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SKELETAL MUSCLE

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Increased resistance to fatigue in creatine kinase deficient muscle is not due to improved contractile economy

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Abstract There has been speculation on the origin of the increased endurance of skeletal muscles in creatine kinase (CK)-deficient mice. Important factors that have been raised include the documented increased mitochondrial capacity and alterations in myosin heavy chain (MyHC) isoform composition in CK-deficient muscle. More recently, the absence of inorganic phosphate release from phosphocreatine hydrolysis in exercising CK-deficient muscle has been postulated to contribute to the lower fatigueability in skeletal muscle. In this study, we tested the hypothesis that the reported shift in MyHC composition to slower isoforms in CK-deficient muscle leads to a decrease in oxygen cost of twitch performance. To that aim, extensor digitorum longus (EDL) and soleus (SOL) muscles were isolated from wild-type (WT) and knock-out mice deficient in the cytoplasmic muscle-type and sarcomeric mitochondrial isoenzymes of CK, and oxygen consumption per twitch time–tension-integral (TTI) was measured. The results show that the adaptive response to loss of CK function does not involve any major change to contractile economy of skeletal muscle.

Keywords Contractile economy · Transgenic mice · Skeletal muscle · Muscle fatigue · Creatine kinase

Abbreviations CK: Creatine kinase · Cr: Creatine · EDL: Extensor digitorum longus · PCr: Phosphocreatine · SOL: Soleus · MyHC: Myosin heavy chain

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Introduction

The creatine kinase (CK) reaction: phosphocreatine + adenosine diphosphate (ADP) + H^+ ↔ creatine + adenosine triphosphate (ATP) is thought to minimize fluctuations in ATP/ADP ratio during transients of muscle activity by acting as a spatial and temporal energy buffer [1]. Genetically deleting CK function, the impairment of local ATP/ADP buffering has been shown to abolish the ability to perform burst-performance, impair free energy homeostasis and calcium handling [2]. However, low intensity stimulation revealed increased endurance compared to the wild type, despite the fact that the buffering function of CK was absent [3–5].

There has been speculation on the origin of this increased stamina in CK-deficient muscle. A first important factor that has been raised is the increased mitochondrial capacity on the energy supply side of muscle energetics [5, 6]. Another explanation may be the reported fast-to-slow alterations in myosin heavy chain (MyHC) isoform composition in CK-deficient fast-twitch muscle [2, 7]. Specifically, in fast-twitch muscle, a near-twofold increase in MyHC type IIA/IIB ratio was found in muscle creatine kinase (M-CK) and cytosolic muscle-type and sarcomeric mitochondrial CK (MiM-CK) knock-out phenotypes. In the mixed fiber-type soleus muscle, there was 50% MyHC type I, 50% MyHC type IIA, however, no change in fiber-type composition was found [2, 7].

Inactivation of CK function using an alternative, non-genomic approach—i.e., depletion of the cellular creatine pool via creatine-analogue β-guanidinopropionic acid (β-GPA) feeding—likewise, caused a transition to slower MyHC isoforms in fast-twitch but also slow-twitch muscle. It was associated with a twofold improvement in oxidative contractile economy (defined as the amount of oxygen consumed per unit integral of tension and time) for mouse soleus (SOL) and extensor digitorum longus (EDL) muscle [8], in a murine model. Remarkably, in a later report, creatine (Cr) analogue feeding was not found to change the contractile economy of rat gastrocnemius, a predominantly fast-twitch muscle [7].

In this study, we determined the oxidative contractile economy of fast EDL and 'slow' SOL muscles of the wild type (WT) and CK-deficient muscles. We tested if the shift in MyHC composition to slower isoforms in CK-deficient EDL muscle is likewise accompanied by a twofold decrease in oxygen cost of twitch contraction reported for β-GPA feeding.

