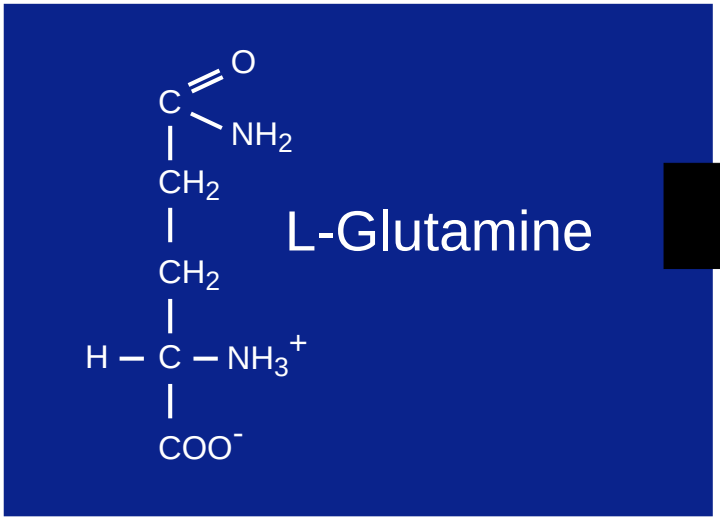

Monograph

L-Glutamine

Introduction

L-glutamine is the most prevalent amino acid in the bloodstream and because human cells readily synthesize it, is usually considered a non-essential amino acid. It is found in high concentration in skeletal muscle, lung, liver, brain, and stomach tissue. Skeletal muscle contains the greatest intracellular concentration of glutamine, comprising up to 60 percent of total body glutamine stores, and is considered the primary storage depot and exporter of glutamine to other tissues. Under certain pathological circumstances the body's tissues need more glutamine than the amount supplied by diet and biosynthesis. During catabolic stress intracellular glutamine levels can drop more than 50 percent, and it is under these circumstances that supplemental glutamine becomes necessary.[1] In times of metabolic stress, glutamine is released into circulation, where it is transported to the tissue in need. Intracellular skeletal muscle glutamine concentration is affected by various insults, including injury, sepsis, prolonged stress, starvation, and the use of glucocorticoids. Therefore, glutamine has been re-classified as a conditionally essential amino acid. Research demonstrates glutamine supplementation may be beneficial when added to total parenteral nutrition (TPN) for surgery, trauma, and cancer patients. In addition, evidence suggests it may provide benefit for certain gastrointestinal conditions, wound healing, critically ill neonates, HIV/AIDS patients, immune enhancement in endurance athletes, and prevention of complications associated with chemotherapy, radiation, and bone marrow transplant.[1,2]

Biochemistry

L-glutamine accounts for 30-35 percent of the amino acid nitrogen in the plasma. It contains two ammonia groups, one from its precursor, glutamate, and the other from free ammonia in the bloodstream. One of glutamine's roles is to protect the body from high levels of ammonia by acting as a "nitrogen shuttle." Thus, glutamine can act as a buffer, accepting, then releasing excess ammonia when needed to form other amino acids, amino sugars, nucleotides, and urea. This capacity to accept and donate nitrogen makes glutamine the major vehicle for nitrogen transfer among tissues. Glutamine is one of the three amino acids involved in glutathione synthesis. Glutathione, an important intracellular antioxidant and hepatic detoxifier, is comprised of glutamic acid, cysteine, and glycine.[1,2]

Clinical Indications

Gastrointestinal Disease

The gastrointestinal tract is by far the greatest user of glutamine in the body, as enterocytes in the intestinal epithelium use glutamine as their principal metabolic fuel. Most of the research on glutamine

and its connection to intestinal permeability has been conducted in conjunction with the use of TPN. Commercially available TPN solutions do not contain glutamine, which can result in atrophy of the mucosa and villi of the small intestine. Addition of glutamine to the TPN solution reverses mucosal atrophy associated with various gastrointestinal conditions.[3] Research has demonstrated glutamine-enriched TPN decreases villous atrophy, increases jejunal weight, and decreases intestinal permeability.[4,5] Trauma, infection, starvation, chemotherapy, and other stressors are all associated with a derangement of normal intestinal permeability. One potential consequence of increased intestinal permeability is microbial translocation. Bacteria, fungi, and their toxins may translocate across the mucosal barrier into the bloodstream and cause sepsis.[6] In numerous animal studies of experimentally induced intestinal hyperpermeability, the addition of glutamine or glutamine dipeptides (stable dipeptides of glutamine with alanine or glycine) to TPN improved gut barrier function, as well as immune activity in the gut.[7] Conditions characterized by increased intestinal permeability that might benefit from glutamine supplementation include food allergies and associated conditions, Crohn's disease, ulcerative colitis, and irritable bowel syndrome. A clinical study of ulcerative colitis patients demonstrated that feeding 30 g daily of glutamine-rich germinated barley foodstuff (GBF) for four weeks resulted in significant clinical and endoscopic improvement, independent of disease state. Disease exacerbation returned when GBF treatment was discontinued.[8] It has also been suggested that cabbage juice consumption may provide benefit to patients with gastric ulcers and gastritis, by virtue of its high glutamine content.

