

Glutamine—The Conditionally Essential Amino Acid



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Abstract

Oxidative stress, sickness, catabolism, and much more, is often the result of inadequate nutrition, compounded with a hardcore workout. There are many ergogenic aids which have been advertised to assist athletes in these times of distress. However, only few have survived the harsh scrutiny of the scientific community. Among these is the conditionally essential amino acid—glutamine. For decades, scientists have marveled at its ability to decrease proteolysis by actions such as minimizing ubiquitin mRNA, and enhancing protein syntheses and osmotic cellular swelling via an electrogenic and electro neutral sodium absorption pathway. Its involvement in leukocyte metabolism and intestinal structure has assisted a great many of ill patients and athletes suffering from OTS, among other scenarios. Indeed, glutamine is only beginning to be understood for its wide range of anabolic traits.

It is the goal of this journal to take the most comprehensive analysis ever on the benefits of GLN, and mechanisms by which these benefits occur.

Introduction

The athlete is a unique creature with unique requirements. To the normal population, phrases such as, "I realized that pain could become pleasure," by Arnold Schwarzenegger would be described in a word as—deranged. However, once the reader truly understand the benefits of pain, this quote indeed makes sense. This psychological analysis is known as ABC. Let's analyze this term:

- A=Antecedent: this is a preceding experience, condition, cause, feeling, or thought, which effects whether or not a behavior will occur. The antecedent can be changed, and will likewise effect your subsequent behavior.
- B= Behavior: an action, or response. The way in which one acts, or behaves themselves.
- C=Consequence: this is the result of the behavior. Consequences always follow a behavior, and change the probability of that behavior reoccurring. There are different forms of consequences. They can be immediate or long-term, positive or negative, certain or uncertain, and important or unimportant consequences. A positive consequence is more likely to cause a repeat in the antecedent, while a negative one will not.

Now, using the full quote from Arnold, let's apply the ABC principle:

That was when I realized that pain could become pleasure. We were benefiting from pain. We were breaking

Through the pain barrier and shocking the muscles. I looked at this pain as a positive thing, because I grew.

It was a fantastic feeling to gain size from pain. All of a sudden I was looking forward to it as something pleasurable. The whole idea of pain became a pleasure trip. I couldn't tell anybody about it then, because I knew they would say I was weird. Which wasn't true, I had just converted the pain into pleasure - not for its own sake but because it meant growing. We bragged to each other about how much our workouts hurt. --- Arnold Schwarzenegger

Since Arnold states that he came to the epiphany that pain was actually good, and considering the fact that most starting athletics translate it as bad, it is safe to assume that his original antecedent was that pain was dreadful. However, a change occurred in his thought process. Let's take a look at Arnold's ABC.

Antecedent: Pain is Pleasurable. This came about by his results in growth.

Behavior: Destroying himself in the gym.

Consequence: 7 time Mr. Olympia!

And this, friends, is one of the most logical and effective thought processes you can use. Almost every situation can be analyzed using ABC. Let's look at another example of ABC.

John 3:16-21

16 For God so loved the world, that he gave his only begotten Son, that whosoever believeth in him should not perish, but have everlasting life.

17 For God sent not his Son into the world to condemn the world; but that the world through him might be saved. 18 He that believeth on him is not condemned: but he that believeth not is condemned already, because he hath

not believed in the name of the only begotten Son of God. 19 And this is the condemnation, that light is come into the world, and men loved darkness rather than light, because their deeds were evil. 20 For every one that doeth evil hateth the light, neither cometh to the light, lest his deeds should be reproved. 21 But he that doeth truth cometh to the light, that his deeds may be made manifest, that they are wrought in God.

Now, let's analyze the heathens' thought processes according the Word of the Living God:

Antecedent: They hate God (or the light, refer to John 1:4-9) because of their sinful lifestyle.

Behavior: Fulfilling the lust of the flesh.

Consequence: Short-term positive: enjoying the pleasures of sin for a season (Hebrews 11:25). Short-term negative: without hope, empty soul, all labor is vanity (Ephesians 2:12, Psalms 127:1). Long-term positive: nothing. Long-term negative: eternal damnation and separation from God almighty (Revelation 20:14).

Why one would choose such a path is against all logic.

Finally, this mindset can be applied to nutrition. The athlete's antecedent needs to be, "nutrition is vital to my success." We'll propose that this realization came by reading JHR. The athlete's behavior will be in accordance with this frame of mind, and the results, in combination with the weight room, among other factors, will be insane growth!

Training is vital to our success, but without proper nutrition, it will accomplish absolutely nothing. As a matter of fact, it will hurt you, leading to an impaired immune system, over training, and such like side effects. This is why JHR stresses proper post-exercise nutrition. No other time in the day is more vital in your diet. As my fellow JHR writer Nick once said referring to a post-workout shake, "Not spiking is like letting an open wound bleed for a few hours before doing something about it." And with your newfound knowledge, I am sure you can analyze the ABC of this mindset.

Now, let's move on to one of the most vital components in proper nutrition—protein.

Amino Acids

The word "amino acid" is synonymous with anabolism. These compounds are composed of carbon, hydrogen, oxygen, and nitrogen atoms. The short term for this is CHON. They are literally the building blocks of proteins.



The sum of these is 20, eight of which are essential nutrients, which means they must be supplied through diet because the body cannot provide them. The remaining 12 are non-essential amino acids, termed so because the body can manufacture them from other compounds at hand [58].

However, at times, there is a ninth essential amino acid. You see, under severe stress (such as a vomiting-inducing session of squats), your ability to produce this amino acid falls well short of your bodily needs. Hence, it has been termed a “conditionally essential” amino acid. This anabolic amino is none other than our topic of discussion—glutamine [75].

