

Review of Spaceflight and Hindlimb Suspension Unloading Induced Sarcomere Damage and Repair

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Abstract

Hindlimb suspension unloading (HSU) and spaceflight microgravity induce atrophy of the slow adductor longus muscle fibers which, following reloading, exhibit eccentric contraction (EC)-like lesions (abnormal widening of sarcomeres with A band disruption and excessively wavy, extracted Z lines). These lesions are similar morphologically to those produced in normal muscles after strenuous eccentric exercise. It appears that atrophic muscles exhibit increased susceptibility to eccentric damage because lesions are produced during nonstressful voluntary movements upon return to weightbearing. The EC-like lesions are absent in the unweighted conditions, but appear in HSU rats 15-60 minutes after reloading and in spaceflown rats about 4 hrs after landing. By 12 hours, many EC-like lesioned sarcomeres are fully covered by longitudinal patches of Z line-like material which increases in density by 48 hours, producing the so-called "Z line streaming" morphology. In this case, Z line streaming is indicative of rapid repair of damaged sarcomeres rather than the onset of sarcomere breakdown. Immunoelectron microscopy is necessary to determine the composition of this dense material. By 9 days of reloading at 1 gravity, sarcomeres have regained normal structure, except for very rare persistence of faint Z patches. The morphological data indicate that Z patches serve at least two functions: 1) to permit contractile force to be transmitted across the damaged sarcomeres and 2) to provide a scaffold upon which sarcomeres are reconstructed in an active functional muscle.

Key words: eccentric contraction-like lesions, Z line streaming, rat skeletal muscle, microgravity.

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Postflight changes in atrophic skeletal muscles

With the exception of the recent 1993 Space Life Sciences-2 (SLS-2) mission achieving inflight tissue acquisition from rats, the past 20 years of studying the effects of spaceflight have relied on tissues from animals flown in space for 1 to 3 weeks and killed hours to days postflight [19-24, 31, 34]. The results of reloading stress, that is, returning to terrestrial gravity weightbearing, have been extremely informative because they have revealed weaknesses in muscle resulting from microgravity adaptation. Humans returning to Earth after 1-2 weeks of spaceflight experience delayed-onset soreness and weakness of leg muscles indicating postflight skeletal muscle damage, commonly associated with strenuous eccentrically-biased exercise (lengthening of a contracting muscle) [7, 10, 26, 27]. Safe transition between different gravity environments is an essential requirement for space travel, explor-

ation of planets and return to Earth. Our laboratory has participated in three Spacelab Life Sciences missions (Spacelab-3, SLS-1, SLS-2) and two Cosmos biosatellite missions (1887, 2044) permitting examination of atrophic skeletal muscles from spaceflown rats killed 2 hours to 14 days postflight [Table 1]. Collectively, these investigations provide specimens for defining the temporal changes induced in atrophic antigravity muscles re-exposed to the physical stress of gravity reloading. As discussed in this review, it is clear from our recent SLS-2 observations of rat muscles obtained in microgravity (no reloading) that sarcomere damage is strictly a postflight phenomenon [22, 23].

We first detected sarcomere damage in the adductor longus (AL) and soleus muscles of 5 rats (Cosmos 1887) killed 2 days postflight [24]. In addition to 38% fiber atrophy, there was severe segmental fragmentation of

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Table 1. Spaceflight mission and postflight reloading durations.

