Muscle Protein Metabolism in the Elderly: Influence of Exercise and Nutrition

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Catalog Data

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Abstract/Résumé
Although the causes of sarcopenia are multi-factorial, at least some, such as poor nutrition and inactivity, may be preventable. Changes in muscle mass must be a result of net muscle protein breakdown over that particular time period. Stable isotope methodology has been used to examine the metabolic basis of muscle loss. Net muscle protein breakdown may occur due to a decrease in the basal level of muscle protein synthesis. However, changes of this type would likely be of small magnitude and undetectable by current methodology. Hormonal mediators may also be important, especially in association with forced inactivity. Net muscle protein breakdown may be also attributed to alterations in the periods of net muscle protein synthesis and breakdown each day. Reduced activity, combined with ineffectual nutrient intake, could lead to decreased net muscle protein balance. Chronic resistance exercise training clearly is an effective means of increasing muscle mass and strength in elderly individuals. Although sometimes limited, acute metabolic studies provide valuable information for maintenance of muscle mass with age.

Deux des multiples causes de la sarcopénie peuvent faire l’objet d’une intervention préventive : mauvaise alimentation et inactivité. La perte de masse musculaire est le résultat d’une perte nette de protéines musculaires durant une certaine période. La méthode des isotopes stables est utilisée pour analyser les fondements métaboliques de la fonte musculaire.

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La perte nette de protéines musculaires peut être due à la réduction du niveau de base de synthèse des protéines. Une telle réduction serait vraisemblablement de faible importance et non détectable par les méthodes actuelles. Les médiateurs hormonaux ont probablement leur importance, surtout dans le cas d’une inactivité forcée. La perte nette de protéines musculaires peut aussi être due à des modifications quotidiennes des périodes de synthèse et de dégradation des protéines. Une mauvaise alimentation combinée à moins d’activité peut modifier le bilan protéique net. L’entraînement à la force est manifestement un moyen d’augmenter la masse et la force musculaires chez les personnes âgées. Malgré leurs limites, les études métaboliques sur l’entraînement à court terme nous procurent des informations précieuses au sujet du maintien de la masse musculaire avec l’âge.

Introduction

Disability and impaired functional capacity are often associated with aging (Evans and Cyr-Campbell, 1997). Diminished muscle mass and reduced strength contribute to impaired functional capacity (Bassey et al., 1992; Hyatt et al., 1990; Rantanen et al., 1999a, 1999b) leading to reduced independence and quality of life (Daley and Spinks, 2000; Winograd et al., 1991). The reduction in muscle mass and strength with age is commonly referred to as sarcopenia (Evans, 1995). Sarcopenia is considered a serious health care issue. It has been estimated that the health care costs due to sarcopenia approach $300 billion (Booth et al., 2000).

The cause of sarcopenia is undoubtedly multi-factorial. Contributing factors could include intrinsic age-related changes of the muscles, genetics, hormonal changes, undernutrition, and increased inactivity. The relative importance of each of these factors is extremely complex and variable and has yet to be completely resolved. However, prevention of many of the detrimental aspects of sarcopenia may best be accomplished by focusing on nutrition and inactivity. It is commonly believed that disuse accounts for as much as 50% of the decline in work capacity with aging (Smith and Gilligan, 1983). Loss of muscle mass due to aging is remarkably similar to that due to inactivity (Bortz, 1982). Thus, given the decreased level of activity as the population ages (Roth et al., 2000; Voorrips et al., 1993), it may be appropriate to redefine the physiology of aging as the physiology of disuse (Wilmore, 1991).

