Effect of dietary supplementation with glutamic acid or glutamine on the splanchnic and muscle metabolism of glucogenic amino acids in the rat

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The aim of the present study was to examine the metabolic effects of a high availability of dietary glutamic acid or glutamine. A 15% casein diet was supplemented with 7.2% glutamic acid or glutamine. The present results show that both supplementations produced only a slight modification in the circulating concentrations of glutamate. Glutamic acid supplementation noticeably enhanced (+ 19%) the arterial concentrations of glutamine, but to a lesser extent than glutamine supplementation itself (+ 54%). Large amounts of alanine were released by the digestive tract in rats fed the various diets; this release was enhanced by glutamine (+ 33%) and, more markedly, by glutamic acid (+ 80%) supplementation. In the liver, glutamic acid and glutamine supplementation produced an increase in the catabolism of glycine, serine, and threonine that resulted in a drop of their peripheral concentrations, especially in muscles. The decrease in serine and threonine concentrations could be ascribed to the elevation of the serine(threonine)dehydratase activity (three fold), and the drop in glycine concentration seems to be connected to serine metabolism. It appears that the administration of glutamine (but not of glutamic acid) by the oral route could be effective in increasing its availability in peripheral tissues.

Keywords: glutamine; glutamate; dietary supplementation; glucogenic amino acids

Introduction

The two dispensable aminoacids glutamate and glutamine occupy unique positions in the intermediary metabolism, notably in the metabolism of ammonia and aminoacids. Glutamate is involved in various transamination processes, energy production, urea and glutathione synthesis, and some tissues can contain considerable quantities of this amino acid. Furthermore, the fact that plasma glutamate concentrations are low and tightly controlled might be connected to its role as a neurotransmitter in the central nervous system.[1,2]

It is generally accepted that the large quantities of glutamate released from dietary proteins are extensively metabolized by the enterocytes, but it has been suggested that the added free glutamate is metabolized less rapidly than the peptide-bound glutamate.[3,4] A considerable fraction of this amino acid is transaminated during the absorptive stage,[5] resulting in a concomitant release in portal blood of alanine, which is further metabolized by the liver. Supplementation studies have shown that, even when large doses of glutamate (up to 10% of the diet) were fed to adult rodents, neuronal necrosis did not occur.[6]

Glutamine is also widely distributed in various mammalian tissues and is, together with alanine, the most abundant amino acid found in plasma. Glutamine is a central compound in nitrogen metabolism and is involved in the uptake, transport, and formation of ammonia, as well as in the homeostatic control of amino acid balance.[7] Glutamine is also a precursor of purines, pyrimidines, glucosamine, and ornithine.[8] The phys-

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iological functions of glutamine depend on the tissue or the cell type; furthermore, it is now well established that the liver can switch from a net utilization to a net production, depending on the physiological or nutritional conditions.[9]

The effect of glutamate supplementation has been extensively studied because it is commonly added to human food as a flavor enhancer. In the case of glutamine, the lack of stability of this amino acid has somewhat precluded its utilization for supplementation studies. The aim of this work was to study the adaptation of interorganal relationships, when a basal (15% casein) diet is supplemented with glutamic acid or glutamine. It was particularly interesting to examine whether a substantial part of glutamic acid or glutamine could escape splanchnic metabolism, and contribute to elevated glutamine concentrations in peripheral tissues, especially muscles. Furthermore, it was examined whether glutamic acid (or glutamine) addition could affect the metabolism of some essential aminoacids, because a previous study reported that the supplementation of a low protein diet with various glucogenic aminoacids produced a decrease of both plasmatic and hepatic pools of threonine.[10]

