

Anabolic Effects of Branched-Chain Amino Acids

Contributed by Robbie J. Durand, MA
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Supplement Edge

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There's little doubt that efficient recovery of protein metabolism is critical to the anabolic process and preservation of skeletal muscle hypertrophy. Amino acid supplementation has been demonstrated to heighten recovery during weight training by increasing protein synthesis, reducing muscle protein breakdown and reducing muscle damage.

Free amino acids in humans are classified as essential amino acids and non-essential. Essential amino acids need to be obtained from the diet, whereas non-essential amino acids are endogenous (produced by the body). In terms of muscle protein synthesis, only the essential amino acids are needed. For example, after an intense resistance exercise program,

where subjects are administered either a mixture of non-essential or essential amino acids alone, only essential amino acids increased protein synthesis rates; non-essential amino acids had no effect.²⁰ Amino acids are well known to stimulate insulin, growth hormone and IGF-1- and may even enhance testosterone production.

Amino Acids, Training & Testosterone

In the journal *Metabolism* the anabolic effects of essential amino acids were documented as they prevented strength loss during an intense overreaching program. Overreaching is an accumulation of training stress, resulting in a short-term decrement in performance capacity followed by a super-compensation effect. In that study, 17 resistance-trained men were randomly assigned to either an essential amino acid group or placebo group before embarking on a five-week overtraining program. Each participant ingested the amino acid supplement separate from meals (i.e., one hour before a meal and two hours after a meal).

In relation to the exercise bout, supplement doses were taken one to two hours pre- and post-exercise. Thus, the sequence was a morning dose, afternoon dose before workout, afternoon dose after workout and evening dose. After one week of overreaching, 1 RM on the bench press had decreased in the placebo group, but not the essential amino acid group. Both groups then showed similar increases in strength in weeks three to five, but total testosterone levels were higher in the amino acid group during most of the study.⁶

The study indicates that amino acid supplementation is effective in preventing the initial strength loss seen when first starting a high-volume program, probably by creating an anabolic environment and reducing muscle damage. It's also been demonstrated that ingestion or infusion of essential amino acids provides a potent anabolic stimulus in both healthy young subjects and elderly subjects.^{1,2,3,4} Two studies have reported that when whey protein or essential amino acids are matched for their effects on net muscle protein synthesis, both supplements stimulated protein synthesis rates, but the increase was greatest in the essential amino acid group.^{5,41} Other studies have shown that consuming essential amino acids (15 grams of essential amino acids and 30 grams of sucrose) between whole meals produces a greater anabolic effect than ingestion of a liquid meal replacement (23 grams protein, 126 grams carbohydrate and 30 grams fat).¹

Amino Acids, Resistance Exercise & Protein Synthesis

High-protein intakes increase the retention of nitrogen and place weight trainers in a more anabolic environment. For example, Tarnopolsky and colleagues found that when strength lifters were administered 0.8, 1.4 and 2.4 grams of protein per kilogram of bodyweight, nitrogen balance was negative in the low-protein condition and increased from moderate- to high-protein conditions.⁷

Protein is broken down into amino acids. Gym rats know that you need protein and sufficient calories to increase muscle mass, but new research suggests that the timing of amino acid intake is essential for this increase. For years, fitness enthusiasts were told that there was a heightened 45-minute "window of opportunity" after exercise in which anabolic reactions take place. So, why is it so important to get essential amino acids into your system quickly after exercise? One reason is that heavy, intense exercise stimulates cortisol production, which results in increases in muscle-protein breakdown. Researchers wanted to know what happened when you infused subjects with cortisol and the effects

essential amino acids have on cortisol. Administration of essential amino acids not only increased protein synthesis after cortisol infusions, but acutely reversed the effects of cortisol.⁴

After resistance exercise, increased protein synthesis has been documented for up to 48 hours following an intense resistance exercise program.¹⁹ However, there's some truth to the "window of opportunity" theory. Studies have reported that a delay in protein consumption after exercise may delay protein synthesis rates. For example, after intense leg exercise, subjects were fed an oral nutrient supplement (10 grams protein, 8 grams carbohydrate and 3 grams fat), which was administered either immediately after exercise or three hours after exercise.

