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The role of glutamine in the immune system and in intestinal function in catabolic states

Review Article

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Summary. Glutamine is designated a non-essential amino acid: however, evidence is accumulating that glutamine becomes essential when catabolic conditions prevail.

It has been established that glutamine is an important fuel for lymphocytes and macrophages, even when resting. Plasma and muscle glutamine concentrations are decreased after trauma such as burns, major surgery, and in sepsis. The effectiveness of the immune system is decreased after trauma: this may be due, in part, to the decrease in plasma glutamine concentrations.

Most studies on sepsis in humans have shown plasma glutamine concentrations to be *decreased*: this may be due to an increased rate of utilization of glutamine by lymphocytes and macrophages during proliferation or phagocytosis. In contrast, several studies on rats show *increased* plasma glutamine levels in sepsis. A species difference in the way in which glutamine is metabolised could be the main reason for the conflicting results. Other contributory factors could be diurnal variation and timing of sample collection.

A substantial amount of dietary glutamine is taken up by intestinal cells. When the supply of glutamine via the diet is decreased, glutamine is taken up from the circulation by the intestine. In total parenteral nutrition (TPN) sepsis can sometimes occur because the gut is "rested", leading to villous atrophy and increased gut mucosal barrier permeability. There is now a move towards the use of enteral nutrition in preference to TPN. Provision of exogenous glutamine has had beneficial effects in humans and animals, particularly in improving intestinal function. The safety and efficacy of glutamine administration to humans is discussed in detail.

Keywords: Amino acids – Glutamine – Immune system function – Intestinal function – Sepsis

Glutamine utilization by cells of the immune system

Glutamine is designated a non-essential amino acid: however, evidence is accumulating that glutamine should be considered to be a "conditionally essential" amino acid. That is, it becomes essential when catabolic conditions prevail.

Traditionally, it was always assumed that only 4 major tissues are involved in glutamine metabolism – namely muscle, liver, intestine and kidney. However, only about 50% of the total glutamine production in man is utilized by the intestine and kidney; the liver consumes glutamine in the post-absorptive state but releases it in critical illness; muscle is considered to be a major site of glutamine synthesis. Work carried out by Ardawi and Newsholme (1983; 1985a) and Newsholme et al. (1987) established that glutamine is used at a high rate by some key cells of the immune system, *i.e.* lymphocytes and macrophages, even when resting (Fig. 1). For example, the rates of utilization of glutamine by quiescent lymphocytes is about 25% of the rate of glucose utilized by a heart working at maximum physical capacity *in vitro*. The oxidation of glutamine is only partial, and has thus been termed glutaminolysis.

The role of glutaminolysis in rapidly-dividing cells has been considered to be the provision of both nitrogen and carbon for the synthesis of purine and pyrimidine nucleotides, which are required for DNA and RNA synthesis in these cells, as well as for energy (Kovacevic and McGivan, 1983). However, the rate of glutaminolysis is markedly in excess of the actual rate of pyrimidine nucleotide synthesis (Szondy and Newsholme, 1991), so that only a small proportion of the glutamine metabolised is required for this task. Furthermore, if glutamine was

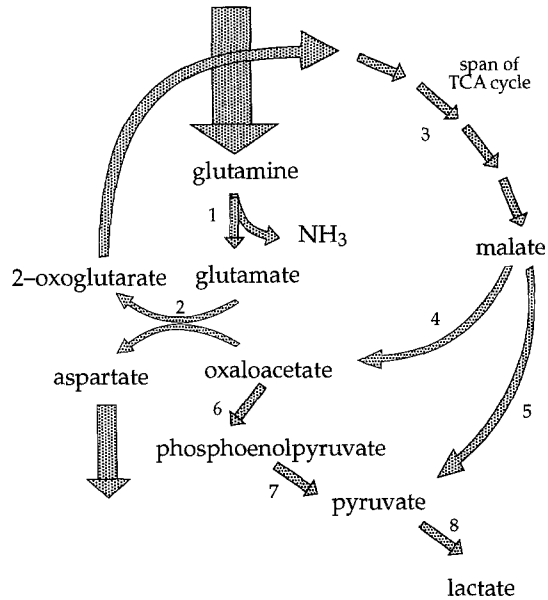

Fig. 1. The proposed pathway of glutamine metabolism in cells of the immune system. The reactions are as follows: *1* Glutaminase; *2* Aspartate aminotransferase; *3* Enzymes of the Krebs cycle converting 2-oxoglutarate to malate; *4* Malate dehydrogenase (NAD+-linked); *5* Malic enzyme [NAD(P)+-linked]; *6* Phosphenolpyruvate carboxykinase; *7* Pyruvate kinase; *8* Lactate dehydrogenase. (From Newsholme et al., 1985b)

important for energy generation, it would be expected that most of the glutamine would be fully oxidised.

