External Potassium and Action Potential Propagation in Rat Fast and Slow Twitch Muscles

F. KÖSSLER, F. LANGE, G. CAFFIER and G. KÜCHLER

Dept. of Work Physiology
Central Institute of Occupational Medicine
Nöldnerstrasse 40/42, Berlin, 1134, FRG

Abstract. The role of extracellular K^+ concentration in the propagation velocity of action potential was tested in isolated rat skeletal muscles. Different K^+ concentrations were produced by KCl additions to extracellular solution. Action potentials were measured extracellulary by means of two annular platinum electrodes. Fibre bundles of m. soleus (SOL), m. extensor digitorum longus (EDL), red (SM_R) and white (SM_W) part of m. sternomastoideus were maximum stimulated. The conduction velocity (c.v.) was calculated from the distance between the electrodes and the time delay of the potentials measured at 22°C. In Tyrode solution containing 5 mmol/l K^+, the c.v. was close to 1 $m.s^{-1}$. Bundles of the fast muscle type seemed to have a somewhat higher c.v. The differences observed in these studies were not significant. At higher temperatures, the c.v. increased (Q_{10} of approx. 2) and a dissociation between SM_R and SM_W muscles appeared. An elevation of K^+ concentration to 10 mmol/l induced a drop of the c.v. by approx. 25% and 15% in EDL and SOL muscles, respectively. After return to normal solution, the recovery was not complete within 30 min. In K^+ free solution the c.v. of EDL and SM muscles rose by a factor of 1.5, but less in SOL muscles. The weaker response of SOL to K^+ modification was related to the higher resistance of this muscle to fatigue. This suggestion was supported by experiments on fatigued fibre bundles. Immediately after a tetanic stimulation producing fatigue, the c.v. of EDL and SOL muscles dropped similarly as in 10 mmol/l K^+; again, the drop was less for SOL muscles. Adrenaline (0.5–10.0 μmol/l) enhanced both the c.v. and the twitch amplitude. The results support the suggestion that extracellular K^+ accumulation during activity is an essential factor of muscle fatigue.

Key words: Rat muscles — Fibre types — Conduction velocity — Potassium — Fatigue — Adrenaline

Introduction

The reduction of force generation in the course of muscle activity cannot be explained either by depletion of energy stores or by accumulation of lactate or a shift of pH (Edwards et al. 1977; Nassar-Gentina et al. 1978; Hultman and Spriet 1986; Sjøgaard 1987; Bergström and Hultman 1988; Cote et al. 1988; Vollestad and Sejersted 1988). Shifts of membrane resting potentials, action potential, and ion gradients have been shown to occur during muscle activity (Juel 1986, 1988 a, 1988 b). Using ion sensitive microelectrodes a fall of intracellular K^+ accompanied by a rise of intracellular Na^+ was observed after repetitive stimulation of isolated muscles (Juel 1986, 1988 b). In corresponding experiments on dog and human muscles *in situ* accumulation of interstitial K^+ from approx. 5 (resting value) to 10 mmol/l was measured (Vyskočil et al. 1983, Hník et al. 1986). Similar or even more pronounced increases of extracellular K^+ have been suggested for T-tubules (Almers 1980; Lännergren and Westerblad 1986; Howell and Oetliker 1987). The accumulation of K^+ was thought to be related to an insufficient capacity of the Na^+K^+-ATPase during long-lasting muscle activity (Clausen 1986; Sjøgaard 1987). Increased extracellular K^+ concentrations decrease the K^+ gradient across the membrane, depolarize the membrane, reduce the membrane resistance, and shift the threshold of membrane activation. The conduction velocity of the action potentials can be expected to decrease (Juel 1988 c). Also, failure of the inward spread of activation and of the neuromuscular transmission have been discussed (Pagala et al. 1984; Juel 1988 c; Glavinovic 1988). To elucidate the role of K^+ accumulation in muscle fatigue, experiments were performed on several muscle types exposed to different extracellular K^+ concentrations. Additionally, measurements of c.v. in fatigued muscles were compared with the results obtained in high K^+ solution. Effects of adrenaline which stimulates the Na^+K^+ ATPase were also studied. Preliminary results were communicated during the Second Symposium of Muscle Physiology, Reinhardsbrunn (Kössler et al. 1989) and during the XIXth Symposium on Muscle and Cell Motility, Brussels 1990.