Mission	Launched	Duration	Body Wgt*	Time Killed
Spacelab-3	4/85	7.0 days	380g	pf 12-16 hrs
SLS-1	6/91	9.0 days	330g	pf 2-7 hrs pf 9 days
Cosmos 1887	9/87	12.5 days	300g	pf 48-54 hrs
Cosmos 2044	9/89	14.0 days	340g	pf 8-11 hrs
SLS-2	10/93	14.0 days	330g	if day 13 pf 2-7 hrs pf 14 days

Wgt* - postflight body weights of male rats

SLS - Spacelab Life Sciences

pf- postflight

if- inflight

fibers, contraction clots, and Z line-like streaming. Z line streaming is the presence of material with an electron density similar to Z lines that extends from the Z lines into the sarcomere to varying degrees [5, 8, 9, 13, 17, 18, 26]. Thrombosis, extravasation of red blood cells, interstitial inflammatory edema and severe tissue disruption suggested that some of these changes were secondary to ischemic/anoxic necrosis [24]. Thrombosis in the capillaries and postcapillary venules was present 6 to 7 hrs postflight for SLS-1 flight rats and much more extensive by 8 to 11 hours for Cosmos 2044 [20, 23]. Interstitial edema occurred in AL 2.3 hrs postflight and showed progressive worsening following mast cell degranulation 5-7 hrs postflight [23]. Defining to what degree ischemia/anoxia contributes to sarcomere damage postflight will require further studies.

The AL muscles of 5 rats orbited 14 days aboard Cosmos biosatellite 2044 and killed 8-11 hr postflight exhibited 23% fiber atrophy and sarcomere disruptions that were morphologically similar to eccentric contraction (EC) lesions detected in both humans and non-humans exposed to unaccustomed high load exercises [2, 3, 6, 8, 9, 14, 17, 18, 26]. At the light microscopic level, EC-like lesions are abnormally widened sarcomeres with lucent areas of missing A bands (Fig. 1). Ultrastructurally, there is fragmentation of A band thick filaments and wavy, somewhat extracted, Z lines (Fig. 2). EC-like lesions were present in about 44% of the muscle fibers examined and, on average, were $33 \pm 6 \mu\text{m}$ in length, involving an estimated 10 sarcomeres in series [20].

For SLS-1, 15 flight rats were videotaped and killed at approximately 15 minute intervals over a 2.3-6.8 hour postflight period, and muscles were processed for light and electron microscopy [22, 23]. The AL and soleus muscles both atrophied about 40% based on fiber cross sectional area measurements. Lucent EC-like lesions, involving 2 or more sarcomeres, first appeared in AL muscles 4 hrs after

reloading; none were detected in the soleus. Video recording of the movements of flight and ground control rats suggested that the AL muscles of spaceflown rats were subjected to eccentrically loaded contractions because the hindlimbs were abnormally flexed and splayed out (abducted) at the hip joint during standing. Plantarflexion, necessitating loaded contractions of soleus, was rare because the spaceflown rats shifted weightbearing to their heels with the foot dorsiflexed rather than the normal posture of standing on the digits and soles of the feet. This postflight abnormal locomotion for ≈ 300 g male rats was apparently not seen in younger (62 g at launch) female rats flown 6 days aboard STS-48 [34, M.E. Tischler personal communication]. McCully and Faulkner showed that muscles of mice were damaged by EC stimulation only when the muscle was actively contracting [15]. Passive stretching within physiological ranges did not produce damage. A future spaceflight experiment videotaping movements and monitoring EMG activities of the AL and soleus muscles is being developed to directly compare postflight use of these muscles. The prediction is that AL will be actively contracting during weightbearing to keep the hindlimbs from splaying out during standing. In contrast, the soleus will be recruited infrequently for standing upon return to Earth.

Regional occurrence and fiber type susceptibility of sarcomere lesions

For AL muscles of SLS-1 rats, EC-like lesions occurred in four times more fibers in the most proximal quarter ($4.3 \pm 4.0\%$) than in the most distal quarter ($1.0 \pm 0.7\%$) of the muscle [22]. In contrast, lesions were equally distributed in the midbelly and ends of the AL muscles of Cosmos 2044 rats [20]. Lesion distribution appears dependent upon the type of hindlimb movements (joint angles, muscle lengths, and peak tension loading) because Ogilvie et al. reported that EC lesions in rat solei were located predomi-

