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Research Institute for the Biology of Farm Animals (FBN), Dummerstorf, Germany

ULRICH KÜCHENMEISTER, MARTINA LANGHAMMER, ULLA RENNE, GERD NÜRNBERG and KLAUS ENDER

Effect of exercise on sarcoplasmic reticulum Ca^{2+} transport in muscle of mouse lines long-term selected for different performance traits

Dedicated to Prof. Dr. Dr. h. c. mult. Horst Kräußlich on the occasion of his 75th birthday

Summary

Mouse lines used were long-term selected for high (DU-hTP) or low treadmill performance (DU-lTP), or high locomotor open field activity (DU-hOF). The control line DU-Ks was maintained unselected. For each line 30 mice were used at 42 days of age. All lines were split into three groups: the first group was investigated without running exercise, the second had to run 500 m, and the third had to run until exhaustion on the treadmill. Compared to mice without running, in exhausted mice the maximal rate of SR Ca^{2+} uptake of the *m. rectus femoris* decreases were only found in the mouse lines DU-lTP, and DU-hOF (28.5 %, and 36.3 %, respectively; $p<0.05$). The effect of the 500 m run was significant ($p<0.05$) in DU-hTP, but not in the other lines. An effect of exhausting exercise on Ca^{2+} ATPase was detected only in DU-hOF with increased values after the exhaustive run. The hypothesis, that exercise induced alterations in Ca^{2+} transport in muscle of mice selected for high activity (DU-hOF) or high running performance (DU-hTP) are attenuated compared to mice which were not selected (DU-Ks) or selected for low performance (DU-lTP), could not be verified.

Key Words: mouse, selection, exercise, muscle, sarcoplasmic reticulum, calcium, adenosine triphosphatase

Zusammenfassung

Titel der Arbeit: **Auswirkung physischer Belastung auf den Ca^{2+} Transport im Muskel von Mäusen, die auf verschiedene Leistungsparameter selektiert wurden**

In dem Experiment wurden Mäuse verwendet, die über 67 bis 99 Generationen auf hohe (DU-hTP) oder niedrige Laufbandleistung (DU-lTP) oder hohe Open-Field-Aktivität (DU-hOF) selektiert worden sind. Bei der Kontrollinie DU-Ks erfolgte keine Selektion. Je Linie wurden 30 Mäuse im Alter von 42 Tagen verwendet. Es erfolgte eine Aufteilung der Tiere jeder Linie in drei Gruppen: die erste Gruppe wurde ohne zusätzliche Belastung untersucht, die zweite nach einem 500 m Lauf und die dritte nach einem Lauf bis zur Erschöpfung. Die maximale Rate der Ca^{2+} Aufnahme durch das sarkoplasmatische Retikulum (SR) des *m. rectus femoris* war gegenüber der in den Gruppen ohne Lauf nur bei den Mäuselinien DU-lTP und DU-hOF verringert (um 28,5 % und 36,3 %; $p<0,05$). Nach dem 500 m Lauf zeigte sich eine verringerte Ca^{2+} Aufnahme nur bei der Linie DU-hTP. Auf die SR-Ca^{2+} ATPase hatte nur der Lauf bis zur Erschöpfung und nur in der Linie DU-hOF einen Effekt mit einer Erhöhung der ATPase-Aktivität.

Die Hypothese, dass hohe physische Aktivität bei den auf hohe Laufleistung oder hohe Aktivität selektierten Mäusen geringere Veränderungen im Ca^{2+} Transport im Muskel gegenüber dem in unselektierten oder auf geringe Laufleistung selektierten Mäusen hervorrufen würde, konnte nicht bestätigt werden.

Schlüsselwörter: Maus, physische Aktivität, Muskel, sarkoplasmatisches Retikulum, Calcium, ATPase

Introduction

Prolonged physical activity of moderate intensity to high intensity leads to skeletal muscle fatigue. Several mechanisms have been proposed to be responsible for the

force decline (GREEN, 1997). Muscle damage (BYRD, 1992), characterised by Z-band streaming, myofibrilar disorganisation (FRIDEN et al., 1983), and membrane disruption (YASUDA et al., 1997) can all be exercise-induced. Reactive oxygen species produced during strenuous skeletal muscle work contribute to the development of muscle fatigue (DIAZ et al., 1998). The accumulation of metabolic by-products affects different cellular events (FAVERO et al., 1995), and glycogen depletion as well as an inappropriate low activity of the Na^+,-K^+ pump (CLAUSEN and NIELSEN, 1994) are associated with fatigue during prolonged exercise.

