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Changes in intracellular ion activities induced by adrenaline in human and rat skeletal muscle*

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Abstract. To study the stimulating effect of adrenaline (ADR) on active Na^+/K^+ transport we used double-barrelled ion-sensitive micro-electrodes to measure the activities of extracellular K^+ (aK_e) and intracellular Na^+ (aNa_i) in isolated preparations of rat soleus muscle, normal human intercostal muscle and one case of hyperkalemic periodic paralysis (h.p.p.). In these preparations, bath-application of ADR (10^{-6} M) resulted in a membrane hyperpolarization and transient decreases aK_e and aNa_i which could be blocked by ouabain (3×10^{-4} M). In the h.p.p. muslce a continuous rise of aNa_i induced by elevation of aK_e to 5.2 mM could be stopped by ADR. In addition, the intracellular K^+ activity (aK_i), the free intracellular Ca^{2+} concentration (pCa_i) and intracellular pH (pH_i) were monitored in rat soleus muscle. During ADR aK_i increased, pH_i remained constant and intracellular Ca^{2+} apparently decreased. In conclusion, our data show that ADR primarily stimulates the Na^+/K^+ pump in mammalian skeletal muscle. This stimulating action is not impaired in the h.p.p. muscle.

Key words: Ion activities – Na^+/K^+ pump – Adrenaline – Skeletal muscle – Hyperkalemic periodic paralysis

Introduction

Catecholamines have a facilitating action on the active Na^+/K^+ transport in striated muscle (Clausen 1986). This stimulating effect is relevant for the K^+ homeostasis in skeletal muscle. In humans, hyperkalemia induced by either work or KCl infusion is accentuated by propanolol and reduced by phentolamine (Williams et al. 1985) or by epinephrine (Rosa et al. 1980). In patients suffering from hyperkalemic periodic paralysis (h.p.p.) hyperkalemia can be suppressed by inhalation of salbutamol (Wang and Clausen 1976; Clausen et al. 1980).

Most of the data concerning catecholamine-induced modulation of muscular K^+ homeostasis was obtained by flame photometry or radioactive tracer studies. At present, no information is available about the behaviour of the ion activities in mammalian and, especially, in human skeletal muscle in the presence of catecholamines. Therefore, we have measured the activities of extracellular K^+ (aK_e) as well as intracellular Na^+ (aNa_i) with double-barrelled ion-sensitive micro-electrodes in rat soleus muscle, in normal human intercostal muscle, and in one case of h.p.p. In addition, the intracellular K^+ activity (aK_i), the free intracellular Ca^{2+} concentration (pCa_i) and intracellular pH (pH_i) were measured in the rat muscle during adrenaline (ADR), in order to see possible effects of catecholamines on ion transport mechanisms other than the Na^+/K^+ pump.

The data show that im mammalian skeletal muscle ADR mainly affects the Na^+ and K^+ activities as a result of Na^+/K^+ pump stimulation. This facilitating action of ADR is not impaired in muscle fibers of one patient suffering from h.p.p.

Materials and methods

The experiments were performed on isolated preparations of rat soleus muscle, of normal external intercostal muscle from patients without muscle diseases who had to undergo thoracic surgery and of external intercostal muscle from one patient who had suffered from attacks of hyperkalemic periodic paralysis (h.p.p.). The clinical and laboratory findings of this patient and his relatives have been described previously (Camacho 1984). The patient gave informed consent for an external intercostal muscle biopsy to be taken. The specimen was obtained under general anaesthesia without the use of muscle relaxants. The study was approved by the Ethics Commission of the Technical University of Munich and carried out in abidance with the Helsinki-convention.

The preparations were placed into a perspex chamber (volume 2 ml) and superfused at 37° C with a solution of the following composition (concentrations in mM): NaCl 118, KCl 3, $NaHCO_3$ 25, NaH_2PO_4 1.2, $MgCl_2$ 1.0, $CaCl_2$ 1.5 and glucose 10 (gassed with 95% O_2, 5% CO_2; pH 7.4). A high K^+ solution was obtained by addition of 4 mM KCl to the standard solution. In the NH_4Cl solution 15 mM NaCl was substituted by NH_4Cl. ADR, tetrodotoxin (TTX) and ouabain were added to the superfusion fluid (all chemicals in this study were purchased from Sigma, Munich, FRG).

