Annu. Rev. Nutr. 1991. 11:285–308

GLUTAMINE: A Key Substrate for the Splanchnic Bed

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KEY WORDS: glutamine, splanchnic bed, gut, liver, nutrition

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INTRODUCTION

The amino acid glutamine has received considerable attention in the past decade, partly because of new knowledge demonstrating that its metabolism

0199-9885/91/0715-0285$02.00

changes markedly during critical illness and also because of studies suggesting that it may be a conditionally essential amino acid. Relatively little was known about glutamine until 1935 when Sir Hans Krebs first described the capacity for glutamine breakdown and synthesis in the mammalian kidney (44). Twenty years later, Dr. Harry Eagle reviewed the nutritional needs of mammalian cells in culture and emphasized the importance of glutamine as a nutrient (18). Its importance in nitrogen metabolism was more recently emphasized by Krebs who stated, "most amino acids have multiple functions, but glutamine appears to be the most versatile" (45).

Glutamine is found in relatively high concentrations in many mammalian cells where it serves as an ammonia scavenger and as a nitrogen donor for the biosynthesis of a number of important compounds such as nucleotides, amino sugars, and amino acids (76). In addition, it is the most abundant amino acid in the blood and has been viewed as a vehicle of nitrogen transport for ammoniagenesis in the kidney and for ureagenesis in the liver (78). However, arteriovenous difference measurements in dogs in the late 1960s indicated a substantial net uptake of glutamine by the portal-drained viscera (19). Subsequent studies demonstrated that the mucosa of the small intestine plays the dominant role in this phenomenon (28, 95–98). Additional studies have shown that the liver plays an equally important role in glutamine metabolism because of its ability to function either as a net glutamine consumer or as a net glutamine producer (9, 29). Glutamine aroused considerable interest among clinicians and nutritionists after studies demonstrated conclusively that interorgan glutamine metabolism changes markedly during critical illness (77, 81, 85) and that profound glutamine depletion may be a hallmark of catabolic diseases (5, 68, 91). More recent studies have enhanced our knowledge of the complexity of glutamine handling by the splanchnic bed since it is now clear that a portion of the glutamine consumed by the portal-drained viscera may occur in the gut lymphatic tissue and in the pancreas.

This overview summarizes our current knowledge on the role of glutamine as a splanchnic substrate. Emphasis is placed on how glutamine metabolism changes during different disease states. Metabolism of glutamine by the various tissues that compose the splanchnic bed is reviewed as well as data suggesting that glutamine may be a conditionally essential amino.

PHYSIOLOGIC IMPORTANCE AND BIOCHEMISTRY OF GLUTAMINE

Glutamine has numerous important and unique metabolic functions, and its physiologic significance has been recently reviewed (76). These properties suggest that glutamine plays an important role in health and during critical

illness. It is the most important vehicle for the transfer of nitrogen between organs and transports one third of circulating amino acid nitrogen (78). Its concentrations in whole blood and tissues decrease significantly during critical illness, leading to a state of marked glutamine depletion (5, 81, 91). In septic patients, intracellular glutamine stores in skeletal muscle may fall by 75%, and the extent of this fall correlates with survival (68). Glutamine is the most important substrate for renal ammoniagenesis (93), a regulator of protein synthesis (38, 51), an essential precursor for the synthesis of nucleotides (53), and an important substrate for hepatic ureagenesis and gluconeogenesis (67). Glutamine is avidly consumed by replicating cells such as gut mucosal cells (95) and by hepatocytes (39), both of which have the capacity to proliferate following liver damage. This observation appears to be of significance in patients with gastrointestinal dysfunction or ileus, which precludes enteral feeding (12, 35), and in patients with hepatocellular damage (6).

Two principal enzymes regulate intracellular glutamine metabolism (85). The enzyme glutaminase catalyzes the hydrolysis of glutamine to glutamate while glutamine synthetase catalyzes the synthesis of glutamine from glutamate and ammonia. Replicating cells, such as enterocytes, lymphocytes, endothelial cells, and tumor cells, tend to be avid glutamine consumers and in general have much greater amounts of glutaminase than glutamine synthetase. Skeletal muscle and lung, which synthesize and release net amounts of glutamine into the bloodstream, have substantial amounts of glutamine synthetase.

SPLANCHNIC GLUTAMINE METABOLISM IN THE BASAL (POSTABSORPTIVE) STATE

Intestinal Tract

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 (95–98). The small intestine of the rat, for example, extracts about 25% of circulating glutamine. The extraction of circulating glutamine is smaller in dogs and humans but is still substantial (33, 88). The gut mucosal cells have high glutaminase activity consistent with their avid rate of uptake and metabolism (65). This enzyme is subject to regulation by several factors (Table 1). Only recently have the characteristics of glutamine transport across the brush border been characterized using brush border membrane vesicles. Jejunal brush border transport of glutamine occurred predominantly via a Na^+-dependent pathway and to a lesser extent by a Na^+-independent process (11, 69). Transport of glutamine across the basolateral membrane is also pH and sodium dependent (25). Other recent studies suggest that the Na^+-

Table 1 Modulation of brush border glutamine transport and intracellular metabolism

Mucosal glutaminase		Brush border glutamine transport	
Increased activity	Decreased activity	Increased activity	Decreased activity
Oral glutamine	Starvation	Oral glutamine	Sepsis
i.v. glutamine	Endotoxin	i.v. glutamine	Starvation
Glucocorticoids	Interleukin-1	EGF	Glucocorticoids
Glucagon	Malignancy	Malignancy	Endotoxin

dependent carrier-mediated glutamine uptake in the brush border occurs via a pathway that resembles System N, based on the pH profile and inhibition studies (73).

