Alterations in Protein Metabolism During Space Flight and Inactivity

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Space flight and the accompanying diminished muscular activity lead to a loss of body nitrogen and muscle function. These losses may affect crew capabilities and health in long-duration missions. Space flight alters protein metabolism such that the body is unable to maintain protein synthetic rates. A concomitant hypocaloric intake and altered anabolic/catabolic hormonal profiles may contribute to or exacerbate this problem. The inactivity associated with bedrest also reduces muscle and whole-body protein synthesis. For this reason, bedrest provides a good model for the investigation of potential exercise and nutritional countermeasures to restore muscle protein synthesis. We have demonstrated that minimal resistance exercise preserves muscle protein synthesis throughout bedrest. In addition, ongoing work indicates that an essential amino acid and carbohydrate supplement may ameliorate the loss of lean body mass and muscle strength associated with 28 d of bedrest. The investigation of inactivity-induced alterations in protein metabolism, during space flight or prolonged bedrest, is applicable to clinical populations and, in a more general sense, to the problems associated with the decreased activity that occur with aging. Nutrition 2002;18:837–841. ©Elsevier Science Inc. 2002

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INTRODUCTION

The most consistent and physiologically relevant finding with space flight or forced inactivity is the loss of lean body mass (LBM). The loss of body protein and nitrogen during space flight affects crew function and crew health. The loss appears to be fairly rapid and affects muscle strength and function. After only 8 d aboard the Shuttle, magnetic resonance imaging demonstrated a muscle volume loss of 6% to 10% in locomotive (soleus-gastrocnemius, quadriceps) and postural (intrinsic back) muscle groups.1 An accompanying loss of muscle strength in the calf, for example, has been demonstrated after flights ranging from 72 to 237 d. A decrease in these muscles is expected because they are used minimally in zero gravity. However, the 28-d Skylab mission found a decrease in arm strength.4 Functionally, this decrement in muscle performance compromises crew capabilities during extravehicular activities and during emergency egress. These impairments are more significant when considering the proposed flight duration of the International Space Station and Mars projects, which entail extravehicular activities after months or years of microgravity exposure.

Not only are crew capabilities compromised, but clinical experience demonstrates that the loss of LBM will eventually affect crew health. Injury or trauma, and the accompanying forced inactivity, also result in a precipitous loss of LBM. This loss of LBM affects patient morbidity and mortality. Losses of LBM in excess of 10% are associated with an impaired immune function, and greater losses can inhibit wound healing and rehabilitation outcomes.5 As the loss approaches 40%, mortality is imminent.5 Although longer flights have yet to demonstrate LBM losses this severe, it is not clear when a new homeostasis of body protein is achieved. However, it is reasonable to suggest that the continued loss of LBM during longer-duration flights could compromise crew health in addition to crew function. When forced to adapt to the unique environment of space, human protein metabolism is altered such that net protein loss occurs.

PROTEIN ALTERATIONS DURING SPACE FLIGHT

Skeletal muscle protein turnover is a dynamic process that in part allows the body to maximize the use of a limited supply of amino acids.6 This continuous process of protein synthesis and breakdown enables the body to regulate enzymatic systems, remove defective proteins, and regulate metabolic processes.6 In terms of skeletal muscle proteins, the synthetic (anabolic) and breakdown (catabolic) processes strike a balance in a healthy individual on Earth. However, in space, this balance is perturbed such that the net balance (synthesis minus breakdown) is negative. A negative net balance equates to a loss of muscle nitrogen and can be achieved by an increase in breakdown or a decrease in synthesis. The investigations to date during space flight suggest that the primary adaptive response of muscle protein is a decrease in protein synthesis.

Despite almost 40 y of microgravity experience for the US and Soviet/Russian programs, there is limited understanding of the mechanisms responsible for the loss of LBM. The inherent difficulties and logistical constraints of conducting research in a zero-gravity environment are exacerbated by the limited opportunities for investigation. Although ground-based models, such as bedrest, have delineated some of these mechanisms in simulated microgravity,7,8 the requisite invasive techniques are unsuitable for space flight. Therefore, investigations of protein metabolism in space flight have used whole-body measures. These methods, although limited in the nature of data generated, are ideally suited...
for performance during space flight. Measures of whole-body protein synthesis during the space life science missions demonstrated an increase in synthesis early in flight. Concomitant with these data, Stein et al. found an increase in cortisol and cytokine secretion. This initial response in flight resolved between flight days 2 and 8. At mission lengths longer than 8 d, the primary alteration in protein metabolism becomes a decrease in whole-body protein synthesis.

