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The relation between glutamine and the immunodepression observed in exercise

Review Article

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Summary. Glutamine is the most abundant amino acid in the body. It is an important fuel for some key cells of the immune system. Both the plasma concentration of glutamine and the functional ability of immune cells in the blood are decreased after prolonged, exhaustive exercise. Glutamine feeding has had beneficial effects in clinical situations, and the provision of glutamine after intensive exercise has decreased the incidence of infections, particularly of upper respiratory tract infections. However, the precise effect of glutamine on immunodepression in this situation is not yet established.

Keywords: Amino acids – Glutamine – Exhaustive exercise – Immunodepression

Glutamine

Glutamine, the most abundant amino acid in the body, was originally classified as a non-essential amino acid. However, more recently it has been considered that glutamine is "conditionally essential" (Lacey and Wilmore, 1990) particularly after clinical trauma such as major surgery or burns where a marked decrease (35–50%) in the concentration of plasma glutamine occurs and is often maintained for several days (Parry-Billing et al., 1990b, 1992). It is worth noting that a similar drop in blood glucose levels would bring about a diabetic coma. It was established in the early 1980s that glutamine is an important fuel for some key cells of the immune system (Ardawi and Newsholme, 1983).

In exercise, a decrease in plasma glutamine of ca. 25% has been observed after prolonged, exhaustive exercise such as marathon running (Parry-Billings et al., 1990a; Castell et al., 1996). This decrease is relatively transient, lasting perhaps for 6–9 hrs after a marathon.

There is substantial evidence that prolonged, exhaustive exercise, such as a marathon, is associated with adverse effects on immune function

Table 1. A "contemporary" view of non-essential and essential amino acids

Category	Amino acid
Totally essential	Lysine, threonine
Oxoacid essential[1]	Branched chain amino acids, methionine, phenylalanine, tryptophan
Conditionally essential[2]	Cysteine, tyrosine
Conditionally essential[3]	Arginine, cysteine, glutamine, glycine, histidine, serine
Non-essential[4]	Alanine, asparagine, aspartate, glutamate

[1] The carbon skeleton of these amino acids cannot be synthesised by the body. However, if the oxo(keto) acids are provided, the amino acids can be synthesised from the oxoacids via the process of transamination. The oxoacids can be provided artificially.
[2] These are produced from other amino acids – cysteine from methionine and tyrosine from phenylalanine, provided that these amino acids are present in excess.
[3] The demand for these amino acids can increase markedly under some conditions, e.g. infection, severe trauma, burns and in some premature babies.
[4] It is assumed that all these amino acids can be synthesised at sufficient rates in the body to satisfy all requirements. It is now beginning to be appreciated that this may not always be the case for glutamine.
(Modified from Newsholme and Leech, 2000)

(Fitzgerald, 1991; Pedersen, 1991; Noakes, 1992; Shepherd et al., 1994; Castell et al., 1997; Nieman et al., 1990, 1997). These effects include:

decreased cytolytic activity of natural killer (NK) cells;
lower circulating numbers of T-lymphocytes for 3–4 h after exercise;
a decrease in the proliferative ability of lymphocytes;
impaired antibody synthesis;
decreased immunoglobulin levels in blood and saliva;
a decreased ratio of CD4 to CD8 cells

Most of the response does not appear to last longer than a few hours, though some parameters remain affected for 24–48 hours after prolonged, exhaustive exercise. Thus, undertaking intensive exercise sessions within two days of, for example, running a marathon may give insufficient time for the immune system to "recover" sufficiently to function normally.

It has been suggested that athletes may be vulnerable to opportunistic infections for several hours after prolonged, exhaustive exercise such as intensive training and that this may be partly due to a decreased availability of glutamine in the blood at a time when immune cells are being challenged (Parry-Billings et al., 1990a). Parry-Billings et al. (1990a) also reported that athletes suffering from the overtraining syndrome had low plasma glutamine which remained low even after several weeks of rest: recent evidence supports their findings (Rowbottom et al., 1997).

