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The effect of taurine depletion on the contractile properties and fatigue in fast-twitch skeletal muscle of the mouse

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Summary. Taurine increases force production in skeletal muscle, and taurine levels may fall during exercise. The contractile properties and fatigability of extensor digitorum longus (EDL) muscles depleted of taurine by guanodinoethane sulfonate (GES) treatment were investigated. GES treatment decreased muscle taurine levels to <40% of controls. Peak twitch force levels were 23% of controls in GES treated EDL muscles ($p < 0.05$), but maximal specific force was unaffected. The force–frequency relationship was examined and significantly less force was produced by the GES treated muscles compared to controls at stimulation frequencies from 50 to 100 Hz ($p < 0.05$). GES treated EDL muscles exhibited significantly slower rates of fatigue than controls ($p < 0.05$). In skinned fibres, 20 mM GES had a small but significant effect on force production, indicating that GES may have some minor taurine-like effects. In this study, a fall in taurine levels decreased force output, and increased the endurance of EDL skeletal muscles.

Keywords: Muscle performance – Ca^{2+} – Extensor digitorum longus

Introduction

Taurine is a sulfonic amino acid that is found in especially high concentrations in skeletal muscle (Chesney et al., 1986; Nieminen et al., 1988; Turner et al., 1994) and other excitable cells (Huxtable, 1992). Evidence is mounting that taurine is essential for the normal function of skeletal muscle (Bakker and Berg, 2002; Warskulat et al., 2004).

Skeletal muscle is activated by a series of events linking electrical activation of the sarcolemma to activation of the contractile filaments, a process known as excitation–contraction coupling. Action potentials generated in the sarcolemma propagate into the transverse-tubular system, where they depolarise transverse-tubular dihydropyridine (DHP) receptors, which act as voltage sensors. Voltage sensor activation in turn elicits Ca^{2+} release from the sarcoplasmic reticulum (SR) via specific Ca^{2+} channels known as ryanodine receptors. Ca^{2+} released from the sarcoplasmic reticulum binds to troponin C on the contractile filaments and activates muscle contraction. After cessation of action potential activity muscle relaxation occurs due to Ca^{2+} resequestration by the SR through the activity of a high affinity Ca^{2+}, Mg^{2+}-ATPase (Lamb, 2000).

In this laboratory, taurine has been shown to increase force production in skinned skeletal muscle fibers, by increasing the Ca^{2+} release from the sarcoplasmic reticulum and increasing the sensitivity of the contractile filaments to Ca^{2+} (Bakker and Berg, 2002). Other groups have shown that taurine can increase the mechanical threshold for skeletal muscle contraction (De Luca et al., 1996), promote intracellular membrane stabilisation (Huxtable and Bressler, 1973) and increase membrane polarisation (Conte-Camerino et al., 1987; Gruener et al., 1975).

These studies are significant because taurine levels may change in skeletal muscle under different conditions. Taurine is actively accumulated by cells via a Na^{+}-dependent high affinity taurine transporter, which is highly expressed in skeletal muscle (Ramamoorthy et al., 1994). Taurine is also reported to be released from muscles during exercise, possibly to counter the increased muscle fiber osmolarity that occurs due to the build up of metabolic by-products (Cuisinier et al., 2002). The release of taurine from skeletal muscle may be triggered by exercise-induced increases in reactive oxygen species and phospholipase A_2 activity (Ortenblad et al., 2003). Considering the marked effects of taurine on enhancing force production (Bakker and Berg, 2002), the loss of taurine could significantly affect skeletal muscle performance. Recently, it was shown that taurine transporter-knockout mice demonstrated an 80% reduction in total

exercise capacity during treadmill experiments (Warskulat et al., 2004).

To date, no one has directly examined the effects of taurine depletion on the contractile performance of intact adult skeletal muscle. Therefore, in this study, we examined the contractile properties and the fatigability of isolated intact extensor digitorum longus (EDL) muscles of mice treated with the taurine uptake inhibitor guanodinoethane sulfonate (GES), a drug which is reported to significantly decrease intracellular taurine levels in mammalian cells (Huxtable, 1982).

Materials and methods

All experimental procedures and methods undertaken in this study were approved by the University of Western Australia Animal Ethics Committee. Taurine depletion experiments were undertaken on intact EDL muscles from 8 week old male mice (C57/BL10). All animals were killed by carbon dioxide inhalation overdose (O_2 maintained at 20%).