Stein et al. investigated protein kinetics during long-duration (>3 mo) flights on the former space station Mir. In contrast to the findings on the space life science missions, whole-body protein synthesis decreased by 45% after 3 mo in orbit when compared with preflight rates. Our limited flight data suggest that the decrease in whole-body protein synthesis occurs much earlier in the exposure to microgravity. In addition to measures of whole-body protein metabolism, we endeavored to estimate skeletal muscle breakdown in space. By using an isotopic tracer of 3-methylhistidine, we adapted previous studies for use during space flight. Because blood draws during space flight are rigorously controlled and logistically difficult, bolus decay kinetics of 3-methylhistidine have been modeled with minimal collection time points. We found that 3-methylhistidine appearance, taken to represent skeletal muscle breakdown, increases early in flight (day 3). These data agree with those of Stein et al. and may be an indication of the early stress response of space flight.

However, Figure 1 shows that whole-body protein synthesis and muscle protein breakdown are decreased by flight day 6. With decreased rates of whole-body synthesis, the decrease in muscle protein breakdown indicates a reduction in muscle protein turnover. Thus, it is reasonable to hypothesize that the primary adaptation to space flight is not an increase in protein breakdown, but the body’s inability to maintain protein synthesis in skeletal muscle. As we have noted with inactivity models, a decrease in net muscle protein synthesis will occur in light of adequate caloric intake and result in a loss of LBM. However, unlike the bedrest model, there are a number of additional factors that contribute to the loss of LBM during space flight.

**CONTRIBUTING FACTORS TO THE LOSS OF LBM**

Given the current knowledge from space flight and ground-based investigations, several factors may contribute to the loss of LBM during microgravity. The first, the body’s inability to maintain protein synthesis during space flight, has been discussed and may be related to other physiologic disruptions. These include a reduced or inadequate dietary intake and an altered hormonal profile. A most apparent factor in the loss of LBM is the reduced energy intake during space flight. The reduction in caloric intake is apparent in short- and long-duration missions. On Shuttle missions ranging from 8 to 14 d, crew members consumed approximately 30% less than the calculated energy requirement. More importantly, these same astronauts consumed 30% less energy than the amount expended during flight. Using double-labeled water methods, Lane et al. noted that an astronaut’s energy requirement during space flight is the same as their requirement on Earth. Therefore, maintenance of ground-based caloric intake is appropriate. It has been proposed that the high work load and rigorous crew schedule of Shuttle missions often interfere with adequate energy intake. These factors also may contribute to the caloric deficit noted during long-duration missions. Stein et al. demonstrated that after 3 mo aboard the Mir space station, crew member caloric intake was 25% below preflight values. Although nitrogen intake was demonstrated to decrease during Shuttle flights, nitrogen intake was similar to preflight values during the Mir missions. An adaptive reduction of whole-body protein synthesis was noted in these Mir crew members, as the change in protein synthesis from preflight correlated with the change in energy intake. Of particular interest was one crew member who actually consumed 20% more calories than preflight; however, whole-body protein synthesis was still 30% below preflight values. The investigators reasoned that the reduction in whole-body synthesis was due to an energy deficit and a reduction in muscle size and activity. These data also may indicate that adequate energy intake alone may not be sufficient to ameliorate the loss of LBM.

There is sufficient evidence to suggest that the exposure to zero gravity alters the body’s hormonal profile. Analogous to a trauma-associated stress response, space flight adversely alters anabolic and catabolic hormonal profiles. Initial entry into microgravity increases cortisol excretion and blood cortisol concentrations, and urinary cortisol excretion remains elevated throughout short- and long-duration flights. Although cortisol may not be elevated to the same extent as in trauma or severe injury, excretion levels remain in the upper normal or above-normal range throughout microgravity exposure. The effects of elevated cortisol on LBM are exacerbated by a decrease in testosterone. Strollo et al. noted that blood testosterone concentrations decreased by 50% after only 5 d in flight. The duration or impact of this decrease has not been determined, but the alteration of the anabolic to catabolic hormone ratio would be expected to affect muscle protein. After trauma, the ratio of cortisol to testosterone is high and contributes to the profound breakdown of muscle protein. In burned patients, the correction of this ratio with testosterone administration restores the anabolic response of muscle to feeding.

