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Glutamine and Its Actions: A Bird's Eye View

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Abstract

Glutamine (Gln) is the most abundant amino acid in the body, playing a versatile role in both maintaining homeostasis and contributing to various pathologies. This review explores the physiological functions of Gln, detailing its enzymatic synthesis and degradation, as well as its role across different organs, tissues and systems in both normal and pathological conditions. This review is a search of relevant topics related with Gln and its actions; its key areas discussed include the immune system, heat shock proteins, skeletal muscle, central nervous system, the intestinal mucosal barrier, liver, kidney, gluconeogenesis, types 1 and 2 diabetes, burns, cancer, and hepatic encephalopathy. While Gln demonstrates numerous beneficial effects, it can also contribute to adverse outcomes in specific diseases, such as cancer and hepatic encephalopathy. Despite these complexities, it is crucial to keep searching for glutamine's role in health and disease. Understanding how Gln supplementation may support patients taking multidrug therapy to reduce the need for certain medications, and enhancing treatment adherence and disease management is particularly important.

Keywords

Glutamine, Metabolism, Immune System, Cancer, Hepatic Encephalopathy, Burns

1. Introduction

Glutamine (Gln) is a non-essential amino acid primarily synthesized in skeletal muscle and the liver through the action of Glutamine synthetase (GS, EC 6.3.1.2),

which catalyzes the addition of ammonia (NH_3) to glutamate. Conversely, Glutaminase (GLS, Glutamine amidohydrolase, EC 3.5.1.2) hydrolyzes Gln, producing glutamate and ammonium ion (NH_4^+) (**Figure 1**). As the most abundant amino acid in the body, glutamine is generally classified as non-essential; however, under certain stress conditions, its endogenous synthesis may become insufficient, needing supplementation [1].

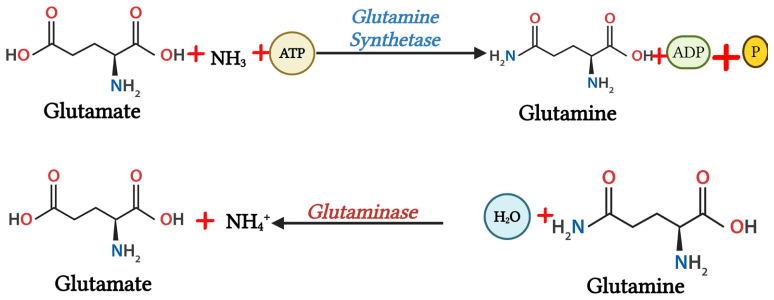

Figure 1. Glutamine metabolism. *Created by AYFD in BioRender.com.*

Glutamine is implicated in numerous critical physiological functions, including ammonia detoxification, pH homeostasis, and the biosynthesis of purines and pyrimidines. In addition, it plays a key role in the expression of proteins such as heat shock proteins (HSPs), under both normal physiological conditions and in pathological states, including sepsis and cancer [2].

The following sections provide a comprehensive overview of glutamine's actions across various organs and systems.

2. Immune System

The immune system is composed of a network of cells and humoral factors, responsible for maintaining the organism's optimal health by detecting pathogens and internal damage [3] [4]. In situations where the organism's well-being is compromised, immune cells have a heightened energy demand, primarily met through glucose metabolism. Concurrently, the utilization of amino acids, particularly Gln, increases. As the most abundant amino acid in the body, Gln is critical for the immune system, being used in amounts comparable to glucose due to its metabolic versatility [2] [5].

Macrophages, the first line of defense in the immune system, are mobile mononuclear cells activated by inflammatory stimuli that produce inflammatory mediators [5]-[7]. There are two main types of macrophages: M1, which initiates a rapid inflammatory response through the secretion of pro-inflammatory cytokines, and M2, which releases anti-inflammatory cytokines and promotes tissue repair. α-Ketoglutarate, a product of glutaminolysis, promotes macrophages differentiation into M2, via IL-4/STAT6/IRF4 signaling [8]-[10].

Macrophages generate large quantities of free radicals to destroy pathogens, using Gln as a precursor of arginine synthesis. Nitric oxide synthase (NOS, EC 1.14.13.39), converts arginine into nitric oxide (NO), a potent free radical [8] [11].

Even though dietary arginine is available, it is depleted during catabolic conditions, such as infections, necessitating the use of endogenous arginine synthesized in the liver via the urea cycle. During endotoxemia macrophages consume large amounts of Gln, which, in conjunction with NOS, converts arginine into NO and citrulline, suggesting that Gln is crucial for NO production during sepsis (**Figure 2**) [12] [13].

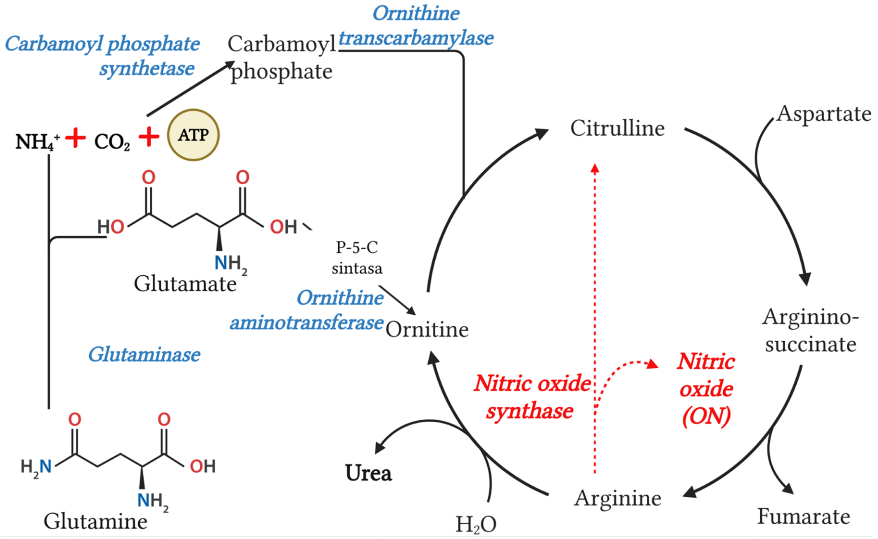

Figure 2. Nitric oxide synthesis in macrophages. *Modified from* [12]. *Created by AYFD in BioRender.com.*