Conversely, exercise interventions, particularly resistance exercise, have been shown to be very successful in reversing the loss of muscle mass and strength in elderly individuals (Fiatarone et al., 1990, 1993; Frontera et al., 1988; Hurley and Roth, 2000; Tracy et al., 1999). After the age of 50 years, muscle mass is lost at a rate of approximately 6% (Lynch et al., 1999) and muscle strength at a rate of approximately 12–14% (Larsson et al., 1979; Metter et al., 1997). In previously untrained elderly individuals, 2–3 months of strength training resulted in muscle mass increases from 6–45% (Fiatarone et al., 1990, 1994; Frontera et al., 1988; Hikida et al., 2000; Tracy et al., 1999). Thus, a short period of strength training may reverse as much as 2–3 decades of muscle loss. Similarly, strength gains ranging from 25–100+% have been reported (Fiatarone et al., 1990, 1994; Frontera et al., 1988; Hikida et al., 2000; Tracy et al., 1999; Welle et al., 1995; Yarasheski et al., 1999) following relatively short-term resistance exercise training. Whereas it is clear that aging leads to decreases in muscle size and strength, it appears that these losses may be reversed by increasing activity.
In order to understand the metabolic mechanisms responsible for the loss of muscle with advancing age, investigators have begun to examine the changes in muscle protein metabolism. Since the major component of muscle, excluding water, is protein, muscle loss over a given time period will occur only if muscle protein breakdown exceeds muscle protein synthesis. Thus, an alteration in muscle protein synthesis, muscle protein breakdown, or both is necessary for the development of muscle loss with aging. That is, a 6% per decade loss of muscle mass (Lynch et al., 1999) can be attributed only to a cumulative net muscle protein breakdown, via either a reduction of muscle protein synthesis and/or an increase in muscle protein breakdown. Perhaps the most parsimonious explanation for net muscle protein breakdown with advancing age would be changes in basal levels of muscle protein synthesis and/or muscle protein breakdown. Alternatively, basal levels of muscle protein metabolism may be unchanged, but alterations due to physical activity and/or nutrition may be responsible for the overall net muscle protein breakdown. Reductions in the quantity or quality of physical activity or nutrient intake could influence muscle protein metabolism, as could the response of muscle protein metabolism to activity or nutrition.

This review will examine the changes in muscle protein metabolism with aging and the influence of nutrient intake and physical activity, or lack thereof, on these metabolic changes as they relate to the loss of muscle mass and strength. The focus will be on studies reporting measurements of muscle protein metabolism in vivo in humans, while animal and in vitro models will be used primarily as supportive evidence.

Methodology

Whereas it is clear that muscle mass and strength are reduced in aged individuals, it is not yet clear that these changes are due to alterations in muscle protein turnover. Changes in muscle mass must be related to a change in the relationship of muscle protein synthesis and muscle protein breakdown. Thus, measurement of both muscle protein synthesis and breakdown is essential for a complete understanding of the metabolic mechanisms behind changes in mass and strength with age. Only recently have methods become available to measure muscle protein synthesis and breakdown in vivo in humans. To date, the majority of the work investigating the effect of aging on muscle protein metabolism is limited to measurement of muscle protein synthesis. Very few studies have determined the rate of muscle protein breakdown in elderly individuals. The most widely used method to measure muscle protein synthesis is the fractional synthetic rate (FSR) of muscle proteins (Carraro et al., 1990; Nair et al., 1988). FSR is determined by infusing stable, isotopically labeled amino acids (usually either leucine or phenylalanine) and measuring the rate of incorporation of the label into muscle protein over time in relation to the enrichment of the precursor during that time. FSR can be determined for the sum of all muscle proteins (usually termed mixed muscle protein), for subfractions of muscle protein (e.g., myofibrillar, sarcoplasmic or mitochondrial), or for individual muscle proteins (e.g., actin or myosin heavy chain). More recently, a method was developed to directly measure both muscle protein synthesis and muscle protein breakdown based on the disappearance and appearance, respectively, of labeled amino acids from the muscle intracellular free amino acid
pool (Biolo et al., 1992, 1994, 1995a). Determination of muscle protein synthesis and breakdown allows a more complete assessment of the metabolic processes that determine net muscle protein balance (muscle protein synthesis minus breakdown) during the aging process. As will be demonstrated, stable isotope methodology is not without its limitations. However, it is a valuable tool with which to examine acute changes in muscle protein metabolism that provides us with information about changes in muscle protein metabolism. Information of this sort may then be utilized to develop and examine interventions that may prevent or reverse age-associated muscle loss.

**Alterations of Muscle Protein Metabolism with Age**

Muscle loss will occur only if net muscle protein balance is negative (i.e., breakdown exceeds synthesis) over a given period of time. This time period would be on the order of decades for sarcopenia. Thus, over decades, periods of net muscle protein breakdown must exceed net muscle protein synthesis. On any given day, there are periods of both net synthesis and net breakdown, given normal feeding cycles. It has been suggested that the basal level of muscle protein synthesis is reduced by aging (Balagopal et al., 1997; Hasten et al., 2000; Rooyackers et al., 1996; Yarasheski et al., 1993), and thus there is a constant decrement in net muscle protein balance that leads to muscle loss. Reductions of mixed muscle protein FSR from 12–40% have been reported. Certainly, it is intuitively satisfying to accept a reduction of muscle protein synthesis as a major mediator for muscle loss with aging. On the other hand, several authors (Balagopal et al., 1997; Hasten et al., 2000; Volpi et al., 1999, 2000, 2001) have reported no difference in mixed muscle protein FSR between young and elderly adults. Interestingly, two studies reported mixed muscle FSR in elderly that was both lower than and similar to young depending on the precursor used to calculate FSR (Balagopal et al., 1997; Hasten et al., 2000). Furthermore, although no direct comparison to young subjects was made, values of mixed muscle FSR in elderly have been reported (Urban et al., 1995; Yarasheski et al., 1999) that are similar to those reported for young adults by others (Biolo et al., 1995b; Phillips et al., 1997, 1999; Volpi et al., 2001). Thus, there is an inconsistency in the literature, even within individual papers. A summary of mixed muscle protein FSR from various studies is presented in Table 1.