The methods for the construction and calibration of the double-barrelled ion-sensitive micro-electrodes are described in detail elsewhere (Ballanyi et al. 1984; Grafe et al. 1985). In brief, theta-capillaries were pulled with a Brown-Flaming type micro-electrode puller (Sutter Instrument Co., San Francisco, CA, USA). Silanization of one barrel with hexamethyldisilazane (Sigma) was performed at 400° C for

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* Parts of the results have been presented to the German Physiological Society (Ballanyi and Grafe 1987)

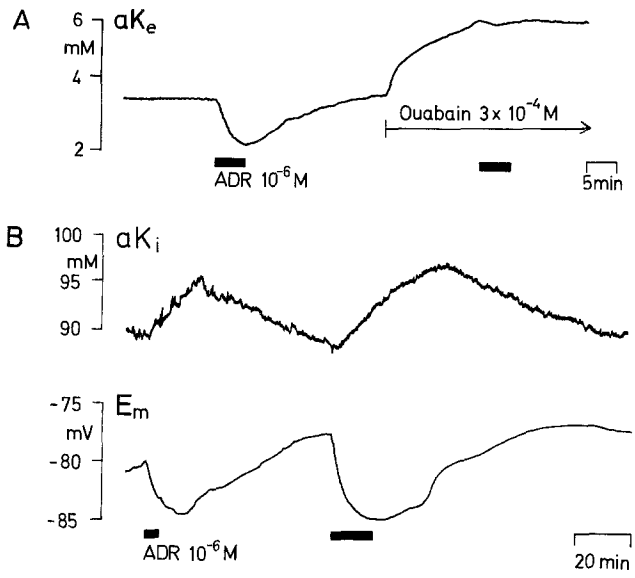

Fig. 1. A Effects of adrenaline (*ADR*) on extracellular K^+ activity (aK_e) in rat soleus muscle. Bath-application of ADR (10^{-6} M) resulted in a transient decrease of aK_e. In the presence of ouabain (3×10^{-4} M) the aK_e decrease was blocked. **B** Effects of ADR on intracellular K^+ activity (aK_i) and membrane potential (E_m) in rat soleus muscle. Two applications of ADR via the bathing solution showed the same effect: transient aK_i increases were accompanied by a membrane hyperpolarization

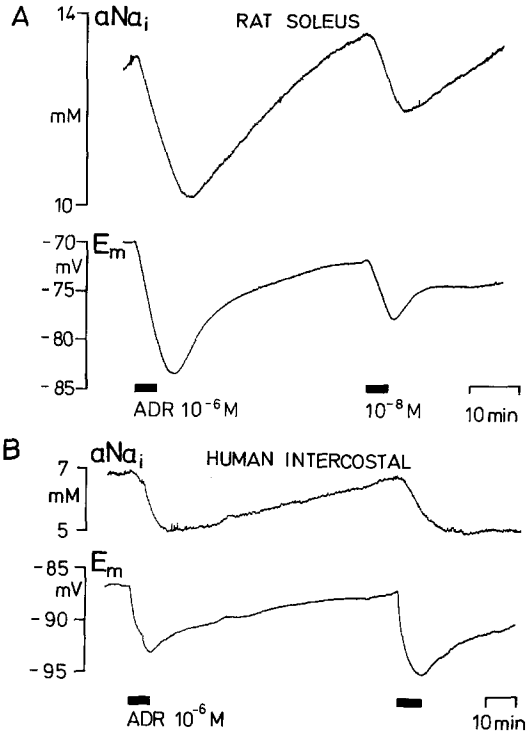

Fig. 2A, B. Effects of adrenaline (*ADR*) on intracellular Na^+ activity (aNa_i) and membrane potential (E_m) in rat soleus (**A**) and human intercostal muscle (**B**). In both, rat and human muscles ADR (10^{-6} M, 5 min) produced very similar hyperpolarizations and transient decreases of aNa_i. Note, that in the rat muscle 10^{-8} M ADR also had a clearly detectable effect on E_m and aNa_i. The kinetics of the aNa_i decreases with respect to the ADR induced membrane hyperpolarizations was considerably variable for each muscle fiber (compare Figs. 2, 3 and 4). Such differences are probably due to the intracellular position of the electrodes or to the volume of individual muscle fibers