M1 macrophages release pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukine-1β (IL-1β) and IL-6, with cytokine production closely linked to extracellular Gln availability. TNF-α, the first cytokine released during infection, activates neutrophils, followed by IL-1, which stimulates T and B lymphocytes; both cytokines subsequently activate IL-6 [14] [15].

Neutrophils, another key immune cell type, are polymorphonuclear leukocytes, with dense chromatin and lobed nucleus, that respond to pathogen infection signals through phagocytosis [7] [16] [17]. Neutrophils also produce reactive oxygen species (ROS) and reactive nitrogen species to eliminate pathogens, utilizing Gln as a substrate to donate NH_4^+ for NO synthesis [12] [13]. In addition, Gln in neutrophils serves as a precursor for superoxide anion (O_2^-) production. α-Ketoglutarate, generated from Gln via Glutamate dehydrogenase (GDH, EC 1.4.1.2), Alanine aminotransferase (EC 2.6.1.2), or Aspartate aminotransferase (formerly Glutamic-oxaloacetic transaminase, GOT or AST, EC 2.6.1.1), enter the tricarboxylic acid (TCA) cycle. Malate dehydrogenase (EC 1.1.1.37) catalyzes the reversible conversion of oxaloacetate, which is necessary for O_2^- formation by the NADPH oxidase (NOX2, EC 1.6.3.1) complex (**Figure 3**) [2] [5].

Immune cells not only produce free radicals but must also maintain redox homeostasis. Gln plays a crucial role in it by serving as a substrate for glutathione synthesis, a key antioxidant [2] [5].

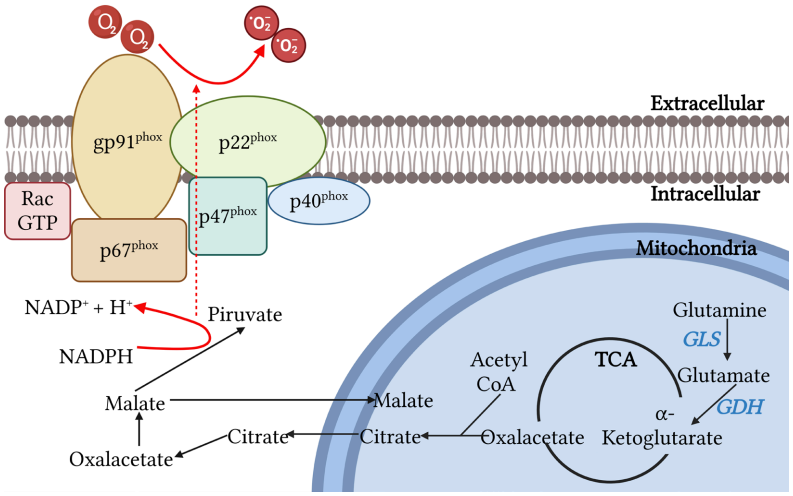

Figure 3. Glutamine as a precursor of superoxide, TCA (tricarboxylic acid cycle). *Modified from* [18]. *Created by AYFD in BioRender.com.*

Moreover, lymphocytes, responsible for immune memory, depend heavily on Gln, and its uptake increases when cells are exposed to mitogens [19]. These small, round cells with large nucleus are divided into two main types: T lymphocytes, which mature in the thymus, and B lymphocytes, which mature in the bone marrow [5] [7]. Lymphocyte maturation is Gln-dependent, and its absence halts cell proliferation. Higher Gln availability enhances lymphocyte differentiation, though the reason for this dependency remains unclear, as Gln cannot be substituted by other amino acids. In addition, Gln metabolism supports the production of various intermediates in the TCA cycle, facilitating continuous energy production. Furthermore, Gln donates nitrogen and carbon for synthesis of DNA, RNA, proteins, and lipids [5] [14] [19]-[21].

3. Heat Shock Proteins

Heat shock proteins (HSPs) are families of proteins classified by their molecular weight, including HSP110, HSP100, HSP90, HSP70, HSP60, HSP40, and small HSPs. These proteins play a key role in maintaining proteostasis (the homeostasis of cell proteins), which is essential for cell survival. HSPs are typically expressed in response to stressful conditions, such as thermal stress, exercise, ischemia, or oxidative stress, and their main function is to act as molecular chaperones. Additionally, HSPs are involved in anti-inflammatory and anti-apoptotic actions [22]-[24].

Glutamine is closely associated with the expression of HSPs, particularly the HSP70 family, which is the most abundant in the organism. This association occurs through the biosynthesis of hexosamines, where Gln interacts with fructose-6-phosphate, catalyzed by Glutamine-fructose 6-phosphate aminotransferase (EC 2.6.1.16), to form eventually UDP-GlcNAc. This pathway activates transcription factors such as Sp1, which induces Heat shock factor 1 (HSF1), thereby enhancing HSP70 expression [2] [24]-[27].