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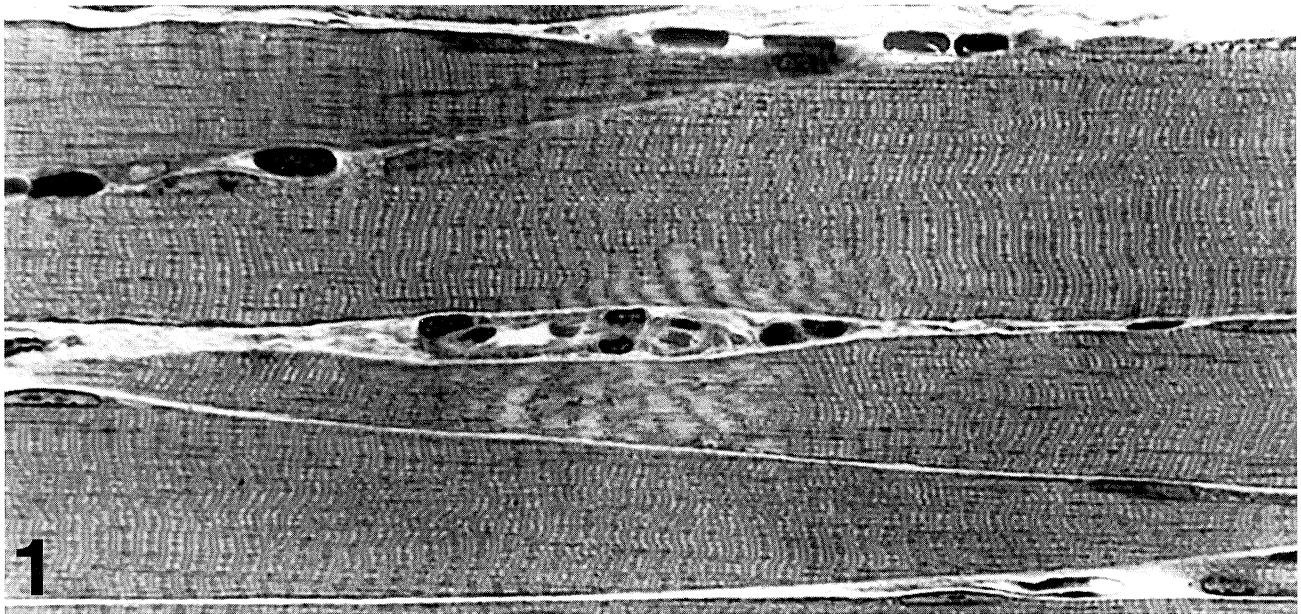


Figure 1. A toluidine blue-stained longitudinal section (0.5 μm) of an AL muscle from a rat flown 9 days in SLS-1 and killed 4 hours postflight. Eccentric contraction-like lesions, representing disruption of A bands and abnormal widening of the sarcomeres, are present at the center of the field in two muscle fibers separated by a blood vessel. Lesions and blood vessels are not independently distributed at the 99% confidence level. X1,000.

nated distally after downhill running and proximally after level running [18]. Moreover, spatial distribution analysis of EC-like lesions at the fiber-to-fiber level in the AL muscles of Cosmos 2044 rats revealed significant grouping of damage [31]. This observation is consistent with the diversion of mechanical loading (tension, strain and shear force) from injured fibers to neighboring fibers via a transmembrane path similar to that described by Tidball [32, 33].

