THE SCIENCE BEHIND

GLUTAMINE

GLUTAMINE: a good all-round amino acid

Key points

- Glutamine is a major intramuscular amino acid
- Glutamine is converted to glucose in the liver and this process (gluconeogenesis) occurs during exercise
- Glutamine helps maintain gut integrity during periods of stress such as exercise and so attenuates uptake of toxins and bacteria
- Glutamine helps the immune system
- Glutamine promotes glycogen storage without raising insulin and blood glucose
- Glucose causes cell swelling, which may stimulate protein accretion and aid recovery
- Glutamine promotes muscle recovery from resistance exercise and reduces muscle soreness

Introduction

Glutamine is a naturally occurring non-essential amino acid which constitutes about 60% of the free amino acids inside muscle cells. Although it is strictly termed a non-essential amino acid (because it can be made from other amino acids we consume in our diet), it becomes a conditionally essential amino acid in circumstances of stress and trauma. Under such conditions, glutamine production cannot be made quickly enough for its many uses within the body and so needs to be added to the diet in sufficient amounts. The main roles of glutamine appear to be for gut health (as it is a major energy source for intestinal cells to grow and replicate), the immune system (as a crucial energy source), for acid-base balance, and for muscle protein synthesis. Other less well-known roles for glutamine include that it can act as an indirect source of energy for muscles during prolonged exercise via the process of gluconeogenesis, that it causes cell swelling by drawing water into a cell, and that it stimulates glycogen synthesis.

Most of the earlier research on glutamine was (and still is) associated with the role of glutamine in 'sick' patients, when it is released from muscle (where it is produced) to 'feed' the immune system, and provide an important source of protein for the gut to remain (or become) healthy (Griffiths et al., 1997). In fact, many studies over the years in seriously ill patients have shown the benefits of providing added glutamine in enteral feeding, resulting in shortening recovery times and even promoting survival (Jones et al., 1999; Wischmeyer et al., 2014).

For athletes ingesting a daily protein intake of around 1.6g/kg body weight there is the likelihood that approximately 6g of glutamine will be consumed. In the various studies on the efficacy of

glutamine intake, doses of up to 30+g a day have been employed. There appears to be no upper level for glutamine ingestion from a safety view. The question arises as to what are the outcomes from these studies.

Glutamine and exercise

During exercise lasting for more than 20-30 minutes the process of gluconeogenesis by the liver ensures that there is a supply of glucose into the blood for organs such as the brain and muscle to utilize. As the duration of exercise becomes longer, gluconeogenesis can contribute around 5-8% of the total energy used – you may not consider this a great deal, but it is important for attempting to keep blood glucose levels from becoming 'hypo' as well as enabling the exercise to continue i.e. delay fatigue. Gluconeogenesis is a process whereby glucose is produced from non-carbohydrate sources – these typically being lactic acid, glycerol (from fat metabolism), and the amino acids alanine and glutamine (from protein breakdown). An increase in the hormone, glucagon, stimulates gluconeogenesis as well as the breakdown of protein in muscle and other tissues. Such an event occurs during prolonged, aerobic activities in line with a decrease in insulin. Feeding carbohydrate during exercise inhibits glucagon secretion and so diminishes gluconeogenesis, but in circumstance where athletes wish to undertake 'fat burning', taking carbohydrate is not desirable, and hence gluconeogenesis takes place.

Figure 1 is a schema illustrating the concept of the glucose-glutamine cycle whereby glutamine is released by the muscle during exercise, and is taken to the liver where glucose is produced. The glucose can then be taken back to muscle (and the brain) to act as an energy source. It is quite conceivable that by supplying glutamine prior to and even during such activities may reduce the requirement for muscle glutamine. The evidence for this is equivocal, and further research is needed.

