Review

Intestinal glutamine metabolism and nutrition

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Introduction

Arteriovenous difference measurements in dogs in the late 1960's indicated a substantial net uptake of glutamine by the portal-drained viscera. Subsequent studies demonstrated that the mucosa of the small intestine plays the dominant role in this process.[1] More recently, glutamine has become of considerable interest to clinicians and nutritionists because intestinal glutamine metabolism may be impaired during critical illness, and that this impairment may be associated with altered intestinal function.[2]

The small intestine is the principal organ of glutamine uptake and metabolism in the body. The majority of studies that have measured in vivo glutamine utilization by the bowel have employed regional flux techniques using indwelling acutely or chronically placed arterial and portal venous catheters. Such studies quantitate the net exchange of substrate by the tissue, but do not provide information about the specific metabolic events or the specific cells that contribute to the total net rate of glutamine utilization. Thus, while regional flux studies are hampered by the disadvantage that only a net exchange measurement is calculated, they are also a valuable tool for the investigator interested in learning how organ utilization of a particular substrate changes in vivo during pathophysiologic states. Combined with the other methods that are commonly used to study intestinal glutamine transport and metabolism, in vivo measurements have substantially increased our knowledge of how intestinal glutamine utilization changes during disease states and how these changes are regulated. In this review the author summarizes the importance of glutamine for gut metabolism and discusses the techniques used to study glutamine utilization by the gut mucosa. In addition, the changes in intestinal glutamine metabolism that occur during several pathophysiologic states are reviewed and the use of glutamine-enriched nutrition as specific metabolic therapy for the gut is discussed.

Models used to study glutamine utilization by the intestine

Three fundamental factors (*Figure 1*) determine the uptake of glutamine by the gut mucosa: (a) the delivery of glutamine to the epithelial cell (delivery via the circulation = flow × arterial concentration; brush border delivery ∝ luminal glutamine concentration);

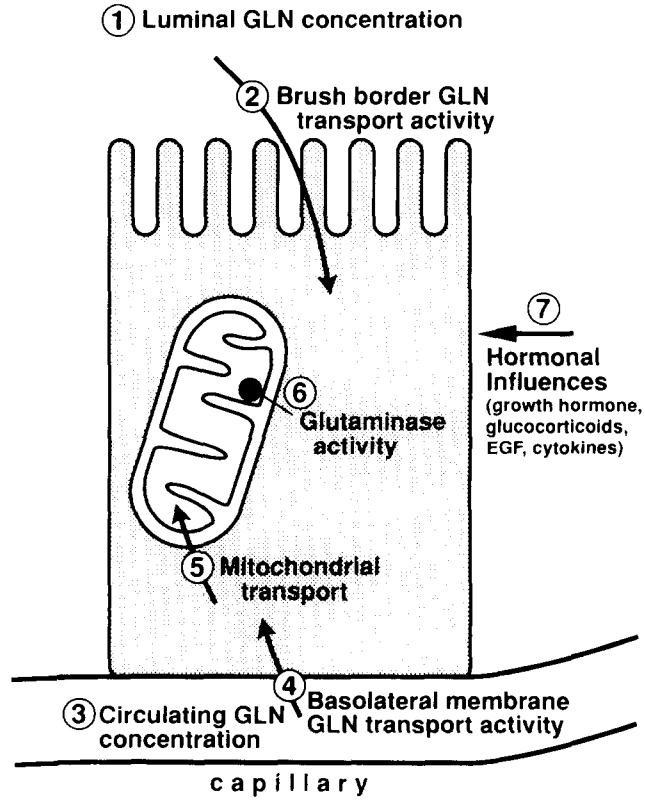

Figure 1 Several factors influence the uptake and release of glutamine by the small intestine epithelial cell. These include substrate delivery, membrane transport, and intracellular metabolism.

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(b) the intrinsic activity of the cell membrane carriers that transport glutamine into the mucosal cell; and (c) the rate of intracellular glutamine metabolism. The precise and relative roles of each of these factors in regulating intestinal glutamine availability varies depending on the physiologic state of the animal (i.e., postabsorptive versus postprandial, catabolic versus anabolic). Several in vivo and in vitro models have been used to study intestinal glutamine utilization. Each of these models has strengths and weaknesses (*Table 1*).

In vivo flux models

In vivo flux models quantitate the net exchange of a substrate across an organ by measuring bloodflow and by sampling the concentration of the substrate (usually with indwelling catheters) in the entering (usually arterial) and exiting (venous) blood. The arterial sample is usually obtained from a representative and easily accessible artery (often the radial in humans or the carotid artery in rats). In the case of glutamine, the net exchange (flux) by the gut in vivo is determined by multiplying portal bloodflow by the arterial-portal venous (A-PV) concentration difference. If the venous sampling catheter is placed in the portal vein, flux across the portal-drained viscera (small and large intestine, pancreas, and spleen) is determined, as opposed to catheter placement in the superior mesenteric vein, which allows quantitation of glutamine uptake by the small intestine and its supporting tissues (mesentery and mesenteric lymph nodes). The resultant exchange rate (often expressed in moles/body weight/time) represents the sum of the various flux rates by the individual cell populations that comprise the organ. Thus, flux rates are crude in that they do not provide information about the relative contributions of the individual cell populations in the tissue to the net overall exchange rate. For example, one cell population may release net amounts of an amino acid, while another may consume net amounts of it. The net flux measurement across the entire organ (uptake, release, or balance) represents a sum of these individual rates. Because bloodflow is always a positive number, the arteriovenous concentration difference (A-V diff) across the organ determines whether the organ is a net consumer (A-V diff is a positive number), a net releaser (A-V diff is a negative number), or is an organ of balance (A-V differ is not different from zero).

