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Catabolism of BCAAs and Application

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by

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ABSTRACT

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Over the past 150 years, amino acids have been found and researched in the nutrition biochemistry field. Over these years, three have been identified; leucine, valine and isoleucine; to make up the branch chain amino acids (BCAAs) that play a crucial role on the anaerobic and aerobic energy systems. The metabolism of BCAAs is a highly complicated process that is regulated by the activation of the alpha-keto acids dehydrogenase complex (BCKDH complex) to complete the catabolic reaction. With exercise, it has been found to increase the metabolism of BCAAs by increasing the BCKDH complex, which will decrease the fatigue and muscle breakdown experienced during training. Additionally, BCAAs have been found to increase insulin uptake in the body and decrease delayed onset muscles that is experienced the days following activity. Although BCAAs have a positive impact on exercise performance and recovery, they can negatively impact the body if not in the correct balance.

KEYWORDS: Amino Acids, Metabolism, Branch Chain Amino Acids, Catabolic reactions, Exercise, Decrease Muscle Fatigue, Leucine, Valine, Isoleucine, Recovery

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CHAPTER ONE:
Introduction

Amino acids have been a topic of study for decades with the first isolation of an amino acid (AAs) being roughly one hundred and fifty years ago (Meister, 2012). Research in nutrition biochemistry has discovered approximately 500 various forms of AAs. AAs are the building blocks of the body's structure and function. According to Meister (2012), an AA is a chemical compound comprised of amino and acid groups . To further elaborate, this means that the AA has a central carbon atom that is bonded to an amino group, primarily NH_2, a carboxyl group and a hydrogen atom. AAs are the monomers of proteins. Of the approximately 500 AAs there is a primary focus on 20 of these AAs that are necessary for hormones, neurotransmitters and proteins synthesis. These 20 AAs can be separated into three groups: essential AAs, conditional AAs, and non-essential AAs. Non-essential AAs are produced by the body without any supplementation in the diet. Conditional AAs can be synthesized on a small scale; however, our bodies require additional supplementation acquired through diets. There are nine essential AAs that cannot be made in the body and have to be fully acquired through diet. Of these nine AAs three form branch chain amino acids (BCAAs), leucine, isoleucine, and valine. BCAAs can be found in all forms of proteins and in supplements i.e., tablets, powders and drinks. Through these forms of supplementation, individuals have benefited by way of reducing recovery time, increasing muscle endurance and reducing bodyfat percentage. With those benefits in mind this paper will first specifically discuss the effects of BCAA metabolism on the aerobic and anerobic energy systems. Secondly, the following will elaborate on the metabolism of BCAAs. Thirdly, the oxidation of BCAAs in skeletal muscle and how the processes discussed effects everyday individuals, explicitly relating to the implication of BCAAs on exercise and diet. Finally, information will be given on who should and should not supplement with BCAAs and why.

CHAPTER TWO:

Metabolism of Branch Chain Amino Acids

Leucine, isoleucine and valine work together in a specific balance to signal protein synthesis, enhance energy, increase endurance, and help with muscle recovery and repair. The average individual requires 40 mg leucine, 17-20 mg valine and 19 mg isoleucine of consumption daily. This provides a balanced 2:1:1 ratio of the respective AAs (Kurpad et al., 2006). The essential AAs each play a unique role in protein synthesis because of their different side chains, shape, and hydrophobicity (Brosnan & Brosnan, 2006). Leucine is the main driver for protein synthesis in the body. Presence of this AA signals to increase the rate of protein synthesis. Valine and isoleucine do not, on their own, promote protein translation. As stated before, all three BCAAs have to be in a balance; two valine for every one isoleucine and for every one leucine; in order for protein synthesis to proceed (Harris et al., 2004). Valine stimulates activity to promote muscle growth and repair in the system. This AA is also known for lowering blood glucose levels and increasing the growth hormones the body produces ("National Center for Biotechnology Information," 2021a). Similar to valine, isoleucine plays a key role in blood glucose levels. Isoleucine has diverse physiological functions which include wound healing, stimulating immune function, secretion of various hormones (e.g. insulin) and discarding nitrogenous waste like ammonia. Isoleucine is necessary for the formation of hemoglobin and control the blood glucose and energy levels. ("National Center for

Biotechnology Information," 2021b). Additionally, it is worth noting that isoleucine and valine may have a correlation with the potential increase of CoA succinyl availability in the tricarboxylic acid cycle (TCA cycle), one of the last steps in the breakdown of BCAAs. (Gualano et al., 2011)