4. Skeletal Muscle

Glutamine synthesis occurs in various organs, including lungs, liver, brain, and skeletal muscle, being this last one the most significant contributor, accounting for around 80% of the body's Gln synthesis due to its larger mass. The concentration of amino acids within skeletal muscle varies by fibers types, with Gln predominantly located in type 1 fibers [2] [28]. Due to its abundance, Gln from skeletal muscle is used throughout the body for the synthesis of purines and pyrimidines, which are essential for DNA and RNA production. In these processes Gln donates NH_4^+ [28] [29]. Under stressful conditions circulating Gln is diminished, and then its synthesis is augmented. Studies have shown that glucocorticoids stimulate both Gln synthesis and transport, promoting its release into extracellular space [27]. In addition, glucocorticoids increase GS mRNA expression, resulting in increased GS activity in response to decreased intracellular Gln [2] [28] [29]. However, the transmembrane gradient for Gln uptake also increases, facilitated by Na^+-dependent channels stimulated by insulin-like growth factors. As intracellular Gln concentration rises, GS expression is subsequently inhibited [29].

5. Central Nervous System

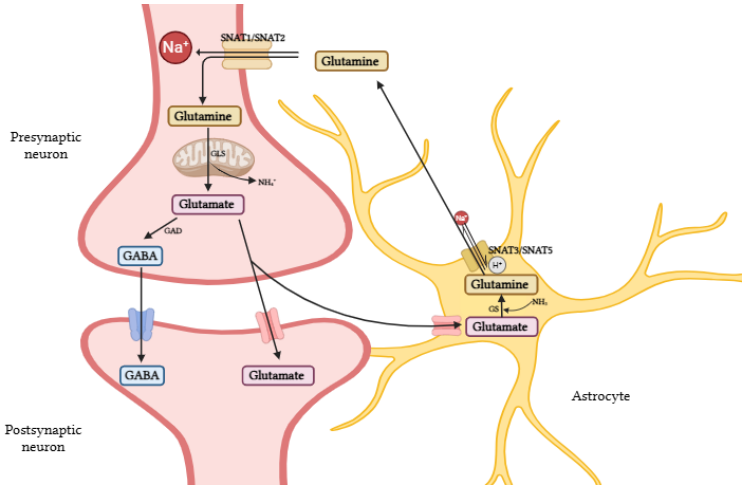

Figure 4. GABA/glutamate/glutamine cycle. In neurons Gln uptake is mediated by SNAT1 and SNAT2, which are Na^+-dependent electrogenic transporters. The Gln enters mitochondria, where it is metabolized by phosphate-dependent GLS, producing glutamate and NH_4^+. Glutamate is decarboxylated by GAD, to produce GABA, or it comes out of the neuron and enters to astrocyte where it is amidated to Gln by the action GS. Gln is transported to the extracellular milieu by SNTA3/SNAT5. *Created by AYFD in BioRender.com.*

In the central nervous system Gln serves as the key intermediary for recycling neurotransmitters, specifically glutamate (Glu) and γ-aminobutiric acid (GABA), through the glutamate/glutamine cycle, which involves interactions between neurons and astrocytes [30] [31] (**Figure 4**). Glutamate, the principal excitatory neurotransmitter released by synaptic neurons enters astrocytes, where it is amidated

to form Gln via the action of GS in the presence of ATP and NH_3. This Gln is subsequently transported into the extracellular space, and taken up by neurons, where it is deaminated in mitochondria by GLS to generate glutamate. Glutamate is decarboxylated by Glutamate decarboxylase (GAD, EC 4.1.1.15), to produce the neurotransmitter GABA, the main inhibitory neurotransmitter [32].

The effective functioning of the glutamate/glutamine cycle in both neurons and astrocytes requires specific Gln transporters. Several transport systems have been identified, with the system N transporters, SNAT3 and SNAT5, playing a key role in astrocytes. These bidirectional transporters facilitate the release of Gln into the extracellular space, accompanied by the exit of one Na^+ and the entry of one H^+ into the cell, making them the main transport mechanism for Gln in astrocytes [30] [33]. In neurons, Gln uptake is mediated by system A transporters SNAT1 and SNAT2, which are Na^+-dependent electrogenic transporters. Unlike system N, they do not exchange H^+, allowing intracellular pH to remain stable during amino acids incorporation (**Figure 4**) [34] [35].

6. Intestinal Mucosal Barrier

While skeletal muscle is the primary site of Gln synthesis, the intestine is the largest consumer of this amino acid, utilizing it as an energy substrate at a higher rate than glucose. Consequently, the intestine lacks Gln reserves due to the high activity of GLS. The interaction between GLS and Gln is decisive for maintaining the integrity of the intestinal mucosal barrier, which avoids the crossing of bacteria towards the bloodstream [2].

In recent decades the role of Gln in preserving intestinal functionality has been extensively studied. Glutamine serves as the primary energy source for enterocytes. For instance, Meynial-Denis *et al*. reported that Gln reduces oxidative stress in enterocytes of old rats, by promoting glutathione synthesis, thereby reducing intestinal mucosal barrier loss, and preventing weight loss [36]. Similarly, Coëffier *et al*. found that Gln administration significantly reduces IL-6 and IL-8 expression in human, suggesting that Gln could be a therapeutic option for mitigating intestinal inflammatory diseases [37]. Comparable results were obtained in rats subjected to exercise and Gln supplementation [38].

