Phenotypic adaptations in human muscle fibers 6 and 24 wk after spinal cord injury

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Talmadge, R. J., M. J. Castro, D. F. Apple Jr., and G. A. Dudley. Phenotypic adaptations in human muscle fibers 6 and 24 wk after spinal cord injury. J Appl Physiol 92: 147–154, 2002.—The effects of spinal cord injury (SCI) on the profile of sarco(endo)plasmic reticulum calcium-ATPase (SERCA) and myosin heavy chain (MHC) isoforms in individual vastus lateralis (VL) muscle fibers were determined. Biopsies from the VL were obtained from SCI subjects 6 and 24 wk postinjury (n = 6). Biopsies from nondisabled (ND) subjects were obtained at two time points 18 wk apart (n = 4). In ND subjects, the proportions of VL fibers containing MHC I, MHC IIA, and MHC IIX were 46 ± 3, 53 ± 3, and 1 ± 1%, respectively. Most MHC I fibers contained SERCA1. All MHC IIX fibers contained SERCA1 exclusively. SCI resulted in significant increases in fibers with MHC IIX (14 ± 4% at 6 wk and 16 ± 2% at 24 wk). In addition, SCI resulted in high proportions of MHC I and MHC IIA fibers with both SERCA isoforms (29% at 6 wk and 54% at 24 wk for MHC I fibers and 16% at 6 wk and 38% at 24 wk for MHC IIA fibers). Thus high proportions of VL fibers were mismatched for SERCA and MHC isoforms after SCI (19 ± 3% at 6 wk and 36 ± 9% at 24 wk) compared with only ~5% in ND subjects. These data suggest that, in the early time period following SCI, fast fiber isoforms of both SERCA and MHC are elevated disproportionately, resulting in fibers that are mismatched for SERCA and MHC isoforms. Thus the adaptations in SERCA and MHC isoforms appear to occur independently.

fatigue; fiber type; myosin heavy chain; sarcoplasmic reticulum; vastus lateralis

IN HUMANS, SPINAL CORD INJURY (SCI) results in adaptations in the physiological characteristics of the paralyzed muscles, including atrophy, loss of maximal force output, transformation toward fast phenotypic protein expression, including type II myosin heavy chain (MHC) isoforms, prolongation of relaxation time, and decreased resistance to fatigue (1, 7–11, 18, 20, 21, 30, 31, 40, 41, 43, 44, 54). The causes for the changes in relaxation time and resistance to fatigue have not been elucidated (9, 10, 43, 44).

Castro and colleagues (9) have demonstrated that both succinate dehydrogenase (SDH, a marker enzyme for oxidative capacity) and α-glycerophosphate dehydrogenase (GPDH, a marker enzyme for glycolytic capacity) activities were increased in human vastus lateralis (VL) muscle fibers, regardless of fiber type, of SCI individuals from 6 to 24 wk after injury. These data suggested that the increased susceptibility to fatigue after SCI in humans was not due to a deficiency in oxidative or glycolytic enzymatic activities related to ATP synthesis. These observations are supported by data from animal models of SCI showing that the activities of SDH and GPDH are elevated in soleus fibers of rats 1, 3, and 6 mo after a complete spinal cord transection (ST) (37).

Fibers containing various isoforms of MHC are associated with distinct contractile characteristics, such that there is an ordered progression in contractile velocities and ATP utilization rates of the fibers during activation. In rodents, the order from slowest to fastest (and lowest-to-highest ATP utilization rate) is MHC I, MHC IIA, MHC IIX, and MHC IIB (4, 5, 6, 17, 39). In humans, a similar relationship exists (24, 26, 27, 29); however, the MHC IIB isoform is not expressed in human limb muscle (14). Because fibers containing fast (MHC II) isoforms of MHC have higher ATP utilization rates than fibers with slow MHC isoforms, the MHC isoform content of the fiber could contribute to a higher ATP utilization rate during activation and an elevated susceptibility to fatigue (22). Dramatic changes in rat muscle MHC isoforms occur after a complete ST. For example, the rat soleus displays pronounced adaptations in whole muscle MHC isoform proportions and in the proportion of fibers containing specific MHC isoforms as early as 15 days following ST (50, 52). Within ~1 yr after ST, the rat soleus undergoes a nearly complete transformation from a predominantly slow (~90% MHC I) to a predominantly fast muscle (~90% MHC II) (52). However, relatively small changes in MHC isoform characteristics and Ca2+ actomyosin ATPase activity of human VL fibers were observed within the first 6 mo after SCI (11). Thus early changes in human muscle fatigability after SCI did not appear...
to be related to enzymes related to ATP synthesis or ATP utilization (9, 11, 19).

