Recover & Build

Goal

To timely supply the branched-chain-amino-acids (BCAAs) valine, isoleucine and most importantly leucine, in amounts consistent with successful clinical trials demonstrating the ability of BCAA supplementation to reduce muscle damage, soreness and potentially enhance recovery and muscle protein synthesis (MPS) initiated from exercise. BCAA supplementation may be especially useful during prolonged energy restriction, continuous high intensity activity, extended exercise bouts or any combination of these conditions. Proper dosing would supply a low calorie, isolated group of amino acids with a high affinity towards peripheral tissues (e.g. skeletal muscles) rather than liver metabolism which happens to most other amino acids involved in MPS. The BCAAs are metabolized to become available for protein synthesis and energy production. Therefore, during exercise, appropriate supplementation may increase BCAAs in the body's "amino acid pool" to spare endogenous BCAA stores from catabolism (reduce muscle breakdown), delay fatigue and help supply additional substrate for MPS and energy.

Note

The dotFIT Recover&Build is a tablet form of isolated BCAAs allowing the user a convenient, low calorie and economical alternative to the dotFIT AminoBoostXXL (AB), which also contains a very high dose of BCAAs (6 g in one 12 g serving). While there may be clinical or other potential conditions where BCAAs supplementation alone may be warranted, the dotFIT R&D team positions the use of Recover&Build (RB) only for the goals described above, which are similar to the actions of AB supplementation. In other words, if you are using AB, we have no rationale to recommend RB other than in relatively high doses for the primary goal of delaying fatigue during strenuous endurance activities.

Rationale

For details on the relationship including mechanisms of actions between amino acids including branched-chain-amino-acids (BCAAs/leucine), exercise and muscle protein synthesis, the reader is referred to the AminoBoostXXL section in this series. This Recover&Build section is dedicated solely to the use of BCAA supplementation during exercise.

Leucine, isoleucine and valine are called branched chain amino acids because of their structure, which includes a side chain of one carbon atom and three hydrogen atoms. These BCAAs are three of the nine essential amino acids (EAAs) that are indispensible for muscle protein synthesis and make up approximately 35% of the EAAs found in skeletal muscle.[1] Ingested BCAA's have a greater availability than other amino acids for skeletal muscle.[2,3]

BCAAs metabolism predominantly takes place in skeletal muscle and therefore escapes splanchnic extraction (liver metabolism) allowing BCAAs to rapidly increase plasma concentrations following ingestion.[4] The three BCAA's are structurally similar thus catabolized in similar metabolic pathways that can result in their by-products being shuttled to the Krebs cycle to re-synthesize adenosine triphosphate (ATP) for energy production.[5] Although the liver has limited ability to metabolize BCAAs, it does contain an active system for the breakdown of one of its by-products, the α-branched-chain-keto acids (BCKA)[6] via the branched-chain α-keto acid dehydrogenase (BCKD) system, which ends up contributing to important gluconeogenesis especially during exercise.4 BCAAs, more than any other amino acids, are metabolized during exercise within skeletal muscle mitochondria.[7] The first step is the transamination of the BCAAs to an alpha-keto acid by the enzyme branched-chain amino transferase (BCAT). The resulting form can remain in the tissue amino acid pool and go one of two ways: 1) further catabolism by the enzyme BCKD (as described above) to form metabolites that can feed the Krebs cycle or 2) preferentially used to re-synthesize muscle protein.[8] This dual role of the BCCAs fate of metabolism (substrate for the energy cycle and MPS) gives rise to the rationale of supplementing additional BCCAs in a timely fashion around exercise to improve long-term outcomes compared to a non-supplemented state and especially during intense training combined with energy restriction. Therefore, the goal of supplementing BCCAs is to increase the amount of free BCAAs in the skeletal muscle amino acid pool.

BCAA in Exercise

Energy Contribution

Branched chain amino acid metabolism clearly contributes to exercise capacity but proper dosing of supplementation to overcome innate rate-limiting production/performance factors has remained elusive. The role of BCAAs in energy contribution relates to its downstream production of metabolites alanine and glutamine and the maintenance of glucose homeostasis. The relationship between BCAAs and glucose metabolism is their association with the glucose-alanine cycle. BCAAs are continuously released from the liver and escorted to skeletal muscle stimulating the transamination of BCAAs, as described above, resulting in the production of glutamine and the transfer of the BCAA nitrogen components to pyruvate to produce alanine. Alanine then can circulate back to the liver to support hepatic gluconeogenesis. The glucose-alanine cycle might account for greater than 40% of the glucose produced during prolonged exercise.[9,10] The oxidation of BCAAs in muscle for energy may increase fivefold during strenuous exercise.[1,11] Therefore, when BCAAs are consumed, they move to the muscle and are oxidized to supply the additional energy and theoretically prolong energetic activity through the longer maintenance of glycogen or less reliance on their stores.[12,13,14] To be sure, impaired BCAA metabolism, as demonstrated by high resting plasma levels, have been shown to be negatively correlated with exercise capacity[15,16] and the inefficiency of BCAT2, the enzyme responsible for the initial transamination step.[17]