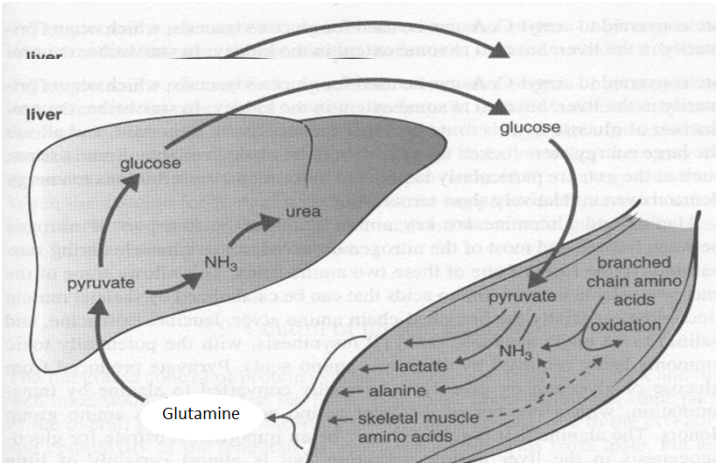

Figure 1 – Glutamine-Glucose cycle which occurs during exercise i.e. glutamine released by muscle is taken up by liver and converted (via gluconeogenesis) to glucose.

Glutamine and muscle glycogen resynthesis

There is some evidence for an effect of glutamine supplements in promoting glycogen synthesis in the first few hours of recovery after exercise. Bowtell et al. (1999) provided 8g of glutamine in addition to 61g of glucose polymer after a glycogen-depleting bout of exercise and compared this with 8g glutamine alone and 61g of glucose polymer alone. The glucose plus glutamine showed a 25% increase in whole body glucose disposal in the 2 hours of recovery compared with glucose polymer alone (most going into liver glycogen). All three drinks resulted in a significant increase in muscle glycogen restoration in a 2 hour period, with no differences between the treatments. It may seem strange that glutamine alone was able to store muscle glycogen, but remember that glutamine is converted to glucose by the liver and so can be taken up by muscle as glucose and then stored as glycogen.

A word of caution needs to be made, the ingestion of 61g of carbohydrate is a suboptimal amount and (in this study) represented 0.8g/kg body mass of carbohydrate - amounts of 1-1.2g/kg are needed after such exercise to achieve the maximum rate of muscle glycogen synthesis over a 2-h post-exercise period. So the need for additional glutamine is not necessary IF good amounts of carbohydrate are ingested post-exercise. However, if an athlete is concerned with not ingesting too much carbohydrate after strenuous (or light) training (maybe because of body fat issues) but wishes to ensure adequate muscle glycogen storage, consideration should be given to adding glutamine to a post-exercise low carbohydrate intake – I would suggest 10-20g. In this manner it is likely that sufficient stores of muscle glycogen may be attained without the likelihood of promoting fat storage. However, for those who wish to maximise muscle glycogen stores after training, the emphasis should be on more carbohydrate ingestion.

Glutamine and the Gut

It has long been recognised that a major function of glutamine is in relation to the gut. The last decade has witnessed accumulating evidence on the beneficial effects of glutamine on gut function and health in humans and other animals. Glutamine is oxidized by the Krebs cycle to produce ATP for rapid dividing cells (including enterocytes and lymphocytes). Furthermore, glutamine activates mTOR signalling and increases protein synthesis in enterocytes, promotes intestinal development, regulates intestinal immunity, and inhibits apoptosis (cell death) induced by oxidative stress (Figure 2).