Alternatively, increased susceptibility to fatigue after SCI may be related to alterations in the Ca\(^{2+}\)-handling properties of the muscle fibers and specifically of the sarcoplasmic reticulum (SR). For instance, alterations in the ability of the SR to release and resequester Ca\(^{2+}\) appear to be related to the onset of fatigue (15, 16, 53). Furthermore, differences in the fatigability of various fiber types may relate to differences in SR properties. For instance, mammalian fast fibers contain the fast-fiber-specific isoform of the sarco(endo)plasmic reticulum Ca\(^{2+}\)-ATPase (SERCA) SERCA1, whereas slow fibers contain the slow-fiber-specific isoform SERCA2. Fibers with SERCA1 typically have higher SR Ca\(^{2+}\)-ATPase activities and Ca\(^{2+}\) uptake rates than fibers with SERCA2. However, the noted differences appear to be primarily a result of differential regulation. Each of the two SERCA isoforms found in mammalian skeletal muscle appears to be regulated by specific proteins that are distributed in a fiber-type-specific fashion. Regulatory proteins include phospholamban, which is thought to impart slow kinetic properties to the SERCA2 pump in slow fibers (23, 28), and sarcoplasm, a protein found in fast fibers that appears to confer fast pump kinetics to the SERCA1 isoform (34). In addition, fast fibers contain higher total amounts of SR (as measured by SR membrane volume percentage) and total SERCA protein (13, 32). Thus different fiber types have both qualitative and quantitative differences in SR properties, each of which may contribute to the greater fatigability of fast fibers (15, 16, 53). Therefore, to determine if changes in the SR were occurring after short-term SCI, we assessed the SERCA isoform content of individual muscle fibers relative to adaptations in MHC isoforms in the VL muscles of SCI subjects at two time points (6 and 24 wk) after SCI. We hypothesized that SCI would result in elevated proportions of VL fibers expressing the fast phenotypic isoforms of MHC and SERCA.

MATERIALS AND METHODS

Experimental subjects and sample preparation. Six clinically complete (aged 18–45 yr) male SCI patients were recruited from the Shepherd Center, Atlanta, GA. Patients included in this study represent a portion of the patients included in a series of previous studies (8–11). Five SCI patients were paraplegic, and one was quadriplegic. All patients were determined to have clinically complete injuries of ASIA Impairment Classification Scale A, i.e., no sensorimotor function detected below the level of the lesion, as determined by a neurological examination (12). Lesion levels were from C\(_6\) to T\(_{10}\). Four age-matched nondisabled (ND) male subjects served as controls. All subjects provided written informed consent after receiving an explanation of the risks and benefits associated with the study. Study protocol was approved by the Institutional Review Boards for Human Research at the Shepherd Center, University of Georgia, and Virginia Polytechnic Institute and State University. Muscle biopsies were taken from the right VL by using the Bergstrom technique (3). Biopsies were taken from the SCI subjects as soon as the subjects were clinically stable (~6 wk, SCI-1) and again at 24 wk post-SCI (SCI-2). Biopsies were taken from ND subjects at two time points 18 wk apart. Biopsies were frozen in isopentane cooled by liquid nitrogen and stored at −70°C until immunohistochemical analyses were performed. With the use of a cryostat microtome, 10-μm-thick serial cross sections were taken from each biopsy and placed on microscope coverslips in preparation for immunohistochemistry.