Additionally, since BCAAs enhance cell signaling pathways of muscle protein synthesis as described in the AminoBoostXXL section of this series, and effect intermediary metabolism as noted above, BCAAs may also indirectly facilitate an enhancement in mitochondrial function including ATP production.[18] Tatpati et al. tested this theory in old and young adults using an infusion of BCAAs which included an equimolar mixture of valine, leucine, and isoleucine that achieved plasma concentrations of these BCAA greater than 3–6 times their baseline concentrations and maintain the leucine concentration 800 µmol/liter or greater.[19] They discovered that the BCAA supplement significantly increased the skeletal muscle mitochondria ATP production ratio (MAPR) in the young participants in comparison with placebo, but not in older subjects.[19]

BCAAs Effects on Fatiguing Substances

Serotonin is involved in many biological functions including appetite, body temperature, sexual behavior, aggression, mood, exercise, memory, fatigue, etc. Serotonin or 5-hydroxytryptamine (5-HT) is a monoamine neurotransmitter biochemically derived from tryptophan.[20] Therefore because the transport of tryptophan across the blood-brain-barrier (BBB) increases levels of 5-HT, this action has been suggested to contribute to fatigue during long-duration exercise (e.g. endurance events).[21,22]

Consuming purified tryptophan increases brain serotonin whereas eating foods containing tryptophan does not[23] because the BBB transport system for tryptophan is also selective for other amino acids contained in protein sources and especially BCAA.[24] Therefore, elevated plasma levels of other large neutral amino acids compete for the same transportation sites and can prevent the respective plasma tryptophan from increasing serotonin synthesis.[25,26] Based on these facts, researchers have postulated that increasing serum BCAAs may reduce uptake of tryptophan during endurance exercise, hence decreasing 5-HT and central fatigue as shown early on by Bloomstrand et al. [27,28] Their latter study showed supplementing BCAAs during 60 minutes of exercise at a given work rate resulted in 7% lower ratings of perceived exertion along with 15% lower ratings of mental fatigue compared to placebo.[28] When BCAA supplementation is supplied to endurance athletes, rates of perceived exertion and mental fatigue have been shown to be reduced during exercise[21,22] while other trials have shown no benefit.[29]

BCAA Studies Related to Fatiguing Factors in Prolonged Exercise

- Mikulski et al. administered 16 g of BCAA with 12 g of L-ornithine L-aspartate (ammonia decreasing agent) supplementation to reduce plasma ammonia concentration and enhance psychomotor performance in healthy

men. Supplementation was found to delay central fatigue during prolonged exhaustive exercise including improvement in multiple choice reaction time (MCRT).[30]

- Gee et al. had 11 resistance-trained males perform baseline measures of a counter movement jump (CMJ) and a seated shot-put throw (SSPT). Subjects were provided with either 20 g of BCAAs or a placebo. Each dose was divided into two equal quantities and ingested before and after a strength training session consisting of various multi-joint barbell exercises. For both conditions, the CMJ and SSPT were repeated at 24 hours post-strength training and participants reported their perceived muscle soreness. The BCAA supplementation compared to placebo demonstrated a significant attenuation in normal decreases in power producing abilities but no difference in muscle soreness. The authors suggested that "BCAAs are an effective ergogenic aid for athletes who require augmented recovery of power-producing ability following intensive strength training."[31]
- Greer et al. studied whether BCAA supplementation impacts aerobic performance, ratings of perceived exertion (RPE), or substrate utilization as compared with an iso-caloric carbohydrate (CHO) beverage or a non-caloric placebo beverage in three 90-minute cycling bouts at 55% VO_2 peak followed by 15-minute time trials. BCAAs supplementation did not positively influence aerobic performance as the CHO group, but did attenuate RPE as compared to placebo.[32]
- Portier et al. tested perceived exertion, mental and physical performance during a sailing race that lasted 32 hours using a standard diet and adding a high protein supplement (40% CHO, 35% protein, 25% fat) with BCAAs fortification (50% valine, 35% leucine, and 15% isoleucine) compared to placebo (standard diet). Before and after the race a vertical jump and a handgrip test were performed, and mental performance was evaluated with a standardized battery of tests. A significant increase in the feeling of fatigue was noted on day two of the race in both groups but registered no change in physical performance. However, the increased perceived exertion was significantly higher in the placebo subjects. Additionally, only the placebo group experienced a decrease in short-term memory performance. The authors concluded that "these detrimental consequences are reduced by a high-protein diet with BCAAs."[33]
- In a study designed to determine changes in multiple-choice reaction time (MCRT) with an application to soccer, Wisnik et al. incorporated treadmill running to simulate locomotor activity during a soccer game and test the effect of BCAAs supplementation on psychomotor performance. BCAA (7 g) or placebo was given one hour before exercise in a double-blind manner. The running test consisted of two 45-minute exercise bouts separated by a 15 minute passive rest period and running speeds varied to match soccer play. While no significant differences were discovered in biochemical indices between trials, during the BCAA trial, subjects MCRT was shorter than during the placebo trial by ~10% ($p < 0.05$) before and during exercise. It was concluded that "BCAA supplementation might be recommended in sport activities that change in intensity and require quick responses to external signals (e.g., soccer and other team games)."[34]