There is evidence that alterations in intracellular Ca^{2+} handling play a major role in the fatigue process (WILLIAMS and KLUG, 1995; FAVERO, 1999). Reduced Ca^{2+} handling of the sarcoplasmic reticulum (SR) has been shown following high intensity exercise of horses (BYRD et al., 1989a), in stimulated frog muscles (WILLIAMS et al., 1998), in exhaustively exercised rats (SEMBROWICH and GOLLNICK, 1977), and exercised man (GOLLNICK et al., 1991). Ca^{2+} handling is fibre-type specific (BYRD et al., 1989b) and depends on exercise duration (SEMBROWICH and GOLLNICK, 1977; BYRD et al., 1989b). Inhibited SR Ca^{2+} release has been identified as a relevant factor in the fatiguing muscle (FAVERO et al., 1993; FAVERO, 1999), probably caused by metabolic end products (FAVERO et al., 1995). Although most investigations indicate a decline of the SR Ca^{2+} transport by exercise, some investigators found no alterations. Ca^{2+} ATPase and Ca^{2+} uptake of rat soleus and gastrocnemius homogenates were unaffected by intermittent running (DOSSETT-MERCER et al., 1994). A short term stimulation elicited no change in Ca^{2+} uptake in white or red rat gastrocnemius tissues but increased Ca^{2+} ATPase activity in white gastrocnemius tissues (DOSSETT-MERCER et al., 1995). With eccentric exercise there were no differences before and after exercise in SR Ca^{2+} uptake, whereas the ATPase activity was increased (ENNS et al., 1999).

Exercise training increases physical fitness (MADSEN et al., 1994), but the effect on the SR Ca^{2+} transport is ambiguous. In trained and non trained rats there was no difference in SR Ca^{2+} uptake either at rest or after exhaustive exercise, but the Ca^{2+} ATPase activity was increased in exhausted muscle of trained rats (BONNER et al., 1976). Intense training did not affect skeletal muscle Ca^{2+} ATPase concentration in human (MADSEN et al., 1994). However, sprint conditioning of horses attenuated the decrease in the calcium transfer rate and in the Ca^{2+} ATPase activity (WILSON et al., 1998), and high-resistance training attenuated exercise induced decreases in SR Ca^{2+} ATPase activity (GREEN et al., 1998). It is suggested that exercise training can retard the onset of fatigue by an attenuation of a disturbance of the Ca^{2+} transport (GREEN et al., 1998; WILSON et al., 1998).

Selection is another way to influence characters of animals. The mouse lines used in this investigation were long-term selected for high or low running performance on a treadmill, or high locomotor open field activity, respectively, with an appreciable selection success (indicated in Tab. 1). The objective of this study was to determine the effect of this selection on Ca^{2+} transport and Ca^{2+} ATPase activity of the skeletal muscle SR at rest, during defined run activity, and after exhaustive exercise with the hypothesis that the effect of exercise on the rate of SR Ca^{2+} uptake in mice selected for high locomotor activity or high running performance is lower than in mice unselected

or selected for low locomotor activity.

Materials and Methods

Animals and exercise

The experiments were carried out in the Mouse Laboratory of the Research Institute for the Biology of Farm Animals in Dummerstorf and based on the outbred strain Fzt:DU, which has been obtained in 1969/1970 by systematic crossbreeding of 4 inbred and 4 outbred lines (SCHÜLER, 1985; RENNE et al., 1985). Four different mouse lines were used. Selection parameters were: high (DU-hTP) or low (DU-lTP) running performance in a treadmill, and high locomotor activity in an open field (line DU-hOF). The selection for high/low treadmill performance resulted in an increase/decrease of the running performance of about 180%/71%, and the open field activity increased by about 110% (Tab. 1).