We previously demonstrated an interaction between muscular inactivity and hormonal alterations patterned after those seen in space flight. Specifically, we demonstrated that the combination of inactivity and hypercortisolism is more catabolic to skeletal muscle than either condition alone. Subjects were made hypercortisolemic for 12 h and studied before and after 14 d of strict bedrest. Before prolonged inactivity, the effects of hypercortisolism on skeletal muscle protein synthesis and breakdown are indistinguishable from those of fasting. However, after 14 d of inactivity, hypercortisolism resulted in a significant increase in muscle protein breakdown. The combined effects of cortisol and inactivity were more catabolic to skeletal muscle than either individual condition. In fact, the combined effects of hypercortisolism and inactivity on skeletal muscle are similar to those noted in patients with severe burns. This interaction of inactivity and hypercortisolism may be applicable to space flight. Muscular inactivity, particularly in the locomotive and postural groups, is minimized in zero gravity. Although the leg muscles are used to propel and stabilize the astronaut while working in zero gravity, the require-
ment for more forceful and continuous muscular contraction is absent. Thus, as demonstrated on Earth, a reduced muscular activity combined with a prevailing hypercortisolemia could contribute to the loss of LBM during space flight.

THE BEDREST MODEL

Like space flight, the loss of LBM has been consistently documented with bedrest. A loss of postural and locomotive muscle mass is evident within 7 d of bedrest and continues throughout 17 wk. In addition to the associated loss of LBM, bedrest and the accompanying muscular inactivity replicate the underlying alteration in protein metabolism found in space flight. Our laboratory investigated the effects of 14 d of strict bedrest on whole-body and skeletal muscle protein metabolism. At the whole-body level, protein synthesis decreased by 14% after 2 wk, and skeletal muscle protein synthesis decreased by almost 50%. Because indices of liver protein synthesis were not changed, the decrease in whole-body synthesis was largely reflective of changes in skeletal muscle. In other words, the decrease in whole-body synthesis was essentially accounted for by the decrease in skeletal muscle protein synthesis. Although this direct relationship has not been definitively established in space flight, it is likely that, similar to the bedrest model, the adaptive decrease in whole-body protein synthesis is reflective of changes at the muscular level.

Although bedrest mimics the qualitative changes in protein metabolism associated with space flight, the model requires modification to accurately reflect the in-flight caloric deficit or hormonal alterations. The hormonal alterations associated with a stress response are not easily duplicated. For example, to imitate the mild hypercortisolemia associated with space flight, a continuous administration of cortisol or glucocorticoid could be used. Unfortunately, in contrast to the usual situation in which endogenous secretion of cortisol is stimulated, continuous administration of cortisol increases insulin production and confounds the interpretation of skeletal muscle protein metabolism. Hypocaloric feeding during bedrest is a plausible model, although not attractive in terms of subject compliance or willingness. Further, it is hard to duplicate the conditions that lead to the in-flight caloric deficit because it may be due to food preference or a decrement in taste sensitivity that cannot be simulated during bedrest. However, despite limitations in the ability to model certain aspects of space flight with bedrest, the effects of muscular inactivity on muscle protein metabolism adequately represent those demonstrated during space flight. In this regard, the bedrest model provides an opportunity to investigate the effects of potential exercise and nutritional countermeasures on skeletal muscle protein metabolism.

