

Glutamine: clinical applications and mechanisms of action

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Supplementation of the conditionally essential amino acid glutamine may be beneficial for individuals who are highly stressed and have minimal energy and protein reserves. This includes elderly individuals, postoperative patients, individuals with cancer and very low birthweight infants. Individuals who are undergoing treatment with catabolic glucocorticoids may also benefit. Unfortunately, confusion exists as to situations in which glutamine may be beneficial because a clearly defined 'glutamine deficiency syndrome' has not been described as for some other nutrients. In this review, we will discuss how glutamine affects protein metabolism under certain stressful conditions, how it affects intestinal mucosal integrity and how this might relate to sepsis and systemic inflammation. We will also discuss nutrients that are closely related to glutamine such as glutamate, nucleotides, arginine, glucosamines, and ornithine alpha-ketoglutarate and how and why they might be used as substitutes for glutamine. *Curr Opin Clin Nutr Metab Care* 5:69-75. © 2002 Lippincott Williams & Wilkins.

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Abbreviations

IgA	immunoglobulin A
IL	interleukin
TPN	total parenteral nutrition
VLBW	very low birthweight

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Introduction

Glutamine is, by far, the most abundant amino acid in the circulation and in the intracellular free amino acid pool. Glutamine was classified as a non-essential amino acid when it was demonstrated that it could be synthesized *de novo* in the body [1]. In more recent years, it has been shown that despite large repositories of glutamine, stores may become depleted particularly in the course of a catabolic insult such as injury, infection, or chronic glucocorticoid treatment [2]. This appears especially important for susceptible individuals, such as the aged, postoperative patients, individuals with cancer and very low birthweight (VLBW) infants, who are highly stressed, have low energy and protein reserves, and may be treated with catabolic glucocorticoids. Despite debate about its therapeutic efficacy in humans [3], considerable evidence supports important metabolic and nutritional roles for glutamine supplementation. Recent studies in critically ill low birthweight infants, children, adults, and athletes are not only focusing on efficacy, but are also exploring mechanisms of glutamine action. The current paper will discuss recent studies of how glutamine affects protein metabolism under certain stressful conditions. It will explore mechanisms of its effects on intestinal mucosal integrity and how this relates to sepsis and systemic inflammation. We will also discuss nutrients that are closely related to glutamine such as glutamate, nucleotides, arginine, glucosamines, and ornithine alpha-ketoglutarate and provide opinions as to why they might be used as effective substitutes for glutamine.

Catabolic stress

Here three areas will be addressed. The first involves critically ill patients whose recovery depends on nutrients that will aid in healing and prevent complications such as hospital acquired sepsis. The second involves patients treated with pharmacologic doses of glucocorticoids, which induce catabolism. Finally, we will discuss strenuous exercise. Athletes often go to great lengths to improve performance, hasten recovery from a strenuous athletic event and prevent the problems associated with strenuous training and competition. Glutamine supplements are currently being examined in the field of sports medicine.

Critically ill patients

Of the several categories of critically ill patients who undergo catabolism, one of the most dramatic is the human VLBW infant. These infants have sparse energy reserves. Despite being highly stressed and 'pro-

grammed' to undergo very rapid growth, they frequently receive little if any enteral nutrition in the first weeks of life and do not receive glutamine from their parenteral nutrition solutions. Because this is such a rapid period of brain growth, nutritional deficiencies during this time could have life-long consequences.

During fetal life, about 19% of total nitrogen accretion is derived from maternal and placental glutamine [4]. The delivery of glutamine from the maternal-placental circulation is interrupted with preterm birth. The infant also frequently receives dexamethasone, a highly catabolic glucocorticoid, in order to hasten weaning from mechanical ventilation. Two studies of glutamine supplementation in VLBW infants have shown that it is safe at the doses used in these studies and have suggested benefits [5,6]. Currently at least three large multicenter trials testing the efficiency of glutamine supplementation in preterm infants are underway.