Materials and Methods

Muscle preparation and solutions

Experiments were carried out on the following muscles of male Wistar rats weighing 250 to 450 g: m.extensor digitorum longus (EDL); m.soleus (SOL); red (SM_R) and white (SM_W) segments of m.sternomastoideus. To maintain sufficient supply of oxygen, fibre-bundles of 30 to 50 fibres were prepared immediately after dissection and stored at 2 °C and resting length (l_0) in Tyrode solution (in mmol/l: NaCl 137.0, KCl 5.0, $MgCl_2$ 1.0; NaH_2PO_4 1.0; $NaHCO_3$ 12.0; $CaCl_2$ 2.0; glucose 11.0) bubbled with carbogen gas (95% O_2, 5% CO_2), pH 7.4. The solution with elevated K^+ content was prepared by addition of KCl to give 7.5, 10 or 15 mmol/l K^+; K^+ free solution was prepared by omitting K^+. K^+-modified

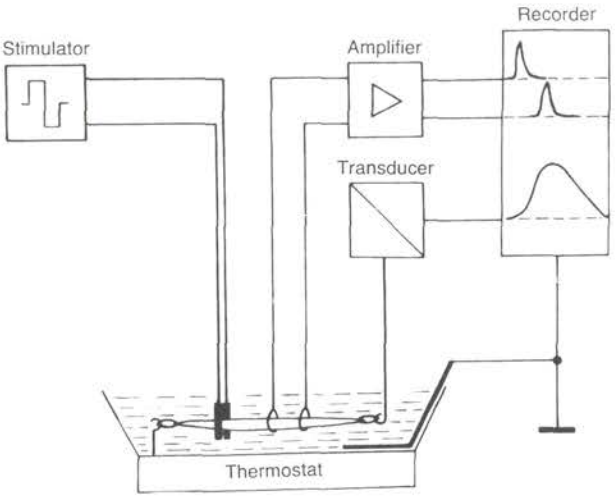

Figure 1. Schematic representation of the layout for measuring conduction velocity in isolated muscles. The perspex chamber (approx. 4 ml) contained the solution, the preparation, the stimulation and extracellular action potential measuring electrodes.

solutions were applied after a period of 30 min allowed for equilibration. The c.v. was measured before and following 2, 4, 8, 12, 16, and 20 min of exposure, as well as during 30 min of recovery in 5 mmol/l K^+. With the exception of temperature experiments, all investigations were performed at 22±1 °C. At this temperature, c.v. remained constant at least over 60 min.

Measurements of muscle contraction and conduction velocity

The fibre bundles were mounted horizontally in a perspex chamber (Fig. 1) (volume 4 ml). Solution could be exchanged within a few seconds. The chamber was inserted in a movable microscope table and was equipped with a thermostat. One end of the fibre bundle was fixed with a platinum hook to the bottom of the chamber, the other one was attached to the lever of a force transducer (RCA 5734 tube or strain gauges). The resting tension was adjusted to maximum twitch tension. Small stimulation electrodes sited close to the fixed end of the preparation were connected to a stimulator (DISA, Type 15 E) delivering supramaximal biphasic pulses of 0.2 ms duration at a frequency of 0.02 Hz. To produce muscle fatigue repeated trains of pulses, 20 s in duration (50 to 100 Hz) were used.

Extracellular action potentials were measured with two different platinum electrodes. The conduction velocity was calculated as the ratio of the distance between the two annular electrodes and the time delay of the two peaks of myoelectric signals (compound action potentials) recorded by an oscilloscope on direct printing paper. Intracellular membrane potentials were measured by the conventional microelectrode technique (Micro-Probe System M 707, W–P Instruments; glass microelectrodes, filled with 3 mol/l KCl, electrode resistance 10–30 MΩ).

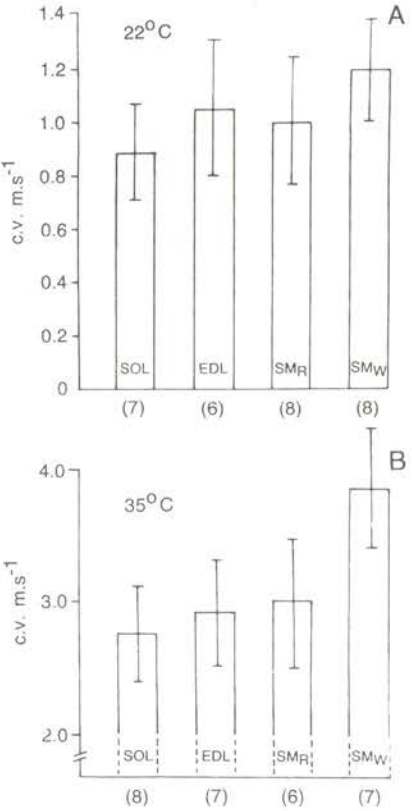

Figure 2. Conduction velocities (c.v.) of four different rat muscles (mean and SD) at 22 °C (*A*) and 35 °C (*B*). For abbreviations see Methods. Numbers of investigated muscles are given in parentheses.

