Nonnutritive Effects of Glutamine¹⁻³

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Abstract
Glutamine is the most abundant free amino acid of the human body. Besides its role as a constituent of proteins and its importance in amino acid transamination, glutamine has regulatory capacity in immune and cell modulation. Glutamine deprivation reduces proliferation of lymphocytes, influences expression of surface activation markers on lymphocytes and monocytes, affects the production of cytokines, and stimulates apoptosis. Moreover, glutamine administration seems to have a positive effect on glucose metabolism in the state of insulin resistance. Glutamine influences a variety of different molecular pathways. Glutamine stimulates the formation of heat shock protein 70 in monocytes by enhancing the stability of mRNA, influences the redox potential of the cell by enhancing the formation of glutathione, induces cellular anabolic effects by increasing the cell volume, activates mitogen-activated protein kinases, and interacts with particular aminoacyl-transfer RNA synthetases in specific glutamine-sensing metabolism. Glutamine is applied under clinical conditions as an oral, parenteral, or enteral supplement either as the single amino acid or in the form of glutamine-containing dipeptides for preventing mucositis/stomatitis and for preventing glutamine-deficiency in critically ill patients. Because of the high turnover rate of glutamine, even high amounts of glutamine up to a daily administration of 30 g can be given without any important side effects. J. Nutr. 138: 2025S–2031S, 2008.

Introduction
Glutamine is a nonessential amino acid that is important as a constituent of proteins and as a central metabolite for amino acid transamination via α-ketoglutarate and glutamic acid. The organ-specific role of glutamine was documented by the work of Krebs (1) showing a different tissue distribution of the key enzymes of glutamine metabolism, namely glutaminase (mainly present in the liver) and glutamine synthetase (mainly present in skeletal muscle). Glutamine is 1 of the 20 proteinogenic amino acids and accounts for 5–6% of bound amino acids. In addition, glutamine is the most abundant amino acid in blood and the free amino acid pool of the body. It is synthesized from other amino acids (mainly the branched-chain amino acids and glutamate) in the cell cytoplasm.

The clinical interest in glutamine research started from 2 major findings. Firstly, glutamine is an important metabolite in ammonia metabolism and is crucial for ammonia detoxification.

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Secondly, the metabolic research group of Bergstrom et al. (2) showed that intracellular free glutamine of skeletal muscle is markedly reduced in the postaggression syndrome after operation, trauma, and inflammatory states. Our group reported that in nonsurviving septic patients, the amount of free glutamine in skeletal muscle is reduced by 90% and is a reliable prognostic marker (3). Moreover, in the septic state, the release of glutamine from skeletal muscle is highly stimulated and glutamine is taken up from the intestine and from blood cells. In this respect, glutamine seems to be an extremely important substrate, especially for proliferating cells. In 1959, Eagle (4) showed that glutamine is the most required substrate for the cultivation of cells under in vitro conditions and surpasses the demand of glutamate considerably. In other words, although glutamine is not considered an essential amino acid in humans, it is absolutely necessary for cultivating human cells. In the postprandial state, glutamine is the only amino acid released from skeletal muscle, which is a continuous producer of glutamine, even using essential amino acids for glutamine synthesis. Therefore, it is of interest to elucidate why glutamine seems to be so important for human metabolism.

Special emphasis should be given to the nonnutritive function of glutamine, as outlined in the title of this review. Principally, nutrition is seen as a means for maintaining nitrogen and energy balance. However, apart from their role in nitrogen and energy homeostasis, nutrients can also serve as immune and cell regulators. Glutamine is a potent immune stimulator, as demonstrated by different in vitro and in vivo experiments (5–7). With respect to the in vitro experiments, biochemical and immunological analyses under glutamine starvation have to be distinguished from those performed under glutamine overfeeding.
Glutamine: influence on immune cells

