Amino Acids As Gluconeogenic Precursors During Prolonged Exercise and Catabolic States

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When liver glycogen levels fall, various structural and non-structural muscle (protein) amino acids are catabolized to form gluconeogenic agents such as alanine, and glutamine. Upon reaching the liver these gluconeogenic precursors are converted into glucose to satisfy the liver's need for carbohydrate energy as well as to serve as glucose for blood sugar, which in turn can be used by peripheral tissues, including exercising muscles. The amide groups (NH2) deaminated from these amino acids is hooked on to glutamate to form glutamine or hooked on to pyruvate to form alanine. Both glutamine and alanine can exit the muscle, travel through the blood stream to the liver, where they can both become deaminated and provide the carbon backbone for glucose synthesis (in the liver alanine forms pyruvate, which can be converted to oxaloacetate and then phosphoenolpyruvate, which is gluconeogenic). In this case, the discarded amide groups form urea, a waste product that is easily excreted from the body in the urine. Due to the catabolism of structural and non structural amino acids associated with exercise, the dietary protein requirement is increased in order to re-store catabolized proteins, and possibly serve as free amino acids for the synthesis of glucose, sparing the catabolism of structural amino acids, as is the case with glutamine.

Recent studies have shown that in a glycogen depleted or carbohydrate-deprived state that up to 10% of the calories burned to produce ATP energy during moderate to strenuous exercise are derived from the breakdown of muscle protein (actin and myosin). However, athletes should strive to prevent glycogen depletion and maintain more ideal intakes of carbohydrates on a daily basis. Thus, the contribution of protein as an energy source during endurance exercise can vary from 2 – 10%, depending upon the intensity of the event, the duration, and the carbohydrate status of the athlete. In addition, the secretion of the stress hormone cortisone, which accompanies intensive endurance training and heavy resistance weight training, further catabolizes muscle protein during the exercise, and continues to play a role in muscle catabolism long after the exercise has ended. Taken together, athletes are known to have a higher dietary protein requirement than sedentary individuals.

Aspartate and Glutamate – in the liver these amino acids serve as precursors to the formation of the keto acids, oxaloacetate and alpha-keto glutarate. When deaminated, glutamate becomes alpha-keto glutarate, which in turn can becomes oxaloacetate. Oxaloacetate is gluconeogenic in that it can be converted to phosphoenolpyruvate, a substance that can back peddle to form glucose. Aspartate can be directly converted to oxaloacetate, and note that asparagine can be converted to aspartate if more aspartate is required as a precursor for oxaloacetate synthesis. Oxaloacetate is the rate-limiting step for gluconeogenesis in that it provides an effective source of substrate in the formation of phosphoenolpyruvate. As such, the oxaloacetate concentration must exceed that required for the citric acid cycle. Thus, in a low energy state (increased ADP and/or GDP) aspartate and glutamate are catabolized to form gluconeogenic precursors.

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Branched-chain Amino Acids (leucine, isoleucine, valine) – within skeletal muscle the branched-chain amino acids are deaminated during exercise. Their amide group (NH2) is hooked on to pyruvate to form the amino acid alanine, which exits the muscle and travels to the liver through the blood stream to serve as a source of glucose. Their carbon backbone can also serve as an energy substrate for oxidation in the production of ATP. In the liver, alanine is first converted back to pyruvate (essentially, the amide group is remove from alanine and used to form urea). Pyruvate is then converted to oxaloacetate, and then to phosphoenolpyruvate, and then to glucose. The deamination of alanine increases the production of urea within the liver.