Statistics

Standard statistical methods were used to estimate mean and standard deviation (SD) from the results of at least 6 tests performed under identical conditions (K^+ concentration, muscle type, temperature). U-test (Wilcoxon, Mann-Whitney) was used for the analysis, and the level of significance was set at $p=0.05$.

Results

Conduction velocity of fast and slow twitch fibre bundles

The type of the preparation (mainly fast twitch, EDL bundles, or slow twitch fibres, SOL bundles) was confirmed by recording the twitch contraction time which in SOL was three times that of EDL (Kössler and Küchler 1987). Red and white

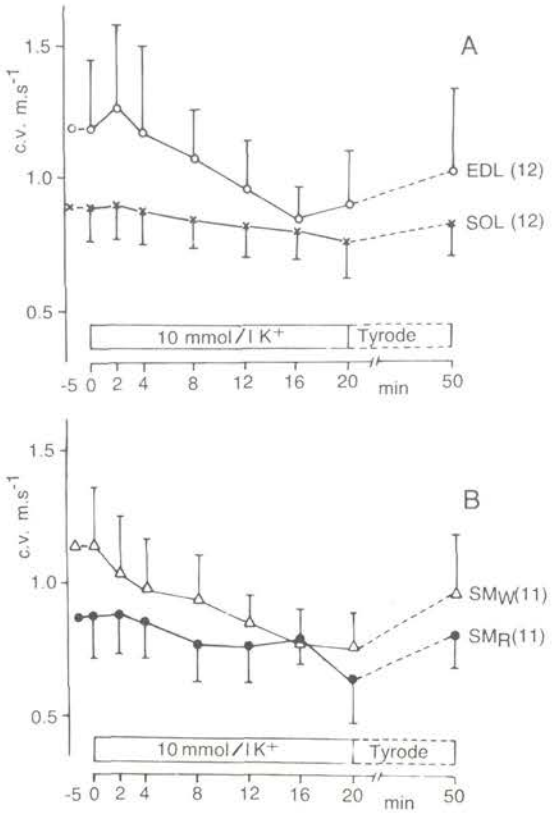

Figure 3. Effects of increased K^+ (from 5 to 10 mmol/l) on the conduction velocity (c.v) of EDL and SOL (A, n =12) and SM_W and SM_R ($B, n = 11$) muscles during 20 min of exposure at 22 °C. Initial values at −5 min; recovery in Tyrode after 30 min.

segments of SM muscles could be separated under a preparation microscope. Their twitch contraction time and fatiguability were hardly distinguishable (Dulhunty and Dlutowski 1979). The conduction velocities of the muscle types tested are illustrated in Fig. 2. Independent of the contraction time, the conduction velocity showed a tendency to higher values in EDL and SM_W muscles, but the differences were not significant. Somewhat higher differences appeared at higher temperatures (Fig. 2 *B*) but no relation to contraction time could be observed. The conduction velocity increased in parallel with the increasing temperature, with a Q_{10} value of approx. 2.0 between 20 °C and 30 °C.

Table 1. Changes of twitch amplitudes (% of control values in Tyrode solution) of rat EDL ($n = 10$) and SOL ($n = 6$) muscles during exposure for 4 to 20 min to 10 mmol/l K^+ and up to 45 min after return to Tyrode; 22 °C

Muscle	Tyrode	K^+ Incubation (min)					Tyrode (min)		
		4	8	12	16	20	15	30	45
EDL	100	99	90	83	77	72	59	56	50
		±7	±8	±6	±5	±4	±6	±10	±17
SOL	100	107	106	98	87	75	77	88	98
		±7	±13	±9	±7	±5	±11	±17	±8

