



NEUROLOGÍA

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INTRODUCTION

Severe trauma and subsequent extensive tissue damage cause a trauma-related excess of oxidative stress and cellular injury. Moreover, the catabolic state induced by stress is associated with the retention of sodium and water and the concomitant expansion of the extracellular fluid compartment (1). The proportion of sodium and water retention is related to the severity of the injury and is aggravated by severe infection (2, 3). These changes are thought to be the result of increased release of catabolic mediators and hormones, such as vasopressin and aldosterone (4). Catabolic stress is also characterized by increased glutamine expenditure, which exceeds glutamine synthesis; therefore, glutamine was reclassified as a conditionally essential amino acid (5). Glutamine provides precursor nitrogen for protein synthesis and serves as a preferred respiratory fuel for rapidly dividing cells (6). It was reported that the provision of glutamine in the catabolic state stimulates intracellular processes (6, 7), improves nitrogen balance (8 – 11), preserves gastrointestinal barrier function (12 – 14), ameliorates the immune response (7, 10, 15, 16), and restores body-fluid distribution (1, 17). Moreover, it was shown that glutamine-enriched enteral feeding reduces the incidence of infectious complications in patients with multiple trauma (18).

The exact mechanisms underlying these events are not fully understood. For example, glutamine supplementation prevents extracellular water retention compared with a control solution (1). In general, osmoregulation involves the regulation of changes in the concentrations of solutes over the cellular membrane. The cytosolic concentration must change in parallel with the osmolarity of the extracellular compartment. To maintain the cell's integrity, it is thus important that concentrations do not change drastically and thereby do not influence the membrane potential, enzyme activities, or other cellular processes. To meet these requirements of an osmoregulator, a metabolically inert compound is needed that requires a minimum of energy in remaining high concentrations across the cell membrane and in responding adequately to osmotic changes. Taurine, a β amino acid, meets these requirements almost ideally (19). Several studies reported that plasma taurine concentrations decrease in response to surgical injury, trauma, sepsis, and critical illnesses (20 –

22). As metabolic and respiratory patterns progressively deteriorate, plasma taurine concentrations decrease even more severely, suggesting an increased expenditure and possibly an increased requirement for taurine (20, 21). Because glutamine-enriched enteral feeding reduces the incidence of infectious complications (18) and restores body-fluid distribution (1), it was hypothesized that glutamine enrichment might have an important effect on adequate plasma taurine concentrations, which are needed to restore the osmolar disturbances observed after trauma. Moreover, because glutamine serves as the preferred fuel for neutrophils (6, 23, 24) and as a precursor of the endogenous antioxidants taurine and glutathione (24), it could be hypothesized that glutamine has a beneficial effect on infectious morbidity by increasing antioxidant availability.

The purpose of this study was to compare the effect of glutamine-enriched enteral nutrition with that of an isocaloric, isonitrogenous control solution on plasma taurine concentrations in patients with multiple trauma. To gather additional information concerning taurine at the organ level, a stressed rat model was also studied. Taurine fluxes in the kidneys, liver, and gut were measured with a radioactive microsphere technique.

SUBJECTS AND METHODS

This study was part of a study of the effects of enteral glutamine supplementation in trauma



patients, which was approved by the Council for Medical Research of the Netherlands Organization for Scientific Research (no. 900-716-064) (18) and by the Institutional Review Board of our institute. Informed consent was obtained from each patient or the patients' closest relative.

Trauma patient study

Patients

Eighty-four patients with multiple traumas admitted to the Intensive Care Unit of the University Hospital Vrije Universiteit of Amsterdam were considered eligible for the study. The patients included were aged 18–65 y and had an expected survival of >48 h and an injury severity score of >20 (18).

The exclusion criteria were as follows: pregnancy or lactation, renal insufficiency, third-degree burns over >15% of body surface, malignancy, genetic disorders, HIV infection, previous splenectomy, liver insufficiency, inflammatory bowel disease, type 1 diabetes, or use of investigational drugs, steroids, or immunosuppressive medication. Circulating plasma taurine and glutamine concentrations were measured during the first 15 d of hospitalization.