In contrast, regular low-intensity exercise appears to be beneficial for the immune system (Fitzgerald, 1991; see Nieman, 1997).

Fuel for immune cells

Originally, it was thought that immune cells such as lymphocytes and macrophages obtained most of their energy from the oxidation of glucose (see Hume and Weidemann, 1980). However, it has now been shown that freshly isolated lymphocytes and macrophages utilise glutamine at a rate which is either similar to, or greater than, that of glucose (Ardawi and Newsholme, 1983). This is supported by the fact that there is a high maximal catalytic activity of glutaminase in these cells, which is the key enzyme in the glutamine utilisation pathway (Fig. 1).

Glutamine is converted almost totally into glutamate, aspartate, alanine and CO_2. However, only some of the carbon of glutamine (10–30%) is completely oxidised by these cells: this partial oxidation of glutamine is known as glutaminolysis. High rates of glutaminolysis and glycolysis (the partial oxidation of glucose) provide energy for these cells. In addition, glutamine provides nitrogen for the synthesis of purine and pyrimidine nucleotides. The nucleotides are needed for the synthesis of new DNA and RNA during proliferation of lymphocytes, and for mRNA synthesis and DNA repair in macrophages. The rate of glutaminolysis in lymphocytes is very markedly in excess of the rates of synthesis of these compounds (Newsholme et al., 1985). They proposed, as an explanation for this phenomenon, that the synthetic

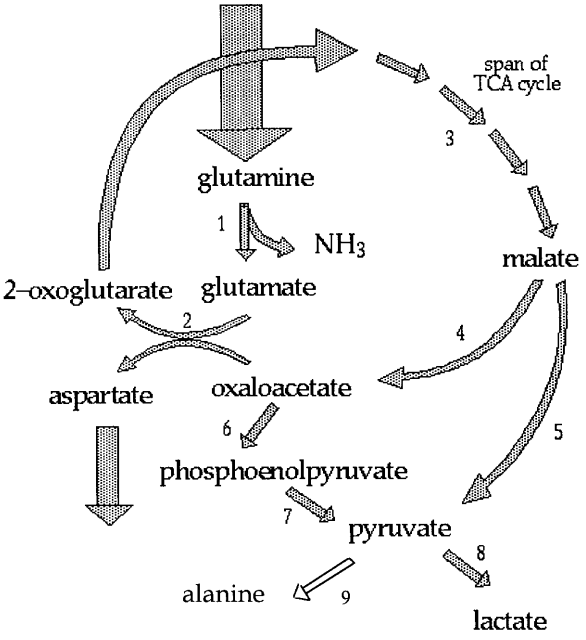

Fig. 1. The proposed pathway of glutamine metabolism in cells of the immune system. The reactions are as follows: *1* Glutaminase; *2* Aspartate aminotransferase; *3* Enzymes of the Krebs cycle converting 2-oxoglutarate to malate; *4* Malate dehydrogenase (NAD+-linked); *5* Malic enzyme [NAD(P)+-linked]; *6* Phosphoenolpyruvate carboxykinase; *7* Pyruvate kinase; *8* Lactate dehydrogenase; *9* Alanine aminotransferase (redrawn from Newsholme et al., 1985)

pathways for *de novo* nucleotide synthesis require specific and precise increases in the rate of synthesis of these nucleotides during the proliferative process. The important point is that glutamine is used at a high rate by some of the cells of the immune system, even when they are not stimulated: these cells would thus be "primed" to respond to any invasion by a foreign organism (Ardawi and Newsholme, 1985). This would require glutamine to be available in the bloodstream at a fairly constant level.