In the case of glutamine consumption by the intestinal tract, the bulk of the glutamine uptake occurs in the small intestinal epithelial cells. While investigators have generally assumed that a change in regional glutamine uptake indicates a change in mucosal glutamine uptake, these assumptions may not always be valid. For example, the diminished intestinal glutamine consumption that occurs after endotoxin treatment is due in part to a decrease in mucosal glutamine uptake, but glutamine uptake by lymphocytes in mesenteric lymph nodes is simultaneously increased.[3] These difficulties

Table 1 Some models used to measure glutamine metabolism by the small intestine

Method	Advantages	Disadvantages
In vivo flux model	1) quantitates net glutamine uptake by the small intestine using indwelling arterial and superior mesenteric vein catheters 2) measurements are made in vivo	1) does not partition the relative contributions of the various cells in the small intestine and its mesentery 2) is a net measurement, hence does not provide information about unidirectional transport rates or rates or intracellular metabolism
Regional perfusion model	1) measures glutamine uptake by the intact small bowel separate from other tissues 2) composition and flow of the perfusate can be controlled	1) does not partition the relative contributions of the various cells in the small intestine and its mesentery 2) is a net measurement, hence does not provide information about unidirectional transport rates or rates or intracellular metabolism
Cultured intestinal cells	1) investigator can study the regulation of glutamine transport or metabolism separate from paracrine or endocrine influences 2) inhibitors of transcription and translation can be utilized 3) substrate concentrations can be controlled	1) primary cultures have been unsuccessful necessitating the use of cell lines 2) measurements are made separate from other cells in the intestine 3) transport may be confounded by subsequent metabolism 4) basal metabolic activity may decay as cells remain in culture
Membrane vesicles	1) transport activity representative of that occurring in intact cells is preserved in vesicles 2) alterations in glutamine transport reflect the changes that occur in vivo 3) can discriminate the intrinsic level of membrane transport activity apart from other confounding influences (e.g., metabolism, substrate delivery, transtimulation effects)	1) examines only one factor that determines glutamine utilization 2) transport measurements are made in a subcellular membrane 3) transport changes may be due to direct or indirect effects

with net regional flux measurements should be kept in mind when flux values are reported. Moreover, they emphasize the importance of using complimentary models to study mucosal glutamine transport and metabolism (*Table 1*). Nevertheless, although flux studies do not provide detailed information about transport and metabolism in individual cells, they do provide important information about how organ handling of specific nutrients changes during feeding, starvation, critical illnesses, and other pathophysiologic states. Combined with data obtained from the other models described below, much can be learned about how amino acids are utilized in health and disease.

In vivo uptake of labeled glutamine

Accumulation of radiolabeled glutamine following an intracardiac injection is a technique that can be used to quantitate its uptake by the intestine. Like the in vivo flux measurements described above, the methodology does not specifically measure transport kinetics, but does provide important clues about relative uptake rates. For example, increased accumulation of the labeled amino acid within the tissue being studied is suggestive of an increase in carrier-mediated transport, but does not provide conclusive data. In the case of glutamine, localization studies have shown that the majority of glutamine consumed by the small intestine occurs in the mucosa, substaining the importance of the gut epithelium in glutamine metabolism.[1] The lack of selective non-metabolizable substrates for the major glutamine transporter in the intestinal basolateral membrane limits this technique for a detailed analysis of discrete transport systems.

Regional perfusion models

Isolated perfusion of the small intestine ex vivo or in continuity to maintain neural innervation is yet another commonly used technique to study the net uptake or release of glutamine by the gut. Again the assumption is safely made that the majority of glutamine uptake occurs in the mucosal cells. The gut and its vasculature may be removed from the body and studied under euthermic conditions or it may be left in situ. The organ is usually studied as an isolated preparation, separated from the rest of the circulation and perfused by an oxygenated solution that contains nutrients and other factors such as hormones. The concentration of substrate in the perfusate can be varied, and extraction rates can be calculated as a function of the concentration in the perfusate. From these data whole organ kinetic uptake parameters for the specific amino acid being studied can be determined. A weakness of this technique is that the relative contributions of the specific cell populations that constitute the whole organ are not partitioned out. The requirement of exogenous hormones to maintain tissue integrity may influence cellular metabolism.