Glutamine

The first significant find on glutamine metabolism was by Sir Hans Krebs in 1930. He displayed the hydrolysis and biosynthesis of glutamine in the kidney. Eight years later, Rose showed that glutamine is a non-essential amino acid [74]. Much more has been discovered since then. Glutamine (GLN) is by far the most abundant amino in our intracellular fluid (ICF), composing more than 60% of its kind within [11, 105]. It has two ammonia groups—one from its precursor, glutamate, and the other from free ammonia in the bloodstream. Throughout muscle cells, the body is able to form GLN with the enzyme glutamine synthetase via the amidation of another amino acid known as glutamate. GLN is also prevalent in the brain, liver, lungs, and stomach tissues. Along with the amino acid alanine, glutamine represents 50% of amino acids unleashed from muscles, while only accounting for 15% of total muscle protein. It is also highly utilized by the gut and kidneys [39, 31].

The metabolic properties of glutamine are mind-blowing. These benefits range from immune system regulation, nitrogen shuttling, oxidative stress, muscle preservation, intestinal health, injuries, and much more [45].

PH Regulation

Excess bodily ammonia (NH₃) is extremely dangerous; side-effects such as coma and brain damage are common. NH₃ is produced by the breakdown of amino acids. Glutamine acts as a nitrogen carrier in the body, transporting ammonia to the stomach in order to convert it to urea in the liver, or excreting it via the kidneys. Approximately 50% of the nitrogen excreted in the urine, as ammonium or urea, is a result of glutamine [115]. The breakdown of GLN in epithelial cells results in bicarbonate ions (a buffer) and NH₃. The bicarbonate is added to the blood, assisting regulation of pH, while the ammonia is released in the kidney by glutaminase. From here, NH₃ rapidly bonds with protons to form ammonium (NH₄⁺), which is then excreted with a co transport of sodium ions. As a result, a buffer is added to the blood stream, and acidic hydrogen ions are released via NH₄⁺, effectively regulating pH [32, 33].

This is very relevant to the athlete. During weight lifting, lactic acid is prevalent and severely inhibits athletic performance, for reasons such as an increased pH. Anything that raises your pH would enhance performance. I explained this in my article, [Active Recovery - A Threefold Breakdown](#). You will see I provide ample evidence to support this therein. Furthermore, the regulation of pH has been supported in several other scientific journals [21, 100]. Therefore, in theory, maintaining high concentrations of GLN would enhance athletic performance.

Lastly, Eiji Nakamura and Susan J. Hagen tested if glutamine could inhibit ammonia from killing epithelial cells. They placed rat epithelial cells with ammonia chloride at pH 7.4, with and without glutamine. The ammonia chloride group had a rapid increase in cell death and vacuolation (increase in cavities, or spaces in a given cell). Both of these results were fortunately inhibited in the glutamine group.

Gluconeogenesis

The production of glucose from non-carbohydrate nutrients is known as gluconeogenesis. Glutamine is one of the most efficient non-carbohydrate substances, which can be used for energy. In certain cells, approximately 30% of degraded GLN can be converted to lactate and carbon dioxide, and 20% of it can be used for macromolecules [106, 137]. Glutamine utilization increases when glucose is low [66, 137]. In fact, under certain conditions, cells may survive and grow in a low glucose environment with an adequate supply of glutamine [3, 13, 46]. Lastly, GLN can be metabolized in the urea cycle, protein synthetic pathways, and the Krebs cycle for energy and production of citrate, lactate, and glucose [42].

Oxidative Stress

Glutathione is a very potent antioxidant that helps protect tissues from free-radical injury [47, 138]. It is a tripeptide made of cysteine, glycine, and glutamate. Glutamine is often converted to the later amino—glutamate. Furthermore, the former amino acid, cysteine, is made from cystine taken in by the removing of glutamate. This twofold production makes GLN a valuable asset for the manufacturing of glutathione [29].



Bannani and Ishii T. tested the hypothesis that glutamine was critical in the utilization of cysteine [12]. They concluded that:

These results are consistent with the view that the intracellular glutamate, of which the source is glutamine in the medium, is released from the cells into the medium in order to take up cysteine and thereby to rotate the cystine-cysteine cycle. In the routine culture one-third to one-half of the total consumption of glutamine seems to be used for the uptake of cysteine.

Nissim I, et al. [90] showed that glutamate is in large part due to glutamine used by the kidney.

An excellent study was performed by Hong RW et al. to display the potency of glutamine in glutathione production, and diminished oxidize stress [47]. Here are the results:

Glutathione (GSH) is a major antioxidant that protects tissues from free radical injury. Glutamine augments host defenses and may be important in GSH synthesis. Acetaminophen toxicity causes hepatic GSH depletion and hepatic necrosis. The authors hypothesized that glutamine-supplemented nutrition would enhance liver GSH stores and diminish hepatic injury and death after acetaminophen overdose...Standard TPN solution animals had a rapid depletion of hepatic glutathione, whereas GLN animals were resistant to this drop and rapidly replenished hepatic GSH stores. Glutamine-supplemented animals maintained higher plasma glutamine concentrations, had lesser elevations in hepatic enzymes, and sustained significantly fewer complications compared with STD animals. The authors conclude that

glutamine-supplemented nutrition preserves hepatic glutathione, protects the liver, and improves survival during acetaminophen toxicity. Glutamine may augment host defenses by enhancing antioxidant protection.

Moreover, after physical exercise, levels of oxidized glutathione increases by 72% [127]. In a study on rats during intense exercise, liver glutathione was depleted by 20% compared to inactive rats [104].