Glutamine – Glutamine can also serve as precursor to glucose synthesis in the liver, and if available in high concentrations, has been shown to reduce the reliance upon alanine formation. Hence, increased ingestion of glutamine or increased glutamine stores can reduce the catabolic effect on the structural amino acids in muscles (leucine, isoleucine and valine). These three amino acids comprise 30% of all the structural amino acids in skeletal muscle. For this reason, glutamine supplementation has been shown to be anti-catabolic in patients experiencing catabolic conditions (burn victims, post-surgery, possibly intensive exercise etc. – see glutamine). In the body, glutamine constitutes the largest single component of the free amino acid pool. Glutamine is the amino acid that is found in highest concentrations in the blood and it also serves as a free amino acid in peripheral tissues, including muscle. Although it contains two amide groups, it is very non-toxic. In fact, one of its roles is to shuttle amide groups to the liver from peripheral tissues, which are in turn converted to urea and discarded by the body. The deamination of amino acid releases ammonia (NH3, NH4), which is a highly toxic compound to the human body. To guard against ammonia toxicity the body attaches these amide (NH2 and NH3) groups to glutamate in peripheral tissues to form glutamine. In this form, these amide groups are non-toxic. Once glutamine travels to the liver from these peripheral tissues, including muscle tissue, the amide groups are extracted forming urea, and the carbon skeleton can be used to make glucose if the body is in a low energy state. Thus, one of endogenous sources of glutamine is the transfer of amide groups to glutamate (to form glutamine), which occurs in the deamination (catabolism) of various amino acids during catabolic states (including exercise)
In review, glutamine formed in peripheral tissues can travel to the liver. After discarding the amide groups to form urea, the carbon skeleton can be used to form glucose if the body is in a low energy state. This occurs as glutamine is first converted to alpha – ketoglutarate (deamination of NH2 and NH3 groups use to form urea). From there, alpha- ketoglutarate is converted to oxaloacetate, then to phosophoenolpyrvate, which can back peddle to glucose. Dietary and supplemental glutamine can also serve as source of glucose in the liver, sparing the catabolism of branched-chain amino acids in skeletal muscle, by reducing the demand for alanine as a glucose precursor. This is one way in which, glutamine supplementation has been shown to be anti-catabolic.

Glutamine supplementation has also been shown to stimulate the release of growth hormone from the pituitary gland, which in turn stimulates the release of insulin-like growth factor-I (IGF-I) from the liver. This hormone (IGF-I) is known to stimulate anabolic processes, including protein synthesis within skeletal muscle. Thus, in older patients, who exhibit lower circulating levels of growth hormone and IGF-I, glutamine

supplementation can act to preserve or increase lean mass, in conjunction with adequate protein intake and resisted exercise training, by raising serum levels of IGF-I as much as 30%. As such, 2,000 to 4,000 mg of glutamine supplementation (usually in conjunction with other amino acids that act as growth hormone releasing factors, or secretagagues), may spare the breakdown of branched-chain and other structural muscle amino acids, and stimulate the further synthesis of myofilaments (muscle protein contractile bands), within the muscle, helping to preserve and increase lean mass. Note that ornithine alpha-ketoglutarate, which the body can convert into glutamine, has been shown to be an even more potent stimulator of growth hormone and IGF- I release upon supplementation at a dose of 10 gm per day. This molecule consists of ornithine bound to two molecules of alpha-ketoglutarate (Grow Young With HGH. R. Klatz. 1997).

Other Considerations – The large free amino acid pool (blood and tissue) in the body ensures the continuous availability of individual amino acids to tissues for the synthesis of proteins, neurotransmitters, and other nitrogen-containing compounds. A well-nourished individual experiences a 300-600 gm protein degradation per day, and about a 100 gm ingestion of dietary protein. From this pool, tissues utilize amino acids for the continuous synthesis of new proteins (300-600 gm) to replace those degraded. The continuous turnover of proteins in the body makes the complete complement of amino acids available for the synthesis of new and different proteins, such as antibodies. It also provides a complete pool of specific amino acids which can be utilized as oxidizable substrates: precursors for gluconeogenesis and the formation of ketones, and for heme, creatine phosphate, purine, pyrimidine, neurotransmitter synthesis, for ammonia-genesis to maintain blood pH (if acidity should increase as in acidosis), and for numerous other functions.

The efflux of amino acids from skeletal muscle supports the essential amino acid pool in the blood. Skeletal muscle oxidizes the branched-chain amino acids to produce energy and the carbon skeleton from which muscles can make more glutamine. Alanine and glutamine account for about 50% of the total alpha-amino nitrogen released by skeletal muscle. The amino groups of branched-chain amino acids and of aspartate and glutamate are transferred out of skeletal muscle in alanine and glutamine. Hence, under hyper-catabolic conditions labile amino acids are degraded in this fashion to support blood sugar (alanine and glutamine converted to glucose in the liver). The formation of glutamine (also from the catabolism of branched-chain amino acids) is also required as a fuel by rapidly dividing immune cells (e.g., lymphocytes and macrophages), and for protein synthesis in cells involved in the immune response and wound healing, as is the case in burn victims and in other hyper-catabolic states.

The hormones primarily involved in the degradation of structural muscle proteins are glucagon and cortisol (cortisol is released under periods of stress). Thus, athletes need to pay attention to the testosterone to cortisone ratio, as over-training increases cortisone release, which encourages the breakdown of muscle protein.

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