Using an isolated, perfused preparation of rat small intestine as well as an in vivo model of autoperfused rat jejunum, Windmueller & Spaeth studied the fate of glutamine carbons and nitrogens using tracer methodology (95–98). Nearly two thirds of the glutamine carbons were oxidized to carbon dioxide, accounting for 40% of the total CO_2 produced by the jejenum of postabsorptive rats. Glutamine nitrogen appeared in ammonia, alanine, citrulline, and proline (Table 2). 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 1). Functionally, glutamine metabolism by the small intestine (*a*) provides a major energy 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. 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

Table 2 Metabolic fates of carbons and nitrogens of glutamine utilized by the rat jejunum[a]

Carbon product released into portal blood	Percent of glutamine carbons	Nitrogen product released into portal blood	Percent of glutamine nitrogens
CO_2	64	NH_4+	38
Lactate	11	Citrulline	28
Citrulline	6	Alanine	24
Proline	5	Proline	7
Others	14	Others	3

[a] Modified from Windmueller (95–98).

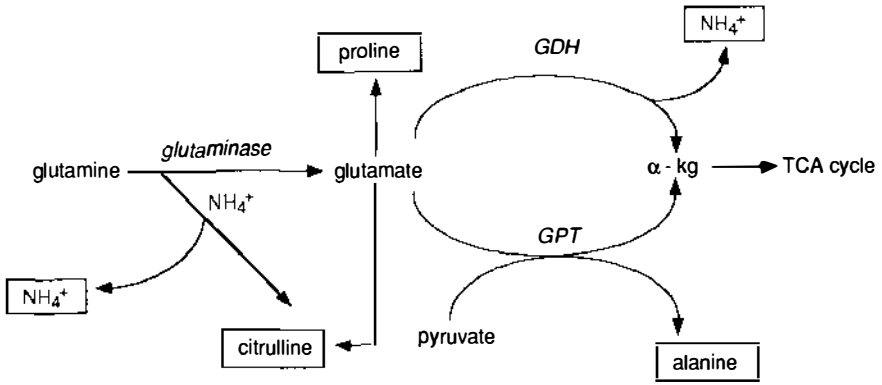

Figure 1 Pathways of glutamine metabolism in the small intestinal epithelial cell. Glutamine is metabolized similarly whether it enters the enterocyte from the lumen or from the bloodstream. Two thirds of the glutamine carbons are oxidized to carbon dioxide in the TCA cycle, while the glutamine nitrogens are released into the portal blood as ammonia, citrulline, alanine, and proline. The ammonia and alanine are extracted in large part by the liver; citrulline is used by the kidneys for arginine biosynthesis.

fuel for both enterocytes and colonocytes (95), although the colon prefers short-chain fatty acids as a primary fuel (66). 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. Portal ammonia removed by the liver is used predominantly for ureagenesis and glutamine synthesis. The liver uses alanine for gluconeogenesis; the alanine generated from glutamine in the intestine accounts for a variable portion of the total hepatic alanine consumed.

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 of body weight per min (33).

Pancreas

Glutamine is an important respiratory fuel for the exocrine and endocrine pancreas (13, 52, 60, 64). In cultured acinar cells and in the isolated perfused pancreas, glutamine is utilized to a much greater extent than any other amino acid. Intravenously administered radiolabeled glutamine is rapidly cleared from the circulation and its metabolites are detected in higher concentrations in the exocrine pancreas than in any other tissue (13). In isolated islet cell preparations, glutamine accounts for nearly one third of islet cell basal respiration (52). These studies suggest that glutamine may be an important fuel or nitrogen source for pancreatic growth and function. Glutamine also

appears to regulate pancreatic islet hormone release. Opara and colleagues (60) examined the direct effects of glutamine on insulin and glucagon release by isolated perfused islets of Langerhans. Their study indicated that glutamine suppressed insulin production but stimulated glucagon release under basal glucose conditions.

Lymphocytes/Macrophages

Although the relative contribution of the lymphatic tissue present in the gut to total gut glutamine utilization by the intestinal tract is unknown, it is important to address this issue since most data on gut glutamine uptake is derived from arterial-portal venous differences across the whole bowel. It has been assumed that most of the glutamine metabolism occurs in the gut mucosa, and although this assumption is supported by studies by Windmueller (95), the intestinal wall is also rich in lymphocytes, macrophages, and Peyer's patches. In addition, the bowel mesentery contains numerous lymph nodes. Ardawi (4) and Newsholme et al (55, 57) demonstrated that lymphocytes and macrophages have high activities of phosphate-dependent glutaminase and utilize significant amounts of glutamine. Newsholme et al (56) and Parry-Billings et al (62) also suggest that glutamine may be essential for lymphocyte proliferation in response to antigenic challenge both as a precursor for nucleotide biosynthesis and as a major energy source. Brand and colleagues (10) showed that glutamine consumption is significantly increased in proliferating lymphocytes.

Liver

The liver plays a central role in interorgan glutamine metabolism as evidenced by its ability to consume or release net amounts of glutamine, depending on prevailing metabolic pressures. It is unique in that it contains some hepatocytes that express glutaminase (periportal cells) and others that contain glutamine synthetase (perivenous cells) (29). This division of labor allows the liver to function as a regulatory site in which net uptake or release of glutamine can be modulated according to the global needs of the body. Although in vivo flux studies across the liver of the healthy dog and the rat indicate that the liver consumes a small amount of glutamine in the postabsorptive state (6, 87), disruptions in homeostasis such as those that occur during critical illness result in marked changes in hepatic glutamine metabolism that reflect the liver's attempt to adjust glutamine balance in extrahepatic tissues (6, 92).

