Review Article

Annals of Nutrition & Metabolism

Ann Nutr Metab 2012;60:17–26
DOI: 10.1159/000334880

Received: October 27, 2011
Accepted: November 3, 2011
Published online: December 30, 2011

Have We Enough Glutamine and How Does It Work? A Clinician's View

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Key Words

Glutamine · Cell proliferation · Redox potential · Anaplerosis · Cataplerosis · Intermediary metabolism · Fluxes · Rate of appearance

Abstract

There is a gap between the scientific basis of the claim that in several disease states glutamine is lacking and the widespread belief that supplementation of glutamine to the nutritional regimen is beneficial in severely ill patients. Glutamine shortage exists when consuming tissues, playing a crucial role in the response to trauma and disease, receive insufficient amounts of glutamine. In these tissues (immune system, wound), glutamine is only partly oxidized but has more specific roles as nontoxic nitrogen carrier, precursor of several crucial metabolites required for cell proliferation and for maintenance of the redox potential, and as osmolyte. In inflammatory states, glutamine concentrations in plasma and tissues are decreased due to many disease-related factors, precluding its use as a reliable indicator of shortage. Isotope studies have yielded equivocal results, precluding their use as a reliable indicator of glutamine shortage or adequacy. The increase in the net release of glutamine from peripheral tissues to central tissues (immune system, liver, spleen, wound) in inflammatory states provides a better basis for the necessity to supplement the organism with extra glutamine in these conditions. Glutamine supplementation was beneficial in a few studies in burn or trauma patients. The clinical benefit of parenteral glutamine supplementation in patients with severe inflammation has been demonstrated more convincingly. The amounts of glutamine supplemented approximate the amounts released by peripheral tissues and utilized by central organs operative in host defense and are therefore in the physiological range.

Introduction

A world of literature exists on scientific aspects of glutamine metabolism in experimental settings on the one hand and on the benefit of glutamine supplementation in human disease on the other hand. There nevertheless remains a gap between the scientific basis of the claim that in several disease states glutamine may be lacking and the widespread belief that supplementation of glutamine to the nutritional regimen of severely ill patients is beneficial.

In the past 4 decades, scientists have gratefully embraced the suggestions of clinicians that in acute and chronic illness the organism presents itself with a different substrate mix compared to the healthy nonstressed

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state. The ability to generate this substrate mix may depend on the nutritional state of the patient and his/her capacity to generate these substrates. If indeed the undernourished organism fails to do this, it might be advantageous to nourish patients with a composition mimicking this mix.

One of the virtues of such hypotheses is that they generate much interest both in basic and in clinical scientists. They also generate funds to intensify research in this area. It is striking, however, that basic research and clinical application of modulated nutritional formulas had simultaneously been undertaken in fact long before metabolism had been clearly defined and shortages confirmed. In practice still today modulated feeds are offered without full knowledge of their metabolism. In many reviews, the benefits of glutamine and its supplementation are described as separate entities without an apparent metabolic connection [1]. Also, proof of certain effects has been derived from experimental work in which glutamine has been found to upregulate mediators or transcription factors, improving survival, whereas knocking out the gene coding for these factors worsens the outcome which cannot be reversed by glutamine supplementation. Interpretation of these data is difficult because they do not allow us to pinpoint the primary biochemical/physiological effect on the cascade of events induced by trauma and disease.

Proposed Working Mechanisms of Glutamine

- Tissue protection has been claimed from enhanced heat shock expression, promotion of intestinal integrity, and decreased cellular apoptosis
- Anti-inflammatory/immune regulation by diminishing activation of nuclear factor-κB and cytokine release
- Preservation of tissue metabolic function by maintenance of ATP levels and upregulation of insulin sensitivity
- Diminished iNOS expression and enhanced GSH levels after stress.
- Provision of NADPH [2]

Interest in glutamine has increased over the last two decades because it was proposed that glutamine lack might interfere with host response and intestinal integrity and therefore should be replenished [3, 4]. In basic research, however, its important role in metabolism in the enterocyte and in immune cells has been appreciated for more than 40 years [5–7]. There are many reasons for the increasing interest in its potential application in clinical practice. Glutamine indeed plays a central role in metabolism, is highly concentrated in plasma and tissues, is therefore an important (nontoxic) nitrogen carrier, highly stimulates proliferation and cell growth in cell and tissue cultures, and could be patented for patient use. Also interest from the industry was greatly enhanced because, being badly soluble and unstable, better soluble and more stable glutamine-containing dipeptides could be produced that could be safely administered to patients.