Immunohistochemical analysis. The MHC and SERCA isoform contents of individual fibers were assessed by using a series of monoclonal antibodies (MAbs) specific to MHC and SERCA isoforms (Table 1). A MAb to the sarcolemmal protein merosin (Vector Laboratories, Burlingame, CA) was also used to facilitate the identification of individual muscle fibers. Binding of the MAb was detected on the serial cryostat sections by using a biotinylated secondary MAb and avidin-biotin amplification procedures (49). Two serial sections were reacted with each MAb. Thus a total of 14 serial sections from each biopsy sample were immunohistochemically stained (including two sections with no primary MAb, which served as negative controls). An area, free from artifact in all 14 serial sections and containing between 40 and 65 fibers, was randomly selected for single-fiber MHC and SERCA composition analysis, and images of the region were generated with a Nikon Eclipse E400 microscope and a GMS-300 gray-scale microscopy system (Scion, Frederick, MD), which consists of a C饽ihu high-performance camera, Scion LG-3 gray-scale frame grabber, and Scion image software. Fibers that were present throughout all of the printed images for each biopsy were analyzed for MHC and SERCA isoform content. Approximately 45 fibers were analyzed per biopsy sample (~900 total fibers). The ~45 fibers sampled per biopsy specimen represent between ~20 and 90% of the total number of fibers within each biopsy specimen that was present throughout all

Table 1. MAb specificity

<table>
<thead>
<tr>
<th>MAb (Working Dilution)</th>
<th>MHC I (slow)</th>
<th>MHC Ila (fast)</th>
<th>MHC IIX (fast)</th>
<th>SERCA2 (slow)</th>
<th>SERCA1 (fast)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BA-D5 (1:10,000)</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BF-13 (1:10,000)</td>
<td>–</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BF-35 (1:20,000)</td>
<td>+</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IID8 (1:100)</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VE12;G9 (1:100)</td>
<td>–</td>
<td>–</td>
<td></td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

By using this series of monoclonal antibodies (MAbs), fibers that contain both myosin heavy chain (MHC) Ila and MHC IIX would label positively with MAb BF-35 and would be classified as MHC Ila fibers. +, Positive MAb-protein interaction; −, negative MAb-protein interaction. SERCA, sarco(endo)plasmic reticulum Ca\(^{2+}\)-ATPase.

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serial sections. The number of fibers analyzed per subject was held at ~45 to maintain consistency across all biopsy specimens. Mismatched fibers were defined as those containing a different isoform (fast vs. slow) or combination of isoforms for MHC vs. SERCA. Thus fibers with multiple SERCA isoforms but only fast or only slow MHC would be considered mismatched. Fibers with both SERCA and both fast and slow MHC isoforms would be considered as matched.

**Statistical procedures.** Statistical analyses (SigmaStat, SPSS) were performed using a two-way (group × time) repeated-measures ANOVA followed by the Student-Newman-Keuls method for significance tests between specific groups. The alpha level was set at $P \leq 0.05$. All data are presented as means ± SE with the number of subjects used as the $n$ value for calculation of the SE in all cases. For presentation purposes, the two ND time points (0 and 18 wk) are treated as one since there were no significant differences between them at an alpha level of $P \leq 0.05$.

**RESULTS**

**MHC composition.** The proportion of fibers containing MHC IIx was increased at both time points (~15-fold increase) after SCI, but no time-dependent increase was observed within SCI subjects (Figs. 1–3). There were no significant differences in the proportions of fibers containing only MHC I between SCI and ND subjects at either time point. In addition, there was no difference in the proportion of MHC I fibers in the SCI subjects between the two time points (40 ± 5% at 6 wk postinjury vs. 32 ± 5% at 24 wk postinjury). A small proportion (~3%) of hybrid fibers containing both MHC I and MHC II were observed only at the second time point after SCI (24 wk postinjury, SCI-2).

**SERCA composition.** As shown in Fig. 4, there were no significant changes in the proportion of fibers containing SERCA1 (fast isoform) exclusively. However, reductions in the proportion of fibers with SERCA2 (slow isoform) were evident at both time points after SCI. The proportion of fibers with SERCA2 alone was decreased by ~30% at 6 wk post-SCI (SCI-1) and ~65% at 24 wk post-SCI (SCI-2). Hybrid SERCA fibers (containing both SERCA1 and SERCA2) were increased in proportion by approximately twofold at 6 wk post-SCI (SCI-1) and nearly fivefold at 24 wk post-SCI (SCI-2). Thus the total percentage of fibers containing at least some SERCA1 (i.e., fibers with only SERCA1 plus fibers with both SERCA1 and SERCA2) was increased from ~60% in

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**Fig. 1.** Representative nondisabled (ND) vastus lateralis (VL) muscle cross sections stained immunohistochemically for the presence of myosin heavy chain (MHC) and sarcoplasmic reticulum Ca$^{2+}$-ATPase (SERCA) isoforms. A: MHC II (BF-13). B: MHC I (BA-D5). C: MHC I and IIa (BF-35). D: SERCA1 (fast). E: SERCA2 (slow). F: merosin (sarcolemma). Two representative fibers are labeled as follows: 1 = MHC I and SERCA2; 2 = MHC IIa and SERCA1. Scale bar in $F$ represents 100 µm.
ND subjects to ~72 and ~86% in SCI subjects 6 and 24 wk after injury, respectively.