Cultured cells

Employing primary cultures of intestinal epithelial cells to study glutamine transport and metabolism allows the investigator to study the regulation of amino acid utilization more directly, i.e., apart from other cells, separate from paracrine or endocrine influences, and independent of changes in the microcirculation. Unfortunately, these attempts have, in general, been unsuccessful. Several attempts have also been made to study cell suspensions, but long-term viability, differentiation status of the various cells that are harvested, and morphologic polarization of isolated enterocytes prevent direct comparison with absorptive events that occur in vivo. Consequently, investigators have used immortalized epithelial cell lines (e.g., Caco-2) to study glutamine uptake and metabolism by gut mucosal cells.[4] The use of transwell cell culture chambers is an attractive method of studying glutamine transport by monolayers of differentiated Caco-2 cells because it permits the formation of a tight epithelium of cells and provides access to both sides (basolateral and apical) of the cell monolayer. Inhibitors of transcription and translation can be utilized in cultured cells to learn whether alterations in transport activity require de novo RNA and/or protein synthesis. A disadvantage of the use of some cultured cells is that enzyme activity may change during the course of the incubation. Furthermore, some cells require the addition of certain hormones (e.g., insulin or glucocorticoids) to maintain optimal viability.

Membrane vesicles

Membrane vesicles are tiny spheres of the cell membrane that can be used to study amino acid transport.[5] They are easily prepared from fresh mucosal scrapings using differential and density gradient centrifugation and offer unique advantages over other approaches. Vesicles can be prepared from the brush border (brush border membrane vesicles, BBMVs) or from the basolateral membrane (BLMVs). Transport activity representative of that occurring in intact cells is adequately preserved in vesicles. Alterations in transport (i.e., following treatment with a hormone, nutrient, or cytokine) reflect the changes that occur in vivo and thus may be secondary to direct or indirect effects of mediators. By employing vesicles, it is possible to clearly discriminate the intrinsic level of membrane transport activity free from other confounding influences (e.g., metabolism, substrate delivery, transtimulation effects, etc.)

Intestinal glutamine metabolism during physiologic and pathophysiologic states

Metabolism of glutamine by the small intestine changes during a variety of disease states. Below, we summarize the changes that occur in catabolic diseases commonly observed in hospitalized patients, some of which may be amenable to nutritional intervention.

The basal postabsorptive state

The gastrointestinal tract is the principal organ of glutamine utilization with most of the uptake occurring in the small intestinal epithelial cells that line the villi. The same intestine of the rat, for example, extracts 20–30% of circulating glutamine,[1] compared to an extraction rate of about 15–20% for the portal-drained viscera.[6] Studies done in healthy patients during elective abdominal surgery have demonstrated that the human gastrointestinal tract extracts approximately 12–13% of circulating glutamine, resulting in a net uptake of glutamine by the human portal-drained viscera of about 1200 nmol/kg BW/min.[7] The enterocytes of the jejunum and ileum have high concentrations of the glutaminase enzyme, the principal of glutamine breakdown, which catalyzes the hydrolysis of glutamine to glutamate and ammonia. This activity of this enzyme is altered in vivo in different pathophysiologic states (*Table 2*).

Table 2 Evidence that glutamine is a conditionally essential amino acid for the gut

A. Concept: Glutamine is a conditionally essential amino acid for the gut if it is not required in the diet under normal circumstances, but is needed for intestinal structure and function during certain disease states.

B. Hypothesis: During certain disease states glutamine is an essential amino acid for the healing or maintenance of gut function and structure.

C. Effects of dietary glutamine absence:

Required effect/criteria	*Evidence/examples*
1. Fall in blood glutamine concentration	Animals treated with whole abdominal radiation (XRT) who receive glutamine-free diets after XRT develop glutamine depletion after radiation damage to the bowel.
2. Atrophy or dysfunction of the gut mucosa	Rats on GLN-free TPN develop bacterial translocation, villous atrophy, and a fall in lamina propria lymphocyte populations.
	Rats treated with radiation or chemotherapy develop a more severe mucosal injury when no glutamine is provided in the diet.

D. Effects of glutamine repletion:

Required effect/criteria	*Evidence/examples*
1. Correct glutamine depletion	Glutamine-enriched diets restore blood glutamine levels after whole abdominal radiation
2. Enhance cellular utilization	Provision of GLN-enriched TPN increases gut uptake of circulating glutamine; feeding a GLN-enriched oral diet to starved rats increases brush border transport.
3. Improvement in tissue morphology and function	GLN-enriched TPN increases villous height in rats and decreases the incidence of spontaneous bacterial translocation to the mesenteric lymph nodes
	Glutamine-enriched enteral diets improve recovery and enhance mucosal healing after chemotherapy or radiation
4. Improvement in protein economy/improvement in outcome	Glutamine-enriched TPN improves nitrogen balance and decreases hospital stay in patients undergoing bone marrow transplantation