Several questions remain:

On what grounds are the claims established that in some disease states glutamine production is becoming deficient, and are these claims justified?

Glutamine plays a central and quantitatively important role in intermediary metabolism but also serves as a precursor of minor but nevertheless potentially important pathways. In view of the fact that recent meta-analyses suggest that glutamine is effective in a variety of disease states, the question of which pathway the benefit is acquired through arises.

In the present review, we will try to answer these questions by describing the role of glutamine in intermediary metabolism in stressed states and its effects on cell proliferation, maintenance of the redox state, and production of radicals operative in dealing with removing the waste of tissue damage and with the killing of bacteria.

Metabolism of Glutamine

Glutamine as a Universal Precursor

Glutamine plays a central and quantitatively important role in intermediary metabolism of carbon skeletons, amino groups, and ammonia in trauma, disease, and growth.

Firstly, glutamine is readily transported into cells and deamidated in several tissues (intestine, liver, spleen, immune cells, kidney) to yield glutamate and NH_3. Glutamate in turn is either transformed to α-ketoglutarate by means of its dehydrogenase or transaminated to equally yield α-ketoglutarate, which serves as an intermediate in the Krebs cycle. In this way, glutamine serves as an anaplerotic substrate, replenishing Krebs cycle intermediates in (especially rapidly) proliferating tissues. In these tissues, the intermediates are only partly regenerated because they branch off at several sites of the Krebs cycle to provide substances supporting cell proliferation in the immune response, wound repair, and growth and to maintain redox balance (see further).

The Krebs cycle operates differently in different tissues. In muscle especially, α-ketoglutarate transaminates with amino acids to yield glutamic acid, which is released as glutamine in the circulation after amidation with ammonia derived from the purine nucleotide cycle or from the circulation (cataplerosis). To allow this branching off, intermediates have to be replenished (anaplerosis). This is largely performed by glucose-derived pyruvate, which carboxylates to produce oxaloacetate, which subsequently with acetyl-coA forms citrate, starting the cycle. These anaplerotic and cataplerotic processes increase quantitatively when the inflammatory response or growth rates are stronger. Altogether, this implies that although glutamine is necessary in proliferating cells its carbon skeleton is largely derived from glucose-derived pyruvate. In turn, this glucose is synthesized in the liver and kidney with muscle-derived amino acids as precursors in trauma or disease states. Although one may expect this to happen especially when the organism is starving, it most likely also occurs in the fed state.

In the tissues responsible for host response, besides glucose, glutamine is taken up as anaplerotic substrate in the TCA cycle. Subsequently intermediates branch off producing pyrimidines, purines, phosphoenopyruvate, glycerol-phosphate, acetyl-coA, and others. These compounds, together with amino acids, taken up from the circulation and released from peripheral tissues, allow production of nucleotides, ATP, phospholipids, sterols, and cellular proteins, all of which are necessary for cell proliferation. Equally important is the glutamine-induced production of NADPH occurring directly by the breakdown of glutamine to α-oxoglutarate or indirectly by, together with glucose, supporting the malate pyruvate cycle.

Summarizing these pathways, in the traumatized/stressed individual peripheral protein is broken down to deliver amino acids (after intramuscular synthesis of glutamine and alanine) to the systemic circulation. They are partly reconverted to glucose in the kidney and liver. This glucose in turn serves to supply the carbon skeleton for glutamine and alanine synthesis in peripheral tissues. Glutamine and alanine are partly used in healing tissues for biosynthetic purposes, partly to produce NADPH for maintenance of the redox potential (see next paragraph). Outside the mitochondrion, glucose also yields NADPH in the first two steps of the pentose phosphate pathway.

The question of why, even in vitro, specifically glutamine is crucial to allow rapid cell proliferation remains. Newsholme [2] has tried to answer this question. In tissue cultures, proliferation and cell growth can only reach optimal levels when both glucose and glutamine are added to the incubation medium [5, 8]. It is suggested that the specific need for glutamine and glucose in immune cells (probably all rapidly proliferating cells) arises from the need to produce NADPH [2]. NADPH is necessary for the enzymes involved in the production of free radicals, superoxide and NO, which are required for pinocytosis and phagocytosis [2]. NADPH is also necessary in fatty acid synthesis, required for cell proliferation, and it is necessary to reduce glutathione and possibly many other molecules once they are oxidized.