Modification of external K^+

Upon increasing the K^+ concentration of the Tyrode solution from 5.0 to 7.5 mmol/l a reduction of the conduction velocity by 10–15% was observed with considerable differences between the muscles. More remarkable effects occurred after increasing the concentration to 10 mmol/l K^+. A summary of the results from these experiments is presented in Fig. 3. In 10 mmol/l K^+ the decrease of the conduction velocity was more pronounced in EDL and SM_W muscles than in SOL and SM_R muscles; 30 min after replacement of the solution the recovery was not complete. No differences in resting membrane potentials were observed between EDL and SOL muscles. In Tyrode solution, -76 ± 3 mV (4 muscles each, 40 impalements) were measured. The membrane potential measured in 5 mmol/l K^+ corresponded to -79 and -80 mV reported for the same muscles in 3.5 mmol/l K^+ (Dulhunty et al. 1987). Upon rising the K^+ concentration from 5 to 10 mmol/l, the cells were depolarized to -63 ± 3 mV. In the presence of 5 mmol/l K^+ the membrane potential returned to the initial values within about 15 min.

In parallel with the slowing down of the conduction velocity the amplitudes of the compound action potentials were diminished and the rate of rise was reduced. An increase to 15 mmol/l K^+ accelerated the flattening of action potentials, and this complicated the analysis.

The twitch amplitudes measured simultaneously with the action potentials were reduced in high K^+ solution by 20–30%. The decrease after 20 min in 10 mmol/l K^+ seemed somewhat deeper in EDL muscles but recovery occurred in SOL muscles only (Table 1). In contrast to the absence of any effect of high K^+ on the time to peak, the half relaxation time—a sensitive indicator of muscle fatigue—was prolonged by approx. 25% in EDL but less than by 10% in SOL muscles.

In K^+ free solution higher values of conduction velocity were measured. With EDL muscles the increase was almost 50%, but it was weaker in SOL (Fig. 4*A*). After returning to 5 mmol/l K^+, all muscle types showed full recovery within 30 min (Fig. 4 *A*, *B*, *C*). In contrast to the rise of the conduction velocity in K^+-

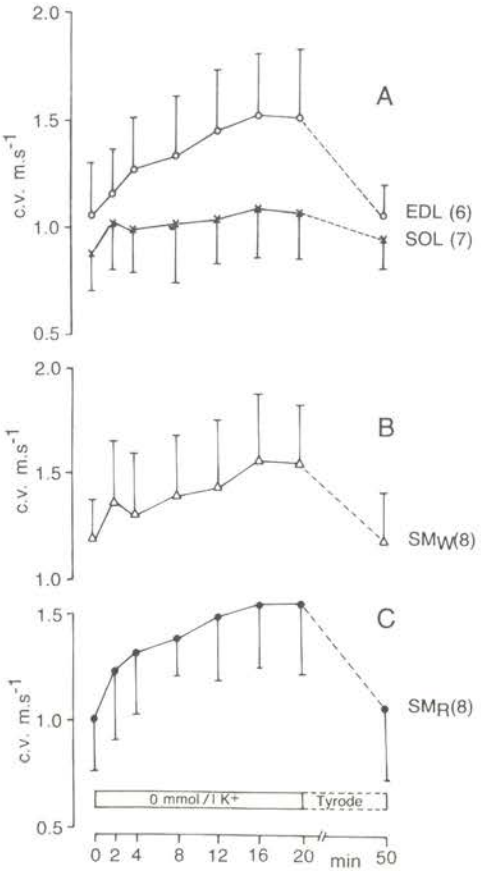

Figure 4. Effect of decreased K^+ in the bath solution (from 5 to 0 mmol/l) on the conduction velocity (c.v.) of EDL and SOL(*A*), SM_W (*B*), and SM_R (*C*) muscles during 20 min and after 30 min recovery in normal Tyrode (mean and SD, $n = 6 - 8$), 22 °C. Values at 0 min are values prior to solution exchange.

free solution the twitch amplitudes dropped by approx. 20% in all muscles. The changes were reversible, again better in SOL muscles. The time parameters of twitches remained almost unchanged in K^+-free solution.

Tetanic stimulation and conduction velocity

To compare the effect of K^+ increase observed in the present experiments with that reported for K^+ accumulation during muscle activity, the isolated muscles were stimulated tetanically by three trains of pulses (50 Hz, 20 s) separated by 1 s intervals. The conduction velocity was measured before the tetanus, immediately