BCAA and Lactate Production

As described above, BCAAs are used as an important energy source during exercise with oxidation increasing with exercise intesity.[35] BCAA metabolites enter the Krebs cycle not by the glycolitc pathway but directly s acetyl-CoA and/or succinyl-CoA and therefore lactate is not produced from BCAA energy metabolism.[36] With this in mind and lactate being a known limiting factor in exercise performance, any energy produced from BCAA supplementation should theoretically decrease lactate production during exercise and potentially raise the work threshold in the case where lactate is rate-limiting. To be sure, De Palo et al. found that BCAA supplementation blunts the increase in blood lactate during exercise.[37]

- Since latate threshold is often used as a measure of endurance exercise capacity,[38] Matsumoto et al. investigated the effect of BCAA supplementation before an incremental loading exercise test following a 7-day supplementation (1.5 g valine, 3 g leucine, 1.5 g isoleucine totaling 6 g BCAA), on the lactate threshold as an index of the endurance exercise capacity in trained subjects.[39] The results found decreases in lactate accumulation (suggesting the expected decrease in carbohydrate oxidation) and a significant increase in the VO_2 max in the

BCAA trial compared to the placebo trial. The study concluded that 6 g/day of BCAA supplementation increased the VO_2 and workload levels at the lactate threshold and onset of blood lactate accumulation (OBLA) and VO_2 max.

- In a different design, Matsumoto et al. also demonstrated BCAA supplementation lowered lactate levels.[40] This study, in the BCAA trial, also found muscle soreness and fatigue sensation during the training period lower than those in the placebo trial (-32% and -24%, respectively). Additionally, they reported the plasma creatine kinase (CK), lactate dehydrogenase (LDH), and granulocyte elastase (GEL) levels (all markers of muscle damage) in the BCAA trial, as lower than those in the placebo trial (-21%, -6%, and -15%, respectively).[40]

Other studies have come up empty on BCAA supplementation and endurance performance, which may be related to dosing protocols including acute versus chronic usage and amounts.[29,39,41]

BCAA Effects in MPS, MPB, DOMS & Recovery

At a minimum BCAAs are three of the nine essential amino acids that must be supplied through diet in order for MPS to occur in humans. BCAAs are both structural components of skeletal muscle (SM) and act as messengers (especially leucine) in the continuous cycling processes of MPS, making them a tempting dietary supplement research topic. However, in regard to exercise and MPS, the elusiveness in their value in isolation beyond being timely supplied in "desired amounts" as part of the EAAs may be moot.

BCAAs Reference Points

While BCAAs make up 35–40% of the essential amino acids in body protein, they account for 14–18% of the total amino acids in muscle protein.1,7 Approximately 40% of the body weight of non-overweight humans is muscle mass, which establishes a large depository of BCAAs in the body. The human body also has a free amino acid (AA) pool that remains fairly constant in which skeletal muscle contains approximately .05 g/lb (0.3 -.55 mmol/lb) of free BCAAs.[42] Compared to the other amino acids, because of the metabolic fates of BCAAs (see above section), the concentration of BCAA in human blood is relatively high (0.3–0.4 mM) but small compared to amounts in muscle proteins.[7,43] However, the free BCAAs and especially leucine play an important role in overall protein metabolism by affecting the activity of intracellular signaling networks such as the mammalian target of rapamycin complex 1 (mTORC1) and the mitogen activated protein kinase (MAPK) cascades.[44] Furthermore, unequivocal evidence has surfaced that both exercise and aging increase the demand for AAs (including the BCAAs), if an individual seeks to maximize MPS throughout the lifespan. In fact, it's clear that increasing plasma and muscle intracellular AA concentrations stimulate MPS with or without exercise.[45] Like exercise, AA ingestion alone also stimulates muscle mTOR signaling but independently through regulators of translation initiation (S6K1 and 4E-BP1) and elongation (eEF2), which strongly and rapidly stimulate muscle protein synthesis (i.e. within 1 hour).[46,47] It is also clear that the essential amino acids[48] are the primary drivers of the signals for protein synthesis, particularly leucine.[49]