In vivo, the use of glutamine is advantageous because it is readily transported in large and varying quantities without toxic side effects, which is not the case for most other individual amino acids. The described trafficking of glutamine serves another purpose. In the first step of the degradation of glutamine NH_3 is generated, which has toxic effects on the brain if it reaches the systemic circulation. When tissues utilize glutamine for purposes other than its incorporation in protein, a substantial proportion of its amide-nitrogen is released into the circulation as NH_3. These tissues are anatomically located in such a way that the NH_3 that is released can be immediately scavenged. This applies to the intestine, the liver, and the kidney. In this way, glutamine serves as a nontoxic nitrogen carrier.

Simultaneously it serves as a precursor of many elements in (rapid) cell proliferation and in maintenance of the redox state. Besides donating its carbon skeleton as intermediate of the TCA cycle for further cataplerosis it also contains two nitrogen atoms, both of which can be inserted into the skeleton of purines and, indirectly, of pyrimidines. Similarly, glutamine may serve to produce nonessential amino acids and other nitrogen-containing compounds (e.g. hexosamine).

A third more specific role of glutamine may be as one of the osmolytes regulating cell homeostasis in hyper- and hypo-osmolar conditions by cell shrinkage and cell swelling, respectively. Cell swelling or shrinkage have been demonstrated to play a role in the regulation of protein synthesis [9]. The original observation that intracellular glutamine concentrations regulate protein synthesis has not consistently been confirmed in later research [10].

It may be concluded that in traumatized/diseased/growth conditions glutamine has a central role in producing substrate for the pathways operative in these conditions. In view of its central place in intermediary metabolism, a shortage in glutamine availability would imply that flux in most if not all of these biosynthetic and redox regulating processes would be compromised. This will specifically be harmful in situations where rapid cell proliferation and host defense are required.

Amino Acid Concentrations and Fluxes

Glutamine is by far the most abundant free amino acid in plasma and tissues in humans. Plasma concentrations vary between 400 and 600 μmol/l and tissue concentrations between 2 and 20 mmol/l intracellular water (ICW) [11]. In ICW of enterocytes, glutamine concentrations range between 2 and 4 mmol/l [12], whereas in muscle and liver these concentrations range between 5 and 20 mmol/l [11, 13].

The steep concentration difference between plasma and tissue levels can only be maintained by active transport. This is primarily made possible by the Na^+/K^+-ATPase-driven ion pump. Several transporters are available for this purpose, including cotransporters for Na^+ and glucose, Na^+ and amino acids, and Na^+ and bile acids. In addition, transporters are available that exchange Na^+ and H^+ and other cations. It is important to note that these primary and secondary active transporters are responsible for the strong uphill gradient for amino acids and specifically glutamine. Intracellular glutamine concentrations are, however, also determined by several other metabolic processes, including intracellular production (from de novo synthesis or protein degradation) and uptake (amino acid degradation and protein synthesis). A last factor determining intracellular concentrations is the transport from inside to outside the cell. However, the 5-fold difference between mucosal and muscle intracellular glutamine concentrations indicates that not only plasma concentrations determine tissue concentrations but that one or several of the other factors must have additional and differing influences on intracellular levels in different tissues. This may also apply to the changes observed in amino acid concentrations in tissues in different metabolic situations, including undernutrition, sepsis [14], trauma [15], or mono-organ failure [16].

In principle, a glutamine shortage is demonstrated by insufficient delivery of glutamine from peripheral tissues to cover requirements in the consuming tissues, playing a crucial role in the response to trauma and disease. As early as 1983, Clowes et al. [17] demonstrated that cirrhotic patients that could not metabolize sufficient amounts of amino acids in their central organs (presumably predominantly the liver) died of sepsis, while those that could survived [18]. It therefore becomes evident that an adequate response of the organism to trauma/disease would be an increased release of glutamine (and other amino acids) by peripheral tissues (muscle, skin, possibly bone). This release can be calculated when arteriovenous differences for the amino acid under study are multiplied by flow across the organ. Subsequently, an estimation is necessary to extrapolate from the flux across a single arm or leg to the flux from all peripheral tissues in the body.