Taurine depletion

The taurine depletion treatment involved exposing the mice to drinking water containing a 1% solution of GES (Toronto Research Chemical Inc.), and 1% glucose ad libitum for a 4-week period (Huxtable, 1982; De Luca et al., 1996). Control animals were maintained on drinking water containing 1% glucose alone. All animals were allowed free access to food and water at room temperature (20–24 °C) and exposed to a light cycle of 12 hours per day.

Measurement of intracellular taurine levels

Analysis of taurine concentrations in control and GES treated mice was undertaken using high pressure liquid chromatography (HPLC) using a similar protocol to that described by Pierno et al. (1998). After removal, EDL muscles were washed in physiological saline solution, and then dried and weighed. The dried muscles were homogenized in $HClO_4$ ($10\,ml \cdot g^{-1}$ tissue) and K_2CO_3 ($5.5\,g \cdot g^{-1}$ tissue). The homogenates were centrifuged at 4 °C for 10 min at $600 \times g$, and the supernatant was removed and stored at −80 °C until required. Samples were derived using *o*-phthalaldehyde and the taurine content determined by HPLC.

Skinned fiber experiments

Mechanically skinned muscle fibres retain normal excitation–contraction coupling due to sealing of the t-system after skinning (Lamb and Stephenson, 1990). These experiments were undertaken using EDL muscles from large (>300 g) wistar rats (Rattus norvegicus), as only large fibers, not available in mice, provide reliable preparations for this technique. EDL fibres from rats and mice have very similar skinned fibre contractile characteristics (Fink et al., 1986). Muscles were removed and placed in paraffin, where single fibres were isolated and the membrane mechanically peeled away (skinning). As the skinned fibres have no membrane, substances added to the bath solution quickly diffuse in to the interior of the fibers. Therefore, the skinned fiber technique can be used to determine the effects of membrane impermeable substances on the contractile physiology of skeletal muscle. The fibers were then mounted on a sensitive force transducer (SI Heidelberg) and maintained in a potassium hexamethylenediamine-tetraacetate (potassium-HDTA) solution (mM): K^+, 125; Na^+, 36; $HDTA^{2-}$, 50; ATP (total), 8; Mg^{2+} (total), 8.6; creatine phosphate, 10; EGTA (total), 0.03; N-2-Hydroxyethyl-piperazine-N′-2-ethanesulphonic acid (HEPES), 90; NaN_3, 1 at pH 7.10 ± 0.01 (Lamb and Stephenson, 1990). The free Mg^{2+} concentration was 1 mM. NaN_3 was added to inhibit mitochondrial Ca^{2+} fluxes. The sealed t-system could be repolarised by a 1 min exposure to the K^+-HDTA solution. Depolarisation induced force responses were elicited by exposing the preparation to a Na^+-HDTA solution, (similar to the K^+-HDTA solution, with Na^+ substituted for K^+). The K^+-HDTA and Na^+-HDTA solutions were weakly buffered to a pCa of approximately 6.7–7.0 using Sol A (to remove residual Ca^{2+}). Twenty mM GES was added to one set of the K^+- and Na^+-based solutions, and 20 mM sucrose was added to the control set to maintain a similar osmolarity. The experiment protocol involved the measurement of a depolarisation-induced force response under control conditions, followed by a response in the presence of GES, and finally, another response under control conditions. The peak and ½ peak width of the depolarisation-induced force responses measured in the presence of 20 mM GES were compared to the mean values of control measurements made before and after exposure to GES.

