Review paper

Current popular ergogenic aids used in sports: a critical review

Graziela Beduschi

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Many athletes make extensive use of ergogenic aids in the hope that they can favourably affect athletic performance and increase lean body mass. Supplementation with creatine, glutamine, carnitine, leucine and its metabolite hydroxymethylbutyrate (HMB), and branched chain amino acids (BCAA) has been hypothesised to assist in the achievement of optimal sports performance. Despite an increasing amount of scientific evidence and popularity, uncertainty about the effectiveness and safety of these supplements still exists.

A survey was undertaken of the supplements being promoted in the most popular sports magazines in Australia. Approximately one quarter of the advertisements for supplements in the magazines surveyed were for creatine (54%), glutamine (24%), HMB (20%), and BCAA (2%). A critical literature review of trials of the effect of these ergogenic aids on exercise performance trials was conducted. Creatine supplementation appears to have substantial scientific support as a safe and effective nutritional strategy to enhance exercise performance and improve training adaptations in high-intensity, short-term (≤ 30 seconds) exercise tasks, with limited recovery time between repetitions. Carnitine supplementation has been reported to increase exercise capacity in disease states. However, in healthy athletes carnitine was not shown to have an ergogenic effect. There was limited evidence that the use of HMB supplementation resulted in gains in strength and body mass. There was an abundance of clinical evidence supporting the requirement for exogenous glutamine in critically ill patients and in the over-training syndrome. However, for healthy subjects, the few scientific studies available suggested that glutamine is only of benefit for athletes with true deficiency. Research findings regarding the effects of BCAA supplementation are somewhat equivocal. Most reviews evaluating the central fatigue hypothesis suggest that BCAA is not an effective ergogenic supplement, nor is it ergolytic. Further research is needed for better evaluation of the safety and efficacy of many of these supplements, especially focussing on their use in specific sporting situations.

Key words: ergogenic aids, hydroxymethylbutyrate, branched chain amino acids, creatine, carnitine, glutamine, sport nutrition, exercise

Introduction

The provision of sports supplements has become a multi-million dollar business and in popular sports magazines (such as Muscular Development, Iron Man, Muscles Magazine Flex, Muscle and Fitness, Muscle Media), creatine, glutamine, hydroxymethylbutyrate (HMB) and branched chain amino acids (BCAA) are among the most promoted supplements.

The process of substantiating the performance benefits or outcomes from nutrient supplementation is difficult. Under specific conditions ergogenic aids can have some positive effects on performance, lean body mass, strength and changes in body composition. Unfortunately there is often inadequate experimental evidence of efficacy or what exists is of poor quality. For some supplements there are sound trials demonstrating efficacy in the laboratory setting but not in the sports setting (1).

The following considerations are relevant when studying the effectiveness of specific sports ergogenic aids:

(1) In appropriate subject population; subjects should be highly trained in the specific sport performance factors that theoretically are enhanced by use of the sports ergogenic. If the sports ergogenic is effective, it should improve performance beyond the effects of training. Highly trained aerobic athletes, such as marathon runners or road cyclists, should serve as subjects, so that the variability in performance measures can be minimised;

(2) the performance tests used should be valid and reliable. Both laboratory (well-controlled) and field (real-world conditions) tests provide valuable information. Subjects should undertake a learning trial or trials to

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G. Beduschi, MSc, BNutrDiet, Lecturer, FEPAR University, Paraná, Brazil
Correspondence: G. Beduschi, R: Augusto Stellfeld, 1387, Bigorrilho, Curitiba – Paraná, Brazil 80430–140. Email: grazibedu@hotmail.com

become proficient in the tests; the treatment should be based on sound theoretical rationale;

(3) an appropriate placebo should be used. The best design involves repeated-measures, crossover approach in which each subject randomly takes both the treatment and placebo, with an appropriate wash-out period between, and a double-blind protocol;

(4) investigators attempt to control extraneous factors and control the test environment that might influence test performance. During the conduct of the study, the athletes should maintain normal dietary and exercise training habits. Factors such as the exact composition and amount of an amino acid, the amount per serving and timing of ingestion in relation to the exercise may all influence study outcome (2);

(5) appropriate statistical techniques should be used to minimise the chance of statistical error (1) and how best to examine the data genreated by the studies (3). It must be considered whether statistical tests will detect the very small differences that can enhance performance.