20 min. During this period nitrogen was applied under pressure to the other barrel in order to prevent the silane from entering. Later on, a drop of liquid ion exchanger was injected into the silanized barrel, which was then backfilled with an internal reference solution. The reference barrel was filled with electrolyte solution (1 M Mg-acetate). The following combinations of ion-exchanger and backfilling solution were used: K^+-sensitive micro-electrodes (Corning 477317, 200 mM KCl); Na^+-sensitive micro-electrodes (Fluka 71176, 200 mM NaCl); Ca^{2+}-sensitive micro-electrodes (Fluka 21048, 200 mM $CaCl_2$); pH-sensitive micro-electrodes (Fluka 82500, KH_2PO_4 40 mM + NaOH 23 mM + NaCl 15 mM).

K^+-sensitive electrodes were calibrated in solutions containing 3, 12 and 60 mM KCl with a constant background of 150 mM NaCl. The mean values for the slope and the selectivity coefficient versus Na^+ were 53.3 ± 4.6 mV and 0.019 ± 0.007 (mean $\pm$ standard deviation, $n = 21$). Na^+-sensitive electrodes were calibrated by comparison of the Na^+ signal in the physiological solution with solutions containing different Na^+ concentrations (1, 3, 12, 30 and 60 mM) with a variable background of K^+ to keep the sum of Na^+ and K^+ at 150 mM. The Ca^{2+} concentration in these calibration solutions was buffered to 10^{-7} M to imitate the Ca^{2+} contribution to the Na^+ signal during impalement. Interference of the Na^+ measurements with Ca^{2+} is negligible as intracellular Ca^{2+} concentration is about 10^{-7} M in skeletal muscle (Weingart and Hess 1984; this study). All values of intracellular Na^+ and K^+ and of extracellular K^+ (aNa_i, aK_i, aK_e) are given in activities assuming an activity coefficient of 0.74 for these ions. The Ca^{2+}-sensitive electrodes were calibrated in terms of free ion concentrations according to calibration solutions given by Tsien and Rink (1981). The Ca^{2+}-electrodes had slopes between 27 and 30 mV at pCa 3–6, between 15 and 24 mV at pCa 6–7, and between 5 and 11 mV at pCa 7–8. Individual calibration curves were plotted for each electrode. The electrodes were also tested for their sensitivity to Na^+. Changing Na^+ from 5 to 10 mM at pCa 7 resulted in a voltage change of the Ca^{2+}-electrodes by about 1 mV indicating an apparent increase of Ca^{2+} (see Fig. 5B). pH-sensitive electrodes were calibrated in different buffer-solutions (HEPES-buffer: pH 7.7; PIPES-buffer: pH 6.7 and TAPS-buffer: pH 8.4). The pH-electrodes had slopes between 56 and 60 mV. Intracellular impalements were achieved by means of a piezo driven micro-manipulator (built by M. Frankenberger, Munich, FRG).