**MHC and SERCA matching.** As shown in Table 2, the majority of MHC I fibers contained SERCA2 in the ND subjects. Likewise, the majority of MHC IIa and IIx fibers contained SERCA1 in the ND VL. However, after SCI, increases in the proportion of MHC I and MHC IIa fibers with both SERCA isoforms were evident. This resulted in significant increases in the total proportion of fibers that were mismatched for MHC and SERCA isoform composition after SCI that ranged from ~5% of all fibers in ND subjects to greater than 35% in SCI subjects 24 wk (SCI-2) after injury (Fig. 5). In addition, we observed that all MHC IIx fibers contained SERCA1, regardless of subject group.

**DISCUSSION**

**MHC isoform adaptations.** As expected, VL muscles of the SCI subjects contained higher proportions of fibers with MHC IIx, consistent with a MHC I or MHC IIa to MHC IIx transformation. Elevations in fast MHC that occur in other species after complete ST are qualitatively similar to those found in this study in humans after SCI. For example, rat, mouse, and cat soleus muscles acquire increased proportions of MHC IIx isoforms after complete ST (47, 48, 50–52). One difference in the transformations among the different species appears to be the time frame for the adaptations. In rats, the only mammal for which a complete time course has been determined, the predominantly slow soleus muscle undergoes a nearly complete transformation to a fast MHC phenotype by 6 mo post-ST (52). The soleus of ST cats, on the other hand, only transforms to ~30% MHC II6 mo post-ST (51). Data from this study, in contrast, suggest that only the initial stages of slow-to-fast fiber MHC transformation (hybrid slow and fast fibers) occur in human muscle by ~6 mo post-SCI. Why the time frame of MHC transformation among the fast fiber types and from slow to fast fibers is much faster in lower mammals is not clear. This may in part reflect the fact that slow muscles in rodents are highly responsive to unloading, whereas a mixed human skeletal muscle was examined in this study (47). However, adaptive responses to unloading appear to be less dependent on skeletal muscle fiber-type composition in humans compared with lower mammals (2, 9, 25, 47).
SERCA isoform adaptations. SCI subjects showed increased proportions of fibers with SERCA1 (fast SERCA) in combination with SERCA2 (slow SERCA) and reductions in fibers with only SERCA2. Thus the direction of adaptation was from slow to fast. The proportion of pure SERCA2 fibers in the VL decreased by \( \frac{40}{96} \) from ND subjects to \( \frac{28}{15} \) and \( \frac{15}{9} \) in SCI subjects 6 and 24 wk postinjury, respectively. This suggests that the onset of SERCA isoform adaptations from slow to fast occurs early after SCI and that the adaptations are progressive beyond 24 wk postinjury. However, the proportion of fibers containing SERCA1 alone was unchanged. This suggests that the adaptations in SERCA isoform expression were incomplete. Multiple possibilities exist for the incompleteness in SERCA adaptations after short-term SCI. First, it is likely that the time needed for complete transformation of the SERCA isoform in a fiber is longer than 24 wk. Second, it is possible that transformations may be complete at the gene transcription level but that additional time is required to completely replace the existing pool of SERCA protein in the SR. Unfortunately, turnover rates for SERCA proteins in human muscle are unknown. Also, the amount of SERCA1 in hybrid SERCA fibers is unknown. The immunohistochemical technique used yields only qualitative information as to the presence or absence of the particular protein isoform and cannot quantify the amounts of a particular isoform in a fiber. Thus it is possible that only small amounts of SERCA1 are present in hybrid fibers. However, due to the very large increase in the total proportion of fibers containing at least some SERCA1 (~60% in ND subjects compared with ~72 and 86% in SCI-1 and SCI-2 subjects, respectively), it is likely that the fibers do express substantial amounts of SERCA1 protein. Third, it is possible that fibers that show a hybrid-SERCA phenotype express both SERCA isoforms at the transcriptional level. It is interesting to note that