In cases of intestinal inflammatory diseases, disruption of the intestinal mucosal barrier can lead to the translocation of microbiota bacteria into the bloodstream [1] [38]. Intestinal permeability is regulated by the ubiquitin-proteasome system, which is involved in protein degradation and regulates several cellular pathways, including apoptosis, cell proliferation, inflammatory response, and antigen presentation [2] [39] [40]. Studies on the relationship between ubiquitin-proteasome activity and Gln supplementation, have shown that Gln modifies protein ubiquitination, leading to reduce inflammation and decrease intestinal permeability [2] [39] [40].

The intestine is particularly sensitive to experience ischemia, making ischemia/reperfusion (I/R) injury a common and severe condition in clinical practice,

and it is considered an abdominal emergency, with high mortality rates [41]-[44]. I/R injury can result from neonatal necrotizing enterocolitis, acute mesenteric ischemia, volvulus, severe trauma, and transplants, making it largely unpreventable [41]-[44]. To explore potential treatments to reduce morbidity and mortality associated with I/R, various animal models have been developed. In one such study, Zabot *et al*. stimulated I/R injury by occluding the mesenteric artery and celiac trunk, then administered a Gln supplement. Their results showed that Gln decreased lipid peroxidation and IL-6 expression, diminishing inflammatory response, lower intestinal permeability, and prevention of multiple organic failure [44].

7. Liver

While the intestine is the primary consumer of Gln under normal conditions, the liver becomes the organ with the highest Gln metabolism during stressful conditions to perform various functions, such as hepatocyte proliferation, gluconeogenesis, blood pH regulation, and ammonia (NH_3) detoxification, among others [2].

Ammonia detoxification is a critical hepatic action, as NH_3 is highly toxic to the body. Under physiological conditions, the hepatic urea cycle facilitates this process, where cytosolic Carbamoyl phosphate synthetase II (EC 6.3.4.16) synthesizes carbamoyl phosphate from Gln-derived NH_3. In hereditary disorders where urea cycle enzymes are deficient, NH_3 accumulates in the bloodstream, necessitating alternative detoxification strategies. One such strategy involves Gln synthesis, in which glutamate binds NH_3. However, this reaction could not be enough, and some patients must be treated with sodium phenylbutyrate, which binds Gln to form phenylacetylglutamine, enabling the elimination of two nitrogen atoms via urine [45] [46].

Like many organs, the liver is susceptible to developing chronic diseases such as hepatitis B and C, as well as nonalcoholic fatty liver disease, which can lead to hepatic fibrosis. This fibrosis might be reversible, but if untreated, it can advance to cirrhosis or hepatocellular carcinoma, a condition with significant clinical relevance, accounting for 1 - 2 million deaths globally each year. This has led to ongoing research focused on developing effective treatments to prevent the progression of hepatic fibrosis [47] [48].

Hepatic fibrosis is caused by the accumulation of hepatic stellate cells. Li *et al*. showed that Gln promotes stellate cells proliferation, thereby contributing to development of hepatic fibrosis [49]. Conversely, Shrestha *et al*. found that Gln protects liver from damage induced by carbon tetrachloride (CCl_4), a free radical producer, highlighting a potential controversy regarding Gln's role in liver health [50].

8. Kidney

To sustain essential functions, such as oxygen exchange or protein synthesis, the

body requires a stable acid-base balance, maintaining a pH between 7.35 and 7.45. However, in pathological conditions, this balance can be disrupted, leading to alkalemia (pH above 7.45), or acidemia (pH below 7.35). These disruptions in homeostasis may cause hospitalization, as they impair the body's ability to maintain critical physiological functions. Acidemia can result from various causes, including metabolic acidosis, where the pH decreases due to untreated diabetes or a reduction in bicarbonate concentration [51] [52].

The kidney plays a major role in maintaining acid-base balance, particularly through ammonia excretion, with Gln serving as a primary source of NH_3. Under normal conditions the kidney metabolizes Gln at a low rate. However, during metabolic acidosis, Gln synthesis in muscle and liver increases rapidly, and the kidney's absorption and metabolism of the Gln also intensify. In the glomerulus plasma Gln is absorbed, while filtered Gln is reabsorbed in the proximal convoluted tubule [53] [54]. Once inside the nephron, Gln is metabolized by phosphate-dependent GLS, producing glutamate and NH_3. Glutamate is further converted into α-ketoglutarate by GDH, releasing NH_4^+ [55] [56]. Both nitrogen atoms are metabolized by the urea cycle for excretion, eliminating H^+ and helping to regulate pH [54]. H^+ elimination is complemented by the formation of bicarbonate. α-Ketoglutarate derived from Gln enters the TCA cycle and participates in gluconeogenesis, resulting in the formation of CO_2/glucose or 2 HCO_3^- [55] [56].