It is uncertain exactly why there are discrepancies in the difference of muscle protein synthesis between studies. However, the most likely explanation is that methodological differences are important. If reduced muscle protein synthesis with age accounts for the associated muscle loss, then it must be very small. A 6% loss of muscle protein per decade, if constant, would be only about 0.0016%/d or 0.00007%/h. FSR measurements simply cannot be made with this kind of precision, thus detection of this type of difference is not possible. A decrease in muscle protein synthesis in the range of 30–40%, without a concomitant equivalent decrease in muscle protein breakdown, would result in a rate of muscle loss much larger than 6% per decade. Normal FSR in young individuals ranges from 0.04–0.06%/h. A 30% decline would be -0.012–0.018%/h, in other words, orders of magnitude greater than the difference (0.00007%/h) that accounts for the observed loss of muscle mass with age. Furthermore, in 86 young subjects from our laboratory (unpublished data) and 22 elderly subjects from our laboratory (Volpi et al.,
Table 1  Summary of Studies Reporting Mixed Muscle Protein Fractional Synthetic Rates (FSR) in %/h

<table>
<thead>
<tr>
<th>Reference</th>
<th>Tracer</th>
<th>Plasma α-KIC precursor</th>
<th>Muscle IC fluid AA precursor</th>
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<tr>
<td></td>
<td></td>
<td>Young Mixed muscle</td>
<td>Elderly protein FSR</td>
</tr>
<tr>
<td>Yarasheski et al., 1993</td>
<td>$^{13}$C-Leu</td>
<td>0.049 ± 0.004</td>
<td>0.03 ± 0.003</td>
</tr>
<tr>
<td>Urban et al., 1995</td>
<td>$^{13}$C$_5$-Phe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rooyackers et al., 1996</td>
<td>$^{13}$C-Leu</td>
<td>0.043 ± 0.002</td>
<td>0.038 ± 0.003</td>
</tr>
<tr>
<td>Balagapol et al., 1997</td>
<td>$^{13}$C-Leu</td>
<td>0.0471 ± 0.0028</td>
<td>0.0359 ± 0.0022</td>
</tr>
<tr>
<td>Volpi et al., 1999</td>
<td>$^2$H$_2$-Phe</td>
<td></td>
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<tr>
<td>Yarasheski et al., 1999</td>
<td>$^{13}$C-Leu</td>
<td></td>
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<tr>
<td>Hasten et al., 2000</td>
<td>$^{13}$C-Leu</td>
<td>0.048 ± 0.003</td>
<td>0.037 ± 0.003</td>
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<td>Volpi et al., 2000</td>
<td>$^2$H$_2$-Phe</td>
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Plasma α-KIC = plasma α-ketoisocaproate enrichment as precursor for FSR calculation; muscle ic fluid aa = muscle intracellular fluid amino acid enrichment as precursor for FSR calculation. Diff = difference between FSR in vastus lateralis of elderly and young subjects in the same study.
and other laboratories (Nair et al., 1988), the coefficient of variation for mixed muscle protein FSR has been reported to be from 28% up to 35–40%. Thus, if a reduction of basal muscle protein synthesis is responsible for the loss of muscle observed with aging, it is likely a very small reduction that would be difficult to detect with the methodology available. In fact, muscle loss associated solely with a reduction of muscle protein synthesis of 35–40% must be catastrophic, up to 60% loss of muscle in one year (Volpi et al., 2001). Intuition, as well as practical experience, renders this an unlikely possibility, thus making a much smaller, undetectable decline in muscle protein synthesis seem more tenable.