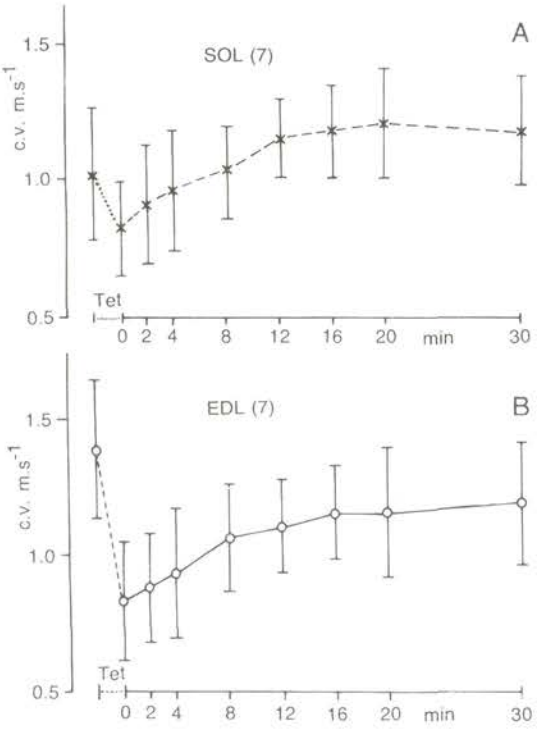

Figure 5. Conduction velocities (c.v.) of SOL (*A*) and EDL (*B*) muscles before and immediately after tetanic stimulation (Tet, 3 × 20 s, 50 Hz) and during 30 min of recovery, 22 °C; mean and SD of 7 experiments.

after the third train, and during 20 min of recovery. At the end of the last tetanus the contraction amplitude reached approx. 1% and 40% of the initial tension for EDL and SOL muscles, respectively. The decrease of the conduction velocity was of the same order of magnitude as that induced by 10 mmol/l K^+; again, it was smaller in SOL than in EDL muscles (Fig. 5). In contrast to the fast recovery and even acceleration of the conduction velocity in SOL muscles, EDL muscles did not reach complete recovery within 30 min.

Stimulation by adrenaline

Catecholamines released during muscular activity *in vivo* support the K^+ re-uptake in order to sustain the K^+ homeostasis. For the present study it was of interest to investigate whether adrenaline *in vitro* might have any effect on the c.v. and on the twitch amplitude. Concentrations of 0.1 μmol/l adrenaline were just above the threshold for the stimulation of c.v. and twitch tension; 0.5 to 10.0 μmol/l

Table 2. Conduction velocity (c.v., $m.s^{-1}$ and %) and twitch amplitudes (F, % of control in Tyrode) of rat EDL and SOL muscles after 20 min exposure to 0.5–10.0 μmol/l adrenaline; means and SD of n preparations, 22 °C

Adrenaline	EDL				SOL			
μmol/l	n	c.v. ($m.s^{-1}$)	(%)	F(%)	n	c.v. ($m.s^{-1}$)	(%)	F(%)
0	4	1.41 ±0.17	100	100	3	1.20	100	100
0.5	4	1.87 ±0.20	133	151 ±27	3	1.34	112	114
0	6	1.72 ±0.31	100	100	5	1.19	100	100
5.0	6	2.05 ±0.25	119	132 ±16	5	1.59 ±0.15	134	152 ±36
0	5	1.43 ±0.37	100	100	7	0.97 ±0.17	100	100
10.0	5	1.64 ±0.37	115	114 ±28	7	1.29 ±0.20	133	124 ±19

markedly enhanced c.v. and the twitch tension (Table 2). As the enhancing effect of adrenaline was opposite to that of 10 mmol/l K^+, a combination of both was tested. In 10 mmol/l K^+ plus 10 μmol/l adrenaline the decrease of c.v. was not attenuated but, after the return to Tyrode the recovery was facilitated, in particular in EDL muscles.

Discussion

Relation to fibre type

Despite the clear differences in the speed of contraction between EDL and SOL fibres (Kössler and Küchler 1987) there was only a small and insignificant difference in the conduction velocity between EDL and SOL muscles at 22 °C. At 35 °C a significantly higher propagation velocity of the action potential was obtained in SM_W muscles. Using a similar temperature and intracellular microelectrodes Juel (1988 c) measured in mouse muscle somewhat higher values in EDL fibres compared with SOL fibres.