In the intact liver acinus, urea synthesis occurs and glutaminase is found only in periportal hepatocytes while glutamine synthetase is located in perivenous cells (Figure 2). As described by Haussinger (29), this intercellular compartmentalization represents the sequence of a periportal low-affinity,

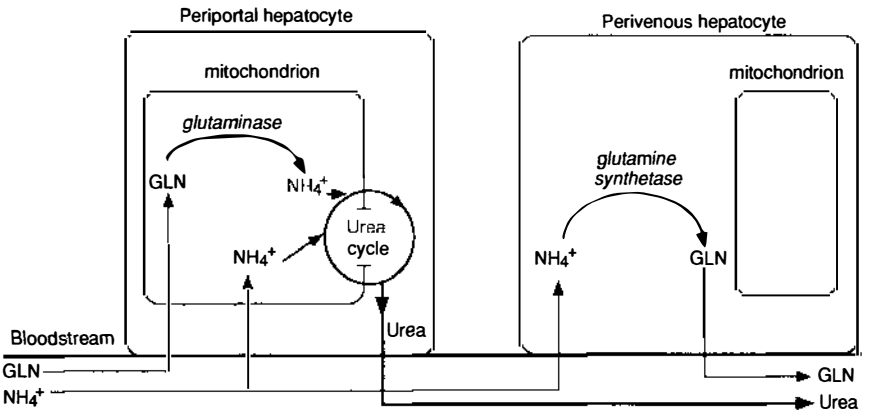

Figure 2 Hepatocyte heterogeneity in the liver. Periportal hepatocytes contain glutaminase and urea cycle enzymes; the perivenous cells express glutamine synthetase. In the periportal cells, glutaminase is activated by ammonia and can therefore control flux through the urea cycle. Glutamine synthetase acts as a downstream scavenger by converting ammonia to glutamine and preventing ammonia intoxication [modified from Haussinger (29)].

high-capacity system of ureagenesis and a perivenous high-affinity system for detoxification of ammonia that has escaped detoxification by urea synthesis. One of the principal regulatory advantages that arises from this structural and functional organization is that flux through the urea cycle can be varied without the danger of developing hyperammonemia, because glutamine synthesis in perivenous cells acts as an effective scavenger system. Modulation of periportal glutaminase activity by the portal ammonia level allows the activity of this enzyme to serve as an amplifier for ammonia inside the mitochondria, which becomes an important determinant of urea cycle flux.

In addition to ammonia, an important site that regulates glutamine metabolism in the hepatocyte is transport across the plasma membrane. Plasma membrane transport of glutamine occurs via the sodium-dependent System N, originally described by Kilberg et al (39). The specific carrier protein has not been identified or isolated, so investigators have relied on kinetic analyses to gain further insight into the regulation of the System N carrier. Despite the relatively high circulating glutamine concentration (600–800 μM), the carrier appears to operate at submaximal capacity. The sodium electrochemical gradient is able to maintain the cytoplasmic concentration of glutamine about 10 times higher than the circulating level, and it has been suggested that the rate-limiting step in the metabolism of glutamine by hepatocytes is delivery or transport rather than metabolism. This hypothesis is strengthened by the observation that intracellular glutamine levels fail to rise in the endotoxin-treated rat despite a tenfold increase in hepatic glutamine uptake (6). The

specific activity of glutaminase far exceeds the rate of uptake, thus indicating that metabolism is generally not rate-limiting.

SPLANCHNIC GLUTAMINE METABOLISM IN PATHOPHYSIOLOGIC STATES

Starvation

Short-term starvation (4 days) in the dog is associated with significant adaptations in glutamine metabolism by the gut and liver; these adaptations are not accompanied by significant changes in the arterial glutamine concentration (14, 15). 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. These adaptive changes in nitrogen metabolism indicate an orchestrated cooperative effort between the gut and liver. Unlike the postabsorptive state in which transamination of glutamine-derived glutamate to yield alanine is a major reaction, the coupling of glutamine metabolism to deamination, catalyzed by the glutamate dehydrogenase complex, is observed in four-day starvation. 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 over that of periportal glutaminase and urea enzymes (1). As a consequence, the liver shifts to release increased amounts of glutamine and less urea. Presumably, these elaborate adaptive changes help spare skeletal muscle from undergoing excessive catabolism in order to support the glutamine requirements of the kidneys and the gut.

Metabolic Acidosis

Metabolic acidosis alters both the magnitude and direction of interorgan glutamine flow. Because glutamine plays such a pivotal role in renal ammoniagenesis, the kidneys become the major organ of glutamine consumption in acidotic states. To meet these renal demands, the splanchnic bed, in particular the liver, undergoes marked changes in glutamine handling. Liver glutamine uptake reverses to net release, effectively canceling gut uptake, such that the overall effect is elimination of net splanchnic removal of glutamine (63, 92). This process essentially allows glutamine derived from skeletal muscle to supply the kidneys.

