Role of Leucine in Protein Metabolism During Exercise and Recovery

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Exercise produces changes in protein and amino acid metabolism. These changes include degradation of the branched-chain amino acids, production of alanine and glutamine, and changes in protein turnover. One of the amino acid most affected by exercise is the branched-chain amino acid leucine. Recently, there has been an increased understanding of the role of leucine in metabolic regulations and remarkable new findings about the role of leucine in intracellular signaling. Leucine appears to exert a synergistic role with insulin as a regulatory factor in the insulin/phosphatidylinositol-3 kinase (PI3-K) signal cascade. Insulin serves to activate the signal pathway, while leucine is essential to enhance or amplify the signal for protein synthesis at the level of peptide initiation. Studies feeding amino acids or leucine soon after exercise suggest that post-exercise consumption of amino acids stimulates recovery of muscle protein synthesis via translation regulations. This review focuses on the unique roles of leucine in amino acid metabolism in skeletal muscle during and after exercise.

L'exercice modifie le métabolisme des protéines et des acides aminés. Parmi les changements, notons la dégradation des acides aminés à chaîne ramifiée, la production d’alanine et de glutamine ainsi que le taux de renouvellement des protéines. La leucine, un acide aminé à chaîne ramifiée, est un des acides aminés les plus touchés par l’exercice. Au cours des dernières années, de nombreuses études ont contribué à l’enrichissement des connaissances sur le rôle de la leucine dans la régulation du métabolisme; les études ont également dévoilé...
les importantes fonctions de cet acide dans la signalisation intracellulaire. La leucine semble jouer un rôle synergique avec l’insuline en tant que facteur de régulation dans la cascade des signaux de l’insuline/phosphatidylinositol-3 kinase. L’insuline enclenche le processus et la leucine est indispensable pour améliorer ou amplifier le signal déclenchant la synthèse des protéines au niveau des peptides. Les études sur la consommation d’acides aminés ou de leucine peu après la fin de l’exercice mettent de l’avant que la consommation d’acides aminés après la fin de l’exercice stimule la récupération des protéines musculaires par des régulations de translation. Cet article met l’accent sur les rôles particuliers de la leucine dans le métabolisme intramusculaire des acides aminés au cours et après un exercice.

Introduction

Dietary protein has been assumed to be important for physical performance since ancient times when consumption of meat was thought to enhance strength and endurance. However, lipids and carbohydrates are clearly established as the major fuels for muscle contraction (Wolfe, 1998) and relatively little additional protein is believed necessary for muscle hypertrophy (RDA, 1989). Still most current day athletes consume copious quantities of protein under the belief that protein intake is a key to muscle development (Hickson and Wolinsky, 1996). For reviews of exercise and protein metabolism see Paul et al. (1997), Wagenmakers (1998a), and Rennie and Tipton (2000).

Evaluating the roles of protein and amino acids in maintaining the structure and function of skeletal muscle is complicated by the diversity of the individual amino acids. For carbohydrates and lipids, the basic molecules are glucose and palmitate and the functions are largely limited to generation of energy via ATP or storage as glycogen or fat. On the other hand, there are twenty different amino acids required for protein structures and many of these amino acids also participate in numerous other metabolic reactions. In skeletal muscle, the amino acid with the most complex of these metabolic roles may be the branched-chain amino acid leucine.

Anabolic effects of leucine on muscle protein have been reported for over twenty years (Buse and Reid, 1975; Li and Jefferson, 1978; Tischler et al, 1982), however, only recently have researchers begun to understand and integrate the overall metabolic roles of this amino acid (Hutson and Harris, 2001). Leucine participates in metabolism in diverse ways including 1) as a substrate for protein synthesis, 2) as a fuel, and 3) as a metabolic signal. The most obvious role for any amino acid is as the fundamental unit for building protein. As a substrate for muscle protein synthesis, leucine’s role is similar to the other twenty amino acids; however, in skeletal muscle leucine is disproportionately incorporated into proteins accounting for approximately 9% of muscle amino acids (RDA, 1989). Leucine also functions as a metabolic fuel in muscle. Skeletal muscle is the principle site for degradation of the three branched-chain amino acids, leucine, isoleucine and valine. Degradation of these three amino acids in muscle provides carbon for use as a direct energy source and also provides the stimulus for synthesis of alanine and glutamine. Finally, the most recent and perhaps most intriguing role for leucine is its participation in intracellular signal transduction as part of the insulin signal cascade. Recent discovery of leucine’s participation in signaling begins to suggest links among the diverse metabolic roles of this essential amino acid.
Collectively, the three branched-chain amino acids (BCAA) make up over 20% of the amino acids in the food supply and account for three of the nine essential amino acids in the diet. Further, the BCAA have the distinction of being the only amino acids that are largely degraded in skeletal muscle. Associated with these properties, the BCAA exhibit rapid changes in blood and tissue concentrations associated with dietary intake, metabolic stress, and exercise (Ahlborg et al., 1974; Harper et al., 1984).

