Review Article

Glutamine: metabolism and application in nutrition support

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Glutamine is the most abundant free amino acid in the body. It is avidly consumed by rapidly dividing cells, such as those lining the gut, because its 5-carbon skeleton can provide energy whilst the nitrogen molecules support the synthesis of nucleic acids. Patients who are maintained using conventional solutions of parenteral nutrients become depleted in glutamine, which has led to the reclassification of glutamine as a conditionally essential nutrient. Unfortunately, glutamine is unstable in solution and produces toxic byproducts on decomposition. This means that solutions of nutrients containing glutamine have a relatively short half-life, which has led to the commercialisation of stable dipeptides containing glutamine. Although it is evident that glutamine enhances nitrogen metabolism, there is a lack of consistent evidence from the initial clinical trials demonstrating that supplementation with glutamine has specific clinical advantages. The next few years will witness the performance of larger scale clinical trials and the results of these studies should define a more certain role for glutamine in routine clinical practice.

Key Words: amino acids, glutamine, enteral nutrition, parenteral nutrition

Introduction

Glutamine, a 5-carbon amino acid with 2 amino groups, is the most abundant free amino acid in the body.[1] Specifically, glutamine accounts for more than 50% of the free amino acid pool in skeletal muscle,[2] 25% of plasma free amino acids[3] and in the cerebrospinal fluid is present in a 10-fold greater concentration than any other amino acid.[4] It was Sir Hans Krebs who, in 1935, first described glutamine metabolism recognising that its commonality between tissues and across species indicated a central metabolic role.[5,6] Glutamine functions as an intermediary in energy metabolism, a substrate in the synthesis of peptide and non-peptide molecules including glutathione, neurotransmitters and nucleotide bases. Glutamine also has a homeostatic role as a regulator of systemic acid-base balance and in the detoxification of ammonia. The concept that the response to critical illness may be modulated by glutamine-supplemented nutritional support has gained a degree of acceptance in clinical practice. This review offers a summary of glutamine metabolism and a discussion of its application in nutrition therapy.

Glutamine is a conditionally essential amino acid

Glutamine was first proposed to be conditionally essential by Lacy and Wilmore in 1990.[7] The reclassification of glutamine was based on the deduction that the fall in the plasma level observed during catabolic stress indicates synthesis is inadequate for demand and that an exogenous supply is required. However Askanazi *et al*. found that, in humans, decreased plasma levels are not always observed during catabolic stress; specifically in sepsis[8] or trauma irrespective of the injury severity.[9] In the same studies the catabolic stress of trauma, but not sepsis, was associated with a significant decrease in muscle glutamine concentration. Since then, using the same criteria, it has been proposed that glutamine is conditionally essential for preterm infants.[10] The biochemical basis accounting for glutamine becoming conditionally essential differs from that of other conditionally essential amino acids. Glutamine may be synthesised from several essential amino acids (Val, Leu, and Ile) whereas the *de novo* synthesis of cysteine and tyrosine are dependent on the availability of a single essential amino acid for their endogenous synthesis, methionine and phenylalanine respectively. Histidine is conditionally essential for a specified age group, infants,[11] whereas glutamine can become conditionally essential for any age group. Cysteine is conditionally essential in low birth weight neonates secondary to an immature synthetic pathway, specifically low cystathionase activity.[12] Some are sceptical about the reclassification of glutamine and require unequivocal evidence of a clinical response to supplementation as proof that endogenous synthesis can be inadequate.[13]

Two key enzymes

The main enzymes related to glutamine metabolism are glutaminase and glutamine synthetase which catalyse the

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rate limiting steps in glutamine utilisation and synthesis respectively (Table 1). Glutaminase is a mitochondrial enzyme which hydrolyses glutamine to glutamate and ammonia. In this way glutamine is trapped for intracellular metabolism because glutamate, which carries a negative charge, cannot freely cross the membrane.[14] Humans possess several different glutaminase isoforms. These are encoded by genes on chromosomes two and twelve and the distribution of different forms in human tissues is an ongoing area of research. Glutamine synthetase catalyses the final step in glutamine *de novo* synthesis. This cytosolic enzyme forms glutamine from glutamate and ammonia. High glutamine synthetase activity is characteristic of ammonia producing tissues and during net glutamine generation such as in catabolic states.[15] Glutaminase and glutamine synthetase activities appear to be regulated, at least in part, by the interaction of an individual's genotype with diet.[16,17] Gene-nutrient interactions affect gene expression[18] and, in turn, the responsiveness to treatment. The elucidation of these interactions is advocated by leaders in nutrition science as a priority area for interdisciplinary research.[19,20]