Results

Effects of adrenaline on extra- and intracellular K^+ activities

Rat soleus muscle. The extracellular K^+ activity (aK_e) was measured with double-barrelled ion-sensitive micro-electrodes in 14 fiber bundles of rat soleus muscle. In some fiber bundles resting aK_e was slightly higher than in the bulk solution probably due to K^+ leakage from injured muscle fibers. In all bundles bath-application of 10^{-6} M adrenaline (ADR, 5 min) revealed a transient decrease in aK_e of 0.9 ± 0.3 mM (mean $\pm$ standard deviation). An example for

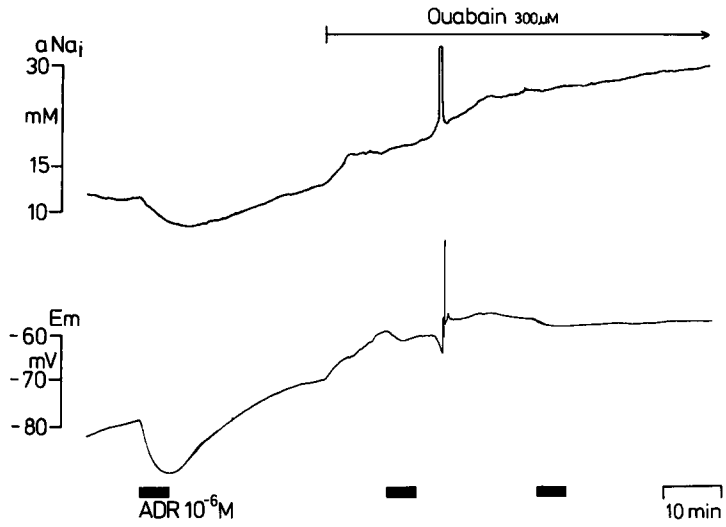

Fig. 3
Effects of ouabain on adrenaline (*ADR*) induced changes of membrane potential (E_m) and intracellular Na^+ activity (aNa_i) in rat soleus muscle. ADR (10^{-6} M, 5 min) resulted in a hyperpolarization of about 12 mV and an aNa_i decrease of 3 mM. After recovery from ADR, ouabain (3×10^{-4}M) was added. E_m depolarized by 15 mV and reached a stable value at -55 mV after about 25 min. In contrast, a continuous rise of aNa_i could be observed in the presence of ouabain. An interpretation of the effects of the first ADR application during ouabain is not possible because of an unstable recording situation. The following application revealed an almost complete blockage of the ADR induced hyperpolarization and aNa_i decrease. The blockage of the hyperpolarization was not due to the ouabain dependent depolarization as the ADR hyperpolarization was not impaired in muscle fibers with low resting potentials or in fibers that were depolarized by elevation of extracellular K^+

such a measurement is given in Fig. 1 A. In the beginning of the recording aK_e decreased from about 3 to 2 mM during ADR. After the recovery of aK_e ouabain (3×10^{-4} M) was added. aK_e baseline increased to 6 mM as a result of Na^+/K^+ pump inhibition. In the presence of ouabain the ADR-induced aK_e decrease was blocked. The mean intracellular K^+ activity (aK_i) as measured in 10 muscle fibers with an average membrane resting potential (E_m) of -78 ± 2.8 mV was 96.9 ± 9.5 mM. ADR (10^{-6} M, 5 min) resulted in an aK_i increase of 4.03 ± 1.8 mM in these fibers accompanied by a membrane hyperpolarization of 8.5 ± 3.1 mV. Figure 1 B illustrates two subsequent applications of ADR. The 16 min superfusion with ADR led to a prolongation of the hyperpolarization as well as of the aK_i increase with respect to the 5 min ADR-application in the beginning of the recording.

Human intercostal muscle. aK_e during ADR was also measured in 5 fiber bundles of normal human intercostal muscle (5 different preparations) and in one case of hyperkalemic periodic paralysis (h.p.p.). ADR (10^{-6} M, 5 min) produced a mean aK_e decrease of 0.27 ± 0.12 mM in normal human muscle. In the h.p.p. muscle very similar aK_e decreases during ADR could be observed (see upper trace in Fig. 4).

Effects of adrenaline on intracellular Na^+ activity

Rat soleus muscle. The mean intracellular Na^+ activity (aNa_i) as measured in 11 fibers of rat soleus muscle with a mean E_m of -79.2 ± 5.4 mV was 11.5 ± 2.4 mM. During ADR (10^{-6} M, 5 min) aNa_i in these fibers transiently decreased by 1.73 ± 0.9 mM accompanied by a membrane hyperpolarization of 11 ± 2.9 mV. Figure 2A shows that 10^{-8} M ADR produced a smaller hyperpolarization and aNa_i decrease with respect to 10^{-6} M ADR applied in the beginning of the recording. In 4 cells tested ouabain (3×10^{-4} M) blocked both the ADR-induced hyperpolarization and the aNa_i decrease as illustrated in Fig. 3.