Experimental

Animals and muscle preparation

Adult wild-type C57BL/6 mice were used as controls. Double knock-out mice, deficient in MiM-CK$^{-/-}$, were generated in the laboratory of Dr. B. Wieringa (Nijmegen University, The Netherlands) by gene-targeting as described previously [9, 10]. Offspring obtained in the breeding program was genotyped by polymerase chain reaction (PCR) analysis on a regular basis. All experimental procedures were approved by the Committee on Animal Experiments of the University Medical Center Utrecht and complied with the principles of good laboratory animal care. Mice (age 21–30 days) were killed by cervical dislocation, EDL and SOL muscles of both hind limbs were prepared free from the surrounding tissue, and a 5.0 silk suture (Ethicon, Norderstedt, Germany) was attached to the muscle tendons.

Muscle contractile performance

One end of the muscle was mounted in a custom-made oxygraph stopper and the other end was connected to an adjustable Harvard Apparatus 60-2995 force transducer (Harvard Instruments, Edenbridge, UK), which allowed the muscle to be stretched to yield its maximum twitch force. Muscles were stimulated via platinum wire electrodes by supramaximal pulses (0.5 ms duration; 6–15 V) by a Grass S88 dual channel stimulator (Astro-med, West Warwick, RI, USA) and force signals were digitized at 1,000 Hz sampling rate. The stimulation protocol started with 10 min of rest to record basal respiratory flux followed by 5 min at 0.5, 1.0 or 2.0 Hz and 1.5 or 3.0 Hz for EDL and SOL muscles, respectively [11]. Episodes of muscle stimulation were separated by 10-min intervals during which non-stimulated basal respiration of the muscle was recorded.

Oxygen consumption of intact EDL and SOL muscle

The rates of oxygen consumption (nmol O_2 · g muscle weight^{-1} · min^{-1}) were determined at 20°C, using a high-resolution oxygraph (Oroboros, Innsbruck, Austria) with a stirring rate of 500 rpm. Respiratory fluxes were corrected for chamber oxygen leak based on an exponential decay of P_{O2} in the oxygraph chamber at 20°C containing Ringer solution (116 mM NaCl, 25.3 mM $NaHCO_3$, 4.6 mM KCl, 2.5 mM $CaCl_2$, 1.16 mM KH_2PO_4, 1.16 mM $MgSO_4$, pH 7.4) according to [12]. Oxygen solubility of 5% CO_2–95% O_2 equilibrated Ringer medium was calculated according to [13] and oxygen electrode response time was constant at 4 s (tested prior to each experiment). All measurements of muscle respiration were performed after 30 min of equilibration, to avoid measurements at high chamber oxygen leak. All measurements of muscle respiration were performed as randomized paired-experiments with simultaneous measurement of one WT and one MiM-CK$^{-/-}$ muscle in a dual-chamber setup. To avoid oxygen limitation of respiration in SOL and EDL muscles at 20°C [14], all measurements were performed above a P_{O2} of 450 Torr. Chamber volume (approximately 5.2 ml) and muscle weight (blotted and tendon free) were determined after each experiment.

Data acquisition, analysis, and statistics

Oxygraph and force transducer data-acquisition was performed with LabView software (National Instruments, Woerden, The Netherlands). Muscle mechanics data were analyzed using LabView software. Time–tension-integrals (TTIs) of twitch force and concomitant oxygen consumption during the 5-min stimulation periods were calculated using Origin 6.0 (Microcal Software, Northhampton, MA, U.S.A.). Reported data are presented as arithmetic means± SE. Statistical analyses were performed using a Student's unpaired *t* test. Differences between MiM-CK$^{-/-}$ and WT muscle were considered significant if $P<0.05$.

Results

Respiratory and contractile stimulation of CK-deficient muscle

Figure 1 shows typical recordings of twitch contraction force and O_2 consumption for a WT and a MiM-CK$^{-/-}$ EDL muscle. Note the higher noise in the recordings from the CK$^{-/-}$ muscle compared to WT because of its smaller size. Initiation of stimulation (2 Hz) at t=300 s led to activation of mitochondrial oxidative phosphorylation. After a rapid early decay followed by stabilization of absolute twitch contraction force [steady-state force (SSF)] in the first minute of contractions, both WT and MiM-CK$^{-/-}$ EDL muscles fatigued. Twitch force after 5 min contractions had fallen to 60% of SSF in WT but less so in MiM-CK$^{-/-}$ EDL (70% of SSF).