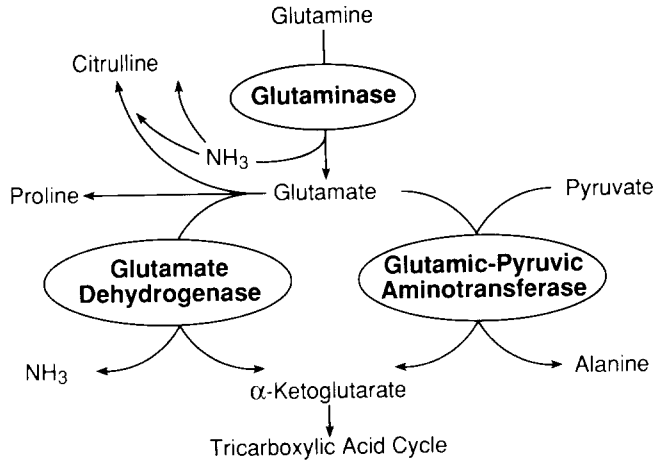

Figure 2 Pathways of glutamine metabolism in the small intestinal mucosa.

Using an isolated, perfused preparation of rat small intestine and an in vivo model of autoperfused rat jejunum, Windmueller studied the fate of glutamine carbons and nitrogens using tracer methodology.[1] Nearly two-thirds of the glutamine carbons were oxidized to carbon dioxide, accounting for 40% of the total CO_2 produced by the jejunum of postabsorptive rats. Glutamine nitrogen appeared in ammonia, alanine, citrulline, and proline. Similar end products were released into the portal circulation following intraluminal glutamine administration. Thus, glutamine is similarly metabolized whether it enters the mucosal cells across the brush border from the lumen or across the basolateral membrane from the arterial blood (*Figure 2*). Glutamine is taken up by the cells of the intestine at a rate that equals that of glucose uptake, and it is even more important than glucose as an oxidative fuel for enterocytes. The gut is well suited to metabolize glutamine because the ammonia produced readily diffuses into the portal blood and is extracted by the liver before reaching the systemic circulation. Functionally, glutamine metabolism by the small intestine (a) provides a major source for the gut, (b) provides amide nitrogen that may support nucleotide biosynthesis, and (c) processes nitrogen and carbon from other tissues for further metabolism in the liver and kidney.

The brush border of the intestinal epithelium also possesses discrete glutamine transporters that function to take up glutamine from the diet. The primary glutamine transporter in the intestinal brush border may be unique to the intestine and has recently been named

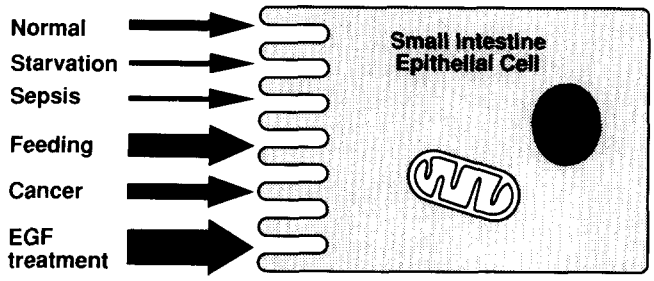

Figure 3 Effects of different physiologic and pathophysiologic states on brush border glutamine transport. EGF, epidermal growth factor.

System B[8] (formerly named system NBB), which has been found in the brush border of the human Caco-2 intestinal epithelial cell line[4] and in human small intestine.[9] System B is sodium-dependent, transports most dipolar amino acids and, in response to increased availability of glutamine in the diet, there appears to be specific upregulation of the System B transporter. The transport of glutamine across the basolateral membrane is also mediated primarily by a sodium-dependent pathway.

Starvation and feeding

Short-term starvation in the dog is associated with significant adaptations in glutamine metabolism by the gut that occur despite no significant changes in the arterial glutamine concentration.[10] Glutamine uptake by the intestinal tract increases, while the liver switches from uptake to release such that the overall effect is one of glutamine balance across the splanchnic viscera. Unlike the postabsorptive state in which transamination of glutamine-derived glutamate to yield alanine is a major reaction, there appears to be a coupling of glutamine metabolism to deamination, catalyzed by the glutamate dehydrogenase complex. This adaptive switch in gut metabolism of glutamine to yield increased amounts of ammonia plays a key role in modulating hepatic glutamine metabolism. The increase in the portal ammonia load, in conjunction with a change in the redox potential of the hepatocytes, results in a preferential increase in the activity of perivenous glutamine synthetase. As a consequence, the liver shifts to release increased amounts of glutamine that supports renal ammoniagenesis. With time, the gut may adapt to using increased amounts of ketones as a primary fuel source, which may also spare glutamine for the kidneys during starvation-induced ketosis/acidosis.