Adam showed last month that anti-oxidants such as vitamin C are valuable for reducing oxidative stress, and maintaining glutathione. As displayed previously, glutamine also plays a vital role in the preservation of this powerful antioxidant tripeptide. For more on the importance of glutathione and the benefits of minimizing oxidative stress, refer to, [Role of Anaerobic Post-Workout Antioxidant Supplementation in Correspondence to Exercise Induced Oxidative Stress.](#)

Intestinal function

70-80% of immune tissues in the body are located in the gastrointestinal tract. Therefore, it is imperative that you maintain health in this area. Consequently, GLN is vital for gut structure and productivity by strengthening the immune system, mucosal growth, and lubrication [30]. For example, Gianotti L tested glutamine supplementation on stomachs infected by bacteria [44]. Here are the results:

BACKGROUND: Glutamine has been shown to be an important dietary component for the maintenance of gut metabolism. The purpose of this study was to assess the potential benefit of glutamine-enriched diets on experimental gut-derived sepsis... **RESULTS:** Mice fed glutamine-enriched diets had a lower degree of translocation (as measured by both radionuclide and bacterial counts) to the tissues than did the other groups and had an improvement in the ability to kill translocated E coli (as measured by the percentage of viable bacteria). Survival was significantly higher in the group fed 2% glutamine (81%) compared with the groups fed 1% glycine (36%), AIN-76A (35%), and Purina Rodent Laboratory Mouse Chow 5001 (36%) diets (p < .004). **CONCLUSIONS:** Glutamine-supplemented enteral diets may exert important benefits in preventing gut-origin sepsis after trauma.

Another study was performed by Burke DJ et al. on glutamine's effect on gut immune functions [14]. They separated 36 rats into three groups: group 1 ate rat chow and water ad libitum, group 2 ingested a hyperalimentation solution, and group 3 consumed a hyperalimentation solution that contained 2% glutamine. They maintained this diet for approximately three weeks. The glutamine-supplemented group was effectively protected against bacterial translocation from the gut. They attributed this effect to secretory IgA immune system. GLN has also been shown to increase intestinal cell reproduction [109]. The benefits on gut mucosa may be partially attributed to enhanced protein synthesis [50]. Additionally, glutamine is used for energy by growing cells such as fibroblasts, reticuloendothelial cells,

malignant cells, and gut epithelial cells [42].

In another experiment, Houdijk et al. fed male Fischer rats with a glutamine-rich diet for two weeks [4]. The results showed an increased blood flow in the small intestine, pancreas, colon, and stomach. It is also important to note that the primary fuel of the small intestine is L-glutamine [42].

Many more studies attest to these results [15, 16, 30 68, 132].

Muscle Sparing

Glutamine has displayed its muscle-sparing effects by protein synthesis and decreased protein degradation, time and time again [52, 71, 140]. Post-operation glutamine supplementation, for example, has been shown to spare glutamine and enhance protein synthesis [48, 88, 123]. Additionally, GLN acts as a nitrogen donor for the synthesis of amino sugars, urea, nucleotides for DNA and RNA, purines, pyrimidines, and other amino acids necessary for cell reproduction [116, 128, 129]. Furthermore, during catabolic states, glutamine release increases rapidly. Skeletal muscle has a glutamine concentration of about 7 mmol/L of ICF water [87]. Your body compensates for decreased concentrations by proteolysis (breaking down protein), and decreasing protein synthesis. This allows other amino acids to be used and converted to glutamine [3, 10, 103, 107]. Additionally, there is evidence that glutamine acts as a substrate for transamination (the reaction between an amino acid and an alpha-keto acid through which the amino group is transferred from the former to the latter) reactions in the liver [114].

Hankard et al. investigated glutamine's benefits in comparison to glycine (an amino acid) [49]. It was concluded that, "glutamine enteral infusion may exert its protein anabolic effect by increasing protein synthesis, whereas an isonitrogenous amount of glycine merely decreases protein turnover with only a small anabolic effect resulting from a greater decrease in proteolysis than protein synthesis." To test glutamine's attenuation of cell apoptosis (programmed cell termination), rat neutrophils were observed for 3, 24, and 48 hours in the absence or presence of glutamine (0.5, 1.0, and 2.0 mM respectively) [131]. The results showed that escherichia coli phagocytosis was much higher, and the maintenances of mitochondrial transmembrane potential was 20-38% higher in the presence of glutamine. Similar results have been shown in humans as well. These effects were additive and helped slow apoptosis. In conclusion, glutamine guards against reactions associated with apoptosis in both rat and human neutrophils.

Alain Lavoinne et al. further investigated glutamine and intestinal protein synthesis/degradation [86]. Two groups of healthy humans were given either glutamine (group 1) or saline (salt containing) or isonitrogenous aminos (group 2). The glutamine group had a significantly greater increase in the rate of mucosal protein synthesis compared to saline. Furthermore, ubiquitin (a protein which promotes proteolysis) mRNA was greatly decreased after taking glutamine in relation to group two. This would effectively limit mucosal (mucous membrane) protein degradation, and may be imperative in prohibiting intestinal inflammation and mucosal damage, which supports the previous topic on gut protection. Furthermore, in an experiment on rats, it was displayed that glutamine significantly inhibited net protein loss and protein breakdown [73]. Thus, glutamine has once again shown to not only have anabolic effects, but anti-catabolic ones as well. Does it get any better than that?

One hypothesis for these benefits was that glutamine enhanced insulin secretion, which has been shown to increase intestinal protein synthesis and reduce the ATP-ubiquitin-dependent proteolytic pathway, as glutamine did [27, 28]. However, this is not likely since both groups displayed an increase in insulin, and glutamine's results were still far superior. It has been suggested that glutamine's ability to increase cell volume is a major element of its anti-catabolic/anabolic traits [136, 54, 55, 56].