In 1974, Ahlborg et al. reported that exercise stimulated movement of amino acids through the blood. They reported that interorgan movement of amino acids was dominated by the three branched-chain amino acids (BCAA) and alanine. The BCAA pass into the blood from the liver and gut and circulate to skeletal muscle for use in synthesis of proteins or for degradation of the amino acids as a source of energy. Degradation of the BCAA to energy results in release of the amino-nitrogen that is transferred from the BCAA on to either pyruvate or α-ketoglutarate to form the non-essential amino acids alanine and glutamine (Figure 1). Alanine and glutamine are released from muscle into the blood and circulate back to visceral tissues (liver and gut) through blood circulation to uptake by skeletal muscle. In muscle tissue, BCAA are used for protein synthesis, production of energy, and synthesis of alanine (Ala) and glutamine (Gln). Alanine and glutamine are released from muscle and return to the liver and gut as substrates for endogenous production of glucose.

**Figure 1.** Picture represents movement of the BCAA from visceral tissues (liver and gut) through blood circulation to uptake by skeletal muscle. In muscle tissue, BCAA are used for protein synthesis, production of energy, and synthesis of alanine (Ala) and glutamine (Gln). Alanine and glutamine are released from muscle and return to the liver and gut as substrates for endogenous production of glucose. Abbreviations: BCAA branched-chain amino acids, α-kg alpha-ketoglutarate.
tissues where the liver removes alanine and the gut, kidney and liver remove glutamine. This interorgan movement of amino acids serves multiple purposes including delivering BCAA to muscle as a source of energy, supplying potential intermediates for the TCA cycle, and providing a constant supply of alanine and glutamine for endogenous production of glucose (Harper et al., 1984; Wagenmaker, 1998a; Young and Ajami, 2001).

Degradation of the three BCAA in skeletal muscle is largely dependent on increases in the concentration of the amino acids (Harper et al., 1984). The first step in degradation is an aminotransferase that is shared by the three BCAA and driven by concentration. The BCAA aminotransferase is predominately found in muscle tissue and essentially absent in liver. Absence of the aminotransferase in liver results in constant release of BCAA from visceral tissues, movement through the blood and extraction by skeletal muscle. Within muscle, the aminotransferase removes the α-amino group from the BCAA and transfers it either to pyruvate forming alanine or to α-ketoglutarate forming glutamate. The second step in degradation of the BCAA is also a shared enzyme known as the branched-chain ketoacid dehydrogenase (BCKAD) (Harris et al., 2001). BCKAD removes the alpha-carbon and commits the amino acid to complete degradation to energy.

Extraction of BCAA from plasma circulation increases during exercise in proportion to intensity and duration (Ahlborg et al., 1974; Paul et al., 1996; Van Hall et al., 1996). Movement of the BCAA into skeletal muscle stimulates their oxidation (Wolfe et al., 1982). Early in exercise, changes in plasma amino acids reflect an increased visceral release of BCAA and increased muscle production of alanine. As the level of work progresses, production of alanine gives way to production of glutamine (Van Hall et al., 1995). These changes in non-essential amino acid products appear to be associated with the availability of pyruvate derived from either blood glucose or muscle glycogen. At the beginning of exercise, pyruvate appears to be readily available resulting in alanine production. As the activity progresses, alanine production is replaced by production of glutamine from α-ketoglutarate and glutamate. These reactions suggest a link between BCAA metabolism and the balance of fuels during exercise (Wagenmaker, 1998a).