Modern technology has allowed measurement of the rate of appearance (Ra) in and disappearance (Rd) from plasma of a certain substrate by the organism. The Ra is a measure of all of the glutamine appearing in the plasma in a given time period and the Rd represents all of the glutamine that disappears from the plasma. Hypothetically, in the diseased state more glutamine should be produced by peripheral tissues and more should be taken up by immune organs like the liver, the spleen, other immune cells in the organism, the wound, or growing tissues. The turnover of glutamine (Ra and Rd) should therefore increase. One might hypothesize that failure to increase turnover after trauma or during illness reflects a shortage.

Is There a Shortage in Disease and Trauma?

Sources of Glutamine in Plasma

Glutamine is a normal constituting amino acid in muscle protein. Muscle protein degradation will therefore yield free glutamine which will appear in the cytosol and subsequently can be exported from the cell into the plasma compartment. Another source of glutamine consists of *de novo synthesis*. This process is enhanced after trauma. A third source of glutamine consists of the free pool, which has been shown to decrease in diseased states and therefore furnishes glutamine to the plasma. The amount released in this manner would cover only the amount metabolized in half a day after trauma and during severe illness. Its release is therefore negligible in longer disease processes. A final source of glutamine consists of exogenous supply as free amino acid, as dipeptide, or as protein.

What Do Depressed Glutamine Concentrations in Plasma and Tissues Mean?

In critical illness, plasma glutamine levels decrease [14, 19]. This phenomenon does not exclusively regard glutamine but applies to most amino acids. In nondepleted patients undergoing elective surgery for colonic cancer, plasma glutamine levels equally drop from 625 ± 22 μmol/l before operation to 431 ± 17 μmol/l on the second day after operation [20]. We measured plasma glutamine levels in a group of patients with intestinal diseases and found that the levels did not correlate with percentage weight loss or percentage ideal body weight but rath-

er with the sedimentation rate and with albumin levels as a measure of inflammatory activity [12]. In patients with severe pancreatitis, plasma glutamine levels decrease to less than 50% of the control values, but so do almost all other amino acids [19].

The general decrease in most amino acids may be due to several factors. There may in fact be a shortage, although this is less likely in view of the fact that the patients undergoing colorectal surgery were not depleted before operation, and similarly because in the pancreatitis patients the decrease in plasma amino acid levels appeared to parallel the severity of the disease rather than the nutritional state.

One important factor potentially influencing the generalized hypoaminoacidemia is the fact that in severe illness the distribution space increases. Both the intravascular volume (due to vasodilatation) and the extravascular volume (due to increased permeability leading to interstitial edema) increase and the amino acids (as well as plasma proteins, electrolytes like sodium, and chloride) dilute in these volumes. These distribution abnormalities are present from the initial stages of the disease and directly correlate with its severity. Indeed, one study in critically ill patients found that glutamine levels in plasma were already decreased on admission and this correlated with poor survival, which could not be explained by preadmission glutamine store depletion but should be explained by the severity of the primary disease or trauma [21].

Summarizing this part, it is unlikely that low plasma levels reflect a shortage, and one should be cautious in interpreting low levels as such, especially in severe acute inflammatory conditions.

Tissue concentrations of glutamine are much higher than plasma levels. Muscle glutamine levels drop, however, immediately after moderate size surgery [20] to 75% of preoperative levels and during severe pancreatitis with multiorgan failure to less than 20% of normal. In the fore mentioned study in elective well-nourished colorectal patients, muscle glutamine levels decreased from 13.2 ± 1.4 before operation to 9.6 ± 2.0 mmol/l ICW [20]. Mucosal glutamine levels were significantly lower in patients exhibiting inflammatory activity, whereas percentage weight loss in the absence of inflammatory activity was not strongly paralleled by a decrease in mucosal glutamine levels [12]. The tissue concentration drop might be due to alterations in membrane potential and transmembrane transport. Indeed, TNF-α, subsequently produced after an endotoxin challenge, has been shown to inhibit the activity of the Na^+/K^+-ATPase pump in the kidney and in the Caco-2 cells of the rat (effects partially reversed by indomethacin) [22, 23]. In fact, generalized inflammation may characteristically lead to/consist of changes of membrane (including gut mucosa) characteristics involving the activity of the sodium pump, secondary active transporters and, importantly, tight junction proteins [24]. It follows that steep uphill gradients of solutes cannot be preserved in critical illness and after trauma, explaining the decrease in several intracellular solutes, including glutamine. We may conclude that tissue concentrations of glutamine should be interpreted with caution as they are very unlikely to specifically represent a shortage.