A correlation of conduction velocity with the fibre type was considered on the basis of a larger diameter of fast twitch fibres. These differences were not consistent in all investigations and they seem to depend on the age of the animals. In some cases variations of fibre diameter was much greater than that of conduction velocity (Sadoyama et al. 1988). Small differences in ionic concentrations and elec-

trical membrane properties between fast and slow twitch fibres (Luff and Atwood 1972; Juel 1986; Dulhunty et al. 1987) were thought to be a reason for different conduction velocities. In the present investigations identical resting membrane potentials were measured for all muscle types and similar diameters were supposed for EDL and SOL fibres in accordance with literary data (Gollnick et al. 1972; Sadoyama et al. 1988). In contrast, cross-sectional areas of SM_R and SM_W fibres differ by a factor of 2 (Dulhunty and Dlutowski 1979). This difference may influence the membrane resistance and the length constant of the fibre resulting in a higher conduction velocity of SM_W muscles at 35 °C. On the other hand, it should be considered that conduction velocity may respond differently under supramaximal electrical stimulation of isolated muscles compared with the *in situ* conditions where the recruitment of fibre types depends on the effort.

K^+ accumulation and muscle fatigue

Muscle fatigue is a process including changes in metabolic pathways and membrane related functions (Dawson et al. 1980; Hultman et al. 1986; Bergström and Hultman 1988; Kushmerick and Meyer 1985; Bigland-Ritchie and Woods 1984; Pagala et al. 1984; Westerblad and Lännergren 1986; Bianchi and Narayan 1982). Also, reduction of cross-bridge cycling has been discussed (de Haan et al. 1989). A mechanism of fatigue at the neuromuscular junction could be excluded by comparing the development of fatigue during indirect and direct stimulation (Roed 1988). This result supports the conclusion that the mechanism underlying fatigue can be expected to be localized distal to the motor endplate.

Changes of EMG (Roed 1988) and of the resting membrane potential (Juel 1986) suggest that this mechanism may be located, at least partly, in the sarcolemma and/or superficial T-tubules. Extracellular potassium ions accumulated during fatigue may modify these structures. A disturbation of E-C coupling has been discussed as a consequence of calcium and/or potassium accumulation in T-tubules which occurs during repetitive activity (Howell and Oetliker 1987). A reduction or failure of conduction velocity along the muscle fibre was postulated. T-tubules and triads of EDL and SOL fibres differ in their morphometric data as well as in their electrophysiological parameters (Dulhunty 1984; Dulhunty et al. 1986). Therefore, the force development in EDL muscles might be more vulnerable to K^+. Some papers (Kwiecinski et al. 1984; Glavinovic 1988; Juel 1988 c) have posed the question whether increased K^+ may change membrane currents and c.v. The decreased propagation and the broadening of the action potential in 10 mmol/l K^+ suggest a slowdown of the regenerative processes of the action potential along the muscle fibre.

The doubling of the K^+ concentration of the solution in the present experiments was comparable to that occurring during intensive muscle activity *in situ* (Hník et al. 1986). The intensity of changes of conduction velocity induced by

increased K^+ correlated with the muscle resistance to fatigue. The responses to both the increased and the decreased K^+ content of the solution were stronger in EDL than in SOL muscles. A greater sensitivity of EDL muscles to K^+ was also observed by Juel (1988 c). Depolarization of the sarcolemma and a decrease of membrane resistance induced by K^+ ions were described earlier (Hodgkin and Huxley 1952; Adrian 1956; Zachar 1971).

The differences in the sensitivity of the different muscle types to K^+ need not be related to different depolarization. Comparative studies of various external K^+ concentrations showed the same degree of depolarization in EDL and SOL muscles (Dulhunty 1980, Fig. 7 therein). In the present studies, the depolarization by approx. 13 mV induced in 10 mmol/l K^+ could partly be responsible for the reduced c.v. and force development. However, it should be emphasized that 1) depolarization occurred faster than depression of c.v. and twitch contraction; 2) the depolarization was similar in both muscle types but there were differences in c.v.; 3) in Tyrode, the depolarization reversed within 10 to 15 min, whereas c.v. and the twitch tension required longer intervals to recover, or the recovery was incomplete. Other membrane functions should also be considered, e.g. Na^+,K^+-ATPase. Higher concentrations of this enzyme important for the ionic balance were found in mouse slow twitch than in fast twitch muscles (Clausen 1986). Moreover, the stimulation of the Na^+-K^+ pump by catecholamines was more pronounced in rat SOL than in EDL muscles (Everts et al. 1988). The known rise of plasma catecholamines during exercise may favour the re-uptake of K^+ released by excitation processes. At stimulation frequencies higher than 5 per second the net loss of K^+ exceeded the maximum capacity of the pump (Clausen 1986). As a consequence, K^+ accumulated within the interstitium during tetanic stimulation (Sreter 1963; Vyskočil et al. 1983; Hník et al. 1986). This accumulated external K^+ may have similar effects on the conduction velocity as did increased K^+ concentration of the Tyrode solution in the present studies. Investigations on stimulated muscles showed approximately the same decrease of the conduction velocity as measured in 10 mmol/l K^+, again, greater in EDL than in SOL muscles.

