INTRODUCTORY REMARKS

Part 18 extends the general amino acids overview in Part 2, by reviewing specifically glutamate and glutathione, and the tripeptide antioxidant, glutathione.

Glutamine supplementation has been well studied in both clinical and exercise situations, particularly in terms of its effects on immune function. Sports drinks containing glutamine as a free amino acid or part of a dipeptide are widely available but the low levels recommended are unlikely to help improve immune or muscle function.

The first product of glutamine metabolism, catalysed by the enzyme glutaminase, is the excitatory neurotransmitter glutamate. The latter has sometimes been used for supplementation. This may seem rather surprising, since its appearance in plasma at a high concentration correlates neurotoxicity and sometimes with clinical problems.

Glutathione, for which glutamine is a precursor via glutamate, is a powerful antioxidant and, in its reduced form, is a good marker of antioxidant capacity, while an increase in its oxidised form is a good marker of oxidative stress.

GLUTATHIONE AND GLUTAMATE

P Newsholme and M Krause

Glutathione (γ-glutamyl-cysteinyl-glycine; GSH) is the predominant low molecular weight thiol (0.5–10 mmol/l) in mammalian cells. Most GSH (85–90%) is cytosolic, with the remainder located in organelles (including mitochondria, nuclear matrix and peroxisomes).1 This tripeptide is a key antioxidant within cells, critical to regulating the reactive oxygen species (ROS) concentration.2 Reduced glutathione (GSH) may be used to remove damaging ROS such as H$_2$O$_2$ and convert it to harmless H$_2$O, generating oxidised glutathione (GSSG) via glutathione peroxidase (figure 1). Disulphide formation and glutathionylation are reversible forms of protein covalent modification dependent on glutathione and can provide mechanisms for regulation of metabolic, signalling and transcriptional processes,3 including skeletal muscle adaptation to exercise and training.4 The cellular redox state is crucial for molecular signalling, and glutathione is a key regulator/sensor for redox status; thus strategies aiming at increasing GSH synthesis should be beneficial to exercise performance.

Exercise, free radical production and dissipation

Exercise stimulates ROS and reactive nitrogen species (RNS) production, dependent on exercise type, duration and intensity, culminating in changes in skeletal muscle redox state.5 ROS/RNS production and various antioxidant roles are summarised in figure 1. Excessive ROS and RNS production is associated with deleterious effects in many diseases including diabetes.6 7 Antioxidant supplementation strategies have been assessed for their ability to decrease ROS levels and the deleterious effects of oxidative/nitrosative damage.8 While excessive ROS and RNS can exert harmful effects within skeletal muscle during exercise, lower levels are crucial for adaptation of metabolic and signalling pathways in response to exercise. For example, redox changes are essential for the production and release of myokines such as interleukin 6 (IL-6), which, in part, optimises fuel provision for sustained activity.9 Although antioxidant supplementation may at first be considered as beneficial, the consequent reduction of ROS/RNS could have negative effects. Muscle redox state may be best improved by providing skeletal muscle cells with key natural precursors for GSH synthesis and allowing the cells to synthesise what they actually require. Exercise-induced free radical production in skeletal muscle is not detrimental to human health; thus endogenous antioxidants may be sufficient to protect against exercise-induced oxidative damage.

Regulation of glutathione synthesis

The synthesis of GSH from glutamate, cysteine and glycine is catalysed sequentially by two key cystolic enzymes, γ-glutamylcysteine synthetase (GCS) and GSH synthetase. The availability of these amino acids is essential for GSH synthesis (figure 2). Supplementation with cysteine precursors, such as N-acetylcysteine, increases glutathione levels.10 However, de novo GSH synthesis depends on glutamate, which is a constituent of the GSH molecule. It also acts as an amino acid donor in serine synthesis, which can subsequently be converted to glycine. GSH is a non-allosteric feedback inhibitor of GCS but competes with glutamate, thus high intracellular glutamate concentrations will enhance GSH synthesis.11

In conclusion, amino acid supplementation that increases intracellular glutamate and cysteine could improve muscle GSH synthesis. Future
Glutamine, the most abundant amino acid in the body, has recently become regarded as conditionally essential rather than non-essential. Glutamine is synthesised, stored and released predominantly by skeletal muscle: it is taken up by intestinal cells, such as enterocytes and colonocytes, by the liver and kidney and by some key immune cells. In clinical studies, the plasma concentration of glutamine (p[Gln]) is decreased in trauma and starvation: glutamine provision has been reported to have a beneficial effect on gut function, morbidity and mortality, and immune cell function. Clinical evidence suggests that glutamine provision helps recovery from surgery and maintains muscle protein mass.

The normal resting, fasting p[Gln] is 500–700 μmol/l and is often higher in athletes: the muscle concentration can reach 20 mM (60% of the intramuscular pool). During short-term strenuous exercise, p[Gln] is usually markedly increased, probably due to the release of glutamine into the circulation from skeletal muscle. However, p[Gln] is often substantially reduced by prolonged, exhaustive exercise: this decrease often occurs concomitantly with relatively transient immunodepression. Decreased p[Gln] may contribute to overtraining. Glutamine supplementation after exercise reduced the self-reported incidence of illness in endurance athletes. However, when glutamine was given to athletes to combat exercise-induced depletion of circulating glutamine, no effects were observed on the immune parameters studied, apart from reduced neutrocytosis and increased circulating IL-6. It remains to be studies need to determine which amino acids can increase intracellular glutamate and glutathione (see main text for further explanations). α-KG, α-ketoglutarate; BCAA, branched chain amino acids; BCKA, branched chain keto acids; GCS, γ-glutamylcysteinyl-glycine. Figure 2 Glutathione synthesis and the possible amino acid candidates which may increase intracellular glutamate and glutathione (see main text for further explanations). α-KG, α-ketoglutarate; BCAA, branched chain amino acids; BCKA, branched chain keto acids; GCS, γ-glutamylcysteinyl-glycine; γ-glutamylcysteine synthetase; GSH, γ-glutamyl-cysteinyl-glycine.