The fall in arterial glutamine that occurs in the acidotic rat and in chronically acidotic humans is regulatory and should not be interpreted as representing an imbalance between supply and demand. The diminished arterial glutamine level exerts its regulatory effect, somewhat like starvation, in part by mod-

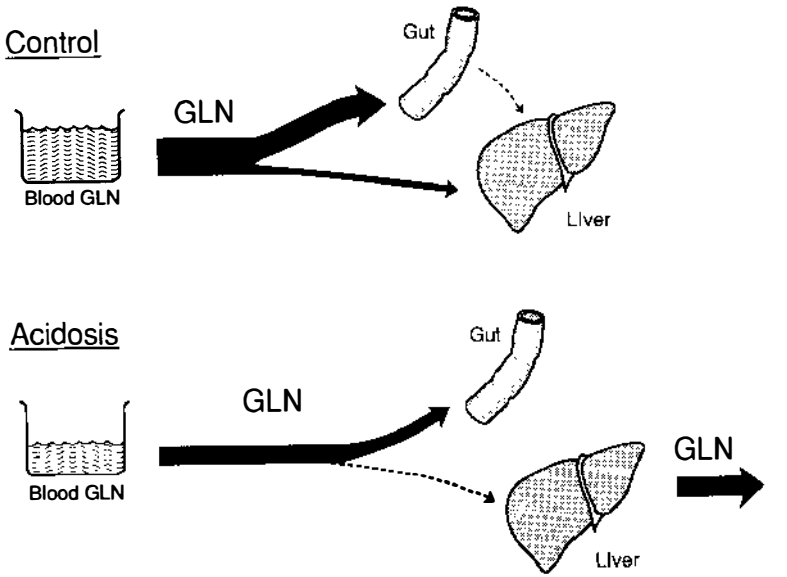

Figure 3 Changes in splanchnic glutamine flux during acidosis. A high portal ammonia load coupled with a relatively low portal glutamine level (such as seen during metabolic acidosis) decreases urea synthesis (and therefore hydrogen ion production) but increases glutamine synthesis and release, which can help support renal ammoniagenesis.

ulating intestinal glutamine metabolism. Consequently, the portal vein profile normally seen (relatively high glutamine and alanine and low ammonia) is skewed to one of low glutamine and alanine with relatively high ammonia (63). The former relationship favors ureagenesis while the latter favors hepatic glutamine synthesis. Therefore, the delivered substrate load appears to dictate net balance. Relatively more ammonia (from the gut) together with periportal glutamate are delivered to the perivenous hepatocytes, thus bypassing incorporation into urea. As emphasized by Haussinger (29), ammonia is diverted into the less energetically expensive high-affinity synthetase pathway. Thus, in metabolic acidosis, hepatic glutamine formation is enhanced at the expense of urea and glucose formation in order to support renal glutamine requirements (Figure 3). A second advantage of the reduced ureagenesis is reduced hydrogen ion production, which complements renal efforts to produce bicarbonate.

"Pure" Operative Stress

Despite the accelerated skeletal muscle release that occurs after operative stress (81), blood glutamine levels fall indicating increased glutamine utilization in other tissues. Studies in awake, chronically catheterized dogs have shown that the consumption of glutamine from the bloodstream nearly dou-

bles following elective abdominal surgery (87). The uptake of glutamine was augmented despite a significant fall in portal blood flow and in the circulating glutamine concentration. Within 96 hr of surgery, intestinal glutamine consumption had normalized. The accelerated gut glutamine consumption cannot be attributed to a fall in food intake, since starvation studies demonstrated that intestinal glutamine uptake is unaffected by food deprivation (54). Concomitant with the increase in the uptake of circulating glutamine was a fall in the consumption of blood glucose. Thus, following clean elective operative stress, the gastrointestinal tract appears to consume more glutamine but less glucose (Figure 4). The explanation for this shift in fuel utilization is unclear, but the gut mucosa may be consuming more glutamine at a time when the bowel lumen tends to be empty due to the anorexia associated with injury.

The observation that intestinal consumption of circulating glutamine is accelerated despite a fall in glutamine delivery suggests that gut glutamine uptake is hormonally regulated in the postoperative period. Characteristic of the postoperative state is an increase in adrenal glucocorticoid production and an increase in pancreatic glucagon output (94). In vivo data generated in chronically catheterized awake dogs indicates that both the glucocorticoid hormones and glucagon are important "stress" mediators of glutamine metabolism. Following dexamethasone treatment, intestinal glutamine uptake

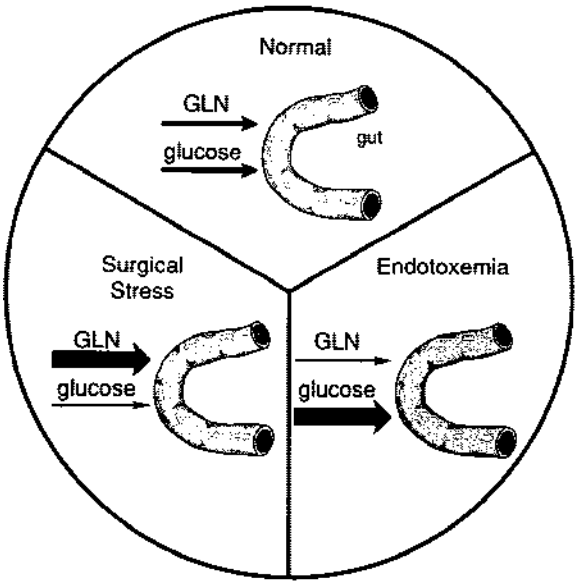

Figure 4 Relative rates of consumption of glutamine and glucose by the gut in normal conditions, following operative stress, and during endotoxemia.