The effect of GES on the sensitivity of the contractile filaments to Ca^{2+} in EDL fibers was determined by exposing fibers to solutions of different free Ca^{2+} concentrations in the presence and absence of 20 mM GES (Han et al., 2003). The strongly Ca^{2+}-buffered solutions of different, known, free Ca^{2+} concentrations were prepared by mixing different proportions of Ca^{2+} EGTA (Sol. A) and EGTA (Sol. B) based solutions (Stephenson and Williams, 1981). Sol. B was composed of: (mM) K^+, 117; Na^+, 36; ATP (total), 8; free Mg^{2+}, 1; creatine phosphate, 10; $EGTA^{2-}$ (total), 50; HEPES, 60; NaN_3, 1 at pH 7.10. Sol. A was similar to Sol. B, with the exception that the $[EGTA^{2-}]$ and $[CaEGTA^{2-}]$ of Sol. A were 0.77 mM and 49.33 mM, respectively. The free $[Ca^{2+}]$ of the solutions was calculated using a K_{app} for EGTA of $4.78 \times 10^6\,M^{-1}$ (Fink et al., 1986). Fibers were exposed to Triton X-100 for two minutes at the start of the experiment, in order to destroy all membranous compartments and stop SR and mitochondrial Ca^{2+} fluxes. During experiments, a brief exposure to Sol. B was used to return the force to base line before the next force response was measured. Measurements in GES were compared to control measurements made before and after GES exposure in order to compensate for the progressive small decline in force that occurs during these experiments. Steady-state force elicited after exposure to solutions of increasing free $[Ca^{2+}]$ were expressed as a percentage of maximum Ca^{2+}-activated force and plotted as a function of pCa ($-\log[Ca^{2+}]$). The data were fitted with sigmoidal curves using GraphPad Prizm (GraphPad Software Inc.), and the slope and pCa_{50} values (pCa value corresponding to 50% of maximum force) of the curves were determined for control conditions and in the presence of taurine. All skinned fiber experiments were conducted at room temperature (22–24 °C).

Contractile properties of isolated intact muscle

The EDL muscles were rapidly removed from the mice and attached with surgical thread to an isometric force transducer (Grass FT03). The muscles were maintained in a 20 ml bathing chamber containing Krebs Ringer solution (mM): NaCl, 121; KCl, 5.4; $MgSO_4$, 1.2; $NaHCO_3$, 25; HEPES, 5; Glucose, 11.5; $CaCl_2$, 2.5, pH 7.3. The Ringer solution was bubbled with carbogen and maintained at 30 °C. This temperature was chosen because it approaches the normal *in vivo* temperature of these muscles, but is within the range of temperatures that are optimal for maintaining isometric force *in vitro* (25–30 °C) (Segal et al., 1985, 1986).

The muscles were initially left to equilibrate for 10 min in the organ bath. The output of the force transducer was recorded and analyzed using a Powerlab 410 (AD Instruments) in chart mode. The muscles were stimulated supra-maximally via platinum electrodes, and the optimum length for active tension generation determined by incrementally stretching the muscle and measuring the maximal twitch force peak after stimulation. Twitch responses were elicited by a single 1 ms supramaximal stimulus pulse. The force–frequency relationship was determined by subjecting the muscles to stimulation frequencies of 10 to 160 Hz at 10 Hz intervals

(1 ms pulse duration, 300 ms burst width). The muscles were left to rest for 3 min between stimulation bouts to ensure recovery from fatigue. Maximal tetanic tension (mN/cm^2) was determined by dividing maximal tension (mN) by the total muscle cross-sectional area, which was determined by dividing the wet mass (mg) by the product of optimal muscle length (mm) and the density of mammalian skeletal muscle ($1.06\,mg/mm^3$).

The muscles were also subjected to a fatiguing stimulation protocol to test the fatigability of the GES-treated and non-treated muscles. This involved stimulation at 70 Hz (1 ms pulse duration), for 250 ms every second. The muscles were fatigued until they produced 30% of the original, pre-fatigue force. Time to fatigue to 75%, 50% and 35% of pre-fatigue peak force was determined from this data.

All measurements were expressed as mean ± S.E.M, unless otherwise stated. Significant difference between two means was evaluated using an unpaired Student's *t*-test. The fatigue and force vs. frequency data, were analysed using a MANOVA with a Newman-Keuls post hoc test. A p-value of 0.05 or less was considered to be significant. Statistical analysis was undertaken using the statistics software packages *GraphPad Instat* and *Statistica*.

Results

GES treatment

GES treatment significantly decreased the taurine content of the EDL muscles to less than 40% of control levels (Control $46.5 \pm 2.6\,\mu mol$ (g wet weight)$^{-1}$, $n = 6$; GES 17.6 ± 8.1 (g wet weight)$^{-1}$, $n = 2$, $p < 0.05$), but had no effect on the mean body mass of the mice (controls; 24.2 ± 0.51 g ($n = 12$), GES treated; 22.6 ± 0.63 g ($n = 10$).

Skinned fibre measurements

As GES is a competitive inhibitor of taurine uptake, and is preferentially accumulated in preference to taurine (Huxtable, 1982), skinned fibre measurements were undertaken to determine whether GES itself had any substantial effects on the excitation–contraction coupling mechanism in skeletal muscle which could confound interpretation of the results of contractile studies with respect to taurine depletion.