Supplementation of BCAA as ergogenic aids for muscle activity has been tested with apparently minimal or no effects on performance (Blomstrand et al., 1991; Jackson et al., 1997; Madsen et al., 1996). However, the rate of BCAA degradation is not insignificant with leucine oxidation ranging from 30 to 70 μmol/kg-hr for cycling activities at intensities of 30 – 55% $\dot{V}O_{2\text{max}}$ (Evans et al., 1983; Wolfe et al., 1982). Depending on the size of the athlete and the intensity of the exercise, leucine oxidation may reach nearly 1.0 g/hr. During intense exercise, we observed a decline in plasma levels of BCAA after 90 minutes of intense cycling and this decline continued into recovery (Paul et al, 1996).

**Impact of Exercise on Muscle Protein Synthesis**

Athletes have intense interest in muscle mass because of the relationship of muscle mass to strength. Muscle mass is influenced by numerous factors but ultimately the amount of protein is determined from the balance between the rates of protein synthesis and protein breakdown. The combination of synthesis and breakdown is called protein turnover. During muscle hypertrophy, the net balance of synthesis
and breakdown is positive producing muscle growth. To maximize muscle hypertrophy, athletes often consume four to five times the RDA for protein (Hickson and Wolinsky, 1996). However, maximum rates of growth or muscle hypertrophy are less than 0.5 kg per week. Assuming that protein accounts for 20% of this weight change, maximum protein accretion is less than 15 grams per day for the entire body, implying that the additional protein needs for muscle hypertrophy are minimal. On the other hand, while the net balance is small, whole body protein turnover accounts for over 300 grams of protein being synthesized and degraded each day (Munro, 1982; Pacy et al., 1994) maximizing the potential for the body to repair and remodel its structure. The discrepancy between the relatively small level of daily protein deposition and the large rate of protein turnover makes evaluation of protein needs challenging.

The individual processes of synthesis and breakdown are regulated by different mechanisms but appear to increase or decrease in a coordinate manner (Millward et al., 1976). The relative importance of regulation of synthesis versus breakdown in determining muscle mass is unknown. Under most conditions, the anabolic response of protein turnover appears to be led by changes in protein synthesis (Phillips et al., 1999). This review focuses on some remarkable new findings about the molecular regulation of protein synthesis and the direct links to insulin signaling and leucine levels.

Exercise is an anabolic stimulus resulting in increased muscle mass and strength. Studies of isolated muscles demonstrate that constant stretch or electrically induced contraction stimulate anabolic changes in muscle protein synthesis at levels of both transcription and translation and produce muscle hypertrophy (Goldspink, 1978; Laurant et al, 1978). While exercise has an anabolic effect on muscle development, changes in protein turnover during exercise and key regulatory steps to achieve maximum muscle development have not been fully elucidated.

In the early 1980’s, a number of laboratories reported that immediately after a bout of exercise muscle protein synthesis was reduced (Dohm et al., 1980; Rennie et al., 1981; Wolfe et al., 1982). Research with rats indicated that the magnitude of the inhibition was proportional to the intensity and duration of the activity such that exhaustive, endurance running could depress muscle protein synthesis by as much as 70% (Dohm et al., 1980). More recent work with experimental animals appears to support these earlier findings (Balon et al., 1990; Davis and Karl, 1986; Gautsch et al., 1998). The time-course for recovery of protein synthesis after exercise is unknown, however, Tipton and Rennie (2000) suggest that protein metabolism may remain negative in the absence of adequate food intake. Recently, we found that protein synthesis remains depressed for at least eight hours after exhaustive exercise if an animal consumes nothing but fluids (Figure 2, unpublished data). In total, these studies suggest that exercise of high intensity and long duration is a metabolic stress that inhibits that rate of protein synthesis. If this is true, then the anabolic effects of exercise must be achieved during post-exercise recovery.