more than doubles, primarily because of an increase in gut extraction of circulating glutamine rather than an increase in portal blood flow (84). Additional studies by Fox and colleagues (20) have shown that dexamethasone increases the specific activity of glutaminase in the small intestinal mucosa of rats. Therefore an increase in mucosal glutamine metabolism in the glucocorticoid-treated animal may account for a portion of the accelerated uptake of blood glutamine, although changes in basolateral membrane transport are also likely to occur. Glucocorticoids also diminish the net rate of glucose uptake by the gastrointestinal tract. In dexamethasone-treated dogs, the gut switched from an organ of glucose uptake to one of balance or slight release (88). This adaptation may provide glucose for obligate glucose users and indicates that the gut and liver cooperate metabolically to augment gluconeogenesis. Although net hepatic glutamine exchange did not significantly change following surgical stress or glucocorticoid treatment (84, 87), glutamate consumption by the liver was markedly increased when dexamethasone was given to healthy dogs. In addition, Gebhardt & Kleeman have demonstrated that dexamethasone increases glutamine uptake in primary hepotocyte cultures more than twofold (23). The purpose of this increased glutamine extraction is unclear, but glutamine is a potential substrate for hepatic gluconeogenesis, a regulator of hepatic protein and glycogen synthesis, and a precursor for the synthesis of nucleotides, proteins, and amino sugars.

The effects of glucocorticoids on luminal glutamine uptake have also been investigated. Although uptake of glutamine by the inverted jejunum of dexamethasone-treated rats is increased (77), this may be due to an increase in intracellular metabolism of glutamine (i.e. stimulation of glutaminase) rather than carrier mediated, since studies using brush border membrane vesicles demonstrate that glucocorticoids decrease luminal transport of glutamine (72). This down-regulation of luminal glutamine transport occurs at a time when uptake of circulating glutamine is increased by approximately twofold (84).

Glucagon also appears to be an important regulator of gut and liver glutamine metabolism. Geer and colleagues (24) studied the effects of a glucagon infusion in dogs with basal pancreatic secretion "clamped" by somatostatin. Studies were done in chronically catheterized dogs that were fasted for 18 to 96 hr. Administration of glucagon diminished circulating glutamine levels by 25%. The reduction in glutamine levels was due in part to a significant increase in hepatic glutamine uptake, which occurred independent of the fasting state. The intestinal response to hyperglucagonemia was not altered by four-day starvation, but in the overnight fasted animals, glucagon stimulated gut glutamine uptake threefold and was associated with a marked increase in portal ammonia production. These findings are consistent

with an important role for glucagon as a regulator of splanchnic glutamine metabolism in the postoperative state.

Sepsis/Endotoxemia

Although for the past 5–10 years the prevailing viewpoint has been that gut glutamine uptake is increased during catabolic states, recent studies indicate that this concept should be further qualified. 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. Studies in patients with severe abdominal infection and in endotoxin-treated rats indicate that intestinal consumption of circulating glutamine is markedly diminished (79). The reduction in glutamine uptake from the bloodstream was associated with a fall in mucosal glutaminase activity and the development of gram-negative bacteremia. Further studies in jejunal and ileal brush border

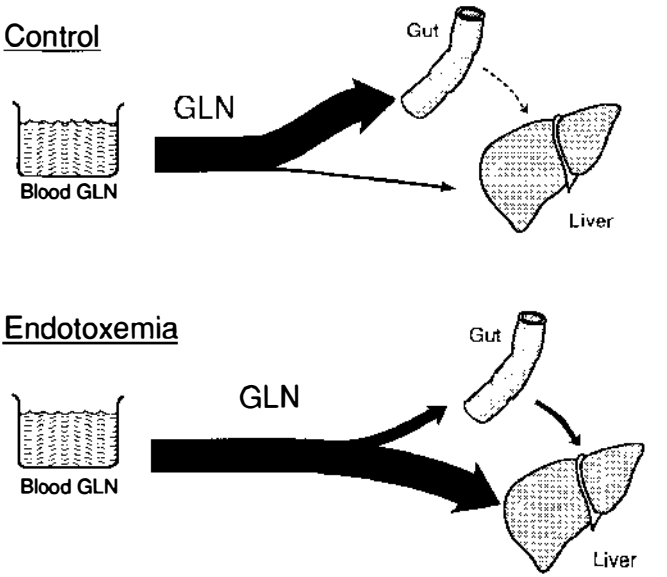

Figure 5 Glutamine utilization by the gut and liver during endotoxemia. Normally the gut is the major glutamine consumer, exceeding hepatic glutamine uptake by threefold. During endotoxemia, intestinal glutamine consumption falls and hepatic glutamine utilization increases tenfold, such that the liver becomes the major organ of glutamine uptake. The huge increase in hepatic glutamine uptake is due to an increase in the rates of hepatic glutamine delivery and intracellular metabolism rather than to a change in hepatocyte plasma membrane activity. The accelerated hepatic glutamine uptake appears to support nucleotide biosynthesis and glutathione biosynthesis as well as ureagenesis and gluconeogenesis.

membrane vesicles from septic patients and endotoxemic rats indicate that mucosal glutamine transport is also diminished by severe infection (W. W. Souba et al, unpublished data).