On the basis of a quantitative approach to metabolic control, it is suggested (Crabtree and Newsholme, 1985) that high rates of glutaminolysis provide ideal conditions for the precise and sensitive control of changes in the rate at which the intermediates of these pathways are used for biosynthesis. Requirements for and availability of biosynthetic precursors are thus precisely matched: *i.e.* purine and pyrimidine synthesis is readily increased when DNA and RNA are needed (Fig. 2). High rates of glutaminolysis can be seen, therefore, as part of a control mechanism to permit specific changes in the rate of synthesis of macromolecules, without the need for complex regulatory mechanisms or for extracellular signals to make more glutamine available for the rapidly dividing cells (Newsholme et al., 1985). The mechanism that provides this precise regulation is known as branched-point sensitivity (Crabtree and Newsholme, 1985).

The hypothesis predicts that, for example, if plasma glutamine is decreased below a physiological level, the function of cells of the immune system would be impaired. A study by Parry-Billings et al. (1990) has demonstrated that the proliferative ability of human lymphocytes is decreased when glutamine levels in culture medium are decreased below physiologically normal concentrations, despite the presence of other amino acids and fuels such as glucose. Macrophage function was found to be similarly affected. The importance of glutamine for the cells of the immune system *in vitro* has been reviewed recently (Calder, 1994).

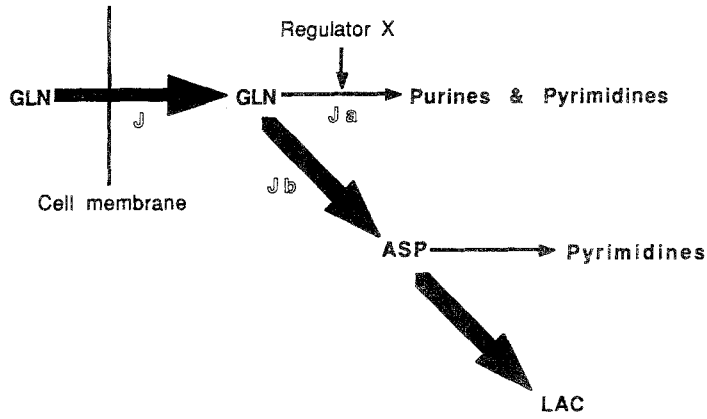

Fig. 2. Regulation of flux through a branched pathway. *Ja* and *Jb* represent metabolic fluxes. Ja is regulated by factor X. The highest sensitivity of Ja to changes in the concentration of X occurs when Jb is very much greater than Ja. Thus, because of the high rate of glutaminolysis and the sensitivity of metabolic control it provides, an increase in flux through these biosynthetic pathways can occur rapidly and precisely when required. *GLN*, Glutamine; *ASP*, Aspartate; *LAC*, Lactate. (From Parry-Billings, 1989, after Newsholme et al., 1985)

Sources of glutamine

Despite the fact that glutamine is the most abundant amino acid in the body (see Felig, 1975), comparatively little dietary glutamine gets into the circulation

(but see Matthews, 1990; Déchelotte et al., 1991). A substantial amount of dietary glutamine is taken up by intestinal cells (Windmueller 1982; Carrie, 1989; Ardawi et al., 1988): their utilization of glutamine far exceeds that of any other amino acid (Weber et al., 1977; Windmueller and Spaeth, 1980). The lung, adipose tissue and the liver are all sources of glutamine. However, the tissue thought to be quantitatively the most important for glutamine synthesis and release is skeletal muscle. Analysis of the processes of glutamine release from muscle and glutamine metabolism by the immune system, using metabolic control logic, indicates that outward glutamine transport across the plasma membrane of muscle is the important "flux generating" step which determines the rate of release and hence, in part, the level of glutamine in the blood. A detailed discussion of the properties of glutamine release from muscle and its relevance to cells of the immune system can be found elsewhere (Newsholme and Parry-Billings, 1990).

