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REVIEW

Cardioprotective and anti-inflammatory effects of glutamine in parenteral nutrition

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Abstract

Glutamine is the most abundant free amino acid with multiple biological functions. The supplementation of this amino acid to parenteral nutrition has been widely used for the management of ICU complications. However, inconclusive reports have generated reluctance in the use of this pharmaco-nutrient. In the last decade, new studies have reported the beneficial effects for the cardiovascular and pulmonary system, besides its classical functions as antioxidant, immunomodulator and substrate for other molecules. From the medical science point of view, considering clinical and in vivo studies, the evidence describes several metabolic pathways in which glutamine plays a beneficial role. These pleiotropic effects support the participation of glutamine as a cardioprotective and anti-inflammatory amino acid.

Introduction

Glutamine is the most abundant free amino acid in the body with concentrations fluctuating around 500-900 μmol/l[1] The biological functions of this amino acid have been widely studied, suggesting several targets in which glutamine could modulate physiological functions. The more accepted activities include immune enhancer, muscular maintainer, nitrogen transporter, neuronal mediator, pH homeostasis, gluconeogenesis, amino sugar synthesis and insulin release modulation.[2]

In 1990 it was demonstrated that glutamine is one of the only conditionally essential amino acids, meaning that in hypercatabolic or stress conditions the body suffers depletion in the pool levels.[3] Moreover, this condition is an independent risk factor for mortality, which correlates with an increase in infection rates and length of hospital stay in ICU patients.[4,5]

This characteristic confers the option of glutamine use as a pharmaco-nutrient, meaning that through its targets it could improve the outcome of patients suffering from a hypercatabolic or hypermetabolic condition.

Molecular targets of glutamine

Several molecular actions of glutamine explain its beneficial effects as a supplement with pharmacological actions. Reverting glutamine depletion would be the main goal for the hypercatabolic patient, causing a normalisation on the abrogated metabolic processes.

The last decades of biomedical research have identified the specific molecular targets in which this amino acid exerts its functions; the main roles are centred in reducing oxidative stress through glutathione biosynthesis, ameliorating the inflammation by heat-shock proteins production, maintenance of enterocyte integrity, enhancing lymphocyte function, modulating the nitrogen balance and regulating the insulin

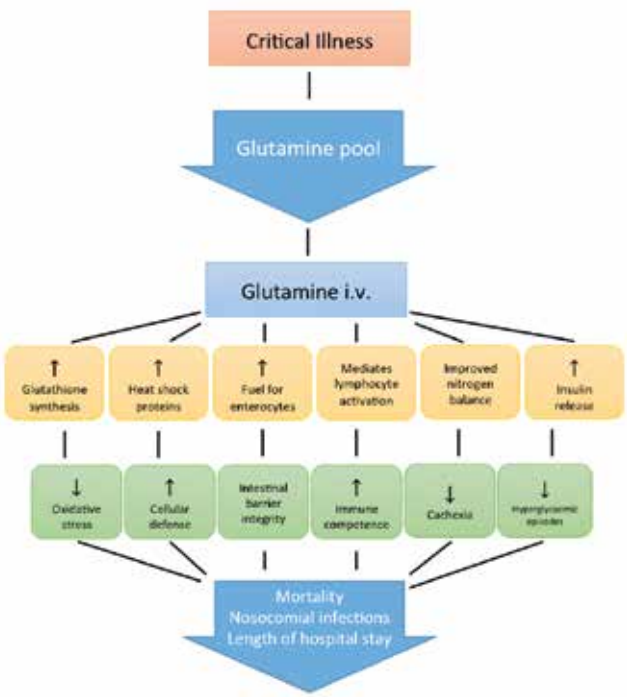

Figure 1. Molecular targets of glutamine supplementation in critical care patients under hypercatabolic depletion

release *(figure 1)*.[6] Importantly, most of these data have emerged from experimental studies; the latest and largest and trials have given controversial results, showing no benefit of the glutamine supplementation in ICU patients.[7-9]

New potentially beneficial effects of glutamine

Cardioprotective effect

Recent clinical, *in vivo and in vitro* studies have reported the cardioprotective role of this amino acid in ischaemic heart disease and diabetic cardiomyopathy.