Of course, if individuals with much larger decrements of FSR with age are studied, then a larger difference may be recorded. There is a broad range of activity and health among the elderly, and differences in the study population chosen may be a factor in the dissimilarity in muscle protein synthesis reported in different studies. In a carefully controlled study, muscle protein synthesis was recently compared in a large sample of elderly and young adults (Volpi et al., 2001). Activity and diet were carefully controlled and muscle protein synthesis was calculated using three separate methods, each with a different set of assumptions. Muscle protein synthesis in the elderly was not less than in the young, but was even slightly greater than in the young. Thus, when a large cohort was studied under carefully controlled diet and activity conditions, the notion that sarcopenia results from a reduction in the basal level of muscle protein synthesis is not supported.

Alternatively, or additionally, the choice of precursor may influence the results of studies examining muscle protein synthesis in elderly and young adults. In each of the studies reporting a significant difference in mixed muscle protein FSR between elderly and young adults, plasma α-ketoisocaproate (KIC) represented the precursor enrichment for the calculation of FSR from 13C-leucine infusions (Nair et al., 1988). Volpi and colleagues (Volpi et al., 1999, 2000, 2001), on the other hand, utilized labeled phenylalanine and muscle intracellular phenylalanine as the precursor for calculating FSR (Table 1). It is conceivable, but unlikely, that the choice of amino acid would contribute to a difference in the rate of muscle protein synthesis between studies. More likely, the choice of precursor is the salient factor. When muscle intracellular leucine was used as the precursor to calculate FSR by the aforementioned authors (Balagopal et al., 1997; Hasten et al., 2000), the differences between young and elderly narrowed (Balagopal et al., 1997; Hasten et al., 2000) and, in fact, in most cases there was no statistically significant difference in mixed muscle protein synthesis (Balagopal et al., 1997; Hasten et al., 2000). These results suggest that there may be a difference in amino acid-ketoacid transport between the young and elderly, rather than a difference in the basal rate of muscle protein synthesis. Unfortunately, measurement of the true precursor for muscle protein synthesis, the amino acyl-tRNA, requires a great deal of muscle tissue, so it is necessary to calculate FSR with surrogate measures, such as the tissue amino acids or KIC (Baumann et al., 1994).

Evidence from rat muscle suggests that protein synthetic rates in different muscle fiber types may respond differentially to aging (Fluckey et al., 1996), so that fiber types of the muscle biopsies used to measure muscle protein synthesis in humans also may affect the reported rates. Furthermore, myofibrillar (Welle et al., 1993, 1994), mitochondrial (Rooyackers et al., 1996), and myosin heavy chain FSR (Balagopal et al., 1997; Hasten et al., 2000) have been reported to be reduced
in elderly individuals, but sarcoplastic FSR was not reduced (Balagopal et al., 1997). Balagopal et al. (1997) and Hasten et al. (2000) measured FSR of myosin heavy chain using both α-KIC and muscle intracellular amino acids as precursor enrichments and found that, unlike mixed muscle FSR, the values for elderly were reduced with both precursors. Thus, it is conceivable that differences in mixed muscle protein FSR reported between studies may be also attributed to the proportion of the various protein fractions sampled.

Nevertheless, it seems clear that, at the very least, an inherent reduction in the basal level of muscle protein synthesis with age must be much smaller than the range of 30–40% that has been reported. Clearly, future work must account for differences in precursor enrichments, as well as study populations, diet, activity, and, perhaps, muscle protein fractions in an attempt to ascertain the effect of age on muscle protein synthesis. It seems most likely that there is a slight reduction in muscle protein synthesis with age that is small, variable, and thus difficult to detect by current methods.

It is important to note that knowledge of the rates of muscle protein synthesis, while valuable, provides only half of the information necessary to determine the influence of age on muscle protein balance and thus the metabolic basis for the loss of muscle with age. Unfortunately, there is only limited information on the effect of aging on muscle protein breakdown. In the only studies to measure muscle protein breakdown in old and young humans in vivo, it was reported to be similar in elderly and young volunteers (Volpi et al., 1999, 2000, 2001). These results are consistent with the notion that muscle protein synthesis is unlikely to be dramatically reduced with aging. Clearly, if muscle protein synthesis is reduced by up to 40% or more, as was reported by other authors (Balagopal et al., 1997; Hasten et al., 2000; Rooyackers et al., 1996; Yarasheski et al., 1993), there also must be an alteration in muscle protein breakdown.