While intense exercise appears to depress protein synthesis in rats, the findings from studies with humans are less clear. Investigators have reported decreases (Rennie et al., 1981, Wolfe et al., 1982), no change (Carraro et al., 1990; Wagenmakers, 1998b), or increases (Tipton et al., 1999) in protein synthesis after exercise. The diversity of these findings has been attributed to differences in the
intensity or duration of the exercise protocol, to methodology differences among isotopic tracers, and to differences between human and rats in their ability to sustain intense exercise (Rennie and Tipton, 2000; Wagenmaker, 1998b). Currently, it is not possible to fully reconcile these differences. An important consideration in comparing animal and human exercise studies is to evaluate the type of exercise. Most animal studies utilize endurance exercise with high intensity (>70% VO₂max), while most human studies use low intensity (40% VO₂max) or resistance exercise. Further, a problem inherent to human metabolic studies is the need to make indirect measurements. Use of stable isotopes has been a tremendous advancement in human metabolic research. However, use of stable isotopes requires prolonged steady-state infusion in sufficient quantities to reach measurable enrichment of the amino acid pool. For these measurements to be interpreted, methods require achieving and maintaining isotopic steady state. For exercise experiments, this requirement is virtually impossible. Beginning with the metabolic conditions at rest, exercise progresses from early metabolic adjustments toward the physiology of exhaustion. Many investigators have attempted to minimize these problems by using prolonged exercise. Unfortunately, prolonged exercise usually requires exercise of lower intensity. Still other methods such as nitrogen balance measurements appear too crude to reach definitive conclusions about short-term regulations of protein synthesis. In the absence of full understanding of protein metabolism during exercise, the molecular mechanisms and regulations obtained from animals studies remain important.

**Leucine Stimulation of Muscle Protein Synthesis**

Regulation of protein synthesis occurs in numerous ways. The amount of protein is controlled at the level of transcription of DNA into messenger and ribosomal
RNA and at the level of translation of individual mRNA into peptides. In general, transcription adjusts the capacity for synthesis of a protein. Short-term, minute-by-minute controls of protein synthesis occur by regulation of the translation of mRNA into individual proteins (Pain, 1996; Figure 3). Short-term controls are modified by factors including hormones and the availability of energy or amino acids. These controls are exerted through at least twelve regulatory proteins called eukaryote initiation factors (eIF). Of these initiation factors, at least two of these factors, eIF2 and eIF4 are subject to physiological regulations (Campbell et al., 1999; Pain, 1996). Within skeletal muscle, the initiation factor eIF4 exhibits unique regulation by the BCAA leucine (Anthony et al., 2001).

The first evidence that leucine could stimulate muscle protein synthesis appeared in the 1970’s. Using isolated diaphragm muscle and perfused hindlimb preparations, researchers demonstrated that supplementing the plasma or media with a complete mixture of essential amino acids stimulated protein synthesis (Fulks et al., 1975; Li and Jefferson, 1978). Further evaluation of the impact of individual amino acids revealed that the stimulatory effect of the complete mixture could be reproduced by the single amino acid leucine (Buse and Reid, 1975; Hong and Layman, 1984; Tischler et al., 1978). Initially, these findings were interpreted to suggest that leucine might have potential to stimulate muscle growth or reduce muscle wasting in the critically ill. However, subsequent studies failed to show anabolic effects of leucine during extended catabolic conditions (McNurlan et al., 1982). Now it is recognized that leucine exerts its effect on short-term transla-

![Figure 3](image-url). Illustration represents translational regulation of protein synthesis emphasizing role of the initiation factors eIF2, eIF3 and eIF4. Initiation factor eIF2 participates in formation of the ternary complex (43S pre-initiation complex) including the 40S ribosomal subunit and methionine-tRNA. The eIF4 is required for recognition and unfolding of secondary structure at the 5’-end of the mRNA. The eIF3 is required to bind to the 40S subunit during termination to maintain the subunit in a form active for protein synthesis.
Leucine in Protein Metabolism