The metabolism of BCAAs begins in skeletal muscle and consists of transamination, oxidative decarboxylation and finishing with the TCA cycle. The system begins with the leucine, isoleucine and valine being catalyzed by branch chain aminotransferase (BCAT) to form branch chain alpha-keto acids (BCKAs). After the production of the BCKAs in the inner mitochondrial membrane, BCKAs are taken in by the muscles then catalyzed by branch chain alpha-keto acids dehydrogenase complex (BCKDH) to make CoA compounds that continue the oxidation process of BCAAs to their respected ketoacids (Shimomura et al., 2004). During its active state, the BCKDH complex, catalyzes the BCKAs. However, the complex is inhibited by BCKDK. In order for the complex to be reactivated, BCKDH phosphatase must add energy back into the system, making the second step involving the BCKDH complex the rate limiting step of the metabolism of BCAAs. The breakdown of BCAAs has a third step, which involves the ketoacids going through the TCA cycle to produce Succinyl CoA and Acetyl CoA (Shimomura et al., 2004). As a result of the catabolism of BCAAs, the AAs that are involved in the process are thought to prevent fatigue during exercise, promote wound healing and stimulate insulin production through oxidation and increasing the glucose transporters in the body.

CHAPTER THREE:

Oxidation of BCAAs in Skeletal Muscle

With the step-by-step process of the metabolism of BCAAs, the BCKDH complex, is the rate limiting enzyme of the entire catabolic pathway. The reaction is irreversible in the second step of the pathway. Only further breakdown of the AAs is allowed after this point (Shimomura et al., 2004). There are few ways to regulate this complex during BCAA metabolism. One process of regulation includes the modification of the BCKDH complex. This occurs during dephosphorylation when a phosphate is removed from Adenosine Triphosphate (ATP) resulting in Adenosine Diphosphate (ADP). This results in the E1 alpha subunit or the α-ketoacid dehydrogenase, and the release of energy. To activate the BCKDH complex, energy must be restored by replenishing ATP within skeletal muscle. (that process is called phosphorylation). In order to active the BCKDH complex, the addition of a phosphate is needed to produce ATP from ADP by a phosphatase enzyme. The complex is also regulated by the amount of BCKAs present. Catabolism of leucine results in alpha-ketoscaproate which is a primary regulator of the complex. Valine and isoleucine are also reduced into regulatory BCKAs but not to the same degree (Brosnan & Brosnan, 2006).

Free fatty acid oxidation

Along with the regulation of the complex, isoleucine and valine increase succinyl-CoA availability which could possibly lead to the increase in concentration of oxalacetate which is thought to increase the free fatty acid (FFA) oxidation (Gualano et al., 2011). A decrease in valine or isoleucine would inhibit BCKAC and lower or even stop the FFA oxidation. To illustrate, a hyperlipidemic drug called Clodibric acid stimulates FFA oxidation by decreasing kinase activity and promoting the breakdown of BCAAs. During exercise, FFA oxidation is also increased because the activation of BCKDH complex increased with endurance activities which suppresses the kinase protein (Shimomura et al., 2004). The increase of activation of BCKDH complex can be justified by the Central fatigue hypothesis. This states that the FFAs are taken from the tissue and transported to the blood into the muscle that is working during an exercise (Gleeson, 2005). This process is working BCAA metabolism, decreasing the fatigue that is experienced during endurance exercise.

CHAPTER FOUR:

Roles of BCAA's in Exercise

Decreasing the fatigue during endurance exercise is beneficial for individuals who are looking to improve their performance during training. The consumption of BCAAs in the muscles results in oxidization of energy and the improvement of plasma glucose levels (Holeček, 2018). Endurance exercise increases oxidation of BCAAs, which then increases the glucose transporters in the blood. This increase in glucose transporters in the body increases the insulin in the body (Holeček, 2018). An increase of insulin in the body then allows for uptake of glucose and glycogen in the muscles. A study performed by Gualano and colleagues showed with completely glucose depleted subjects, that individuals who were supplemented with BCAAs had a higher plasma glucose level at the 20, 25 and 30 minute mark of their work duration than those with the placebo supplement (Gualano et al., 2011). With an increase of plasma glucose levels in the blood, BCAAs have an effect on the aerobic energy system in the body. Even though they are used for energy in the body, it is to note that BCAAs do not have as big of an energy payoff as carbohydrates and fats (Gleeson, 2005). During the BCAA oxidation, energy is only increased by two to three times, while carbohydrates and fats increase energy by 10 to 20 times.