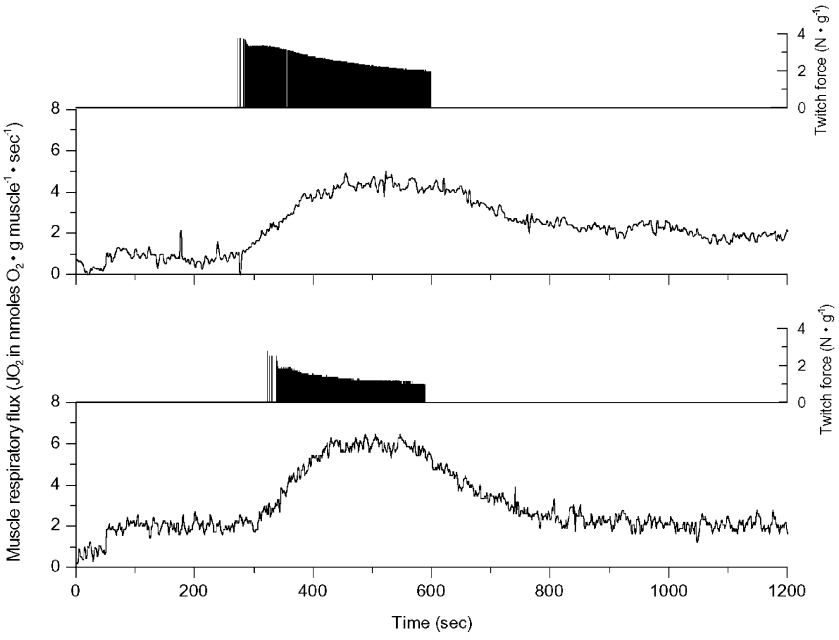

Fig. 1 Representative traces of twitch-force peaks and respiratory flux during a 2 Hz stimulation protocol (from 300 to 600 s) for wild-type (*top two panels*) and MiM-CK$^{-/-}$ (*bottom two panels*) EDL muscle

Mechanical performance of CK-deficient muscle

Initial twitch force per milligram of muscle wet-weight was slightly lower in MiM-CK$^{-/-}$ EDL muscles and significantly lower in MiM-CK$^{-/-}$ SOL muscles, compared to WT (Table 1). The rise time to peak force for MiM-CK$^{-/-}$ EDL and SOL muscles was similar to the WT muscles (Table 1). However, the half-width and relaxation times (ms) were significantly longer in CK-deficient EDL (51.1±2.4 ms (n=4)) for MiM-CK$^{-/-}$, compared to WT (35.8±5.8 ms (n=6) (p=0.05) and 52.1±1.8 ms (n=5)) for MiM-CK$^{-/-}$, compared to WT (40.4±1.8 ms (n=7) (p=0.05), respectively). CK-deficient SOL muscle also displayed significantly prolonged half-width and relaxation times (126.8±3.6 (n=8) vs 166.7±11.7 (n=7) and 166.8±8.9 (n=8) vs 225.6±19.3 (n=7) ms, respectively; WT vs CK$^{-/-}$, respectively, P<0.05).

Figure 2a displays a typical time course of the TTI of twitch contractions of EDL muscles for the WT vs CK$^{-/-}$ phenotypes (single muscles) over the 5-min serial stimulation at 2 Hz. TTI was scaled to average steady-state TTI value prior to fatigue determined for each individual muscle from measurements during stimulation at 0.5 Hz (not shown). During the first 5–10 s of stimulation, WT EDL (thick line) showed typical burst performance, while CK-deficient EDL (thin line) lacked burst performance. Subsequently, TTI stabilized temporarily, after which it gradually declined at constant but markedly different rates for each phenotypes. Fig. 2b shows a detail of this time course (between 60 and 300 s) and specifically the average time course for each group. To objectify muscle endurance from each phenotype, we determined the rate of fatigue (defined as rate of decline of scaled TTI) by applying linear best fits to a 200-s time period for WT (thick line) and CK-deficient (thin line) EDL muscle. The average rate of scaled TTI decline for WT EDL muscle was found to be more than twofold higher than for CK-deficient EDL muscle [−2.79±0.13 (n=5) and −1.16±0.01% · min^{-1} (n=4), for WT and MiM-CK$^{-/-}$, respectively]. Figure 2c shows equivalent data for SOL muscle. Here, TTI was scaled for each individual muscle using the TTI value determined prior to serial stimulation. Similar to CK-deficient EDL muscles, MiM-CK$^{-/-}$ SOL displayed enhanced endurance compared to WT, as objectified by a likewise twofold lower decline of TTI [−2.33±0.63 (n=3) vs −5.54±0.87% · min^{-1} (n=7)].