Materials and methods

Animals and diets

Male Wistar rats (IFFA-CREDO, L'Arbresle, France) weighing 150–160 g were first acclimated for 7 days on a semi-purified diet that contained the following (by dry wt.): 72% wheat starch (Louis François, Paris, France), 15% casein (Louis François), 5% corn oil (C.I.O., Genay, France), 7% mineral mixture (U.A.R., Villemoisson/Orge, France) and 1% vitamin mixture (U.A.R.). The animals were then divided into three groups and fed for 15–21 days the experimental diets: control diet (see above), glutamic acid-supplemented diet (Glu diet), or glutamine-supplemented diet (Gln diet). In the Glu or Gln diets, part of the wheat starch supply was replaced by 7.2% L-glutamic acid (Vegetadrog, Paris, France) or 7.2% L-glutamine (Ajinomoto, Tokyo, Japan), respectively. Thus, the Glu or Gln diets were designed to supply the same amounts of glutamyl units, but were not isonitrogenous. The basal supply of glutamyl units (3.6 g/100 g diet, corresponding to a daily provision of about 2 μmol/100 g body weight) was enhanced three-fold by the supplementation. The animals were housed in wire-bottomed cages in a temperature-controlled room (22° C) with the dark period from 09:00 to 21:00 hr, and the food was available from 09:00 to 17:00 hr.

Sampling and analytical procedures

The rats were sampled 8 hours after the beginning of food intake. The animals were anesthetized with sodium pentobarbital (40 mg/kg) and maintained at 37° C. Blood (about 0.8 mL) was withdrawn from the hepatic vein, portal vein, then abdominal aorta. Portal and hepatic blood flows were determined by an indicator-dilution method, with *p*-aminohippurate as an indicator, using a procedure adapted from that of Katz and Bergman.[11] In parallel, a portion of liver (about 1 g) and of the quadriceps femoris (about 0.4 g) were immediately freeze-clamped, weighed, and stored in liquid nitrogen. The remaining liver was excised and weighted to determine the total liver weight.

Glucose and urea were determined spectrophotometrically on perchloric extracts (2 vol $HClO_4$ 0.4 mol/L : 1 vol plasma) by enzymatic methods.[12,13] The frozen liver and muscles samples were crushed in 5 vol 0.4 mol/L $HClO_4$ then neutralized by K_2CO_3. Amino acids were determined on a Chromakon 500 (Kontron, Zürich, Switzerland) autoanalyzer, using lithium buffers and postcolumn ninhydrin detection.

Measurements of enzyme activities

A fraction of liver (≈0.5 g) was disrupted using a Polytron homogenizer in 11 vol of KH_2PO_4 50 mmol/L, EDTA 1 mmol/L, and dithiothreitol 0.1 mmol/L with 20% glycerol (pH 8.2). The reaction mixture contained KH_2PO_4 200 mmol/L, EDTA 2 mmol/L, L-threonine 100 mmol/L, and pyridoxal phosphate 0.5 mmol/L (pH 8.2). The reaction was allowed for 15 min at 37° C then it was stopped by addition of 24% TCA. The appearance of 2-oxobutyrate was determined using the dinitrophenylhydrazine reaction at 520 nm.[14]

Calculations and data analysis

The digestive balance was ([portal vein]) − [artery] × portal blood flow and the hepatic balance was ([hepatic vein] − [afferent]) × hepatic blood flow. The afferent concentration was calculated from portal vein and artery, considering their respective blood flow (hepatic arterial blood flow was calculated by difference between hepatic and portal blood flows). The fractional extraction was referred to as the ratio ([hepatic vein] − [afferent]) × 100 / [afferent]. The digestive and hepatic balances were calculated using plasma concentration values, because it has been previously established that there is no significant difference between these blood and plasma balances, except for arginine.[15]

Values are given as the means ± SEM, and where appropriate, significance of the differences between mean values was determined by one-way analysis of variance coupled with the Student-Newman-Keuls test.[16]

Results

Effects of dietary glutamic acid or glutamine on food intake and weight gain

Table 1 shows that, compared with the control, the incorporation of glutamic acid or glutamine in the diet did not affect food intake or daily body weight gain (22.1 ± 0.4 and 5.3 ± 0.3 g/day in control rats, respectively); furthermore, the liver weight was not significantly changed by dietary conditions (about 10 g, namely 4% of the body weight).