The adrenaline induced increases of c.v. and twitch amplitudes (Table 2) might be the consequence of Na^+,K^+-ATPase stimulation. The rise of c.v. was similar to that observed in 0 mmol/l K^+ solution (Fig. 4) but opposite to that in high K^+ or during tetanic contractions. Simultaneous application of K^+ and adrenaline could only improve the restoration processes. The results support the concept that K^+ accumulation during muscle activity contributes to muscle fatigue. The mechanisms involved may concern electrophysiological deterioration as well as the capacity of the Na^+-K^+ pump.

References

Adrian R. H. (1956): The effect of internal and external potassium concentration on the membrane potential of frog muscle. J. Physiol. (London) **133**, 631—658

Almers W. (1980): Potassium concentration changes in the transverse tubules of vertebrate skeletal muscle. Fed. Proc. **39**, 1527—1532

Bergström M., Hultman E. (1988): Energy cost and fatigue during intermittent electrical stimulation of human skeletal muscle. J. Appl. Physiol. **65**, 1500—1505

Bianchi C. P., Narayan S. (1982): Muscle fatigue and the role of transverse tubulus. Science **215**, 295—296

Bigland-Ritchie B., Woods J. J. (1984): Changes in muscle contractile properties and neuronal control during human muscular fatigue. Muscle Nerve **7**, 691—699

Clausen T. (1986): Regulation of active Na^+-K^+ transport in skeletal muscle. Physiol. Rev. **66**, 542—580

Cote C., White T. P., Faulkner J. A. (1988): Intramuscular substrate depletion and fatiguability of soleus grafts in rats. Can. J. Physiol. Pharmacol. **66**, 829—832

Dawson H. J., Gadian D. G., Wilkie D. R. (1980): Mechanical relaxation rate and metabolism studied in fatiguing muscle by phosphorus nuclear magnetic resonance. J. Physiol. (London) **299**, 465—484

de Haan A., Jones D. A., Sargeant A. J. (1989): Changes in velocity of shortening power output and relaxation rate during fatigue of rat medial gastrocnemius muscle. Pflügers Arch. **413**, 422—428

Dulhunty A. F. (1980): Potassium contractures and mechanical activation of mammalian skeletal muscles. J. Membrane Biol. **57**, 223—233

Dulhunty A. F. (1984): Heterogeneity of T-tubule geometry in vertebrate skeletal muscle fibres. J. Muscle Res. Cell Motil. **5**, 333—347

Dulhunty A. F., Dlutowski M. (1979): Fiber types in red and white segments of rat sternomastoideus muscle. Amer. J. Anat. **156**, 51—62

Dulhunty A. F., Gage P. W., Lamb G. D. (1986): Differential effects of thyroid hormone on T-tubules and terminal cisternae in rat muscles: an electrophysiological and morphometric analysis. J. Muscle Res. Cell Motil., **7**, 225—236

Dulhunty A. F., Gage P. W., Lamb G. D. (1987): Potassium contractures and asymmetric charge movement in extensor digitorum longus and soleus muscles from thyrotoxic rats. J. Muscle Res. Cell Motil. **8**, 289—296

Edwards R. H. T., Hill D. K., Jones D. A., Merton P. A. (1977): Fatigue of long duration in human skeletal muscle after exercise. J. Physiol. (London) **272**, 769—778

Everts M. E., Retterstøl K., Clausen T. (1988): Effects of adrenaline on excitation-induced stimulation of the sodium-potassium pump in rat skeletal muscle. Acta Physiol. Scand. **134**, 189—198

Glavinovic M. I. (1988): Changes in miniature end-plate currents due to high potassium and calcium at the frog neuromuscular junction. Synapse **2**, 636—643

Gollnick P. D., Armstrong R. B., Saubert IV C. W., Piehl K., Saltin B. (1972): Enzyme activity and fiber composition in skeletal muscle of untrained and trained men. J. Appl. Physiol. **33**, 312—319

Hník P., Vyskočil F., Ujec E., Vejsada R., Rehfeldt H. (1986): Work-induced potassium loss from skeletal muscles and its physiological implications. In: Biochemistry of Exercise VI, (Saltin E. (ed.)) Int. Ser. Sport Sci., 16, pp. 345—363, Hum. Kin. Publ., Champaign, I 11.