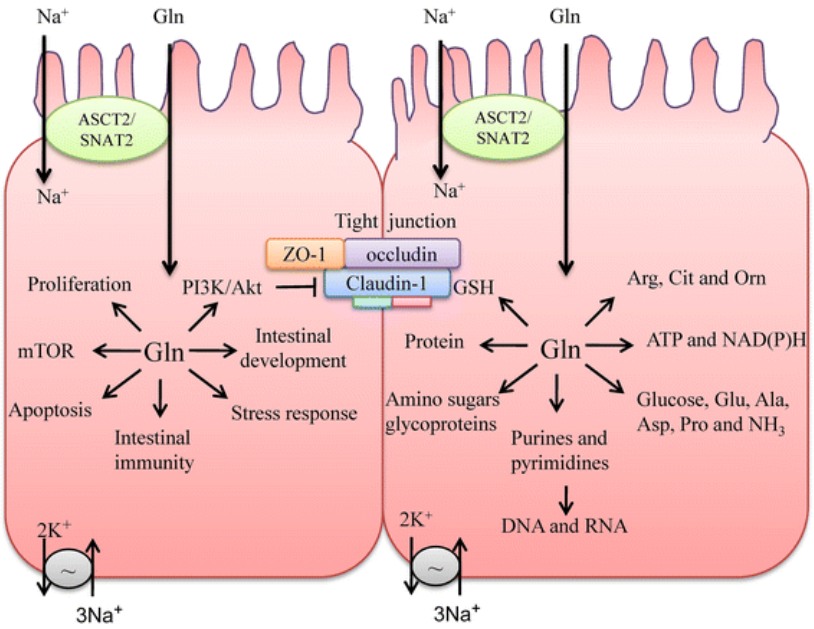

Figure 2 - The likely roles of Glutamine in intestinal epithelial cells

The gut provides an important barrier to the entry of bacteria or toxins – particularly from the colon. Increased intestinal permeability (in which the gut becomes 'leaky' due to damage) is a well-recognised phenomenon in critically ill patients as well as in endurance athletes and those who train vigorously (van Wijck et al., 2011). A consequence of a 'leaky' gut is the potential to enable greater uptake of bacteria and endotoxins into the bloodstream and so weaken the immune system – in effect the body's own immune system is compromised to deal with greater endotoxin levels coming into the blood from the 'leaky' gut. Figure 3 provides an illustration as to the effect of a so-called 'leaky' gut on uncontrolled uptake of pathogens and toxins (note how nutrient uptake is compromised!).

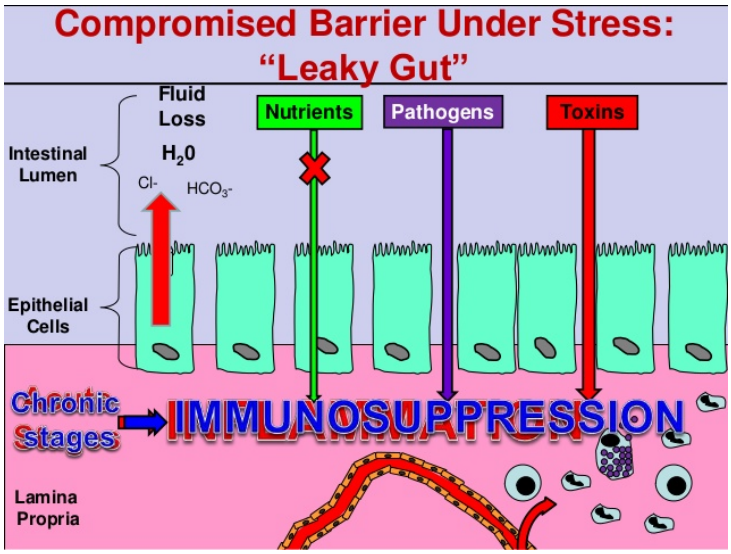

Figure 3 – Illustration of a 'leaky' gut.

Gastrointestinal problems are common, especially in endurance athletes, and often impair performance and subsequent recovery. Studies have demonstrated that 30-50% of athletes experience such complaints (de Oliveira et al., 2014). Most gastrointestinal symptoms during exercise are mild and of no risk to health, but in some cases they can present serious medical challenges. During intense exercise, and especially when dehydrated, blood flow around the gut is reduced (because there is an increase in blood flow to working muscles and maybe the limbs to dissipate heat), and is believed to be one of the main contributors to the development of gastrointestinal symptoms. Reduced gut blood flow has been shown to result in compromised gut permeability in athletes (van Wijck et al., 2011) with all the likely associated problems. Figure 4 illustrates that exercise at high intensities or for prolonged periods can be problematic from a gut perspective.

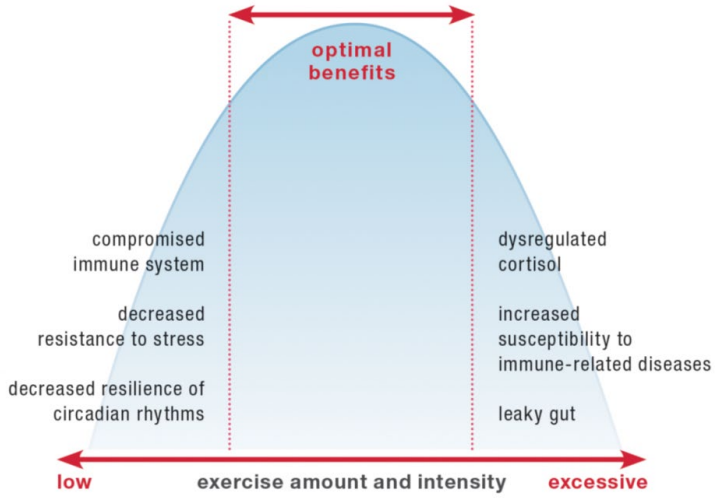

Figure 4 – Illustration of the possible effect of exercise on the gut.