The concentration of glutamine in human skeletal muscle is normally 20 mM, and that of plasma glutamine is *ca* 0.6 mM. Even after an overnight fast the supply of glutamine from the intestinal lumen, via the diet, is decreased, and thus glutamine is taken up from the circulation by the intestine. The importance of glutamine in the intestine is emphasized by the fact that, in several species, intravenous administration of the enzyme glutaminase caused physiologically subnormal levels of glutamine which led to intestinal malfunction, e.g. chronic diarrhoea, villous atrophy etc. (Hambleton et al., 1980). Cellular glutaminase is an important part of the mechanism by which glutamine maintains gut function: intestinal glutaminase activity is increased after glutamine feeding in the septic rat (Dudrick et al., 1992) and the starved rat (Boyd, Parry-Billings and Newsholme, unpublished observations).

Plasma glutamine concentration in stress and catabolism

It has now been clearly established that a substantial decrease in plasma glutamine concentration occurs after trauma such as burns (Stinnet et al., 1982; Parry-Billings et al., 1990; Gottschlich et al., 1993) major surgery and injury (Askanazi et al., 1980; Parry-Billings et al., 1992; Castell et al., 1992), and in sepsis (Clowes et al., 1980; Roth et al., 1982). An even greater decrease has been seen in muscle glutamine concentration in catabolic conditions (see Roth, 1990). The effectiveness of the immune system is decreased after trauma (Baker et al., 1980; Green and Faist, 1988; Brambilla et al., 1970): this may be due, in part, to the decrease in plasma glutamine concentrations observed in these conditions. Glutamine-enriched diets have improved immune function in rats (Alverdy, 1990; Yoshida et al., 1992).

The rate of release of glutamine from muscle is increased following major trauma (Lund et al., 1986; Stjernstrom et al., 1986; Ardawi, 1988) and sepsis (Rosenblatt et al., 1983; Parry-Billings et al., 1989; Austgen et al., 1992) Glutamine uptake by the intestine, however, is decreased in sepsis in humans and rats (Souba et al., 1990a; Ardawi et al., 1990, 1991).

Planas et al. (1992) have suggested that inhibition of glutamine uptake by the gut, coupled with increased release of glutamine from skeletal muscle and

from the lung, may be responsible for the increased serum glutamine concentrations which they observed in sepsis patients. In another study on sepsis in children, plasma glutamine was reportedly increased by 100% (Maldonado et al., 1988). But other studies with human subjects have shown plasma glutamine concentrations in sepsis to be *decreased* (Askanazi et al., 1980; Clowes et al., 1980; Roth et al., 1982; Fong et al., 1990; Martinez and Giraldez, 1993). Mobilisation and activation of cells of the immune system, such as lymphocytes and macrophages, may result in an increased rate of utilization of glutamine during proliferation or phagocytosis, which may account for the observed decrease in plasma glutamine levels. Indeed, increased glutamine utilization by intestinal lymphocytes has been seen in septic rats, while glutamine utilization by enterocytes was decreased (Ardawi et al., 1991).

In contrast to human studies, several studies on rats show *increased* plasma glutamine levels in sepsis (for example, Souba et al., 1990; Ardawi, 1990, 1991; Pacitti et al., 1992). A species difference in the way in which glutamine is metabolised, or in the response to, or the duration of, sepsis, may well be the main reason for the conflicting results.

Other contributory factors could be diurnal variation and timing of samples both during an experiment and during the progression of sepsis. Experiments on both species are usually undertaken during the day. However, rat plasma glutamine concentration is at its highest during the nocturnal period when the animals are most active and consume most food (Parry-Billings, 1989). In humans, maximum concentrations for most plasma amino acids occur in the late afternoon or early evening, although diurnal variation is often lost in critical illness. In addition, the site from which blood samples are taken sometimes differs between species.

Nutrition in intensive care

The attitude towards patient nutrition in intensive care has altered considerably during the past few years. Nevertheless, there are still clinical situations, for example, after bowel surgery, in which the only nourishment for several days post-operatively is about 250 calories from a 5% glucose drip. During starvation of this nature, the intestine has to rely upon the circulation for a supply of glutamine. This could clearly compromise the function of cells of the intestine and the immune system, when plasma glutamine levels are already low from trauma.

Sepsis is a major cause of morbidity and mortality among hospitalized patients – for example, in 1992 the annual incidence in the USA was estimated to be 400,000. There is increasing concern about the way in which sepsis can actually be attributed to total parenteral nutrition (TPN) (see Moore et al., 1992; Arnow et al., 1993). The TPN catheter itself can be a direct source of infection, and the parenteral nutrient is an eminently suitable medium in which bacteria can flourish (Gil et al., 1989; Llop, 1993). Infections can also occur indirectly because the gut is "rested": this leads to villous atrophy, mucosal ulceration and increased gut mucosal barrier permeability (Koga et al., 1975; Hughes and Dowling, 1980; Wilmore et al., 1988; Naber, 1991). It is generally supposed that

subsequent bacterial translocation occurs which gives rise to infections and sepsis (Deitch et al., 1986; Alverdy et al., 1988; Inoue et al., 1993; Frankel et al., 1993). However, although observed in animals, this has not so far been conclusively demonstrated in man.