Evidence to support this hypothesis has been provided by *in vitro* studies (Parry-Billings et al., 1990b). A decrease in the glutamine concentration in culture medium below that normally present in human plasma (600 uM) not only decreased the maximum rate of proliferation in response to mitogenic stimulation in peripheral blood lymphocytes but also slowed the response time (Parry-Billings et al., 1990b). This occurred despite the fact that the culture medium contained all other nutrients and growth factors in excess, including glucose. Similarly, a decrease in glutamine concentration decreased phagocytosis and the rate of cytokine production by macrophages (Parry-Billings et al., 1990b).

Muscle and glutamine release

Glutamine is the main amino acid released during short-term starvation such as an overnight fast. Several tissues including liver, muscle, adipose and lung can synthesize and release glutamine into the bloodstream. However, of the tissues that release glutamine, skeletal muscle is thought to be quantitatively most important, since it both synthesizes and stores glutamine, which is taken up by the intestine, liver and kidney and by some cells of the immune system. The rate of release across the plasma membrane, which occurs via a specific transporter, appears to be controlled by various hormones (Newsholme and Parry-Billings, 1990). About 8–9 g of glutamine per day is released from the entire human musculature (see Elia et al., 1990).

Although glutamine synthesis is important to maintain the store of glutamine in muscle, it is the release from muscle which appears to be the key regulatory step for glutamine release into the bloodstream under normal conditions, rather than glutamine synthesis (Newsholme and Parry-Billings, 1990). Clinical studies have reported that feeding large daily quantities of glutamine appears to have helped to prevent a further decrease in muscle glutamine in patients in a catabolic condition, or to restore muscle glutamine to physiological levels. Given that the muscle concentration of glutamine is 20 mM in humans, compared to 0.6 mM in plasma, unacceptably high amounts of glutamine would have to be consumed orally to have an effect on muscle levels in athletes.

Muscle plays a major role in the provision and regulation of plasma glutamine, via the transporter system in the membrane. Much of this glutamine may be used by some key cells of the immune system. Thus it has been suggested that immune cells may communicate with skeletal muscle in

relation to mediation of the rate of glutamine release via chemical messengers such as cytokines, released from cells of the immune system (Newsholme et al., 1988).

The plasma concentration of glutamine is decreased in clinical situations such as major surgery, burns, starvation and sepsis (Askanazi et al., 1980; Newsholme et al., 1988; Parry-Billings et al., 1990b; 1992). In patients with severe catabolism muscle glutamine is also decreased (Roth et al., 1982). There is evidence that the immune system is suppressed during such clinical trauma. The requirement for glutamine is likely to be increased in these conditions, since there will be increased activity of the immune system, and an increased number of cells involved in proliferation and repair, which use glutamine as a fuel.

Glutamine in exercise

The concentration of plasma glutamine is increased in athletes after short-term exercise (Poortmans et al., 1974; Maughan and Gleeson, 1988; Parry-Billings et al., 1992; Table 2). However, it is decreased in athletes after prolonged, exhaustive exercise such as running a full marathon, or after intensive training sessions (Decombaz et al., 1979; Brodan et al., 1986; Parry-Billings et al., 1992; Table 2). This biphasic response of the plasma glutamine concentration first reported in separate observations by Poortmans et al. (1974) and Decombaz et al. (1979) was subsequently confirmed in a single study in athletes who exercised for 3.75 hrs at 50% V_{O2max}: the plasma glutamine concentration increased at an early stage during the exercise but decreased below pre-exercise levels after 3.75 hrs (Rennie et al., 1981).