Of course, simply measuring muscle protein synthesis, breakdown, and net balance at rest may not be sufficient to explain the loss of muscle with aging. It may not be possible with tracer methods to acutely detect small changes in basal levels of muscle protein metabolism that result in muscle loss over long periods of time. Whereas changes in the basal rate of either muscle protein synthesis or breakdown, or both, can not be excluded as explanations for the decline in muscle mass with age, it does not seem reasonable to accept changes in muscle protein synthesis of the magnitude that has been deemed responsible for muscle loss (Balagopal et al., 1997). Alternatively, muscle protein synthesis, breakdown, or net muscle protein balance measured in the postabsorptive state at rest may not represent the balance over an entire 24-h period. Differences in the response to nutrient intake, exercise, or the lack thereof, are also likely to be important to explain muscle loss with age.

**Muscle Protein Metabolism, Nutrition and Aging**

The response of muscle protein metabolism to feeding may be altered with age, and this could contribute to loss of muscle mass regardless of whether there are changes in basal levels of muscle protein metabolism or not. Loss of muscle would occur if periods of net muscle protein synthesis associated with feeding were not sufficient to outweigh the periods of net muscle protein breakdown. Studies in rats
suggest that the response of muscle protein metabolism to a meal (Mosoni et al., 1995) and to amino acids (Dardevet et al., 2000) is reduced with advanced age. However, data from human studies are more equivocal. Prior to and following a meal, myofibrillar FSR was lower in elderly compared to young humans, but the response to the meal was similar (Welle et al., 1994). Volpi and colleagues (1999) reported that the responses of muscle protein synthesis and breakdown to amino acid ingestion in elderly subjects were no different from young. However, the response of muscle protein synthesis to ingestion of amino acids plus carbohydrates was altered in the elderly (Figure 1), resulting in a reduced anabolic response compared to young subjects (Volpi et al., 2000). These results suggest that an alteration in the response of muscle to the carbohydrate-induced insulin secretion may be

![Graph](image)

**Figure 1.** Change in muscle protein synthesis (mps) and muscle protein breakdown (mpb) from basal (fasted at rest) values in young and elderly volunteers following consumption of amino acids alone (AA) or amino acids plus glucose (AA+Glc). Adapted from Volpi et al. (2000).
responsible for deficits in muscle protein metabolism with feeding in the elderly. If so, then the lack of stimulation of muscle anabolism by a carbohydrate-containing meal may contribute to progressive muscle loss over a long period of time. Unfortunately, since others (Welle et al., 1994) showed no alteration in the response of myofibrillar protein FSR with age, a solid conclusion is difficult to accept. It is possible that differences in meal composition may account for the differences between studies. Welle et al. (1994) fed subjects liquid meal supplements containing protein, carbohydrates, and fats, whereas Volpi et al. (2000) fed subjects free amino acids plus glucose. Alternatively, it is possible that since Welle et al. (1994) measured FSR in myofibrillar proteins, the changes in mixed muscle protein synthesis reported by Volpi et al. (2000) may be attributed to other types of proteins. Certainly, more research must be performed to determine the influence of the response of muscle protein metabolism to nutrient ingestion on muscle loss. Nonetheless, muscle loss does occur with age, so there must be a net decrease in muscle protein balance over the years that the muscle is lost, and proper nutrition may play a role in preventing this muscle loss. Unfortunately, to date, there is not enough information available to make recommendations about specific nutrients and their influence on muscle protein metabolism with age. However, the above information suggests that food sources of amino acids may be especially important.

Muscle Protein Metabolism, Exercise and Aging

ACUTE

In healthy, young adults, stimulation of muscle protein synthesis and breakdown will result from a resistance exercise bout of appropriate intensity (Biolo et al., 1995b; Chesley et al., 1992). Following resistance exercise, the increase in muscle protein synthesis is greater than the increase in breakdown (Biolo et al., 1995b; Phillips et al., 1997), thus resulting in a more favorable situation for muscle growth. However, in the absence of nutrient intake, the net muscle protein balance remains negative (i.e., catabolic). Additionally, the stimulation of muscle protein synthesis (Chesley et al., 1992; Phillips et al., 1997) and breakdown (Phillips et al., 1997) lasts for at least 24 h. Thus, the stimulation of muscle via the exercise bout should interact with the nutrients in any meals consumed in the 24 h following the exercise bout resulting in muscle growth.