The patients were randomly allocated to receive a glutamine-enriched enteral nutrition solution or a balanced isocaloric, isonitrogenous enteral solution. After the study application forms were signed by the patients' physicians, the pharmacist used a computer-generated randomization table based on blocks of 4 to assign patients to the 2 treatment groups, each of which corresponded to the batch numbers on the nutrition pouches. The code for the batch numbers was kept at the supplier's office in the United States, and the codes were broken when the analyses were finished. All participants were unaware of which treatment they were to receive.

The enteral nutrition solution was freshly prepared in the Pharmacy Department by mixing the dry powder with sterile water. The solution was then placed in brown glass bottles labeled with the patient's name, hospital number, and protocol number. To ensure double-blindness, the solutions were indistinguishable by color, smell, and taste.

Study design

The patients were randomly assigned to receive either a glutamine-enriched enteral nutritional solution (30.5 g/100 g protein, AlitraQ; Ross Products Division, Abbott Laboratories, Columbus, OH) (n = 35) or a balanced enteral control solution (n = 37) (18). The control solution was identical except that the following amino acids were added in place of glutamine: alanine, aspartic acid, glycine, proline, and serine.

Both feedings contained similar concentrations of the essential amino acids. After immediate stabilization and surgical treatment, feeding was started within 48 h after admission via a nasoduodenal tube that was inserted endoscopically. Feeding was delivered continuously via a pump with the goal to reach 75% of the calculated basal energy expenditure within 72 h after admission (25). Indirect calorimetry was done with Deltatrac (Datex Division Instrument, Helsinki) to ascertain the caloric need of each patient. The enteral nutrition was continued until the patients tolerated oral feeding. While receiving enteral

nutrition, the patients received no other form of nutrition. A minimum period of 5 d of enteral nutrition was thought necessary for glutamine to have an effect.

Amino acid measurement

Blood samples were obtained between 0800 and 1000. Plasma glutamine and taurine concentrations were measured on days 1, 2, 3, 4, 5, 7, and 14. The blood samples were immediately placed on ice. After centrifugation at 1500 x g for 10 min at 4° C, aliquots of plasma were pipetted into cryovials containing crystallized sulfosalicylic acid (4 mg/100 µL), immediately put in liquid nitrogen, and stored at -70°C before analysis. Taurine and glutamine concentrations were measured in plasma by using HPLC (between-run precision: <5.8%), as previously described (26).

Statistical analysis

Differences in plasma concentrations of amino acids between the glutamine and control patients were analyzed by using the two-factor repeated-measures analysis of variance with interaction. The significance of the differences at each time point were analyzed by using Student's t test with Bonferroni correction. The analyses were done with STATVIEW (version 1.03; Abacus Concepts, Berkeley, CA). All results are expressed as means ± SDs. A P value <0.05 was considered statistically significant.

Rat study

Rats

The Laboratory Animal Ethical Committee of our institute approved the design used for the rat study. Male Wistar rats weighing 250–300 g (n = 24; Harlan CPB,



Zeist, Netherlands) were used. The animals were maintained in accordance with the Guide for the Care of Laboratory Animals used in our institute. After arrival, the animals were allowed to acclimate to the laboratory environment for 5 d. The rats were individually housed in metabolic cages and subjected to a 12-h light and 12-h dark cycle under controlled environmental conditions. Before the experiment began, a 3-d period was allowed for nutritional adaptation of the rats to the pulverized rat food (SRM-A; Hope Farms, Woerden, Netherlands).

Study design

The rats were randomly assigned to receive a glutamine-enriched enteral diet (12.5%, by wt) or an isocaloric, isonitrogenous control diet for 14 d. In the control diet, glutamine was replaced by the following amino acids: asparagine (3.3%), serine (2.4%), glycine (3.9%), proline (2.6%), and alanine (2.0%). Both diets contained arginine (1.3%). Food intake was recorded daily.

Blood-flow measurements and blood sampling were done in the fed state. Organ fluxes were calculated on the basis of arteriovenous differences and blood-flow measurements. Organ blood-flow measurements were performed with the radioactive labeled microsphere method, as described previously (27, 28). In brief, on the morning of the 15th day, animals were anesthetized with ketamine hydrochloride (50 mg/kg) and then placed in the supine position on a heating pad that maintained body temperature at 37°C. The trachea was cannulated with a small piece of polyethylene tubing to facilitate breathing. The right carotid artery and left femoral artery were cannulated with PE-50 tubing (Fisher Scientific, Springfield, NJ). The catheters were connected to P23Db Statham pressure transducers (Gould Inc, Medical Products Division, Oxnard, CA) to monitor the placement of the carotid catheter into the left cardiac ventricle and the femoral artery blood pressure.