Intracellular hormone signaling is under intense investigation by researchers seeking to define the mechanisms of action for growth factors including insulin, insulin-like growth factor (IGF-1) and cytokines (Taha and Klip, 1999). Insulin and other growth factors mediate a wide spectrum of biological responses including cell division, regulation of gene expression, glucose transport, glycogen synthesis, protein synthesis, and antilipolysis. These responses are initiated by the hormone binding to a membrane bound receptor containing tyrosine kinase and triggering a signal cascade beginning with phosphorylation of insulin receptor substrate-1 (IRS-1) (Figure 4). IRS-1 generates metabolic signals by binding to phosphatidylinositol-3 kinase (PI3-K) and production of phosphatidylinositol-3,4,5 phosphate (Tsakiridis et al., 1995). Through these phosphorylated inositol molecules, PI3-K plays a major role in regulation of the metabolic actions of insulin. These actions include stimulation of glucose transport via stimulation of the GLUT4 transporter, synthesis of glycogen via glycogen synthase kinase-3, and stimulation of protein synthesis via activation of downstream initiation factors eIF-4E and p70S6K. Each of these physiological outcomes involves regulation by phosphorylation of key rate-limiting molecules.

While insulin is a primary stimulator of this pathway, chronic exposure of cells to excess insulin produces down-regulation of the initial IRS-1 and PI3-K steps (Cengel and Freund, 1999). These findings may represent important feedback regulations of the signal cascade and may be exerted by a downstream component of the pathway named mTOR (Taha and Klip, 1999; Takano et al., 2001). Further, the insulin signal pathway appears to be modulated by leucine which can directly stimulate downstream components of this signal pathway independent of changes in insulin concentration (Anthony et al., 2000a, 2000b; Gautsch et al., 1998).
The molecular mechanisms linking leucine and the signal pathway to control of muscle protein synthesis have begun to be elucidated (Hara et al., 1998; Patti et al., 1998; Xu et al., 1999). The first critical finding was that leucine modifies translational activity by stimulating a downstream protein kinase recognized as mTOR (mammalian target of rapamycin). Through stimulation of mTOR, leucine has the ability to activate the initiation factor eIF4 and the 70-kDa ribosomal protein S6 kinase (p70\textsuperscript{56}K) (Anthony et al., 2000; Hara et al., 1998; Xu et al., 1999). The initiation factor eIF4 (also known as eIF4F) is a complex of three subunits: eIF4E, eIF4G and eIF4B, required for the initial recognition and unfolding of secondary structure of the 5’-end of mRNA. To activate the eIF4 complex, first requires release of the eIF4E subunit from an inhibitory binding protein (4E-BP1) through phosphorylation of the binding protein by mTOR. Leucine serves to activate mTOR stimulating phosphorylation of 4E-BP1 causing release of the eIF4E subunit. Once eIF4E is released from 4E-BP1, it is free to bind with the remaining subunits (eIF4G and eIF4B) to form the active eIF4 initiation complex. Likewise, mTOR also stimulates phosphorylation of p70\textsuperscript{56}K, which in turn activates the S6 ribosomal protein. Together, activation of eIF4 and p70\textsuperscript{56}K serve to initiate trans-
leucine in protein metabolism

Leucine in Protein Metabolism

The regulation of significant components of muscle mRNA (Kimball and Jefferson, 2000). These findings serve to link the anabolic response of dietary protein to muscle protein synthesis through the ability to mTOR to detect changes in cellular leucine concentrations.

Leucine Stimulates Protein Synthesis After Exercise

While changes in muscle protein turnover associated with exercise remain controversial, studies evaluating changes in protein synthesis after exercise consistently report post-exercise, anabolic responses enhanced by food intake (Farrell et al., 1999; Gautsch et al., 1998; Tipton et al., 1999). Further, the anabolic responses to post-exercise supplements appear to be derived from intake of relatively small amounts of essential amino acids (Anthony et al., 2000; Rasmussen et al., 2000). Recent work suggests that the anabolic response is associated with the signaling role of leucine (Anthony et al., 2000; Gautsch et al., 1998).

As reviewed above, prolonged exercise with animals depresses muscle protein synthesis (Figure 2). Using this animal model, we tested the potential for a pre-exercise meal to prevent the catabolic effects of exercise on protein synthesis (Table 1). Our pre-exercise meal consisted of a complete nutritional drink (Ensure®, Abbott Labs) and provided about 15% of the animal’s daily energy needs. Use of pre-exercise nutritional supplement had no impact on the exercise-induced depression of muscle protein synthesis (Table 1).

