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Chapter 10

Glutamine: A Conditionally Essential Amino Acid with Multiple Biological Functions

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Abstract

Glutamine (Gln) is the most abundant free amino acid (AA) in the body with concentrations fluctuating around 500–900 μmol/L. The biological functions of Gln have been widely studied, and they have opened new targets because Gln could modulate physiological functions such as immune enhancer, muscular maintainer, nitrogen transporter, neuronal mediator, pH homeostasis, gluconeogenesis, amino sugar synthesis, and insulin release modulation. In 1990, it was identified that Gln is a conditionally essential AA, meaning that in hypercatabolic or stress conditions, the body suffers depletion in its circulating levels. Moreover, this condition is an independent risk factor of mortality, has been correlated with increase in infection rates, and length of hospital stay in intensive care units (ICU) patients. This characteristic confers the option of Gln use, meaning that through its targets, it could improve the outcome of patients who are suffering a hypercatabolic or hypermetabolic condition.

Keywords: glutamine, parenteral nutrition, enteral nutrition, amino acid

1. Introduction

L-Glutamine (abbreviated as Gln or Q; encoded by the codons CAA and CAG) is a charge neutral, polar (at physiological pH) α-amino acid. Its free form has limited solubility and is unstable in aqueous solution. Gln solved in aqueous solution constructs the cyclized compound pyroglutamic acid (**Figure 1**), which is an uncommon amino acid associated with metabolism problems [1].

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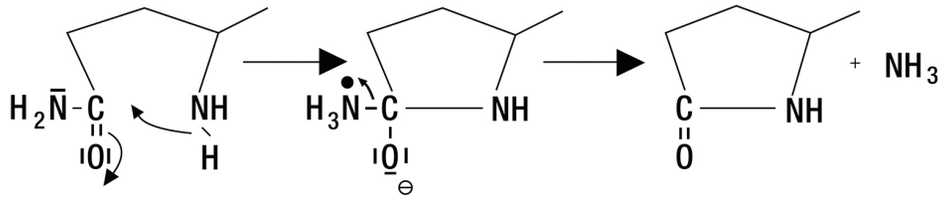

Figure 1. Suggested mechanism for the formation of pyroglutamic acid from glutamine.

Gln is commonly used as a dipetide through a conjugation with L-alanine (Ala-Gln) in the use of nutritional supplement. The dipeptide showed not only dramatically high solubility and stability (**Table 1**) but also can liberate and excrete after absorption into body (**Figure 2**) and ensure the proper excretion [2].

	Solubility (g/L H_2O at 20°C)	Stable in solution
Alanine	167.2	Yes
Cystine	0.1	Yes
Cystine-HCl	252.0	No
Bis-L-analyl-L-cystine	>500.0	Yes
Bis-glycyl-L-cystine	541.0	Yes
Tyrosine	0.4	Yes
L-alanyl-L-tyrosine	14.0	Yes
Glycyl-L-tyrosine	30.0	Yes
Glutamine	36.0	No
L-alanyl-L-glutamine	568.0	Yes
Glycyl-L-glutamine	154.0	Yes

Table 1. Solubility and stability profile of amino acids and conjugations.

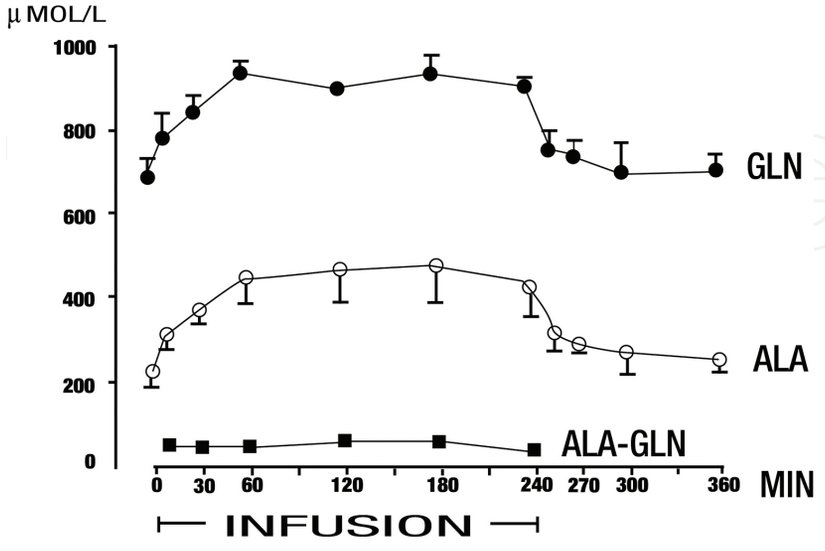

Figure 2. Plasma concentrations of alanine, glutamine, and Ala-Gln during and after continuous intravenous infusion of Ala-Gln (mean ± SD) [2].

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Gln is the most abundant amino acid in the body, representing around 30–35% of the amino acid nitrogen in the plasma. It contains two ammonia groups: one from its precursor glutamate and the other from free ammonia in the bloodstream. Because of it, one of its classic and first described functions was as a "nitrogen shuttle," which helps to protect the body from high concentrations of ammonia: Gln behaves as a buffer, receiving excess ammonia, and then releasing it when needed to form other amino acids, amino sugars, nucleotides, and urea.

Gln is mainly distributed in the skeletal muscle (60% of the total pool), short intestine, brain, kidney, and liver. This amino acid (AA) is supplied by specific organs for its metabolic use and adequate renal excretion (**Figure 3**) [3].