After the surgical procedures were finished, the rats were allowed to stabilize for 20 min before the microspheres were injected. Radiolabeled microspheres (46 Sc; diameter: $\pm 15 \mu\text{m}$; Du Pont–New England Nuclear, Boston) were injected into the left ventricle, and a reference blood sample was drawn from the femoral artery catheter. After the microsphere injection, blood samples (50 μL) were drawn from the femoral catheter for hematocrit and pH determination. After the blood-flow measurement, the abdomen was opened. The blood-flow measurement in the kidney is given as an example of the procedure used for all organs studied. The left renal vein was cannulated with a 12-gauge needle attached to a heparin-containing syringe. The renal vein was clipped at its entrance into the caval vein, and a blood sample (1 mL) was drawn. An additional blood sample was drawn from the abdominal aorta. The rats were killed by an overdose of sodium pentobarbital (100 mg/kg). After verification of the position of the left ventricular catheter, the kidneys were removed, weighed, and placed in counting vials. Larger organs were divided in portions of $\pm 2 \text{ g}$ to ensure good geometric distribution in the counting vials. Radioactivity was counted in a well-type -counter (type LKB-1280, Ultrogamma; Wallac, Turku, Finland). Count rates were corrected for natural background and counter dead time.

Plasma flow through the organ (F) was calculated by using the following equation:

$$F = F_a (Q_o / Q_a)$$

Where F_a is reference flow, Q_o is the count rate of the organ, and Q_a is the count rate of the reference blood sample. Reference flow was computed from the weight of the reference blood sample and the duration of the withdrawal, assuming a whole-blood density of 1.069 g/mL. Plasma flow was calculated according the equation

$$\text{Plasma flow} = \text{blood flow} \times (1 - \text{hematocrit})$$

To determine the blood flow over the gut and liver, similar procedures were used. Gut flow was calculated as the sum of organ blood flow through the splanchnic organs, ie, the stomach, pancreas, spleen, small intestine, and colon. Hepatic artery and portal venous flow were summed to determine the total hepatic flow.

Cardiac output was calculated according to the equation

$$\text{Cardiac output} = F_a (Q_{tot} / Q_a)$$

Where Q_{tot} is the total injected radioactivity determined by subtracting residual activity in the catheter and injection vial from the initially recorded activity. Amino acid measurement Blood samples were immediately placed on ice. After centrifugation at 1500 $\times \text{g}$ for 10 min at 4°C, aliquots of plasma were pipetted into cryovials containing crystallized sulfosalicylic acid (4 mg/100 μL), immediately put in liquid nitrogen, and stored at -70°C before analysis. Taurine and glutamine were measured in plasma by using HPLC (between-run precision: <5.8%), as previously described (26). Aliquots of the arterial plasma samples were used for ammonia and urea



measurements by using standard enzymatic methods.

Calculations

Net taurine fluxes over the kidneys, liver, and gut were calculated with the following equation:

$$\text{Net organ flux (nmol/min)} = [(A) - (V)] \times F$$

Where A is the arterial plasma taurine concentration and V is the plasma taurine concentration in the major vein of the organ. According to this method, a negative value indicates release. The net fractional extraction rate of taurine was calculated as $[A] - [V]/[A]$ (Table 1). [See link](#)

TABLE 1
Net fractional extraction rates of taurine in rats

	Glutamine-fed rats (n = 12)	Controls (n = 12)
Liver	0.25 ± 0.06	0.26 ± 0.05
Kidneys	0.34 ± 0.05	0.36 ± 0.05
Gut	0.13 ± 0.04	0.07 ± 0.05

Statistical analysis

All results are means ± SEMs. Significant differences between means were determined by using Student's t test. A P value <0.05 was considered statistically significant.