Lymphocytes. The importance of glutamine for the proliferation of lymphocytes was first demonstrated by the group of Newsholme studying the metabolism of glucose, glutamine, and long-chain fatty acids, which were thought to function as fuel for lymphocytes (8). Astonishingly, none of these 3 substrates was oxidized in great quantities via acetyl groups and the common Krebs cycle. Whereas glucose is converted almost totally into lactate, the fatty acids are metabolized into ketone bodies. Both lymphocytes and macrophages have high rates of glutamine utilization. Newsholme et al. (8) explained the high rates of glutaminolysis by the need of the cells to be provided with metabolites for the response to an immune challenge at any time. For lymphocytes, this need involves cell proliferation and for macrophages, it is the synthesis of mRNA for secretory proteins, peptide messengers, and protein receptors. Glutamine is a known precursor in purine and pyrimidine synthesis, which are needed rapidly when lymphocytes or macrophages are activated. Indeed, the proliferation of lymphocytes after activation with RNA or mitogenic antibodies directed against the cluster of differentiation (CD)3+ (marker for mature lymphocytes) component of the T-cell receptor is highly dependent on the glutamine concentration of the culture medium (9). A glutamine dependence of lymphocytes was also shown for the expression of the cell surface activation markers CD25 [interleukin (IL)-2 receptor α chain], CD45RO (leukocyte common antigen), and CD71 (transferring receptor), and also for the production of interferon γ and tumor necrosis factor-α (9). Glutamine depletion arrests the cells in 0 and 1 phase (10), reduces lymphokine-activated killer cell activity (11), and impairs cellular stress response (12). (Table 1).

Monocytes. Monocytes and macrophages belong to the mononuclear phagocyte system, are widely distributed in normal tissue and accumulated in inflamed tissue, and play a central role in both specific and nonspecific immunity against bacterial, viral, and fungal infection (13,14). Secretory products of monocytes and macrophages include several proteins and metabolites such as IL, granulocyte-macrophage colony-stimulating factor, platelet-activating factor, prostaglandins, substance P, leukotrienes, proteases, and complement components. A substantial decrease in the number of functional phagocytes has been reported in septic patients. Monocytes express major histocompatibility complex class II molecules which play a crucial role in antigen presentation to T-helper lymphocytes. Recent investigations have shown that changes in major histocompatibility complex class II expression on monocytes are indicative of developing infections after major surgery and that fatality and recovery rates among patients suffering from infection, sepsis, or active ulcerative colitis are linked to levels of human leucocyte antigen on DR locus (HLA-DR) expression.

In an in vitro study, we investigated whether blood monocyte marker expression and function from healthy donors are influenced by glutamine when lowering the glutamine concentration in culture medium from 2 mmol/L to 200 μmol/L (15). We showed that both the expression of various cell surface molecules and the function of monocytes are regulated by glutamine. The expression of HLA-DR, high affinity IgG Fc receptor (FcγRII/CD64), CD11b/CD18, and complement receptor 4 (CR4; CD11c/CD18) was downregulated by glutamine in a concentration-dependent manner. However, the expression of low affinity IgG Fc receptor (FcγRI/CD64), as well as CD14, the lipopolysaccharide-binding protein receptor on the monocytes, and CD71, the transferrin receptor, was not affected by lowering the glutamine concentrations.

Decreasing the concentration of glutamine from 2 mmol/L (commonly used for in vitro cell culture) to 50 μmol/L reduced HLA-DR expression by 58% (15). HLA-DR expression significantly decreased after lowering the glutamine concentration from 600 μmol/L (physiological range of glutamine in the plasma) to 200 μmol/L (plasma concentration found in critically ill patients). Interestingly, reduced HLA-DR expression was paralleled by the diminished capacity of monocytes to present tetanus toxoid antigen to T cells. Intracellular adhesion molecule-1/CD54 is involved in the costimulation of resting T-cells. The constitutive expression of this accessory molecule on monocytes was also significantly downregulated by low concentrations of glutamine.

Reduced glutamine concentrations led to a downregulation of the molecules responsible for the phagocytic capacity of the monocytes, such as the high affinity receptor for IgG (FcγRII/CD64) and CR3 (CD11b/CD18). Previous in vitro studies revealed that the ability of murine peritoneal MΦ to phagocytose 125I-labeled yeast cell walls (Zymosan) or 51Cr-labeled sheep red blood cells is dependent on the concentration of glutamine (16,17). These results are in accordance with our findings. The phagocytosis of sensitized ox erythrocytes and opsonized Escherichia coli was found to be glutamine dependent. However, the phagocytosis of latex particles by human monocytes was not influenced by glutamine.