Other studies are beginning to provide insights gained about the mechanisms of benefits of supplemental glutamine in VLBW and surgical neonates. One effect of glutamine supplementation appears to be that it results in a decrease in endogenous protein breakdown. In one study employing leucine-stable isotope kinetics, intravenous glutamine supplementation in VLBW infants resulted in lower rates of leucine release from muscle breakdown and leucine oxidation and a trend toward a lower rate of non-oxidative leucine disposal, an indicator of protein synthesis, and a trend toward improved protein balance [7]. The authors concluded that although glutamine failed to enhance the rate of protein synthesis, it appears to have a protein-sparing effect [7]. In another study of surgical neonates, parenteral glutamine supplementation reduced whole body protein breakdown by 15% [8].

Studies in children with severe burns assessed the peripheral glutamine kinetic response [9]. A quantification of peripheral glutamine kinetics using glutamine stable isotopes demonstrated significant decreases in plasma glutamine, along with a decreased rate of glutamine turnover, but no change in the net efflux of glutamine in burned children. The decrease in plasma glutamine concentration observed in these burned patients probably results from a deficit in peripheral glutamine release, principally from skeletal muscle, in conjunction with an increased central consumption. This supports the notion that exogenous glutamine supplementation in pediatric patients with severe burns may be needed because of this inadequate skeletal muscle response.

Precursors of glutamine are also being investigated to determine whether they can improve the status of

critically ill patients. This is an issue because glutamine has a low solubility and heat instability that releases toxic products, such as pyroglutamic acid and ammonia during heat sterilization [10]. Supplementation of arginine and glutamate, two precursors of glutamine synthesis, were compared in a group of adult surgical patients to an isonitrogenous, isocaloric control group containing supplemental lipids and glucose [11]. Outcomes included plasma amino acids, urinary excretion of 3-methylhistidine, and nitrogen balance. Despite an increase in glutamine concentration during the perfusion in the supplemented group, the plasma levels remained relatively stable. The urinary excretion of 3-methylhistidine, a measure of muscle myofibrillar catabolism, was decreased in the supplemented group. The nitrogen balance was also increased in the supplemented group. The authors suggest that this solution containing the glutamine precursors is doubly attractive because it provides arginine and generates glutamine through a channeled pathway and may be more easy to use than glutamine.

Pharmacologic glucocorticoids

It is established that the administration of dexamethasone, a synthetic glucocorticoid, initiates catabolism [12]. This response includes increased degradation and decreased synthesis of protein in several tissues [13]. The gastrointestinal tract is particularly susceptible [14,15]. The possibility of glutamine reversing the effects of catabolism is an exciting area of study. Previous studies demonstrated that alanyl-glutamine given to rats reversed hydrocortisone-induced catabolism [16–18]. However, more recent studies of glutamine supplementation on dexamethasone-induced catabolism have been mixed.

In a study designed to examine the benefits of glutamine supplementation during experimentally induced state of hypercatabolism in dogs, glutamine supplementation failed to attenuate protein wasting. In this model dogs were both protein restricted and treated with dexamethasone. This treatment produced a marked increase in proteolysis, increased leucine oxidation, but no change in protein synthesis [19]. A 7-h infusion of glutamine in these dogs failed to attenuate protein wasting despite a 40% increase in plasma glutamine. Thus, this relatively short period of glutamine supplementation did not result in beneficial effects.

In a study of dexamethasone administration to rats, glutamine was administered either as free glutamine or by providing a glutamine-rich protein source (carob protein) [20]. Dexamethasone treatment lowered weight gain, muscle glutamine, and muscle and jejunal protein synthetic rate. Protein synthesis was measured using ¹³C-phenylalanine enrichment in muscle and

plasma and tissue amino acids. Muscle protein synthesis was increased from 15.9% to 24.2% only when glutamine was included in the diet as a free amino acid. Both forms of glutamine supplementation were equally effective in increasing protein synthesis in the jejunum (by 25%). The authors speculated that glutamine provided in dietary protein is extensively metabolized by the splanchnic tissues and does not influence peripheral glutamine status to the same extent as glutamine provided in a free amino acid form.

