Glutamine: The Nonessential Amino Acid for Performance Enhancement

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Glutamine is a popular dietary supplement consumed for purported ergogenic benefits of increased strength, quicker recovery, decreased frequency of respiratory infections, and prevention of overtraining. From a biochemical standpoint, glutamine does play a physiologic role in each of these areas, but it remains only one of a host of factors involved. This review examines the effects of glutamine on exercise and demonstrates a lack of evidence for definitive positive ergogenic benefits as a result of glutamine supplementation.

Introduction

Since the 1994 enactment of the Dietary Supplement Health and Education Act, the dietary supplement industry has become entrenched as a multibillion dollar business with lenient guidelines as to how the purported benefits of various products can be marketed [1]. Amino acids, including glutamine, are a popular product line in the industry, which capitalizes on the role of amino acids as a substrate for protein synthesis that in turn leads to increases in lean muscle mass. Glutamine has been reported to have beneficial health effects on a number of medical conditions, including wound healing after surgery or burns, gut healing in inflammatory bowel disease, and limitation of muscle loss in patients with AIDS [2,3]. Considering these potential benefits on muscle tissue and immune function, it is not surprising that glutamine has become a popular supplement among athletes, including elite college athletes [4]. The ergogenic benefits attributed to glutamine can be categorized as follows: 1) increasing strength and lean muscle mass; 2) prolonging exercise and fostering recovery by buffering acidosis and inhibiting proteolysis; 3) improving immune function and reducing upper respiratory tract infections; and 4) preventing the athlete from reaching an overtrained state. However, research into the athletic applications of glutamine appears to call into question the efficacy of supplementing this nonessential amino acid.

Biochemistry

Glutamine is a nonessential amino acid, meaning the human body is able to synthesize it. However, glutamine is found in many dietary sources, including meats, cheeses, yogurt, spinach, and cabbage. The recommended daily intake for glutamine is up to 1500 mg/d [3], or roughly 0.02 g/kg for the "average" adult. Glutamine is a precursor for glutamate, which has important roles in creating energy via the tricarboxylic acid and purine nucleotide cycles [5]. In the process of converting glutamine to glutamate, ammonium (NH_4^+) ions are released. Renal excretion of ammonium ions may help buffer metabolic acidosis, including lactic acidosis resulting from exercise [6,7]. Glutamine also provides necessary substrate for lymphocyte function, and there is a threshold level of glutamine necessary for appropriate in vitro function [8•].

General Exercise Effects

The relationship of glutamine to exercise is complex. Serum concentrations of glutamine generally fall after exercise, reflecting conversion of glutamine to glutamate. However, this expected decline is not absolute, as Lehmann et al. [9] demonstrated no decrease in glutamine in nine ultra-tri-athletes following a competition. Additionally, significant variance in resting glutamine levels can be seen between athletes of different sports. For example, Hiscock and Mackinnon [10] showed that power lifters had lower baseline glutamine levels than nonathletes, and cyclists had higher baseline glutamine levels than athletes in all other sports studied. These studies illustrate potential difficulties inherent in any study of the possible ergogenic effects of glutamine. Nonetheless, it is accepted that baseline levels of glutamine will increase over time as the result of a progressive training program [11,12]. This finding suggests that increases in glutamine reflect positive benefits of exercise. Researches have extended that relationship to hypothesize that glutamine supplementation would further augment performance gains achieved through training.

Strength Effects

One potential mechanism by which glutamine could exert an ergogenic effect would be a direct effect on muscle cells. Vierck et al. [13] demonstrated in vitro that a growth medium enriched with glutamine had no positive effects on either proliferation or differentiation of muscle satellite cells. This lack of positive effect extends to studies of actual athletes as well. Glutamine supplementation of 0.9 mg/kg lean muscle mass/d combined with 6 weeks of strength training demonstrated no changes in multiple strength measurements and no additional accumulation of lean muscle mass compared with strength training alone [14]. Even when combined with creatine and ribose, glutamine supplementation and 8 weeks of resistance training showed no additional increases in lean muscle mass, one-repetition maximum resistance, or the maximal number of endurance repetitions performed as compared with resistance training and placebo [15]. Other studies have focused on maximal endurance repetitions or time to fatigue. These studies will be considered later with other measures of recovery.