Information on the response of muscle protein metabolism to exercise in the elderly is limited to muscle protein synthesis. In a series of studies, Yarasheski and colleagues reported increases of 50–180% for mixed muscle protein FSR in healthy and frail elderly subjects following resistance exercise (Hasten et al., 2000; Yarasheski et al., 1993, 1999). Interestingly, the increase in mixed muscle FSR in elderly was greater than that reported for young subjects (Hasten et al., 2000; Yarasheski et al., 1993). The measurement of FSR post-exercise was performed following a period of resistance exercise training, so that the interpretation of the results is somewhat confounded. Nonetheless, these studies demonstrate unequivocally that elderly muscle has the same, if not greater, capacity to respond to an acute bout of resistance exercise as young muscle under similar circumstances. Individual protein fractions of elderly muscle also seem to respond similarly to that of young volunteers to resistance exercise. Increased myofibrillar (~30%; Welle and Thornton, 1998) and myosin heavy chain (~144%; Hasten et al., 2000) FSR.
have been reported for elderly volunteers. Unfortunately, to date, there are no reports of muscle protein breakdown in response to exercise in elderly subjects.

The interaction of nutrient intake and resistance exercise has been demonstrated to increase muscle protein synthesis (Figure 2) without a concomitant increase in muscle protein breakdown, thus stimulating positive net muscle protein balance in young subjects (Biolo et al., 1997; Rasmussen et al., 2000; Tipton et al., 1999). Similar information is unavailable for elderly humans at this juncture; however, it seems reasonable to expect a similar response. The response of FSR to resistance exercise in elderly volunteers is similar to young volunteers (Hasten et al., 2000; Yarasheski et al., 1993, 1999). Whereas net muscle protein balance in elderly in response to a meal may be less than in young, muscle synthesis is stimulated, and thus net balance is stimulated from negative to positive by meals in both populations (Volpi et al., 1998, 1999, 2000; Welle et al., 1994). Thus it seems unlikely that the response to the interaction of resistance exercise and nutrient intake would be dramatically different and a positive net muscle protein balance would be expected in elderly as in the young. These results suggest that acute bouts of resistance exercise, combined with meals, will stimulate periods of positive net muscle protein balance in the elderly. Repeated bouts of exercise plus meal consumption over time should provide periods of net muscle protein synthesis sufficient to explain muscle growth during training. These results provide a metabolic explanation for the success of resistance training for increasing muscle mass and strength in elderly individuals (Fiatarone et al., 1990, 1993; Frontera et al., 1988; Hurley and Roth, 2000; Tracy et al., 1999).

CHRONIC

It is clear that exercise training, particularly resistance exercise training, results in increases in muscle mass and strength in the elderly (Fiatarone et al., 1990, 1993; Frontera et al., 1988; Hurley and Roth, 2000; Tracy et al., 1999). However, the
metabolic changes in muscle protein that account for the changes during training have yet to be elucidated. It is often suggested that muscle hypertrophy due to resistance exercise training results from an increase in the basal level of muscle protein synthesis such that during much of the day, the muscle is in a more positive net protein balance. To date, there is no information on the response of muscle protein breakdown to chronic resistance exercise training in young or elderly humans. Without knowledge of muscle protein breakdown, we cannot definitively determine the impact of resistance exercise training on basal net muscle protein balance. Studies have concluded that resistance exercise training, even for as little as 2 weeks, results in an increase in the basal level of muscle protein synthesis in both young and elderly individuals (Hasten et al., 2000; Yarasheski et al., 1992, 1993, 1995, 1999), thus supporting the view that hypertrophy results from an increase in the basal level of muscle protein synthesis. However, as mentioned above, the design of these studies renders such a conclusion somewhat uncertain. Whereas the initial, pre-training measurement of muscle protein synthesis was made at rest, the final, post-training measurement was made shortly (3–24 h) following the final bout of resistance exercise (Hasten et al., 2000; Yarasheski et al., 1992, 1993, 1995, 1999). The response of muscle protein synthesis to an acute bout of resistance exercise lasts up to 48 h in young humans (MacDougall et al., 1995; Phillips et al., 1997). Since the pre- and post-training measurements of muscle protein synthesis in these studies were made at rest and following resistance exercise, respectively (Hasten et al., 2000; Yarasheski et al., 1992, 1993, 1995, 1999), it is not possible to distinguish the effect of training on muscle protein synthesis from the effect of the final acute resistance exercise bout. Therefore, the increase in muscle protein synthesis attributed to resistance training may have been, at least in part, due to the previous exercise bout. Furthermore, in a cross-sectional study, the resting muscle protein synthesis, breakdown, and net muscle protein balance of young, resistance-trained subjects were no different from that of untrained subjects (Phillips et al., 1999). Moreover, Welle et al. (1995) demonstrated that resting, basal myofibrillar FSR of elderly subjects did not change over a 3-month period of resistance exercise training. Taken together, these studies do not support the notion that training-induced muscle hypertrophy is the result of an increase in the basal level of muscle protein synthesis in young or elderly individuals. A determination of muscle protein synthesis and breakdown in response to resistance training in well-controlled studies must be made before any firm conclusion can be made about the influence of the training on basal levels of net muscle protein synthesis. Even so, as with the changes in muscle protein synthesis due to aging, it is possible that an increase in muscle protein synthesis that accounts for increased muscle mass due to chronic resistance exercise training may be small and thus difficult to detect with available methodology. For example, even the extreme case of an increase in muscle fiber mass as large as 30% in 16 weeks (Hikida et al., 2000) would result only from an increase in mixed muscle FSR of ~0.0112% h, an increase of ~22% over normal, resting values. Even with a large increase in muscle mass such as in this example, a very large number of subjects would be necessary to discern a statistically significant difference given the 30% or greater coefficient of variability typically associated with the methodology.