Lastly, another study displayed a fascinating aspect of glutamine. MacLennan PA et al. [36] increased glutamine concentrations from 0.67 to 5.0 Mm [84]. This resulted in a 200% increase in ICF glutamine concentrations, and a 66% increase in protein synthesis! However, the addition of insulin led to a 30% higher GLN concentration and an 80% increase in protein synthesis, displaying that they may have synergistic effects, and definitely showing that a combination of both, post-exercise for example, will sky rocket protein synthesis.

Glycogen Storage

Several studies have been composed to test the effect of glutamine on post-exercise glycogen re-synthesis [70]. For example, Varnier M et al. sampled six subjects who cycled for 90 min at a high intensity to deplete glycogen stores [124]. They then fed them either alanine+glycine, NaCl, or glutamine. The glutamine group showed a much greater increase in muscle glycogen storage. Glutamine with carbohydrates has additionally been shown to enhance total body carbohydrate storage [59]. Furthermore, glutamine increases the insulinogenic effect of a post-workout shake [125, 126].

These results have been contributed to several aspects of glutamine. Possibly by a cell volumizing action, glutamine stimulates hepatic glycogen synthase (the key enzyme in the synthesis of glycogen) [7, 85]. Glutamine is rapidly absorbed by skeletal muscle via a sodium dependent transport [8]. This augments glutamine ICF concentrations, promoting cell swelling [69]. Meijer et al. showed that cell volume and increased GLN concentrations activates glycogen synthase phosphatase, increasing an action in glycogen synthase via dephosphorylation (removal of a phosphate group) [85]. It also has been proposed that glutamine increases glycogen storage by gluconeogenesis [124].

Immune System

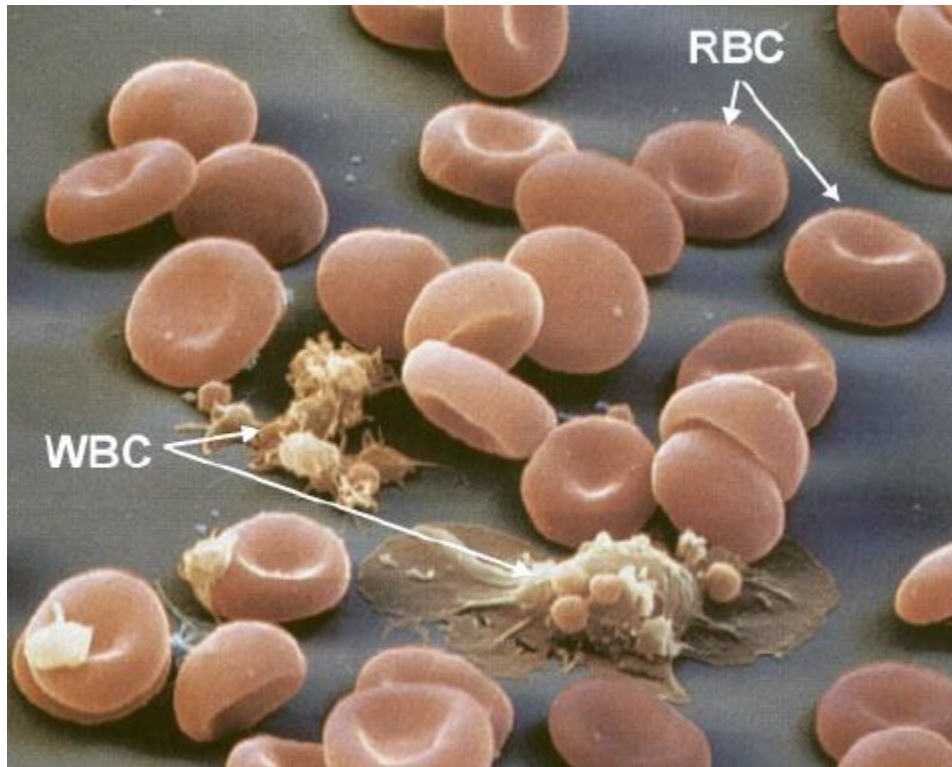
The immune system is a magnificent structure of irreducible complexity, which requires several articles in itself to do it justice. However, for this journal entry, I will analyze three aspects of the immune system, as they are directly affected by glutamine. These are:

- Lymphocytes
- Neutrophils
- Monocytes (which develop into Macrophages)

Leukocytes

Our immune system is composed of two main features known as leukocytes and lymphoid tissues. The former group are commonly known as white blood cells

(WBC'S). As I am sure you are aware, white blood cells perform a wide range of tasks in the immune system. Five general categories of WBC'S exist. These are: basophils, eosinophils, neutrophils, lymphocytes, and monocytes. The first three are known as granulocytes because they have protein vesicles in their cytoplasm, which is called the cytoplasmic granules. The later two lack these granules and are thus called agranulocytes. Our focus will be on agranulocytes and neutrophils. There will also be some discussion on lymphoid tissues.



Lymphocytes

These cells make up 30% of all leukocytes in the blood, and 99% of all cells found in interstitial fluid (fluid spaces between cell tissues, also called tissue fluid). In addition to their T-Cells, two other cells, which make up lymphocytes are B lymphocytes (B-Cells) and null cells (they are called this because they do not have cell membranes characteristic of the former two cells).

B-cells play a vital role in the immune system. When encountered with antigens (foreign bodies) they turn into plasma cells and release anti-bodies. Anti-bodies help destroy antigens such as bacteria.

Null cells compose a small portion of lymphocytes, but are extremely potent in waging war against virus infection. Another name for these cells is "natural killer cells (NK)." In order to repopulate, viruses must infiltrate cells. To stop this, NK cells kill viruses. They are the extremely nimble in response (much faster than the former two cells), making them a vital part of the body's first line of immune defense. They also help eliminate mutant cells, which may later develop into diseases such as cancer [101, 102].