Cell regulatory capacity of glutamine

Regulation of cell volume. There is a close relationship between the regulation of cell volume, glutamine levels, and...
protein catabolism. The administration of glutamine to hepatocytes stimulates anabolic processes within the cell involving an increased synthesis of DNA, RNA, and proteins (18). Furthermore, the mitogenic stimulation or immunological activation of lymphocytes or macrophages may result from the concomitant increase in cell volume which is related to an increase in glutamine metabolism (19). The addition of glutamine to the culture medium causes cell swelling. Previously, we demonstrated that both glutamine and heat shock protein (Hsp) are protective against hypertonic challenge in a human monocyte cell line (U937) (20). The observed cytoprotective effect of both Hsp and glutamine seems to result from influencing ion transport across the cell membrane and maintaining (protecting) the intracellular ion milieu. Glutamine-induced cell swelling also activates extracellular signal-regulated kinases and p38 (mitogen-activated protein kinase). A similar relation of glutamine to osmosignaling pathways is described also in other cell types, including myelocytic human promyelocytic leukemia cells and adipocytes. Therefore, it seems that the osmo-regulatory effect of glutamine is not restricted to glutamine-consuming cells.

**Stimulation of Hsp.** Cells express a group of proteins that are essential to cellular survival under stressful conditions, the Hsp (21). Hsp70 induction protects cells against cytotoxic mediators and reduces organ dysfunction and mortality in animal models of sepsis (22). Under conditions with low plasma glutamine, such as polytrauma, severe sepsis, and acute respiratory distress syndrome, Hsp70 expression was impaired in granulocytes (23), monocytes (24), and lymphocytes (25). Hsp70 shows a reduced inducibility (−47%) at pathological glutamine levels (0.2 mM/L). This indicates that glutamine-starved cells are unable to express normal amounts of Hsp70. Proteomic analysis revealed that especially in short-duration glutamine starvation, the protein expression of Hsp70 is reduced. Therefore, we investigated at which molecular level the glutamine starvation interferes with Hsp70 expression. We tested the glutamine dependence of transfer RNA (tRNA) association and the influence of glutamine on the stimulation of heat-shock factor 1 and on transcription and translation of Hsp70 (26,27). Our results revealed that the overall level of tRNA-bound glutamine remained unaffected as did the formation of heat-shock factor 1 (27). Also the transcriptional and the translational control of Hsp70 expression remained unchanged. However, glutamine starvation enhanced mRNA decay. U937 cells cultured with low amounts of glutamine had a drastically shortened half-life of Hsp70 mRNA (45 min vs. 4 h). Therefore, in U937 cells the lower expression of Hsp70 seems to be related to a reduced half-life of mRNA (27). It has to be mentioned that the molecular mechanism responsible for the decrease in Hsp70 expression in U937 due to glutamine starvation must not be pertinent to other cell populations such as lymphocytes or neutrophils.

The group of Wischmeyer et al. (28) investigated the role of Hsp with respect to glutamine in sepsis and lung injury. In a recent publication, they were able to show that glutamine administration improved survival after cecal ligation and puncture-induced sepsis only in wild-type mice but not in mice with a deletion of the Hsp70 gene. These results confirm the hypothesis that Hsp70 expression is required for the beneficial glutamine effect on survival, tissue injury, and the inflammatory response after systemic inflammatory injury.

**Glutathione metabolism**

Glutamine (via glutamate), cysteine, and glycine are the precursor amino acids for glutathione, which is present within the cell in a reduced (GSH) and an oxidized form (GSSG). The ratio of GSH:GSSG is the most important regulator of the cellular redox potential. GSH synthesis can be altered via the administration of glutathione precursors or via the activity of GSH peroxidase and GSH reductase. The synthesis of inflammatory cytokines and adhesion molecules is dependent on the activation of the transcription factor nuclear factor κB, which relies on the cellular redox potential and therefore on the intracellular ratio of GSH:GSSG (29–31). Furthermore, the SH-containing tripeptide glutathione is effective in the protection of SH-carrying proteins against oxygen radicals and may thereby be especially important for dividing cells, because they are particularly susceptible to reactive oxygen intermediates. It should be mentioned that the GSH concentration in cancer cells is 10–50 times higher than in nonmalignant cells, which gives the cancer cell an additional protection against oxygen radicals.