In contrast to operative stress, gut glucose uptake is increased during endotoxemia (6) (Figure 4). Simultaneously, hepatic glutamine uptake increased tenfold owing to an increase in hepatic blood flow and in glutamine extraction from the bloodstream (6) (Figure 5). Complementary studies have shown that the increase in hepatic glutamine uptake is due to an increase in the delivered hepatic load rather than to a change in System N transport activity (W. W. Souba et al, unpublished data). The increase in liver glutamine utilization that occurs during endotoxemia was associated with small increases in hepatic DNA levels and an increase in glutathione and urea release into the systemic circulation. The specific mediators responsible for these alterations are unclear, but interleukin-1 administration, like endotoxin treatment, decreases gut glutamine uptake and mucosal glutaminase activity and appears to lead to bacterial translocation (W. W. Souba et al, unpublished data).

Advanced Malignant Disease

Studies in tumor-bearing rats have enhanced our understanding of how interorgan glutamine flow changes with progressive neoplastic growth (16, 17, 82, 86). The majority of the studies have been done in rats with fast-growing tumors that are avid glutamine consumers. The changes in interorgan glutamine flow that occur appear to be designed in large part to maintain the blood glutamine concentration as the tumor grows and utilizes more glutamine (Figure 6). Many of the adaptive changes that occur in the various organs result in increases in net glutamine release or a reduction in glutamine utilization. With time the tumor becomes the principal glutamine consumer, exceeding glutamine uptake by the intestinal tract. Progressive glutamine depletion develops, particularly in skeletal muscle, which is associated with cachexia and anorexia.

Intestinal glutamine uptake from the bloodstream falls as the tumor grows, and eventually it becomes the principal consumer of glutamine (16). This fall in uptake is associated with a marked fall in mucosal glutaminase activity, the major enzyme of glutamine hydrolysis in the gut epithelium (82). Interestingly, the presence of the growing tumor does not alter mucosal protein content or the activities of five other jejunal mucosal enzymes (W. W. Souba, et al, unpublished data). The decrease in gut glutaminase was due to a reduction in enzyme synthesis rather than to a change in enzyme-substrate affinity. One mechanism by which fast-growing tumors with an absolute

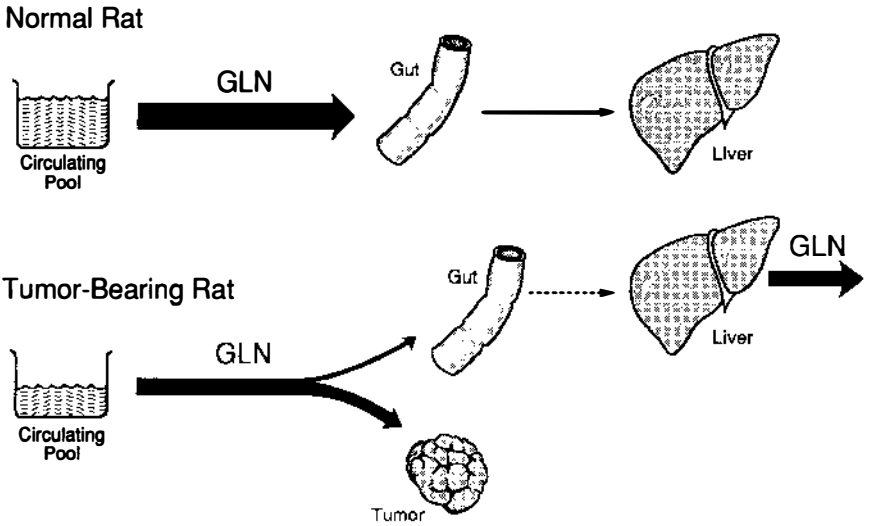

Figure 6 Splanchnic glutamine metabolism in advanced malignant disease. In tumor-bearing rats, intestinal glutamine uptake falls and the liver reverses to an organ of net glutamine release. With time the tumor becomes the major organ of glutamine uptake.

requirement for glutamine may diminish gut glutamine utilization is by decreasing glutaminase biosynthesis. This effect appears to be specific and distinct for glutaminase and may be designed to spare glutamine for the growing tumor. Interestingly, the brush border membrane transporter adapts to this decreased utilization of circulating glutamine by increasing its activity nearly twofold (70). 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 liver switches from an organ of slight glutamine uptake to one of glutamine release in the tumor-bearing rat, but this response appears to differ from that occurring during acidosis or starvation, since portal ammonia levels are unchanged (8, 17). The regulation of this change appears to be partially due to a fall in glutaminase activity and to a significant increase in hepatic glutamine levels (17). This increase in hepatic glutamine content coupled with a fall in blood glutamine resulted in a 68% increase in the intracellular/circulating concentration gradient, which effectively drove glutamine out of the hepatocyte and into the bloodstream. Simultaneously, a 30% increase was observed in the activity of the sodium-independent System L carrier, which transports glutamine out of hepatocytes (W. W. Souba et al, unpublished data).

GLUTAMINE NUTRITION AND REQUIREMENTS

Is Glutamine a Conditionally Essential Amino Acid?

In textbooks of biochemistry and nutrition, glutamine has been classified as a nonessential or nutritionally dispensable amino acid. Since this categorization implies that glutamine can be synthesized in adequate quantities from other amino acids and precursors, it has not been considered necessary to include glutamine in nutritional formulas. Glutamine has been eliminated from total parenteral nutrition (TPN) solutions because of its relative instability and short shelf-life compared to other amino acids. With few exceptions, glutamine is present in oral and enteral diets only at the relatively low levels characteristic of its concentration in most naturally occurring proteins (about 7% of total amino acids) (46). This view of glutamine as a dispensable nutrient underestimates its qualitative and quantitative importance in mammalian metabolic pathways. In critically ill patients, glutamine concentrations in the body not only are quite high but also are very labile. The decrease in glutamine concentrations is greater than for any other amino acid, correlates in general to the severity of the underlying insult, and is reversed only late in the course of recovery (81).