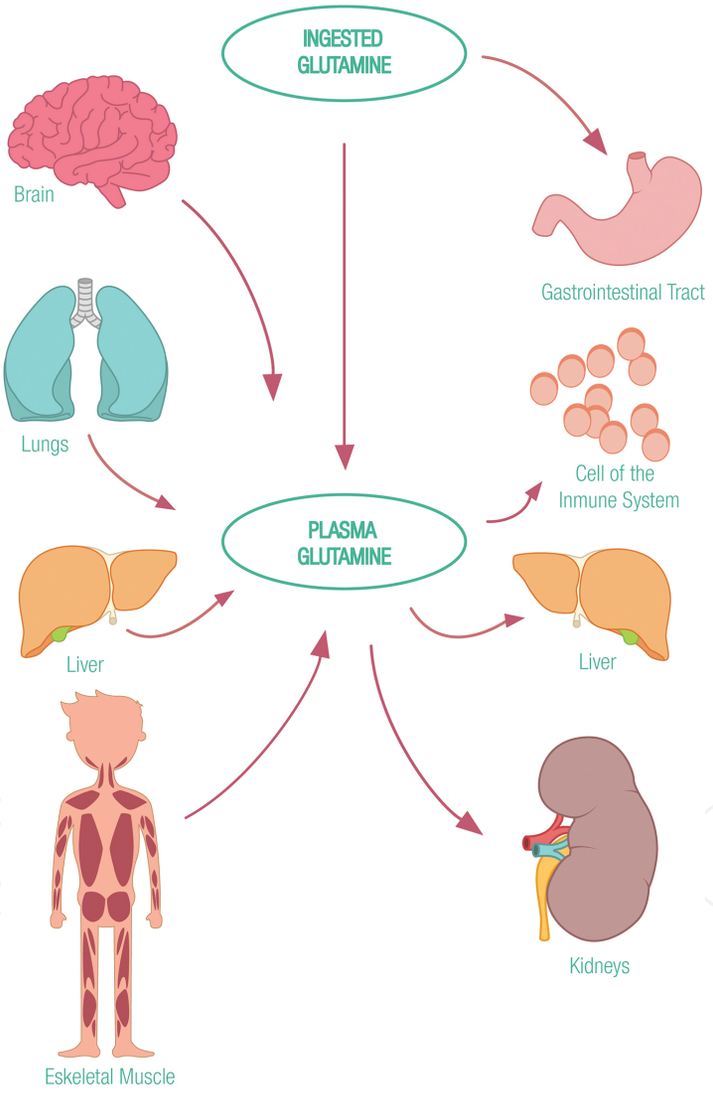

Figure 3. Glutamine distribution in the body.

The role of nutrition in the Gln metabolism has been widely studied. The initial studies on its physiological role suggested that Gln is not always necessary to be ingested from diet because it can accumulate to a high amount; however, this concept has changed in the recent years. In

fact, when 5–10 g \ day of Gln is consumed in the diet, the de novo synthesis of Gln is regulated by a demand to maintain a balance [4].

An extensive study that evaluated the glutamine content of a wide range of food has been performed. The results showed that the content varied from 0.01 to 9.49 g/100 g of food and a ratio of Gln contained in total protein reached around 1–33% of the intake. The most Gln-enriched foods were the one directed from beef meat, milk, tofu, white rice, corn protein, among others [5].

As mentioned above, the food containing Gln at high concentrations may be used as superfood. In this chapter, we precisely introduce the role of AA in the body, its possibility to be considered as a super nutrient, and we discuss its effectiveness in clinical practice.

2. Glutamine metabolism

Gln is considered to be a nonessential amino acid that was coined by Lacey JM and Wilmore in 1990, as human cells can readily synthesize by glutamine synthetase present in the skeletal muscles, liver, brain, and stomach tissues (**Figure 4**) [6].

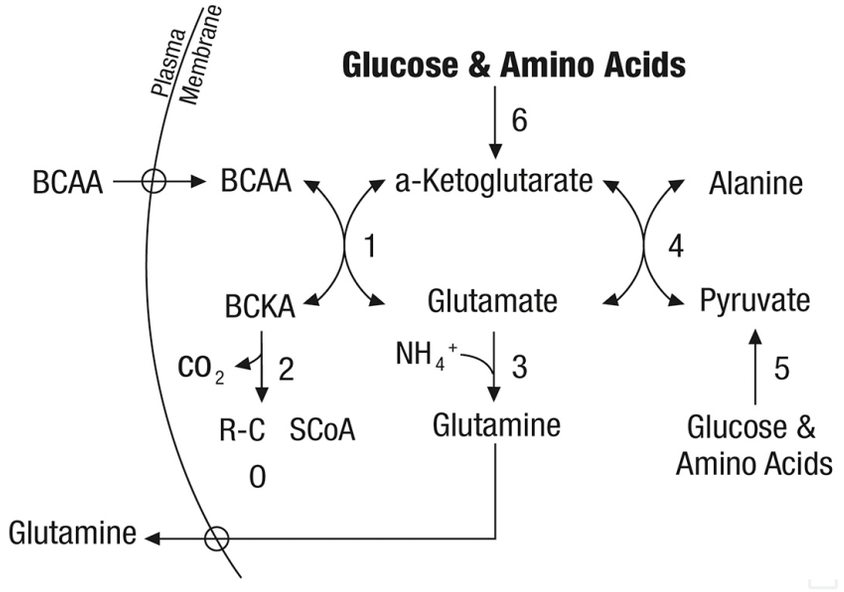

Figure 4. Glutamine biosynthesis process.

Gln is a highly versatile AA as shown in **Figure 5**: it can be converted to other amino acids, to glucose in the liver, and contributes amino groups to nucleotide, amino sugar, and protein biosynthesis. Moreover, it is related to multiple functions and molecular targets in physiological pathways [7].

The uptake into cellular compartments is mediated by several membrane transporters that regulate the homeostasis by coordinating the absorption, reabsorption, and delivery to tissues.

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These redundant and ubiquitous located transporters belong to different protein families. The complex interplay between the cell polarity and types of Gln transporters have been sophistically reviewed by Pochini et al. They described the role of the glutamine transporters linked to their different transport modes and coupling with Na^+ and H^+. Most transporters share the specific transport capacity with other neutral or cationic amino acids. Na^+-dependent co-transporters efficiently accumulate glutamine, while antiporters regulate the pools of glutamine and other amino acids.