There is a significant correlation between glutamine supply, the rate of lymphocyte proliferation, and intracellular glutathione content. The importance of glutathione for lymphocyte function especially in HIV-infected patients was reviewed by Dröge et al. (32). A depletion of the intracellular glutathione pool reduces blast transformation and the proliferation and generation of cytotoxic T cells. Cultivation of peripheral blood mononuclear cells with glutamine and IL-2 revealed a maximum of growth stimulation that was accompanied by increasing intracellular GSH content (31). A dysfunction of lymphocytes in the septic state may be related to a 60% decreased glutathione synthesis as shown in septic pediatric patients (33). Moreover, glutamine is able to preserve hepatic glutathione levels after hepatic injury (34). In recent studies, we fed mice with either glutamine or a mixture of glutamine, glycine, arginine, and (n-3) fatty acids (eicosapentaenoic acid, docosahexaenoic acid) and measured the lymphocyte numbers and also the GSH content in the spleen and in Peyer’s patches (PP) (35,36). We showed that glutamine-fed mice had increased GSH content in both tissues and that the number of lymphocytes in the PP positively correlated with the GSH content. The administration of buthionine sulfoximine, an inhibitor of GSH synthesis, led to a reduced number of lymphocytes in the PP. These studies indicated that glutamine is an effective precursor for GSH synthesis in lymphocytes of PP and the spleen, which seems to be associated with an enlarged number of lymphocytes in the respective organs. These results are supported by in vitro experiments and in rats after depletion of glutathione stores by diethyl maleate (37,38).

**Glucose metabolism**

In vitro studies as well as experiments in animals have shown glutamine to be one of the most effective substrates for gluconeogenesis (39,40). Glutamine is the major gluconeogenic precursor in the kidney. In contrast to alanine, the carbon skeleton of glutamine originates mainly from protein and other amino acids and may therefore provide more to the new glucose pool than alanine (41). Tracer studies revealed that nearly twice as much of the carbon in glucose is transferred from protein-derived glutamine than from alanine. Infusion of large amounts of glutamine (28 g/4 h) resulting in 3-fold increased plasma glutamine concentrations caused a 7-fold increase in glucose formation without changes in plasma insulin and glucagon levels (42). These results provide evidence that, in humans, glutamine may act both as a substrate as well as a modulator of its metabolism to glucose. In contrast, in mice genetically predisposed to become overweight and develop hyperglycemia, the administration of glutamine as part of a high-fat diet reduced body weight (BW) and attenuated hyperglycemia and hyperin-
sulinenia (43). This glucose-lowering effect of glutamine may be in relation to the known effect of glutamine on fat metabolism such as inhibition of fatty acid oxidation and lipolysis and is possibly involved in the attenuation of insulin resistance induced by fat. Therefore, it was hypothesized that glutamine may be useful as an antiobesity and antidiabetic agent in prediabetic and diabetic subjects. This assumption was recently confirmed in intensive care unit patients, because parenterally administered glutamine (in the form of alanyl-glutamine) prevented worsening of insulin sensitivity in multiple-trauma patients (44). A possible explanation of these results would be that glutamine improved the sensitivity of adipose tissue to insulin, decreased lipolysis, and subsequently improved glucose metabolism.

**Effect on signaling and amino acid sensing**

Glutamine-utilizing cells react in a specific manner in the case of glutamine deprivation. The data described above show that glutamine deprivation influences glutathione metabolism, decreases the mRNA half-life of Hsp70, leads to cell shrinkage, and lowers intracellular ATP content. It remains remarkable that the reduced concentration of 1 amino acid causes such a variety of different effects. A possible explanation is that the signaling pathways via AMP-activated protein kinase or mammalian target of rapamycin seem to be influenced by amino acid deprivation. Furthermore, translational initiation is influenced by amino acid metabolism in the form of an amino acid sensing. The existing data are mainly derived from basic research, e.g. from yeast physiology, and must be confirmed for other cell types. A specific way of glutamine sensing can be achieved via aminoacyl-tRNA synthetases, which catalyze the attachment of specific amino acids to their cognate tRNAs, thereby ensuring the faithful translation of the genetic code. In addition to their specific aminoacyl-tRNA synthetases, which catalyze the attachment of amino acid metabolism in the form of an amino acid sensing. The existing data are mainly derived from basic research, e.g. from yeast physiology, and must be confirmed for other cell types. A specific way of glutamine sensing can be achieved via aminoacyl-tRNA synthetases, which catalyze the attachment of specific amino acids to their cognate tRNAs, thereby ensuring the faithful translation of the genetic code. In addition to their enzymatic function, these enzymes have been discovered to regulate various cellular functions such as tRNA export, ribosomal RNA synthesis, apoptosis, inflammation, and angiogenesis (45). Various aminoacyl-tRNA synthetase species can interact directly with a number of different regulatory proteins: Ile-tRNA synthetase (RS) binds to Hsp90, Lys-RS to superoxide dismutase, Val-RS and His-RS to various translation factors, and glutaminyl-RS to apoptotic signal-regulating kinase 1 (ASK1). In the latter case, glutaminyl-RS binds directly to the catalytic domain of ASK1, which thereby loses its ability to phosphorylate c-Jun N-terminal kinase (46). The suppressive association of glutaminyl-RS with ASK1 is controlled by the presence of glutamine. Because glutaminyl-RS can recognize glutamine specifically, it is considered a glutamine-sensor protein that renders the ASK1 activity glutamine sensitive.