Several recent studies have demonstrated that glutamine may be a conditionally essential amino acid during critical illness, particularly as it relates to supporting the metabolic requirements of the intestinal mucosa. In general, these studies demonstrate that glutamine is not required during states of health but appears to be beneficial when glutamine depletion is severe and/or when the intestinal mucosa is damaged by insults such as starvation (74), chemotherapy (21, 37, 58), and radiation therapy (40, 41, 80). The potential therapeutic impact of glutamine-enriched diets may be greatest in patients who are critically ill and at high risk for developing gut and liver dysfunction and other complications.

Effects of Glutamine Nutrition on the Intestinal Tract

Glutamine plays an important role in the maintenance of intestinal metabolism, structure, and function. Shive et al (75) demonstrated its use in the treatment of peptic ulcers more than 30 years ago, and Okabe et al (59), demonstrated that glutamine protects against aspirin-induced gastric ulceration. Ten years ago, Baskerville et al (8) infused the enzyme glutaminase systemically and noted the development of diarrhea, mild villous atrophy, mucosal ulcerations, and intestinal necrosis in several animal species. Blood glutamine levels in these animals were nearly undetectable.

Although glutamine is present in some enteral feedings, it is probably provided in insufficient quantities to adequately support mucosal growth

under certain circumstances. Furthermore, current TPN solutions are glutamine free. A short-term infusion of glutamine in dogs results in a threefold increase in gut uptake of this amino acid (83). Interestingly, parenteral glutamine also stimulates brush border glutamine transport (71). Klimberg et al (43) showed that provision of glutamine-supplemented TPN to rats for one week upregulated gut glutaminase activity and stimulated gut glutamine utilization. Hwang et al (35) demonstrated that glutamine supplementation of TPN solutions resulted in an increase in jejunal mucosal weight and DNA content and significantly decreased the villous atrophy associated with standard intravenous feedings; further increases in mucosal DNA were noted when glutamine and epidermal growth factor were given synergistically (36). Additional studies by Grant (26) also demonstrated that glutamine supplementation of TPN solutions increased villous height and gut nitrogen content. Salloum et al (74) demonstrated the ability of glutamine-supplemented elemental diets to accelerate mucosal regeneration after starvation. Burke and associates (12) showed that TPN promotes bacterial translocation from the gut in rats, a phenomenon that was reversed when glutamine-enriched TPN was provided (12). This decrease in translocation was associated with a normalization of secretory-IgA levels and a decrease in bacterial adherence to enterocytes, suggesting that glutamine-supplemented TPN may enhance gut immune function.

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 and colleagues (20) 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. In addition, they demonstrated that provision of glutamine reduced endotoxin transmigration from the gut lumen. Similar benefits were reported by Jacobs and associates (37), who demonstrated that a glutamine-enriched intravenous diet accelerated healing of the gut mucosa in rats receiving 5-fluorouracil (5-FU). O'Dwyer et al (58) also showed that after receiving 5-FU, rats maintained on glutamine-enriched TPN demonstrated greater mean jejunal villous height and had increased mucosal DNA content. When glutamine-supplemented TPN was given before the administration of 5-FU, the effect on mucosal cellularity was even more marked and the rate of mortality was significantly lower than that of animals maintained on standard TPN.

Others studied the effects of supplemental glutamine on the incidence of bacterial translocation in an experimental radiationenteritis model (Table 3). Administration of glutamine-enriched oral diets prior to abdominal radiation

Table 3 Benefits of oral glutamine provided after whole abdominal radiation in rats[a]

Diet provided	Gut glutamine extraction (%)	Number of animals surviving for 8 days	Number of animals with culture-positive MLNs[b] (day 4)	Jejunal villous height (mm)	Jejunal villous number (#/cm bowel)
Control	12 ± 7	5/11	8/9	0.29 ± 0.03	79 ± 11
Glutamine	35 ± 8[c]	11/11[d]	2/10[c]	0.54 ± 0.05[d]	101 ± 4[d]

[a] Modified from Klimberg et al (40) and Souba et al (80).
[b] MLNs = mesenteric lymph nodes.
[c] $p < 0.05$ versus controls.
[d] $p < 0.01$ versus controls.

afforded small bowel mucosal protection (41), and postradiation glutamine-enriched oral diets decreased translocation of luminal bacteria (80), accelerated healing of the gut mucosa, and improved survival (40).

Effects of Glutamine Nutrition on Gut Immune Function

Burke and colleagues have studied the effects of glutamine-enriched total parenteral nutrition on gut immune function (12). When rats received parenteral feedings that were isonitrogenous and isocaloric but glutamine-enriched, significant improvements in gut immune function were observed. In contrast to the glutamine-supplemented group, animals fed standard glutamine-free total parenteral nutrition developed bacterial translocation to the mesenteric lymph nodes, marked increases in bacterial adherence to the cecal mucosa, and a 50% fall in the concentration of secretory IgA in the bile. Addition of glutamine to the diet resulted in biliary s-IgA levels and translocation rates similar to those observed in control chow-fed animals. Examination of the gut lamina propria cell population demonstrated that glutamine-supplemented parenteral nutrition prevented depletion of these IgA-producing cells (3).