Do Glutamine Fluxes Represent a Shortage?

At present, it is well accepted that the normal metabolic response to trauma and disease includes a net loss of muscle protein and a net uptake of amino acids by central organs (liver, spleen, immune system, wound) that play a crucial role in the healing response by producing proteins and cells that promote this healing. Focusing on protein metabolism, loss of muscle protein is achieved by increasing protein degradation, whereas simultaneously muscle protein synthesis does not increase or even decreases. At the same time, a net uptake of amino acids is achieved by increasing protein synthesis in the liver, other parts of the immune system, and the wound and by increasing the uptake of glutamine and alanine by these tissues [25] (fig. 1a, b). This explains why organisms subject to both stress and starvation are more catabolic than organisms that exclusively starve. In a pig model of operative trauma, we measured net glutamine fluxes across the hindquarter, the portal drained viscera (intestine), the liver, and the spleen [26]. We confirmed the hypothesized net efflux from peripheral tissues and the increased uptake by liver and spleen, whereas the uptake of glutamine by the intestine decreased (fig. 2). This finding furnishes strong support that immune cells (as represented by the spleen and also to a substantial extent by the liver) preferentially take up glutamine (along with glucose) in vivo. In conclusion, release of amino acids and specifically glutamine by peripheral tissues may be viewed as a measure of the adequacy of the metabolic response to trauma.

Data in this respect are limited (table 1). The net efflux of glutamine from the arm or leg, considered to represent largely muscle metabolism, is increased in traumatized and septic states. Unfortunately, no data exist regarding the efflux of glutamine in severely undernourished patients. We must conclude that although this measure

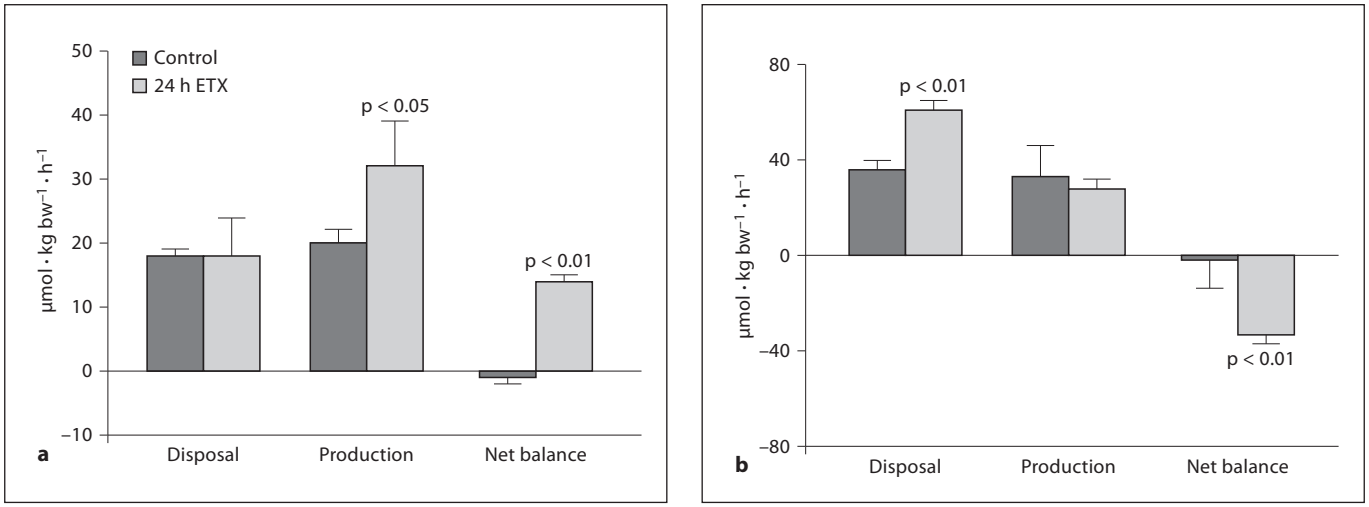

Fig. 1. a Disposal (protein synthesis) and production (protein degradation) of phenylalanine in muscle of pigs 24 h after an endotoxin challenge. **b** Disposal (protein synthesis) and production (protein degradation) of phenylalanine, corrected for oxidation in liver of pigs 24 h after an endotoxin challenge. The net balance represents the release of amino acids in the hindquarter and uptake in the liver. [25].

