Branched Chain Amino Acid, Leucine:

The Effects of Leucine on Skeletal Tissue in Relation to Aerobic Exercise

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Table of Contents

I. INTRODUCTION .................................................................2

II. REVIEW OF LITERATURE .............................................................3

A. The Branched Chain Amino Acids .............................................3
   i. Catabolism of Branched chain amino acids .........................4

B. Metabolic roles of Leucine .......................................................5
   i. Signaling translation initiation .........................................5
   ii. Regulation of BCKDH activity by the Derivative of Leucine, α-
       ketoisocaproate (KIC) ...................................................6

C. Exercise ..............................................................................7
   i. Implications of aerobic exercise on skeletal tissue ...............7
   ii. Physiological consequences of leucine metabolism on recovery
       from aerobic exercise ...................................................8

III. CONCLUSION .................................................................10

IV. REFERENCE LIST .............................................................11
INTRODUCTION

The branched chain amino acids (BCAA), Leucine, Isoleucine and Valine, have been studied for their essential role in protein synthesis. Unlike the other essential amino acids, the branched chain amino acids can be oxidized in the skeletal muscle, and exercise, whether it is aerobic or anaerobic, increases the oxidation of branched chain amino acids. Conversely, leucine has been shown to encourage muscle protein synthesis thereby generating interest in the effects of branched chain amino acids on skeletal muscle in relation to recovery from aerobic exercise. This paper will focus on the mechanism through which leucine promotes muscle protein synthesis and the stimulation of BCAA catabolism/protein degradation of muscle protein in relation to aerobic exercise.
REVIEW OF LITERATURE

The Branched Chain Amino Acids

Humans are unable to synthesize 9 of the 20 amino acids found in nature making it essential that humans consume them in their diet. Three of these essential amino acids make up the branched chain amino acids which features an open, branched carbon chain. Isoleucine, valine, and leucine are the most aliphatic of the essential amino acids which gives them a critical role in the secondary structure of proteins, most notably in globular proteins (1). One characteristic of the BCAA’s that are unique to the other essential amino acids is that they are catabolized in the skeletal muscle rather than in the liver (2). A study performed in 1974 by Ahlborg reported that the movement of BCAA’s from the liver to the skeletal muscle is stimulated by exercise. Once the BCAAs reach the skeletal muscle they are used in protein synthesis or they are degraded and used as an energy source (3). This catabolism of BCAA’s for energy use is directly correlated to the intensity of physical activity which is why consuming essential amino acids is important in avoiding significant loss of lean tissue. The exact mechanism as to how BCAAs promote muscle protein synthesis is still not fully understood but multiple studies performed on rats and humans indicate that BCAA administration to test subjects results in change in protein metabolism by either increasing the rate of protein synthesis or decreasing the rate of protein catabolism (4).

Although leucine, isoleucine, and valine similarly are the most hydrophobic of the essential amino acids, they are not identical in nature. While isoleucine and valine prefer β structures, leucine prefers α helix structures. This is due to differing size, shape and hydrophobicity of their different side chains (1). Of the three BCAAs metabolized in skeletal
muscle, leucine has been found to have the biggest impact on the anabolism of skeletal tissue accounting for 9% of the amino acids found in muscle and through its participation in multiple metabolic processes (5, 3). One of the most important metabolic roles of leucine is regulating translation initiation of protein synthesis (6).

Catabolism of Branched Chain Amino Acids

Skeletal muscle is the primary site for the catabolism of isoleucine, leucine and valine as they provide carbons to be used as an energy source (3). Branched chain amino acids are unique in that the first 2 steps of their catabolism are the same for all three. The catabolism of isoleucine, valine and leucine begins with the transamination of the specific amino acid to its appropriate α-keto acid by branched-chain aminotransferase (BCKA) and this is a reversible step. Next is an irreversible decarboxylation reaction of the α-keto acid that is catalyzed by branched-chain α-keto acid dehydrogenase complex (BCKDH). Coenzyme A is formed by the oxidative decarboxylation of BCKA. This is followed by the reaction that has been highly studied in rats; it is the phosphorylation or dephosphorylation of the BCKDH complex. When the E1 component of the BCKDH complex is phosphorylated, the complex has been inactivated. BCKDH kinase is the enzyme that is responsible for the inactivation reaction. Conversely, BCKDH phosphatase is the enzyme responsible for activating the BCKDH complex by dephosphorylating the E1 complex (7,2).
Metabolism of Leucine

Signaling translation initiation

Leucine has been marked as being the most anabolic of the essential amino acids in protein synthesis as it elicits the initiation of translation (8). Studies assessing leucine’s role in skeletal muscle protein have shown that leucine promotes the construction of the eIF4F complex and the stimulation of the ribosomal protein S6 Kinase (9). The promotion of these two pathways is made possible because leucine is responsible for stimulating the protein kinase mammalian target of rapamycin (mTOR). When the mTOR pathway is initiated by leucine, the phosphorylation of 4E-BP1, an inhibitory binding protein, activates the release of subunit eIF4E which in turn activates the eIF4 complex. Once this inhibitory binding protein is phosphorylated, the eIF4E subunit is free to bind two other subunits (eIF4G and eIF4B) forming the eIF4 in its active form. The mTOR is also responsible for activating the ribosomal protein S6 kinase by prompting the phosphorylation of p70^56K. The synergistic stimulation of these two pathways assists the commencement of translation, an important constituent of the mRNA binding step of the protein synthesis process (9, 3).
Regulation of BCKDH activity by the Derivative of Leucine, α-ketoisocaproate (KIC)