9. Gluconeogenesis

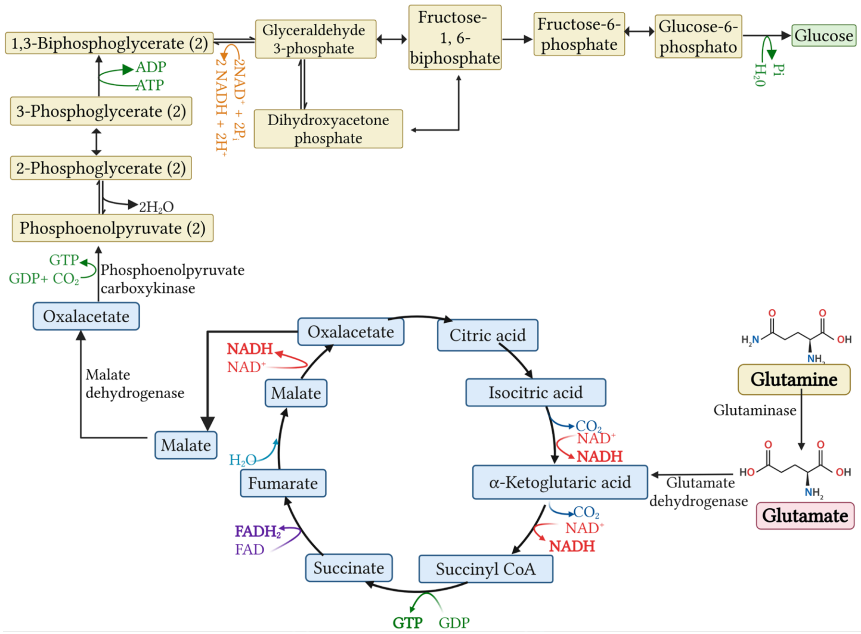

Figure 5. Glutamine as a precursor of gluconeogenesis. *Created by AYFD in BioRender.com.*

Glucose is the body's primary energy source, typically obtained from food, though is not the only source of glucose [57]. Gluconeogenesis is a metabolic

pathway that produces glucose from non-carbohydrate metabolites, and during prolonged fasting around half of the blood glucose is produced through this pathway. Although gluconeogenesis predominantly occurs in the liver, the kidneys also contribute significantly to this process. These are the only two organs capable of releasing glucose into the bloodstream, as they express Glucose-6-phosphatase (G6Pase, EC 3.1.3.9) [58]-[60]. Among the substrates for gluconeogenesis are the glucogenic amino acids, including Gln. Glutamine is converted to glutamate, which is then transaminated to α-ketoglutarate. This intermediate enters the TCA cycle, eventually forming oxaloacetate. When energy charge is low oxaloacetate can be converted to malate, which exits the mitochondria via the malate-aspartate shuttle. In the cytosol, malate is reconstituted into oxaloacetate, and then converted to phosphoenolpyruvate by the enzyme Phosphoenolpyruvate carboxykinase (PEPCK, EC 4.1.1.32), to continue the pathway toward glucose production and eventual release into the bloodstream (**Figure 5**) [57] [58] [61] [62].

10. Type 1 Diabetes

Type 1 diabetes (T1D) is a condition characterized by the destruction of β-cells in the pancreatic islets of Langerhans, leading to a progressive deficiency in insulin production and resulting in chronic hyperglycemia. This condition is managed with exogenous insulin therapy, which is often associated with episodes of insulin-induced hypoglycemia (IIH) [63]-[65]. In healthy individuals, IIH can be counteracted by the release of glucagon, catecholamines or cortisol stimuli, which stimulate glucose production. However, in individuals with T1D, this counterregulatory response is impaired, necessitating alternative strategies to prevent hypoglycemic episodes. IIH typically occurs at night, when patients are unaware of the hypoglycemia and unable to consume food to mitigate it. However, in recent years, it has been observed that the consumption of Gln, in combination with insulin therapy, can prevent IIH by stimulating gluconeogenesis [65] [66]. Moreover, Felisberto-Junior *et al*. demonstrated that the administration of glutamine-alanine dipeptide in rats with IIH, resulted in increased glycaemia due to hepatic gluconeogenesis stimulation. However, the exact amount of dipeptide entering the liver remains unknown. Therefore, caution is necessary with Gln supplementation, as high doses can increase both gluconeogenesis and the ureogenesis pathway, necessitating careful dose management [66].

11. Type 2 Diabetes

Type 2 diabetes (T2D) is a chronic non-communicable disease, characterized by the progressive loss of insulin secretion from the pancreatic β-cells or by insulin resistance (IR), leading to hyperglycemia. Unlike type 1 diabetes, T2D is not an autoimmune condition; it is multifactorial, with obesity as a main risk factor [63] [67] [68]. Obesity, a complex condition, is characterized by hypertrophy of adipocytes, resulting from an imbalance between caloric intake *vs*. energetic expenditure. This hypertrophy is accompanied by a low-grade inflammation, which

triggers the release of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, and C-reactive protein, among others [67] [69]-[72]. Following cytokine activation, adipose tissue-derived adipokines like leptin and resistin are also activated. Leptin regulates satiety and macrophages activation, while resistin inhibits adipocyte differentiation, promotes pro-inflammatory cytokines production, and reduces insulin sensitivity [72] [73]. In addition to cytokines activation, hypertrophied adipocytes in obese patients often exhibit increase in bacteria-derived lipopolysaccharide (LPS), which further stimulates inflammatory pathways, leading to the overexpression of inducible Nitric oxide synthase (iNOS, E.C. 1.14.13.39), and NO production. This promotes S-nitrosylation, leading to IR in adipose tissue, liver and skeletal muscle [74] [75].

Given the complex relationship between T2D and obesity, there is ongoing research to identify alternative treatments that can improve patient adherence and reduce polypharmacy. One such option is Gln supplementation, which has been shown to reduce LPS and waist circumference, as well as the liberation of pro-inflammatory cytokines, thereby improving insulin sensitivity and glucose homeostasis [68] [76]. However, participants in these studies did not exhibit significant weight loss, which may be attributed to IR. In IR, protein synthesis diminishes, leading to muscle mass loss in the individual. Gln supplement, however, can stimulate protein synthesis, potentially restoring muscle mass and maintaining overall body weight despite the reduction in adipose tissue (**Figure 6**) [77]-[79].