Table 1
Characterization of mouse lines and responses to long-term selection for different traits (Charakterisierung der Mauslinien und Erfolge der Langzeitselektion)

Line	Generation	Selection trait	Selection response		
			start	end	change (%)
DU-Ks *	98	randomly mated	28.7 g	31.3 g	9
DU-hTP	67	high treadmill performance	1020 m	2875 m	182
DU-lTP	67	low treadmill performance	933 m	266 m	- 71
DU-hOF	68	high locomotor open field activity	37.3 m	78.7 m	111

* the group DU-Ks was randomly mated, the selection response is shown as change in body weight

At the day of exercise all mice were 42 ± 2 days of age. Altogether 120 female mice were used, with 30 mice per selection line. One third of each mouse line was assigned as control without exercise (Con), the second had to run 500 m on a treadmill (500 m), and the third had to run until exhaustion (Exh). The rationale for the 500 m run was to compare the effects of identical loads (same running speed and interval) opposed to the exhaustive run (with expected different running distances) on the investigated parameters. In each of the three activity groups within the lines full sibs were investigated. Because of their refusal to run six mice had to be excluded from the evaluations. For standardising the treadmill test the mice were running only in the morning (8.00 to 10.00 a.m.). The treadmill test was a computer controlled submaximal test. Mice ran on the treadmill (10 % incline) at a rate of about 22.8 m min^{-1} (start speed: 15 m min^{-1}, final speed: 38 m min^{-1}) according to a special test plan (RENNE et al., 1997). The test stop depended on remaining of the mice on the stimulating equipment of the treadmill.

Sample preparation

The animals were killed by cervical dislocation either without exercise (Con) or immediately after exercise (500 m; Exh), the skin was removed, and the *m. rectus femoris* from both legs were excised. The muscles were freed of fat and as far as possible of connective tissue, immediately frozen in liquid nitrogen, and stored at -70° C. The time interval from the end of exercise to sample freezing was no longer than 5

min. Later, the samples were thawed, finely minced with scissors, and homogenised with a glass/glass Potter-Elvejem type homogeniser in 9 vol of 100 mM KCl, buffered with 20 mM MOPS (pH 7.5), filtered through 3 layers of cheese cloth, and used for immediate measurements of Ca^{2+} uptake and SR Ca^{2+}ATPase. The protein content of the homogenates was estimated by a modified biuret method (GORNALL et al., 1949), using bovine serum albumin as standard.

Ca^{2+} uptake and Ca^{2+} ATPase activity

The rate of Ca^{2+} uptake was measured at 30°C with a calcium sensitive minielectrode in 0.5 ml medium containing 100 mM KCl, 5 mM K-oxalate, 5 mM $MgCl_2$, 5 mM NaN_3, 5 mM ATP, and 10 mM HEPES, pH 6.8 (KÜCHENMEISTER et al., 1999). The uptake was initiated by 10 µl homogenate and duplicate measurements were performed. The data acquisition system DaisyLab (DASYTEC GmbH, Mönchengladbach, Germany) was used to determine the highest rate of Ca^{2+} uptake by the homogenate (nM min^{-1} mg^{-1} homogenate protein), i.e. the maximum value of the first deviation of the change in calcium concentration. This rate of Ca^{2+} uptake will sometimes be referred to as uptake only.

Ca^{2+} ATPase activity of the homogenates was measured spectrophotometrically with a coupled enzyme assay at 30°C by a modified method described previously (SIMONIDES and VAN HARDEVELD, 1990). The 0.8 ml reaction mixture consisted of 20 mM HEPES (pH 7.5), 200 mM KCl, 2 mM ATP, 5 mM $MgCl_2$, 1 mM EGTA, 1 mM $CaCl_2$, 10 mM NaN_3, 0.2 mM NADH, 16 IU lactate dehydrogenase, 10 IU pyruvate dehydrogenase, 10 mM phosphoenolpyruvate with 2 µM Ca^{2+} ionophore A23187. As confirmed by variations of the Ca^{2+} concentration, at the chosen Ca^{2+} concentration the activity was maximal. The reaction was initiated by the addition of 10 µl homogenate. After about 1 min the change of absorbance was essentially linear and after a further run of 3 minutes 2 µM cyclopiazonic acid (CPA) was added to inhibit the SR Ca^{2+} ATPase selectively. The absorbance was measured for another 3 min. The activity of the Ca^{2+} ATPase was determined as the difference of activities before and after the addition of CPA.