The presence of 20 mM GES significantly increased the peaks of depolarisation-induced force responses by $6.6 \pm 1.8\%$ ($p < 0.05$) ($n = 13$) (Fig. 1). This effect is considerably smaller than the effect of taurine on the peaks of depolarisation-induced force responses ($121 \pm 5\%$ of controls) measured under similar conditions previously in this laboratory (Bakker and Berg, 2002). This result indicates that GES-treatment should lead to a significant decrease in taurine-mediated effects on excitation–contraction coupling in skeletal muscle.

In order to examine whether GES was enhancing force production by altering the Ca^{2+} sensitivity of the myofilaments, the effect of GES on the force–Ca^{2+} relationship was examined in skinned fibres. Twenty mM GES significantly affected the force–Ca^{2+} relationship, producing a small decrease in the mean pCa_{50} value (control pCa_{50}: 6.18 ± 0.02, GES pCa_{50}: 6.12 ± 0.02, $p < 0.05$, $n = 9$), indicating a small decrease in the sensitivity of the contractile filaments to Ca^{2+} (Fig. 2). GES had no significant effect on the slope of the force–Ca^{2+} curves. This result indicates that GES must be increasing force output by altering events before Ca^{2+} activation of the myofilaments, such as SR Ca^{2+} release and/or uptake.

Contractile properties of intact EDL muscles

Peak twitch force levels were 23% lower in EDL skeletal muscles from GES treated mice than controls ($p < 0.05$)

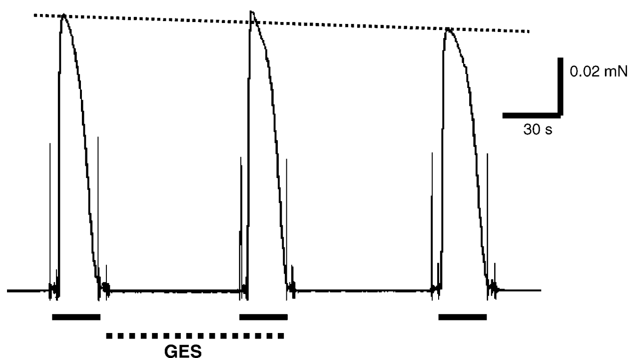

Fig. 1. An example of the effect of GES on depolarisation-induced force responses in skinned fibres. The solid black bars below the force responses represent exposure to the depolarisation solution. The presence of GES is shown by the lower dotted line. The upper dotted line represents the small gradual rundown in peak force that occurs under control conditions in these fibres

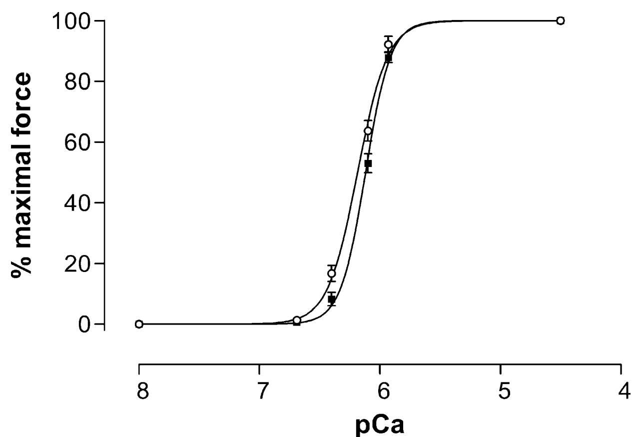

Fig. 2. Sigmoidal curves fitted to mean force values measured in skinned skeletal muscle fibres at different free Ca^{2+} concentrations in the presence (■) or absence (○) of acutely applied GES (20 mM). GES produced a small but significant decrease in the sensitivity of the contractile filaments to Ca^{2+} ($p < 0.05$, $n = 9$)

Table 1. Contractile properties of EDL skeletal muscles from control and GES treated mice

	Control	GES
Peak twitch force (P_t) (N/cm^2)	2.30 ± 0.17	1.77 ± 0.16*
Maximal specific force (P_o) (N/cm^2)	13.44 ± 0.6	11.54 ± 0.77
Ratio P_t/P_o	0.17 ± 0.009	0.15 ± 0.004

* $p < 0.05$

(Table 1). However, there was no significant difference in maximal specific force (maximal force per cross-sectional area) ($p = 0.0644$) or the twitch–tetanus ratio ($p = 0.9862$) (Table 1).