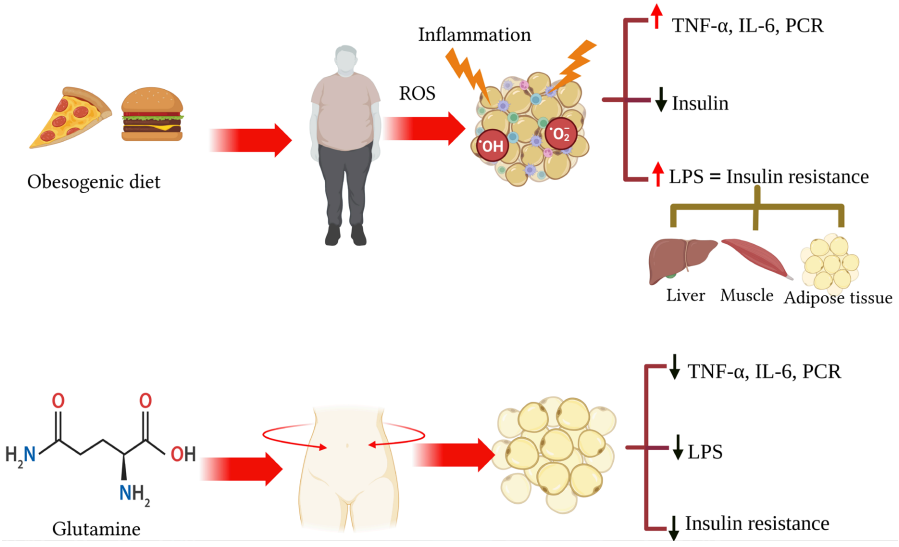

Figure 6. Glutamine contributes to the reduction of inflammation in adipose tissue. *AYFL and SCSF creation.*

T2D also involves a reduction in glucagon-like peptide 1 (GLP-1), a peptide secreted by intestinal L cells in response to food intake or oral glucose. GLP-1 is an incretin that promotes postprandial glucose-dependent insulin secretion, and is a therapeutic target for reducing hyperglycemia [80]-[82]. Furthermore, GLP-1 contributes to β-cells proliferation and decreases intestinal motility, reduces

glucose availability in the bloodstream and promotes normoglycemia [80]. Studies have shown that combining Gln supplementation (15 or 30 g) with sitagliptin increases GLP-1, and reduces postprandial glycaemia in well-controlled T2D patients [83]-[86].

Several studies have shown that Gln supplementation (0.5 g per kilogram of body weight) is not associated with adverse effects on kidney or liver function, although it does increase lactate and ammonia concentrations [83]. Notably, one study observed a relationship between Gln supplementation and a slight decrease in hemoglobin, albumin concentration, and hematocrit [84]. T2D patients are also at a higher risk for developing cardiovascular diseases, leading to increased mortality compared to non-diabetic individuals. Atherogenesis is the main cause of cardiovascular diseases [71], a condition secondary to the loss of antilipolytic action of insulin in T2D due to IR, which induces lipolysis and augments very low density lipoproteins (VLDL). In addition, obesity-related inflammation increases free fatty acids due to TNF-α, contributing to the formation of the atherosclerotic plaque, which lead cardiovascular diseases secondary to T2D [87]-[89]. Since inflammation is closely associated with atherogenesis, Gln supplementation may offer a preventive treatment to cardiovascular diseases development in T2D patients. However, it also suggests that Gln participation in the TCA cycle could exacerbate cardiovascular damage, underscoring the need for further research to elucidate its specific mechanism [79] [90].

12. Burns

Burns are injuries caused by chemical agents, electrical discharge, or heat (fire), resulting in damage to the skin and underlying tissues, leading to localized or systemic functional impairment. The World Health Organization (WHO) considers burns as a significant global public health problem, with approximately 180,000 deaths annually attributed to severe burns [91] [92]. The high mortality rate associated with burns is largely due to the hypermetabolic response that occurs in severe cases. This response is characterized by hyperglycemia, lipolysis, proteolysis, and inflammation, and can persist from the first day of the burn up to 24 to 36 months. Hypermetabolism often induces a catabolic state, compromising the functions of multiple organs, including the heart, skeletal muscle, immune system, and liver [93] [94].

In burns affecting more than 20% of body surface area, there is a significant increase in the synthesis of inflammatory cytokines such as TNF-α, IL-6 and IL-1β. These cytokines promote IR, leading to hyperglycemia even in non-diabetic patients, which is associated with a higher incidence of infections and sepsis. Furthermore, burns injuries increase proteolysis in skeletal muscle, releasing amino acids that fuel hepatic gluconeogenesis, generating a vicious circle of increased pro-inflammatory cytokines production and gluconeogenesis, ultimately resulting in muscular mass loss and hyperglycemia [93]-[95].

It has been suggested that the damage caused by hypermetabolism might be

exacerbated by hypoglutaminemia, which occurs following severe burns. This has led to investigations into the effect of Gln supplementation as a complementary treatment in burns protocols. Several studies have reported that the consumption of Gln decreases muscular mass loss by promoting protein synthesis, and reducing proteolysis caused by burns injury [96]-[98]. In addition, during severe burn injuries, intestinal integrity is often compromised, increasing the risk of bacterial translocation into the bloodstream and subsequent sepsis, which significantly elevates post-burn mortality. Research has shown that exogenous Gln administration helps preserve intestinal integrity, thereby reducing the risk of endotoxemia [96] [99].