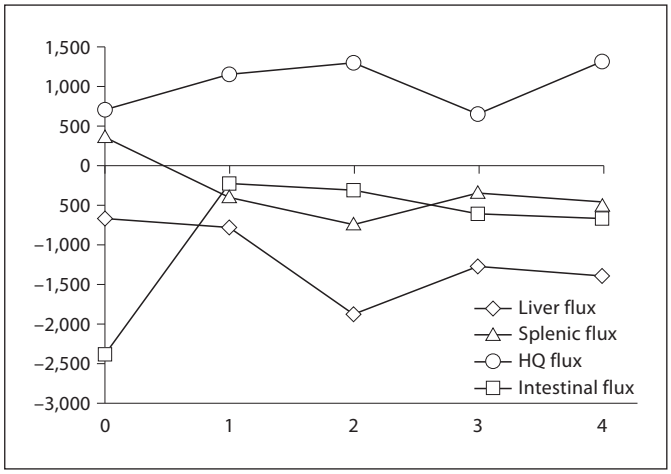

Fig. 2. Fluxes of glutamine across liver, intestine, hindquarter (muscle) and spleen in nmol/kg/min measured 1, 2, 3 and 4 days after operation. Control values were obtained 12 days after operation. [26].

might throw light on whether the body furnishes sufficient quantities of amino acids (specifically glutamine) to central tissues, such studies were not continued.

Does (Diminished) Appearance of Glutamine Indicate a Shortage?

One reason why net glutamine release by muscle was not further investigated may be that two decades ago stable isotope technology was applied increasingly, which promised to allow more in-depth metabolic research without necessitating use of unpopular invasive techniques in patients. As indicated previously, glutamine labeled with stable isotopes was used to measure the Ra of glutamine in plasma (see table 2). Amounts appearing in plasma ranged between 60 and 100 g/24 h, which means that the normal amount of approximately 20–40 g of glutamine that is usually administered as free amino acid or as dipeptide should be considered to be a supplemental dose rather than a pharmacological dose. We found in well-nourished patients undergoing elective surgery no increase in Ra 2 days after surgery, although we had hypothesized that the Ra (and Rd) into plasma should increase (fig. 3) [20]. In view of the findings that in traumatized or septic patients the net release of glutamine from muscle increases (table 1), we can only explain the absence of an increased whole-body Ra of glutamine into the plasma by assuming that the net release from muscle to central tissues is generated by decreasing the uptake (Rd) in muscle and concomitantly decreasing production (Ra) in central tissues (fig. 4).

The physiological significance of the Ra of glutamine into plasma is uncertain (table 2). While there is a significant increase in the Ra of glutamine in burns, weight-losing patients with GI disease, and wasting AIDS patients, there is no increase in glutamine turnover in weight-stable short bowel patients or in diabetic and ICU patients [27–31].

Table 1. Net production (arteriovenous difference times flow) of glutamine from arm or leg, considered to represent predominantly muscle

First authors	Unit of measurement	Control	Trauma	Sepsis
Clowes [41]	μM/m^2/min	5.82 ± 1.82	12.46 ± 2.51*	14.29 ± 2.5*
Fong [42]	nmol/100 ml/min	265 ± 32		311 ± 58
Carli [43]	nmol/100 ml/min	242 ± 95	528 ± 339	
Mjaaland [44]	nmol/100 ml/min	58 ± 23	137 ± 43*	

* $p < 0.05$ vs. control.