Since exercise does not cause loss of muscle mass, the catabolic period during exercise must be followed by an anabolic recovery period (Tipton and Rennie, 1999). We hypothesized that recovery of muscle protein synthesis after exercise would require provision of protein or amino acids (Anthony et al., 1997). Consumption of a complete nutrition supplement within the first 10 minutes after

Table 1 The Relationship of Endurance Exercise and a Pre-exercise Meal on Muscle Protein Synthesis

<table>
<thead>
<tr>
<th>Protein Synthesis¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (no exercise)</td>
</tr>
<tr>
<td>Post-exercise²</td>
</tr>
<tr>
<td>Post-exercise with pre-exercise meal³</td>
</tr>
<tr>
<td>12 hrs</td>
</tr>
<tr>
<td>5 hrs</td>
</tr>
<tr>
<td>1.5 hrs</td>
</tr>
</tbody>
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¹Protein synthesis determined by incorporation of ³H-isoleucine into muscle protein and expressed as a percentage of the control. ²Rats were exercised for 2 hrs on a motor-driven treadmill at 36 m/min (~70% VO₂max) after a 12-hour fast. ³The meal consisted of 5 ml of Ensure® administered by oral gavage at the times indicated. (Unpublished data, Anthony, Gautsch and Layman.)
exercise produced complete recovery of muscle protein synthesis within an hour (Gautsch et al., 1998, data summarized in Table 2). On the other hand, use of a carbohydrate drink with the same energy content produced dramatic increases in blood glucose and insulin but failed to stimulate muscle protein synthesis (Anthony et al., 1999; Gautsch et al., 1998). These data suggested that recovery of muscle’s ability to build protein after exercise requires dietary intake of protein and that carbohydrate supplements alone are not sufficient to stimulate recovery of muscle protein synthesis.

Similar post-exercise effects of amino acid supplements on muscle protein synthesis have been reported for resistance exercise (Biolo et al., 1997; Rasmussen et al., 2000) and dynamic exercise (Levenhagen et al., 2001) with humans. Biolo et al. (1997) utilized normal volunteers who were not highly trained and examined the effects of intravenous infusion of amino acids after 60 minutes of an intense leg resistance exercise regimen. They reported that post-exercise infusion of amino acids produced elevation of blood amino acids and a dramatic increase in muscle protein synthesis (Biolo et al., 1997). They concluded that post-exercise intake of amino acids may be important to anabolic recovery after exercise. Subsequently, they showed that oral administration of amino acids produced a comparable increase in protein synthesis (Tipton et al., 1999). In this experiment, subjects drank a supplement containing either 40 grams of a complete mixture of essential and

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**Table 2. Effects of Nutrient Supplements on Muscle Protein Synthesis During Recovery After Exercise**

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Protein Synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (no exercise)</td>
<td>100%</td>
</tr>
<tr>
<td>Post-exercise</td>
<td>71%</td>
</tr>
<tr>
<td>Post-exercise with recovery meal</td>
<td></td>
</tr>
<tr>
<td>Complete meal</td>
<td>98%</td>
</tr>
<tr>
<td>Carbohydrate supplement</td>
<td>70%</td>
</tr>
<tr>
<td>Protein supplement (unpublished)</td>
<td>92%</td>
</tr>
<tr>
<td>Leucine supplement</td>
<td>99%</td>
</tr>
<tr>
<td>Leucine + carbohydrate</td>
<td>108%</td>
</tr>
</tbody>
</table>