As a consequence of these problems, there is now a move away from the use of total parenteral nutrition to enteral nutrition. Enteral nutrition also has some failings, however, mainly problems with gastric emptying (see Payne-James and Grimble, 1994) absorption and diarrhoea, particularly when opiates are being administered concurrently. Nevertheless, there is convincing evidence for this more natural form of nutrition being more efficacious than TPN in some clinical situations (Saito et al., 1987; Moore et al., 1992; Scott and Moellman, 1992; Inoue et al., 1993).

Recently it has been suggested that it is important for glutamine to be regarded as an *essential* ingredient when nutritional supplements are provided for patients (for review see Ziegler et al. (1993)). Provision of exogenous glutamine, either free or as a dipeptide (see below), in humans and animals, has already been shown to improve intestinal function, including increased or maintained villous heights, and/or to decrease bacterial translocation across the intestine (Hwang et al., 1986; Fox et al., 1988; Klimberg et al., 1990; Souba et al., 1990; Platell et al., 1991; Ardawi, 1992; Jiang et al., 1993; van der Hulst et al., 1993; Frankel et al., 1993; Inoue et al., 1993; see also Smith and Wilmore, 1990).

The safety and efficacy of glutamine administration to humans

Originally glutamine was omitted from parenteral nutrition solutions because of fears of its breakdown to pyroglutamate during sterilisation at high temperatures. Dipeptides, *e.g.* alanyl-glutamine, glycyl-glutamine, have been found to tolerate heat sterilization and have been used as a source of supplementary glutamine in several studies. Now that solutions can be sterilised using cold filtration, parenteral feeding enriched with glutamine has become more widespread.

The decomposition to ammonia and glutamate is slow in glutamine-supplemented TPN solutions, and the concentration of glutamine diminished by 2% over 14 days when stored at 4°C (Khan et al., 1991; Hardy et al., 1993). Ziegler et al. (1990) reported similar stability data; no appreciable accumulation of ammonia was observed when glutamine was stored in solution at 4°C. At room temperature glutamine losses were estimated to be 0.1% per day.

Aseptically prepared and filter-sterilized solutions of free glutamine have also been shown to be stable: in a 3 litre oxygen-impermeable bag, 98.2% of the glutamine remained after 30 days at 4°C (Hardy et al., 1992a,b). Conversion to glutamate was negligible, pyroglutamate production was less than 0.02% and ammonia formation was less than 0.01 mM per day.

Glutamine infusion studies in healthy male subjects have been undertaken by Wilmore and co-workers (Ziegler et al., 1990): they infused glutamine (in 0.2% saline) in healthy male subjects for 4 h at rates of 0.0125 and 0.025 g/kg body wt/h. The glutamine concentration in plasma peaked between 30–45 min after

the onset of the infusion and the half-life of glutamine was estimated to be 67 min. No significant changes in the plasma concentrations of ammonia, glutamate or hormones were observed.

The safety of long-term intravenous glutamine administration in healthy individuals has been investigated in a 5-day study (see Ziegler et al., 1990). Glutamine was given at two doses: – 0.285 and 0.57 g/kg body wt/day (20 g & 40 g of glutamine per day in a typical subject). Up to 57 g glutamine per day was administered parenterally with no reports of side effects, toxic symptoms, central nervous system disturbances, or alterations in blood chemistry, apart from the plasma glutamine concentration which increased by about 30% after 5 days treatment. Plasma ammonia concentration was unchanged.

In enteral studies, glutamine has been taken by healthy volunteers as an oral drink at 0.1 g/kg body wt (Ziegler et al., 1990; Castell et al., 1994) or 0.3 g/kg body wt (Ziegler et al., 1990) without any observed adverse reactions. In both studies the glutamine concentration in the plasma peaked at 30–45 min afterwards and returned to basal levels 2–4 h later. The half-life of glutamine was estimated to be 110 min (Ziegler et al., 1990) and 65 min (Castell et al., 1994). No differences in plasma glutamine concentrations were observed between male and female subjects after the glutamine drink (Castell, unpublished observations). In the study by Ziegler et al. (1990), growth hormone and insulin levels were elevated in response to the glutamine drink, but plasma glutamate and ammonia concentrations remained unchanged.