Exercise and Amino Acids

Increasing exogenous AAs with exercise potentiates the MPS response, initiated through mechanical loading, by further enhancing mTORC1 activation as discussed, and other intracellular AA sensing mechanisms such as the human vacuolar protein sorting-34, (hVps34)[50,51,52] and also by increasing AA transporter expression.[53,54,55] In simple terms, exercise leads to muscle protein breakdown, which induces a heightened nutrient demand and their respective receptor sensitivity, allowing exogenous AAs to be delivered timely in the right amounts (specifically EAA, including a relatively high leucine content) to maximize an individual's MPS potential, leading to enhanced size and/or performance training induced results when all else is equal (e.g. training and overall diet).[56,57,58]

Essential Amino Acids

The stimulation of MPS from AAs is dependent on the EAAs.[59] Although non-essential amino acids are necessary components of complete muscle tissue, they are not required to stimulate MPS.[46,48,51,60] Additionally, it's been shown that EAA feeding stimulates protein synthesis independently of all other mechanisms,[61,62,63,64] and EAA formulas

enriched with leucine have further demonstrated leucine's unique and potentially additive role in MPS.[65,66,67] *The reader is referred to page 2-3 of the AminoBoostXXL section for further details on EAAs, including leucine mechanisms of actions.*

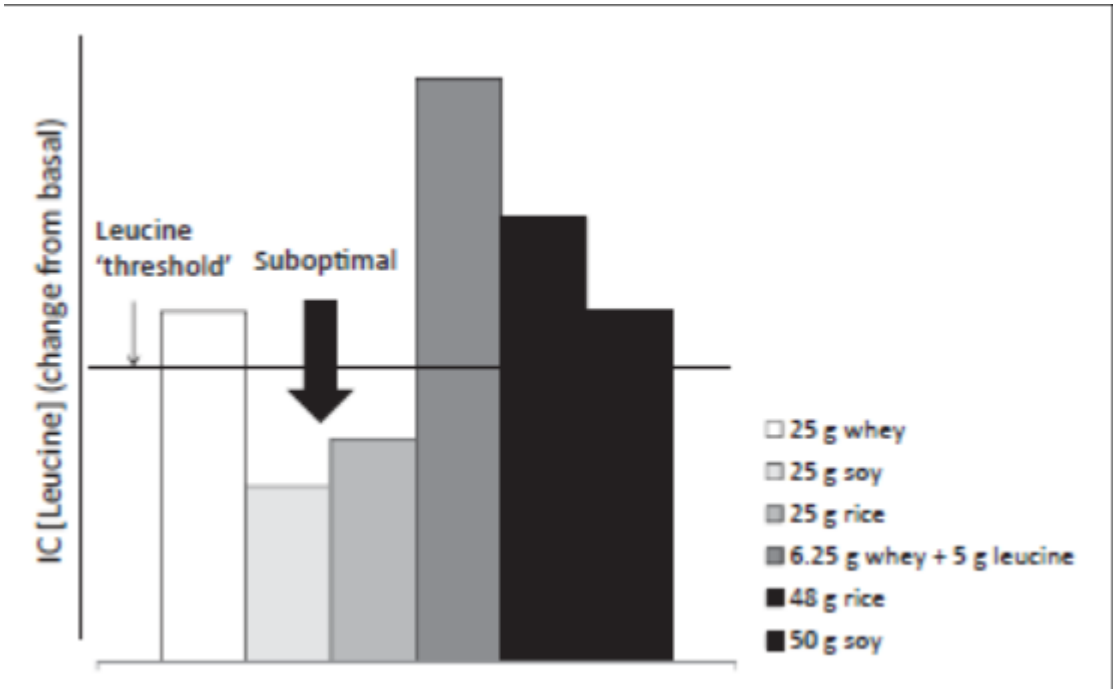
Leucine

Leucine is one of the two exclusively ketogenic AAs in humans (lysine is the other). A ketogenic AA can be degraded directly into acetyl-CoA, which is the precursor of ketone bodies.[68] In contrast, the glucogenic amino acids are converted into glucose. Ketogenic AAs cannot be converted to glucose because both carbon atoms in the ketone body are eventually degraded to carbon dioxide in the Krebs cycle.[68,69] Leucine is an essential amino acid necessary for growth and one of 20 amino acids common in proteins. It has a non-polar 'R' structure and is relatively insoluble in water.[68,70]

Leucine in MPS (see **Amino Boost** and **WheySmooth** sections for details)