Nutrient delivery has been shown to influence transport activity in the gut mucosa. Selective starvation of the bowel allows the investigator to examine gut glutamine metabolism in the absence of total body starvation. Long-term exclusion of a segment of jejunum from the flow of luminal nutrients results in a significant decrease in the activities of several brush border amino acid transporters as well as the glucose carrier.[11] In this model, luminal transport of glutamine was studied in greatest depth because of its importance in small intestinal metabolism. Excluding the limb of jejunum from the remainder of the small intestine did not change the affinity of the Na^+-dependent cotransporter for glutamine (the apparent K_m was unchanged) but the V_{max} decreased to one-half the incontinuity value. This most likely represents fewer copies of transporters expressed on the brush border membrane as a consequence of limb defunctionalization. On the other hand, feeding a diet rich in glutamine resulted in an increase in transport activity.[12] These responses are most likely adaptive and represent the basal, nonstimulated level of transport in the bowel that is not subjected to luminal substrate regulation and the stimulated level of transport that occurs in response to feeding *(Figure 3)*. Although the functional significance of this regulation is not entirely clear, evidence exists that the activity of brush border nutrient transporters is regulated, at least in part, by their respective substrates. Diamond et al.[13] studied the influence of diet on the adaptive regulation of intestinal nutrient transporters and they suggested that fluctuations in transport activity are based on trade-offs among factors such as cost of transporter synthesis and nutrient requirements. Their work indicated that this constitutive luminal transport activity can be upregulated by a factor of two by dietary substrate, but that this response is relatively slow (i.e., 1–3 days). Maintenance of a baseline level transporter activity in the excluded limb may be adaptive and appropriate if it diminishes the metabolic cost of synthesizing and maintaining the membrane transport protein. Unlike the differences in Na^+-dependent glutamine transport that occurred in the two jejunal segments, brush border functions that were unaffected by surgical exclusion included Na^+-independent glutamine transport via carriers and passive diffusion.

Surgical stress

Circulating concentrations of glutamine are diminished after operative stress despite an augmented release of glutamine by skeletal muscle.[14] These observations are consistent with an accelerated postoperative uptake of glutamine in other tissues. Studies in catheterized dogs have demonstrated that following the stress of a standard laparotomy, glutamine consumption by the intestinal tract in vivo is increased by 75%.[15] The augmented intestinal glutamine uptake appears to be unique to the postoperative period; it is not attributable to a decrease in food intake, and during recovery from operation intestinal glutamine uptake returns to normal utilization rates. Uptake of this amino acid is increased in the postoperative period despite a reduc-

Table 3 Mucosal glutaminase activity

Increases	Decreases
Glutamine feeding	Sepsis/Interleukin-1
Glucocorticoids	Starvation
Glucagon	Advanced cancer

tion in portal blood flow and a fall in arterial glutamine concentration, consistent with hormonal regulation.

The augmented intestinal glutamine metabolism that occurs after surgical stress appears to be mediated in part by the glucocorticoid hormones.[16] Following administration of dexamethasone, intestinal uptake of circulating glutamine increases more than two-fold. Simultaneously, the expression of the glutaminase enzyme increases, secondary to an increase in glutaminase mRNA and specific activity[17] *(Table 3)*. Glucocorticoid treatment causes the intestine to switch from an organ of glucose uptake to one of glucose release[16], an adaptation that may spare glucose for the wound or other tissues that are obligate glucose users. This ability of the intestine to spare or to produce glucose attests to the elaborate metabolic cooperation between the intestine and the liver during the accelerated gluconeogenesis that characterizes catabolic illnesses.

Sepsis

In marked contrast to surgical stress, the ability of the intestinal tract to consume circulating and luminal glutamine appears to be markedly impaired during sepsis and endotoxemia.[7,18] Studies in patients with severe abdominal infection and in endotoxin-treated rats indicate that intestinal consumption of circulating glutamine is markedly diminished. The reduction in glutamine uptake from the bloodstream was associated with a fall in mucosal glutaminase activity and the development of bacterial translocation, alterations that may be mediated by the cytokine interleukin-1.[19] Further studies in jejunal and ileal brush border membrane vesicles from septic patients and endotoxemic rats indicate that luminal glutamine transport is also diminished by severe infection.[18] These alterations also appear to be cytokine mediated, at least in part, and suggest that intestinal glutamine metabolism is under different regulation during infection than after elective surgery, when cytokine levels in blood and tissues are low or undetectable. Studies in the human intestinal Caco-2 cell line indicated that a combination of cytokines and dexamethasone could diminish brush border glutamine transport.[4] Interferon-γ alone also decreased GLN transport by 30% by reducing carrier V_{max}. These data suggest that cytokines and glucocorticoids may work independently and synergistically in regulating Na^+-dependent brush border glutamine transport in human intestinal cells.