The lower twitch force output in the GES treated muscle suggested that decreased taurine levels may have significant effects at lower frequencies of stimulation, so we measured the force–frequency relationship in EDL muscles from control and GES treated mice. Force output increased in a sigmoidal manner with increased frequencies of stimulation (Fig. 3). The amount of force produced in the control EDL muscles ($n = 20$) was found to differ significantly from that produced by muscles from the GES-treated mice ($n = 13$) (Fig. 3) over the range of 50–100 Hz ($p < 0.05$), indicating that GES-treatment produces a significant shift to the right in the force frequency curve in EDL skeletal muscles. The GES muscles must be stimulated at higher frequencies to produce the same force output as control muscles.

In order to determine the effects of taurine depletion on fatigue in EDL skeletal muscle, the muscles from control and GES-treated mice were exposed to a stimulation frequency of 70 Hz for approximately 2–3 min. This frequency corresponds to the mean motorneuron output frequency

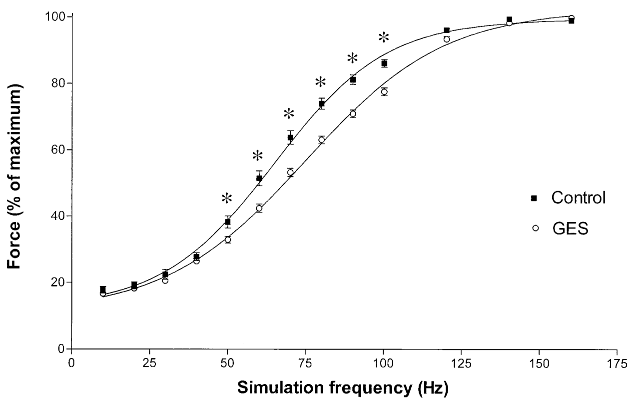

Fig. 3. The relationship between peak force (% of maximum force) and stimulation frequency in EDL muscles from control mice and mice chronically exposed to GES. The force–frequency relationships was shifted to the right by GES treatment *$p < 0.05$

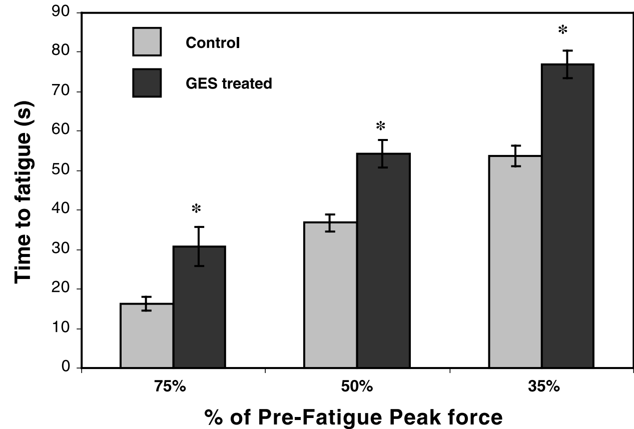

Fig. 4. Time to fatigue of EDL muscles from control mice and mice chronically exposed to GES. The time taken for peak force to drop to 75, 50 and 35% of the original pre-fatigue force level was measured during repeated stimulation at 70 Hz *$p < 0.05$

experienced by these muscles *in vivo* (Hennig and Lomo, 1987), and as expected, corresponds to the mid region of the force frequency curve (Fig. 3). Rates of fatigue at 70 Hz stimulation for 250 ms every second produced a rapid decline in force in EDL muscles from both the control ($n = 13$) and GES-treated groups ($n = 5$). The time to 75%, 50% and 35% of the initial pre-fatigue force was calculated, and muscles from the GES treated group showed slower times to fatigue ($p < 0.05$) (Fig. 4), suggesting that taurine depletion significantly slows fatigue in response to 70 Hz stimulation in EDL skeletal muscles.

Discussion

The results of this study show that taurine depletion has marked effects on the contractile physiology of mammalian skeletal muscle. Decreased taurine levels lead to a loss of force production at stimulation frequencies of 50 to 100 Hz. This result indicates that if taurine is lost during exercise, skeletal muscle force output will be compromised at stimulation frequency levels similar to that might be experienced by these animals during normal activity (Hennig and Lomo, 1987).