Principal sites of glutamine metabolism

Skeletal muscle is the largest tissue reservoir of glutamine and quantitatively the most important site of synthesis. About 90% of plasma glutamine is derived from the intracellular free glutamine pool within skeletal muscle via glutamate derived from branched chain amino acids.[21,22] There is no significant gender difference in the concentration of either the skeletal muscle free or structural glutamine, so the net tissue flux is a function of muscle mass.[21,23] The effect of muscle mass on the capacity for prolonged glutamine synthesis may be clinically relevant during catabolic stress in the very young,[24] the elderly[25] and where there is a muscle wasting disease.[26] The rate of muscle protein synthesis relative to catabolism is regulated by hormones and cytokines. During hypermetabolism net muscle proteolysis and muscle glutamine synthesis and release diverts amino acids to gluconeogenesis and the synthesis of acute phase proteins. In this way nitrogen is transferred from the muscle-reserve to sites of increased utilisation. Further, it appears that this transfer meets a specific glutamine demand by the gut and immune tissues.[27] Intracellular glutamine concentration may be a secondary regulator of muscle protein synthesis and breakdown rates.[28]

Glutamine release from the lungs is part of a homeostatic mechanism that regulates the plasma ammonia concentration.[29] During normal metabolism, including non-hypermetabolic hospital patients, the lungs are said to be in balance with only a slight glutamine release.[30,31] Lung glutamine synthesis and release is markedly increased during the postoperative period of major surgery[30] and the hypermetabolic states such as sepsis.[31] Glutamine synthetase activity shows upregulation by the glucocorticoid hormones released endogenously during catabolic stress and by agents such as dexamethasone delivered as a part of therapy.[32]

In the liver, glutamine is utilised as a substrate for gluconeogenesis and for the synthesis of urea, acute phase proteins, and glutathione. The liver shows net glutamine uptake after a protein meal but changes to net release during catabolic states such as uncontrolled diabetes, sepsis and starvation.[33] During increased protein turnover more ammonium reaches the liver, increasing the supply of substrate for the synthesis of glutamine. When dietary protein is limited the activity of the urea synthesising enzymes is reduced and this may channel ammonia and glutamate towards glutamine synthesis. On the basis of their work Remesy and colleagues suggest that this shift in liver glutamine metabolism constitutes an important mechanism for N-salvage.[34,35]

Renal glutamine metabolism is important in acid/base homeostasis and in gluconeogenesis.[36] During chronic mild acidosis renal glutamine utilisation is increased with a concomitant increase in ammonia production.[37] The ammonia combines with hydrogen ions and is excreted as ammonium. In consequence there is a net disposal of hydrogen ions and an amelioration of acidosis. Glutamine is the preferred substrate for renal gluconeogenesis, 73% of uptake is converted to glucose.[38,39] Glucose production by the renal cortex represents 20% of the total glucose release into the circulation in postabsorptive humans. Renal gluconeogenesis is important after as little as 12 hours of fasting,[40] in hypoglycaemia,[41] and, in Type 1 and Type 2 diabetes mellitus.[42] Cano[43] has proposed 'that renal gluconeogenesis from glutamine released by the muscle realises a glutamine-glucose cycle similar to the alanine-glucose cycle involving the muscle and the liver.'

Glutamine is important in both the non-specific and cellular aspects of immunological defence. It is linked to the functional activities of cells of the immune system; proliferation, phagocytosis, antigen presentation and the production of cytokines, nitric oxide and superoxide, and glutathione synthesis.[44-46] The formation of N-acetyl-glucosamine is glutamine dependent.[47,48] This glycoprotein is a component of the mucin that protects mucosal surfaces. During an immune response there is a marked increase in the uptake of plasma glutamine by immunocytes.[49,50] Glutamine provides pyrimidine nucleotides for the synthesis of nucleic acids.[51]

Table 1. Features of glutaminase and glutamine synthetase

Glutaminase
Glutamine + H_2O → Glutamate + NH_3
Mitochondrial
Highest activity in enterocytes, immunocytes, kidney and liver (periportal hepatocytes)
Several isoenzymes identified
Regulated at the post-transcriptional level
Glutamine Synthetase
Glutamate + NH_3 + ATP → Glutamine + ADP + Pi
Cytosolic
Highest activity in skeletal muscle, lung and liver (perivenous hepatocytes)
One known isoenzyme
Regulated at the pre and post-transcriptional levels

Glutamine is a key intestinal nutrient

One third of total glutamine utilisation occurs in the intestine.[52] The intestinal mucosa contains enterocytes and immune cells that require glutamine for nitrogen and energy.[53-55] Glutamine is withdrawn from both blood and the intestinal lumen. In normal, healthy adults 74%[56] of enterally administered glutamine is absorbed into the splanchnic tissues and most of this is rapidly metabolised within the intestine.[57,58] About 25% of the glutamine in blood is removed each time it passes through the small intestine.[58] While any biological significance of the independence of mucosal glutamine supply from dietary intake is not established it is nonetheless clinically relevant that lumenal glutamine spares the utilisation of arterial glutamine[59] and therefore endogenous protein.[60] Further, the high capacity of the intestinal mucosa to remove glutamine from the arterial and dietary supply suggests that the intestine competes with the other organs for glutamine.