Although human muscle protein synthesis requires 20 AAs including nine EAAs that must be supplied through diet, leucine clearly has the most prominent role in net muscle protein synthesis.[71] The many important actions of leucine are certainly in part associated with absence of the branched-chain aminotransferase enzyme in liver as described above. Therefore, dietary BCAAs appear in the blood virtually equal to intake, allowing leucine to reach skeletal muscle in their proportion within dietary intake.[72] In western diets the BCAAs makeup ~20% of total dietary protein and considering the BCAAs account for approximately one-third of muscle protein,[72] it is logical that leucine evolved with humans to play a more prominent role in the regulation of protein turnover than other AAs. Leucine not only independently enhances mTORC1 signaling to promote growth but also inhibits MPB through down-regulation of proteolysis and suppression of the ubiquitin/proteasome pathway.[73] The importance of leucine synergistically (with other AAs) and independently stimulating MPS is well established,[74,75,76,77,78] and therefore researchers conceptualize a leucine threshold for maximizing MPS as shown in Figure 1. The leucine threshold ("trigger") proposes that for maximum MPS to take place following protein ingestion, the muscular intracellular leucine concentration needs to reach a given level – i.e. "the leucine threshold."[79] In order to maximize protein synthesis, this leucine threshold, depending on age, size and activity, may be in amounts greater than 2.5 g per protein dose.[65,66,67,80]

Figure 1 - Leucine Intracellular Concentration from Various Protein Sources



Intracellular (IC) leucine concentration following the consumption of varied doses of protein in relation to the proposed "leucine threshold." This data is gathered from young, resistance-trained subjects therefore this "leucine threshold" would increase with age and physical inactivity.[79] The leucine threshold proposes that for maximum MPS to take place following protein ingestion, the muscle intracellular leucine concentration needs to reach a given level and the amount of leucine should be >2.5 g. – i.e. "the leucine threshold.[65,66,67,80]

Isoleucine

Isoleucine is an α-amino acid that is used in the biosynthesis of proteins. It contains an α-amino group, an α-carboxylic acid group and a hydrocarbon side chain, classifying it as a non-polar, uncharged aliphatic amino acid. Isoleucine is both a glucogenic and a ketogenic amino acid.[81,82] Following transamination with alpha-ketoglutarate, the carbon skeleton can be converted to either Succinyl CoA, and shuttled into the Krebs cycle for oxidation or converted into oxaloacetate for gluconeogenesis – thus glucogenic. Additionally, isoleucine can be converted into Acetyl CoA and enter the Krebs cycle by condensing with oxaloacetate to form citrate. In humans Acetyl CoA cannot be converted back to carbohydrate but can be used in the synthesis of ketone bodies or fatty acids –thus ketogenic.[81,82]

Valine

Valine is a glucogenic, aliphatic and extremely hydrophobic essential amino acid related to leucine. Valine is a BCAA with stimulant activity and helps maintains mental vigor, muscle coordination, and emotional calm.[83] Valine acts with leucine and isoleucine to enhance energy, increase endurance, and aid in muscle tissue recovery and repair.[71] This group also lowers elevated blood sugar levels and increases growth hormone production. Clinically (not necessarily for MPS or energy), supplemental valine should be combined with isoleucine and leucine at a respective milligram ratio of 2:1:2.[84]

BCAAs in Synergy Beyond Leucine

Clearly, leucine has unique anabolic properties and MPS contribution, however evidence suggests leucine alone would not be responsible for the entire anabolic effect from a proper mixture of EAA.[71] Early on, in vitro studies showed that the stimulation of S6K1 in skeletal muscle cells is mediated by the entire BCAA group[85] and BCAA supplementation strongly stimulates mTORC1 signaling suggesting a synergistic MPS relationship.[86,87] Additionally, Apro and Mogerg et al. demonstrated that the consumption of EAAs in combination with resistance training, stimulated the actions of 70-