Alternatively, it may be that training-induced muscle hypertrophy is due to a series of transient increases in net muscle protein balance in response to individual
workouts. That is, the accretion of muscle protein over the length of a training period is the sum of the accretion due to each exercise bout performed during that period. Muscle protein synthesis and net muscle protein balance remain elevated above resting levels for up to 48 h following an intense, resistance-exercise bout (MacDougall et al., 1995; Phillips et al., 1997). The sum of these responses repeated many times over a period of training could be expected to add up to an appreciable gain in muscle mass without an inherent change in the basal level of muscle protein synthesis. These acute responses were measured primarily in the fasted state; however, muscle growth over a chronic training period would be the result of the response of muscle to the interaction of exercise and any meals consumed during the training period. Young, and likely elderly, muscle responds to the interaction of resistance exercise and nutrient intake by switching from negative to positive muscle protein balance (Biolo et al., 1997; Rasmussen et al., 2000; Tipton et al., 1999). An accumulation of these periods of positive net muscle protein balance could explain the training induced accretion of muscle protein that results in muscle hypertrophy in the elderly.

**Muscle Protein Metabolism and Inactivity**

Activity decreases with advancing age for a variety of reasons (Roth et al., 2000; Voorrips et al., 1993). Many of the problems attributed to aging may be due to inactivity (Bortz, 1982). Clearly, muscular activity can stimulate muscle protein metabolism. Conversely, inactivity has a depressive effect on muscle protein metabolism, hence it is possible that this depression may influence muscle protein balance and muscle loss (Ferrando et al., 1996). Inactivity in the form of prolonged bed rest decreases muscle protein metabolism almost entirely by decreasing muscle protein synthesis (Ferrando et al., 1996). However, the decline in muscle protein synthesis by prolonged inactivity can be effectively countered by only a relatively small amount of exercise. Ferrando et al. (1997) demonstrated that FSR declined 46% in subjects following 2 weeks of bed rest. However, performance of 5 sets or less of knee extensor exercise every other day during the 14-day bed rest resulted in no decline in FSR (Figure 3). Clearly, inactivity results in a decline of muscle protein synthesis and net muscle protein balance that leads to muscle loss. On the other hand, a relatively small volume of exercise seems to be enough to ameliorate the decrease of muscle protein synthesis.

There is evidence to support the notion that an increase in muscle protein synthesis may be a result of regenerating fibers or satellite cells. Conversely, the depression of muscle protein synthesis with inactivity could be due to a loss of regenerating fibers. Satellite cells are important for muscle growth and repair (Seale and Rudnicki, 2000). Decreased satellite cell proliferation and muscle regeneration have been demonstrated in aging humans (Decary et al., 1997) and rats (Carlson and Faulkner, 1998; Delp and Duan, 1996). The importance of satellite cell proliferation has been theorized to be part of the process of sarcopenia via periods of inactivity that require satellite cell proliferation to initiate regrowth (Chakravarthy et al., 2000; Delp and Duan, 1996). In rats that were immobilized to induce limb atrophy, the number of regenerating fibers almost disappeared (Wanek and Snow, 2000), and proliferative potential of satellite cells was decreased (Chakravarthy et al., 2000). However, return to a normal level of activity resulted in the reappearance
of new regenerating fibers in these rats (Wanek and Snow, 2000). The mechanisms for the reappearance of regenerating fibers with renewed activity have not been determined. Furthermore, in frail, elderly humans that began a resistance exercise program, evidence of regeneration was found in previously atrophied muscles (Singh et al., 1999). The concept that the degree of muscle fiber degeneration is related to a subtle change in activity level is supported by these studies and might apply to muscle loss in the elderly. Regeneration of new muscle must certainly involve changes in muscle protein synthesis that change the cumulative net muscle protein balance over long periods of time.