Researchers found that the net uptake of amino acids and glucose immediately after exercise led to more substrate and energy availability within the leg for protein synthesis. Although leg protein breakdown wasn't significantly different between the two supplementations, leg protein synthesis increased more than threefold when a protein supplement was consumed immediately after exercise versus three hours later.¹³

For an even greater effect, researchers discovered that using an amino acid/carbohydrate beverage before exercise leads to greater protein synthesis than taking it immediately after exercise.¹⁴ It seems that in order to receive the optimal effects of protein supplementation, the "window of opportunity" theory should be changed to consuming protein supplements or amino acid supplements before and after exercise for optimal anabolic gains. The anabolic response of muscle protein synthesis to exercise is a result of the metabolic changes induced by the muscular concentration and the availability of amino acids. Although many Arnold wannabes are still using protein supplements, remember that only essential amino acids are needed for increasing protein synthesis rates. Of the eight essential amino acids, researchers have further narrowed the anabolic activity of essential amino acids down to the branched-chain amino acids (often found in whey protein supplements).

Anabolic Effects of Branched-chain Amino Acids

The branched-chain amino acids (BCAAs) are leucine, isoleucine and valine. In many gym circles, BCAAs seem to have been pushed aside in favor of creatine and other products for muscle growth. Creatine is a great product, but it has no effect on human protein synthesis rates after resistance exercise,⁴² whereas the anabolic effect of BCAAs on muscle growth, protein synthesis and recovery is undisputable. One study reported that when BCAAs were administered before a one-hour run, it resulted in post-recovery elevations in GH and testosterone. The T response wasn't modified during the running exercise, but increased during the recovery period- after BCAA administration.⁴³

BCAAs are needed for the maintenance of muscle tissue and appear to preserve muscle stores of glycogen (a storage form of carbohydrate that can be converted into energy). BCAAs also help prevent muscle protein breakdown during exercise. Protein synthesis in skeletal muscle is produced by intake of a mixed meal and is largely due to BCAAs. For example, infusions of a mixture of amino acids containing all the amino acids except BCAAs have no effect on protein synthesis.²⁹ BCAAs have an advantage for someone who wants to add muscle and who's dieting, as they have minimal calories, they're metabolized strictly in muscle and they're highly anabolic.

Of all three BCAAs, leucine appears to be the most important for stimulating protein. More recent studies have extended the earlier investigation to show that leucine is the most potent of the BCAAs in enhancing mRNA translation of protein synthesis. In contrast to administration of either isoleucine or valine alone, which have no effect on protein synthesis, leucine is unique as it's the most important regulator of protein synthesis in skeletal muscle.¹⁷ In fact, a recent study reported that administration of leucine alone to fasted rats invoked the same stimulation of protein synthesis in skeletal muscle as observed after consumption of a complete meal.¹⁶ Additionally, studies using isolated muscle preparations have reported that leucine alone is sufficient to enhance protein synthesis rates.²⁷

What's interesting about leucine is that it appears to be specific for muscle protein synthesis as opposed to other organs. For example, oral administration of leucine has no effect on global rates of protein synthesis in the liver, which many amino acids have. This means muscle seems to have first dibs on leucine absorption, in contrast to other amino acids that are metabolized in the gut. Thus, it seems that the regulatory role of leucine may be specific to muscle.¹⁸ Leucine has a much greater impact on being incorporated into muscle than any other amino acid. A Swedish research study reported that when patients had leucine infusions followed by muscle biopsies, increases in muscle protein synthesis rates were observed and the intracellular concentrations of leucine increased threefold in muscle, but the concentrations of most other intracellular amino acids had no change.⁴⁰ The research suggests that leucine is capable of stimulating muscle protein synthesis by itself.