RESULTS

Trauma patient study

In total, 84 patients with multiple trauma were admitted to our hospital during the study period. Eighty patients were randomly assigned to our nutritional intervention study: 39 patients to a control group and 41 patients to a glutamine group. The control group consisted of 28 men and 9 women with a mean age of 34.5 ± 11.8 y, and the glutamine group consisted of 29 men and 6 women with a mean age of 35.1 ± 11.8 y. No significant differences in sex or age distribution were observed between the 2 groups. The mean injury severity score was 31.8 ± 10.6 in the control group and 32.4 ± 11.3 in the glutamine group. The sites of injury and the surgical procedures performed to stabilize the patients were similar in both groups (18).

The mean basal energy expenditure was calculated as 2598.9 ± 476.8 kcal/d in the control group and as 2646.1 ± 396.5 kcal/d in the glutamine group. The volume of nutritional intake was similar in both groups, and no significant difference in the mean number of days of enteral nutrition was observed between the 2 groups (glutamine group: 12.8 ± 1.1 d; control group: 11.9 ± 1.0 d).

A significantly lower incidence of pneumonia, bacteremia, and sepsis was found in the glutamine group than in the control group (18). No significant difference in the duration of hospitalization was reported between the groups (18).

Glutamine depletion was seen in both patient groups, as evidenced by low plasma glutamine concentrations on day 1 (Figure 1). [See link](#). The reference range for glutamine was determined as 482–938 $\mu\text{mol/L}$. In the glutamine group, plasma glutamine concentrations increased after treatment and were significantly greater than those of the control group on days 3 ($P < 0.003$), 4 ($P < 0.02$), and 5 ($P < 0.04$). In the control group, glutamine concentrations also increased after treatment, resulting in plasma concentrations that were not significantly different between groups from day 7 onward.

DISCUSSION

Plasma taurine concentrations increased more in the patients who received enteral glutamine supplementation than in the patients who received the balanced control diet in the first week after trauma. Previous results in these patients with severe trauma showed that glutamine-enriched enteral nutrition reduced the incidence of pneumonia, bacteremia, and sepsis in severely injured patients (18). In the rat study, the plasma taurine concentration was greater in the glutamine-fed rats than in the control rats. Organ fluxes, as measured by the radioactive microsphere technique in rats, showed an increased uptake of taurine by the gut, the liver, and the kidney.

In relation to the present study in trauma patients, several other studies reported that plasma taurine concentrations decreased in response to surgical injury, trauma, sepsis, and critical illnesses (20–22). Furthermore, as metabolic and respiratory patterns progressively



declined, plasma taurine concentrations were even more severely decreased, suggesting an increased taurine requirement under these conditions (20, 21). The observed increased plasma taurine concentrations in the patient population fed the glutamine-enriched enteral diet might partly explain the reduced incidence of infectious complications seen in these patients. The higher plasma taurine concentrations suggest an improved taurine availability at the whole-body level, and this subsequently may play a role in preserving the osmotic balance and, thereby, cell protection. Furthermore, adequate taurine availability could also play a role in a decreased susceptibility to tissue damage by hypochlorous acid released by inflammatory cells (20, 29).

Our rat model also confirmed that consumption of a glutamine-enriched diet increases plasma taurine concentrations. In a previous publication by our group, it was shown that a glutamine-enriched diet could significantly increase the plasma glutamine concentrations in rats (28). Additionally, the rat model used in the present study was developed to investigate to what extent a glutamine-enriched diet influences taurine uptake at the organ level and the possible implications of the measured higher uptake of taurine by the gut. During periods of stress, such as trauma and surgery, the integrity of the intestine is compromised because of a significant reduction in nutritive blood flow, which might result in intestinal tissue damage (ischemia or reperfusion) and increased mucosal permeability. Glutamine is suggested to play an important role in the protection of the gut mucosal wall by providing respiratory fuel for rapidly dividing cells—such as enterocytes, colonocytes, and lymphocytes (6)—and by increasing intestinal blood flow to maintain normal intestinal structure and permeability (28, 30). A protective mechanism against endotoxins in the gut is based on the binding of bile acids with taurine. Taurine promotes bile flow, increases the activity of the rate-limiting enzyme for bile acids synthesis, and prevents cholestasis (22, 31 – 34). Bacteria in the gut mucosal wall transform bile acids into secondary acids, which are capable of binding endotoxins, thus protecting the gut against mucosal damage (35). The hepatic conjugation of bile acids proceeds within the limitations of taurine availability (33, 36, 37). Because an increased taurine flux was found toward the liver and the gut, it might be suggested to implicate that an increased deconjugation of taurine-conjugated bile acids in the gut took place, which could possibly result in an increased reabsorption of taurine (37).