In the AL muscles of reloaded HSU and SLS-1 flight rats, 92% and 68%, respectively of EC-like lesions observed occurred in the caudal region [12, 23]. The caudal region is composed predominantly of slow oxidative fibers, and the rostral portion contains a mixture of fast oxidative glycolytic and slow fibers [20]. This implies that slow fibers may be preferentially lesioned. Since slow fibers are lower threshold motor units compared to fast units, intense recruitment of slow fibers upon reloading and relatively less participation of fast fibers could explain the apparent selective disruption of slow fibers. Humans performing unaccustomed EC exercise showed lesions mostly in fast glycolytic fibers [3, 8, 9, 12, 26]. Fiber type involvement may depend on the type of exercise (e.g., running to exhaustion, eccentric bicycle exercise, resisted forearm extension) [2, 3, 9, 11, 12]. Fast fibers were also disrupted in the tibialis anterior muscles of rabbits and extensor digitorum longus muscles of mice following electrical stimulation and forced lengthening [14, 15]. Thus, sarcomere lesions may not be fiber type-specific per se, but limited to actively contracting fibers. Additionally, fiber susceptibility to EC lesions may depend upon whether

muscle fibers are atrophic or normal. Understanding fiber type differential susceptibility will be advanced by electrical stimulation studies which activate all fibers synchronously and eliminate the undefined variable of motor unit recruitment [14, 15, 29]. The issue of sarcomere damage is more complex because, following EC stimulation and exercise training, there are multiple morphologically distinct types of sarcomere lesions in addition to the EC-like lesions illustrated in figures 1 and 2 [9, 14, 29]. Studies are in progress to investigate fiber type susceptibility to lesion formation and determine whether the varieties of lesion types represent separate scenarios of primary sarcomere damage or different stages of a single process [30].

In addition to apparent fiber type susceptibility and regional variation in EC-like lesion occurrence, the AL muscles of SLS-1 flight rats showed that EC-like lesions and blood vessel location were not independent ($p < 0.01$, Fisher Exact test) (Fig. 1) [23]. From a stress/strain loading perspective, blood vessel lumens, essentially non-load-bearing "holes", may divert greater stress to the adjacent connective tissue and muscle fibers. Another possibility is that the chemical composition in the extracellular matrix surrounding blood vessels differs from non-vessel areas conferring unique stress/strain properties, leading to neighboring sarcomere disruption.

Sarcomere lesions following hindlimb suspension unloading

Simulations of the 12.5 day Cosmos 1887 and the 14 day Cosmos 2044 missions by hindlimb suspension unloading (HSU) of rats and inspection of AL muscles after 0, 1, 6, 12, and 48 hrs of reloading have provided further under-