Table 2. Whole-body glutamine rate of appearance in healthy subjects (μmol/kg/h)

First authors	Glutamine tracer used				
	2-^{15}N	5-^{15}N	1-^{13}C	U-^{14}C	3,4-^{3}H
Darmaun [45]	348 ± 17	283 ± 16			
Darmaun [46]	325 ± 28				
Matthews [47]	317 ± 13				
Darmaun [48]	320 ± 9				
Matthews [49]	343 ± 26				
Matthews [50]	295 ± 13				
Darmaun [51]	335 ± 7				
Hankard [52]			355 ± 24	373 ± 19	393 ± 24
Biolo [53]		305 ± 26			
Nurjhan [54]				346 ± 16	
Kreider [55]	280 ± 23			343 ± 32	368 ± 32

One potentially disturbing factor in the previous account is that Ra into plasma only roughly reflects what is happening in tissue, where intracellular cycles may be operative. Furthermore, the rapid and widespread metabolism of glutamine in a multitude of reactions central in intermediary metabolism may obviate the validity of the conclusions drawn from the data of Ra and Rd in plasma [32]. Therefore, the Ra of glutamine into plasma is not a reliable indicator of glutamine shortage or adequacy.

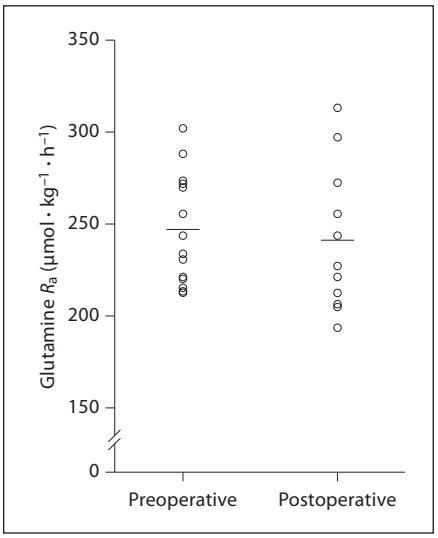

Fig. 3. Whole-body glutamine rate of appearance (*R*a) of patients before and 2 days after surgery. Individual data are given before surgery and on the second postoperative day. Mean values are represented by a horizontal line, n = 14. Wilcoxon signed ranks test, preoperative vs. postoperative: $p \geq 0.05$. [20].

When Is Extra Glutamine Necessary and What for?

Theoretical Reasons for Increased Glutamine Requirements

On the basis of the foregoing lines, glutamine as well as glucose is required to achieve efficient operation of the immune system, the wound, and proliferating tissues. This may require supplementation if the endogenous supply is deficient.

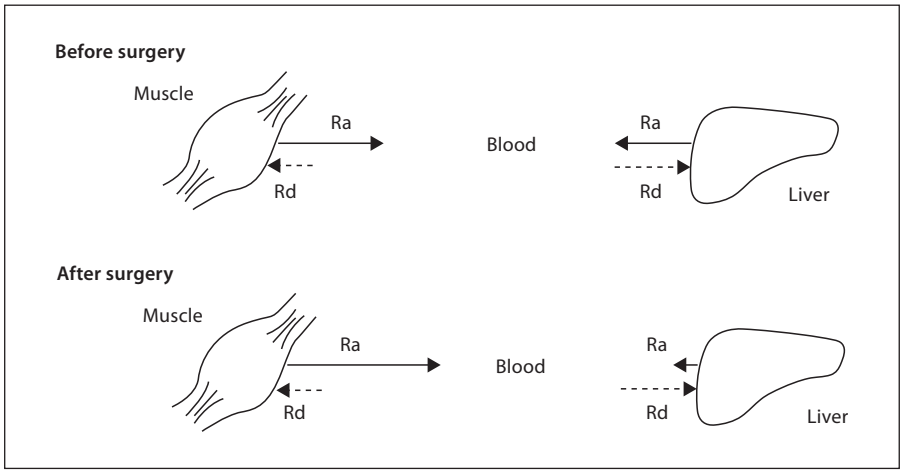

Fig. 4. Potential kinetics of glutamine after surgical trauma. In view of the fact that turnover did not increase and net release from muscle must have increased, the figure proposes that flux is generated by increasing the rate of appearance (Ra) in muscle and simultaneously decreasing the Ra in the other organs. In this way, flux can be generated without increasing whole-body turnover.

In theory, glutamine production by peripheral tissues may be compromised in the severely malnourished state, in which diminished muscle mass precludes sufficient release of amino acids for the production of glucose and subsequently glutamine, as well as an amino acid mixture to synthesize protein in proliferating cells operative in host response.