Table 2. SERCA isoform content of MHC-based fiber types in VL fibers from ND and SCI subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>MHC Isoform (%) of Fibers</th>
<th>SERCA Isoform (%) of Fibers</th>
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<tbody>
<tr>
<td></td>
<td>I (46%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>I and IIa (0%)</td>
<td>97 ± 2</td>
</tr>
<tr>
<td></td>
<td>IIa (53%)</td>
<td>100</td>
</tr>
<tr>
<td>SCI-1</td>
<td>I (40%)</td>
<td>29 ± 4*</td>
</tr>
<tr>
<td></td>
<td>I and IIa (0%)</td>
<td>84 ± 9</td>
</tr>
<tr>
<td></td>
<td>IIa (46%)</td>
<td>100</td>
</tr>
<tr>
<td>SCI-2</td>
<td>I (32%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>I and IIa (3%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>IIa (49%)</td>
<td>62 ± 14*</td>
</tr>
<tr>
<td></td>
<td>IIx (14%)</td>
<td>100</td>
</tr>
</tbody>
</table>

Values are means ± SE for the proportion of fibers of a given MHC isoform content that contains a specific SERCA isoform or combination. ND, nondisabled subjects; SCI, spinal cord injury; SCI-1, 6-wk SCI subjects; SCI-2, 24-wk SCI subjects. *Significantly different from ND (\( P \leq 0.05 \)).

Fig. 3. MHC-based fiber-type composition of VL muscles from ND and SCI subjects, as determined by immunohistochemistry. SCI-1, 6-wk SCI subjects; SCI-2, 24-wk SCI subjects. *Significantly different from ND (\( P \leq 0.05 \)).

Fig. 4. Quantification of fibers containing a given SERCA isoform in VL muscles from ND and SCI subjects, as determined by immunohistochemistry. *Significantly different from ND (\( P \leq 0.05 \)). †Significantly different from SCI-1 (\( P \leq 0.05 \)).

Fig. 5. Proportions of mismatched fibers (i.e., those that contain fast SERCA and slow MHC or vice versa) in VL muscles from ND and SCI subjects, as determined by immunohistochemistry. *Significantly different from ND (\( P \leq 0.05 \)). †Significantly different from SCI-1 (\( P \leq 0.05 \)).
MHC-based hybrid fibers become more prominent and appear to persist for long periods of time in rat muscles paralyzed for up to 1 yr (52). Thus SCI and ST may cause a discoordination of expression of phenotypic proteins that results in the generation of a stable population of phenotypically hybrid fibers.

**MHC and SERCA isofrom interrelationships.** The observation that large proportions of SERCA hybrid fibers were observed after SCI despite the presence of very few MHC hybrid fibers suggests that these two protein systems are differentially regulated. If differences in transformation of SERCA and MHC were simply due to differences in protein turnover time for the two systems, then reductions in the proportions of pure slow fibers for each protein (MHC and SERCA) would follow a similar time course, and differences should only be observed in the relative proportions of hybrid and pure fast fibers for each protein. In other words, the onset of adaptation would be similar for MHC and SERCA (i.e., loss of fibers with purely slow isoforms), but the completion of transformation would be different (i.e., generation of fibers with purely fast isoforms). The fact that SCI resulted in a significant reduction in the proportion of pure SERCA2 (slow) fibers despite no significant reduction in the proportion of pure MHC I (slow) fibers suggests that the differences in transformation of the two systems are, in part, due to new (i.e., fast) protein isoform expression and synthesis, not simply existing protein turnover. In fact, multiple signaling and transcriptional control mechanisms have been identified for the regulation of various phenotypic protein isoforms. These include the calcineurin and nuclear factor of activated T-cell system, myocyte enhancer factor (MEF)-2, MEF-3, myogenic regulatory factors, Ras, nuclear factor-1, and MUS-TRD1 (33, 35, 36, 42, 46, 55). It is now becoming clear that multiple pathways likely act in concert to alter the expression of various phenotypic protein systems. Just as the milieu of extracellular signals (electrical activation, load-bearing status, cell-cell contact, neural connectivity, thyroid hormone state, etc.) interact to control phenotypic gene expression, it is likely that multiple intracellular signaling mechanisms interact to mediate these adaptations.