Nutritional training and appropriate nutrition choices can reduce the risk of gastrointestinal discomfort during exercise by ensuring rapid gastric emptying and the absorption of water and nutrients, and by maintaining adequate perfusion of the gut blood supply. Glutamine ingestion has been shown to improve gut integrity by reducing leakiness (Wischmeyer, 2006), and in a recent review (Wang et al., 2015) concluded that "glutamine holds great promise in protecting the gut from atrophy and injury under various stress conditions". To date only one study has reported on the benefits of glutamine ingestion (0.9g/kg/day for 7 days) on reduced gut permeability during exercise (Zuhl et al., 2014). Such a dose represents 72g of glutamine for an 80kg person – a dose very much higher than reported in any other study. In fact the dose was so high that it was given as 0.3g/kg three times day i.e. 24g x 3 per day for an 80kg athlete. Figure 4 below shows the results of glutamine on intestinal permeability from this study i.e. the leakiness of the gut (represented by intestinal permeability) after glutamine ingestion (GLN) and exercise was similar to being at rest, whereas with placebo (PLA) the gut became 'leaky'.

I should report that work is currently being undertaken by Professor Graeme Close (NutritionX consultant) at Liverpool John Moores University on the efficacy of giving lower doses of glutamine and gut function. Early findings confirm that lower doses of glutamine appear to offer protection from exercise-induced gut injury.

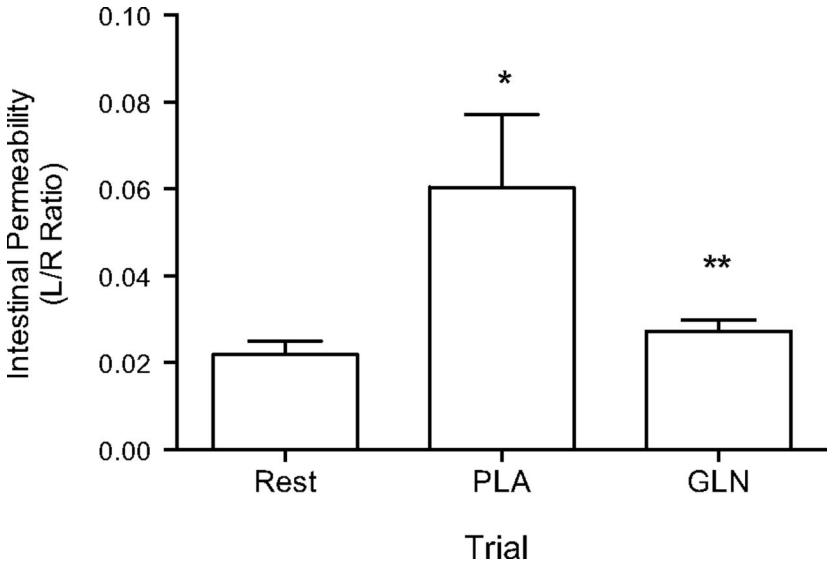

Figure 4 - Glutamine (GLN) prevented a rise in intestinal permeability during exercise compared with placebo (PLA).

Glutamine and Immune Function

Glutamine is used at high rates by immune cells in the body such as leukocytes (or white blood cells) for energy and to help in cell proliferation. In fact, leukocytes are totally reliant on glutamine being provided in the blood (from breakdown of muscle or from diet), and in circumstances of reduced blood concentrations, these cells may be compromised. Prolonged exercise is associated with reduced intramuscular and blood concentrations of glutamine, and this has been hypothesized to impair immune function (Parry-Billings et al., 1992).