The pharmacokinetics of enterally delivered glutamine in healthy subjects following an overnight fast was studied by Déchelotte et al. (1991). A range of graded infusion rates were employed and a dose-dependent increase in the plasma glutamine concentration was observed. The concentrations of alanine, glutamate, aspartate, citrulline and urea were also elevated, but no adverse effects were reported. An antilipolytic action of glutamine was apparent, as reflected by a decrease in the concentration of plasma free fatty acids and glycerol.

Despite an obligatory requirement for glutamine by enterocytes (Carrie, 1989), enteral feeding still appears to be an efficient means of increasing the concentration of glutamine in the systemic circulation. Studies on healthy adults suggest that 40–50% of radioactively labelled glutamine enters the circulating pool, while the remaining 50–60% is consumed by the splanchnic bed (Matthews, 1990; Déchelotte et al., 1991).

This review has concentrated mainly on the results observed when supplementary glutamine is administered to patients with functional problems of the gastrointestinal tract. However, a number of other studies on therapeutic glutamine feeding have been reported, some of which are discussed below. A survey of glutamine feeding in clinical situations appears in the review by Ziegler et al. (1993).

Enteral feeding regimes supplemented with glutamine have been employed for the treatment of burns patients. Gottschlich et al. (1993) administered glutamine at 2 g/l, 4 g/l and 6 g/l [the total daily intake of glutamine was not stated] for 4 weeks after burn injury but failed to demonstrate any positive beneficial effects of the amino acid.

Infusions of glutamine at doses up to 480 mg/kg/day were well tolerated in very low birth weight infants without any apparent complications (Crouch and Wilmore, 1991). Plasma glutamine concentrations were elevated without any observed increases in the concentrations of ammonia or glutamate in the plasma.

Glutamine-supplemented TPN (0.57 g/kg/day) has been administered to bone marrow transplant patients, following standard high dose chemotherapy and whole body irradiation. Clinical benefits of the treatment included an improvement in nitrogen balance, protection from an expansion of the extracellular fluid compartment (commonly observed after standard TPN), a diminished incidence of infection and a shortened hospital stay. No adverse effects of glutamine were reported (Scheltinga et al., 1991; Ziegler et al., 1992).

Glutamine-supplemented TPN (0.285 g/kg/day) has also been administered post-operatively to patients undergoing elective abdominal surgery with no adverse effects reported. Patients receiving glutamine exhibited an improvement in nitrogen balance and a sparing of the intramuscular glutamine pool (Hammarqvist et al., 1989).

Most of the studies on glutamine feeding reported increased concentrations of plasma glutamine. Following glutamine administration in the form of dipeptides, Kweon et al. (1991) reported an increase in muscle glutamine in rats, while Stehle et al. (1989) and Hammerqvist et al. (1990) reported improved nitrogen balance and a sparing effect on muscle glutamine concentration and muscle protein synthesis in man. Improved nitrogen balance and reduced loss of muscle glutamine after alanylglutamine feeding has also been seen in dogs (Roth et al., 1988).

In rats, reports of improved immune response after glutamine feeding include increased lymphocyte proliferation (Yoshida et al., 1992), increased white blood cell counts (Klimberg et al., 1992), increased macrophage activity (Kweon et al., 1991) and an increase in secretory IgA, the most abundant immunoglobulin (Alverdy, 1990).

Concluding remarks

Naber (1991) commented that the most traditional method for estimating requirements of a TPN solution is based on calculations developed from healthy individuals, and that the real caloric demands of a patient are not always met. Physiologically, the patient in a catabolic state is, of course, very different from the healthy individual and thus has very different requirements.

The provision of optimal conditions for cells of the immune system should, ideally, be the first line of defence against infection. Approximately 25% of the gastrointestinal cells are immune system cells. Glutamine is an important fuel for these cells and is now regarded by many workers as being an essential ingredient for inclusion in nutritional supplements for patients. Enteral feeding is regarded as being preferable to parenteral feeding in many cases (see, for example, Alverdy, 1990; Alexander, 1990). Early enteral feeding, from Day 1 if possible, is recommended in some clinical situations (Epstein et al., 1992; Moore et al., 1992).

When there is a decrease in plasma glutamine to below physiologically normal levels it is important to restore the *status quo*. This will provide nutrition for proliferation of the cells which are involved in the body's defensive and digestive mechanisms.

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