Human intercostal muscle. aNa_i in 6 fibers of normal human intercostal muscle (3 different preparations) with a mean E_m of -81.8 ± 3.8 mV was 9.6 ± 1.2 mM. ADR (10^{-6} M, 5 min) hyperpolarized these fibers by 9.8 ± 2.2 mV and decreased aNa_i by 2.3 ± 1.1 mM. Figure 2B illustrates the effects of two subsequent applications of ADR on E_m and aNa_i.

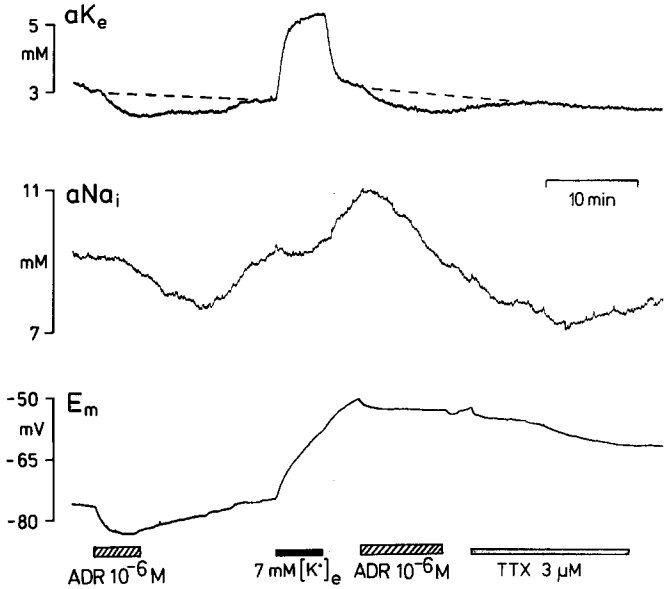

Fig. 4. Effects of adrenaline (*ADR*) on membrane potential (E_m) and the activitites of extracellular K^+ (aK_e) and intracellular Na^+ (aNa_i) in an intercostal muscle fiber of a patient with hyperkalemic periodic paralysis (h.p.p.). ADR (10^{-6} M, 5 min) decreased aK_e and aNa_i and hyperpolarized E_m. A short-time increase of the K^+ concentration of the superfusion-fluid to 7 mM elicited an excessive depolarization and aNa_i increase. In this situation, ADR could stop the depolarization and decreased aNa_i below its resting level. Subsequently, tetrodotoxin (TTX) was applied to restore resting potential (see Lehmann-Horn et al. 1987)

Effects of adrenaline on aK_e and aNa_i in human h.p.p. muscle

aK_e, aNa_i and E_m were measured simultaneously in fiber bundles of human intercostal muscle from a patient with hyperkalemic periodic paralysis (h.p.p.). In the beginning of Fig. 4 it is shown that ADR (10^{-6} M, 5 min) produced the typical effects on aK_e, aNa_i and E_m. A subsequent increase of the K^+ concentration of the superfusion fluid to 7 mM