GLUTAMINE

L M Castell, P Newsholme and E A Newsholme

Glutamine, the most abundant amino acid in the body, has recently become regarded as conditionally essential rather than non-essential. Glutamine is synthesised, stored and released predominantly by skeletal muscle: it is taken up by intestinal cells, such as enterocytes and colonocytes, by the liver and kidney and by some key immune cells. In clinical studies, the plasma concentration of glutamine (p[Gln]) is decreased in trauma and starvation: glutamine provision has been reported to have a beneficial effect on gut function, morbidity and mortality, and immune cell function. Clinical evidence suggests that glutamine provision helps recovery from surgery and maintains muscle protein mass.

The normal resting, fasting p[Gln] is 500–700 μmol/l and is often higher in athletes: the muscle concentration can reach 20 mM (60% of the intramuscular pool). During short-term strenuous exercise, p[Gln] is usually markedly increased, probably due to the release of glutamine into the circulation from skeletal muscle. However, p[Gln] is often substantially reduced by prolonged, exhaustive exercise: this decrease often occurs concomitantly with relatively transient immunodepression. Decreased p[Gln] may contribute to overtraining. Glutamine supplementation after exercise reduced the self-reported incidence of illness in endurance athletes. However, when glutamine was given to athletes to combat exercise-induced depletion of circulating glutamine, no effects were observed on the immune parameters studied, apart from reduced neutrocytosis and increased circulating IL-6. It remains to be...
determined which other aspects of exercise-induced immuno- 
depression might be altered by glutamine supplementa- 
tion. Although the main focus of the series and this article 
is the ergogenic effects of supplementation, immunodepres- 
sion must also be taken into account, since its elimination will 
allow more effective training and thus better performance. 

After endurance exercise, muscle glycogen depletion is an 
important factor in recovery and subsequent performance. 
Post-exercise intake of carbohydrate provides a substrate 
for glycogen synthesis and also stimulates insulin secretion, 
which subsequently activates glucose transport and the gly- 
cogen synthase enzyme in muscle. Varnier et al14 and Bowtell et al15 suggested that glutamine supplementation might also 
promote glycogen synthesis—perhaps an indirect effect via 
promotion of insulin secretion? However, Marwood and 
Bowtell16 found no effect of glutamine supplementation 
(0.125g/kg) on performance in high-intensity exercise after 
glycogen depletion.

Glutamine supplementation ([l-alanyl-l-glutamine dipeptide, 
at 0.05 and 0.2 g/kg] led to a significant ergogenic benefit by 
increasing time to exhaustion during a mild hydration stress.17 
This ergogenic effect was thought likely to be mediated by an 
enhanced fluid and electrolyte uptake. 

There is evidence of a role for glutamine, versus alanine, in pro- 
tecting footballers against an exercise-induced increase in blood ammonia,18 which would have an impact on fatigue. Earlier, 
the same group also observed that glutamine+carbohydrate reduced blood ammonia accumulation in endurance athletes. 
A mixture containing vitamins and minerals, and 12 amino 
acids, including glutamine, was provided to improve train- 
ing efficiency in athletes.9 However, it cannot be deduced whether any one amino acid had a more specific effect than 
another. When BCAAs (precursors for glutamine) were given, although p[Gln] was increased, and muscle recovery was 
helped, the supplementation did not actually enhance athletic 
performance.20 

Welbourne21 found that acute glutamine administration (16–36 mg/kg) increased both plasma bicarbonate and growth 
hormone amino acid supplementation. However, glutamine administration (0.03 g/kg 90 min pre-exercise) did not improve 
maximum effort on a bicycle ergometer.22 By contrast, 
Lehmkuhl et al23 observed an enhanced initial rate of power 
production during cycle ergometer bouts (4 g glutamine/day), 
combined with creatine monohydrate, but no significant dif- 
fERENCE was observed in the combined supplement group com- 
pared with creatine monohydrate alone. 

Overall, there is no consensus or unifying concept to explain 
the efficacy of exogenous provision of glutamine alone on 
performance in athletes, although in combination with carbohy- 
drate or other amino acids, significant improvements have been 
reported.

CONCLUDING COMMENTS

Although there is some evidence that glutamine is effective in 
DEcreasing the self-reported incidence of upper respiratory 
tract illness, it has been difficult to obtain evidence of an effect 
on any specific aspect of the immune system. There is no doubt 
that it is important for the athlete to combat immunodepres- 
sion, and glutamine would be particularly advantageous if it 
could be proved useful in this way, since it is not a banned 
substance. Its effects on performance per se are not convincing 
and, although space precludes citing every study, it is clear that 
more studies are needed to back up the small amount of evi- 
dence already reported.

Because of the importance of glutathione as a key regulator 
or sensor for redox status, increasing GSH synthesis may be 
beneficial to exercise performance. Thus, amino acid supplement- 
ation that increases intracellular glutamate and cysteine 
might improve muscle GSH synthesis.

Competing interests None.

Provenance and peer review Commissioned; not externally peer reviewed.

REFERENCES

Nutritional supplement series
BJSM reviews: A to Z of nutritional supplements: dietary supplements, sports nutrition foods and ergogenic aids for health and performance — Part 18


doi: 10.1136/bjsm.2010.080978

Updated information and services can be found at:
http://bjsm.bmj.com/content/45/3/230.full.html

These include:

References
This article cites 23 articles, 7 of which can be accessed free at:
http://bjsm.bmj.com/content/45/3/230.full.html#ref-list-1

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/