Estimation of the contractile economy of CK-deficient muscle

Contractile economy was estimated by plotting the total amount of oxygen consumed during muscle activity

Table 1 Kinetics of force development of wild-type and CK-deficient (MiM-CK$^{-/-}$) EDL and SOL muscles

	Wild-type EDL	MiM-CK$^{-/-}$ EDL	Wild-type SOL	MiM-CK$^{-/-}$ SOL
Initial force (N/g)	3.4±0.2 (n=7)	2.9±0.3 (n=5)	2.9±0.2 (n=5)	2.1±0.2* (n=5)
Rise time (ms)	10.5±0.3 (n=7)	9.3±1.1 (n=5)	25.3±0.8 (n=8)	30.2±2.8 (n=7)
Half-width time (ms)	35.8±5.8 (n=6)	51.1±2.4* (n=4)	126.8±3.6 (n=8)	166.7±11.7 (n=7)
Relaxation time (ms)	40.4±1.8 (n=7)	52.1±5.0* (n=5)	166.8±8.9 (n=8)	225.6±19.3* (n=7)

Values are means±SE
*P<0.05 compared to WT

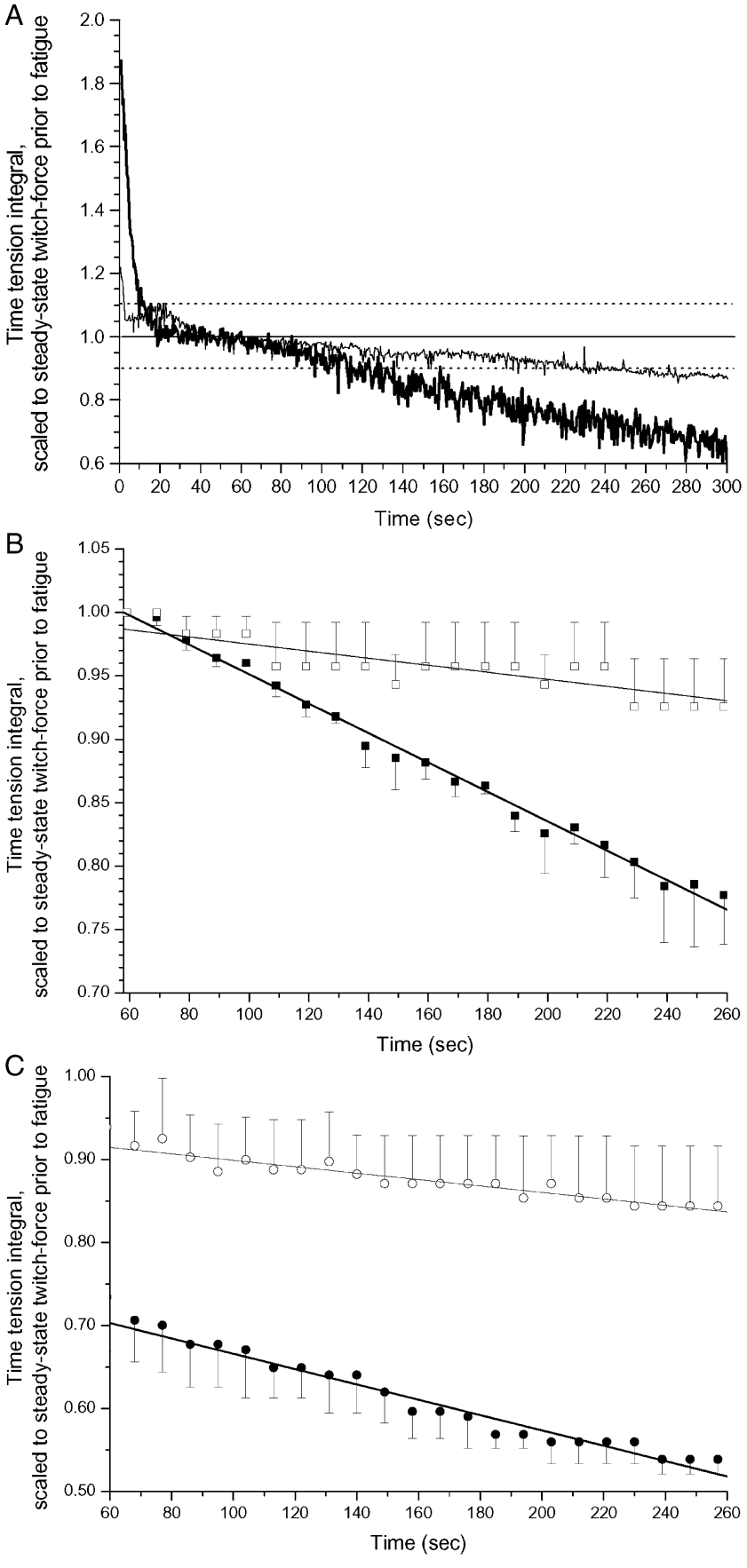

Fig. 2 **a** Typical results of twitch time–tension integral (scaled to steady-state twitch-force prior to fatigue) during 5 min of 2 Hz stimulation in a wild-type (*thick line*) and a MiM-CK$^{-/-}$ (thin line) EDL muscle. Dashed lines