Neutrophils

These white blood cells make up 60-80% of its kind, and act as one of the most effective weapons for the immune system—phagocytosis. A phagocyte refers to an eating cell. As a phagocyte, neutrophils literally inhale microorganisms, along with foreign cells and particles present in the blood stream. During sickness, neutrophils rapidly increase, providing great assistance for the immune system. A high neutrophil count is an easy way of telling there is infection in the body [101, 102].

Monocytes and Macrophages

Monocytes compose 5% of total leukocyte cells. They act as phagocytes. When born, they circulate in the blood for a couple of hours, then travel into tissues, which transform them into monster cells up to ten times in size. These cells are extremely powerful phagocytes. They are named macrophages. Some macrophages wander through the body, while others stay in certain spots. They are potent in the gastrointestinal tract, lungs, lymph nodes, liver, spleen, and connective tissue [101, 102].

With this newfound knowledge, you will be able to more efficiently comprehend the benefits glutamine has on the immune system, which is our next topic.

Leukocyte Fuel

Maintaining a healthy immune system is imperative for the athlete. Not doing so will promote overtraining (discussed further on), sickness, disease, slow recovery from illness, and such like inflictions [101].

In order to perform their many anabolic tasks, however, immune cells require a source of energy. The metabolism of leukocytes is a relatively new study. It was first discovered by Eric Newsholme et al. in the mid 80's that glutamine played an intricate role as a fuel source for white blood cells [91, 92, 6, 26, 93]. Going back even further to 1949, Ehrensvarid et al. discovered that glutamine promotes cell survival and reproduction [37]. Eight years later, Eagle et al. gave even stronger support for this [38].

It has now been confirmed that glutamine is used tremendously by immune cells [94, 25, 139]. Mechanisms, by which this occurs, along with a great deal of empirical support, will be displayed in the following paragraphs.

Macrophages

To test glutamine's effect on macrophages, Spittler et al. composed an experiment in vivo on healthy macrophages [120]. They decreased glutamine concentration from 2 to .2 mmol and reported that HLA-DR expression decreased by 40%, and phagocytosis was greatly diminished. One thing they attributed this to was a severe decrease in ATP. Consequently, macrophages have a high oxidative capacity and hunger, if you will. As such, they require large amounts of fuel to function [95]. To test this, in vitro, glutamine and glucose were given to these cells [95]. Glucose contributed 62% and glutamine 38% of the cell's energy, which supports the idea that these cells are dependent on glutamine for fuel. Another proposed mechanism

for increased GLN needs in activated macrophages is that glutamine's conversion rate to arginine increases in response to arginine's heightened utilization by macrophages in action [95].

Neutrophils

Neutrophils, as with macrophages, heavily depend on glucose and glutamine for energy sources [40, 128]. To further investigate glutamine's function in neutrophils (as well as monocytes), Furukawa teamed up with eight other scientists [40]. Eleven patients who had gastrointestinal surgery were used. He administered glutamine over seven days and found that phagocytosis was increased, as well as super oxide, which is a powerful free radical needed for bacterial termination. Saito et al. displayed similar results in his experiment [121]. The neutrophils of post-operative patients were placed in either a .5 or 1mmol glutamine environment. Bacteria decreased an amazing 26% as the ECF of glutamine increased. Garcia et al. elaborated on glutamine mechanisms when he showed that a 2 mmol concentration of extra cellular glutamine helped slow the adrenaline-inflicted decrease in super oxide [43]. Additionally, it was displayed that adrenaline reduces the glucose 6-phosphate dehydrogenase utilization of macrophages, and glutamine also increases NADPH [22]. This is a vital process. Results show glutamine can produce a large amount of NADPH for cells. NADPH is required for super oxide production (which accounts for another mechanism of its assembly), as well as making proteins, RNA, or DNA. Glutamine can also be catalyzed with the help of NADP+ and result in NADPH production for the cell, and lactate or acetyl-CoA, which is utilized in the Krebs cycle for energy [101]. Philip Newsholme believes this is a huge part of glutamine's immune benefits stating [101],

More recently, glutamine utilization has been linked to functional activities of cells of the immune system such as proliferation, antigen presentation, cytokine production, nitric oxide production, superoxide production and phagocytosis. Many of these functional parameters appear to be directly or indirectly dependent upon the intracellular supply of NADPH. The initial pathway of glutamine metabolism, which is common to all cells of the immune system, can generate NADPH from NADP+, thus providing a possible link between high rates of glutamine utilization and the beneficial effect on the many diverse functions of immune cells.

T Lymphocytes

Results show glutamine plays a major role in T-cell proliferation and function. Yaqoob P and Calder PC tested this [144]. Using rat spleen, they surrounded them in several extra cellular concentrations of glutamine, and T-Cells. As the glutamine concentration rose, there was a 39 fold increase in interleukin-2 production (IL-2). There was a 15% increase in the amount of IL-2 receptors, and a 20% increase in transferring receptors, and the IL-2 use was also dependent on glutamine. Thus IL-2 production, use, receptor expression, and transferring receptor expressions were reliant on glutamine concentrations. To clarify on IL-2, it is a hormone-like substance produced by T-Cells, and promotes the action of other t-cells. It also promotes the

proliferation of certain disease-fighting red blood cells.