The effects of acute exercise on plasma glutamine concentration appear to be largely dependent on the duration and intensity of exercise. There is a consistent body of evidence showing that the plasma glutamine levels fall after prolonged exercise (Gleeson, 2008). Prolonged exercise is known to cause an elevation in plasma cortisol concentration, which stimulates not only protein breakdown and glutamine release but also increases gluconeogenesis. As previously described, the hormone glucagon (increased during exercise when insulin levels decrease) also results in enhanced muscle protein breakdown and stimulation of gluconeogenesis. The overall effect is that prolonged, strenuous exercise may compromise the total glutamine pool possibly resulting in impaired immune function. Consequently, suggestions have been made that supplementing with glutamine may act as an insurance policy during periods of exercise stress (Castell et al., 1996).

The glutamine hypothesis proposes that a decrease in plasma glutamine concentrations, brought about by heavy exercise and training, limits the availability of glutamine for cells of the immune system that require glutamine for energy and nucleotide biosynthesis (in effect cell proliferation). Thus, the glutamine hypothesis provides a mechanism to explain exercise-induced immune impairment and increased susceptibility to infection in endurance athletes. The time course of the decrease in plasma glutamine concentrations after prolonged strenuous exercise coincides with the decreases in many immune parameters; in addition, it is prolonged moderate-high intensity exercise that most often results in the greatest immune impairment and this type of exercise also results in the greatest reduction in plasma glutamine concentration.

The glutamine hypothesis is based predominantly on in vitro work by Parry-Billings et al. (1990), which showed that mitogen-stimulated lymphocyte proliferation is enhanced by glutamine in a concentration-dependent manner. Evidence showing that the provision of glutamine-supplemented, total parenteral nutrition to severely ill surgical patients improves immune responses also provides further support for the 'glutamine hypothesis' (O'Riordain et al., 1996). However, more recent evidence has emerged that lymphocytes function equally well when plasma glutamine are concentrations are low as when at normal levels (Hiscock & Pedersen, 2002).

The majority of studies have found no beneficial effects of maintaining plasma glutamine concentration, with glutamine supplements during exercise and recovery, on various immune responses after exercise. So the evidence does not support a role for decreased plasma glutamine concentrations causing exercise-induced immune depression. More research is required to elucidate the mechanism(s) by which oral glutamine supplements may have positive effects in prolonged, intense exercise bouts. Having said that, glutamine may have an indirect effect on immune function and infection incidence by preserving and maintaining gut barrier function. It may also be that the doses given in the majority of the studies to date are in fact too low, and that further studies using dose in excess of 20-30g/day should be explored!

Glutamine and Cell Swelling

Cellular swelling results from a change in the osmotic gradient within the cell. This occurs when an osmotically active compound (such as glutamine) is at a higher concentration within the cell than the outside. The effect results in movement of water molecules into the cell and hence swelling.

Recent evidence suggests that the state of cellular hydration (cell volume) is an import factor in the control of many important cellular functions. These include modulation of hormones, oxidative stress, and gene expression. Several compounds (such as glutamine) have been shown to have a significant effect on cellular volume, and so the effect glutamine has on glycogen synthesis and inhibition of protein breakdown can be mimicked by bringing about similar changes in cell volume.

Figures 5 highlights the fact that glutamine can promote cell swelling (↑ Cell Volume) and so result in positive changes with regard to protein accretion.

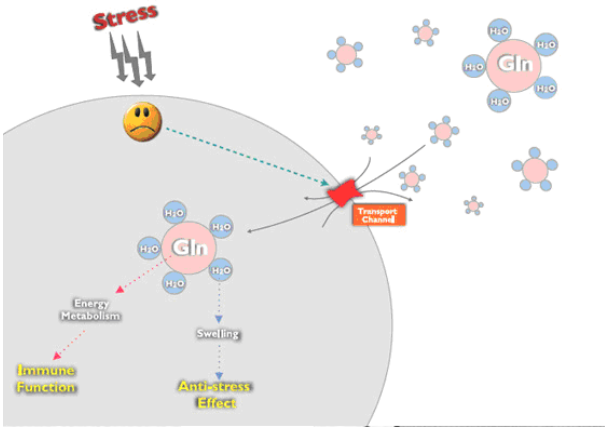

Figure 5 – Schema of effect of glutamine on cell swelling.

A more complex schema is shown in Figure 6 whereby the roles of glutamine (as well as BCAAs and arginine) can be realised.