Wound Healing

The gastrointestinal tract has a large number of immune cells along its length — fibroblasts, lymphocytes, and macrophages. The ability of glutamine to nourish these immune cells may account for its positive impact on the gastrointestinal tract and immunity. Healing of surgical wounds, trauma injuries, and burns is accomplished in part by the actions of these immune cells. Their proper functioning is dependent on glutamine as a metabolic fuel for growth and proliferation. Therefore, a depletion of intracellular glutamine can slow growth of these cells, and ultimately prolong healing.[1] A small clinical study conducted recently in Poland demonstrated glutamine-supplemented TPN rapidly improved a number of immune parameters in malnourished surgical patients with sepsis.[9] Additional clinical trials also suggest that glutamine supplementation, as well as arginine and omega-3 fatty acids, may promote restoration of normal tissue function and intestinal permeability in post-operative patients.[10,11]

Infection and Immunity

Decreases in glutamine concentrations may result in an increased rate of infection in certain stressed patient populations. Critically ill newborn infants frequently display protein-calorie malnutrition due to the demands of sepsis and respiratory failure. A study of nine critically ill infants given a glutamine-supplemented enteral formula (0.3 g/kg glutamine daily) for five days demonstrated a significant decrease in infection and septic complications (20% in the glutamine group versus 75% in the control group).[12]

Endurance athletes also have decreased plasma glutamine concentrations after prolonged, strenuous exercise. This post-exercise glutamine depletion and associated immunosuppression may render the athlete more susceptible to infection. A group of 151 elite runners and rowers were given two drinks containing either glutamine or placebo immediately after, and two hours post-exercise, and then asked to complete questionnaires regarding the incidence of infection during the seven days post-exercise. The percentage of patients infection-free during the seven days was significantly higher in the glutamine group (81%) than in the placebo group (49%).[13]

HIV/AIDS

HIV infection appears to induce glutamine deficiency, resulting in muscle protein wasting, particularly in the AIDS stage of the infection.[14] Approximately 20 percent of AIDS patients also have abnormal intestinal permeability.[15] Clinical studies have demonstrated glutamine supplementation has significant benefit in these patients. A double-blind, placebo-controlled study was conducted with 68 HIV-infected patients having documented weight loss who were given a nutrient mixture containing 14 g L-glutamine twice daily for eight weeks. Body weight, lean body mass, and fat mass were measured throughout the eight-week period. At eight weeks, patients taking the glutamine mixture had gained 3.0 ± 0.5 kg of body weight compared to 0.37 ± 0.84 kg in the placebo group. The body weight gain in the glutamine group was primarily lean body mass while the placebo group lost lean body mass. An additional benefit in the supplemented group was improved immune status as evidenced by increased CD3 and CD8 cell counts, and decreased HIV viral load.[16] In another double-blind, placebo controlled study of AIDS patients with abnormal intestinal permeability, glutamine supplementation (8 g daily for 28 days) resulted in stabilization of intestinal permeability and enhanced intestinal absorption.[15]

Cancer and Bone Marrow Transplantation

Like enterocytes, rapidly growing tumors have high glutaminase activity, using glutamine as their main fuel source.[17] Consequently, glutamine supplementation has been controversial in cancer patients. *In vitro* research has found glutamine added to tumor cell cultures increased cellular growth.[18,19] On the other hand, *in vivo* animal studies have not found glutamine increases tumor growth. In fact, one animal study demonstrated that glutamine supplementation actually reduced tumor growth by 40 percent and stimulated natural killer cell activity.[20]

Research has also suggested that rapidly growing tumors can become "glutamine traps" and deplete muscle glutamine and glutathione,[17] although a clinical study of 32 colon cancer patients demonstrated colon tumors did not extract or "trap" more glutamine than intestinal tissue without tumor.[21]

Fluoruoracil/folinic acid chemotherapy for colorectal cancer often causes diarrhea. In a double-blind, placebo-controlled, randomized trial, glutamine (18 g daily) was given to 70 colorectal cancer patients five days prior to their first cycle of chemotherapy. Treatment continued for a total of 15 days and intestinal permeability and absorption were measured. When compared to baseline values, glutamine reduced changes in permeability and absorption induced by chemotherapy and may be of benefit in preventing chemotherapy-induced diarrhea.[22] A similar effect was seen in esophageal cancer patients undergoing radiation and chemotherapy, but the daily glutamine dose was higher at 30 grams daily.[23]

Studies of glutamine's benefit in parenteral nutrition during and after bone marrow transplant (BMT) have yielded mixed results. Three earlier studies demonstrated glutamine supplementation during BMT was of some benefit in minimizing side effects of high-dose cytotoxic chemotherapy, namely oropharyngeal mucositis, decreased lymphocyte counts, and hepatic veno-occlusive disease.[24-26] More recent studies, however, demonstrated glutamine-enriched TPN solutions had only limited benefit in BMT patients, in regard to number of days on TPN, length of hospital stay, degree of mucositis, white blood cell counts, infection, and diarrhea.[27,28]

Dosage and Toxicity

Numerous clinical trials in humans demonstrate that even at high doses, glutamine administration is without side effects and well tolerated, even during times of physiologic stress. Glutamine is administered orally in bulk powder or in encapsulated form. Dosages vary greatly depending on the clinical situation, but are in the range of two to four grams daily in divided doses for general wound healing and intestinal support. For critically ill adults, cancer, and HIV patients, the dosage is much

higher, ranging from 10-40 grams per day in divided doses. For these patients, the bulk powder form of glutamine eases administration of large doses.

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