Strenuous exercise

Prolonged exercise is associated with a fall in the plasma concentration of glutamine [21] and it has been suggested that this may be partly responsible for the immunosuppression seen with over-training. Provision of glutamine supplements may be beneficial by preventing the impairment of immune function following prolonged exercise. Castell *et al.* have shown that oral glutamine supplements consumed immediately after and 2 h after a marathon reduce the incidence of upper respiratory tract infections in the 7 days following the race [22]. However, several more recent studies investigating the effect of glutamine supplementation during exercise on specific indicators of positive immune function such as immunoglobulin A (IgA), have failed to find beneficial effects. One study examined the possibility of abolishing the exercise-induced (cycle ergometer) decrease in salivary IgA through glutamine supplementation during and after intense exercise. The exercise protocol induced a decrease in salivary IgA. The plasma concentration of glutamine was decreased by 15% 2 h-post exercise in the placebo group, whereas this decline was abolished in groups supplemented with glutamine or protein. However, neither protein nor glutamine supplements were able to abolish the decline in salivary IgA [23••]. These results are similar to those seen in marathon runners, which demonstrated that glutamine supplementation prevented a fall in plasma glutamine, but did not prevent a fall in immune modulators like mitogen-induced lymphocyte proliferation and lymphocyte-activated killer cell activity [24], nor did it prevent the fall in neutrophil function [25].

The effects of glutamine supplementation on human skeletal muscle energy metabolism have also recently been studied. Provision of glutamine 1 h before exercise increased tricarboxylic acid intermediate pool expansion after 10 min of moderate-intensity exercise, but did not reduce muscle phosphocreatine utilization or muscle lactate accumulation. This suggests that, at the onset of exercise, energy production is not limited by tricarboxylic acid intermediate pool size but by some other factor, possibly muscle oxygen availability or delivery of acetyl groups to the tricarboxylic acid cycle [26••].

The cellular mechanisms of these effects remains poorly understood and are a fertile area of investigation. New tools that are being developed to examine protein synthesis via signaling molecules, transcription, and translation pathways should provide clues about glutamine-mediated amelioration of catabolism. These may also help us learn specific mechanisms about how glutamine improves immune function during intensive exercise.

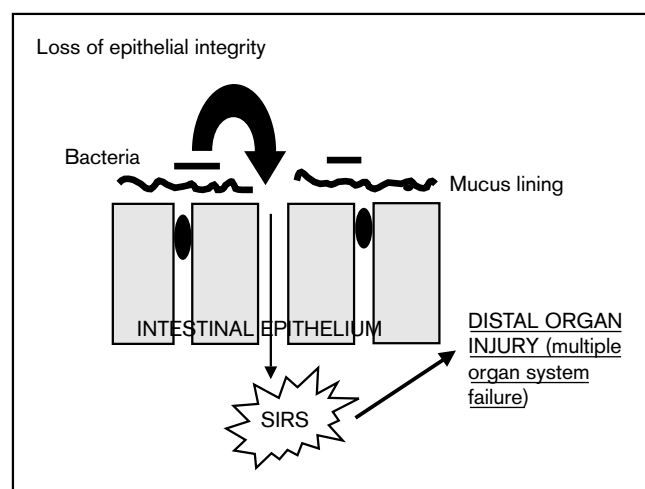
The gastrointestinal tract–intercellular junctions, mucosal integrity, translocation and systemic inflammation

Previous studies have demonstrated that glutamine supplementation in critically ill adults [27,28] and VLBW infants [5] decreases hospital-acquired sepsis. Two of these studies also suggested that systemic inflammation might also be decreased with glutamine supplementation [5,28]. These studies in humans, animals, and cell cultures laid the groundwork for the hypothesis that glutamine stabilizes the intestinal barrier by preventing translocation of bacteria or other toxins and ameliorating the subsequent induction of a systemic inflammatory response [29] (Fig. 1)

Gut-derived sepsis, glutamine and the inflammatory response syndrome

Despite a paucity of data from human studies, many forms of hospital-acquired sepsis and other infections are attributed to intestinal bacterial translocation, sometimes termed gut-derived sepsis [30•,31,32••]. This is thought to be especially prevalent in patients with extensive