Along similar lines, very severe inflammation may require large quantities of glutamine, which may fail to be produced in prolonged or chronic states of severe inflammation.

Another reason may be the situation in which the organism is unable to increase protein and glutamine turnover despite relatively well-preserved muscle mass. This may be the case in patients that are already subject to inflammatory activity and cannot adequately respond to a renewed challenge (second hit).

All of these theoretical considerations might be supported in practice by studies showing a better effect of glutamine when supplemented for a longer period of time, for as long as the patient stays in a critical condition [33]. Vice versa, a too short period of supplementation or a too low dose failed to show any clinical benefit in a recent large, multicenter RCT in ICU patients [34].

Practical Facts Supporting a Shortage of Glutamine

There is some support for the contention that enteral glutamine supplementation is beneficial in patients with burns or trauma, while studies looking at other categories of critically ill patients failed to prove benefit [35]. This might be due to a relatively well-preserved enteral tolerance in patients with trauma and burns, while in patients with severe sepsis or septic shock, intolerance to enteral route for nutrition provision is a common finding. Moreover, a pilot prospective randomized trial showed improved gastrointestinal tolerance when glutamine was added to enteral nutrition in severe trauma patients during shock resuscitation [36].

More evidence supports routine parenteral glutamine supplementation in critically ill patients receiving parenteral nutrition, i.e. patients with substantial inflammatory activity [37–39]. This might be due to a better availability of the glutamine supplemented through this route, as the amount reaching the target organs is not dependent on gastrointestinal tract function.

No unequivocal benefit is observed while studying the effect of glutamine supplementation on bowel integrity. These results may be skewed by the fact that only a proportion of patients receiving glutamine supplementation did suffer from inflammatory activity [12, 40].

Interestingly, in some of the studies referred to, insulin sensitivity appears to be improved in critically ill patients receiving supplemental alanyl-glutamine in their parenteral nutrition mixture [38, 39].

In summary, the results of glutamine supplementation suggest that benefit is only achieved in the presence of overt inflammation, a situation in which clinical research has shown that more glutamine is utilized by the liver and other parts of the immune system, as well as healing tissues. This beneficial effect supports the claim that, in these conditions, the organism may suffer from glutamine shortage. The amounts of glutamine supplemented represent approximately 30–40% of the amount of glutamine appearing in the plasma without supplementation and are in the same order of magnitude as the amounts released by peripheral tissues, reported in the literature

(tables 1, 2). This implies that glutamine effects do not result from the administration of pharmacological dosages.

Conclusions

Solid scientific data supporting an absolute shortage of glutamine in patients are lacking. Decreased plasma concentrations are determined by many factors, including acute inflammatory activity and consecutive distribution abnormalities, and therefore are not a good indicator of glutamine shortage. Release of glutamine by peripheral tissues (especially muscle) in disease states and especially in the depleted state might be a good indicator, but this has not been thoroughly explored. The same applies for the Ra of glutamine in plasma in well- or undernourished individuals in inflammatory and control conditions.

Sufficient data exist showing that glutamine is an essential nutrient in all rapidly proliferating cells including immune cells and proliferating cells in growing tissues. It provides many different building blocks for these cells and simultaneously maintains redox balance by providing reducing equivalents, which are also necessary to allow the immune system to repair tissue damage. Theoretically, therefore, glutamine supplementation may be beneficial in patients with long-standing inflammatory activity that are not producing sufficient quantities of glutamine either due to malnutrition or because they cannot meet the demands of the extremely severe inflammatory illnesses of patients in our present day ICU. In line with this, clinical data show that benefit of parenteral glutamine supplementation is especially achieved in critically ill patients, i.e. patients with substantial inflammation or sepsis. Benefit may possibly also be achieved in traumatized or burn patients receiving extra glutamine enterally. In large multicenter studies in critically ill patients, infectious complications have been shown to be decreased and, interestingly, insulin sensitivity has been shown to be improved. On the basis of these beneficial effects, one may assume that these patients suffer from glutamine shortage. This is supported by the fact that the amounts supplemented are of the same order of magnitude as the amounts newly produced by the body itself and therefore are not in the pharmacological range.

Disclosure Statement

None.

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