Can Glutamine Modify the Apparent Immunodepression Observed After Prolonged, Exhaustive Exercise?

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Glutamine is an important fuel for some cells of the immune system. In situations of stress, such as clinical trauma, starvation, or prolonged, strenuous exercise, the concentration of glutamine in blood is decreased, often substantially. In endurance athletes this decrease occurs concomitantly with relatively transient immunodepression. Provision of glutamine or a glutamine precursor has been found to decrease the incidence of illness in endurance athletes. To date, it has not been established precisely which aspect of the immune system is affected by glutamine feeding during the transient immunodepression that occurs after prolonged, strenuous exercise. However, there is increasing evidence that neutrophils may be implicated. *Nutrition* 2002;18:371–375. ©Elsevier Science Inc. 2002

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GLUTAMINE AS A FUEL FOR IMMUNE CELLS

Glutamine was classified in the 1950s as a non-essential amino acid. However, more recently, it has been considered "conditionally essential" (for a contemporary review of this classification, see Newsholme and Castell[1]). After major clinical trauma a marked decrease (35% to 50%) has been seen in the concentration of plasma glutamine, which is often maintained for several days. Exogenous provision of glutamine may be "essential" in these circumstances.

Ardawi and Newsholme[2] established that glutamine is an important fuel for some key cells of the immune system. Lymphocytes and macrophages, for example, were originally thought to obtain most of their energy from the oxidation of glucose.[3] However, it has now been shown that freshly isolated lymphocytes, T- and B-lymphocyte–derived cell lines, and macrophages use glutamine at a rate that is either similar to, or greater than, that of glucose.[2,4] 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 utilization pathway.[1,2,4]

Only some of the carbon of glutamine is completely oxidized by these cells; this partial oxidation of glutamine is known as *glutaminolysis*. In addition to providing energy, glutamine provides nitrogen for the synthesis of purine and pyrimidine nucleotides. The nucleotides are needed for the synthesis of new DNA and RNA during lymphocyte proliferation and, in macrophages, for mRNA synthesis and DNA repair. However, the rate of glutaminolysis in lymphocytes is substantially higher than the rates of synthesis of these compounds. Newsholme et al.[5] proposed that the synthetic pathways for de novo nucleotide synthesis require specific and precise increases in the rate of synthesis of these nucleotides during the proliferative process. A high rate of glutamine use by some of the cells of the immune system, even when unstimulated, would thus enable a rapid response to an immune challenge.[4] This would require glutamine to be available in the bloodstream at a fairly constant level.

In vitro studies have provided evidence to support this hypothesis. A decrease in the glutamine concentration in culture medium below that normally present in human plasma (600 μM) decreased the maximum rate of proliferation in response to mitogenic stimulation in peripheral blood lymphocytes and slowed the response time.[6] 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.[6]

GLUTAMINE RELEASE FROM SKELETAL MUSCLE

Of the tissues that release glutamine (liver, muscle, adipose, and lung), skeletal muscle is thought to be quantitatively most important. It synthesizes and stores glutamine, which is taken up by the intestine, liver, kidney and some cells of the immune system. Glutamine is released across the plasma membrane via a specific transporter, and the rate of release appears to be controlled by various hormones.[7] The release of glutamine from muscle, rather than glutamine synthesis per se, appears to be the key regulatory step for glutamine release into the bloodstream under normal conditions.[7,26] About 8 to 9 g of glutamine per day is released from the entire human musculature.[8]

Much of the glutamine released by muscle is thought to be used by some key cells of the immune system. Newsholme et al.[11] proposed that immune cells might use chemical messengers such as cytokines, released from different cells of the immune system, to communicate with skeletal muscle in relation to regulating the rate of glutamine release. The plasma concentration of glutamine is markedly decreased in clinical situations such as major surgery, burns, starvation, and sepsis[6,9–13] There is also evidence that the immune system is suppressed during such clinical trauma. The requirement for glutamine is likely to be increased in these conditions because 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.

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TABLE I.