Statistical Methods

The data were analysed with the procedure GLM of the Statistical Analysis Package SAS®. The statistical model included the fixed effect "mouse line" and the random effect "exercise level". Differences were considered to be significant if $p < 0.05$. The tables and figures contain least-squares means (LSM) and the standard error (SE).

Results

Running performance and weights

Table 2 shows the running distance until the mice were exhausted and characterizes the body weight and the weight of the muscle (*m. rectus femoris)* used for this investigation. Despite the long-term selection, within each mouse line there was a very high variability in the running distance. Only the running performance of the line DU-hOF showed significantly higher values compared to the other lines. Even though the

mean running distance of DU-hTP was more than twice of that DU-lTP, no significance could be ascertained. The live body weight of DU-lTP was highest followed by DU-Ks. The mice with the high OF-activity and high treadmill performance are the lightest. The weights of the *m. rectus femoris* were determined from other animals of the same lines to get information about differences between the lines. Related to the body weight the percentage of the *m. rectus femoris* was lowest in DU-Ks but not significantly different from DU-lTP muscle and was not different between exercise groups (data not shown).

Table 2
Running performance, body weight, and weight of *m. rectus femoris* of mice long- term selected for different performances (LSM ± SE) (Laufleistung, Körpergewicht und Gewicht des *m. rectus femoris* der selektierten Mäuselinien)

Mouse-lines	Run to exhaustion (meter)	Body weight at day 42 (g)	*weight *m. rectus femoris* (g)	*relative weight *m. rectus femoris* (%)
DU-Ks	1024 ± 382 a	26.9 ± 0.41 b	0.117 ± 0.009 b	0.53 ± 0.02 b
DU-hTP	1733 ± 364 a	24.0 ± 0.43 c	0.140 ± 0.009 b	0.60 ± 0.02 a
DU-lTP	765 ± 348 a	30.2 ± 0.42 d	0.177 ± 0.009 d	0.57 ± 0.02 a,b
DU-hOF	3005 ± 348 b	24.5 ± 0.42 c	0.141 ± 0.009 c	0.59 ± 0.02 a

different letters indicate significant differences between mouse lines ($p<0.05$)
* muscle weights were determined from mice of identical lines used for another investigation

Ca^{2+} uptake and Ca^{2+} ATPase activities

Without exercise the rate of Ca^{2+} uptake in muscle homogenates was lowest in DU-Ks mice followed by Du-lTP (Fig. 1). The uptake of the homogenate of DU-hOF and DU-hTP was not different at rest but was significantly higher than in the unselected line DU-Ks or in the line DU-lTP, selected for low treadmill performance.

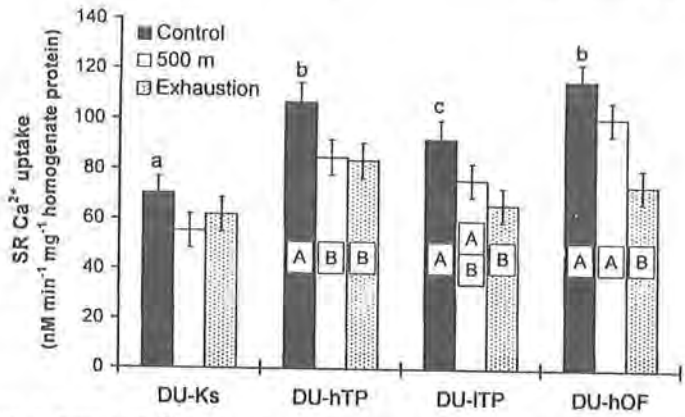

Fig. 1: Rates of Ca^{2+} uptake of muscle homogenates of different long term selected mouse lines at rest (Control), following running 500 m (500 m), and following an exhaustive run (Exhaustion). Values are LSM ± SE. Different lower case letters (a, b, c) indicate significant uptake differences ($p<0.05$) between mouse lines at rest, whereas different upper case letters (A, B) indicate significant uptake differences between exercise levels within mouse lines (Raten der Ca^{2+} Aufnahme von Muskelhomogenat der verschiedenen selektierten Mäuselinien in Ruhe {Control}, nach einem 500 m Lauf {500 m} und nach einem Lauf bis zur Erschöpfung {Exhaustion}. Werte sind in LSM ± SE angegeben. Unterschiedliche kleine Buchstaben weisen auf signifikante Unterschiede ($p<0,05$) zwischen den Mäuselinien in Ruhe hin, während unterschiedliche Großbuchstaben auf signifikante Unterschiede zwischen den Belastungen innerhalb der Mäuselinien hinweisen)