As mentioned before, the activity state of the BCKDH complex is the most regulated step in BCAA catabolism as it controls the promotion of catabolism or conservation of BCAAs. BCKDH kinase is considered the primary regulator of BCAA catabolism as it is responsible for inhibiting the BCKDH complex by phosphorylation of the E1 component of the BCKDH complex. Conversely, the metabolite of leucine, α-ketoisocaproate (KIC) is an inhibitor of the BCKDH kinase. Therefore, α-ketoisocaproate inhibits the phosphorylation of the E1 component of BCKDH complex and allows the dephosphorylation, consequently promoting BCAA catabolism (10,2). A study reported that when rats were fed a diet rich in leucine and low in isoleucine and valine, blood concentrations of isoleucine and valine were further decreased, causing the activation of the BCKDH complex. This demonstrates that when there is an imbalance of BCAA, leucine being in the highest concentration, the accumulation of leucine’s metabolite, α-ketoisocaproate, causes the BCKDH kinase to be inhibited, stimulating BCAA/protein catabolism (2).
Exercise

Implications of aerobic exercise on skeletal tissue

Energy requirements increase during aerobic exercise activities such as running, cycling and swimming, which in turn stimulates the catabolism of amino acids and proteins. Studies conducted on rats have found that the intensity and duration of exercise is directly proportional to the extent of inhibition of protein synthesis (3). Branched chain amino acids make up 35% of the amino acids found in muscle proteins so they account for the amino acids being broken down during exercise (2). It has been demonstrated that the oxidation of the branched chain amino acids is regulated by the BCKDH complex and the activation of this complex through the inhibition of the BCKDH kinase enzyme enhances their catabolism and protein degradation. Shimomura et al measured the activity of the BCKDH complex in relation to aerobic (running) conditions vs. resting conditions in rats. The rats were divided into two groups, trained and untrained (placebo group). The trained rats were to initially run on a treadmill for 30 minutes each day for the first 5 weeks then 60 minutes per day for another 7 weeks. Twenty four hours after the concluding day of exercise, the rats were anesthetized and their gastrocnemius muscle was removed for testing. Results showed that BCKDH complex was activated in the aerobically trained rats by 70-80% which was attributed to the dephosphorylation of the E1 complex (11). Aerobic exercise, whether done at low frequency for a prolonged period of time or in short exhaustive bouts, has also been shown to effect protein status post exercise by inhibiting the mTOR pathway of translation and therefore protein synthesis (6).
Physiological consequences of leucine metabolism on recovery from aerobic exercise

Because aerobic exercise increases the catabolism of muscle protein and therefore protein breakdown, it is important athletes and those participating in regular exercise, meets or exceeds their protein requirements to induce synthesis of skeletal muscle protein for recovery. Bloomstrand et al conducted a study on rats to test the prevention of protein catabolism induced by aerobic exercise in relation to the timing of a nutritional supplement composed mostly of leucine. One group of rats that were to be exercised on a treadmill for 2 hours were given a pre-exercise nutritional supplement and a second group of rats were given a post exercise nutritional supplement 10 minutes after the 2 hour treadmill time. According to the results, pre exercise nutritional supplement had no impact on decreasing the exercise induced protein degradation as the post exercise protein synthesis was only measured to 72% recovery which was the same percentage of protein synthesis recovery in the control group that received no nutritional supplement after the exercise regimen. Conversely, the post exercise nutritional supplement caused a 108% recovery in protein synthesis within an hour of the onset of post exercise recovery time (3). Another researcher conducted a study on rats to test the effect of feeding a leucine supplement to a one group of rats after they had been exercising on a treadmill for 2 hours. Once again, the results showed complete restoration of muscle protein synthesis and even showed an increase in the availability of eIF4E needed for the eIF4E:eIF4G complex in translation initiation (12). This shows that leucine’s anabolic character is most utilized in post-exercise recovery.

These findings along with many more studies imply a few factors to consider regarding the timing of BCAA or leucine supplement and the status of muscle protein synthesis recovery.
The most important factor in reducing the rate and duration of muscle protein degradation post aerobic exercise is eating a nutritionally adequate meal (foods high in BCAAs; meats and dairy) or BCAA/leucine supplement shortly after exercising. Recovery is shown to be dependent on the timing of BCAA/leucine supplementation because consumption of leucine increases intramuscular concentration of leucine which is needed to activate the mTOR pathway and therefore the initiation factors (eIF4E) of translation (6).

Although exercise does not have a direct effect on the function of leucine, supplementation or balanced meals effect the concentration of leucine in circulation. Because of the catabolic effect of aerobic exercise on muscle, it is important athletes, especially of the elite or competitive level, consume adequate amounts of protein to avoid muscle protein degradation. It’s also important to account for the gains in lean body mass associated with exercise when estimating protein/BCAA needs.
CONCLUSION

While the metabolism of the branched chain amino acids have been of high interest since the 1980’s it wasn’t until the early 2000’s that leucine’s role in protein synthesis following aerobic activity was fully understood. The increase in energy expenditure causes the activation of the BCKDH complex which in turn increases BCAA catabolism within the skeletal muscle. Of the three branched chain amino acids, leucine possesses the most anabolic characteristics as it acts as a signal for the initiation of translation in the protein synthesis pathway. It is important to consume supplements with a proper balance between the branched chain amino acids to obtain the beneficial effects of leucine. Otherwise, a supplement of leucine alone causes the accumulation of α-ketoisocaproate and therefore stimulation BCAA catabolism. When consumed in proper balance with isoleucine and valine in BCAA supplement form or dietary meals shortly after aerobic exercise, BCAA’s, most notably leucine, aids in the recovery from exercise induced muscle protein catabolism.
IV. REFERENCE LIST