represent 10% plus or minus deviation from average steady-state force, prior to fatigue. Twitch time tension integral (*TTI*, scaled to steady-state twitch-force prior to fatigue) at 60 s into the stimulation protocol of 5 min at 2 and 3 Hz in wild-type (*closed symbols*) and MiM-CK$^{-/-}$ (*open symbols*) EDL (**b**) and SOL (**c**) muscle, respectively (for reasons of clarity, 1/10 of the actual data-point sampling-rate are displayed. *Error bars* represent SE). Linear best fits of TTI decline over time are indicated for wild-type (*thick lines*) and MiM-CK$^{-/-}$ (*thin lines*) muscle

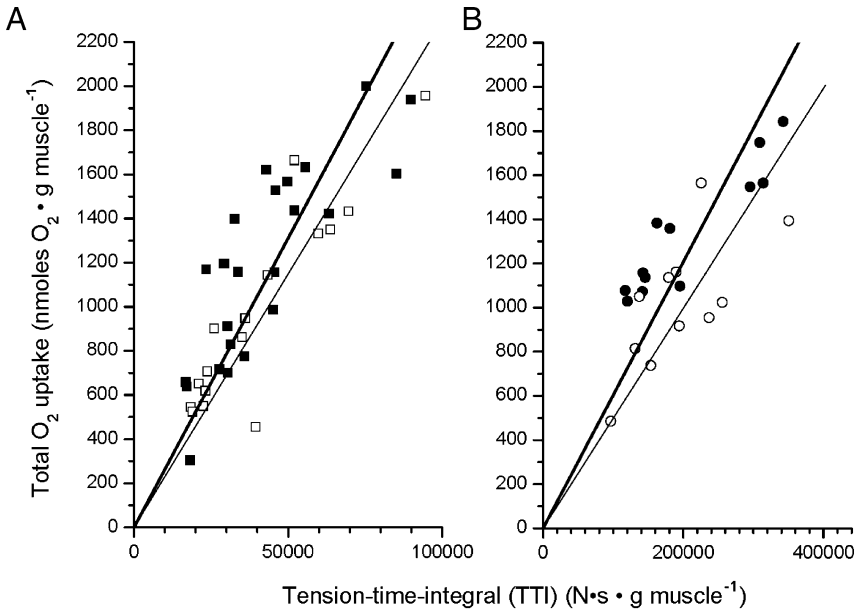

Fig. 3 Total amount of oxygen consumed vs twitch time–tension-integral during 5 min of stimulation in wild-type (*closed symbols*) and CK-deficient (*open symbols*) **a** EDL (*squares*) and **b** SOL (*circles*) muscles. Best linear fits to the data points are indicated as *solid* and *dashed lines* for wild-type and CK-deficient muscle, respectively