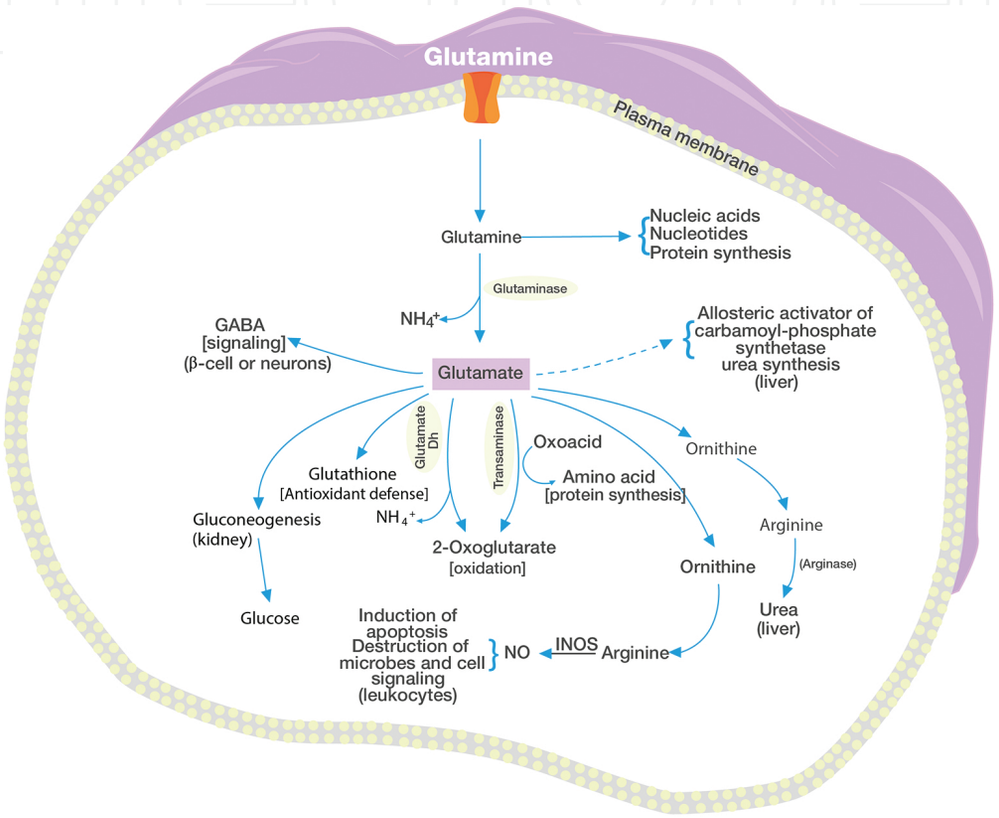

Figure 5. Glutamine intracellular metabolic pathway.

The most studied subfamilies of Gln transporters are the SLC1, 6, 7, and 38. The members involved in the homeostasis are the co-transporters B0AT1 and the SNAT members 1, 2, 3, 5, and 7; the antiporters ASCT2, LAT1 and 2 (**Figure 6**) [8].

Additionally, limited information on glycosylation and/or phosphorylation regulatory sites of the Gln transporters has been described. More studies in the field are needed to fully understand their associated mechanisms.

As shown in **Figure 7**, the metabolic pathway of Gln is a complex network of transport, and the hyperglutaminemia is a highly cytotoxic state classically reported in kidney and liver failure [9]. The proper function of these organs is to ensure the safe excretion. Gln is transformed to urea through the metabolic hepatic pathway and is excreted by the kidney. Additionally, in the intestine, muscle, and liver the Gln is converted to other compounds by chemical

reactions. At those organs, Gln is degraded and converted to glutamate, aspartate, CO_2, pyruvate, lactate, alanine, and citrate, among other metabolites [10].

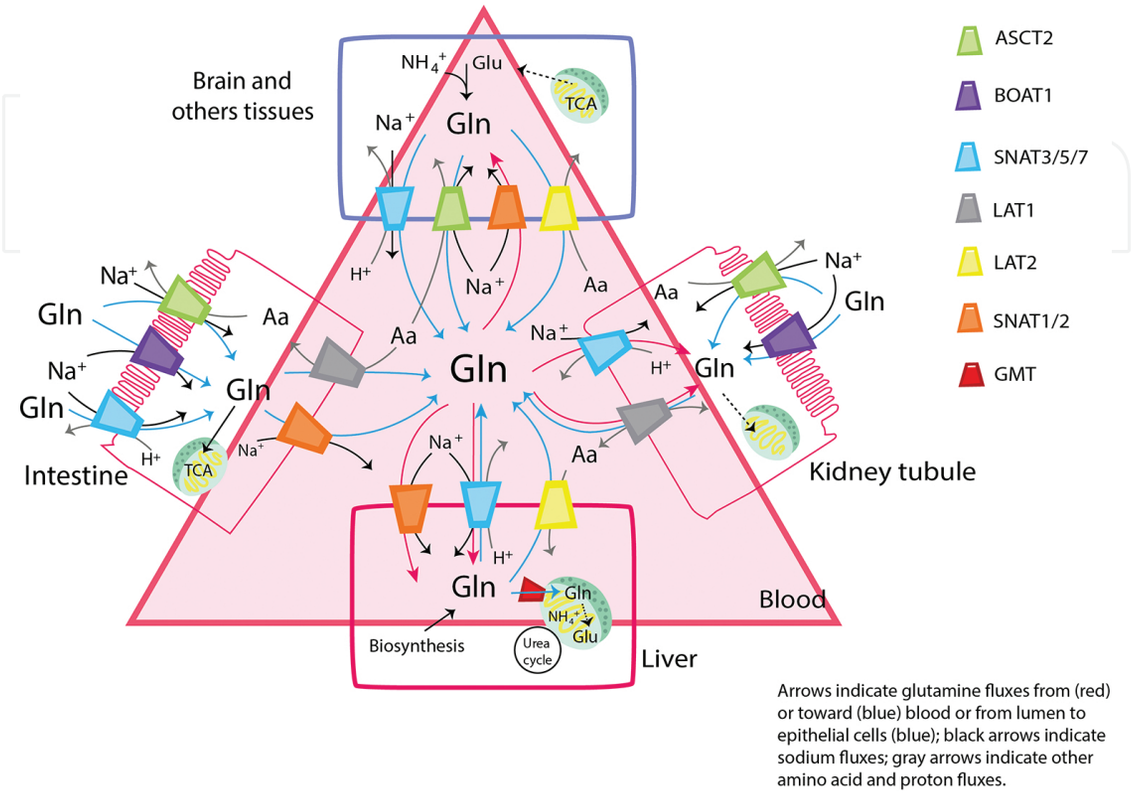

Figure 6. Glutamine transporters, modified from Pochini et al. [8].

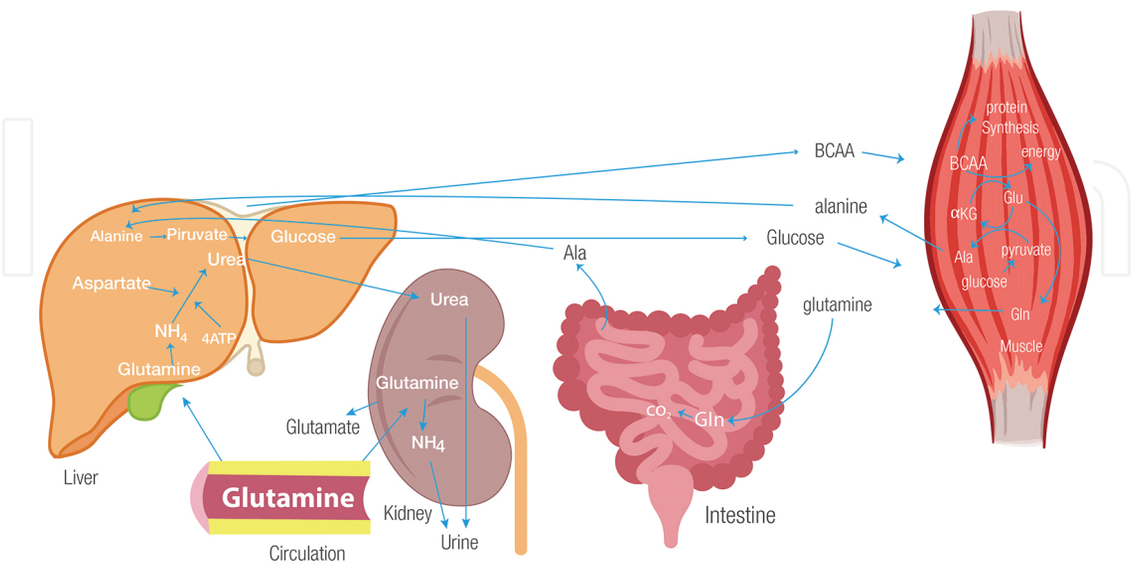

Figure 7. Glutamine transport and excretion system (Ala: alanine, BCAA: Branched Chain Amino Acids, αKG: alpha ketoglutarate).

