fiber CV.

The transmembrane resting potential increased with increasing extracellular potassium concentration, Figure 1, consistent with previous experimental studies in frog and guinea pig skeletal muscle [9], [10].

Increasing the extracellular potassium caused a broadening of the action potential and a reduction in its amplitude and CV, Figures 2 and 3. Similar results have been observed experimentally [3], [11], [12]. In isolated muscle fibers in basic Ringers solution extracellular potassium concentration changes affected the sarcolemma action potential CV, in which a broadening of the action potential was associated with a decrease in muscle fiber CV. Increasing the extracellular potassium concentration broadened and delayed the sodium and delayed rectifier currents and reduced their amplitude, Figure 4.

In this model, the relationship between extracellular potassium concentration and muscle fiber CV was eliminated with the complete removal of the inward rectifier channel, but was maintained following the removal of the delayed rectifier channel, the sodium-potassium pump and the t-tubular system, Figure 3. This suggests that the inward rectifier current is largely responsible for the reduction in CV with changing extracellular potassium in this model.

The inward rectifier current is known to have a strong role in changes related to extracellular potassium concentration [5]. The shape of the action potential and the sodium and delayed rectifier currents showed little change for different values of extracellular potassium when the inward rectifier channel was removed, Figure 3 and 4. This is consistent with a recent study in cardiac cells, in which an increase in potassium accumulation caused a decrease in CV in ventricular myocytes but not in atrial myocytes. The increase in CV in the ventricular myocytes was eliminated by Ba^{2+}, suggesting that the increase was due to the inward rectifier channel [15].

As muscle temperature was increased, the muscle fiber CV was observed to increase non-linearly as in previous experimental studies [13], [14]. There was little change in the relationship between extracellular potassium concentration and CV, although an increase in CV was observed consistently as shown in Figure 5.

One of the main advantages of the model is that model parameters can be changed in isolation, allowing the individual mechanisms responsible for the changes observed to be identified. Furthermore, the model can be used to simulate the accumulation of extracellular potassium during sustained contraction and can be incorporated in a model of the surface EMG signal to capture changes in the transmembrane action potential during sustained contraction. However the limitations of the model should also be considered. It has been found in a recent study that more than 80% of inward rectification occurs in the t-tubules [5], [4]. However, in this study the ionic concentrations have been considered to be the same in both the sarcolemma and the tubular systems, although the conductances were scaled appropriately to account for the difference in channel densities between the sarcolemma and the tubular system. If, instead the potassium accumulation was simulated to occur predominantly in the t-tubules, the removal of the tubular system would have produced a much greater effect on the CV and shape of the action potential.

The accumulation of the extracellular potassium ions during the action potential has also not been considered and although the sodium-potassium pump has been included in this study, the model of the pump has been simplified and does not fully capture the behavior of increased pump activity with extracellular potassium accumulation. The effect of changes in the calcium gradient has not been considered although the activation of Ca^{2+} -sensitive K^+ channel, due to small depolarizations of the transmembrane resting potential caused by increasing K^+, may influence membrane properties [3]. Finally, the effect of changes in the sodium gradient on the transmembrane action potential was not examined in this study. However previous studies have found that the action potential was only slightly altered with large changes in external sodium concentration [3].

V. Conclusion

A model was developed to examine the effect of extracellular potassium concentration on the muscle fiber transmembrane action potential. The model simulation results illustrate a progressive decrease in transmembrane action potential amplitude, a broadening of the action potential and a reduction in CV with increasing extracellular potassium concentration. These simulation results follow closely the results of previous experimental studies where extracellular potassium was increased *in vitro*. The results in this study suggest that the inward rectifier has a considerable effect on the action potential shape and CV due to its sensitivity to the extracellular potassium concentration.

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