B lymphocytes

Crawford J and Cohen HJ performed an excellent experiment on the effect glutamine and other proteins had on the immune system [24]. ³H-thymidine was maximally used at .08 mmL of glutamine. When at a 2mmL GLN concentration, plasma cell differentiation occurred. Additionally, immunoglobulin (a protein made by plasma cells which fights infection) synthesis and secretion increased 2-5 and 3-10 fold, respectively, in cells with a 2mmL GLN conc. Rough endoplasmic reticulum (a result of increased immunoglobulin) was increased only with glutamine. The other proteins displayed few beneficial results. Furthermore, in 1995 these two scientists teamed up again, showing that glutamine is absolutely essential for b-cell antibody synthesis and cell secretion, and again a multitude of amino acids were tested and could not duplicate the benefits of glutamine [23].

Activated killer cells

Juretic et al. displayed that glutamine assists killer cells to eliminate their viral targets. Moreover, deficiency in GLN diminished the amount of these cells used in response to infection [61].

Results

There are a multitude of results that display glutamine's effectiveness in enhancing the immune system. Studies on abdominal surgeries, bowel diseases, and such like, have all displayed that supplementing with GLN enhances nitrogen balance, muscle mass, and gut integrity [62, 122]. Several other cases of sicknesses have also been treated effectively by glutamine [131, 119, 34, 51, 96, 145].

Most importantly, glutamine has been shown to assist athletes in immune regulation. This is vital because plasma glutamine decreases after strenuous work. Keast et al. performed a great experiment to test this [64]. He utilized two exercising groups. Group 1 consisted of seven randomly selected male athletes who utilized a treadmill at 0, 30%, 60%, 90% and 120% of their VO₂ max. The latter group was composed of five advanced male athletes. They performed two gut-wrenching interval training sessions per day for ten days, followed by a six-day recovery period. Glutamine concentrations dropped rapidly from 1244 +/- 121 mumol/L on average to 702 +/- 101 mumol/L after exercise at 90% VO₂max (P < 0.05) and to 560 +/- 79 mumol/L at 120% VO₂max (P < 0.001). They concluded that, "Reduced plasma glutamine concentrations may provide a good indication of severe exercise stress."

Castell et al. performed an experiment on several athletes (200 runners) to test the infection rate of each [20]. The runners received either a placebo drink or glutamine immediately after and 2 hours after exercise. The results were staggering! 81% of the athletes who supplemented with glutamine reported no infections, while only 49% of the athletes who did not have glutamine reported no infections. This tremendously supports glutamine's involvement in the immune system.

Moreover, a 2003 study by Hiscock et al. tested how glutamine effected the release of interleukin-6 (IL-6) from skeletal muscles [97]. To elaborate the importance of this, IL-6 is a cytokine that stimulates the growth and differentiation of human B-

cells (discussed earlier). Eight healthy men participated in a randomized, double-blind, crossover study in which they performed 2 hours of cycling at 75% of their VO₂ max. They received glutamine, glutamine-rich protein, or placebo supplementation at intervals during and 2 hours after exercise. The doses were given in order to help maintain plasma glutamine concentration. The results showed glutamine was superior to the placebo, enhancing IL6 at a sevenfold higher rate; the glutamine rich protein did so at a threefold higher rate.

Overtraining

Several scientific authorities have postulated and demonstrated that diminished glutamine concentrations are an effective indicator of being overtrained. Oftentimes during and after intense exercise, these concentrations are greatly reduced, and the immune system, among other functions, are hindered [64, 110, 111, 141, 53]. Before we get into these studies, it's important that you understand what exactly overtraining is. Two general forms of overtraining are sympathetic and parasympathetic. The former displays signs of edginess, insomnia, and lack of hunger, while the latter gives polar opposite afflictions: being tired, weak, etc. These two share a common ground, however, as they are accompanied with a hindered immune system. An impaired immune system promotes overtraining, and is further hurt when in such stressful states. For much more on overtraining, you will want to read OldSchool's article, [Muscle Mind Doctrine - Theoretical Concepts of Strategization](#) [5].



Intense training sessions can result in a weak immune system. This includes decreased lymphocytes, immunoglobulins, phagocyte cells, leukocytes and cytokines, IL-1, IL-2, IL-6 and TNF cells. Now to the studies.

Sharp and Koutedakis showed that overtrained muscles in many cases may not be supplying enough glutamine for immune cells [118]. Antonio and Street also came to this conclusion in their study of glutamine [2]. Additionally, heavy training may have a cumulative effect on glutamine depletion, as results have shown such activities to reduce GLN concentrations to 500 $\mu\text{mol/L}$, and take long periods for ample recovery [141].

Rowbottom DG et al. composed an excellent experiment with ten athletes who were suffering from the overtraining syndrome (OTS) [113]. Blood samples taken demonstrated that the only measurement which was impaired in comparison to non overtrained individuals was plasma glutamine levels, further demonstrating the effect GLN has on OTS.

As I am sure you are aware, athletes often wake up in the morning and perform a cardio session while their glycogen stores are depleted. To test the effect this had on glutamine stores, eight well-trained males woke up after a night of sleeping (fasting for several hours), and hopped on the bike for one hour. The session consisted of 20 1-min periods at 100% VO₂max, each separated by 2 min of recovery at 30% VO₂max. Several hours after the session, GLN fell extremely low—572 microM. Since glutamine is essential in immune function, this would certainly inhibit your body's defense against disease, promoting sickness and overtraining, as displayed in the previous study on infection rates. To conclude this, here is a great quote from Rowbottom et al. in the Journal Sports Medicine [111]:

If recovery between exercise bouts is inadequate, the acute effects of exercise on plasma glutamine level may be cumulative, since overload training has been shown to result in low plasma glutamine levels requiring prolonged recovery. Athletes suffering from the overtraining syndrome (OTS) appear to maintain low plasma glutamine levels for months or years. All these observations have important implications for organ functions in these athletes, particularly with regard to the gut and the cells of the immune system, which may be adversely affected. In conclusion, if methodological issues are carefully considered, plasma glutamine level may be useful as an indicator of an over trained state.