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3. Glutamine depletion in hypercatabolism

The depletion of glutamine is a generally accepted phenomenon particularly observed in the intensive care units (ICU) patients [11]. However, no clear mechanism of the onset of this alteration have been investigated. During hypercatabolic stress, proliferating lymphocytes and immune-stimulated macrophages are major glutamine consumers [12]. The increased demands of Gln in hypercatabolic stress cause high secretion of Gln from skeletal muscle leading to muscle mass loss, a prevalent feature of ICU patients [13].

Of all AA, muscular Gln levels is the most important indicator to determine the restoring forth or surviving rate in ICU patients with prolonged sepsis [14], even more it has been reported that low Gln levels are an independent mortality predictor [11]. The decreased Gln plasma levels in ICU patients are around the 50% of normal levels and negatively correlated with the severity of the pathology.

Based on the clinical observations, the reduction in Gln is associated with higher mortality, length of hospital stay (LOS), and infection [15]. The clinical experts have suggested a series of metabolic alternations that in concentration would explain the poor outcome that an ICU patient with this depletion present (**Figure 8**).

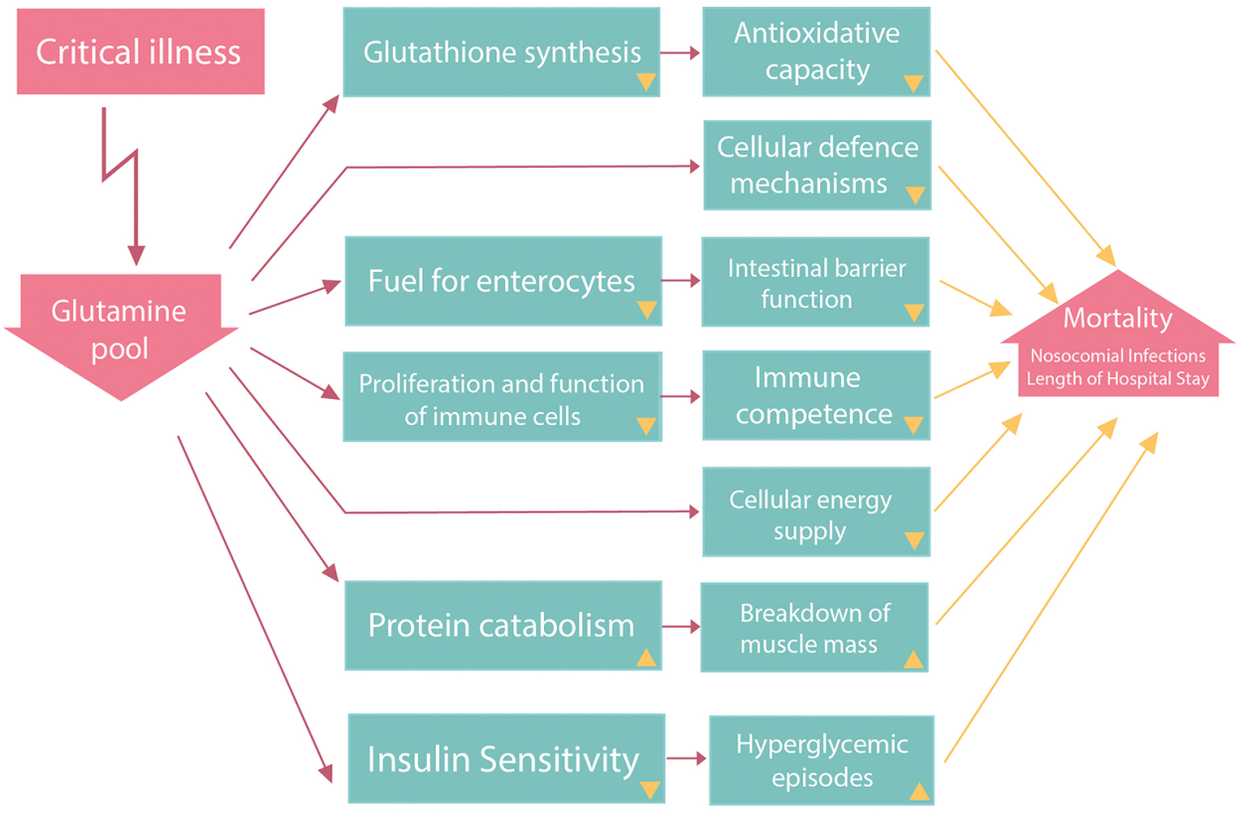

Figure 8. Consequences of glutamine depletion for the organism, modified Stehle et al. [15].

4. Molecular targets of glutamine

Several molecular actions of the Gln [16] have beneficial effects as a supplement with pharmaco logical actions. A supplement of Gln is effective for normalizing the metabolic processes that are altered in hypercatabolic patients. The last decades of biomedical research have identified the specific molecular targets in which this AA exerts its functions[1].

4.1. Glutathione biosynthesis

Glutathione (GSHis) is a reduced nonprotein thiol, which is present in all mammalian tissues and has important antioxidant and detoxification functions. Gln is a precursor of GSHis when combined with glycine and cysteine in the cytoplasmic compartment of the cell. This reduced metabolite has strong affinity to free radicals and toxins, via reaction to oxidized glutathione disulphide (GSSG). GSSG can be converted again to GSHis or be translocated to the vacuole for degradation. This conversion capacity confers its antioxidant and detoxicant effects to the cells (**Figure 9**).