Cancer

Intestinal glutamine transport and metabolism change with progressive neoplastic growth. The majority of the studies have been done in rats implanted with a fast-growing sarcoma. Intestinal glutamine extraction from the bloodstream falls as the tumor grows and the tumor eventually becomes the principal tissue of glutamine consumption.[20] This fall in uptake is associated with a marked fall in mucosal glutaminase activity, an alteration that is at least partially selective because the activities of several other mucosal enzymes are preserved.[21] The decrease in gut glutaminase was due to a reduction in enzyme synthesis rather than a change in enzyme-substrate affinity. It thus appears that one mechanism by which fast growing tumors that have an absolute requirement for glutamine may diminish gut glutamine utilization is by decreasing glutaminase biosynthesis. Interestingly, the brush border membrane transporter adapts to this decreased utilization of circulating glutamine by increasing its activity nearly two-fold.[22] The affinity of the carrier was unchanged by the tumor, but the number of transporters was increased by 70% in the rats with tumors. This adaptive response may help provide glutamine to the mucosal cells at a time when gut uptake of glutamine from the bloodstream is diminished.

The role of glutamine in gut nutrition

Because glutamine is classified as a nutritionally dispensable amino acid, it has not been considered necessary to include glutamine in nutritional formulas. It has been eliminated from TPN (total parenteral nutrition) solutions because of its relative instability and short shelf-life compared to other amino acids. Glutamine is present in most oral and enteral diets at the relatively low levels characteristic of its concentration in most animal and plant proteins (about 3–10% of total amino acids).[23] However, several studies from different laboratories indicate that glutamine may be a conditionally essential amino acid for the intestine during critical illness, particularly as it relates to supporting the metabolic requirements of the intestinal mucosa.

Why should the gut exhibit high rates of glutamine utilization?

It remains unclear exactly why replicating cells such as intestinal epithelial cells should have such high rates of glutamine uptake and metabolism. Clearly, such cells require glutamine for energy, but characteristic of their metabolism is that only a small portion of the glutamine consumed is actually fully oxidized. Newsholme[24] has pointed out that the quantitatively important pathway of glutamine metabolism by replicating cells is the conversion of alpha-ketoglutarate to oxaloacetate, which is subsequently converted to pyruvate. Very little of the pyruvate that is produced from glutamine carbons is further oxidized via the tricarboxylic acid cycle (TCA) cycle, despite the observation that proliferating cells have high activities of all TCA enzymes. Newsholme[24] suggests that this occurs because large quantities of ATP (produced from complete oxidation of glutamine) would, via feedback inhibition, decrease the rates of glutamine utilization. High rates of glutamine utilization provide optimal conditions for regulating the use of TCA cycle intermediates for the synthesis of purine and pyrimidine nucleotides during the cell cycle. A decrease in the rate of glutamine utilization could decrease the rate of cell proliferation. Thus, glutamine must be used at a

high rate by proliferating intestinal epithelia cells to insure that cell division and mucosal cell renewal can take place.

Impact of glutamine nutrition on the gut

Glutamine has been shown to be beneficial in several models of bowel injury, but it has been difficult to differentiate whether these benefits are due to improvements in enterocyte function or to enhancement of gut immune function. Both tissues (mucosal cells and immune cells) may be impacted favorably because glutamine is an important fuel and precursor for nucleotide biosynthesis in both of these rapidly replicating cell populations. Early phenomenologic studies reported interesting findings consistent with the importance of glutamine for the bowel. For example, a clinical study demonstrating beneficial effects of glutamine in the treatment of peptic ulcer disease was reported three decades ago.[25] Similar benefits were made in rats with aspirin-induced gastric erosions.[26]

Although some glutamine is present in most enteral feedings, it may be provided in insufficient quantities to adequately support mucosal growth under certain circumstances. Glutamine comprises 5–8% of dietary protein and hence most enteral feedings may provide as little as 2–3 grams of glutamine daily. In addition, current TPN solutions are glutamine free, which may explain in part the development of villous atrophy in patients receiving long-term TPN. Glutamine supplementation of TPN solutions increases jejunal mucosal weight and DNA content, and significantly decreases the villous atrophy associated with regular TPN.[27] Simultaneously, glutamine-enriched TPN stimulates gut glutaminase activity and gut glutamine consumption.[28] Salloum et al. demonstrated the ability of glutamine-supplemented elemental diets in stimulating intestinal mucosal growth following starvation.[29]

Standard TPN promotes bacterial translocation from the gut in rats,[30] a process that is reversed when glutamine is added to the feeding solution.[31] The decrease in translocation was associated with a normalization of S-IgA levels and a decrease in bacterial adherence to enterocytes, suggesting that glutamine-supplemented TPN may enhance gut immune function. Consistent with this observation are studies that demonstrate the important role of glutamine in supporting lymphocyte metabolism.[32] In the absence of glutamine, concanavalin-stimulated thymidine incorporation into DNA of cultured lymphocytes was very low.

Other studies have shown that provision of glutamine-supplemented nutritional support may be an important adjunct to the therapy of patients with an intestinal mucosal injury secondary to chemotherapy and radiation therapy. Fox et al. showed that the addition of glutamine to an elemental, enteral diet resulted in a significant reduction in the severity of methotrexate-induced enterocolitis, as reflected by improved morphometric parameters in the jejunum and colon.[33] In addition, they demonstrated that provision of glutamine reduced endotoxin transmigration from the gut lumen. The effects of supplemental glutamine on gut structure and function have also been examined in an abdominal radiation model. Jejunum from radiated rats receiving a glutamine diet demonstrated increased villous height and number and nearly twice the number of mitoses per crypt.[34] Similarly, administration of glutamine-enriched oral diets prior to abdominal radiation affords small bowel mucosal protection.[35] Additional studies have shown that the provision of oral glutamine following abdominal irradiation supports gut glutamine metabolism and decreases the morbidity and mortality associated with abdominal radiation.