Supplementing BCAAs before or during exercise also reduces muscle damage during the activity. Supplementation decreases the endogenous muscle breakdown by suppressing the rise of serum creatine kinase activity for multiple days in a row. By suppressing creatine kinase activity, it prevents creatine kinase from being released into the blood when there is muscle damage (Shimomura et al., 2006). With the decrease in muscle damage, the supplements also reduced delayed onset muscle soreness (DOMS) and muscle fatigue. With males and females being supplemented with BCAAs and a placebo, were given specific exercises to determine the effect of BCAAs on their recovery (Shimomura et al., 2006). The females in the study that were given the placebo supplement, displayed DOMS on the second and third day of exercise. The BCAA experimental group experienced DOMS but the peak soreness was significantly lower and only on the second day. For the males, similar data was collected. In both genders, DOMS was lower with BCAA supplementation and muscle fatigue was highest right after exercise. After the fourth day, muscle fatigue was less with BCAA supplementation than placebo. Indicating from the study, that the ingestion of BCAAs before a workout will decrease muscle damage, lower the DOMS and reduce the how long an individual is sore for both males and females (Shimomura et al., 2006).

CHAPTER FIVE:

Applications

Now with an understanding of the science behind BCAA metabolism, oxidation skeletal muscles and BCAAs roles in the exercise, an explanation will be given how of this process is applicable to individuals in exercise and health related situations. First, the effects of BCAAs on exercise will be discussed, secondly the dietary implications, and lastly who should and should not supplement.

The Effect of BCAAs on Exercise

The timing of BCAA consumption is very important for the stimulation of anaerobic and aerobic energy systems during training. Prior to training the focus needs to be fueling the body with proper nutrients to ensure maximal energy payout during a workout. These nutrients should be carbohydrates and fats because they give about 10 to 20 times more energy payout during exercise compared to baseline energy outputs (Gleeson, 2005). BCAAs can be supplemented but should not be the primary energy source due to the fact that the oxidation of BCAAs will only give about two to three times more energy during exercise (Gleeson, 2005). Although BCAAs are not as effective in supplying adequate energy as carbohydrates, their consumption prior to or during exercise has its benefits including enhanced muscle endurance during training, this simply means an individual muscles will be able to contract for a longer period of time (Shimomura et al., 2004). During exercise there is increased cardiac output, which allows for greater AA delivery to the skeletal muscles. This increased delivery to the skeletal muscles increases the rate limiting step, BKCDH complex, allowing for increased BCAA oxidation. Increased oxidation promotes protein synthesis therefore leading to decrease of muscle breakdown i.e increase muscle endurance during training. An additional benefit to combating muscle breakdown is decreasing DOMS and minimizing overall muscle fatigue during exercise (Shimomura et al., 2006). With the decrease of DOMS and overall muscle fatigue the individual will be able to recover faster and more efficiently during and after their training sessions (Shimomura et al., 2006). Quick recovery is conducive to minimizing injury therefore supports a healthy lifestyle.

Besides the training benefits of BCAAs, in order to maintain a healthy lifestyle, there needs to be a balance between the BCAAs and micronutrients (e.g., vitamins, minerals) in one’s diet. If the balance between BCAAs and other nutrients in a diet is off, serious risks can occur like cardiovascular disease (Mertz et al., 2018). When BCAAs and micronutrients are in balance there is evidence that show that there is a decrease in fat and it helps individuals conserve muscle mass (Harris et al., 2004). Therefore, with a balanced diet an individual will be able to maintain a healthier body for a longer period of time.

Dietary Implications of BCAAs and Impact on Performance

The dietary protein intake of an average individual consists of about 20% BCAAs. That 20% forms the dietary make up of 35% of the necessary AAs required in an individual (Brosnan & Brosnan, 2006). Research shows strong evidence that the intake of BCAAs in the diet of mammals can help conserve muscle mass and even decrease body fat percentage. However, overconsumption of BCAAs can lead to various diseases such as Type 2 Diabetes and cardiovascular disease (Mertz et al., 2018). The over-consumption of BCAAs, along with other metabolites, has been linked to insulin resistance in the body. Newgard et. al researched a study which observed 73 obese and 67 lean individuals. This study used Principle Component Analysis to identify the linkage between the components of BCAA's, aromatic amino acids, and the by-products of BCAAs to obesity and insulin resistance among the selected population (Lu et al., 2013; Newgard et al., 2009). In addition, different studies were conducted, including a study that found the reduction of leucine and or isoleucine along with glycerol was a strong indicator of insulin sensitivity (Lu et al., 2013). The study also suggested that the baseline BCAAs were associated with identifying future diabetics, and can predict diabetic tendencies twelve years before an official diagnosis (Lu et al., 2013). The insulin resistance was found not because of how much protein was being consumed but rather that the BCAA degradation was impaired in the tissue or skeletal muscle.

An enzyme called mTOR (serine/threonine kinase) which is primarily used for cell growth regulation through protein synthesis, is now considered the mediating molecule between AAs and insulin. The supplementation of BCAAs, will increase the activation of the mTOR enzyme coupled with other pathways, which will ultimately decrease the insulin signaling in human skeletal muscles (Lu et al., 2013). Therefore, the dietary implication of BCAAs shows that there is need for balance between high protein foods and BCAA degradation in order to maintain a healthy lifestyle.