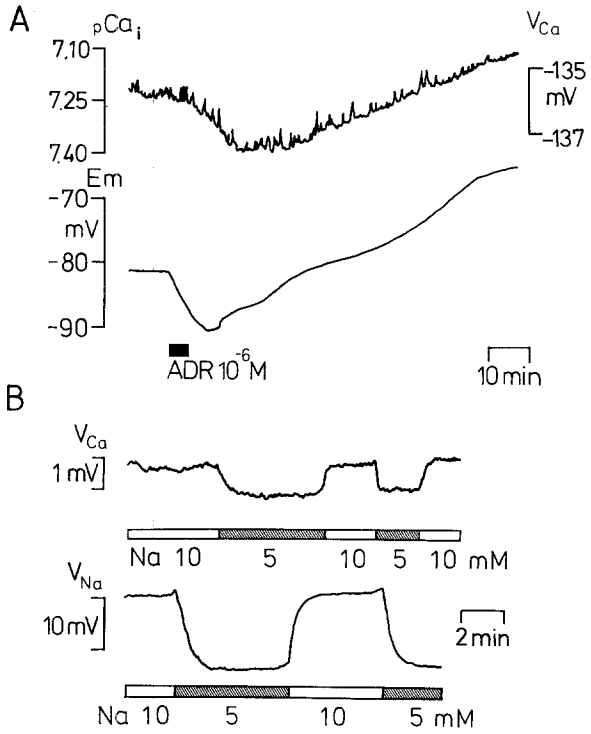

Fig. 5A, B. Effects of adrenaline (*ADR*) on intracellular free Ca^{2+} concentration (pCa_i) and membrane potential (E_m) in rat soleus muscle. **A** ADR (10^{-6} M, 5 min) resulted in a hyperpolarization of about 10 mV accompanied by a change of the difference signal of the Ca^{2+}-sensitive micro-electrode from about -136 to -138 mV indicating a decrease of intracellular Ca^{2+}. **B** Testing of the Na^+ sensitivity of a typical Ca^{2+}-sensitive (*upper trace*) and Na^+-sensitive micro-electrode (*lower trace*) in solutions with pCa 7 and 5 or 10 mM Na^+ concentration. The Ca^{2+}-electrode responded with 1 mV to the change between 5 and 10 mM Na^+ whereas the Na^+-electrode responded with the typical voltage jump of about 15 mV

elicited an excessive depolarization and an aNa_i increase, which is typical for h.p.p. muscle (Lehmann-Horn et al. 1987). ADR, applied in this situation, reversed the aNa_i increase into the typical aNa_i decrease. Due to the long depolarization tetrodotoxin only slowly restored E_m in this h.p.p. muscle fiber.

Effects of adrenaline on intracellular Ca^{2+} and pH in rat soleus muscle

The free intracellular Ca^{2+} concentration (pCa_i) as measured in 6 rat soleus muscle fibers with an average E_m of -82.7 ± 2.5 mV was 6.84 ± 0.33 as derived from a mean intracellular difference signal of the Ca^{2+}-sensitive micro-electrodes (V_{Ca}) of -129.7 ± 6.1 mV. This pCa_i value corresponds to a free intracellular Ca^{2+} concentration of 145 nM. In the presence of ADR (10^{-6} M, 5 min) V_{Ca} decreased by 1.8 ± 0.09 mV indicating an apparent decrease of intracellular Ca^{2+}. An example of such measurements is given in Fig. 5A. Due to interference of the Ca^{2+}-sensitive resin with Na^+ some portion of the Ca^{2+} signal during ADR might result from the transient decrease of aNa_i (compare Fig. 2A). V_{Ca} is changing by about 1 mV in test solutions with 5 and 10 mM Na^+ (pCa 7) as illustrated in Fig. 5B. However, one observation argues for a real decrease of intracellular Ca^{2+} during ADR. In most cases the observed fall