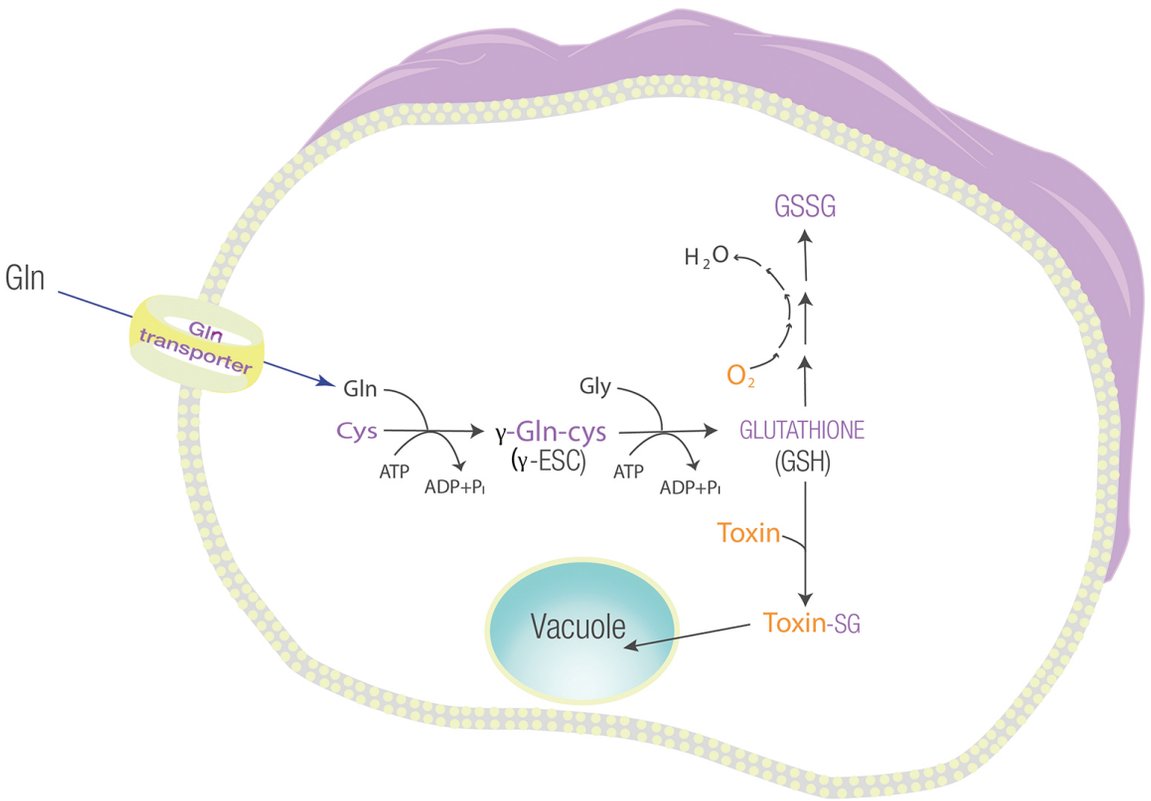

Figure 9. Antioxidant and detoxicant mechanism of glutathione (Cys: cysteine, ATP: adenosine triphosphate, ADP: adenosine diphosphate, y-ESC: gamma glutaminecystein dipeptide, Glu: glutamine, Gly: glycine, SG: glutathione disulfide).

[1] From Leguina-Ruzzi [16]. For the full compilation of references please check the cited article.

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4.2. Heat Shock Proteins genetic regulation

The Heat Shock Proteins (HSP) (also known as stress response proteins) are chaperones that are highly conserved and present in all cells. The important role of HSP is to participate in protein folding, assembly, and correct transport, enabling them to act normally. It has been shown that in sepsis or in inflammatory response syndrome, there is a significant reduction in the intracellular levels of HSP70, which correlates with severity of illness and mortality. Interestingly, administration of Gln enhanced the HSP70 expression through the crosstalk with the hexosamine pathway (**Figure 10**). An *in vitro* study demonstrated that the promotion in HSP70 synthesis by Gln is accompanied by a favorable inflammatory response mediated by IL-8 and IL-10 [17].

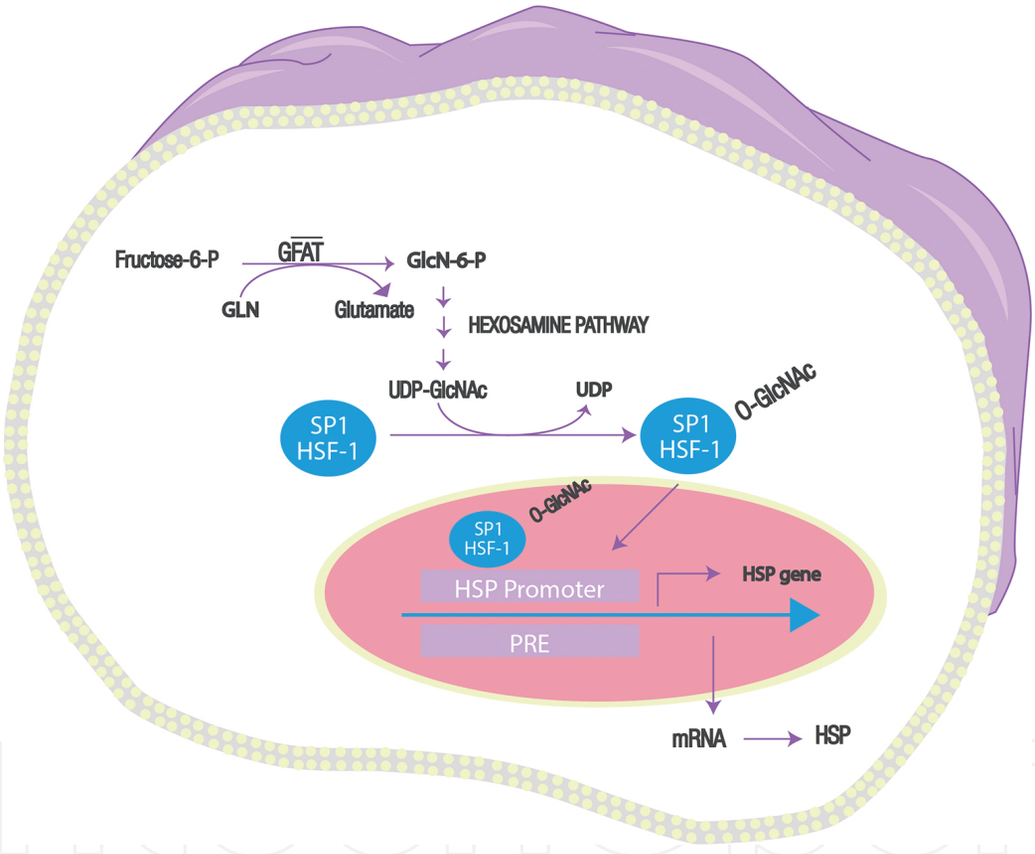

Figure 10. Enhancement of HSP synthesis by glutamine and hexosamine cross-talk (GFAT: glutamine fructose-6-phospate aminotransferase, GlcN-6-P: glucosamine-6-phospato, UDP-GlcNAc: uridine diphosphate N-acetylglucosamine, UDP: uridine di phosphate, SP1: specific protein 1, HSF-1: heat shock transcription factor 1, O-GlcNAc: O-linked N-acetylglucosamine, PRE: promotor regulatory elements).