Changes in arterial amino acid concentrations

The arterial glycemia was similar in the three experimental groups (in the range of 8.0–8.5 mmol/L) whereas plasma urea was enhanced by glutamic acid (+ 46%) or glutamine (+ 112%) supplementation *(Table 2)*. In rats fed the Glu diet, there was a limited but significant increase in glutamate concentration (+ 0.06 mmol/L) together with a rise in glutamine concentration (+ 0.12 mmol/L). In rats fed the Gln diet, the concentra-

Table 1 Effects of supplementation of 15% casein diets with glutamic acid or glutamine (7.2% of the diet) on the body and liver weight, on daily food intake, weight gain, and on liver blood flow

Diets	Control	+ Glutamic acid	+ Glutamine
Body weight (g)	267 ± 11	249 ± 15	251 ± 10
Food intake (g/day)	22.1 ± 0.4	21.1 ± 0.7	21.3 ± 0.6
Weight gain (g/day)	5.3 ± 0.3	4.5 ± 0.4	4.6 ± 0.4
Liver weight (g)	10.4 ± 1.1	9.4 ± 1.3	10.2 ± 1.2
Hepatic blood flow (mL/min)	26.0 ± 3.1	25.1 ± 2.9	25.8 ± 3.0
(mL/g liver)	(2.50)	(2.67)	(2.53)

Results are means ± SEM for 10 rats in each group

Table 2 Arterial glucose, urea, and aminoacid concentrations in rats fed a control diet (15% casein) or diets supplemented with glutamic acid or glutamine (7.2 % of the diet)

Diets	Control	+ Glutamic acid	+ Glutamine
Plasma concentrations (mmol/L)			
Glucose	8.60 ± 0.73	8.12 ± 0.62	8.70 ± 0.70
Urea	3.41 ± 0.25	4.98 ± 0.28†	7.23 ± 0.44†
Glutamate	0.11 ± 0.01	0.17 ± 0.02*	0.14 ± 0.01*
Glutamine	0.63 ± 0.03	0.75 ± 0.03*	0.97 ± 0.04†
Alanine	0.92 ± 0.07	1.09 ± 0.09	0.96 ± 0.10
Threonine	0.60 ± 0.03	0.46 ± 0.02†	0.40 ± 0.02†
Serine	0.40 ± 0.02	0.32 ± 0.02*	0.32 ± 0.01†
Glycine	0.22 ± 0.01	0.16 ± 0.01†	0.15 ± 0.01†

Results are means ± SEM for 10 rats in each group.
* and †, different from control, $P < 0.05$ and $P < 0.01$, respectively.

Table 3 Liver and muscle concentrations of aminoacids in rats fed a control diet (15% casein) or diets supplemented with glutamic acid or glutamine (7.2% of the diet)

Diets	Control	+ Glutamic acid	+ Glutamine
Liver (μmol/g)			
Aspartate	2.27 ± 0.14	2.46 ± 0.23	2.00 ± 0.14
Glutamate	2.31 ± 0.14	2.83 ± 0.17*	3.50 ± 0.16†
Glutamine	5.16 ± 0.24	5.65 ± 0.20	7.12 ± 0.30†
Alanine	3.37 ± 0.09	2.70 ± 0.11†	2.67 ± 0.24*
Threonine	1.05 ± 0.06	0.73 ± 0.06†	0.75 ± 0.04†
Serine	1.53 ± 0.03	1.10 ± 0.10†	1.22 ± 0.06†
Glycine	2.28 ± 0.07	1.43 ± 0.09†	1.60 ± 0.13†
Muscle (μmol/g)			
Glutamate	1.21 ± 0.06	1.40 ± 0.03*	1.30 ± 0.08
Glutamine	4.18 ± 0.23	5.18 ± 0.18†	6.90 ± 0.57†
Alanine	3.09 ± 0.05	4.11 ± 0.11†	3.56 ± 0.21*
Threonine	1.49 ± 0.05	1.08 ± 0.07†	1.14 ± 0.06†
Serine	1.66 ± 0.05	1.21 ± 0.01†	1.36 ± 0.08*
Glycine	3.88 ± 0.06	2.70 ± 0.05†	2.70 ± 0.04†