Glutamine depletion is associated with impaired intestinal structure and function. Baskerville and others demonstrated *in vivo* that a lack of glutamine, due to experimentally induced excessive glutamine hydrolysis, results in intestinal degradation.[61] Recent work has examined the response of the intestine to a graded glutamine supply. In cell culture enterocytes have an increased rate of protein synthesis with increased glutamine supply.[62] A number of animal studies have demonstrated that glutamine availability benefits intestinal functional and structural indices. Parenterally nourished rats show less mucosal atrophy when the solution is supplemented with glutamine.[63] These findings have been reproduced in models of starvation,[64] surgical stress,[65] and sepsis.[66] Parenterally nourished rats have a positively graded relationship between glutamine supply and intestinal mucosal indices.[63,67] Intracellular glutamine appears to be treated the same metabolically irrespective of its arterial or lumenal origin.[68-70] Either route is metabolically suitable for glutamine supplementation targeted at the intestine.

Dietary glutamine

Glutamine is not distinguished from other amino acids by its occurrence in foods where it comprises four to six percent of protein. In contrast, the amino acid profile of breast milk shows that glutamine is set apart by its quantitative importance. Glutamine is the most abundant amino acid in milks across primate and non-primate species.[71] In humans, depending on lactational stage, glutamine contributes 20-40% of the total free amino acid content.[72] While suggestive of a specific demand for glutamine by the developing gastrointestinal tract,[73] this remains to be defined but is of keen interest given that glutamine depletion during fetal and neonatal life is associated with adverse intestinal effects.

The chemical form of glutamine in a food, not just concentration, affects its availability to enterocyte metabolism. It has been appreciated that small peptides are absorbed more efficiently across the human upper small intestine than are free amino acids.[74] Boza and colleagues showed with human subjects that dietary free glutamine produces a significantly greater postprandial rise in plasma glutamine than does protein-bound glutamine.[75] The authors concluded, somewhat controversially,[76] that glutamine in food proteins is more fully metabolised by the splanchnic tissues than free glutamine which passes readily and unchanged to the circulation. While amino acid bioavailability studies are of commercial interest, free glutamine has repeatedly been shown to affect mucosal indices, therefore the chemical form in which it is delivered does not appear crucial in terms of clinical effect.

Glutamine in nutrition support

Clinical trials have evaluated glutamine as both an enteral nutrient and a parenteral nutrient (Table 2). In general, enteral supplementation is less likely to increase the plasma glutamine level and parenteral supplementation is more likely to enhance nitrogen balance and provide a benefit in clinical outcome. Indeed, a recent systematic review of the evidence examining the relationship between glutamine supplementation and hospital length of stay, complication rates and mortality in patients undergoing surgery and experiencing critical illness found that the greatest benefit was in patients receiving high-dose, parenteral glutamine. In surgical patients supplementation may be associated with a reduction in infectious complication rates and shorter hospital stay whereas in critically ill patients a trend towards a reduction in complication and mortality rates was indicated.[89] The incidence of infectious complications, a surrogate outcome, is a valuable goal because it has the potential to affect other endpoints in particular length of intensive care unit (ICU) stay, duration of mechanical ventilation and antibiotic treatment.[90] In intensive care patients, Griffiths found that patients who had been randomly allocated to receive parenteral glutamine showed an improved survival at 6 months (P<0.027) which, they concluded, appeared related mostly to reduced mortality in the intensive care unit from multiple organ failure.[88] Similarly, Conejero found that of patients with systemic inflammatory response syndrome, fewer of those receiving a glutamine-enriched enteral diet developed nosocomial pneumonia (P<0.04), although there were no significant differences with respect to other infections, mortality or length of stay.[87] In a randomised, double blind controlled trial in 168 patients Powell-Tuck found that glutamine supplementation of parenteral nutrition was associated with a significant (P<0.03) reduction in length of stay. An interesting finding, however, the authors concluded that further trials are required to clarify the suggestion of an advantage of glutamine supplementation in this patient group.[80]