(corrected for basal oxygen consumption) against the TTI of all individual twitches [8] during the 5-min stimulation period. The energetic economy of isometric contractions was found to be identical in WT and MiM-CK$^{-/-}$ EDL based on the similar slope of 26.2±1.4 and 23.0±1.2 μmol $O_2 \cdot Ns^{-1}$ for WT and MiM-CK$^{-/-}$ EDL, respectively (Fig. 3a). The total amount of oxygen consumed per TTI in WT SOL muscles was 6.04±0.37 μmol $O_2 \cdot Ns^{-1}$ which was not significantly different from MiM-CK$^{-/-}$ SOL muscles (4.98±0.39 μmol $O_2 \cdot Ns^{-1}$) (Fig. 3b).

Discussion

The main finding of this study is the similar oxidative energy demand of contraction by the sum of the myosin ATPase machinery and cation pumps in CK-deficient and wild-type muscle.

Many physiological studies that addressed the loss of creatine kinase function in muscle have measured the MyHC composition to explore possible adaptive alterations in the energy demand of the muscle contractile apparatus. In muscle lacking a fully functional CK system, either due to β-GPA feeding [7, 15–17] or by deletion of CK enzymes [2, 18], a shift to slower MyHC isoforms (type I and IIa increase) has been observed in fast-twitch gastrocnemius and EDL muscles. The energetic cost to maintain tension is known to depend on the myosin isoform composition due to intrinsic differences in the cross-bridge cycle rates and the myosin ATPase activities [14, 19, 20]. However, depending on the type and duration of muscle work performed (e.g. twitch or tetanus) the contribution of other components, such as Ca^{2+} handling in determining the total energetic cost may vary [21]. Moerland et al. studied the contractile economy based on the poststimulatory oxygen consumption during recovery in EDL and SOL muscles of β-GPA fed mice and observed a 50% decrease in energetic cost to maintain tetanus tension in both muscle types [8]. They related their findings to the more cost-efficient myosins present in these β-GPA treated muscles [15] and concluded that the observed myosin shift led to a twofold increase in contractile economy. Based on these findings and a similar MyHC type IIa/IIb ratio, increase of 119 and 116% in CK-deficient and β-GPA treated fast-twitch EDL muscles [15, 22], respectively, we expected to, likewise, find a twofold increased contractile economy in MiM-CK$^{-/-}$ EDL muscle. This hypothesis was tested.

We conducted our experiments on muscles from 3- to 4-week old mice. This particular age range was chosen because it offered a middle ground between, on the one hand, minimizing the muscle diameter and on the other hand, maximizing phenotypical maturation with respect to myosin composition. The former was important because the muscles in the chambers were superfused and therefore, oxygen had to diffuse from the bath into the muscle. Simulations showed that for the particular conditions (i.e., T=20°C and superfusate pO_2 >450 Torr) and range of stimulation frequencies (and thus, ATP consumption rates) studied here, muscle radius should not exceed 0.5 mm (data not shown). Diameters of WT EDL and SOL muscles from 3- to 4-week old mice were typically on the order of 0.8 mm, and CK-deficient muscles were typically smaller (data not shown). Maximizing phenotypical differentiation with respect to myosin composition was important because the MyHC type IIa/IIb shift in CK-deficient EDL muscle was determined in 2- to 4-months old mice [2]. It was recently shown for EDL and SOL muscles from the same inbred strain used here (i.e., C57BL/6), however, that by days 21 and 28 of postnatal development, both SOL and EDL are devoid of any neonatal MyHC isoform, and no further major changes occur between days 28 and 49 [23].

Therefore, we do not believe that our use of relatively young mice affected the outcome of the test of the hypothesis under investigation.