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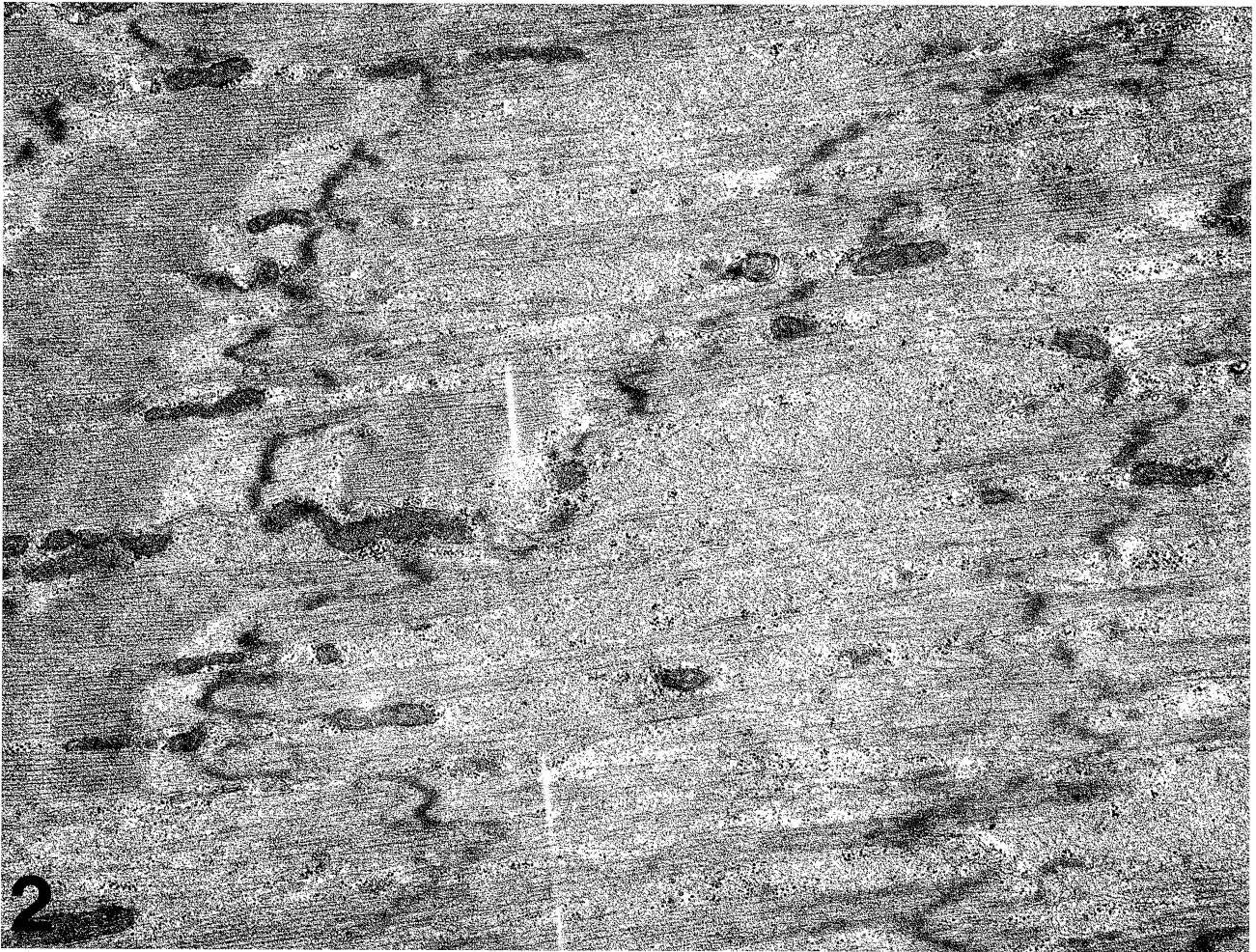


Figure 2. An electron micrograph of an eccentric contraction-like lesion in an AL muscle fiber of an SLS-1 flight rat returned to Earth for 4 hours. The damaged sarcomeres exhibit loss of A band thick filaments and diminished and excessively wavy Z lines. X20,000.