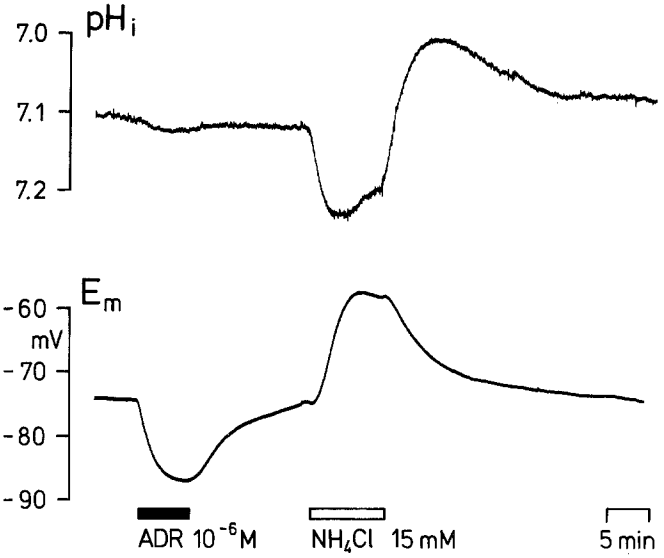

Fig. 6. Effects of adrenaline (*ADR*) on intracellular pH (pH_i) and membrane potential (E_m) in rat soleus muscle. In spite of a prominent hyperpolarization, pH_i remained constant during ADR (10^{-6} M, 5 min). The sensitivity of the pH-sensitive micro-electrode was tested by superfusing the muscle with a solution containing 15 mM NH_4Cl which is known to cause a biphasic alkaline-acid going shift of pH_i

in aNa_i in the presence of ADR was considerably smaller than 5 mM. Nevertheless, V_{Ca} changes were almost twice as large compared to the voltage reading of a Ca^{2+}-sensitive micro-electrode when the Na^+ concentration decreased from 10 to 5 mM (see Discussion).

Intracellular pH (pH_i) as measured in 7 rat soleus muscle fibers with a mean E_m of -76 ± 2.9 mV was 7.04 ± 0.37. During ADR (10^{-6} M, 5 min) pH_i in these fibers remained constant despite of the typical ADR-induced hyperpolarization of 8.8 ± 1.4 mV. Figure 6 illustrates that application of 10^{-6} M ADR had almost no effect on intracellular pH although this muscle fiber hyperpolarized by more than 10 mV. In contrast, superfusion with a solution containing 15 mM NH_4Cl had the typical effects on pH_i (Thomas 1984). An initial alkalinization was followed by an acidification after the washout of NH_4Cl.

Discussion

In the present study measurements of extra- and intracellular ion activities were used to investigate the catecholamine-induced stimulation of the Na^+/K^+ pump in rat soleus muscle, in normal human intercostal muscle and in one case of hyperkalemic periodic paralysis (h.p.p.). The ion activities that were primarily affected by the action of adrenaline (ADR) were aNa_i, aK_i and aK_e. The observed decreases of aK_e and aNa_i as well as the membrane hyperpolarization during ADR were very similar in these preparations. In addition, ADR resulted in an increase of the intracellular K^+ activity (aK_i) as measured in rat soleus muscle. These results confirm earlier measurements of cellular Na^+ content, serum K^+ concentrations, and of Na^+ and K^+ fluxes in rat soleus muscle (Dockry et al. 1966; Clausen and Flatman 1977, 1980; Pfliegler et al. 1983). Furthermore, the magnitude of the average decreases of aNa_i (1.73 mM in rat soleus

and 2.3 mM in human intercostal muscle) very closely resembled catecholamine-induced decreases of $a\mathrm{Na}_i$ as measured with Na^+-sensitive micro-electrodes in different heart tissues as dog heart Purkinje and ventricular trabecular muscle fibers (Wasserstrom et al. 1982), canine Purkinje fibers (Lee and Vasalle 1983) and isolated myocytes of the rabbit (Désilets and Baumgarten 1986). In contrast, in sheep heart Purkinje fibers noradrenaline leads to a small $a\mathrm{Na}_i$ increase (Glitsch and Rasch 1986). A quantitative comparison of the $a\mathrm{Na}_i$ and $a\mathrm{K}_i$ changes in this study with intracellular concentration changes of Na^+ and K^+ as calculated from flux measurements is difficult because of controversies concerning the intracellular activity coefficients, especially for Na^+, in muscle tissue (MacDermott 1984).