Analysis of *total* oxygen consumption during 5 min of twitch contraction at 0.5, 1 and 2 Hz, we found a similar, not different energetic cost in CK-deficient and WT EDL muscle (Fig. 3a). Analysis of the equivalent dataset for SOL, a muscle in which no phenotypic change in MyHC composition has been found in response to CK-deficiency, showed a similar variation of the regression for WT and MiM-CK$^{-/-}$ muscles (Fig. 3b). Analysis of the measurement of oxygen consumption during *recovery* (poststimulatory oxygen consumption during recovery (i.e., starting at t=600 s; see Fig. 1), however, indicated a near-twofold increase of contractile economy (oxygen consumption after isometric contractions was 13.1±0.9 and 7.7±0.5 μmol $O_2 \cdot Ns^{-1}$ for WT and MiM-CK$^{-/-}$ EDL, respectively). Clearly, both answers could not be true at the same time.

We have previously found in analogous experiments that MiM-CK deficiency leads to a threefold faster return of mitochondrial oxidative flux to basal respiration during recovery from contractile activity [11]. This absence of prolonged activation of mitochondrial respiration after stimulation illustrates the lack of so-called 'oxygen debt' in CK-deficient muscle during which the muscle 'repays' the use of phosphocreatine (PCr) during demand [24]. Phosphorous NMR studies have established that, unlike in wild-type muscle, PCr is inert in CK-deficient muscle during periods of increased workload [5]. Oxygen consumption thus lacks the 'oxygen-debt' component during recovery in CK-deficient muscle, and the decline of the respiratory activity to basal values, therefore, occurs faster. By only measuring oxygen consumption during recovery one, therefore, underestimates *total* oxygen cost in the absence of CK-function. Consequently, we concluded that the second, positive answer we obtained regarding any change in contractile economy of CK-deficient EDL muscle was wrong.

Further evidence supporting our conclusion came from the 'post-recovery' analysis of our SOL data. We found that muscle poststimulatory oxygen consumption during recovery was 2.2±0.1 in WT vs 1.4±0.2 μmol $O_2 \cdot Ns^{-1}$ in MiM-CK$^{-/-}$ SOL muscle. Consequently, the contractile economy of CK-deficient SOL muscle should be near-twofold higher than WT. However, WT and CK-deficient SOL muscles have identical MyHC profiles [2, 10]. Therefore, analysis of recovery oxygen consumption only leads to a false conclusion with respect to the particular issue under investigation.

To better understand the physiological impact of alterations in MyHC isoform composition, we estimated contractile economy for isometric twitch force based on tension-cost values for rat single fibers provided by Bottinelli et al. [19]. The increase in MyHC type IIa/IIb ratio of 100% that was observed for CK-deficient fast-twitch muscle was estimated to improve contractile economy by only 10%. This calculation included the minor increase in type I MyHC. Based on the reported shifts in MyHC composition in CK-deficient muscles it was therefore, no longer any surprise to *not* find any increased economy (even with extremely low noise on the experimental data points). The twofold change in contractile economy, as observed by Moerland et al. [8], can be excluded. Furthermore, based on ^{31}P NMR measurements on fast-twitch gastrocnemius muscle from β-GPA fed rats the ATP cost of both twitch and tetanic contractions was found to be similar to wild-type muscle [7].

We did find significantly longer twitch durations, as reflected by the parameters 'twitch half width time' and relaxation time (both in ms) for CK-deficient EDL and SOL muscles (Table 1). However, this observation more likely points to compromised Ca^{2+} handling in CK-deficient muscle, as has been reported previously [5], than any slowing in cross-bridge cycling as a result of the shift in EDL MyHC composition towards more type IIa.

The implications of our findings for the understanding of the plasticity of the ATP metabolic network in skeletal muscle are that cellular adaptations to counterbalance impaired capacity for dynamic energy homeostasis due to loss of CK function, appear to mainly impact the supply side on a physiological level [5, 6, 25]). We have shown that the deletion of CK function and consequently, the reported adaptive MyHC shift in fast-twitch muscle do not alter the contractile economy of EDL muscles to any appreciable extent.

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