kDa ribosomal protein S6 kinase 1 in skeletal muscle greater than leucine alone.[88] Furthermore, in rat muscle, isoleucine alone enhances the phosphorylation of S6K1 and the eukaryotic translation initiation factor 4E (eIF4E)-binding protein 1 (4E-BP1)[89], which may be from the leucyltRNA synthetase sensing the presence of isoleucine.[90]
Apro and Mogerg et al. followed their previous research demonstrating greater activation of specific MPS signaling (e.g. S6K1 and 4E-BP1phosphorylation and mTORC1, etc.) with EAA (including BCAA) compared to leucine.[88] To elucidate the value of BCAAs supplementation versus an EAA mixture (with BCAAs) or leucine alone in different MPS signaling pathways, the researchers had weight-trained subjects consumed one of four drinks: placebo, leucine alone (leucine), all three BCAAs, or essential amino acids including the BCAAs during each exercise trial.[71]
The EAA supplementation (132 mg/lb) consisted of eight essential amino acids (see AminoBoostXXL section for analogous formula); 13.6% L-histidine, 9.5% L-isoleucine, 17.1% L-leucine, 17.8% L-lysine, 2.9% L-methionine, 14.3% L-phenylalanine, 13.6% L-threonine, and 11.4% L-valine. The BCAA supplement (50 mg/lb) contained 25% L-isoleucine, 45% L-leucine, and 30% L-valine. To make sure that the leucine content of all amino acids supplements was equal, the leucine alone supplement was 22.75 mg/lb.
The study findings showed that EAA supplement resulted in a greater activation of S6K1 kinase activity than ingestion of the BCAA, with the effect of leucine alone being the least potent. Additionally, the EAA trials showed the highest phosphorylation of 4E-BP1 along with a greater reduction of its interaction with eIF4E. At the end of the recovery periods both the BCAA and EAA groups showed equal S6K1 and 4E-BP1 activity and both higher than leucine alone thus again demonstrating synergistic effects of EAA including the BCAAs. Collectively, strong evidence supports that BCAAs are superior to leucine alone in activating mTORC1 and that EAA trump both at least as long as leucine is supplied in equal quantities (see also AminoBoostXXL section in this series).[71] These results also appear to refute the notion that isoleucine and valine may antagonize the muscle uptake of leucine[55,67] since in all three AA trials the muscle leucine levels were similar.[71] The contradictions may have been from dosing protocols (smaller frequent dosing versus a large single dose).
In summary, activation of MPS by amino acids is dependent on mTORC1 signaling,[91] and enhanced S6K1 phosphorylation is associated with increases in protein synthesis.[47] Therefore, the enhanced stimulation of S6K1 and 4E-BP1 shown in the EAA trial following exercise (indicative of a significant stimulation of the rate limiting step in translation), would be expected to produce an increased rate of protein synthesis over time through chronic supplementation.

Related Studies

- Shimomura et al. used 5 g (42 mg/lb for females; 35 mg/lb males) of BCAAs (iso:leu:val= 1:2.3:1.2) 15 minutes before squat exercise (plasma BCAAs in solution elevate within 15 minute and peak at ~30 minutes) to test effects on delayed onset muscle soreness (DOMS) and fatigue. Results showed both fatigue and DOMS were attenuated by supplementation versus placebo with females attaining greater benefits presumably from a higher intake per pound of body weight.[7]
- Daneille et al. in a similar design as Shimomura, with both men and women performing squat exercise, found similar results in attenuating DOMS using only 1.2 g of supplemental BCAAs (9 mg/lb for females; 7.5 mg/lb males) combined with glucose.[92]
- Dong-Hee Kim et al. using a more appropriate dosage (37 mg/lb of 20% iso, 24% val, 46% leu) tested BCAA supplementation during endurance exercises on muscle damage markers. They concluded BCAAs decreased serum concentrations of the intramuscular enzymes creatine kinase (CK) and lactate dehydrogenase (LDH) following exhaustive exercise suggesting that BCAA supplementation may reduce the muscle damage associated with endurance exercise.[14]
- Song-Gyu Ra et al. tested the combined effects of 3.2 g (iso:leu:val= 1:2:1) of BCAAs with 2 g of taurine taken three times daily on highly intense eccentric exercise-induced DOMS and muscle damage in a randomized, placebo-controlled, double-blind trial. They found in the exercise induced DOMS and muscle damage, subjective and objective parameters including visual analog scale (VAS) scores, upper arm circumference, and serum levels of LDH

and 8-hydroxydeoxyguanosine (8-OHdG) were significantly improved by the combination of BCAA and taurine supplementation.[93]

- Areces et al. found that seven days of supplementing 5 g/day of BCAAs (1:0.5:0.5 leucine:isoleucine:valine) did not increase the running performance during a marathon, was ineffective at preventing muscle power loss, muscle damage or perceived muscle pain during a marathon race.[94] It is unclear why the authors chose to use this dosing given the evidence that significantly higher doses are necessary to accomplish these particular goals.
- DOMS was reduced in a study by Shimomura et al. which used supplemental BCAAs at 45.5 mg/lb body weight.[95]
- Bassit et al. using acute and chronic BCAA supplementation (about 6 g/d) with endurance athletes attenuated the decline in plasma L-glutamine concentration and also modified the normal immune suppression promoted by exercise.[96] Stimulation by BCAA supplementation presumably led to cellular L-leucine uptake enhancing the synthesis and availability of L-glutamine by providing glutamate in the intracellular environment.[97]
- Howatson et al. examined the effects of BCAA supplementation on markers of muscle damage elicited through a sport specific bout of damaging exercise in 12 trained, young adult athletes randomly assigned to a supplement or placebo group. The exercise consisted of 100 consecutive drop-jumps. Participants ingested 10 g, twice per day (morning and evening) of either BCAA (2:1:1 leucine, isoleucine and valine, respectively) or placebo. The principle findings show BCAA can reduce the negative effects of damaging exercise by attenuating creatine kinase (CK) efflux, reducing residual muscle soreness and improving recovery of muscle function compared to placebo.[98]
- Ikeda et al. examined the effects of BCAAs and exercise on physical function in frail and pre-frail elderly people by testing upper and lower limb isometric strength, performance on the Functional Reach Test (FRT) and the Timed Up and Go test, and activity level. 6 g of BCAAs or 6 g of placebo were ingested 10 minutes before starting exercise. Results showed the improvement rates in gross lower limb muscle strength (leg press, knee extension) and FRT performance were significantly greater (~10%) in the BCAA group. Significant effects were demonstrated for the leg press in both groups only when BCAAs were given. The authors concluded that the combination of BCAA intake and exercise therapy yielded significant improvements in gross lower limb muscle strength and dynamic balance ability.[99]
- Dudgeon et al. studied a BCAA supplement, in conjunction with heavy resistance training and a carbohydrate caloric-restricted "bodybuilding-type diet" on body composition and muscle fitness. Seventeen resistance-trained adult males were randomized to a BCAA group (7 g before and 7 g after exercise) or a carbohydrate (CHO) group while all subjects followed 8-weeks of a prescribed body building style resistance training protocol and hypocaloric diet. The BCAA subjects maintained lean mass, while the CHO group lost ~2 lbs. Both groups increased 1 repetition maximum (RM) squat, but the increase in the BCAA group was significantly greater. The BCAA group also increased 1 RM bench press (~15 lbs), while the CHO group decreased strength (~8 lb).[100]