For direct measures of strength, it seems clear that glutamine does not have a direct ergogenic effect. Additionally, although glutamine has been demonstrated to have slightly positive effects on hemoglobin and hematocrit concentrations, it has also been shown to significantly increase total cholesterol and low-density lipoprotein levels with use for as little as 90 days [16]. Therefore, the argument to supplement glutamine in order to increase muscle strength appears to lack credence at this time.

Measures of Recovery

As mentioned earlier, glutamine normally provides substrate for energy production, with a buffering ability created as a byproduct. These physiologic effects could contribute to longer exercise sessions or faster recovery time, which could potentially account for a positive indirect ergogenic effect of glutamine. However, research has failed to consistently demonstrate such effects. In a study of eight male cyclists, Marwood and Bowtell [17] found decreased plasma lactate concentrations after exercise with glutamine supplementation when compared with control subjects; this buffering effect was not linked to positive changes in oxygen uptake or oxidative metabolism. By contrast, when 10 trained male athletes were asked to exercise at 100% VO_{2max} with a cycle ergometer, no changes in serum pH, bicarbonate concentration, or lactic acid concentrations were found with glutamine supplementation versus control [18]. Kargotich et al. [19] demonstrated that lactic acid can equilibrate in as little as 2 hours after high-intensity exercise, whereas glutamine levels may take 6 to 8 hours to recover. Therefore, although the conversion of glutamine to glutamate has the potential to buffer metabolic acidosis, overall acid–base balance remains a complex process that glutamine supplementation alone cannot reliably affect or control.

In the study by Haub et al. [18] of trained athletes maximally exercising with cycle ergometers, no change in time to fatigue was observed with glutamine supplementation. In another study, supplementation of 0.3 g/kg (~ 15 times normal daily intake) 1 hour after exercise was not shown to be effective in increasing the number of maximal repetitions of leg press or bench press performed by trained athletes [6]. At 0.9 mg/kg lean muscle mass/d, no increase in training volume was seen when compared with control subjects after 6 weeks of resistance training [14]. Ohtani et al. [20] investigated effects of a mixed amino acid supplement containing 14% glutamine on various measures of elbow flexor and extensor strength. An earlier recovery time was shown for isometric strength of elbow extensors only. No benefit for elbow extensor concentric or eccentric strength was demonstrated, and no measure of elbow flexor strength showed earlier recovery [20].

Even using protein breakdown as a measure of recovery, the effects of glutamine are mixed at best. Though one investigation demonstrated an inhibition of total body proteolysis as measured by improved leucine flux after glutamine supplementation [21], a separate study showed glutamine supplementation did not affect urinary levels of 3-methylhistidine, another marker of protein degradation [14]. Therefore, whether considering buffering capacity, time to fatigue, or protein balance, glutamine supplementation fails to consistently demonstrate any positive ergogenic benefit on measures of recovery from exercise.

Immune Function and Upper Respiratory Tract Infections

A relationship between highly strenuous exercise, such as a marathon, and increased incidence of upper respiratory tract infections (URTI) has been highlighted by multiple authors [2,8•,22–27]. This relationship is most commonly attributed to changes in circulating leukocytes after exercise: leukocytosis, neutrophilia, and lymphopenia. Because glutamine does serve as a substrate for lymphocytes, it is a reasonable hypothesis that glutamine supplementation would limit or counter the exercise-induced lymphopenia, resulting in fewer URTI after marathons or other high-demand activities. However, at least eight different studies have examined the potential effects of glutamine supplementation on altered immune function secondary to exercise; no consistent effect of glutamine supplementation on incidence of URTI after exercise has been demonstrated [27]. Castell and Newsholme [24] performed a survey of self-reported URTI among marathoners within 7 days of a race that suggested a decrease in URTI frequency among glutamine users, but blood samples demonstrated no significant differences in total leukocyte or lymphocyte counts between glutamine or placebo users.