BCAA/Leucine & Insulin: A Powerful Anabolic Combination

Leucine appears to regulate the energy status of the cell and intracellular concentrations of several growth factors.²¹ Dietary levels of BCAAs or leucine reach the blood virtually unaltered from the levels in the diet; thus, leucine reaches the peripheral muscle in direct proportion to the diet.²²

Supplemental leucine allows for a muscle to achieve maximum protein synthesis and anabolic recovery.^{23,24} Insulin and amino acids are needed for a synergistic effect to create an anabolic environment in muscle. Researchers tested how anabolic insulin was by itself and in conjunction with amino acids. They found that insulin by itself was anti-catabolic in muscle by inhibiting protein breakdown, whereas amino acids plus insulin largely increased protein anabolism by stimulating protein synthesis and reducing muscle tissue breakdown. Thus, there's a synergistic effect between insulin and amino acids. This is why it's so important to consume a combination carbohydrate/amino acid beverage after exercise.

Subsequent studies have reported that insulin infused in the brachial artery in a fasted state caused a 20-fold increase, but failed to stimulate muscle protein synthesis and inhibited muscle protein breakdown.³² The results support the concept that both insulin and amino acids are needed to increase muscle protein synthesis rates as insulin by itself does not increase muscle protein synthesis rates.

To further support this research, if rats are administered diazoxide, which prevents a rise in insulin, the stimulatory effects of protein synthesis by amino acid infusion are suppressed.¹⁵ An interesting property of leucine is that it can stimulate protein synthesis through an insulin-independent mechanism. For example, protein synthesis in diabetic rats is suppressed 35 percent, however, leucine administration to diabetic rats increases protein synthesis by approximately 50

percent, but the rate remains below that of non-diabetic rats.³⁸ Overall, the results demonstrate that leucine can cause increases in protein synthesis rates that are independent of insulin.¹⁸

One of the problems researchers discovered when trying to identify the mechanism whereby leucine increases protein synthesis is that leucine can stimulate insulin release. It was speculated that leucine administration might have caused a rise in insulin, which enhanced protein synthesis rates. Subsequent studies have shown that when arterial levels of leucine are measured after ingestion of BCAAs, no significant increase in arterial insulin was detected. This suggests that leucine has a direct effect on muscle protein synthesis rates without insulin.³¹ Overall, the research suggests that leucine can stimulate protein synthesis in skeletal muscle through both insulin-dependent and independent mechanisms.

Fasting and calorie restriction result in an increase in leucine appearance rate in the blood- an index of whole body protein breakdown. The increase in leucine appearance is consistent with a decline in insulin, because insulin normally suppresses protein breakdown. Additionally, fasting increases the hormone glucagons, which has a catabolic effect on leucine.⁸ In skeletal muscle, exposure to glucocorticoids such as cortisol is characterized by a reduction in protein synthetic rate coincident with hampered protein synthesis rates. However, oral administration of leucine reversed the catabolic effects of dexamethasone within one hour of administration.²⁸

Get Your Swell on for Increased Protein Synthesis Rates!!

So, what is it about exercise that increases protein synthesis rates? Blood flow to working muscles is greatly enhanced after exercise and blood is shunted away from other organs. This results in a greater delivery of amino acids to muscle tissue and a low percentage of amino acids being absorbed by the gut. Therefore pre-workout leucine or BCAA timing is essential for creating an anabolic response.

In animal studies, BCAAs, including leucine, were highly influenced by blood flow to muscles that occurs during exercise, suggesting that leucine or BCAAs taken before exercise will greatly enhance muscle protein synthesis rates due to enhanced blood flow to muscle. A recent study reported that when insulin was infused into subjects, the change in muscle protein synthesis was predicted by changes in muscle blood flow and amino acid availability, whereas insulin concentrations and delivery didn't significantly predict the response of protein synthesis.³³ Taken together, these studies suggest that leucine, along with enhanced blood flow, significantly increases protein synthesis rates.

Leucine Increases mTOR

Leucine plays multiple roles in metabolism beyond the minimum requirement as an essential substrate for synthesis of

new proteins. The potential for leucine to impact protein synthesis, insulin signaling and production of alanine and glutamine is dependent on dietary intake and increasing leucine concentration in skeletal muscle.^{35,36} In terms of anabolic activity, leucine could be called the "Highlander amino acid: There can be only one!"