The GES treatment effectively decreased muscle taurine by approximately 60% in this study, a finding similar to the 50% reduction found in previous studies using this strategy (Huxtable, 1982; De Luca et al., 1996). Skinned fibre experiments undertaken in this study showed for the first time that GES also has an affect on excitation–contraction coupling in skeletal muscle, a possibility not considered by earlier studies (Huxtable, 1982; De Luca et al., 1996), and not surprising considering the structural

similarities between GES and taurine. However, the effect of acute GES on the peak of the depolarisation-induced force responses (Fig. 1), and the sensitivity of the contractile apparatus to Ca^{2+} (Fig. 2) was very small, and the physiological consequences should be minor.

Considering the minimal effects of GES, the force deficits shown in this study (Table 1, Fig. 3), are likely to be due to taurine depletion rather than GES accumulation as GES was considerably less potent than taurine at modulating excitation–contraction coupling (GES increased the peak of depolarization-induced force responses by only 6.6%, whereas taurine increased the peaks by over 3 times this amount: 21%, Bakker and Berg, 2002). Furthermore, as GES did produce a small taurine-like effect on force production in the skeletal muscle fibres, the effects of taurine depletion reported in this study may be slightly underestimated.

The effects of taurine depletion shown in this study are consistent with a reduction in the known effects of taurine on excitation–contraction coupling in skeletal muscle reported from cellular studies. Taurine has been shown to enhance SR Ca^{2+} release (Bakker and Berg, 2002) and SR Ca^{2+} uptake (Bakker and Berg, 2002; Huxtable and Bressler, 1973) in skinned fibres. Increased rate of SR Ca^{2+} release and increased SR Ca^{2+} content, due to enhanced SR Ca^{2+} uptake, would both act to increase the Ca^{2+} release and force produced in response to a single action potential. This conclusion concerning the intracellular action of taurine is supported by findings in cardiac muscle, where addition of taurine has also been shown to modulate the excitation–contraction coupling process by altering sarcoplasmic reticulum calcium handling, leading to increased cellular calcium release and increased force production (Franconi et al., 1982; Steele et al., 1990). In addition, depletion of taurine also led to a 2-fold decrease in the plasmalemmal calcium ATPase pumping activity in cardiac muscle (Harada et al., 1988).

Therefore, in this study taurine depletion should lead to less SR Ca^{2+} release per action potential-induced stimulation, which would mean that a greater action potential frequency would be required to release the same amount of Ca^{2+} as that triggered under control conditions. This decreased Ca^{2+} release would explain the shift in the force frequency curve to the right and the decreased specific twitch force found in this study in taurine depleted muscles. At high rates of stimulation (>100 Hz), Ca^{2+} release is likely to become so great that the effects of taurine become negligible, hence the lack of a significant difference in the maximal specific force values found between taurine depleted muscles and controls in this study.

The effect of taurine on decreasing the rate of fatigue was surprising. One of the main mechanisms thought to be responsible for fatigue is a decrease in the release of Ca^{2+} from the sarcoplasmic reticulum. This is likely to be due to ATP utilisation and the accumulation of the metabolic by-products of ATP hydrolysis, i.e., ADP, phosphate and increased free Mg^{2+} (Fryer et al., 1995; Westerblad and Allen, 2002; Steele and Duke, 2003). As taurine has been shown to increase SR Ca^{2+} release, taurine depletion might be expected to exacerbate the rate of fatigue in the EDL muscles, although this was not observed in this study. However, it must be kept in mind that the muscles were stimulated at 70 Hz, the mean frequency experienced by these muscles *in vivo* (Hennig and Lomo, 1987). At this physiological stimulation frequency, the initial force output during fatiguing stimulation at 70 Hz was approximately 53% of maximal force in the taurine depleted muscles and 63% of maximal force in the control muscles (Fig. 3). This means that the amount of work performed by the taurine-depleted muscles will have been 16% less than that performed by the controls. Less work performed by the taurine-depleted muscles means less ATP will have been utilised and therefore, lower levels of the fatigue-inducing metabolic bi-products of ATP hydrolysis will have been produced. This could then result in a reduction in the rate of fatigue in the taurine-depleted muscles.

The results of this study indicate that the loss of taurine during exercise at physiologically relevant stimulation frequencies may have two important effects on skeletal muscle performance, a reduced force output, and a decreased susceptibility to fatigue. This raises the possibility that *in vivo*, the loss of taurine could act as a molecular switch converting muscles from a power mode to an endurance mode.

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