**Supply of glutamine under clinical conditions**

Glutamine administration can be performed orally, enterally, or parenterally. Because glutamine is not stable in aqueous solution, for parenteral or enteral products, stable glutamine-containing dipeptides such as alanyl-glutamine or glycylyl-glutamine are used. Information on the maximum upper limits of glutamine supply is available from clinical data and from volunteers receiving glutamine (or the corresponding glycylyl- or alanyl-glutamine dipeptides) in dose-finding studies (Table 2).

**Healthy volunteers.** Wilmore et al. (47,48) infused increasing doses of glutamine up to 0.570 g·kg⁻¹·d⁻¹. Plasma glutamine concentrations increased significantly with glutamine administration but reached a plateau at concentrations ~25% above control values. They reported that the diets were well tolerated and neither ammonia nor glutamate, potentially toxic metabolites of glutamine, increased significantly.

**Cancer patients.** An oral glutamine dosage of 7.5 g for 3 wk administered for preventing mucositis/stomatitis of breast cancer patients receiving anthracycline-based chemotherapy did not cause any side effects but reduced the incidence of clinically

### TABLE 2 Supply of glutamine under clinical conditions

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Glutamine supply, unit/70 kg BW</th>
<th>Probants, n</th>
<th>Administered as</th>
<th>Mode of supply</th>
<th>Duration of study</th>
<th>Change in plasma GLN, %</th>
<th>Side effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>28 g/4 h</td>
<td>16</td>
<td>Glutamine</td>
<td>Parenteral</td>
<td>4 h</td>
<td>+200</td>
<td>None</td>
<td>Perriello et al. (42)</td>
</tr>
<tr>
<td>Healthy volunteers</td>
<td>40 g/d</td>
<td>12</td>
<td>Glutamine</td>
<td>Parenteral</td>
<td>5 d</td>
<td>+25</td>
<td>None</td>
<td>Lowe et al. (47)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>7.5 g/d</td>
<td>183</td>
<td>Glutamine</td>
<td>Oral</td>
<td>3 wk</td>
<td>n.d.</td>
<td>None</td>
<td>Peterson et al. (49)</td>
</tr>
<tr>
<td>Metastatic cancer</td>
<td>30 g/d</td>
<td>51</td>
<td>Glutamine</td>
<td>Oral</td>
<td>15 d</td>
<td>n.d.</td>
<td>None</td>
<td>Choi et al. (50)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>30 g/d</td>
<td>86</td>
<td>Glutamine</td>
<td>Oral</td>
<td>7 d</td>
<td>n.d.</td>
<td>None</td>
<td>Wang et al. (51)</td>
</tr>
<tr>
<td>Cancer/intestinal failure</td>
<td>20 g/d</td>
<td>7</td>
<td>Glutamine</td>
<td>Home parenteral</td>
<td>4 wk</td>
<td>Elevated liver enzymes in 3/7</td>
<td>None</td>
<td>Hornsby-Lewis et al. (52)</td>
</tr>
<tr>
<td>Liver diseases</td>
<td>11.2 g/4 h</td>
<td>16</td>
<td>Glycyl-glutamine</td>
<td>Enteral vs. parenteral</td>
<td>4 h</td>
<td>n.d.</td>
<td>Increased NH₃ levels</td>
<td>Plauth et al. (53)</td>
</tr>
<tr>
<td>Polytrauma</td>
<td>28 g/d</td>
<td>9</td>
<td>Glycyl-glutamine</td>
<td>Parenteral</td>
<td>3 d</td>
<td>+70</td>
<td>None</td>
<td>Weingartmann et al. (54)</td>
</tr>
<tr>
<td>Critically ill</td>
<td>24 g/4 h</td>
<td>20</td>
<td>Alanyl-glutamine</td>
<td>Parenteral peripher</td>
<td>3 d</td>
<td>+200</td>
<td>None</td>
<td>Berg et al. (55)</td>
</tr>
<tr>
<td>Head trauma</td>
<td>24 g/20 h</td>
<td>8</td>
<td>Alanyl-glutamine</td>
<td>Parenteral</td>
<td>20 h</td>
<td>n.d.</td>
<td>None</td>
<td>Berg et al. (56)</td>
</tr>
<tr>
<td>Postoperative</td>
<td>30 g/d</td>
<td>14</td>
<td>Alanyl-glutamine + glycyl-glutamine</td>
<td>Enteral</td>
<td>5 d</td>
<td>n.d.</td>
<td>Nausea, hiccups, flatulence in 3/14</td>
<td>None</td>
</tr>
<tr>
<td>Postoperative</td>
<td>30 g/d</td>
<td>20</td>
<td>Alanyl-glutamine + glycyl-glutamine</td>
<td>Enteral</td>
<td>3 d</td>
<td>n.d.</td>
<td>None</td>
<td>Senkal et al. (58)</td>
</tr>
<tr>
<td>Postoperative, posttraumatic</td>
<td>42 g/d</td>
<td>61</td>
<td>Glutamine</td>
<td>Enteral</td>
<td>3 d</td>
<td>n.d.</td>
<td>None</td>
<td>Schulman et al. (59)</td>
</tr>
</tbody>
</table>