Using an isoprenaline-induced myocardial infarction rat model, Kumar et al. suggested that the cardioprotective effect of glutamine is related to strengthening the myocardial membrane by its stabilising action, counteracting the free radicals by its antioxidant property, or to its ability to maintain a near to normal status of the activities of free radical scavenging enzymes and the level of glutathione, which protect the myocardial membrane against oxidative damage by decreasing lipid peroxidation.[10] Also, it was reported that glutamine treatment improved the electrocardiographic and haemodynamic parameters; left ventricular contractile function; biological markers; oxidative stress levels and histological alterations in STZ-induced diabetic rats.[11] Additionally, using the same model, Ugurlucan et al. concluded that in diabetes mellitus the levels of Hsp70 increase in the myocardium of rats, as a protective mechanism, and these levels are augmented with parenteral administration of glutamine; furthermore, the efficacy of the amino acid is more pronounced in left heart structures.[12] A study in the healthy working heart beyond anaplerosis revealed that a metabolic role of physiological concentration of glutamine appears to involve the hexosamine biosynthetic pathway and regulation of fatty acid entry and metabolism via CD36 upregulation *(figure 2)*.[13] Furthermore, an interventional study reported that glutamine is a cardioprotective amino acid that reduces the plasma levels of troponin I, the main marker of heart damage that correlates with myocardial infarction size.[14] Two years later the authors reported their results from a double-blind, placebo-controlled, randomised study that included 64 patients with diabetes mellitus type 2 who were scheduled for on-pump coronary artery bypass graft surgery using 0.4 g/kg/day of glutamine in TPN for 48 hours. Their results failed to confirm the cardioprotective properties and modulatory effect on perioperative insulin resistance;[15] however, this could be attributable to the short period of use and route of administration. Most of the studies that report an improvement of the clinical outcomes among ICU patients are using at least one week of glutamine supplementation.

Two clinical trials titled 'Effects of Glutamine in Ischemic Heart Disease Patients Following Cardiopulmonary Bypass'[16] and 'Oral Glutamine in Cardiopulmonary Bypass'[17] were completed in the last two years; however, no results have been documented by the responsible researchers.

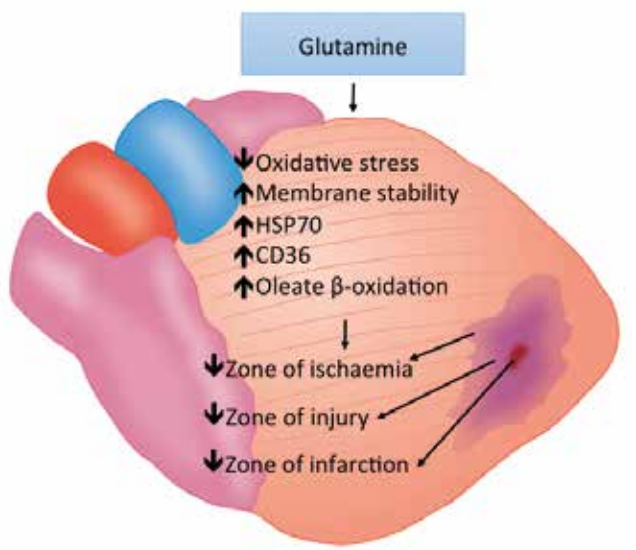

Figure 2. Molecular mechanisms of glutamine as a cardioprotective amino acid

Respiratory anti-inflammatory agent

The lungs maintain amino acid homeostasis and play a key role in glutamine flow in both normal and catabolic states. In this field, Sanli et al. have shown, in a surgically induced rat model, that the injection of glutamine enhances the healing of lung parenchymal injuries reducing air leakage.[18] Interestingly, similar results were obtained in two studies: the first in a rat model of acute lung injury caused by acid aspiration and the second using lipopolysaccharide-challenged rats ventilated with a high tidal volume. The authors suggest that the mechanism is mediated by the reduction of the local levels of IL-1β, IL-6, IL-10, TNF-α and CXCL-1.[19-21]

These experimental settings looked to emulate acute respiratory distress syndrome, a catastrophic syndrome among critically ill patients that has been independently associated with total parental nutrition.[22]

A recent review from Oliveira et al.[23] summarises the evidence regarding the beneficial effects of glutamine in other respiratory diseases such as asthma, chronic obstructive pulmonary disease and cystic fibrosis; however, the data reported are still inconclusive and mainly related to oral ingestion or intraperitoneal injection glutamine.

On the contrary, controversial reports have shown paradoxical effects of glutamine in lung cancer: the amino acid reinforces the pathological activity of cancer cell growth and maintains the proliferative signalling pathways;[24] however, clinical studies have demonstrated that the toxic effects of chemotherapeutic agents and radiotherapy further aggravate glutamine depletion. Oral glutamine supplementation during concurrent chemo-radiotherapy had a beneficial effect in preventing weight loss and reducing the severity and incidence of acute and late radiation-induced oesophagitis. Likewise, in lung cancer patients treated with thoracic radiotherapy, oral glutamine decreased the severity of acute radiotherapy-induced oesophagitis.[25-28]

Conclusion and personal opinion

The multiple functions of this amino acid confer the possibility of its use as a pharmaco-nutrient in hypercatabolic conditions. Strong evidence emerges from the basic and clinical science showing the beneficial effects of glutamine in the metabolism of subjects suffering from a catabolic stress condition. New evidence is emerging regarding beneficial effects of this amino acid in the cardiovascular and pulmonary system, opening a promising opportunity for the management of complications in ICU patients.

However, clinical data are still inconclusive and weak, underlining the need for the development of new research in this field. There is still controversy regarding glutamine supplementation, mainly because the new clinical evidence does not show an effect; however, new studies are required to clarify the specific issues regarding the use of this amino acid in total parental nutrition.

Disclosures

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The author declares no other competing interests.

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