Results are means ± SEM for 10 rats in each group.
* and †, different from control, $P < 0.05$ and $P < 0.01$, respectively.

tion of glutamate was slightly affected (+ 0.03 mmol/L), whereas that of glutamine was markedly elevated (+ 0.34 mmol/L, representing +54%). There was no significant change in the arterial concentrations of alanine, whereas a significant decrease in the arterial concentrations of serine, glycine, and threonine (about −30%) was observed in rats fed the two supplemented diets.

Intrahepatic and intramuscular concentrations of aminoacids

As shown in *Table 3,* high concentrations of glutamate and glutamine are present in the liver in basal conditions. In rats fed the Glu diet, the hepatic concentration of glutamate was enhanced (+ 23%), but glutamine was not significantly modified. On the other hand, in

rats fed the Gln diet, both glutamate and glutamine concentrations were markedly enhanced. With both types of supplementation, the other glucogenic amino acids (alanine, glycine, serine, and threonine) were significantly depressed in the liver (in the range of −30%).

In muscles, the glutamate concentration was slightly enhanced only in rats fed the Glu diet. Muscle glutamine concentration was significantly enhanced in rats fed the Glu diet or the Gln diet (+ 65% with this last diet). In contrast to the liver, muscle alanine was enhanced in rats fed diets supplemented with glutamic acid or glutamine, but glutamic acid was more potent in this respect. However, as in liver, the concentrations of threonine, serine, and glycine were noticeably depressed.

Digestive balance

In control conditions, in spite of the fact that glutamate and glutamine are the major amino acids in casein (besides proline), there was no net absorption of glutamate and a negative balance of glutamine across the portal-drained viscera *(Table 4)*. On the other hand, alanine was found in amounts disproportionate to its percentage in casein (which is close to that of serine, for example). This reflects the extensive metabolism of glutamate and glutamine by the intestine, chiefly towards alanine production. In rats fed the Glu diet, in which the dietary glutamic acid supply was threefold enhanced, there was a noticeable but limited appearance of glutamate in the portal vein and a less negative balance of glutamine. Concomitantly, the supply of alanine in the portal vein was dramatically enhanced (+ 80%). In rats adapted to the Gln diet, there was a shift of glutamine balance toward net absorption (+ 6.08 μmol/min), whereas alanine production was moderately elevated (+ 33%) compared with the Glu diet. The digestive balance of glutamate was slightly enhanced by glutamine supplementation. The digestive balances of threonine, serine, and glycine were not significantly affected by glutamic acid or glutamine supplementation.

Liver metabolism

As shown in *Table 5*, the afferent concentration of glutamate (very low in control rats) was markedly enhanced in rats fed the Glu diet, the afferent glutamine concentration was also slightly elevated (+ 24%). Glutamine supplementation led to a striking increase in afferent glutamine concentration (from 0.58 to 1.20 mmol/L), but afferent glutamate was unchanged. In keeping with data about the digestive balances, afferent alanine was strongly increased in rats fed the Glu diet but not in those fed the Gln diet. The afferent concentrations of threonine were markedly depressed in rats fed the supplemented diets (in the range of −35%) as well as (to a lesser extent) serine concentrations (−20%). The afferent concentrations of glycine were significantly lower only in rats fed the Gln diet.