Table 2. Plasma glutamine concentrations in runners undertaking different levels of exercise. Means ±SEM; [a]$p < 0.05$; [b]$p < 0.01$ (from Parry-Billings, 1989; Castell, 1996)

Exercise	Plasma glutamine (μM)	
	Pre-ex	Post-ex
Marathon race	669 ± 25 n = 18	533 ± 29[b] n = 18
30 km indoor race	532 ± 23 n = 6	503 ± 24 n = 6
15-mile training run	699 ± 21 n = 9	679 ± 20 n = 9
30 km treadmill run	641 ± 17 n = 12	694 ± 29 n = 12
Sprints (10 × 6 sec)	556 ± 21 n = 10	616 ± 21[a] n = 10
Rowers (5 km ergotest)	663 ± 21 n = 13	778 ± 24[b] n = 13

Hiscock and Mackinnon (1998) compared the resting plasma glutamine concentrations of athletes participating in different types of sport, and found a considerable variation. For example, cyclists had a markedly higher resting plasma glutamine than all other sports studied. Interestingly, these authors observed an inverse correlation between plasma glutamine concentration and dietary protein relative to body mass.

Given that the concentration of plasma glutamine is decreased in prolonged, exhaustive exercise (Parry-Billings et al., 1990a; Castell et al., 1996; Brouns, 1997) and in overtraining (Parry-Billings et al., 1990a; Rowbottom et al., 1996), the question arises whether muscle, together with other tissues, can always respond sufficiently to release enough glutamine to maintain the normal blood concentration. This would be particularly important in the event of muscle damage during excessive exercise. Muscle damage may present an area of tissue to which immune cells might migrate, which is larger than normal. MacIntyre et al. (1996) observed a significantly greater number of radiolabelled white blood cells in the right quadriceps after exhaustive eccentric exercise than in the non-exercised muscle. As the numbers of these cells increase, activity increases and/or proliferation of some cells which, in turn, increases the local demand for glutamine. Thus, it is reasonable to suggest that it might be important for extra glutamine to be provided after exhaustive exercise.

Exercise and upper respiratory tract infections

Upper respiratory tract infections (URTI) occur more frequently in athletes after prolonged, exhaustive exercise than in sedentary individuals, or in athletes undertaking moderate exercise, or with non-competing athletes in endurance events (for reviews see Weidner, 1994; Nieman, 1994; Brenner et al., 1994). It has been suggested that moderate, regular exercise helps to reduce the level of infection in sedentary individuals, whereas, in individuals who undertake intensive or excessive training, the incidence of infection increases markedly (Fitzgerald, 1991; Nieman, 1994 1997). The high incidence of infections after prolonged, exhaustive exercise therefore suggests that immunodepression may occur in some athletes due to the stress of hard training and/or competition.

The majority of the studies which showed an increased incidence of URTI after physical activity have been performed on runners (Weidner, 1994). A longitudinal study on 530 male and female runners suggested that a URTI was more likely to occur with higher training mileage (Heath et al., 1991). Similarly, the risk of illness increased in endurance runners when training exceeded 97 km/week (Nieman et al., 1990). In marathon runners, it has been demonstrated that the mental stress of competition more than doubled the risk of getting a URTI (O'Connor et al., 1979). Heath et al. (1991) suggested that a low body mass may be another risk factor for infections. In military personnel in winter, there is a 50% increase in the number of respiratory infections attributable to adenovirus compared with that observed during

summer. Exposure to the cold virus in crowded dormitories, classrooms and gymnasiums might account for the higher incidence of colds in some individuals during winter (Weidner, 1994).

One problem associated with prolonged exercise is that athletes start to breathe through the mouth rather than through the nose, thus bypassing the nasal filter mechanism (Niinima et al., 1980), and consequently impairing the protective effects of mucosal secretions. Furthermore, these mucosal secretions contain IgA, which is known to be decreased after intensive exercise (Tomasi et al., 1982; Pyne and Gleeson, 1998).

The immune response to exhaustive exercise

Cells of the immune system are normally present as circulating cells in the blood and lymph. When an infectious agent attacks, in the first instance the inflammatory response acts together with the innate immune response; this is accompanied by the adaptive immune response, involving T- (thymus-derived) and B- (derived from bone marrow) lymphocytes. The specificity of immune responses is due to the lymphocytes, which are the only cells in the body intrinsically capable of specifically recognizing and distinguishing different antigenic determinants.