Glucocorticoids

Glucocorticoids are a group of hormones secreted by cells of the middle zone, zona fasciculata. They are used in response to stress. The most abundant glucocorticoid is cortisol [63]. Consequently, cortisol plays a major factor in glutamine degradation. For example, Nick et al. tested on weaning pigs (in whom cortisol is prevalent) whether cortisol promoted glutamine catabolism. In several groups he administered a glucocorticoid receptor antagonist; in others, he let the pigs alone. As expected, adding the antagonist receptor effectively inhibited glutamine degradation. In another experiment by Tamarappoo et al. [130], he injected cortisol into rats and observed that glutamine was extracted from the liver and utilized for energy.

This fact further explains how exercise decreases glutamine levels, and why it is vital to replenish afterward. Decreased plasma glutamine levels will promote protein degradation and decrease cell volume [98], which is our next discussion.

Myofibril Hydration

Glutamine has been shown to enhance cellular hydration, which is absolutely vital to athletic performance [134]. SY Low et al. tested the connection between glutamine

transport, and cellular hydration [117]. He induced glutamine uptake into rat myotubes at osmolalities of 170, 320 or 430 mosmol. Glutamine at 320 mosmol increased cell volume by 36%. When insulin was administered, it additionally enhanced cell volume by 22%, and glutamine transport by 40%. They noted that the effects of both glutamine and insulin were additive to cell volume. At 170 mosmol there was also a huge increase in cell volume and glutamine transport. At 430 mosmol, however, cell volume and glutamine transport was diminished. These benefits were attributed to an increase in the Na(+)-dependent glutamine transport system.

To elaborate on this, glutamine uses a sodium transport system, which results in osmotic cellular swelling. This is vital for post-workout oral rehydration! To test this hypothesis, Rhoads et al. gave 30 mmol/L of glutamine to his participants [112]. It was shown that glutamine stimulated large amounts of electrogenic and electro neutral NaCl absorption rates. This would likewise result in a major increase in cellular water absorption. They concluded that glutamine is an effective method of oral re-hydration. Such knowledge can be applied to several scenarios, most importantly, post-workout nutrition. Moreover, using patients with diarrhea, Van Loon et al. tested several oral rehydration solutions [135]. He utilized 3 groups: glucose, sodium (group 1), sodium, glucose, and glutamine (group 2), or alanine, glucose, and salt (group 3). The glutamine, sodium, glucose group was the most proficient one, showing a significant reduction in water and sodium secretion, while increasing fluid absorption.

Another experiment by Islam S et al. showed glutamine, in his words, is "superior to glucose in stimulating water and electrolyte absorption [57]." Bold talk for a one-eyed fat man! Oops; excuse me, been watching too many John Wayne movies, but I digress. Islam did, however, back his words up with results. He applied 50 mM of L-glutamine (group 1) and 50 mM D-glucose (group 2) to electrolyte water solutions. He found that the absorption of water ($P = 0.000$), sodium ($P = 0.002$), potassium ($P = 0.001$), and chloride ($P = 0.003$) from the glutamine electrolyte solution was much greater than from the glucose electrolyte solution in the ileum. He concluded that, "L-glutamine may be a useful component to be tested in oral re-hydration solutions." Now, considering that glucose greatly benefits oral re-hydration, especially when accompanied with sodium, due to the Glucose/Sodium co transport system [134, 80, 81, 82, 83], this gives immense support to glutamine supplementation post-exercise. And when you take into account Van Loon's findings, you see that taking both glucose and glutamine will give you the best of both worlds.

These findings are of the utmost importance to post-workout nutrition. For more on the anabolism of cellular swelling, refer to, [Effect of Plasma Volume on Myofibril Hydration, Nutrient Delivery, and Athletic Performance](#). Lastly, to understand the sodium transport systems mentioned above, you will want to read, [Sodium - A comprehensive Analysis](#).

Creatine and Glutamine

Creatine and Glutamine are two of the few supplements which actually contribute significant ergogenic benefits without adverse side-effects. To test these two powerhouses in combination with each other; an eight-week experiment was performed on 29 athletes by Mark Lehmkuhl et al. [73]. They utilized three groups: a placebo (P) group (.03 g of placebo per kg of body mass, and 4 more grams of placebo per day) a creatine monohydrate (CM) group (.03 g of CM per kg of body

mass, and 4 more grams of placebo per day) and a creatine/glutamine (CG) group (.03 g of CM per kg of body mass, and 4 more grams of glutamine per day). Furthermore, they used a double blind test, which means that the subjects and scientists performing the experiment did not know which group they were in; only those overseeing the tests did. Additionally, the diet and training programs were identical for each group. The results showed that the CM and CG group displayed the highest level of performance, and further that the CG group achieved better results than the CM group. The CG and CM groups displayed a significant increase in body mass, LBM, and initial rate of power production during multiple cycle ergometer bouts. The results of the CG group were better than the CM and P groups. However, the authors suggested the results may have been much better with a higher dosage, as only 4 grams is rather small.

Toxicity

Glutamine has proven to be a perfectly safe and effective supplement [17, 42, 79, 142]. To further solidify this, Lowe et al. performed an experiment using seven normal people over three five-day trials [72]. They were given 0.285, and 0.570 g per kg of body weight. 2.2 kilograms= 1 pound. So if a 200 pound man were in the experiment, that would mean they would give him approximately 50 grams of glutamine. Mental status and other performance tests were standard and consistent throughout the three periods. There were no signs of toxicity whatsoever—all doses were well-tolerated by the subjects. In another test, E Ward et al. gave 13 patients 0.35, 0.5 and 0.65 g per kg of body weight [35]. Again, no side effects were reported. It was concluded that .65 g of glutamine per kg of body weight is perfectly fine to ingest. This would convert to 60 grams of glutamine for a 200 pound man. Therefore, very high levels of glutamine are indeed safe.