The heart is also vulnerable to damage due to hypoxia following severe burns, as indicated by elevated activity of Creatine kinase-MB (CK-MB, EC 2.7.3.2) and Lactate dehydrogenase (LDH, EC 1.1.1.27). Gln supplementation has been found to reduce the activity of these enzymes, suggesting a decrease in burn-induced cardiac damage [96] [99].

13. Cancer

Cancer is characterized by abnormal cell growth, where these cells divide faster than normal cells, potentially due to genetic defects in proteins that regulate the cell cycle or in response to environmental carcinogens/mitogens. Most cases of cancer appear to result from a combination of hereditary and environmental factors [100] [101]. While glucose metabolism is fundamental for cancer cells, it is often altered, and glucose is not their sole energy source. Many cancer cells are Gln-dependent and increase its uptake, and in the absence of this amino acid, they are prone to cell death [19] [101]-[103].

Gln metabolism provides tumor cells with nitrogen and carbon atoms that are used in several critical metabolic pathways, supporting their survival and proliferation [19]. Gln enters the cell via specific carriers and is deaminated by GLS, producing glutamate and NH_4^+. Glutamate then serves as a precursor for other pathways, including glutathione synthesis, non-essential amino acids synthesis, and α-ketoglutarate production [102]-[104].

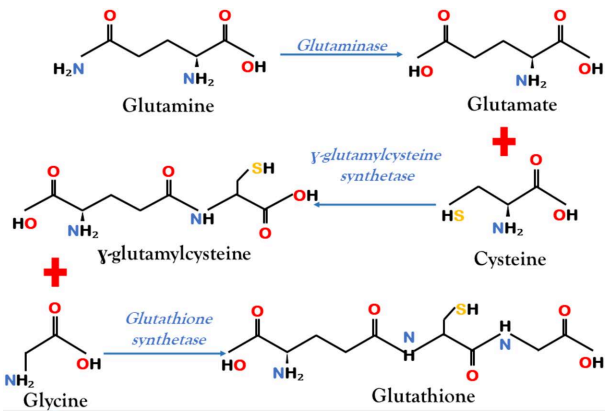

Figure 7. Glutathione synthesis. *A YFD creation.*

Glutathione synthesis involves the combination of glutamate, cysteine and glycine, catalyzed by γ-Glutamylcysteine synthetase (Glutamate-cysteine ligase, GCL, EC 6.3.2.2), to form γ-Glutamylcysteine. This compound is then converted to glutathione by Glutathione synthetase (GSS, EC 6.3.2.3). Glutathione is a key endogenous antioxidant that regulates ROS, counteracting free radicals through its oxidized form, glutathione disulfide (GSSG) (**Figure 7**) [102] [103] [105]-[107].

Glutamate also serves as a precursor to α-ketoglutarate, which can be produced via transamination or by Glutamate dehydrogenase. α-Ketoglutarate, derived from Gln/glutamate, functions as an anaplerotic intermediate in the TCA cycle, contributing to oxidative phosphorylation and generating reducing equivalents for the electron transport chain, as well as forming oxaloacetate. From transamination, α-ketoglutarate is also a precursor for non-essential amino acids [103] [104]. Additionally, Gln donates nitrogen for the synthesis of amino acids, such as aspartate and alanine, with aspartate-derived nitrogen playing a key role in nucleotide synthesis, protein production, and tumor cell proliferation [102] [103].

Oncogenes drive various mutations in proteins that modify cellular functions, leading to tumor cell proliferation. For example, oncogenes influence Gln metabolism, because the requirement of this amino acid is higher for intracellular synthesis. Consequently, tumor cells favor the uptake and catabolism of extracellular Gln. The c-Myc oncogene, related with tumor aggressiveness and chemotherapy resistance, binds to Gln carriers, promoting Gln uptake. Moreover, it boosts glutaminolysis, making Gln indispensable for the continuous function of the TCA cycle, thereby inducing Gln-dependence in tumor cells to support their metabolic needs and proliferation [19] [102] [103] [108].

The K-ras oncogene reprograms Gln metabolism by altering the expression of diverse enzymes, such as reducing GDH while increasing Aspartate transaminase activity. This increases aspartate and NADH production, contributing to redox balance in tumor cells [102] [103] [109].

Under hypoxic conditions, hypoxia inducible factor (HIF) promotes glycolysis to lactate, diminishing pyruvate availability as an energy source. In response, tumor cells use other metabolites, such as Gln, to continue proliferation [110] [111]. Tumor suppressors such as p53 also modulates Gln metabolism. p53 supports energy metabolism and antioxidant defense by promoting Glutaminase 2 (GLS2) expression, which augments glutathione via Gln-derived glutamate, enhancing antioxidant functions of glutathione, reducing ROS and oxidative stress, and enhancing genomic stability [106] [112] [113].

Since Gln is involved in cancer development and proliferation, recent research has explored targeting Gln metabolism as an alternative treatment strategy. Unfortunately, inhibiting enzymes involved in Gln metabolism has not proven to be an effective therapy, due to tumor cells' adaptability [114]-[116].

14. Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a cluster of clinic and sub-clinic symptoms that

characterize the main neurological disorder, resulting from severe chronic or acute liver failure. Chronic HE typically arises secondary to liver cirrhosis, often due to alcoholism, and manifests as neurological impairments, such as personality changes, mood disturbances, diminished intellectual ability, and sleep disorders. In contrast, acute HE is associated with conditions as viral hepatitis B or C, liver neoplasia, or paracetamol toxicity, with symptoms including delirium, seizures, or coma [117]-[119].