There is a substantial increase in numbers of circulating white blood cells (WBC) known as leucocytosis as a result of prolonged, exhaustive exercise. This phenomenon was first observed by Larrabee (1902), who deduced that it was mainly due to a large increase in circulating neutrophils. More recently it has been observed that, within the leucocytosis immediately after a marathon or intensive training, there is also a transient increase in circulating lymphocyte numbers at the start of the recovery period. However, numbers of lymphocytes subsequently decrease below pre-exercise levels within 30 min after strenuous exercise (see Nieman, 1994; Castell et al., 1997).

The majority of *in vitro* studies on athletes after exercise have reported decreased rates of lymphocyte proliferation (Tvede et al., 1989; MacNeil et al., 1991; Field et al., 1991; Nieman et al., 1995; Castell and Newsholme, 1998).

In studies on lymphocyte subsets, a decreased ratio of T-helper to T-cytotoxic (CD4:CD8) cells in athletes after acute exhaustive exercise observed by Berk et al., in 1986, has also been confirmed by Lewicki et al. (1988) and Haq et al. (1993). It has been suggested that a ratio of CD4:CD8 cells below 1.5 is subnormal, and may be a cause of and an indicator of, immunosuppression (Nash, 1986; Keast et al., 1988; Shepherd et al., 1991).

Dehydration and circulating cells

The marked leucocytosis which occurs in the circulation after endurance events may be affected by dehydration, i.e. the cell numbers may be more concentrated in a lower plasma volume. However, in a study by McCarthy and Dale (1988) it was concluded that less than 10% of the leucocytosis could be attributed to dehydration, on the basis of little or no change in haematocrit

levels. This view is confirmed by others (Maron et al., 1975; Haq et al., 1993; Castell and Newsholme, 1998).

Neutrophils

Neutrophils, together with macrophages, are responsible for ingesting invading organisms by phagocytosis. They are the first cells to respond to such an invasion. Unlike most lymphocytes, neutrophils die within a few days of leaving the bloodstream. There appears to be an increased release of immature neutrophils from bone marrow (Hansen et al., 1991) in response to strenuous exercise. Acute mobilisation of neutrophils from bone marrow and blood occurs in response to a more vigorous circulation of the blood.

In *in vitro* studies, the depressed bactericidal ability of neutrophils in samples from burns patients was not only restored but enhanced by the addition of glutamine to the culture medium (Ogle et al., 1994). A similar effect has been reported by Furukawa et al. (1997).

Neutrophil activity, as measured by the oxidative burst technique, was decreased one hour after cycling to exhaustion (mean duration 40 min) at 80% V_{O2max}, and 2.5 hrs after cycling at 55% V_{O2max} for 3 hrs (Robson et al., 1999). After a 100 km race, the percentage of neutrophils incorporating bacteria (the phagocytic rate) was unchanged but the phagocytic activity (the amount of bacteria incorporated per cell) decreased by 34% (Gabriel et al., 1995): nevertheless, the total phagocytic capacity was increased 2–3-fold after this endurance exercise. Fukatsu et al. (1996) found that neutrophil bactericidal activity decreased after a 50-mile walking race: they deduced that this was due to an increase in cortisol and ketone bodies.

Glutamine feeding in clinical situations

Evidence that both parenteral and enteral glutamine feeding can have beneficial effects on gut function and/or the immune system in both humans and animals, comes from several clinical studies. Findings in human studies include a decreased incidence of infections and increased T-cell recovery in bone marrow transplant patients, and enhanced T-cell response in patients undergoing surgery or suffering from acute pancreatitis. Studies on animals include findings of increased alveolar macrophage phagocytosis, reversal of biliary IgA suppression, and increased numbers and function of lymphocytes during sepsis. There are more than one hundred published reports on glutamine feeding studies: no problems of toxicity have been observed.