The benefits of glutamine-enriched TPN on recovery after bone marrow transplantation have recently been reported in patients.[36,37] Patients received bone marrow transplantation and were randomized to receive standard TPN or glutamine-enriched TPN for 25–30 days. Provision of glutamine-enriched TPN improved nitrogen balance, decreased the infection rate, and prevented the extracellular fluid expansion that occurs after a catabolic stress. These changes were associated with a decrease in hospital stay by 1 week, which translated into a hospital savings of thousands of dollars. Animal studies have failed to demonstrate stimulation of tumor growth when glutamine-enriched TPN is provided.[38]

Studies to date have failed to demonstrate any toxicity associated with glutamine-supplemented nutrition.[39,40] Glutamine in solution undergoes hydrolysis in a relatively short period of time, but this process can be slowed considerably by adjusting the pH and temperature of the solution. Therefore, it appears that breakdown is negligible when the glutamine is added to the TPN mixture at the time the pharmacist prepares the final solution.

References

1 Windmueller, H.G. (1982). Glutamine utilization by the small intestine. *Adv. Enzymol.* **53**, 201–237

2 Souba, W.W., Klimberg, V.S., Plumley, D.A., et al. (1990). The role of glutamine in maintaining gut structure and function and supporting the metabolic response to injury and infection. *J. Surg. Res.* **48**, 383–391

3 Sarantos, P., Ockert, K., and Souba, W.W. Endotoxin stimulates lymphocyte glutaminase expression. *Arch. Surg.* (in press)

4 Souba, W.W. and Copeland, E.M. (1992). Cytokine modulation of sodium-dependent glutamine transport across the brush border membrane of monolayers of human intestinal Caco-2 cells. *Ann. Surg.* **215,** 536–545

5 Stevens, B.R., Wright, S.H., Hirayama, B.S., et al. (1982). Organic and inorganic solute transport in renal and intestinal membrane vesicles preserved in liquid nitrogen. *Membrane Biochem.* **4**, 271–281

6 Austgen, T.R., Chen, M.K., Flynn, T.C., Souba, W.W. (1991). The effects of endotoxin on the splanchnic metabolism of glutamine and related substrates. *J. Trauma* **31**, 742–752

7 Souba, W.W., Herskowitz, K., Klimberg, V.S., et al. (1990). The effects of sepsis and endotoxemia on gut glutamine metabolism. *Ann. Surg.* **211**, 543–551

8 Stevens, B.R. (in press). Amino acid transport in intestine. In *Mammalian Amino Acid Transport: Mechanisms and Control,* (D. Haussinger and M. Kilberg, eds.) Plenum, New York, NY, USA

9 Said, H.M., Van Voorhis, K., Ghishan, F.K., et al. (1989). Transport characteristics of glutamine in human intestinal brush-border membrane vesicles. *Am. J. Physiol.* **256**, G240–G245

10 Miller, B.M., Cersosimo, E., McRae, J., et al. Interorgan relationships of alanine and glutamine during fasting in the conscious dog. *J. Surg. Res.* **35**, 310–318

11 Salloum, R.M., Stevens, B.R., and Souba, W.W. (1991). Adaptive regulation of brush border amino acid transport in a chronic excluded jejunal limb. *Am. J. Physiol.* **261**, G22–G27

12 Salloum, R.M., Souba, W.W., Fernandez, A., et al. (1990). Dietary modulation of small intestinal glutamine transport in intestinal brush border membrane vesicles of rats. *J. Surg. Res.* **48**, 635–638

13 Diamond, J.M., and Karasov, W.H. (1987). Adaptive regulation of intestinal nutrient transporters. *Proc. Natl. Acad. Sci. USA* **84**, 2242–2245

14 Kapadia, C.R., Muhlbacher, F., Smith, R.J., et al. (1982). Alterations in glutamine metabolism in response to operative stress and food deprivation. *Surg. Forum* **33**, 19–21

15 Souba, W.W. and Wilmore, D.W. (1983). Postoperative alteration of arteriovenous exchange of amino acids across the gastrointestinal tract. *Surgery* **94**, 342-350

16 Souba, W.W., Smith, R.J., Wilmore, D.W. (1985). Effect of glucocorticoids on glutamine metabolism in visceral organs. *Metabolism* **34**, 450–456

17 Sarantos, P., Abouhamze, A., and Souba, W.W. (1992). Glucocorticoids regulate intestinal glutaminase expression. *Surgery* **112:** 278–283

18 Salloum, R.M., Copeland, E.M., III, and Souba, W.W. (1991). Brush border transport of glutamine and other substrates during sepsis and endotoxemia. *Ann. Surg.* **213**, 401–410