In some cases, hormonal mediators may also be important contributors to muscle loss due to inactivity. A slight increase in circulating cortisol is associated with aging, but it is probably not enough to account for muscle loss (Laughlin and Barrett-Connor, 2000). Yet, elevated glucocorticoids may be associated with increased muscle loss during periods of forced inactivity. In healthy volunteers, forced inactivity results in muscle loss primarily through a decrease in muscle protein synthesis with no change in muscle protein breakdown (Ferrando et al., 1996). However, in many circumstances (e.g., during recovery from injury, microgravity, trauma, burns or prolonged hospital stays), cortisol levels are increased (Ferrando, 2000) and hypercortisolemia could have an impact on muscle loss due to inactivity. Prior to prolonged inactivity, hypercortisolemia did not have any measurable effect on muscle protein synthesis or breakdown, but following 14 days of inactivity, muscle protein breakdown was significantly increased during hypercortisolemia (Ferrando et al., 1999). Thus, it appears that inactivity primes the muscle for muscle loss mediated by cortisol.
This process may be exacerbated by reductions in testosterone levels with aging and inactivity (Abbasi et al., 1993). Although no direct measures on muscle protein metabolism exist, testosterone administration has been shown to preserve lean body mass and whole body protein balance during prolonged bed rest (Zachwieja et al., 2000). Testosterone increases muscle protein synthesis directly by stimulating an efficient reutilization of intracellular amino acids from muscle protein breakdown (Ferrando et al., 1998). Moreover, normalization of physiological testosterone levels in elderly men has been shown to increase muscle protein synthesis (Urban et al., 1995). In many cases, muscle loss may also be exacerbated by hypercortisolemia-induced increases in muscle protein breakdown when inactivity is forced due to trauma or illness. In other words, not only is there an increased susceptibility to muscle protein breakdown when inactivity and hypercortisolemia are combined, but a lessening of the anabolic stimulus exacerbates negative protein balance.

Hence, it appears that inactivity may contribute to muscle loss through reductions of muscle protein synthesis, perhaps due to a reduction in proliferative potential of satellite cells and a reduction in testosterone. Even small amounts of activity may be sufficient to ameliorate the loss of muscle mass. On the other hand, it is equally clear that not all exercise is appropriate to prevent muscle loss, and it may not be possible to completely stop the decline in muscle mass with age. Even master athletes who endurance train on a regular basis lose muscle mass as they age, while strength trained athletes maintain muscle size and function with age (Klitgaard et al., 1990).

**Summary**

It is clear that aging is associated with a loss of muscle mass and strength. Undoubtedly, the causes of this muscle loss are multi-factorial, and we are only beginning to understand the physiological mechanisms responsible for muscle loss. Recent advances in stable isotopic tracer methodology have been used to examine the metabolic basis for muscle loss and to investigate interventions designed to counter aging associated muscle loss. The association of advancing age with a decline in muscle protein synthesis is somewhat equivocal, at least to the extremely high level that has often been reported. It seems more likely that any change in the basal level of muscle protein metabolism is very small and undetectable by current methods. This notion is consistent with the rate of muscle loss (~6%/decade) reported in cross-sectional studies.

Alternatively, muscle loss with age could be, at least in part, due to alterations in the response of muscle protein metabolism to nutrient ingestion, to increased inactivity, or to an interaction of the two. Clearly, exercise, particularly resistance exercise, has been proven to be a very effective countermeasure to loss of muscle mass and strength. However, metabolic studies have been unable to unequivocally determine the mechanism behind the increase in muscle mass. Certainly, increased inactivity has been implicated in the loss of muscle mass associated with aging, but it is not certain if increased inactivity causes muscle loss or if muscle loss contributes to increased inactivity. Although many aspects have yet to be determined, examination of the acute responses of muscle protein metabolism to nutrient ingestion, exercise, and the interaction of the two has begun to give us
insight into the metabolic mechanisms behind the loss of muscle with advancing age. Whereas acute studies of muscle protein metabolism may not always definitively delineate the types of metabolic perturbations that result in long-term loss of muscle, they may be well utilized to examine potential countermeasures that could lead to interventions important for increasing or maintaining muscle mass and strength. It is clear from longitudinal studies that resistance exercise training, even relatively modest amounts in all age groups up to nonagenarians is an extremely effective countermeasure to muscle loss. Obviously, maintenance of muscle mass and strength as we age would lead to much improved functional capacity and quality of life.

References


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