A significant effect of the 500 m run on the rate of uptake (Fig. 1) could only be detected in one line (DU-hTP). The exhaustive run reduced the rate of Ca^{2+} uptake in DU-hOF (36.3 %), in DU-hTP (21.8 %), and in DU-lTP (28.5 %). Uptake reduction in DU-Ks did not attain statistical significance.
Figure 2 illustrates the effect of exercise on the SR Ca^{2+} ATPase activity (measured with inclusion of an ionophore) of the different mouse lines. Pre-exercise values of the activities of Ca^{2+} ATPase between mouse lines were not different.

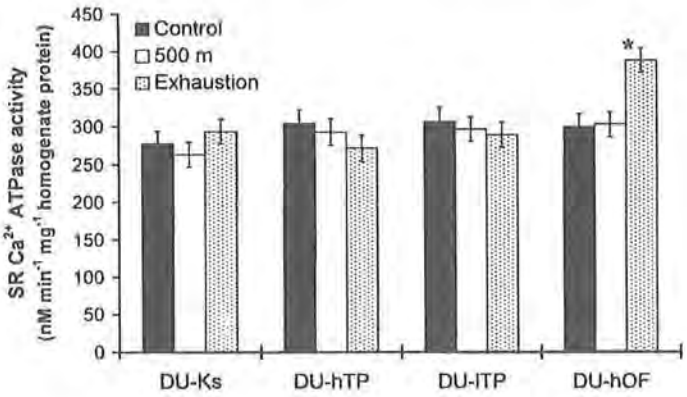

Fig. 2: Sarcoplasmic reticulum Ca^{2+} ATPase activity in muscle homogenates of different long term selected mouse lines at rest (Control), following running 500 m (500 m), and following an exhaustive run (Exhaustion). Values are LSM ± SE. * significantly different from Control and 500 m in the line DU-hOF ($p<0,05$) (Aktivität der Ca^{2+} ATPase des sarkoplasmatischen Retikulums im Muskelhomogenat der selektierten Mäuselinien in Ruhe (Control), nach einem 500 m Lauf (500 m) und nach einem Lauf bis zur Erschöpfung (Exhaustion). Werte sind in LSM ± SE angegeben.
* signifikant verschieden von Control und 500 m ($p<0,05$) in der Linie DU-hOF

The effect of exercise on the activity of the Ca^{2+} ATPase was minor and not uniform. An exercise for 500 m had no effect. Only the exhaustive run of DU-hOF mice augmented the Ca^{2+} ATPase by 29 % whereas exercise for 500 m had no significant effect (Fig. 2).

Discussion

Using the same muscle of the species mouse our aim was to investigate the effect of long-term selection on the Ca^{2+} transport at rest and following exercise. We originally hypothesized, that exercise induced alterations in SR Ca^{2+} transport in muscle of mice long-term selected for high locomotor activity or running performance are attenuated compared to mice which were not selected or selected for low performance. This hypothesis could not be verified.
Contradictory results concerning Ca^{2+} uptake and Ca^{2+} ATPase are intensely discussed to be at least in part a result of different sample preparation (CHIN et al., 1995; DOSSETT-MERCER et al., 1995; CHIN and GREEN, 1996). To circumvent uncertainties in the SR isolation technique, homogenates were used in this investigation.

At rest, the rate of Ca^{2+} uptake was lowest in DU-Ks muscle (unselected line), which could be interpreted that low performance is related to a low SR sequestering function. However, the line selected for low treadmill performance (DU-lTP) had comparable low running performances. Also, the minor differences in Ca^{2+} ATPase activities at rest do not lead to the conclusion that the selection had the expected effect on SR Ca^{2+} transport. This is in agreement with training experiments, showing an increased performance but no change in Ca^{2+} transport (SEMBROWICH et al., 1978; MADSEN et al., 1994; GREEN et al., 1998), but not with other investigations, indicating a reduced uptake and ATPase activity by long-term training (BELCASTRO, 1987), or an increased uptake and ATPase activity (WILSON et al., 1998), determined at rest.