1Rats were exercised for 2 hrs on a motor-driven treadmill at 36 m/min (~70% VO_{max}) after a 12-hour fast. Protein synthesis determined by incorporation of ^3^H-isoleucine into muscle protein and expressed as a percentage of the control. Measurements were made 1 hr after completion of exercise. Complete meal provided 43.9 kJ and consisted of 5 ml of Ensure administered by oral gavage immediately after exercise. Carbohydrate supplement provided 43.9 kJ and consisted of 5 ml of a mixture of 50% glucose and 50% sucrose in water (525g/L) administered by oral gavage immediately after exercise. Protein supplement provided 0.5 g protein in 5 ml water. Leucine supplement provided 0.27 g leu in 5 ml water. Mixture of leu and carbohydrate provided 43.9 kJ and consisted of 0.27 g leu in the Carbohydrate supplement. (Summarized from Gautsch et al., 1998 and Anthony et al., 1999.)
non-essential amino acids, or 40 grams of a mixture containing just the essential amino acids immediately after the exercise. They found that the post-exercise supplement of just the nine essential amino acids was sufficient to produce anabolic recovery of muscle protein synthesis. Recently, Rasmussen et al. (2000) reported that post-exercise stimulation of muscle protein synthesis can be achieved with a supplement containing only 6 grams of a mixture of the essential amino acids plus 35 grams of sucrose. In total, the post-exercise effects on muscle protein synthesis appear similar for humans and animals. In each case, the research suggests that intake of amino acids soon after exercise stimulates muscle protein synthesis.

To further evaluate these findings, we examined the impact of protein and leucine on recovery (Anthony et al., 1999). Using the same experimental design, we found that animals fed only the protein fraction of the supplement or only leucine could fully recover normal rates of protein synthesis within an hour after exhaustive exercise (Table 2). These data are in agreement with reports suggesting a unique effect of leucine on short-term recovery of muscle protein synthesis. A second important finding from this study was that the leucine stimulated protein synthesis in the absence of elevated plasma insulin. Subsequent research suggests that insulin may be increased early after the amino acid supplement and that this transient increase in insulin is sufficient to potentiate the signaling pathway (Anthony et al., 2001).

Examining the molecular mechanism, we found that the response of muscle protein synthesis was closely tied to changes in the initiation factor eIF4. At the end of exercise, activation level of eIF4 was reduced by 70%. Feeding the carbohydrate supplement had no effect on the activity state of eIF4, while consumption of the complete meal produced full recovery of eIF4 activity (Gautsch et al., 1998). This was the first report identifying an initiation factor, eIF4, as a critical regulator of muscle protein synthesis during and after exercise. It is now clear that the stimulatory effect of the meal on protein synthesis is produced by increased muscle levels of leucine (Anthony et al., 1999) resulting in stimulation of mTOR and activation of eIF4 and p70S6K (Anthony et al., 2001). These findings point toward a mechanism that may allow the body to integrate metabolic signals of insulin with nutrition to optimize muscle development.

Summary

Exercise produces changes in protein and amino acid metabolism, however the impact of these changes on amino acid requirements remains unclear. Current evidence indicates that supplementation of amino acids during exercise has little or no beneficial effects on performance. On the other hand, emerging data suggests that supplementation of amino acids soon after exercise may enhance the anabolic nature of the post-exercise period.

During exercise, there is increased oxidation of the three branched-chain amino acids in skeletal muscle. While oxidation of the BCAA contributes to muscle energy needs the contribution appears minimal. A more likely role for the BCAA in energy balance appears either through maintenance of TCA cycle intermediates or through contributions to production of alanine and glutamine. Among the three BCAA, oxidation of leucine appears to be the most dramatic reaching levels of
perhaps 1 g of leucine per hour of exercise. Still, supplementation of the BCAA during endurance exercise does not appear to enhance performance.

Changes in protein turnover associated with a bout of exercise remain controversial. The majority of studies report that a single bout of intense or exhaustive exercise produces a catabolic period for whole body protein turnover. This catabolic period may be caused by depression in the rate of protein synthesis, increases in protein breakdown, or both. While understanding changes in protein synthesis and breakdown are of equal importance, current methods limit our evaluation of molecular mechanism to studies of protein synthesis. Recently, there has been an increased understanding of the role of leucine in metabolic regulations and remarkable new findings about the role of leucine in intracellular signaling. It now appears that leucine has a synergistic role with insulin as regulatory factors in the PI3-K signal cascade. Insulin serves to activate the signal pathway, while leucine is essential to enhance or amplify the signal for protein synthesis at the level of peptide initiation factors. Studies feeding amino acids soon after exercise suggest that post-exercise consumption of protein or amino acids stimulates recovery of muscle protein synthesis via translation regulations. Presently the significance of these molecular findings with experimental animal models to human performance or muscle development is unknown. It will be important to test these new findings as components of defined training programs.

References