Figure 1. Glutamine stabilizes the intestinal barrier



Loss of epithelial integrity secondary to the lack of glutamine may lead to a disrupted mucus lining and intercellular junctions, allowing bacteria and/or toxins to translocate to the subepithelium, thereby inciting the systemic inflammatory response syndrome (SIRS), which may cause distal organ damage.

surgery, burns, patients undergoing chemo- and radiotherapy, short-gut patients, and in VLBW infants. Assuming bacterial translocation does occur in humans, the intestine becomes a potential target for interventions that will stabilize its barrier function via promotion of intercellular junction integrity, provision of a protective mucus, and providing the ability for new cells to proliferate after injury. Glutamine has received considerable attention in this regard. Although much attention is placed on the role of glutamine as an energy substrate for the intestine, this may not be the primary mechanism underlying its protective role in the intestine. The amide nitrogen of glutamine appears to play an important role. It is a major component for the biosynthesis of nucleotides and amino sugars, the former playing a major role in proliferation and the latter in formation of the protective lining of the gastrointestinal tract. Glutamine (via glutamate) also appears to play an important role in the intestine via the production of glutathione [33*,34**], which may play a role in preventing oxidative damage to the gut.

The exciting possibility that supplementation of specific nutrients such as glutamine might reduce the systemic inflammatory response was initially raised by studies in adult trauma patients and in VLBW infants [5,28]. Adult trauma patients supplemented with enteral glutamine had lower concentrations of the soluble tumor necrosis receptors p55 and p75 in their plasma than controls. This was associated with a lower incidence of sepsis and pneumonia [28]. Studies in low birthweight infants showed that glutamine supplementation decreased the relative percentage of several activated T-cell subsets [5]. Although suggestive, these studies only provided circumstantial evidence of this response being mediated via a decrease in the translocation of intestinal microorganisms or their toxins.

Dysfunction of the intestinal barrier is thought to allow translocation of both endotoxin and whole bacterial organisms from the intestinal lumen into the immune system of the gut or the circulation. This allows access of these foreign materials to the cells that are involved in initiation of the systemic inflammatory response, which in turn plays an important role in the development of multiple system organ failure. Malnutrition *per se* compromises the gut barrier function. Controlled trials now support the concept of very early enteral nutrition (within 24 h after trauma) of providing enteral nutrition to decrease the rate of complications and infections [35].

The effect of exogenous glutamine on pro-inflammatory cytokine production by intestinal mucosa has been examined in humans. In one study nine fasted volunteers received either enteral glutamine or saline over 6 h. Duodenal biopsies were taken and cultured for

24 h with or without glutamine. Quantification of interleukin (IL)-6 and IL-8 in culture media by enzyme-linked immunosorbent assay and reverse transcription-polymerase chain reaction was performed. This study demonstrated that glutamine pre-treatment *in vivo* and *in vitro* significantly decreased production of pro-inflammatory cytokines by the human intestinal mucosa [36**].

In another study, the ability of parenteral glutamine to normalize respiratory and intestinal markers of immune function was measured. Mice were cannulated and randomly assigned to receive chow, total parenteral nutrition (TPN; glutamine-free) or an isonitrogenous, isocaloric TPN solution formulated by removing the appropriate amount of amino acids and replacing them with 2% glutamine for 5 days. TPN decreased intestinal and respiratory IgA in association with decreases in intestinal IL-4 and IL-10 compared with chow-fed animals. Glutamine, on the other hand, significantly improved respiratory and intestinal IgA levels, significantly improved IL-4 compared with TPN-treated animals and maintained IL-10 levels midway between chow-fed and TPN animals. Thus, glutamine enriched TPN preserved both extra-intestinal and intestinal IgA levels and had a normalizing effect on T helper type 2 (anti-inflammatory) IgA-stimulating cytokines [37*].