There are certainly other mechanisms that may explain the increased risk of URTI after high-intensity

exercise. Exercise may lead to impairment of other host defense mechanisms, such as mucociliary clearance or mucosal phagocytic activity, which do not have clear associations with glutamine [22]. Secretory IgA plays a key role in respiratory tract defenses, and lymphocyte production of secretory IgA could be enhanced by glutamine. Using salivary IgA as a convenient measure, Krzywkowski et al. [23] showed that glutamine supplementation did not limit decreases in total salivary IgA output or salivary IgA concentration following exercise. In a study of eight triathletes, Rhode et al. [26] did show that serum glutamine concentrations directly correlated with the function of lymphokine-activated killer cells. However, the effect of endurance running on cytokines such as interleukin-6 is contradictory between studies [25,26]. Therefore, the positive correlation of glutamine with lymphokine-activated killer cell function may not be as promising as it appears for enhancing host defenses against URTI. The current body of evidence in the literature does not prove any significant benefit of glutamine supplementation on immune function.

The Overtrained Athlete

In fact, examining the relationship between URTI and high-intensity exercise may be slightly misguided, for many athletes train rigorously but do not experience greater numbers of URTI. As mentioned previously, in vitro studies suggest that intense exercise does not decrease glutamine concentrations to a level that impairs lymphocyte function [8•]. Perhaps then, frequent URTI reflect the overtrained athlete, along with other traits such as lack of performance improvement with training or delayed recovery from training or performance. Accordingly, one could hypothesize that glutamine may reflect the overtrained state; if so, perhaps glutamine supplementation could be used to prevent or treat this condition.

However, the evidence from several studies casts doubt on this relationship as well. In a study of 24 swimmers, Mackinnon and Hooper [28] demonstrated that not only was there no relationship between glutamine concentrations and URTI, but that more well-trained than overtrained athletes experienced URTI and glutamine concentrations did not predict whether an athlete would be well-trained or overtrained. Smith and Norris [7] studied 52 elite athletes from six different sports and found that although the average glutamine levels decreased after heavy training, this trend was not uniformly seen across all the sports involved. Additionally, the overtrained athletes in the study had resting glutamine concentrations comparable with their well-trained peers and post-training concentrations lower on average than the well-trained athletes in only two of the six sports studied [7]. Such contradictory evidence has led experts to conclude that glutamine alone cannot be used as a standard for determining if an athlete is in an overtrained state; it is likely that no one metabolic marker for the overtrained state exists [2].

However, Smith and Norris [7] did show that the ratio of glutamine to glutamate was a better predictor of the overtrained state or training tolerance. As you will recall, glutamine is converted to glutamate during exercise, which would lower the ratio; this decline mirrors the ratios found in the study by Smith and Norris [7]. In recovery, glutamate can be used to synthesize glutamine. Hence, the well-trained athlete should maintain a ratio below an at-rest or sedentary baseline, but above a ratio seen in overtrained athletes. It is hypothesized that because glutamine synthesis primarily takes place in skeletal muscle, muscle damage at the cellular level negatively impacts the glutamine-to-glutamate ratio and can result in overtraining [7]. This may be a promising area for future study, but at this time there has been no demonstrated evidence that glutamine supplementation prevents an athlete from becoming overtrained or helps one escape the overtrained state.

Conclusions

Based on its biochemical functions, glutamine has been marketed as a beneficial supplement with ergogenic properties of increasing strength, improving recovery, boosting immune function, and preventing overtraining. However, a review of the relevant literature fails to demonstrate consistent evidence for any ergogenic effects of glutamine. The ratio of glutamine to glutamate may become an effective marker of overtraining, but the ability to manipulate that ratio with glutamine supplementation has yet to be determined. Finally, although glutamine supplementation seems relatively well tolerated, its negative impact on lipid metabolism calls into serious question the appropriateness of glutamine as a dietary supplement. Unfortunately, this appears to be another example of commercial marketing trumping scientific evidence that in this case demonstrates how nonessential glutamine supplementation is to athletic performance.

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