The exact mechanism behind neurological damage in severe liver failure remains unclear, though hyperammonemia elevating brain NH_3 is thought to be a key factor, potentially due to portosystemic shunting that increases NH_3 in the bloodstream, allowing it to cross the blood-brain barrier (BBB) [117] [120]. In the brain, NH_3 concentration is regulated by Gln synthesis in astrocytes [117] [121], where Gln serves as non-toxic carrier for NH_3, protecting astrocytes from elevated NH_3 concentration. However, Gln can also contribute to NH_3-induced neurotoxicity. Historical studies by Warren and Schenker showed that the administration of methionine sulfoximine, a GS inhibitor, mitigated the toxic effects of NH_3, like brain edema, coma, and diminished glucose uptake, improving survival [122] [123]. Albrecht and Norenberg later proposed the "Trojan horse" hypothesis, suggesting that Gln enters astrocyte via specific Gln carriers (SNAT3/SNAT5), and once inside mitochondria, Gln is hydrolyzed by phosphate-activated Glutaminase, producing glutamate and NH_4^+, increasing mitochondrial NH_4^+ [122] [124] [125].

In patients with severe liver failure with portal hypertension, increased BBB permeability allows solutes such as glutamate and water to enter the brain. The rapid increase in glutamate, coupled with the activation of SNAT3/SNAT5 transporters, removes magnesium or zinc, exacerbating NMDA receptors activity in astrocytes. This leads to increased intracellular Ca^{2+}, which binds to calmodulin, activating neuronal NOS (nNOS), and producing NO. NO then activates soluble guanylate cyclase to produce cGMP and enters the mitochondria, increasing ROS production [117] [122] [125]-[128]. The combination of oxidative stress and elevated intracellular Ca^{2+} induces the formation of the mitochondrial permeability transition pore (mPT), increasing mitochondrial membrane permeability and leading to astrocyte inflammation [119]. In some patients with HE, brain edema occurs due to excess of mitochondrial NH_3, which inhibits α-Ketoglutarate dehydrogenase, blocking the TCA cycle and forcing cells to rely on glycolysis for energy. This metabolic shift results in increased lactate production, lowering intracellular pH and upregulating aquaporin 4 expression, allowing extracellular water to enter astrocytes. The inhibition of the TCA cycle and electron transport chain depletes ATP, as continuous Gln synthesis consumes available energy [129]-[131]. Moreover, excessive NMDA receptor requires constant Na^+ influx into the cytoplasm, increasing Na^+/K^+ ATPase activity to maintain ionic balance, further straining ATP reserves (**Figure 8**) [129].

Some cirrhotic patients could have minimal hepatic encephalopathy (MHE),

the earliest stage of HE. MHE is characterized by neuropsychological alterations that are undetectable through routine psychometric tests but can significantly impact quality of life. If not diagnosed early, MHE can progress to full-blown hepatic encephalopathy, increasing mortality. Early diagnosis of MHE is crucial to reducing mortality in these patients [120] [132]. One alternative diagnostic test for MHE involves administering an oral Gln load (10 - 20 grams), which results in a transient increase in systemic NH_4^+ followed by its diminution. This test is considered useful because it does not produce adverse effects neither alters the course of HE in cirrhotic patients, nor does it affect cognition in healthy individuals [120] [133].

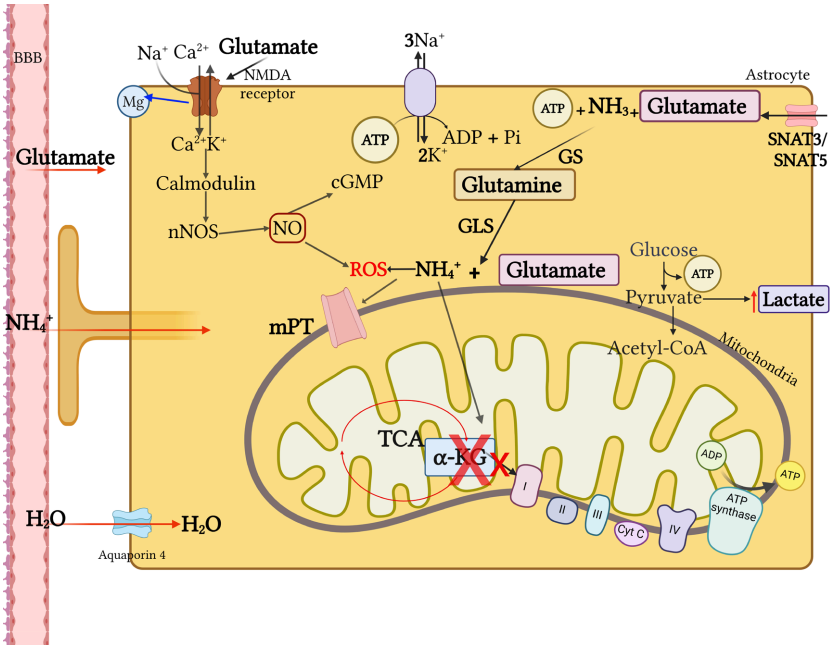

Figure 8. Pathogenesis of hepatic encephalopathy. *Created by AYFD in BioRender.com.*

15. Conclusion

Glutamine is the most abundant amino acid in the human body, and has been extensively studied due to its numerous beneficial effects across various physiological systems. However, glutamine can also have detrimental effects in certain pathological conditions, such as cancer or hepatic encephalopathy. Despite these complexities, it remains crucial to continue researching glutamine's role in health and disease. Further studies may reveal how Gln supplementation could benefit patients undergoing multidrug therapy, potentially reducing the need for some medications, and improving overall treatment adherence and disease management.

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Conflicts of Interest

The authors declare no conflict of interest.

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