Glutamate and glutamine were released by the liver in control rats. Glutamate was taken up by the liver (0.80 μmol/min) in rats fed the Glu diet and glutamine was only taken up (4.36 μmol/min) in rats fed the Gln diet. Alanine uptake was practically doubled in rats fed the Glu diet, but it was only 26% enhanced in rats fed the Gln diet. In both cases, the fractional extraction of alanine was enhanced. In parallel, the hepatic uptake of threonine and serine was increased (although the afferent concentrations were depressed) due to the rise in the fractional extraction by the liver, especially threonine. The hepatic uptake of glycine was not affected by the dietary conditions, but its fractional extraction (relatively high in basal conditions) was also enhanced.

Changes in serine(threonine)dehydratase activity

There was a noticeable induction of the serine (threonine)dehydratase activity (control: 0.49 ± 0.08 μmol/min/g liver) in rats fed the supplemented diets (Glu diet: 1.52 ± 0.25 and Gln diet: 1.33 ± 0.23 μmol/min/g liver). The magnitude of the induction was thus similar in rats fed the Glu or Gln diets (2.5–3 fold). It is noteworthy that the activities of the two major transaminases in the liver (alanine and aspartate ami-

Table 4 Digestive balance of the major glucogenic aminoacids in rats fed a control diet (15% casein) or diets supplemented with glutamic acid or glutamine (7.2% of the diet)

Diets	Control	+ Glutamic acid	+ Glutamine
Digestive balance (μmol/min)			
Glutamate	+0.37 ± 0.03	+2.63 ± 0.15†	+0.76 ± 0.07†
Glutamine	−1.49 ± 0.09	−0.68 ± 0.07†	+6.08 ± 0.56†
Alanine	+7.29 ± 0.78	+13.10 ± 1.02†	+9.69 ± 0.85*
Threonine	+0.94 ± 0.09	+1.05 ± 0.09	+0.95 ± 0.07
Serine	+1.31 ± 0.11	+1.22 ± 0.12	+1.14 ± 0.08
Glycine	+2.24 ± 0.19	+2.04 ± 0.18	+2.28 ± 0.13

Results are means ± SEM for 10 rats in each group.
* and †, different from control, $P < 0.05$ and $P < 0.01$, respectively.

Table 5 Liver metabolism of the major glucogenic aminoacid in rats fed a control diet (15% casein) or diets supplemented with glutamic acid or glutamine (7.2% of the diet)

	Control	+ Glutamic acid	+ Glutamine
Afferent concentration (mmol/L)			
Glutamate	0.13 ± 0.02	0.36 ± 0.04†	0.13 ± 0.02
Glutamine	0.58 ± 0.03	0.72 ± 0.06*	1.20 ± 0.11†
Alanine	1.25 ± 0.09	1.77 ± 0.13†	1.31 ± 0.08
Threonine	0.64 ± 0.02	0.45 ± 0.03†	0.41 ± 0.02†
Serine	0.44 ± 0.03	0.37 ± 0.02*	0.33 ± 0.03*
Glycine	0.32 ± 0.03	0.27 ± 0.02	0.24 ± 0.02*
Hepatic balance (μmol/min)			
Glutamate	+0.73 ± 0.10	−0.80 ± 0.06†	+1.02 ± 0.03*
Glutamine	+1.56 ± 0.25	+1.60 ± 0.04	−4.36 ± 0.06†
Alanine	−8.12 ± 0.70	−16.10 ± 0.98†	−10.20 ± 0.06*
Threonine	−0.66 ± 0.06	−0.90 ± 0.08*	−0.85 ± 0.07*
Serine	−1.26 ± 0.12	−1.60 ± 0.11*	−1.53 ± 0.13
Glycine	−2.39 ± 0.30	−2.39 ± 0.22	−2.37 ± 0.20
Fractional extraction (%)			
Glutamate	—	8	—
Glutamine	—	—	14
Alanine	25	35	31
Threonine	4	8	8
Serine	11	17	18
Glycine	28	36	38

Results are means ± SEM for 10 rats in each group. The hepatic balance is referred to as: ([hepatic vein] − [afferent]) × hepatic blood flow, and the fractional extraction as: (hepatic balance × 100)/([afferent] × hepatic blood flow.
* and †, different from control, $P < 0.05$ and $P < 0.01$, respectively.

notransferase) were unmodified by the dietary conditions (data not shown).