**Potential relationships to muscle fatigue.** Human skeletal muscle becomes more fatigable shortly after SCI (9, 43). For example, Castro and colleagues (9) demonstrated a significantly greater loss of knee extension torque over two bouts of submaximal contractions (20 contractions/bout, 2-s rest between contractions, and 2-min rest between the 2 bouts) in electrically stimulated quadriceps femoris (primarily fast fibers) of SCI (−20–30% loss of force in subjects paralyzed for 6–24 wk) vs. ND subjects (−10% loss in force). Similarly, Shields (43) reported a significant reduction (−75% loss) in plantar flexion torque by the soleus muscle (primarily slow fibers) within 1–2 min after supramaximal activation (contractions elicited at 1 Hz for 4 min) in SCI subjects paralyzed for periods of >1 yr. In contrast, only a modest reduction (−20% loss) in torque was observed in SCI subjects paralyzed for periods of <6 wk. Thus both fast and slow muscles become more fatigable after SCI; however, the time course for the onset of fatigability may be specific for muscles of varying fiber type.

At present, the mechanisms leading to enhanced fatigability of human muscle after SCI are unknown (9, 11). However, it appears that the enhanced fatigability does not result from deficits in oxidative or glycolytic enzymes associated with ATP synthesis. This is suggested by data demonstrating that single VL-fiber activities of SDH (mitochondrial oxidative enzyme maker) and GPDH (glycolytic marker) increased to or above normal from 6 to 24 wk after SCI despite greater fatigability of SCI muscle (9). Thus the increased fatigability observed in human muscle after SCI appears to be unrelated to changes in metabolic enzymes associated with ATP synthesis. Other studies have also shown a dissociation between oxidative enzyme capacity and fatigability. For instance, chronic stimulation of rat or rabbit fast glycolytic muscle results in improvements in fatigue resistance that follow a different time course than increases in oxidative enzyme capacity (45). In fact, oxidative enzyme capacity continued to increase at time points after fatigue resistance had plateaued. This suggests that 1) oxidative enzyme levels are not the limiting factor with respect to at least some types of fatiguing stimulation and 2) factors other than oxidative enzyme levels contribute to the fatigability of transforming skeletal muscle.

Multiple studies have shown a link between SR function and the onset of fatigue of a muscle (for reviews, see Refs. 15, 16, 53). For instance, Ca$^{2+}$ cycling between the myoplasm and the SR is thought to be responsible for about one-third of all ATP consumed during contraction (38). Because the SERCA pump is the primary ATPase associated with Ca$^{2+}$ cycling, changes in its activity brought about by changes in isoform composition or other regulatory processes could significantly alter ATP utilization rates and contribute to the fatigability of a muscle. The relationship between SR function and fatigue appears to involve reductions in both Ca$^{2+}$ release from the SR and Ca$^{2+}$ uptake by the SR during and immediately after fatiguing contractions (15, 16, 53). It is possible that the fast muscle SERCA isofrom (SERCA1) is more susceptible to repeated contractile stimuli, resulting in decreased Ca$^{2+}$ uptake by the SR between contractions, which may result in reduced SR Ca$^{2+}$ stores available for release and subsequently reduce the amount of Ca$^{2+}$ released by the terminal cisternae of the SR and depress force production on activation (53). It is also possible that the presence of SERCA1 in a fiber is merely indicative of a fast SR phenotype and that other components of the SR (potentially including the ryanodine receptor, sarcoplasm, FK-binding proteins, etc.) are directly responsible for the enhanced fatigability of fast fibers. Regardless, SCI clearly resulted in enhanced proportions of fibers with SERCA1, and because, in general, fast fibers (those that contain SERCA1) are more highly fatigable than slow fibers (those with SERCA2), the switch in SERCA phenotype...
may indicate the transformation to a more fatigable SR profile. The present study demonstrates that the fast isoform of SERCA is upregulated soon after SCI in paralyzed human muscle. Adaptations in SERCA and MHC isoform expression appear to be asynchronous, resulting in the generation of high proportions of fibers with mismatched SERCA and MHC isoforms compared with muscle from ND subjects. The functional capacity of the mismatched fibers is presently unknown; however, because fibers containing the fast SERCA isoform are typically more fatigable than fibers with the slow isoform, it is reasonable to predict that the mismatched fibers (those containing fast SERCA) may have an increased susceptibility to fatigue. Future studies are needed to assess the functional capacity of these mismatched fibers with respect to fatigue resistance and the relative contribution of the SERCA isoform to fatigue resistance.

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