The analysis by Kuhn *et al.* showed that usual delivery of standard enteral nutrition support provides 6 to 8g glutamine/day therefore falling short of the estimated requirement of 10-20g of exogenous glutamine in the critically ill patient.[91] There is a practical explanation as to why elemental glutamine is not added to standard enteral and parenteral formulae. Compared with other amino acids, glutamine is relatively unstable in solution,[92] for it undergoes cyclisation to form pyroglutamate, (5-oxoproline, 5-pyrrolidone-2-carboxylic acid), a neurotoxin. The reaction occurs at room temperature but is

accelerated by heat.[93] thereby making glutamine unsuitable for use in preparations such as parenteral nutrition components which require sterilisation. While some have suggested that this concern is theoretical it has sufficiently inhibited the pharmaceutical industry such that free glutamine has not been added to enteral or parenteral nutrition solutions. The biotechnology for the synthesis of glutamine-containing dipeptides using plant proteases was developed and commercialised in Germany.[94] This has permitted the safe addition of glutamine as alanyl- or glycyl- glutamine to parenteral nutrition solutions. Ad hoc supplementation of enteral nutrition solutions at the time of delivery has been practised at medical discretion. It is L-glutamine, not the D-glutamine optical isomer that is used for this purpose on the basis of better *in vivo* utilisation, although cells in tissue culture can metabolise both isomers. Certain, relatively new, enteral products are supplemented with mixed glutamine-containing peptides of various lengths. These peptides are derived from the acid hydrolysis of glutamine-rich proteins such as gliadin, the process accounting for the variety in resultant peptide composition.

There has been an absence of reported adverse clinical events due to the glutamine component of commercially available enteral feeding products. Information from clinical trials of enteral glutamine supplementation (0.3-0.86g/kg/d) in adults and pre-term infants has been free of reports of adverse effects. However the remarks made by Ziegler in 1996 are still applicable.[95] He urged that some caution needs to be given because the number of trials remains small and typically those patients where there is risk of changed protein metabolism secondary to impaired hepatic or renal function are excluded from study. Glutamine-supplemented parenteral nutrition appeared safe in healthy volunteers over a five day treatment.[96] However, four weeks of glutamine-supplemented TPN in home-TPN patients was associated with a significant elevation in patient hepatic amino transferase level.[97] The levels were normalised after cessation of glutamine administration.

Product regulation

In the United States parenteral glutamine is regulated by the Food and Drug Administration and is not currently approved for use in intravenous solutions. Parenteral dipeptide solutions are approved for use throughout Europe. In Australia parenteral products are regulated under the Therapeutic Goods Act 1989. A glutamine-supplemented parenteral solution was listed on the Australian Register of Therapeutic Goods in May 2002. In the United States enteral and oral glutamine-supplemented products are permitted as long as no claims of specific medical benefit are made. General claims that enteral glutamine helps maintain normal bodily functions do not require approval. In Australia products for enteral use are considered foods and fall under the Australia New Zealand Food Standards Code (FSC). The FSC does not, at present, explicitly recognise these types of products. A set of regulations, Foods for Special Medical Purposes have been developed and an Initial Assessment Report produced.

Conclusion

The science in support of the use of glutamine supplements is compelling. There is ample evidence that glutamine enhances the nitrogen metabolism of patients in a wide range of catabolic circumstances. However, clinical trials have provided contradictory results and there is no consensus view that supports the routine clinical use of glutamine supplements in any specific situation. Future directions will involve the use of glutamine supplementation in combination with biologically active molecules that moderate the systemic effects of catabolism.

Table 2. Some clinical trials evaluating glutamine supplementation

	Patient group	Route	Major findings
Lacey JM *et al.,* 1996[77]	44 premature infants	Parenteral	The < 800g cohort had less ventilation days and less time to full feeds.
Griffiths *et al.,* 1997[78]	84 critically ill adults	Parenteral	Improved survival after 6 months and reduced costs.
Neu J *et al.,* 1997[79]	68 very low birth weight neonates.	Enteral	Decrease in nosocomial infections.
Houdijk AP *et al.,* 1998 [80]	72 patients with multiple trauma	Enteral	Significantly lower incidence of pneumonia, bacteraemia and sepsis. No significant effect on mortality rate.
Anderson PM *et al.,* 1998 [81]	193 bone marrow transplant patients	Enteral	Less mouth pain.
Powell-Tuck J *et al.,* 1999 [82]	168 critically ill adults	Parenteral	No appreciable difference between the groups.
Mertes N *et al.,* 2000 [83]	37 adults undergoing major abdominal surgery	Parenteral	Reduced length of hospital stay.
Akobeng *et al.,* 2000 [84]	18 children with active Crohn's disease	Enteral	Improved Crohn's disease activity index.
Wischmeyer *et al.,* 2001 [85]	26 severely burned patients.	Parenteral	Reduction in Gram-negative bacteremia.
Goeters C *et al.,* 2002 [86]	95 critically ill patients	Parenteral	Improved survival after 6 months for patients treated > 9 days
Conejero R *et al.,* 2002 [87]	84 SIRS patients	Enteral	Reduced nosocomial pneumonia
Griffiths RD *et al.,* 2002 [88]	84 critically ill patients	Parenteral	Improved survival after 6 months

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