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III. MISSION OVERVIEW AND SUMMARIES OF EXPERIMENTS

EFFECTS OF MICROGRAVITY ON RAT MUSCLE

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It is well known that humans exposed to long term spaceflight experience undesirable progressive muscle weakness and increased fatigability. This problem has prompted the implementation of inflight exercise programs because most investigators believe that the major cause of diminished muscle performance is a combination of disuse and decreased workload. Inflight exercise has improved muscle health, but deficits have persisted, indicating that either the regimens utilized were suboptimal or there existed additional debilitating factors which were not remedied by exercise.

Clarification of this question requires an improved understanding of the cellular and molecular basis of spaceflight-induced muscle deterioration. To this end, multiple investigations have been performed on the muscles from rats orbited 5-22 days in Cosmos biosatellites and Spacelab-3 (2,4,5,8,10-14,16,18,19, 21-23,25,27,28).

The eight Cosmos 1887 investigations that follow examined the structural and biochemical changes in skeletal and cardiac muscles of rats exposed to microgravity for 12.5 days and returned to terrestrial gravity 2.3 days before tissues were collected. Even though interpretation of these results was complicated by the combination of inflight and postflight induced alterations, the consensus is that there is marked heterogeneity in both the degree and type of responses from the whole muscle level down to the molecular level. Consistent with previous reports, red (oxidative) antigravity muscles (such as soleus, adductor longus, and vastus intermedius) were more atrophic than white (glycolytic) non-antigravity muscles (extensor digitorum longus, tibialis anterior, vastus lateralis and medialis) (2,4,5,13,14,16,17, 19,23,25,27). To some extent, fiber type composition predicts the degree of muscle atrophy. The most affected muscles were composed primarily of slow oxidative fibers whereas fast oxidative glycolytic and fast glycolytic fibers predominated in the least affected muscles. However, at another level of complexity, fibers of a given type located deep in a muscle (closer to the bone) exhibited greater atrophy than fibers of the same type located superficially in the same muscle (7). More limited in occurrence than muscle atrophy was the degeneration of muscle fibers, nerves, and micro-vessels which only involved the adductor longus and soleus muscles (24). Within the adductor longus, the pathology affected the mid-belly or endplate region more extensively than the ends or myotendinous zones.

Generally speaking, muscle enzyme properties shifted from slow oxidative toward fast glycolytic, but microheterogeneity was evident. During atrophy, contractile proteins, especially slow myosin, were preferentially lost relative to cytoplasmic non-contractile proteins (1,7,28). Increased ubiquitination of contractile proteins was observed (24). This process is postulated to promote selective protein degradation (26). Within slow oxidative fibers, slow myosin was replaced by fast myosin resulting in hybrid slow/fast fibers with elevated myosin ATPase activity (1,7). The shifts in cytoplasmic enzymes were not uniform. In soleus muscles, oxidative enzymes (citrate synthase and malate, beta-hydroxyacyl CoA, and

succinate dehydrogenases) decreased in step with muscle atrophy so that their concentrations were minimally altered (15). In contrast, glycogenolytic enzymes (glycogen phosphorylase, glycerophosphate dehydrogenase, lactate dehydrogenase, and pyruvate kinase) were not lost and their amounts per fiber increased during atrophy. In contrast to soleus, individual muscle fibers of the tibialis anterior showed elevated oxidative enzymes in atrophic fibers whereas glycogenolytic enzymes minimally changed in concentration (15). Mitochondrial enzyme changes were not uniform across the diameter of a muscle fiber. Mitochondria and their associated enzyme activities were essentially unchanged centrally but showed a marked decrease in the peripheral subsarcolemmal population (7,24). The mechanism by which proteins are turned over selectively and enzyme levels are altered within specific regions of atrophic muscle fibers are not understood.

The absence of detectable shifts in alpha-actin and cytochrome c mRNA levels may have resulted from the postflight muscle contractile activity because messenger levels can easily be altered within two days (29). Other parameters, such as atrophy, do not change markedly in two days and therefore, more accurately reflect microgravity induced changes. Distinguishing between microgravity induced and postflight readaptation induced alterations is a primary objective for the proposed studies in which muscles are harvested immediately (within 4 to 9 hours) upon landing (Cosmos July 1989, SLS-1) or inflight (SLS-2).

The muscle atrophy associated with spaceflight is most likely due to disuse and reduced workload. The observed decrease in mature collagen cross-links, collagen concentration and DNA concentration in the patellar tendons of flight rats is consistent with lowered workload (30). However, the Achilles tendon, serving the gastrocnemius/soleus/plantaris complex, was unchanged in the same animals (3). Again, these findings illustrate the diversity of skeletal muscle tissue responses. Activity and workload can be assessed by instrumenting muscles with electromyographic electrodes and tendon tension transducers. Systematic factors may have also contributed to atrophy. The suspected lower levels of growth hormone would have had a general catabolic effect on a skeletal muscle and elevated glucocorticoids, indicated by adrenal cortex hypertrophy, would have specifically induced fast fiber atrophy (9).

Some cardiac and skeletal muscle fibers were necrotic (20,24). The motor innervation of skeletal muscle was partially degenerated (24). Microcirculatory vessels were disrupted in skeletal muscle and abnormal in cardiac muscle (20,24). Repair of necrotic muscle fibers, motor axons, and blood vessels is dependent upon the effectiveness of complex processes of regeneration. Ground-based evidence predicts that regeneration may be compromised in space because of reduced active muscle tension and exposure of the dividing stem cells to damaging cosmic radiation (3,6,13). The ability of tissues to regenerate effectively during spaceflight is important to address in future missions.

Collectively, the muscle investigations of Cosmos 1887 clearly illustrate the wide diversity of muscle tissue responses to spaceflight. Judging from the summary report of this mission, heterogeneity of responses is not unique to muscle tissue. Elucidating the mechanism underlying this heterogeneity holds the key to explaining adaptation of the organism to prolonged spaceflight.

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