1 n.d., Not determined.

2028S Supplement
significant oral mucositis (49). In another study, patients with advanced or metastatic cancer receiving fluorouracil/leucovorin in chemotherapy were supplemented with glutamine at 30 g/d for 15 d for preventing mucositis/stomatitis (50). In this study, a reduction of mucositis/stomatitis was also observed without any side effects attributable to glutamine supplementation. Similarly, 30 g oral glutamine given daily to colorectal cancer patients receiving oxaliplatin reduced the incidence and severity of peripheral neuropathy and also did not cause any side effects (51). In a mixed patient group (cancer or intestinal failure) on home total parenteral nutrition due to colonic resection or inflammatory enteropathy, the parenteral infusion of glutamine at a dose of 0.285 g/kg BW (equivalent to 20 g/70 kg BW) for 4 wk resulted in the elevation of liver enzymes in 3 patients (52). Those abnormalities subsided after discontinuation of the glutamine-total parenteral nutrition administration. Interestingly, during the course of the study, plasma levels of glutamine did not increase. Therefore, it seems questionable whether the increase in liver enzymes was due to glutamine or to the concomitant overload of fat application [n=6 fatty acids] or glucose supply. Both factors increase liver enzymes under certain conditions. Interestingly, the 3 patients received a rather high level of total energy (2888, 2574, and 2314 kcal\(^5\), respectively), which, rather than the glutamine supplementation, may have triggered the deterioration of hepatic metabolism.

Patients with liver failure. Patients with liver diseases seem to be more sensitive to glutamine administration. In cirrhotic patients (pre- and postliver transplantation), the administration of 10 g glutamine significantly increased venous blood ammonia and impaired reaction time following oral glutamine challenge (60). We compared enteral and parenteral glutamine supply in patients with transjugular intrahepatic portosystemic shunt and liver cirrhosis and measured mesenteric venous-arterial concentration differences of ammonia and glutamine (53). Our data demonstrated that enteral glutamine supply resulted in a higher portal ammonia load and a higher degree of systemic hyperammonemia. Therefore, oral/enteral glutamine administration can significantly affect ammonia metabolism in patients with an impaired liver function and therefore influence hepatic coma. Recent publications propose that elevation in plasma and brain glutamine levels associated with hepatic failure may, by increasing \(y\)-aminobutyric acid release, produce some of the manifestations of hepatic encephalopathy (61,62).

Critically ill patients. Both enteral and parenteral supply of glutamine (dipeptides) was investigated in critically ill patients. Our group infused increasing daily dosages of glycyl-glutamine up to 570 mg glycy-glutamine (equivalent to 28 g glutamine for a 70-kg BW patient) in polytraumatized patients (54). This dosage caused a sustained rise in arterial glutamine concentrations, which remained stable during the 4-d study period. No pathological accumulation of free glycine or the dipeptide was detected and no side effects occurred. The group of Wernerman et al. (55,63) performed extensive studies on the safety of alanyl-dipeptide infused to severely ill patients. In this respect, it was shown that the infusion of 0.5 g/kg alanyl-glutamine (equivalent to 27 g glutamine/70 kg BW) over 4 h in a peripheral vein on 3 consecutive days was safe and did not cause thrombophlebitis. Patients on continuous renal replacement therapy were also not affected by i.v. glutamine supplementation (64). Glutamine infusions to neuro-

\(5 \quad 1 \text{ kcal} = 4.184 \text{ kJ}\).