19 Austgen, T.R., Chen, M.K., Dudrick, P.S., Copeland, E.M., III, and Souba, W.W. (1992). Cytokine regulation of intestinal glutamine metabolism in vivo. *Am. J. Surg.* **163**, 174–180

20 Chen, M.K., Austgen, T.R., Klimberg, V.S., Copeland, E.M., and Souba, W.W. (1990). Tumor glutamine use exceeds intestinal glutamine use in cachectic tumor-bearing rats. *Surg. Forum* **41**, 12–14

21 Salloum, R.M., Sitren, H.S., Bland, K.I., Copeland, E.M., and Souba, W.W. (1991). Selective inhibition of intestinal glutaminase activity in the tumor-bearing rat. *Surg. Forum* **50**, 115–117

22 Salloum, R.M., Copeland, E.M., III, Bland, K.I., and Souba, W.W. (1991). Selective stimulation of brush border glutamine transport in the tumor-bearing rat. *J. Surg. Res.* **50**, 391–397

23 Lacey, J. and Wilmore, D.W. (1990). Is glutamine a conditionally essential amino acid? *Nutr. Rev.* **48**, 297–313

24 Newsholme, E.A., Crabtree, B., and Ardawi, M.S.M. (1985). The role of high rates of glycolysis and glutamine utilization in rapidly replicating cells. *Biosci. Rep.* **4**, 393–400

25 Shive, W., Snider, R.N., DuBilier, B., et al. (1957). Glutamine in treatment of peptic ulcer. *Texas State J. Med.* 840–843

26 Okabe, S., Honda, K., Takeuchi, K. (1975). Inhibitory effect of L-glutamine on gastric irritation and back diffusion of gastric acid in response to aspirin in the rat. *Digest. Dis.* **20**, 626

27 Hwang, T.L., O'Dwyer, S.T., Smith, R.J., et al. (1987). Preservation of small bowel mucosa using glutamine-enriched parenteral nutrition. *Surg. Forum* **38**, 56

28 Klimberg, V.S., Souba, W.W., Sitren, H., et al. (1989). Glutamine-enriched total parenteral nutrition supports gut metabolism. *Surg. Forum* **40**, 175–177

29 Salloum, R.M., Souba, W.W., Klimberg, V.S., Plumley, D.A., Dolson, D.J., Bland, K.I., Copeland, E.M., III. (1989). Glutamine is superior to glutamate in supporting gut metabolism, stimulating intestinal glutaminase activity and preventing bacterial translocation. *Surg. Forum* **40**, 6–8

30 Alverdy, J.C., Aoys, E., and Moss, G.S. (1988). Total parenteral nutrition promotes bacterial translocation from the gut. *Surgery* **104**, 185–190

31 Burke D., Alverdy J.C., Aoys E., et al. (1989). Glutamine supplemented TPN improves gut immune function. *Arch. Surg.* **124**, 1396–1399

32 Ardawi, M.S.M. and Newsholme, E.A. (1983). Glutamine metabolism in lymphocytes of the rat. *Biochem. J.* **212**, 835–842

33 Fox, A.D., Kripke, S.A., DePaula, J., et al. (1988). Effect of a glutamine supplemented enteral diet on methotrexate-induced enterocolitis. *J. Parent Ent. Nutr.* **12**, 325–331

34 Klimberg, V.S., Salloum, R.M., Kasper, M., et al. (1990). Oral glutamine accelerates healing of the small intestine and improves outcome following whole abdominal radiation. *Arch. Surg.* **125**, 1040–1045

35 Klimberg, V.S., Souba, W.W., Dolson, D.J., et al. (1990). Prophylactic glutamine protects the intestinal mucosa from radiation injury. *Cancer* **66**, 62–68

36 Scheltinga, M.R., Young, L.S., Benfell, K., et al. (1991). Glutamine-enriched intravenous feedings attenuate extracellular fluid expansion after standard stress. *Ann. Surg.* **214**, 385–395

37 Ziegler, T.R., Young, L.S., Benfell, K., et al. (1992). Clinical and metabolic efficacy of glutamine-supplemented parenteral nutrition after bone marrow transplantation: a randomized, double-blind, controlled study. *Ann. Int. Med.* **116:** 821–828

38 Austgen, T.R., Dudrick, P.S., Sitren, H.S., Bland, K.I., Copeland, E.M., III, and Souba W.W. (1992). The effects of glutamine-enriched total parenteral nutrition on tumor growth and host tissues. *Ann. Surg.* **215**, 107–113

39 Ziegler, T.R., Benfell, K., Smith, R.J., et al. (1990). Safety and metabolic effects of L-glutamine administration in humans. *J. Parent Ent. Nutr.* **14**, 137S–146S (suppl)

40 Lowe, D.L., Benfell K., Smith, R.J., et al. (1989). Glutamine-enriched total parenteral nutrition is safe in normal humans. *Surg. Forum* **40**, 9–11