4.3. Enterocyte integrity

The bacterial translocation (BT) is mainly occurring under pathological conditions because the passage of viable bacteria from the gastrointestinal tract to extraintestinal sites is opened in such conditions.

ICU patients are at higher risk of bacterial translocation: 15% of these patients is affected. BT is one of the main causes of sepsis and multiorgan failure.

It has been reported that the supplementation of Gln to the total parenteral nutrition (TPN) reduces the prevalence of BT and prevents inflammatory intestinal complications. *In vivo* and *in vitro* studies have reported that the enterocyte uses Gln as its principal energy source and enhances its growth and proliferation. Moreover, the enterocyte is capable of transporting Gln to and from the intestinal circulation, creating a bidirectional supply of this AA. This process uses a series of antiporters coupled with Na^+ and H^+ from the family of ASCT2. On the other hand, a deprivation of Gln facilitates BT, which suggests the importance of Gln in the intestinal barrier integrity (**Figure 11**.)

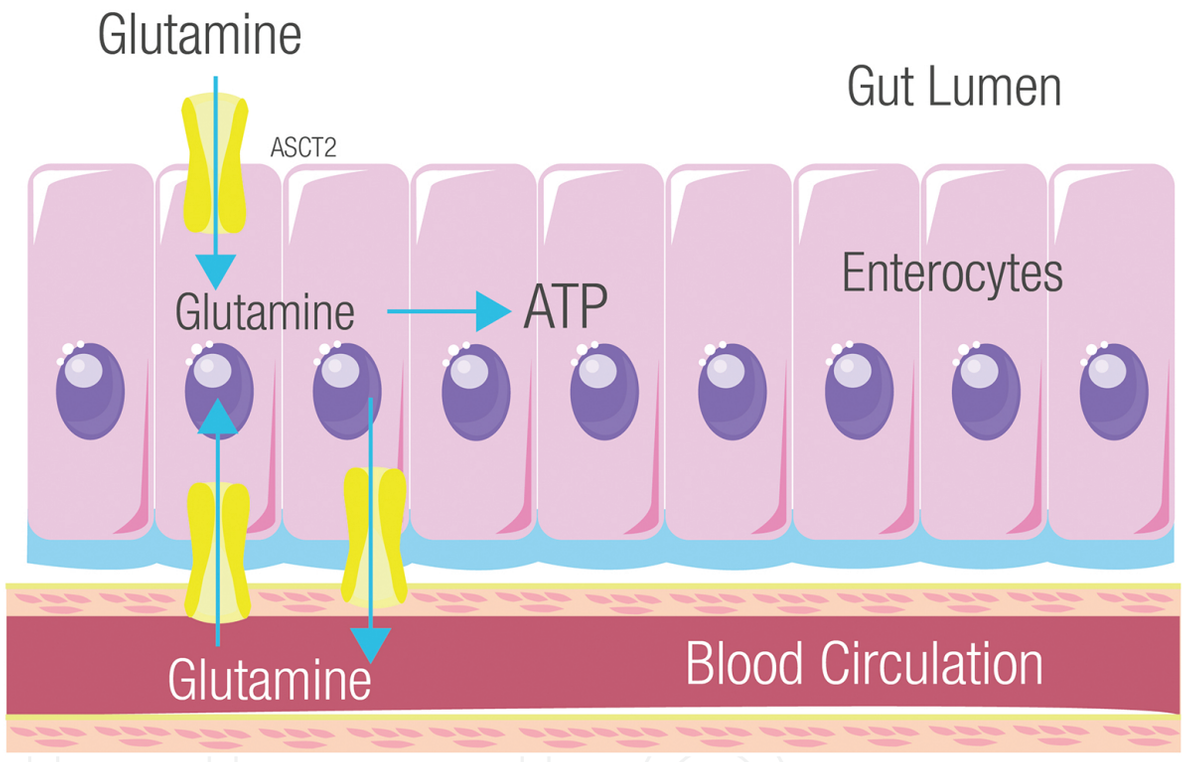

Figure 11. Glutamine transport and metabolism in the enterocyte.

4.4. Lymphocyte function

The activation of naive T cells is a pivotal process for the immune response and is a highly energetic event in which T cells require an increase in nutrient metabolism. For the series of processes required, Gln uptake is a fundamental step highly regulated by the extracellular signal-regulated kinases (ERK)/MAPK pathway (**Figure 12**).

In vitro studies have demonstrated that the Gln supplementation modulates the proliferation of the naive T cells, and the extracellular Gln is essential as a respiratory fuel. The supplementation of Gln has a prominent effect on both activations of lymphocyte and modulation of secretory functions as well as killing bacteria by neutrophils and macrophage phagocytosis.

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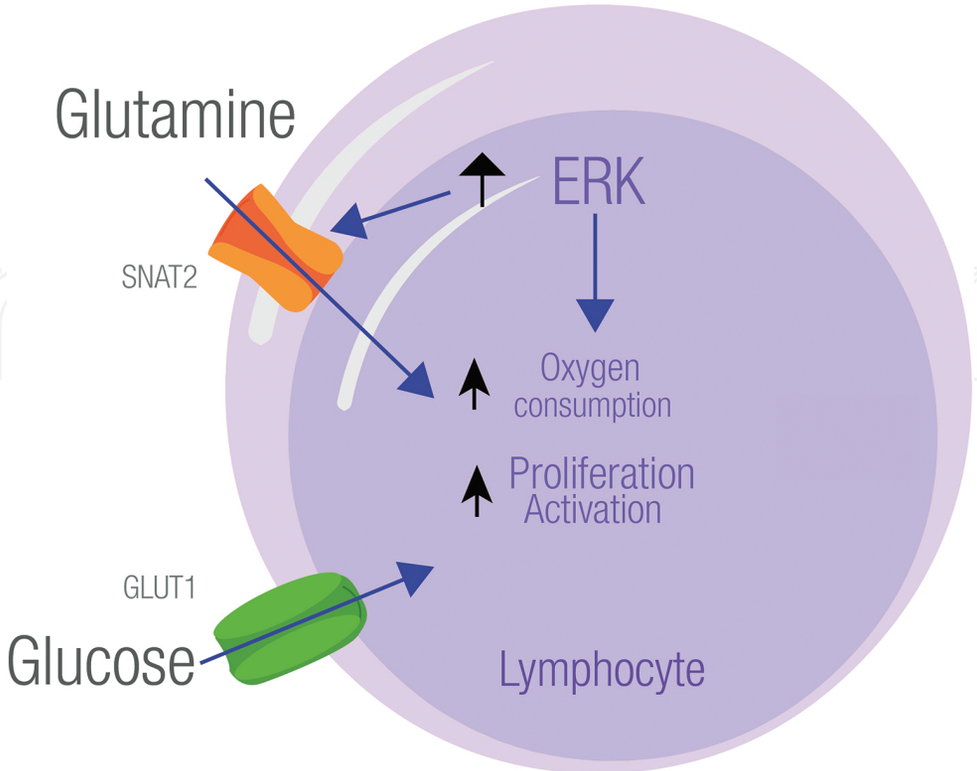

Figure 12. Metabolic processes required for lymphocyte activation (GLUT1: glucose transporter 1, ERK: extracellular signal-regulated kinases).