COUNTERMEASURE INVESTIGATION IN THE BEDREST MODEL

Because muscular inactivity has been demonstrated to decrease skeletal muscle protein synthesis, interventions known to increase net muscle protein synthesis would be of potential benefit. Our laboratory and others found that resistance exercise increases muscle protein synthesis. Thus, it was reasonable to expect that resistance exercise throughout bedrest could ameliorate the reduction in muscle protein synthesis. With the understanding that inactivity is no longer applicable at a certain volume of exercise, the key is to find a sufficient amount of exercise, or muscular activity, that will maintain muscle protein synthesis. This is particularly applicable to space flight because mission requirements and constraints allow for limited exercise opportunities. We studied the effects of resistance exercise, accomplished every other day throughout 14 d of bedrest, on muscle protein synthesis. The knee extensors were exercised from a supine position with the use of a horizontal leg-training device. Training volume progressively increased such that, by the third session, subjects performed five sets of eight repetitions. Considering familiarization, the progression of training volume, and the use of a minimal volume on day 13 to preclude the interference of acute exercise effects, five sets of eight repetitions were performed only three times throughout the 14-d bedrest period. This protocol was sufficient to maintain the protein synthetic rate in subjects who exercised, whereas muscle protein synthesis decreased in non-exercising subjects by almost 50%. The maintenance in protein synthetic rate was associated with a maintenance in muscle strength. Although the minimal activity and required time commitment of this exercise protocol would be attractive during space flight, it is possible that a lower exercise volume would suffice in maintaining muscle protein synthesis and strength. The exercise group demonstrated a non-significant 30% increase in protein synthesis, indicating that a lesser training volume may be effective in maintaining protein synthesis. Although the optimal volume and paradigm have yet been developed, resistance exercise is an attractive countermeasure to ameliorate the inactivity-related decrease in muscle protein synthesis and strength.

A nutritional intervention that stimulates muscle protein synthesis might benefit astronauts. In addition to its effects on muscle protein, a nutritional supplement could ameliorate the hypocaloric intake that is so common with space flight. We have long studied the effects of amino acids on muscle protein metabolism. Our laboratory showed that administration of essential amino acids, whether by infusion or oral ingestion, stimulates net protein synthesis in skeletal muscle. Further, we found that the addition of carbohydrate to an amino acid solution enhances the synthetic response of muscle protein. Based on these findings, we proposed that the daily administration of an essential amino acid/carbohydrate supplement during 4 wk of bedrest would preserve body protein and muscle function. Although this work is ongoing, preliminary results are encouraging. Preliminary data on three treatment and two placebo subjects indicated that the amino acid/carbohydrate supplement maintains leg muscle fiber diameter, whereas the placebo group demonstrated an approximate 50% decline in fiber diameter (Fig. 2). The maintenance of muscle fiber diameter translates to a diminished loss of LBM in the legs. Figure 3 shows that the loss of lean mass in the legs was markedly greater in the placebo group than in the treatment group. While the supplement is capable of ameliorating the loss of LBM, its effect on muscle strength is not as clear. Although the data are incomplete in both groups, muscle function and strength measures in the treatment group may decline over the first 2 wk and then remain constant until week 4, whereas the decline in the placebo group
continues throughout the entire period. If this trend continues, the combination of exercise and nutritional supplementation provides a reasonable next step in the effort to maintain muscle mass and function during inactivity.

Taken together, these studies demonstrate the capability and practicality of the ground-based bedrest model in the investigation of potential in-flight countermeasures. This model of muscular inactivity produces alterations in muscle protein metabolism that are similar to those during space flight. In addition, this model allows for strict scientific control, use of more invasive procedures to study protein kinetics, and timely investigation of interventions.

EARTH-RELATED BENEFITS

The study of muscle protein alteration in microgravity is of great potential benefit to Earth-bound populations. The stress response and required adaptation to muscular inactivity are analogous to patients recovering from trauma, injury, or major orthopedic surgery. Further, the inherent muscular inactivity and hormonal alterations that accompany these insults on Earth are similar to those experienced in space flight. However, the study of space flight offers a unique model for the study of muscle protein loss without accompanying insult or injury. This is particularly beneficial in the study of potential interventions designed to ameliorate muscle protein loss. Although the constraints of space flight present research challenges, the ability to study a stress state in an otherwise healthy individual allows for initial investigations of interventions designed to counteract the loss of muscle protein. If these perspective interventions prove efficacious in astronauts, then it is reasonable to extend these examinations to patient populations. Further, models of space flight designed to assess the role of inactivity on muscle mass are particularly relevant to the study of sarcopenia, i.e., the loss of muscle mass with aging. It is clear from the results of recent studies that, rather than being entirely an inevitable course of aging, sarcopenia in part results from inactivity. Understanding the mechanisms operative in bedrest are thus likely to be applicable to the elderly population.

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