The close relationship between the time courses of the observed Na^+ and K^+ activity and membrane potential changes favours a stimulation of the electrogenic Na^+/K^+ pump as the ionic mechanism for the effects of ADR as proposed for the majority of previous investigations (Clausen 1986). A shift of the K^+ equilibrium potential towards a more negative value also contributes to the membrane hyperpolarization during ADR (Clausen and Flatman 1977). An increase of the K^+ permeability by catecholamines (Zemkova et al. 1985) is not likely as such an effect should result in an, at least initial, decrease of $a\mathrm{K}_i$ and an increase of $a\mathrm{K}_e$. $a\mathrm{Na}_i$ according to this assumption, should not decrease but increase during ADR due to an increased driving force for Na^+ facilitating Na^+ entry into the muscle fibers. Furthermore, the decreases of $a\mathrm{K}_e$ and $a\mathrm{Na}_i$ as well as the hyperpolarization could be blocked by ouabain, a specific inhibitor of the Na^+/K^+ pump.

In the h.p.p. muscle an elevation of the extracellular K^+ concentration to 7 mM elicited an excessive membrane depolarization and a continuous $a\mathrm{Na}_i$ increase similar to observations in intercostal muscle fibers of a different h.p.p. patient (Lehmann-Horn et al. 1987). In this situation, ADR could restore $a\mathrm{Na}_i$ resting level. This stimulating effect of ADR is in accordance with other studies on h.p.p. (Wang and Clausen 1976; Clausen et al. 1980; Bendheim et al. 1985) and indicates that the Na^+/K^+ pump is not impaired in this muscle disease as proposed by Brooks (1969). However, ADR did not completely repolarize the membrane in spite of a return of $a\mathrm{K}_e$ and $a\mathrm{Na}_i$ to normal levels. This supports the idea that an abnormal increase in a TTX-sensitive Na^+-conductance may be the primary cause for the excessive membrane depolarization seen in h.p.p. muscle fibers (Lehmann-Horn et al. 1987).

Previous reports established an involvement of Ca^{2+} in catecholamine-elicited hyperpolarization in skeletal muscle (Kozachuk and Phillis 1978). Therefore, intracellular Ca^{2+} ($p\mathrm{Ca}_i$) was measured in rat soleus muscle. The interpretation of the observed apparent decrease of intracellular Ca^{2+} during ADR is complicated by the sensitivity of the Ca^{2+} sensor (Fluka 21048) for Na^+. The Ca^{2+}-sensitive micro-electrodes responded to calibration solutions with 5 and 10 mM Na^+ concentration (pCa7) with a voltage-signal of 1 mV. The average change of the intracellular Ca^{2+} signal during ADR was 1.8 mV. As the observed decreases of $a\mathrm{Na}_i$ in soleus muscle were considerably smaller than 5 mM (1.73 mM) the contribution of Na^+ to the Ca^{2+} signal should be less than 1 mV. Several mechanisms could be responsible for a decrease of muscular Ca^{2+} during ADR. A Na^+/Ca^{2+} exchange normally extruding cellular Ca^{2+} by use of the energy stored in the transmembraneous Na^+ gradient would be stimulated by a decrease of $a\mathrm{Na}_i$. The opposite mechanism i.e. an increase of cytosolic free calcium due to an inhibition of Na^+/K^+ pump has been reported for rat ventricular myocytes (Sheu et al. 1984). Alternatively, Ca^{2+} could be taken up into the sarcoplasmic reticulum as it is known for heart tissue. The Ca^{2+} measurements argue against the hypotheses that catecholamines in mammalian skeletal muscle lead to a release of Ca^{2+} from intracellular stores like sarcoplasmic reticulum or mitochondria (Rasmussen and Clausen 1982) or significantly increase intracellular Ca^{2+} concentration as a result of an enhanced probability of single Ca^{2+} channel activation as suggested by Zemkova et al. (1985).

Using pH-sensitive micro-electrodes no changes of intracellular pH (pH_i) could be detected in rat soleus muscle during ADR. Therefore, stimulation of the Na^+/K^+ pump by ADR does not seem to be accompanied by a massive energy consumption and subsequent lactate production as it is the case in working muscle (Steinhagen et al. 1976). This is in accordance with the finding that the total energetic cost of active Na^+/K^+ transport remains low even during stimulation with ADR (Chinet and Clausen 1984).

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