PLASMA GLUTAMINE CONCENTRATIONS IN RUNNERS UNDERTAKING DIFFERENT LEVELS OF EXERCISE*

	Plasma glutamine (μM)	
Exercise	Pre-exercise	Postexercise
Marathon race	669 ± 25	533 ± 29‡
n	18	18
30-km indoor race	532 ± 23	503 ± 24
n	6	6
15-mile training run	699 ± 21	679 ± 20
n	9	9
30-km treadmill run	641 ± 17	694 ± 29
n	12	12
Sprints (10 × 6 s)	556 ± 21	616 ± 21†
n	10	10
Rowers (5-km ergotest)	663 ± 21	778 ± 24‡
n	13	13

* Data are presented as means ± standard error of the mean.
† $P < 0.05$.
‡ $P < 0.01$.[26,27]

GLUTAMINE IN EXERCISE

The blood concentration of glutamine is increased in athletes after short-term exercise[14–16] (Table I). Conversely, in athletes undertaking prolonged, exhaustive exercise such as running a full marathon or intensive training sessions, it is decreased[16–19] (Table I). The biphasic nature of the plasma glutamine response to exercise was first reported in separate observations.[14,17] It was subsequently confirmed in athletes who exercised on a treadmill for 3.75 h at 50% maximum oxygen consumption ($V_{O_{2max}}$): the plasma glutamine concentration increased at an early stage during the exercise but, at the end of the exercise, decreased below preexercise levels.[21] The decrease in plasma glutamine after running a marathon is relatively transient, lasting perhaps for 6 to 9 h after a marathon.

The resting, fasting plasma glutamine concentration in athletes participating in different types of sport has been found to vary considerably.[22] Cyclists had a markedly higher resting plasma glutamine concentration than all other athletes studied, and powerlifters had the lowest. Those investigators also observed an inverse correlation between plasma glutamine concentration and dietary protein relative to body mass. Parry-Billings et al.[23] reported that athletes with the overtraining syndrome had low plasma glutamine that remained low even after several weeks of rest; recent evidence supports their findings.[24]

It has been suggested that athletes may be vulnerable to infectious agents for several hours after prolonged, exhaustive exercise, and that this may be partly due to a decreased availability of blood glutamine at a time when immune cells are being challenged.[23] In contrast, regular low-intensity exercise appears to be beneficial for the immune system.[25] An important factor may be that the blood glutamine concentration remains unaltered at that level of exercise.

Thus, in terms of prolonged, strenuous exercise, the question arises as to whether muscle and 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 a larger than normal area of tissue, to which immune cells migrate. For example, MacIntyre et al.[28] observed a significantly greater number of radiolabeled 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 or proliferation of some cells increases. This in turn increases the local demand for glutamine. Thus, it is reasonable to suggest that the provision of exogenous glutamine after exhaustive exercise might boost immune function.

THE INCIDENCE OF ILLNESS IN ENDURANCE ATHLETES

There is a high incidence of illness in endurance athletes, in particular upper respiratory tract infections (URTIs), compared with athletes undertaking moderate exercise or sedentary individuals (for reviews see[29–31]). It appears that moderate, regular exercise reduces the incidence of illness in sedentary individuals, whereas the incidence of infection increases markedly in individuals who undertake intensive or excessive training.[25,30,32] This suggests that some immunodepression may occur in some athletes due to the stress of hard training and/or competition.

Rhinoviruses are responsible for approximately 40% of URTIs in adults and are more prevalent during autumn and spring. In winter, the adenovirus is more prevalent. A 50% increase in the number of respiratory infections attributable to adenovirus compared with that observed during summer has been observed in military personnel in winter.[29,33] The main transmission of rhinoviruses is via aerosol routes. However, viruses are also spread very efficiently by hand-to-hand transmission, for example, by playing contact sports or handling contaminated sports equipment. Gwaltney et al.[34] undertook an experiment in which a subject whose hands were contaminated with rhinovirus shook hands with 15 individuals. Eleven of the 15 were infected via this direct hand-to-hand contact.

There are other factors that can increase the risk of illness in endurance athletes. It has been suggested that a URTI is more likely to occur with higher training mileage; indeed, the incidence of illness increased in endurance runners when training exceeded 97 km/wk.[35,36] Low body mass has been suggested as a risk factor for infections,[36] and the mental stress of competition more than doubled the risk of marathon runners getting a URTI.[37]

EXHAUSTIVE EXERCISE AND THE IMMUNE RESPONSE

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 with the innate immune response; this is accompanied by the adaptive immune response, involving T (derived from the thymus) 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.