The liver is known to be a major site of taurine biosynthesis and releases taurine into the plasma (37). The hydration of the hepatocytes is described to change within minutes in response to hormones, amino acids, bile acids, and metabolites of oxidative stress (38). A variety of mediators of inflammation and oxidative stress might cause hepatocellular shrinkage, which occurs by opening K^+ channels in the plasma membrane (39), resulting in a hepatocellular K^+ efflux and a release of antioxidants, such as taurine (40). The hepatic hydration state is an important determinant of metabolic liver function and gene expression (41). The liver cells use organic osmolytes, such as taurine, in response to hyper-osmotic cell shrinkage or hypo-osmotic cell swelling to maintain cell volume homeostasis (41). Taurine is the major osmolyte released in response to hypo-osmotic stress and is the most important osmolyte under normo-osmolar conditions (41). Taurine seems to have a direct beneficial effect on liver parenchymal cells, because it was shown that taurine is protective against several toxic compounds.

Oxidative stress is known to induce cholestasis, probably caused by hepatic glutathione depletion. It is conceivable that the oxidation of the glutathione–glutathione disulfide system triggers K^+ channel activation and cell shrinkage (39, 40). Glutamine provides the source of glutamate and has been shown to preserve total glutathione concentrations after injury or ischemia of the liver (42).

Restoration of the glutathione content is followed by increased synthesis of this tripeptide, with a concomitant need for cysteine and a reduction in taurine, because the substrate cysteine is the precursor for glutathione and taurine. Thus, enhanced glutathione synthesis has been suggested to explain the decrease in plasma taurine after trauma or stress (43).

Stress is associated with the retention of sodium and water and consequently with the expansion of the extracellular fluid compartment (1). Additionally, the proportion of the water and sodium retention is related to the severity of the injury and is enhanced by infections (2, 3). Furthermore, stress is known to be associated with an increased production of free oxygen radicals, which results in an increased H^+ concentration that may enhance Na^+ reabsorption; water is also absorbed in this process. Glutamine is necessary to donate NH_3 , to couple with H^+ to form urinary NH_4^+ and possibly as a fuel for kidney cells to eliminate this H^+ overshoot (44). Glutamine, thus, is not only important in providing substrate for antioxidant protection, but may also diminish extravasation of fluids by preventing leakage through the



endothelial cells; overall, this results in a better clinical outcome (1).

In the rat model, we found an increased uptake of taurine by the kidney when the rats were fed the enteral glutamine-enriched diet. The kidney is the organ that excretes taurine in the urine and thereby maintains sulfur balance and subsequently taurine homeostasis (36, 45, 46). Renal transport of taurine adapts to perturbed taurine homeostasis by reducing or increasing the Na⁺-taurine symport (cotransport) activity (47, 48). If extracellular sodium increases, the taurine influx increases (49). This cotransport of taurine and sodium via the β-amino acid transporter could explain the increased taurine influx in the kidney under conditions of stress (50).

The other major function of taurine is to trap chlorinated oxidants by producing the nontoxic, long-lived taurine-chloroamine, and thus protect the cell from self-destruction during processes that produce oxidants (29, 51, 52). Because taurine is exceptionally abundant in the cytosol of inflammatory cells, especially in neutrophils, taurine will travel with the migrating neutrophils to the damaged organs to combat free radicals (53). It is known that sufficient glutamine concentrations maintain an adequate neutrophil function (6, 23) and thus might play an indirect role in transporting intracellular taurine to the damaged focus (21) for osmoregulation and oxidant trapping.

In conclusion, glutamine-supplemented enteral nutrition is efficacious in increasing glutamine (18) and plasma taurine concentrations after trauma compared with a balanced control diet. In the glutamine-fed rats, organ fluxes showed an increased uptake of taurine in the liver, kidneys, and gut. This suggests that glutamine may serve as substrate and facilitate the availability of taurine in plasma and at the organ level. It is likely that when actual and potential losses of taurine are elevated, eg, in trauma patients, the taurine requirement increases and taurine becomes a conditionally essential amino acid (36).



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