Discussion

The splanchnic tissues in mammals usually metabolize large amounts of dietary glutamic acid (together with other glutamic-yielding amino acids such as glutamine or proline). Glutamic acid is abundant in most protein sources, such as casein, and it reaches very high levels in some plant proteins such as gliadin[17]; however, the percentage of glutamyl units present as glutamine in dietary proteins is seldom available (in casein, 46% as glutamine).[18] Free glutamate is also present in significant amounts (up to 1%) in foods such as tomato extracts and some cheeses. In addition, sodium glutamate is often used in human nutrition as a flavor enhancer. In the present conditions, with a basal dietary supply of about 0.75 g/day total glutamic acid for a 15% casein diet, the supply obtained in the supplemented diets mimicked a 45% casein diet. The diets supplemented with glutamic acid or glutamine were well tolerated by the animals, as shown by the data on body weight gain and food consumption. This is in keeping with previous investigations showing that the above amino acids should not exert adverse effects provided that the percentage added does not exceed 8–10%.[19] It is noteworthy that adverse effects of glutamic acid supplementation may be observed at a lower percentage in the diet (5%) when the basal diet is a low-protein diet.[20,21] On the other hand, a parenteral supply of about 1 g glutamine/day has recently been reported in septic rats.[22]

It is well established that most of ingested glutamate and glutamine is metabolized by the digestive tract[23] and that there is practically no net appearance of these amino acids in portal blood when there is a moderate level of protein in the diet.[24] A large part of the carbon moiety of glutamate (or glutamine) gives rise chiefly to alanine, and to small amounts of citrulline, ornithine, and proline.[23] These metabolic properties of the digestive tract may represent a handicap when glutamine is orally or enterally administered, to enhance its availability for glutamine-demanding tissues. In fact, substantial amounts of glutamine appeared in the portal vein in rats fed the Gln diet, whereas, for the same level of supplementation, the appearance of glutamate in portal vein of rats fed the Glu diet was quite limited. This could reflect the slower rate of absorption of glutamate by the digestive tract, compared with that of glutamine.[25] Furthermore, this indicates that glutamate is extensively transaminated, as shown by the high rate of alanine production. This could be viewed as a feature that protects the organism against the possible neurotoxic effects of glutamate. In rats fed the Glu diet, the digestive balance of glutamine was less negative. Because no glutamine synthase activity has been reported in the small intestine mucosa, the above effect should be primarily ascribed to an inhibition of glutaminolysis via an enhanced availability of glutamate in enterocytes. This is in keeping with data suggesting that the intestinal glutaminase resembles the glutaminase of kidney in many of its properties and thus could be inhibited by high concentrations of glutamate.[26,27] In rats fed the Gln diet, a substantial part of glutamine escaped the intestinal hydrolysis and

appeared in the portal vein; yet it has been shown that feeding a glutamine-enriched diet may stimulate glutaminase activity,[28] but it is also conceivable that the provision of glutamine to the intestine by the oral route may decrease the uptake of glutamine from the circulation.