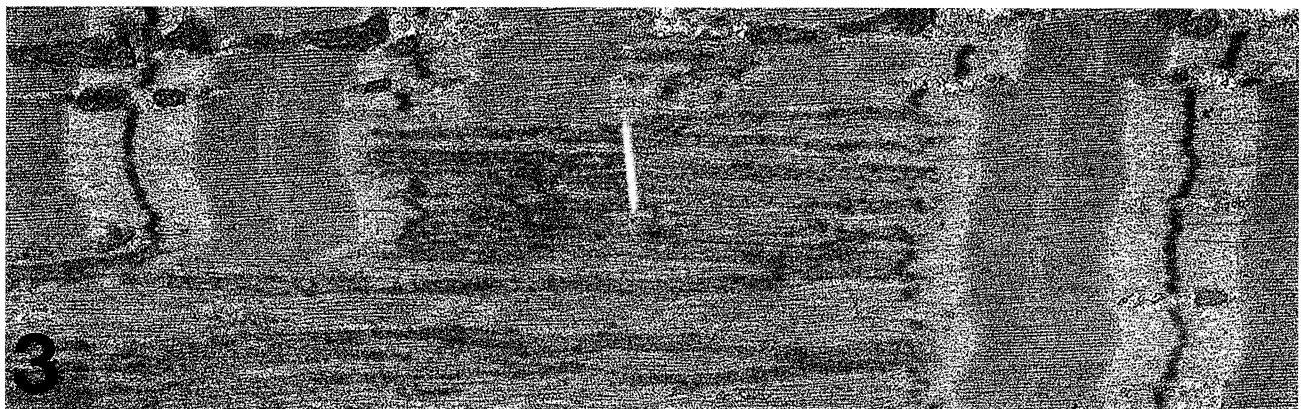


Figure 3. Extensive longitudinal patches of dense Z line-like material cover disrupted sarcomeres in an atrophic muscle fiber of a rat subjected to 12.5 days of hindlimb suspension unloading and killed after 48 hrs of reloading. X13,000.

standing of the temporal onset and resolution of EC-like sarcomere lesions [13, 20]. In these simulations, the AL muscles atrophied 28-36% and showed lesions in 9-15% of the fibers by 1 hr after reloading. Reloading consisted of simply allowing the suspended rats to return to voluntary weightbearing undisturbed in a vivarium cage [20]. By 12 hrs, and more extensively at 48 hrs, dense Z line-like material covered the lesioned sarcomeres suggesting major restructuring (Fig. 3) [13]. These times for HSU are consistent with postflight results, i.e., an early occurrence of EC-like lucent lesions (Cosmos 2044) and a late onset of Z line-like streaming (Cosmos 1887) [20, 24].

"Z line streaming" may be a misnomer for the 48 hour post HSU condition because the amount of Z line-like material appears too extensive to be simple redistribution (streaming) from Z bands, and multiple polyribosomes are prevalent at 12 hrs in the lesions, suggesting localized protein synthesis [13, 20, 26]. Ribosomes were also associated with damaged sarcomeres in humans after eccentric exercise [17]. A milder form of Z line streaming, not covering the full length (Z to Z) of damaged sarcomeres, can result immediately (< 1.5 hrs) after eccentric exercise in normal (nonatrophic) muscle fibers. In this case, physical disruption appears to widen Z lines by longitudinal displacement, although some accumulation of dense material is indicated by the ultrastructural appearance [14]. The temporal evidence of our reloading study clearly shows that EC-like lucent sarcomere disruption occurs first followed by rapid deposition of Z line-like material [13].

The extensive patches of Z line-like material are postulated to represent structural repair that serves to transmit contractile tension across the damaged sarcomeres, without which fibers may be pulled further apart at the lesions, disrupting the cell membrane and resulting in segmental fiber necrosis. The ischemia/anoxia associated with Cosmos 1887 may have retarded sarcomere repair and promoted segmental necrosis [24]. The rate of sarcomere repair may be faster when muscle activity is low following the initial damage; extensive patching was present in rats anesthetized for 1 hour after eccentric contractions of 25% strain [14]. Continued contractile activity may exacerbate sarcomere disruption, promoting proteolysis leading to lucent wide A bands.

It will be of interest to determine in future experiments whether the patches provide a period of immunity against sarcomere damage analogous to the 1-6 weeks of protection against inflammatory necrosis afforded by a single session of eccentric exercise [25]. Fridé'n postulated that sarcomere turnover was a mechanism of inserting new sarcomeres along the length of the myofibrils to better responded to the eccentric loading [6]. Interestingly, exercise weight training regimens typically recommend working different groups of muscles on alternate days to avoid injury. A rest period would permit patching of damaged sarcomeres and possibly reduce injury during subsequent training.