In further studies by the same group, the effects of glutamine supplementation on IL-4 and IL-10 cytokine mRNA expression within isolated gut associated lymphoid tissue lamina propria cells after lipopolysaccharide stimulation was evaluated [38*]. Both IL-4 and IL-10 mRNA expression decreased significantly in intravenous-TPN mice compared to chow or complex enteral diet feeding. Glutamine preserved IL-4 and IL-10 mRNA levels, which correlated with intestinal IgA levels. Glutamine supplementation also decreased TPN-induced intracellular adhesion molecule-1 (a molecule that promotes neutrophil attachment to the vascular endothelium and can cause injury) expression in the gut [39*]. Therefore, glutamine supplementation can promote anti-inflammatory effects by increasing T helper type 2 cytokines and decreasing the stimulus for neutrophil attachment to the intestinal vascular endothelium.

The energy substrate for neutrophils has long been thought to be glucose, but it has also been suggested that neutrophils can use glutamine during severe infection where glucose use is restricted. However, the effects of glutamine on neutrophil function remain to be clarified. Macrophages also ingest and kill bacteria within phagocytic vacuoles by using reactive oxygen intermediates. The effects of glutamine on phagocytosis and reactive oxygen intermediate production by monocytes

from 11 postoperative patients who had undergone major gastrointestinal surgery were examined *in vitro* [40•]. Incubation of blood from these patients at 1, 3 and 7 days postoperatively demonstrated that phagocytosis and reactive oxygen intermediates were greater at 2000 μM than at 0 μM glutamine at each time point. The authors concluded that supplemental glutamine enhances both phagocytosis and reactive oxygen intermediate production by neutrophils from postoperative patients *in vitro* [40•].

In a study designed to determine the effects of glutamine supplementation on septic mediators in the liver, a target organ for septic complications, hepatocytes were isolated from suckling rats and O_2 consumption was measured polarographically. The ability of 10 mM glutamine to reverse the inhibitory effects of H_2O_2 and *N*-nitroso-*N*-acetylpenicillamine (a nitric oxide donor) on O_2 consumption was studied. This study showed that glutamine and its dipeptides are unique in reversing the effects of septic mediators on neonatal rat liver oxidative metabolism. This effectiveness appears to be mediated via glutathione synthesis. The authors concluded that addition of glutamine, glutamine dipeptides or glutathione to TPN may be beneficial in preventing liver damage in neonatal sepsis. These studies support the hypothesis that glutamine may function to counteract the morbidity encountered after loss of intestinal epithelial integrity in critically ill individuals, as depicted in Fig. 1 [41].

Several closely related metabolites of glutamine are also demonstrating benefits. Ornithine alpha-ketoglutarate supplementation in rats that had bacterial translocation induced with lipopolysaccharide had reduced bacterial dissemination and metabolic changes, thus suggesting its potential in prevention of gut-derived sepsis in critically ill patients [42••]. A few studies have suggested that nucleotide supplementation will spare the need for glutamine [43,44]. However, whether other amino acids such as arginine, glutamate or closely related metabolites such as glucosamine will effectively and safely substitute for glutamine remains to be investigated.

Conclusion

In this review, we have discussed the possibility of reversing the effects of critical illness and athletic overtraining with the use of glutamine or closely related metabolites. Several studies were cited that suggest benefits, but their mechanisms remain poorly defined. For the future, new tools are being developed to investigate control of protein synthesis signaling pathways [45•]. These pathways appear to be important in glucocorticoid-induced catabolism [46•–48•] and could serve as targets for reversal with glutamine or related metabolites. Synergy between glutamine and growth factors in signaling processes is also likely to play an

important role [49•]. The protein degradative pathway induced by mediators such as cytokines and affected by the ubiquitin-proteasome pathways [50] remains to be explored in the context of supplementation with glutamine or its metabolites.

We have also discussed the intestine as a gatekeeper to infectious agents and other toxins and how glutamine and related metabolites might be aimed at preventing hospital acquired sepsis and systemic inflammatory conditions associated with breakdown of this barrier during stress. New studies demonstrating how nutrients interact with genes [51••] and elucidating microbial-intestinal relationships [52] will provide us with insights and exciting new directions for use of nutrients such as glutamine in preventing disease.

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