Neutrophils and 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. Acute mobilization of neutrophils from bone marrow and blood occurs in response to a more vigorous circulation of the blood. There appears to be an increased release of immature neutrophils from bone marrow in response to strenuous exercise.[57]

There is substantial evidence associating prolonged, exhaustive exercise, such as a marathon, with adverse effects on immune function.[25,30,32,38–45] These effects include:

- decreased cytolytic activity of natural killer cells
- lower circulating numbers of T lymphocytes for 3 to 4 h after exercise
- a decreased ratio of CD4 to CD8 cells
- a decrease in the proliferative ability of lymphocytes
- decreased neutrophil activity

- impaired antibody synthesis
- decreased immunoglobulin levels in blood and saliva

In most cases the response appears relatively transient, lasting only a few hours. However, some parameters remain affected for 24 to 48 h after prolonged, exhaustive exercise. Thus, undertaking intensive exercise sessions within 2 d of, for example, running a marathon, may give insufficient time for some aspects of the immune system to "recover" sufficiently to function normally. Some evidence of this has been observed after repeated bouts of high-intensity exercise,[24] and after a short bout of intensive exercise ($V_{O_{2max}}$) undertaken after 8 wk of training in endurance runners in preparation for a major competition.[46]

Strenuous exercise markedly increases the numbers of circulating white blood cells (leucocytosis). This phenomenon was first observed by Larrabee[47] who deduced that it was due mainly to a large increase in circulating neutrophils, and it is now well documented.[48] 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 15 to 30 min after strenuous exercise.[30,44,57] It has been suggested that leucocytosis after endurance events may be affected by dehydration. However, several studies on endurance exercise have observed little or no change in hematocrit levels. Thus it is likely that only a minor amount of the increase in circulating cell numbers is attributable to dehydration[48–51]; but see also Kargotich et al.[69]

In vitro studies on athletes after exercise have reported decreased rates of lymphocyte proliferation.[25,38,39,40,51] A decreased ratio of T-helper to T-cytotoxic (CD4:CD8) cells in athletes after acute exhaustive exercise was observed by Berk et al.[52] and has since been confirmed.[50,53] A ratio of CD4:CD8 cells below 1.5 has been suggested to be a cause of and an indicator of immunodepression.[54–56]

Neutrophil activity, measured with elastase release and oxidative burst, was decreased 1 h after cycling to exhaustion (mean duration 40 min) at 80% $V_{O_{2max}}$ and 2.5 h after cycling at 55% $V_{O_{2max}}$.[45] After a 100-km race, the percentage of neutrophils incorporating bacteria (the phagocytic rate) was unchanged, but phagocytic activity (the amount of bacteria incorporated per cell) decreased by 34%.[58] Fukatsu et al.[59] 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.

In in vitro studies, the depressed bactericidal ability of neutrophils in samples from burn patients was not only restored but also enhanced by the addition of glutamine to the culture medium.[60] A similar effect has been reported more recently.[61] Recent studies in my laboratory have shown oxidative burst in human neutrophils to be enhanced by the addition of glutamine in vitro by using a novel chemiluminescent assay and two different stimuli.[68]

GLUTAMINE FEEDING IN CLINICAL SITUATIONS

Both parenteral and enteral glutamine feeding in clinical situations have been shown to have beneficial effects on gut function in particular (as described elsewhere in this issue) and on the immune system in humans and animals. 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 immunoglobulin A suppression, and increased numbers and function of lymphocytes during sepsis (Table II). Recent observations in my laboratory have included an increase in lymphocyte proliferation (as measured by ^{3}H-thymidine incorporation into DNA) and increased interleukin-2 production in intensive care patients receiving daily enteral glutamine.[62]

GLUTAMINE FEEDING AFTER PROLONGED, EXHAUSTIVE EXERCISE

In collaboration with Newsholme, I made a series of studies in which supplementary glutamine was administered at rest or after prolonged exercise, such as a marathon. About 50% of dietary glutamine is used by the intestine. Thus, it was of interest to observe that, after ingestion of a bolus dose of glutamine (0.1 g/kg body weight) in water, an increase (ca. two-fold) in the plasma glutamine concentration was observed within 30 min in eight healthy control subjects after an overnight fast.[63] Two hours after ingestion, this concentration returned almost to the baseline concentration.

Subsequently, in double-blind studies, marathon runners were given two drinks of glutamine (5 g of L-glutamine or placebo) immediately after and 1 or 2 h after a race. Measurements included plasma glutamine, whole blood counts, some inflammatory response markers, and cytokines.[44,63] Although plasma glutamine appeared slightly higher in the glutamine group 1 h after the bolus dose, the difference was not significant. As described earlier, a significantly elevated plasma glutamine concentration was observed in a sample taken from subjects at rest 30 min after ingestion of glutamine.[63] The plasma concentration of glutamine was decreased (23%) 1 h after the marathon compared with fasting, resting control levels but had returned to normal the next morning.[44]

The plasma concentration of the acute-phase response markers, interleukin-6 and complement C5a, were markedly increased after a marathon.[44] There was a four-fold increase in plasma C-reactive protein 16 h after the race (the next morning), which is indicative of muscle damage after strenuous exercise. The production of interleukin-8, a chemoattractant for neutrophils, has been consistently observed to be decreased in the glutamine group compared with placebo[27,64] (see also Table II). There is increasing evidence from in vitro and in vivo studies that the exogenous supply of glutamine may have a beneficial effect on neutrophil function.