In agreement with the majority of investigations Ca^{2+} uptake was affected by the level of exercise. However, whereas the overall (all mouse lines) decrease in the rate of uptake in our experiment by 14.3% for the 500 m run and 24.1% for the exhaustive run (data not shown) attained statistical significance, the effect of exercise on the uptake between the different mouse lines is not as clear. Contrary to our hypothesis we can not recognize unequivocal differences in the uptake between the different performance lines either by a 500 m run or the exhaustive run. Comparing training experiments with our selection experiments for different running performances the effects are confusing in either treatment. Endurance training of rats decreased the Ca^{2+} uptake at rest (BELCASTRO, 1987) and a fibre type dependence has been shown (KIM et al., 1981). Sprint conditioning of horses increased the SR Ca^{2+} uptake at rest and attenuated an exercise induced decrease in Ca^{2+} transport (WILSON et al., 1998). Following endurance training of rats the Ca^{2+} uptake of isolated SR was reduced, but not so in muscle homogenates (SEMBROWICH et al., 1978). Training had no significant effect on SR Ca^{2+} uptake either at rest or following exercise (BONNER et al., 1976).

There was hardly any significant effect of exercise on SR Ca^{2+} ATPase, except for the line DU-hOF with an increase in activity by 29.3 % following an exhaustive run (Fig. 2). The reason for this increase is not obvious. These animals run an average distance of 3005 m (corresponding to an average run period of 84 min). It can be speculated that this significantly longer running period compared to the other lines and exercise groups resulted in an activation of latent ATPase enzyme. The muscle used in our investigation, the *m. rectus femoris*, contains about 64 % white, and 36 % red and intermediate fibres (REHFELDT et al., 1987). An increase in the SR Ca^{2+} ATPase activity has been found following a continuous intense run in the soleus and the red gastrocnemius, but not in white gastrocnemius muscle (GREEN et al., 1996). On the other hand, short term stimulation increased Ca^{2+} ATPase activity in white gastrocnemius, but not soleus or red gastrocnemius (DOSSETT-MERCER et al., 1995). An increase in Ca^{2+} ATPase shortly after exercise following 2 h of running was suggested to be the result of increasing the proportion of functional SR Ca^{2+} ATPase proteins (FERRINGTON et al., 1996). Ca^{2+} ATPase activity was elevated in female vastus lateralis immediately following eccentric exercise (ENNS et al., 1999). Possibly, an insufficient supply of blood and energy may have initiated an ATPase activity increase in exhausted DU-hOF mice. Ischemia for 1 to 3 h induced elevations of the SR Ca^{2+} ATPase activity dependent on the fibre type composition with greater

effects in white muscle, suggesting a recruitment of a latent pool of the enzyme (GREEN et al., 1996). The combination of a decreased uptake rate (Fig. 1) and increased Ca^{2+} ATPase activity in exhaustively exercised DU-hOF mice (Fig. 2), means that there is at least in vitro an unexplained Ca^{2+} ATPase activity not resulting in Ca^{2+} pumping. A comparable effect has been found (DOSSETT-MERCER et al., 1995) which mechanistic basis remained unknown.

In summary, previous results indicate a great variability in the effect of exercise and training on SR Ca^{2+} transport, depending on species, age, muscle type, exercise protocol, training, use of homogenates or purified SR, and analytical techniques. The long-term selection of mice, resulting in differences in running performances of about 400 %, seems not to change muscle sarcoplasmic reticulum Ca^{2+} transport properties to a corresponding extent.

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Authors' address
Dr. ULRICH KÜCHENMEISTER[1], Dr. MARTINA LANGHAMMER[2], Dr. ULLA RENNE[2], Dr. GERD NÜRNBERG[2], Prof. Dr. habil. KLAUS ENDER[1]
Forschungsinstitut für die Biologie landwirtschaftlicher Nutztiere Dummerstorf
FB Muskelbiologie und Wachstum[1]
FB Genetik und Biometrie[2]
Wilhelm-Stahl-Allee 2
D-18196 Dummerstorf
Germany