Eccentric exercise-induced sarcomere disruptions in normal muscles

More than 10 years ago, eccentric exercise of normal muscle was demonstrated to produce immediate (< 1 hr) and long lasting (many days) decreases in maximum force output and sarcomere damage for both humans and non-humans [17]. The degeneration/regeneration scenario for normal muscles is qualitatively similar to that observed postflight for atrophic rat muscles [20, 23, 24]. One major difference is that damage to normal muscle requires high intensity exercise whereas atrophic muscles are disrupted in rats during simple voluntary movements. This suggests that atrophic muscles adapting to unloading are more sensitive to eccentric contraction damage, although it does not necessarily follow that the primary failure mechanisms are identical. The A band and Z line disruptions indicate at least two types of failures: one involving the passive cytoskeletal structural elements and the other contractile proteins. The passive elements include desmin and titin, and the active components are myosin and actin [7, 35]. Tidball showed that the damage site varied with the state of activation i.e., passive lengthening an inactive muscle produced disrupted Z lines, and the same strain rate applied to a contracting muscle spared the Z lines but caused myotendinous junction failure [33]. According to Morgan, sarcomeres in the middle of a fiber are lengthened at the expense of shortening sarcomeres at the ends [33]. Sarcomere stretched beyond actin myosin overlap would load the structural components and lead to the commonly seen Z line damage [16]. On the other hand, breakage of the thick filaments at the M line is also possible because titins do not connect with each other across the M line and transfer the load to the middle of the thick filament [35]. Breakage could be either mechanical rupture of, otherwise normal, proteins in response to the strain or structural failure due to proteins weakened by protease nicking. A likely player is calcium activated protease stimulated by Ca^{2+} released from internal stores by shear forces acting on the sarcoplasmic reticulum and derived extracellularly through a leaky cell membrane [1, 4, 21, 36]. Reduction of damage by drugs chelating Ca^{2+} supports this latter hypothesis [4].

Numerous exercise studies have reported Z line alterations, ranging from simple wavy morphology, to marked broadening, streaming and complete dissolution [6, 8, 9, 14, 17, 18]. The electron dense material similar to Z lines may represent a variety of protein aggregates such as actin, myosin and tropomyosin, a host of proteins in addition to or other than Z line proteins such as desmin, spectrin, α actinin [8, 28, 35, 36]. Identifying the material for different lesion types will aid in understanding the mechanism of its formation. To elucidate the mechanisms of sarcomere disruption, it is necessary to investigate the earliest (primary) events in a temporal manner. These studies will be aided by controlled muscle stimulation and lengthening to generate damage reproducibly, and structural analysis of

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high resolution immunoelectron microscopy to identify the involved proteins.

Fates of sarcomere lesions

The ultimate fates of sarcomere lesions are currently under study. In rats flown on SLS-1, Z line-like streaming in AL muscles was only rarely detected 9 days postflight [23]. Muscle fibers had normal appearing sarcomeres even though they had to have experienced EC-like lesions and Z patching at 4-48 hrs postflight based on studies of flight rats killed at those times. Eccentrically damaged normal muscles are also eventually repaired [17]. Thus, Z patching may also provide a scaffold on which sarcomeres are reconstituted [13].

Thresholds for sarcomere lesions

The ability of sarcomeres to bear loads without structural failure may be regulated by the workload history of the muscle fibers which sets a hypothetical injury threshold [8]. Adaptation to low loads as in spaceflight and HSU would be predicted to lower the threshold for injury relative to 1G, and chronic hyper G would be expected to raise the threshold. On the other hand, threshold to injury may not be lowered during spaceflight and HSU. Rather, muscle atrophy with an unchanged body weight may reduce the muscle weight to body weight ratio and produce higher loading of the weaker antigravity muscle whose fixed threshold to injury is exceeded. Studies are in progress to distinguish between these possibilities.

Concluding remarks

The spaceflight investigations with inflight and post-flight muscle tissue acquisition have demonstrated that sarcomere disruptions result postflight, most likely in response to the stress and strain of reloading in terrestrial gravity. The hindlimb suspension model simulates this process with very high fidelity when rats are studied both unloaded and after return to weightbearing. Skeletal muscle is markedly resilient to injury; damaged sarcomeres show morphological signs of advanced repair within a few hours following disruption. The results of spaceflight and HSU studies on rats should aid development of protocols for reducing or eliminating muscle injury in humans who must function in different gravity environments.

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