As anticipated, numbers of circulating leukocytes increased markedly immediately after the marathon, mainly due to a large increase in neutrophil numbers.[44] There was a 30% decrease in total circulating lymphocytes within 15 min after the race. However, in a subset of marathon runners, numbers of circulating lymphocytes were restored to baseline levels 16 h after the marathon (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.[51] The CD4:CD8 cell ratio was decreased 2 h after the marathon but the decrease was less ($P < 0.02$) in the glutamine group than in the placebo group.[63] An important issue is whether measurements of the numbers and activities of leukocytes 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.

The incidence of illness during the 7 d after strenuous exercise was investigated. More than 200 athletes in 14 studies participating in rowing or marathon or middle-distance running completed self-reported questionnaires. The levels of infection were lowest in middle-distance runners and highest in runners after a full or ultramarathon and in elite rowers after a period of intensive winter training. The majority of illnesses reported were URTIs.[19] The self-reported incidence of illness in marathon runners in the glutamine group was significantly lower (32%) than in the placebo group ($n = 151$).[19]

Further evidence in support of this finding comes from a study by Bassit et al.[65] who observed a similar magnitude of decrease (40%) in the incidence of infections in triathletes after daily supplementation with branched chain amino acids. As precursors

TABLE II.

BENEFICIAL EFFECTS OF GLUTAMINE FEEDING IN CLINICAL SITUATIONS ON SOME ASPECTS OF IMMUNE FUNCTION*

Recipients	Clinical situation	Method of feeding	Beneficial effects
Humans	Bone marrow transplant†	TPN (L-glutamine)	Decreased number of positive microbial cultures Decreased number of clinical infections Enhanced recovery of circulating lymphocytes, total T-lymphocytes, CD4 helper, CD8 suppressor
Humans	Colorectal cancer‡	TPN (glycyl-glutamine dipeptide)	Enhanced postoperative T-lymphocyte DNA synthesis
Humans	Severe, acute pancreatitis§	TPN	Enhanced T-cell response, decreased IL-8 production
Rats	Healthy, suppressed biliary IgA‖	TPN (L-glutamine)	Increased biliary concentration of IgA normally suppressed by TPN
Rats	Tumor bearing¶	TPN (alanyl-glutamine dipeptide)	Increased phagocytic activity of alveolar macrophages
Rats	Tumor bearing#	Oral	Increased mitogenic response in splenocytes, increased NK cell numbers but not activity in the spleen
Rats	Sepsis**	TPN (alanyl-glutamine dipeptide)	Increased rate of lymphocyte proliferation and increased number of lymphocytes
Rats	Chemotherapy††	Oral	Decreased sepsis defined as decreased white blood cell count plus decreased positive blood cultures
Mice	Healthy‡‡	Oral	Increased macrophage production of TNF-α and IL-6; enhanced Thl response

* Modified from Newsholme and Castell, with permission.[1]
† Ziegler et al. Ann Intern Med 1992;116:821; Ziegler et al. JPEN 1994;18:17S.
‡ O'Riordan et al. Ann Surg 1994;220:212.
§ O'Riordain et al. Nutrition 1996;12:S82.
‖ Burke et al. Arch Surg 1989;124:1396.
¶ Kweon et al. Amino Acids 1991;1:7.
# Shewchuk et al. J Nutr 1997;127:158.
** Yoshida et al. Am J Physiol 1992;263:E368.
†† Klimberg JPEN 1992;16:83S.
‡‡ Yaqoob et al. Clin Nutr. 1998;17:O15.
IgA, immunoglobulin A; IL-6, interleukin-6; IL-8, interleukin-8; NK, natural killer: TNF-α. tumor necrosis factor-α; TPN, total parenteral nutrition

for glutamine, the branched chain amino acids maintained the plasma glutamine levels, and Bassit et al. attributed the decrease in incidence of illness to this.

Despite these interesting findings, some recent studies[66,67] have failed to show an effect of glutamine feeding on the specific immune parameters investigated after strenuous exercise. There is good evidence that glutamine has a marked effect on some functions of the immune system in clinical situations (see Table II and other articles in this issue). Glutamine feeding may well prove beneficial to the athlete by improving intestinal function and enhancing the functional ability of some immune cells at a critical period when athletes are vulnerable to opportunistic infections. However, the cellular and molecular mechanisms of the beneficial effect of glutamine supplementation observed on the incidence of illness in placebo-controlled field studies have yet to be established.

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