Dosing and Composition

Although intertwined, regardless of the desired goal (delay fatigue or primarily recovery), BCAA supplementation of 5-20 g taken always before and sometimes split both before, during and after exercise have been shown to be generally successful. This vast dosing range, as mentioned at the onset of this section, is confusing but probably a result of body weight, type and duration of selected trial activities and, as with all diet supplement interventions, the physiological state of the recipient (e.g. current diet, energy restriction, genetic variants, etc.). That said, a BCAA supplement supplied at 50 mg/day per pound of body weight, with at least 50% being leucine (up to ~75% of total mgs) and the remainder split between isoleucine and valine, probably offers the greatest potential to deliver the goal. For example, the appropriate dose for a 175 lb athlete would be 8.75 g of total BCAAs with 4-6 g leucine, 1-2 g isoleucine and 1-2 g valine.

Note: *When delaying fatigue in an endurance activity is the primary goal, it appears ≥6g 15-30 minutes (depending on pill or in solution form) before exercise would be necessary and if possible a smaller second dose (3-5 g) during (mid-point) the activity.*

Safety

There is no Upper Limit (UL) established for BCAAs. The estimated average requirement (EAR) is 31 mg/lb/day (leucine 15.5 mg, isoleucine 6.8 mg, valine 8.6 mg) for adults with many researchers believing it should be doubled since the EAR is only a starting point for health or survival.[101] Earlier reports have summarized studies of BCAA administration in athletes, normal adults, and patients with clinical disorders.[102] Daily intakes of 15–60 g total of BCAA supplementation (91-390 mg/lb/day for a 154 lb male) did not result in adverse event outcomes for the monitored variables.[103,104]

Leucine

Since the relatively recent discoveries of leucine's potent stimulation of MPS, it has become a popular supplement, giving rise to a need to discover a potential upper limit (UL) where chronic use may lead to adverse reactions. Hence, Elango et al.[105] proposed that a reasonable marker to define the upper limit of tolerance for an amino acid would be the intake where maximum oxidation level was exceeded.[106] The trial method was to increase leucine intake until the oxidation of leucine reached a maximum (i.e. plateau), thus surmising that greater intakes may result in increasing risk of adverse effects. They found when subjects reached intakes >230 mg/lb/day (~40 g for a 175 lb individual) there was an increase in blood ammonia concentrations above normal values (<35 µmol/L) with simultaneous increases in plasma leucine concentration and urinary leucine excretion suggesting higher intakes might be harmful.[105] Therefore, with proper dosing of BCAAs in combination with typical western diets, this proposed UL would be unattainable.

Data Summary

At the very minimum BCAA supplementation can timely increase the supply of the most important essential amino acids (including leucine) necessary for muscle protein synthesis (MPS) in an extremely low-calorie delivery system. Beyond that, BCAA's supplementation appears to be effective in suppressing exercise-induced muscle damage with the potential to concurrently improve recovery with the goal of delivering greater long-term training outcomes. Additionally, BCAA supplementation during strenuous endurance-type activities may help reduce fatigue and improve multiple choice reaction times (MCRT) through its ability to contribute as an energy source during prolonged training, potential to block serotonin production and reduce lactate levels. BCAA supplementation supplied at 45 mg/lb/day, with at least 50% being leucine (up to ~75% of total mg) and the remainder split between isoleucine and valine, probably offers the greatest potential to deliver the goal.