Supplementation Specific to Individuals

Although for most individuals the supplementation of BCAAs is beneficial for muscle recovery, others may experience negative side effects. As previously explained, the oxidation of BCAAs releases insulin in the body allowing for glucose and glycogen to be absorbed in the muscles. Individuals that are insulin resistant (IR) or in another words, people who cannot use insulin properly for uptake of glucose will experience an increase insulin with the supplementation of BCAAs (Mertz et al., 2018). In addition to the already high levels of insulin being produced in IR individuals, BCAAs will signal more insulin to be released by the pancreas due to the increase of glucose transporters in the blood. The supplementation with BCAAs increases the concentration of insulin to dangerously high levels. This also goes for individuals with Type 2 diabetes, especially in the earlier years of diagnosis, which is an extreme version of insulin resistance.

Another group that should stay clear of BCAA supplementation, are those with cardiovascular disease and people with cardiovascular disease in their family tree. People that have the disease are going to block the catabolism of BCAAs in the myocardial cells. This blockage then results in the buildup of AAs in the myocardium and through different process can lead to cardiovascular disease (Mertz et al., 2018). Lastly, those that personally struggle or have family members that struggle with depression or other disorders that are along the same line should not supplement with BCAAs. These individuals could be affected by the supplementation of BCAAs because they reduce another amino acid called tryptophan (Choi et al., 2013). Tryptophan is the main building block of the serotonin hormone that regulates the mood eating, sleeping and digestion. Tryptophan is reduced with the catabolism of BCAAs and exercise (Choi et al., 2013). Low tryptophan means low serotonin levels, resulting in a low mood or even depression.

While BCAAs are beneficial to almost all individuals, there especially important for individuals who perform aerobic or anaerobic exercise. Aerobic exercise is any training style that uses oxygen in order to meet energy demands. This includes but is not limited too long-distance running, jogging, rowing, cross country skiing etc. Over these periods of exercise, an individual muscles begin to break down and they become physically and mentally fatigued (Gleeson, 2005; Shimomura et al., 2006). When individuals supplement with BCAAs during the training period they will experience increased muscle endurance. With the increased cardiac output during training, BCAA will be moved into the muscles and begin oxidation. This oxidation with signal for protein synthesis and reduction of serum creatine kinase. The individual will experience less pain or soreness after endurance exercise and promote repair of the muscles (Shimomura et al., 2004).

Anaerobic exercise, which is in simple terms is activity that does not use oxygen to meet energy demands, like sprinters, heavy weightlifters, and individuals that do high intensity interval training. These individuals will experience similar affects is those who part take in aerobic style training but to a different degree. Anaerobic exercisers will experience less soreness, increased muscle endurance, but most importantly muscle repair. For example, a study by Wesley David Dudgeon and colleagues, showed that individuals who were in a calorie deficit state while strength training, improved muscle recovery and growth while maintain a lean body weight (Dudgeon et al., 2016). The individuals studied also experienced weight lose while losing minimal muscle mass (Dudgeon et al., 2016). In essence, not only are BCAAs great for endurance training, but for anyone who is trying to lose weight but maintain as much muscle mass as possible, like bodybuilders. It is important to note that there is insufficient evidence to supporting BCAAs as a supplement to increase strength.

CHAPTER 6:

Conclusion

BCAA oxidation is crucial to the proper functioning of the aerobic and anerobic energy systems during exercise. The metabolism process has two crucial steps. The first being a required balance ratio of 2:1:1 between AAs, and second, the rate limiting step, BKCDH complex, which is an irreversible reaction. During exercise, the rate limiting step increases, allowing for FFAs to be transported from the tissues to the blood and then to the muscles. The result of this transfer is a decrease of muscle fatigue. BCAAs play an important role in exercise by increasing the glucose transporters in the blood. This increase in glucose transporters in the blood increases the insulin throughout the body. An increase of insulin in the body allows for uptake of glucose and glycogen in the muscles, producing a small energy payout. Supplementing BCAAs before exercise suppresses serum creatine kinase that helps reduce muscle damage during the activity. With the decrease in muscle damage, the supplements also reduced DOMS and muscle fatigue. Although the intake of BCAAs has positive effects for individuals participating in aerobic and anerobic exercise, such as decreasing the body fat composition, maintain muscle and increasing muscle endurance, negative side effects can occur from over-consumption including cardiovascular disease and diabetes. The relationship between insulin and BCAAs has been found to be both positive and negative. Positive in that baseline BCAAs have been shown to detect future diabetics, and negative in that over-consumption promotes insulin resistance. In essence a healthy balance of BCAAs is vital for an individual's over all well-being.

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