Glutamine feeding after prolonged, exhaustive exercise

The plasma concentration of glutamine is decreased by ca. 25% in endurance runners after a marathon. A series of studies was therefore undertaken by the author in which supplementary glutamine was administered at rest or after

prolonged, exhaustive exercise. The first study established a suitable glutamine does and timing in resting, normal subjects. About 50% of dietary glutamine is utilised by the intestine. Thus it was of interest to observe that, following the provision of 5 g glutamine as a drink, there was a two-fold increase in the plasma glutamine concentration within 30 min in eight healthy fasting humans. This level returned to almost baseline levels after approximately 2 h.

Double-blind studies were subsequently undertaken in marathon runners to investigate the effects of giving glutamine or a placebo. Athletes took two drinks of either glutamine (5 g L-glutamine) or placebo, immediately after, and one or two hrs after a race. Blood samples were taken after exercise. Plasma glutamine and numbers of leucocytes and lymphocytes were measured, as well as some inflammatory response markers (Castell et al., 1997; Castell and Newsholme, 1997). The plasma concentration of glutamine was decreased (23%) one hour after the marathon but had returned to normal the next morning (Castell et al., 1997).

Increases were also demonstrated in the acute phase response markers, the cytokine interleukin-6 and complement C5a, in blood samples taken after a marathon race (Castell et al., 1997). The four-fold increase in the plasma concentration of CRP observed 16 h after the race, is consistent with damage to muscle after prolonged, exhaustive exercise.

Circulating leucocytes increased three-fold in blood samples taken from runners immediately after the marathon: this was mainly due to an elevation in neutrophil numbers (Castell et al., 1997). There was a 30% decrease in total circulating lymphocytes within 15 minutes after the race but there was no significant difference in leucocyte or lymphocyte numbers between the glutamine and the placebo group. However, numbers of circulating lymphocytes were restored to baseline levels the next morning in the glutamine group, compared with the placebo group. At the same time point, numbers of circulating neutrophils had returned to baseline in the glutamine group, compared with the placebo group, in whom they were still slightly elevated (Castell and Newsholme, 1998). In another marathon study, the decrease in the CD4:CD8 ratio 2 hr after the marathon was less ($p < 0.02$) in runners who took glutamine as opposed to placebo (Castell and Newsholme, 1997).

Completed questionnaires on the incidence of infection for seven days after exercise were received from more than 200 individuals in fourteen studies, who participated in rowing, or endurance or middle-distance running (Castell et al., 1996). The levels of infection were lowest in middle-distance runners, and were highest in runners after a full or ultra-marathon and in elite rowers after a period of intensive winter training. Among the infections reported, the majority were associated with URTI.

The marathon runners who participated in the glutamine feeding study also completed 7-day questionnaires ($n = 151$). Overall, the percentage of participants in the glutamine group who reported being free of infections was significantly greater (81%) than in the placebo group (49%) (Castell et al., 1996). It is suggested that the provision of glutamine after prolonged, exhaus-

tive exercise might increase its availability for some cells of the immune system at a critical period when athletes are vulnerable to opportunistic infections.

Bassit et al. (1999) have shown a similar magnitude of decrease in the incidence of infections in triathletes as that observed by the present author. This decrease was in the group supplemented with branched chain amino acids which, as precursors for glutamine, maintained the plasma glutamine levels, and was compared with a placebo group. Some recent studies have, however, failed to show an effect of glutamine feeding on the immune parameters they studied (see Nieman and Pedersen, 1999). Thus, it remains to be established precisely how glutamine supplementation affects the incidence of infections in field studies. In this context, an important issue is whether measurements of the numbers and activities of leucocytes in the blood properly reflect the performance of the immune system in the whole body. In human studies, it is the only measurable link we have with the much larger number of cells in the whole immune system. Further study is required on different types of supplementation and the consequent effects on immune function. In particular, more field studies should be undertaken.

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