Ardawi & Newsholme (4) and Newsholme & Parry-Billings (57) noted that incorporation of radiolabeled thymidine into conconavalin-A–stimulated lymphocytes requires the presence of glutamine in the cell culture media. Cell culture studies demonstrate that failure to supplement the culture media with glutamine impairs the ability of lymphocytes to respond to mitogenic stimulation (90). In terminally differentiated macrophages, glutamine may be required for the synthesis of mRNA in order to produce secretory proteins (such as tumor necrosis factor or interleukin-1) during immune challenge or phospholipid to support cell membrane activity during pinocytosis or phagocytosis (56).

The route of glutamine administration also may play an important role in modulating the intestinal immune system (3). Oral provision of glutamine is

preferential to intravenous administration. When animals were fed a glutamine-enriched diet orally, mortality from methotrexate was only 10%, compared to 90% in animals administered the identical solution parenterally. The authors acknowledge that this study raises as many questions as it answers, but the data lend further credence to the hypothesis that supplemental glutamine, under certain circumstances, may be an important amino acid for maintenance of gut lymphatic tissue and for the synthesis of secretory-IgA.

Effects of Glutamine Nutrition on the Pancreas

Helton et al demonstrated that glutamine also supports pancreatic growth and function during elemental enteral feeding (31). They also studied the effects of glutamine-enriched total parenteral nutrition on the exocrine pancreas in laboratory rats with and without a 60% small bowel resection (30). In both resected and unresected animals, addition of glutamine significantly increased pancreatic weight, DNA content, and protein content. Glutamine supplementation also increased total pancreatic trypsinogen and lipase content. These beneficial effects of glutamine resulted in pancreatic acinar hyperplasia rather than hypertrophy.

Effects of Glutamine Nutrition on the Liver

Li et al have studied the effects of glutamine-enriched total parenteral nutrition (TPN) on hepatic steatosis (48). Their work focused on the observation that the infusion of excess carbohydrate calories leads to hepatic steatosis in rats and is associated with an elevated portal insulin/glucagon molar ratio. Their studies indicated that addition of L-glutamine to hypertonic dextrose prevents the development of hepatic steatosis, probably by stimulating glucagon secretion and thus lowering the portal insulin/glucagon ratio and increasing hepatic lipid export (48). Helton and colleagues also demonstrated the beneficial effects of glutamine-enriched enteral elemental diets in attenuating the gain in liver weight and fat content that follow massive small bowel resection (31). These two studies are consistent with the work of Ostenson & Grebing (61) and Opara et al (60), who showed that pancreatic endocrine function can be regulated by exogenous glutamine.

HUMAN STUDIES ON GLUTAMINE METABOLISM AND NUTRITION

Two recent European studies suggest that glutamine-supplemented TPN is safe and potentially useful. Hammarqvist et al (27) studied patients following cholecystectomy and demonstrated the ability of glutamine-enriched TPN to improve nitrogen balance. Provision of approximately 20 g of free glutamine as a TPN additive significantly diminished the fall in muscle glutamine

content and intracellular ribosomal concentration that characterizes operative stress. Similar benefits were reported by Stehle et al (89), who administered the stable dipeptide L-alanyl-L-glutamine to postoperative patients and reported an improvement in nitrogen balance.

To date, the best-designed study for evaluating the use of glutamine-enriched TPN in the clinical setting is in progress at the Brigham and Women's Hospital in Boston. The patients being evaluated have undergone bone marrow transplantation and have therefore received intensive treatment with chemotherapy and whole body radiation. The patients have been randomized in a completely blinded fashion to receive standard TPN solutions or parenteral feedings that are glutamine-supplemented. Large doses of intravenous glutamine have been administered (20–40 gm per day). The preliminary data suggest that the provision of glutamine-enriched nutrition to this group of patients decreases the number of antibiotic days as well as hospital stay (D. W. Wilmore, personal communication).

Safety and Toxicity of Glutamine Feedings

Studies to date have failed to demonstrate any toxicity associated with glutamine-supplemented parenteral nutrition (50, 99). Concern exists about infusing glutamine because of its biochemical relationship to ammonia, but elevated circulating levels of ammonia have not been reported to date. Certainly, administration of glutamine to the patient with hepatic insufficiency may be contraindicated. Although tumors may be major glutamine consumers, studies to date indicate that glutamine-enriched nutrition does not stimulate tumor growth but may support muscle and gut glutamine metabolism (7, 42).

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. L-glutamine is relatively insoluble, and therefore it may be more practical to utilize much more stable and soluble glutamine dipeptides (2, 22, 49).

SUMMARY AND INTEGRATION

The splanchnic bed plays a pivotal role in regulating interorgan glutamine metabolism in normal and catabolic states. Glutamine appears to be essential for mucosal turnover and function. The liver occupies a key position in glutamine metabolism because of its capacity to consume or release net amounts of this amino acid, depending on prevailing metabolic pressures. Data from several laboratories indicate the important role that glutamine plays in maintaining pancreatic function and in supporting the immune system.

More recent studies indicate that the lungs also contribute to the maintenance of glutamine homeostasis (32, 34, 47, 81).

Further studies are required to determine whether glutamine-enriched diets should be used in the clinical setting and, if so, under what circumstances. Such trials should focus on significant end points such as patient morbidity and mortality as well as length of hospital stay.

ACKNOWLEDGMENTS

W. W. S. is supported by NIH grants CA 45327 and HL 44986, a grant from the Veterans Administration Merit Review Board, and a Career Development Award from the American Cancer Society.

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