Practical Applications

A multitude of benefits have been laid out for you concerning glutamine supplementation. Now all that's left is to instruct you about is how to take it—let's get to it.

Post-Workout

Post workout is the most essential time for glutamine supplementation. As displayed above, this will enhance glycogen storage, reduce exercise-induced oxidative stress, strengthen the immune system, promote myofibril hydration and protein synthesis, and decrease protein degradation, among other benefits. At this time of the day, such factors as hydration are absolutely vital to your success.

Pre-Sleep

The goal here is to try to sustain as high a plasma glutamine level as possible. Fasting for several hours at night puts your body in a highly catabolic state, and glutamine levels are quickly depleted. By supplementing with GLN here, you will promote its preservation, and proper immune function. I would recommend you utilize OldSchool's sleep stack (which includes glutamine) for maximum results. See [Enter The Z Factor](#).

Post-Sleep

If you were to have a massive carbohydrate meal before sleep, your glycogen stores would still be diminished, and catabolism prevalent after fasting for several hours at night. This is why breakfast is one of the most vital meals of the day. The same applies to glutamine. Even if you supplement the night before, your stores will still be diminished in the morning. Several studies have displayed glutamine concentrations are severely reduced (around 500 to 750 $\mu\text{mol/L}$) after a night of sleeping [65, 143]. As such, I recommend taking glutamine in the morning as well, to get your body back into a state of anabolism.

Pre-Workout

Another logical time to supplement with glutamine would be pre-workout. Due to its gluconeogenic effects, you would help spare muscle mass during a training session. Additionally, maintaining high GLN concentrations would promote glutathione preservation, enhancing your body's defense against oxidative stress, among immune benefits. Moreover, in theory you would help maintain a stable pH, which is raised during exercise due to lactic acid.

Sick

Any time you are sick you should increase your glutamine supplementation, as it plays an absolutely vital role in this area.

Overtrained

As stated earlier, being overtrained can oftentimes be a sign of depleted glutamine stores. Moreover, your immune system is always torn down when in a stressful state such as overtraining. This would further help boost your leukocytes and speed recovery.

Final Suggestions

I would recommend you utilize the powder form of glutamine, as pills are much less potent, and would cost you a fortune. If you are on a very tight budget, you should have glutamine at least post-exercise. Otherwise, I would recommend having it a minimum of 3 times a day: in the morning, post exercise, and pre-sleep. Pre-exercise would be another time to implement this conditionally essential amino. Other than that, there is no particular portion in the day for glutamine supplementation; one time is as good as another. In states of stress, such as sickness and overtraining, or if you feel you are nearing overtraining, you may want to double your dosage, depending on your previous consumption; regardless, definitely make a substantial increase in your GLN intake. Lastly, the majority of scientific authorities recommend 5 grams of glutamine per serving [19, 78, 18, 73].

Conclusion

It has been clearly displayed that glutamine supplementation is essential for the athlete that seeks to obtain optimal results. Now, before we close, it's imperative that you understand what the term "essential" really means. Webster's dictionary defines it as [76]:

1 : of, relating to, or constituting essence : **INHERENT**

2 : of the utmost importance : **BASIC, INDISPENSABLE, NECESSARY** <essential

foods> <an essential requirement for admission to college>

Synonyms ESSENTIAL, FUNDAMENTAL, VITAL, CARDINAL mean so important as to be indispensable. ESSENTIAL implies belonging to the very nature of a thing and therefore being incapable of removal without destroying the thing itself or its character <conflict is essential in drama>. FUNDAMENTAL applies to something that is a foundation without which an entire system or complex whole would collapse <fundamental applies to something that is a foundation without which an entire system or complex whole would collapse <fundamental principles of algebra>. VITAL suggests something that is necessary to a thing's continued existence or operation <cut off from vital supplies>. CARDINAL suggests something on which an outcome turns or depends <a cardinal rule in buying a home>.

In summary, something that is essential is absolutely necessary to have—there is no substitute for it. Consequently, millions of people today are missing out on the essential key to each of our lives [1]:

Luke 10:38-42

38 Now it came to pass, as they went, that he entered into a certain village: and a certain woman named Martha received him into her house. 39 And she had a sister called Mary, which also sat at Jesus' feet, and heard his word. 40 But Martha was cumbered about much serving, and came to him, and said, Lord, dost thou not care that my sister hath left me to serve alone? bid her therefore that she help me. 41 And Jesus answered and said unto her, Martha, Martha, thou art careful and troubled about many things: 42 But one thing is needful: and Mary hath chosen that good part, which shall not be taken away from her.

Mark 4:18-19

18 And these are they which are sown among thorns; such as hear the word, 19 And the cares of this world, and the deceitfulness of riches, and the lusts of other things entering in, choke the word, and it becometh unfruitful.

I don't know how many times I have heard people make excuses for not turning to Christ, or not studying the word, or continuing to willfully sin. What these people do not understand is that they are cutting out the only thing that really matters—a relationship with the Lord of all the living. Jesus said, "But seek ye first the kingdom of God, and his righteousness; and all these things shall be added unto you." I implore all those who are reading this to reflect their lives and get your priorities straight. If you are on this path, everything else will fall into place.

Mark 8:34-36

34 And when he had called the people unto him with his disciples also, he said unto them, Whosoever will come after me, let him deny himself, and take up his cross, and follow me. 35 For whosoever will save his life shall lose

it; but whosoever shall lose his life for my sake and the gospel's, the same shall save it. 36 For what shall it profit a man, if he shall gain the whole world, and lose his own soul?

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