Authors note: *as mentioned in the goal section of this paper, the dotFIT essential amino acid formula, AminoBoostXXL, contains the BCAAs in appropriate doses and may be of greater overall value for MPS than BCAA alone.*[71] *Therefore any additional supplementation with BCAA is most likely not necessary unless there is a desire for continuous daily isolated BCAA dosing to maintain high plasma/muscle levels of BCAAs in support of the supplement's putative anti-fatigue benefits during strenuous endurance activities.*

Typical Use

- Athletes and exercisers of any fitness level, during intense or excessive training bouts to decrease muscle breakdown and enhance recovery, and not using AminoBoostXXL (AB)
- Anyone attempting body fat reduction while maintaining or increasing LBM not using AB
- Intermittent (most team sports >1.5 hours – i.e. combined intermittent aerobic and anaerobic activity such as football, soccer, basketball, baseball, rugby, hockey, etc.) and strenuous endurance athletes for reducing fatigue factors (rates of perceived exertion and mental fatigue)
- Minimum dose: take 8 tabs 20-30 minutes before workout
- If over 175 lbs, take 8 tabs 20 -30 minutes before workout and 2-4 tabs during activity (~midpoint)
    - Body weight increases the need or ability to utilize as shown above

Precautions

Presently, insufficient data exists to use the risk assessment model for determining an upper limit (UL) for any of the amino acids. Furthermore, chronic excessive use of individual amino acids is likely to be highly unusual in athletes (no perceived value at levels that may lead to danger) and potentially uncomfortable (e.g., stomach distress). Consequently, collecting data on amino acid toxicity is difficult and possibly unnecessary. Reported adverse events from acute and chronic high-level intake of amino acids are extremely rare.[107] Amino acid supplementation safety appears to have survived the "test of time" as it relates to use by athletes. Despite the lack of adverse events reported by athletes who use amino acid products and the lack of UL values for amino acids, the safety of chronic high intakes of amino acids is unknown. However, the risk/benefit ratio appears to be extremely low and the amounts present in the Recover&Build formula do not approach any level of amino acid intake that may lead to adverse events.

Contraindications

BCAA's are contraindicated for those with the hereditary disorder Maple Syrup Urine Disease.[108] This product, as with any protein or creatine-containing supplement, is contraindicated for users with kidney or liver disease.[104] Recover&Build is also contraindicated for pregnant or lactating females because it has not been tested in these groups and because protein can be adequately supplied by the diet for fetal growth or lactation needs.

Adverse Reactions

There is no Upper Limit (UL) established for BCAAs and no known adverse reactions in healthy users at the recommended doses. Daily intakes of 15–60 g total of BCAA supplementation (91-390 mg/lb/day for a 154 lb male) did not result in adverse-event outcomes for the monitored variables.[103,104,109]

Upper Limit/Toxicity

- There is no established UL for BCAAs[101,107]
- Amino acid blends and protein supplements have been studied for use in numerous disease states and to improve sports performance for decades with a large margin of safety between the typical doses and those needed for toxic effects in healthy users.[110,111,112]
- A proposed upper limit for leucine (only based on plasma and urinary variables, not an adverse reaction) is >230 mg/lb/day (~40 g for a 175 lb person).[105] We should be mindful that even at this proposed level there are no known side effects. It was proposed because at this intake maximum oxidation level was exceeded in the subjects under the conditions of the study.
- In addition, all BCAAs appear on the Generally Regarded As Safe (GRAS) list and are in forms which may be safely used when added to foods[113]

Summary

Purpose

Body stores of BCAAs are metabolized to become available for protein synthesis and energy production. Therefore, during exercise, appropriate timely supplementation may increase BCAAs availability (amino acid pools) to spare endogenous BCAA stores from catabolism (reduce muscle breakdown and subsequent soreness) and help supply additional substrate for muscle protein synthesis (speed and enhance recovery) and energy (improve specific markers of performance).

Potential Users

- Athletes and exercisers of any fitness level, during intense or excessive training bouts to decrease muscle breakdown and enhance recovery, and not using AminoBoostXXL (AB)
- Anyone attempting body fat reduction while maintaining or increasing LBM and not using AB

- Intermittent (most team sports >1.5 hours – i.e. combined intermittent aerobic and anaerobic activity such as football, soccer, basketball, baseball, rugby, hockey) and strenuous endurance athletes for reducing fatigue factors (rates of perceived exertion and mental fatigue)

Unique Features

- Contains leucine, isoleucine and valine in a ratio and potency supported by clinical evidence
- Manufactured in a regularly inspected NSF certified facility in compliance with Good Manufacturing Practices (GMPs) and 3rd party tested exclusively for dotFIT, LLC

Supplement Facts Panel

SUPPLEMENT FACTS

Serving Size: 8 Tablets
Servings Per Container: 20

Amount Per Serving	% Daily Value
L-Leucine	5600 mg **
L-Isoleucine	1920 mg **
L-Valine	1920 mg **

** % Daily Value not established.

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