4.5. Nitrogen balance

The regulation of protein concentration in the body at a relatively normal level is a physiologically favorable process to maintain the cellular integrity. It is widely accepted that ICU patients with TPN present a negative balance that correlates with the clinical outcome. The capacity of Gln pool and nitrogen balance was improved by its supplementation has shown the capacity to recover the nitrogen balance in three days after supplementation. Furthermore, the Gln-supplemented diet did not affect portal ammonia concentration, showing that it does not affect the excretion pathway and did not cause anabolic effects that are associated with cardiovascular alterations [18].

Consequently, these clinical observations could be explained in part by the capacity of the Gln to act as a substrate for other AA or to construct more protein at the muscle.

4.6. Insulin release

The hyperglycemic condition is a metabolic emergency commonly associated with uncontrolled diabetes mellitus, which may result in significant morbidity and death. The prevalence in UCI patients is approximately 40% and classically was presumed to be an adaptive response to the hypercatabolism. However, more recent reports have shown that hyperglycemia is associated with unfavorable clinical outcomes.

The role of Gln in insulin sensitivity and hyperglycemia is a hot topic that has been actively studied. A recent randomized clinical trial demonstrated that the supplementation of Gln to the TPN for more than 7 days reduces significantly the hyperglycemic episodes and the insulin requirement in ICU polytrauma patients. *In vivo* and *in vitro* studies have demonstrated the Gln stimulates calcium-dependent insulin secretion and beta-cell depolarization and enhances the insulin glucose response. The improved process involves the metabolism of the gamma-glutamyl cycle, the glutathione synthesis, and the mitochondrial function (**Figure 13**).

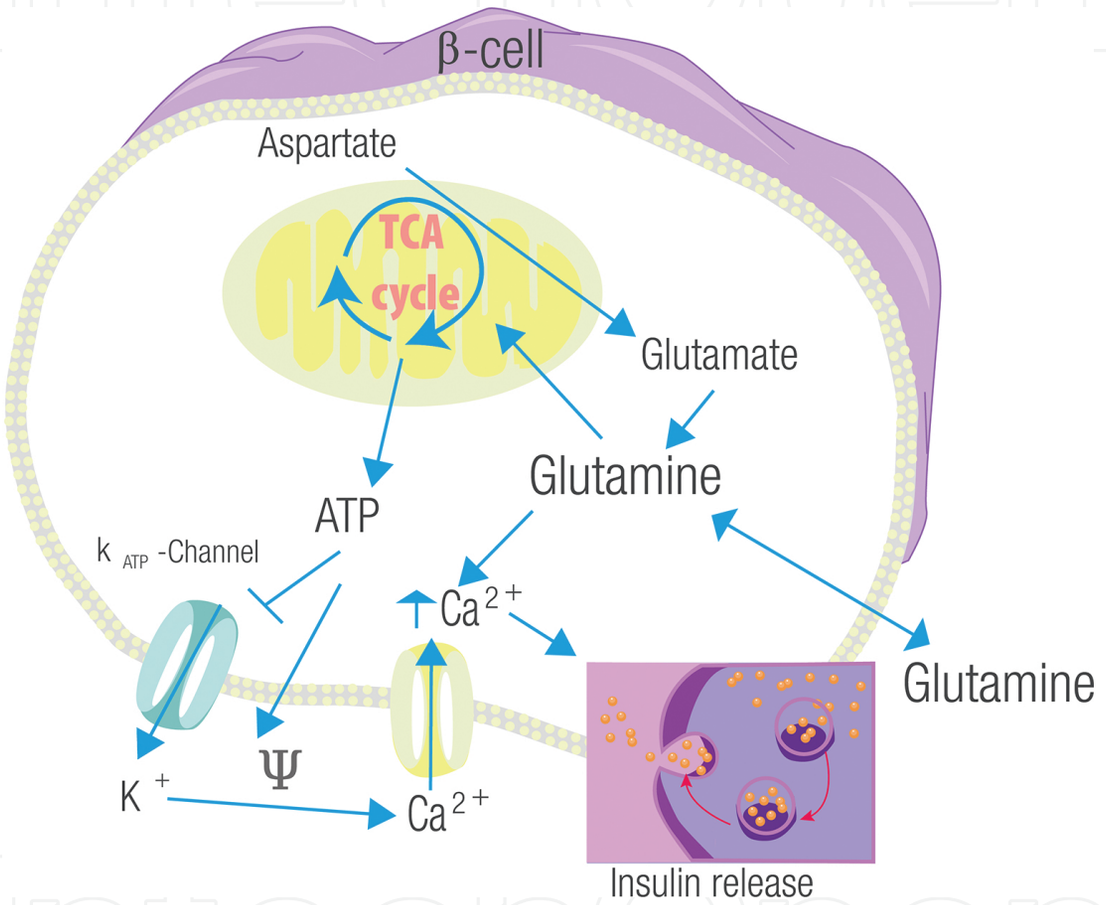

Figure 13. Glutamine-dependent insulin release (TCA: tricarboxylic acid cycle, ATP: adenosine triphosphate, K_{ATP}-channel: ATP-sensitive potassium channel).

4.7. Others beneficial effects of glutamine

The scientific community has been eager to understand the beneficial effects of Gln. Recent clinical, *in vivo* and *in vitro* studies have suggested the cardio protective role of Gln [19, 20] in ischemic heart disease and diabetic cardiomyopathy [21]. Additionally, studies suggest that the supplementation of Gln enhances the healing of the lung parenchymal injuries, reducing the air leakage [22], also regulates the pulmonary infiltration in sepsis, modulating the immunological function [23], and endogenous levels of this AA modulates the vasoactive response of the nitric oxide (NO) in pulmonary hypertension [24].

5. Enteral and parenteral glutamine supplementation

The benefits of parenteral and enteral Gln supplementation in critically ill patients have been shown in numerous clinical trials. Many authors reported in systematic reviews and meta-analyses that Gln supplementation, combined with enteral nutrition (EN) and parenteral nutrition (PN), is associated with reduced infectious morbidity and improved recovery from critical illness compared with standard [25]. The most relevant results have been observed with parenteral supplementation, a phenomenon that might be explained by highly regulated metabolism of the AA and the enterocyte participation (**Figure 11**).