Hodgkin A. L., Huxley A. F. (1952): The dual effect of membrane potential on sodium conductance in the giant axon of Loligo. J. Physiol. (London) **133**, 631—658

Howell J. N., Oetliker H. (1987): Effects of repetitive activity, ruthenium red, and elevated extracellular calcium on frog skeletal muscle: implication for T-tubule conduction. Can. J. Physiol. Pharmacol. **65**, 691—696

Hultman E., Spriet L. (1986): Skeletal muscle metabolism, contraction force and glycogen utilization during prolonged electrical stimulation in humans. J. Physiol. (London) **374**, 493—501

Hultman E., Spriet L. L., Söderlund K. (1986): Biochemistry of muscle fatigue. Biomed. Biochim. Acta **45**, 97—106

Juel C. (1986): Potassium and sodium shifts during *in vitro* isometric muscle contractions, and the time course of the ion gradient. Pflügers Arch. **406**, 458—463

Juel C. (1988 a): Intracellular pH recovery and lactate efflux in mouse soleus muscles stimulated *in vitro*: the involvement of sodium/proton exchange and a lactate carrier. Acta Physiol. Scand. **132**, 363—371

Juel C. (1988 b): The effect of β_2-adrenoceptor activation on ion-shifts and fatigue in mouse soleus muscles stimulated *in vitro*. Acta Physiol. Scand. **134**, 209—216

Juel C. (1988 c): Muscle action potential propagation velocity changes during activity. Muscle Nerve **11**, 714—719

Kössler F., Küchler G. (1987): Contractile properties of fast and slow twitch muscles of the rat at temperatures between 6 and 42 °C. Biomed. Biochim. Acta **46**, 815—822

Kössler F., Lange F., Caffier G., Küchler G. (1989): Changes of the conduction velocity of isolated muscles induced by altered external potassium concentration. Biomed. Biochim. Acta **48**, 465—470

Kushmerick H. J., Meyer R. A. (1985): Chemical changes in rat leg muscle by phosphorus nuclear magnetic resonance. Amer. J. Physiol. **248**, C542—C549

Kwiecinski H., Lehmann-Horn F., Rüdel R. (1984): Membrane currents in human intercostal muscle at varied extracellular potassium. Muscle Nerve **7**, 465—469

Lännergren J., Westerblad H. (1986): Force and membrane potential during and after fatiguing, continuous high frequency stimulation of single *Xenopus* muscle fibres. Acta Physiol. Scand. **128**, 359—368

Luff A. R., Atwood H. L. (1972): Membrane properties and contraction of single fibres in the mouse. Amer. J. Physiol **222**, 1435—1440

Nassar-Gentina V., Passoneau J. V., Vergara J. L., Rapoport S. I. (1978): Metabolic correlates of fatigue and recovery from fatigue in single frog muscle fibres. J. Gen. Physiol. **72**, 593—606

Pagala M. K. D., Namba T., Grob D. (1984): Failure of neuromuscular transmission and contractility during muscle fatigue. Muscle Nerve **7**, 454—464

Roed A. (1988): Fatigue during continuous 20 Hz stimulation of the rat phrenic nerve diaphragm preparation. Acta Physiol. Scand. **134**, 217—221

Sadoyama T., Masuda T., Miyata H., Katsuta S. (1988): Fibre conduction velocity and fibre composition in human vastus lateralis. Eur. J. Appl. Physiol. Occup. Phys. **57**, 767—771

Sjøgaard G. (1987): Muscle fatigue. Medicine Sport Sci. **26**, 98—109

Sreter F. A. (1963): Cell water, sodium, and potassium in stimulated white and red mammalian muscles. Amer. J. Physiol. **205**, 1295—1298

Vollestad N. K., Sejersted O. M. (1988): Biochemical correlates of fatigue. Eur. J. Appl. Physiol. Occup. Phys. **57**, 336—347

Vyskočil F., Hník P., Rehfeldt H., Vejsada R., Ujec E. (1983): The measurement of the K_e^+ concentration changes in human muscles during volitional contractions. Pflügers Arch. **399**, 235—237

Westerblad H., Lännergren J. (1986): Force and membrane potential during and after fatiguing, intermittent tetanic stimulation of single *Xenopus* muscle fibres. Acta Physiol. Scand. **128**, 369—378

Zachar J. (1971): Electrogenesis and Contractility in Skeletal Muscle Cells. Univ. Park Press, London

Final version accepted May 20, 1991