In basal conditions, the hepatic balance of glutamate and glutamine correspond to a slight release (+ 0.73 and + 1.56 μmoles/min, respectively); however, in rats fed the high-protein diet, an effective uptake (40–50% of afferent) of glutamine and glutamate was observed, due to the induction of various enzymes (transaminases, glutaminase, enzymes of urea cycle) and, to some extent, of membrane carriers.[24] Acute experiments of glutamine infusion in portal vein have shown that the elevation of afferent glutamine shifted the hepatic balance toward net uptake but, for comparable concentrations in portal vein, the fractional extraction was much lower than in rats adapted to a high protein diet.[15,24] In the present experiment, the fractional extraction of afferent glutamine was relatively low in rats fed the Gln diet, probably in connection with the lack of induction of the enzymes involved in ureogenesis. This point is interesting because it indicates that most of glutamine escaping intestinal metabolism should be available for extrasplanchnic tissues. Nevertheless, the hepatic uptake of glutamine was substantial (4.4 μmol/min); most of it was likely utilized for urea production because glutamate release was poorly modified. Various factors (glutamine accumulation, ammonia concentration, etc.) participate in an amplifier function of glutaminase when the plasma concentration of glutamine is enhanced.[29] In rats fed the Glu diet, only small amounts of glutamate were found in afferent plasma (0.36 mmol/L), and its hepatic uptake was low (fractional extraction 8%) when compared with glutamate uptake in rats fed high-protein diets.[15,24] It has been reported that the glutamate transporter activity is located mainly in perivenous hepatocytes, the sites of glutamine synthase activity.[29] Yet, the uptake of glutamate in rats fed the Glu diet failed to affect the hepatic balance of glutamine, which suggests that the above process was not quantitatively important.

The supplemented diets enhanced the digestive production of alanine, especially the Glu diet, and the major part of this production was removed by the liver. The enhanced uptake of alanine is not consecutive to an induction of alanine aminotransferase because the activity of this enzyme was found unchanged in rats fed the supplemented diets; whether the activity of membrane transport (via system A) might be enhanced is still undetermined. It is noteworthy that the hepatic uptake of the other glucogenic amino acids (threonine, serine, and glycine) was elevated, parallel to a slight induction of the serine (threonine) dehydratase. Nevertheless, this induction (about three fold) is moderate compared with that observed with high-protein diets (more than 40 fold).[10] In peripheral tissues, it turns out that glutamic acid or glutamine supplementation may be effective in enhancing the concentration of glutamine in muscles, but glutamine itself was more effective. This point is important because skeletal muscle is the primary site of nitrogen loss after injury and disease.[30] In rats fed the Gln diet, it is conceivable that the enhanced availability of glutamine in arterial blood would increase its uptake by muscle cells. However, the question arises as to the origin of glutamine accumulation in rats fed the Glu diet: circulating glutamate could be a source of glutamine under such conditions. On the other hand, the accumulation of alanine (which is, with glutamine, a major end-product of amino acids catabolism in muscles)[31] could (via equilibrium reactions) channel endogenous glutamate towards glutamine.

Recent studies indicate that glutamine appears to be an essential amino acid for rapidly dividing cells such as those of the intestinal mucosa[32] and lymphocytes.[33] It has also been proposed that glutamine may be of therapeutic value to minimize protein losses in muscles,[34,35] which could be relevant in the case of sepsis, surgery, trauma, or burns. Generally, glutamine is not added in amino acid solutions because it is considered as unstable in free form (decomposing into toxic compounds like pyroglutamic acid and ammonia). However, it has been reported that glutamine in solution may be considered stable for some uses in humans.[36] Attempts have also been made to provide glutamine under a peptide bound form (for example, L-alanyl-L-glutamine). However, a major site of uptake of this form has rather been found in kidneys,[37] although Stehle et al.[38] have also shown that visceral organs and muscles exhibit a high ^{14}C incorporation after intravenous administration of L-alanyl-L-[^{14}C]glutamine. The administration of glutamine in free form seems relatively efficient to increase the plasma and tissue (liver, muscles) concentrations of glutamine, even if a substantial part is to be broken down by the small intestine, in agreement with recent investigations using enterally administered glutamine in humans.[39] Whether detrimental effects associated with excessive ureogenesis might outweigh the beneficial effects of glutamine administration is probably tightly dependent on the integrity of renal function. With low doses of glutamine, even if the direct provision of exogenous glutamine to peripheral tissues is quite limited, there should be at least a sparing effect of endogenous glutamine in the intestine.

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