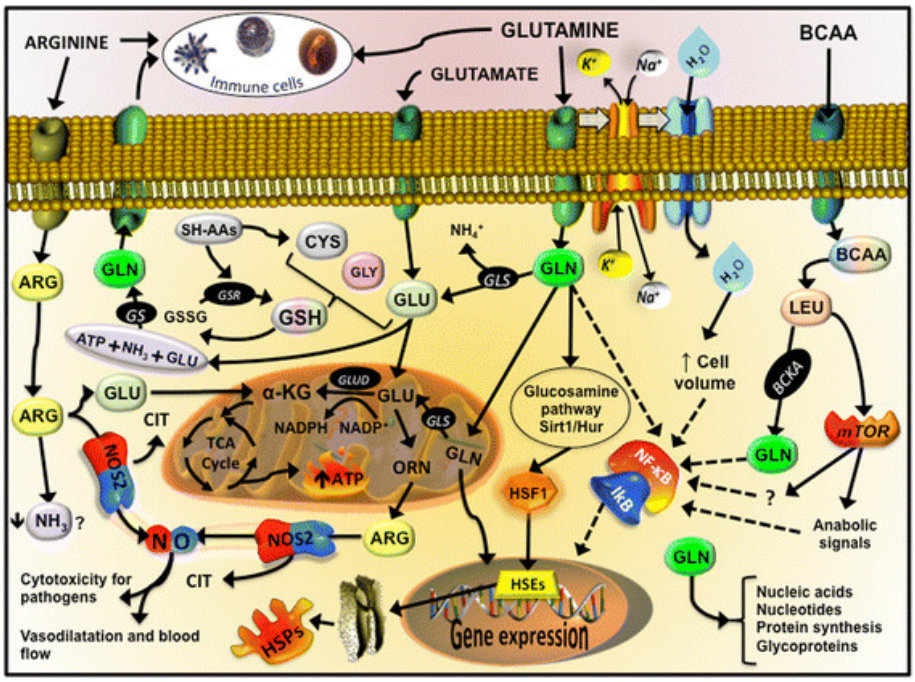

Figure 6 - **Immune, antioxidant and inflammatory targets that L-glutamine, L-arginine and BCAA are involved.** L-glutamine is transported inside the cell through active transport with sodium (Na^+) potassium (K^+) ATPase, which augment the absorption of water, altering the volume of the cell and stimulate the resistance to damage.

Glutamine and muscle recovery

Only a few studies have explored the efficacy of glutamine on muscle function following exercise. In one study there was a positive effect of ingesting 0.3g/kg body weight a day of glutamine in the 3 days after doing 100 box jumps and there was also a reduced rating of muscle soreness (Street et al., 2011). Similar findings were reported in a more recent study (Legault et al., 2015) in which muscle recovery was significantly faster and muscle soreness lower 3 days after a bout of eccentric exercise when 0.3g/kg body weight per day of glutamine was ingested (this equated to approximately 20-25g of glutamine per day). Figure 7 shows the data on recovery of muscle peak torque in the days following the exercise bout, and clearly demonstrates the advantages of glutamine supplementation (especially for males).

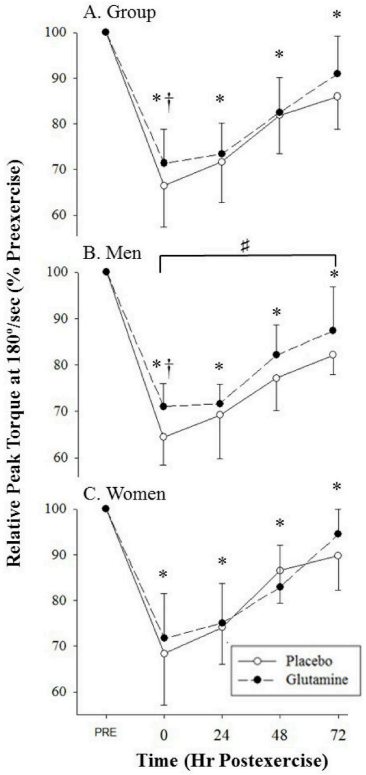

Figure 7 – Recovery of peak muscle torque in 72 hours after eccentric exercise, with and without glutamine supplementation (after, Legault et al., 2015)

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