Standard PN and EN formulations do not contain Gln as monopeptide due to the poor solubility and the instability in heat sterilization as described in Section 2. The solubility is limited to 35 g/l (3.5%) at 20°C, and the recommendation is not to use solutions of 2.5%, to avoid precipitation that could affect the proper nutritional administration. To solve these problems, the clinical use by parenteral formulation has been supported in the administration of the Gln dipeptides with other AA, which is more stable and allow prolonged conservation. The dipeptides are rapidly hydrolyzed by serum peptidases, allowing the utilization of 100% of Gln (**Figure 2**). The dipeptides are more soluble than Gln alone; the solubility of Gly-L-Gln is 154 g/l (15.4%) and the solubility of L-Ala-L-Gln is 568 g/l (56.8%). Importantly, parenteral formulations contain 200 g/l (20%) of dipeptide L-Ala-L-Gln which is equivalent to 134 g/l of Gln and enteral formulations contain 2–4 g/l (0.02–0.04%) [26].

Currently, the most commercially used Gln products are Dipeptiven® for PN and Reconvan® for EN produced by Fresenius Kabi Co.; however, it is important to mention that the basic enteral formulations contain Gln as a part of the protein composition and under low concentrations; for example, the Fresubin® line by Fresenius Kabi (Bad Homburg vor der Höhe, Germany) fluctuates around 3.5—9.4 g per presentation bag.

The early enteral feeding has been associated with a substantial reduction in length of hospital stay (LOS) with a significant reduction in the frequency of acquired infections. The enteral Gln supplementation has been shown to be safe and well tolerated and may help to reduce infectious complications, oxidative stress, intestinal permeability, mortality, and LOS [27]. Houdijk [28]. However, in 2015, Van Zanten et al. published a systematic review and meta-analysis with a total of 11 studies involving 1079 adult critical ill patients and enteral Gln supplementation was not associated with a reduction of hospital mortality, infectious complications, or stay in the intensive care unit. In the subset of patients with burns, there may be a significant benefit in hospital mortality [29].

The effective concentration of Gln in TPN has been suggested by different multidisciplinary medical groups. According to the ESPEN guideline, "when PN is indicated in ICU patients the amino acid solution should contain 0.2–0.4 g/kg/day of L-glutamine (e.g. 0.3–0.6 g/kg/day alanyl-glutamine dipeptide)" [30] and "glutamine should be added to a standard enteral formulation in burned patients and trauma patients" [31]. It is important to consider that the main contraindications are renal failure (Creatinine clearance <20 mL/min), metabolic acidosis, and liver failure (Liver function tests International Normalized Ratio >1.5) [32]. Interestingly,

Helling et al. evidenced the association between liver failure and high plasma Gln levels [33], a medical situation that needs to be taken into consideration at the moment to prescribe Gln supplementation.

The use of EN with Gln may not be enough to full up plasma concentration up to normal level; new remarkable data showed that enteral supplementation only is not enough to revert the Gln depletion [34]. The values and data accumulated in PN cannot be directly extrapolated to EN supplementation and, therefore, cannot be used as the base for recommendation. According to the trials, high protein enteral nutrition enriched with immuno modulator nutrients, such as Gln, did not improve infectious complications or other clinical end points compared to standard EN [35].

On the other hand, administration of TPN with Gln is effective. In 2002, Goether showed improvement in a 6-month survival in a patient with at least 9 days of parenteral Gln supplementation [28]. Until 2014, several trials showed that PN with Gln supplementation given in conjunction with nutrition support continues to be associated with a significant reduction in hospital mortality and hospital LOS. A systematic review published by Wischmeyer et al. in 2014 summarized all randomized controlled trials conducted from 1997 to 2013, showing the benefits of parenteral glutamine [36]. However, in 2013, the Reducing Deaths Due to Oxidative Stress (REDOX) study, the largest trial to date showed that the supplementation of Gln was associated with higher mortality and no beneficial effects were seen [37]. The results of this trial awaken a question to the safety and efficacy of the use of glutamine in critically ill patients, in high doses (much higher than recommended) may produce adverse effects. In this study, they used a combined enteral and IV Gln supplementation in higher doses than the recommended ones: the intervention setting was the Gln enteral 30 g/day plus parenteral 15 g/day giving around 1 g/kg/day, doses higher than the classically recommended by the clinical guidelines of the date. Furthermore, the heterogeneous enrolment included patients that fulfilled contraindication criteria for its supplementation.

A year later, the authors published a new analysis of the data (post hoc study) concluding that high doses of Gln may be associated with higher mortality in patients with multiorgan failure and particularly renal dysfunction [38]. These conclusions had a high impact not only on the pharmaceutical industry but also on the clinical practice: two of the most important guidelines changed dramatically the recommendation of the use of Gln. The Canadian Clinical Practice Guidelines (2016) [39] and ASPEN (2016) [40] downgraded the Gln supplementation based of the REDOX results and a series of studies that do not justify this.

It is important to highlight that even after these dramatic results, the research has given important steps in the years follow the REDOX. It gave not only answers to the basic questions such as the glutamine plasmatic levels in ICU patients and its safe use as supplement to TPN but also opened a whole perspective for further research and use. Pérez-Bárcena et al. [41], in 2014, showed that low doses of IV Gln for 5 days did not show beneficial effects in the ICU patients, without causing any derogative effect. Additionally, plasmatic Gln measurement in the patients showed that those with lower levels presented a worse outcome (mortality, LOS, and infections) in which a supplementation with higher doses might be necessary.

In the same year, Grintescu et al. [42] showed that Gln supplementation in trauma patients reduces hyperglycemic episodes and improves insulin response. The conclusions suggest a role for Gln as an insulin sensitizer.

Despite the controversy, when parenteral nutrition is prescribed, the Gln supplementation is still recommended in critically ill patients. There are insufficient data to generate recommendations for IV glutamine in critically ill patients who are receiving EN. New large, multicenter, prospective randomized clinical trials are needed to confirm the beneficial effects of Gln in the mortality, LOS, and infections rates as main clinical outcomes are highly relevant in the critical care unit.

6. Conclusion

The multiple functions of Gln and the possibility of its use as a pharmaco-nutrient under the hypercatabolic condition were introduced in this chapter. The studies on basic and clinical science showed the beneficial effects of Gln in the metabolism of subjects suffering from a catabolic stress condition. *In vitro* data performed under concentration ranges from 500 to 2000 μmol/L of Gln, and it could represent supplementation and supports the clinical findings. Gln pleiotropic functions make it a great candidate for its use in pathological conditions; however, important lessons have to be learned from the controversial evidence that impacts negatively on its use. Still nonconclusive data have weakened it role in oral and enteral supplementation making mandatory new research in this field.

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Authors contributions: A. Leguina-Ruzzi conceptualized and prepared the chapter. M. Cariqueo.

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