Leucine stimulates protein synthesis rates greater than any other amino acid. Additionally, a recent study reported that the addition of leucine to a protein-based supplement led to a greater protein synthesis than intake of the protein supplement alone when it was taken after a resistance exercise program.³⁰

It has now been established that leucine stimulates protein synthesis through signaling pathways that involve mTOR.^{10,11} What the hell is mTOR? mTOR stands for the mammalian target of rapamycin. mTOR is a master regulator of muscle growth (cell size and division) by sensing amino acid availability and cellular energy level.²⁵ mTOR itself is thought to serve as an ATP sensor. mTOR appears to have important effects on stimulating a variety of growth signals, resulting in increased protein synthesis rates. Resistance exercise, amino acids or a combination of both, are all known regulators of mTOR. When BCAAs were administered to subjects during and after one session of leg extensions, an increase in mTOR was found during the recovery period.²⁹ The exact mechanism by which mTOR regulates muscle hypertrophy is unknown. Interestingly, IGF-1-dependent muscle hypertrophy is dependent on the mTOR pathway. Studies have reported that if mTOR is inhibited by drugs, neither insulin, amino acids or resistance exercise will cause increases in proteins synthesis rates.²⁶ Overall, the available evidence strongly suggests that mTOR plays a crucial role in controlling muscle cell growth.

Leucine for Reducing Appetite and Maintaining an Anabolic Environment

Another benefit of leucine has been found for weight training. mTOR is not only found in muscle, but also in brain areas that regulate food intake. The research is still premature, but rats administered leucine have a reduction in appetite. In several experiments, leucine decreases food intake.

Interestingly, another BCAA- valine- had no effect on food intake and didn't stimulate mTOR activity in the brain areas regulating food intake.³⁴ Leucine is now known to interact with the insulin-signaling pathway with apparent modulation of the downstream signal for control of protein synthesis, resulting in maintenance of muscle protein during periods of restricted energy intake.

Oral intake of 2.5 grams of leucine stimulates muscle protein synthesis after exercise or an overnight fast.^{23,37} These studies support the role of leucine as a key amino acid for reversing catabolic conditions. Two weight-loss trials using diets designed to provide 10 grams per day of leucine (125 grams per day of dietary protein) with a minimum of 2.5 grams of leucine at each of three meals. In comparisons with subjects following the USDA Food Guide Pyramid, subjects consuming the protein-rich diets lost more weight and were more effective in correcting body composition during weight loss.³⁹ Consumption of the protein-rich diet resulted in greater loss of body fat and attenuated loss of lean tissue consistent with a protein-sparing mechanism for leucine. It seems reasonable that if a strength competitor is getting ready for a competition, adding a few grams of leucine to his diet may reduce appetite, yet still maintain an anabolic environment.

Leucine & Aging

Aging is associated with a decrease in muscle mass along with concomitant decrease in anabolic hormones. In addition, there's also a decrease in protein synthesis, which has been termed "anabolic resistance." This is shown by a decreased sensitivity and responsiveness of protein synthesis in muscle both in rats and humans.

A recent study examined younger rats (8 months old) and older rats (22 months old) and found that protein breakdown rates were higher in older rats compared to younger rats. But when older rats are fed a diet supplemented with 5 percent leucine, there's a rejuvenation of muscle and an inhibition of protein breakdown similar to young rats.¹² Thus, aging seems to be associated with a decrease in leucine-induced stimulation of muscle protein synthesis. When older animals are fed a high-leucine supplemented meal, it will not only restore a significant stimulation of muscle protein synthesis, but also maintain the effect for 10 days.³⁰ The long-term utilization of leucine-rich diets may therefore limit muscle protein wasting during aging.

Before creatine, BCAA supplements were the most popular muscle-building supplement in the early '90s. The reported anabolic effects of BCAAs, particularly leucine, have caught the eye of many researchers in terms of increasing muscle mass and reducing muscle breakdown. It's been known for many years that muscle hypertrophy comes about via an increase in the rate of protein synthesis. Leucine and BCAA have potent anabolic effects by increasing mTOR activity, resulting in enhanced activation of muscle proteins. Carbohydrates, nonessential amino acids and other amino acids don't have the stimulatory effects on protein synthesis when compared with leucine. However, in most cases, the combination of BCAAs with carbohydrates produces an additive effect on the stimulation of the mTOR pathway, producing maximal rates of protein synthesis during recovery.