Methods

A comprehensive literature review was conducted to find studies that examined the relationship between sports or ergogenic supplementation and changes in performance, strength and any other physiological metabolic response. The following databases were searched: MEDLINE (1996 to Week 3 September 2001, whole file), ProQuest 5000, American Physiological Society, Sprunger, SwetsNet Navigator and High Wire Press. Information about study design, method, sample size, subject characteristics, dose-effect and study outcomes published in peer-reviewed journals were summarised. Given the limited number of studies found and the heterogeneity of study design and characteristics, discussion of each supplement was conducted using the most credible evidence available to build a critical review of the state of the science at the current time. Assessment of quality and content was undertaken by the author. Information about study design, method, sample size, subject characteristics, dose-effect and study outcomes were considered.

Results and discussion

Creatine

Creatine is a naturally occurring amino acid derived from the amino acids glycine, arginine, and methionine. Most creatine is stored in skeletal muscle, primarily as phosphocreatine; the remainder is found in the heart, brain, and testes (4,5). The daily creatine requirement is approximately two to three grams; half is obtained from diet, primarily from meat (500 g of uncooked steak contains about two grams of creatine) (6) and fish, while the remainder is synthesised (7). The amount of phosphocreatine in the skeletal muscle partially determines the length of time that maximum muscle work can be done (8). In theory, an increased store of creatine or phosphocreatine could improve the ability to produce energy during high-intensity exercise as well as improve the speed of recovery from high-intensity exercise (9). Creatine may also independently result in increased body mass (10), although in the first few weeks much of this increase may be due to increased water retention (8). Its use as a supplement to enhance sport performance has not been prohibited by the International Olympic Committee (8). Nevertheless, the US Food and Drug Administration recently warned consumers to consult a health professional before using creatine, and bodies such as the American College of Sports Medicine have taken a cautious view on the benefits and side effects of nutritional ergogenics aids (14). The safety of prolonged creatine supplementation has not been established, however, short-term supplementation (up to eight weeks) has not been associated with major health risks (3,6). Whether there are side effects from long-term use of creatine, particularly with high doses associated with rapid loading, remains to be determined. Some undocumented anecdotal reports indicate creatine supplementation may lead to muscle cramps, nausea, gastrointestinal upset, headache and possible muscle strains (3,6).

Table 1 shows the results of 35 studies on creatine supplementation. Most studies were undertaken using an experimental design, using a placebo control with the subjects supplemented with creatine at 0 to 25 g per day. In only one study subjects were administered 40 g of creatine per day (12). The creatine trials were from three days to 11 weeks in duration and included both healthy males and females, elite and untrained subjects (in the specific sport performance factors), active and sedentary participants. Of 35 studies ten did not find any significant effect of creatine supplementation on metabolism, performance or strength, nor any ergogenic effects or changes in body composition (13–22).

High-intensity ergometer protocols

In six studies using exercise tests ranging in duration from six to 30 seconds, the creatine group experienced a significantly lower decrease in performance compared to the placebo group (23–29). However, in four studies the investigators reported that creatine supplements produced no significant differences in peak or maximum power, time to exhaustion, performance or any other work measure (13,14,18,19). These more recent studies support the review by Williams (1) of 17 earlier studies, using cycle ergometer performance in a laboratory setting, 11 of which reported an ergogenic effect of creatine. Four of the 11 studies using cycle ergometer test summarised in Table 1 did not find improvements in the groups supplemented with creatine. In three of these studies the reason for the lack of effect may be that subjects were untrained (13,18,19) and in the other study a possible explanation for the negative result could be the cycle ergometry test, because the maximal performance was evaluated in a single test (a single ten-second test), one prior to and the other following, the supplementation period (14). Creatine is not usually considered ergogenic for single-bout or first-bout of exercise, because the likely benefit is too small to be detected (3).

Isokinetic protocols

Recent trials investigating the influence of creatine on isokinetic torque (elbow flexion) did not find significant effects (16,21), but earlier studies in the laboratory setting have shown that supplementation with 20 to 40 g per day for four to seven days may improve isokinetic torque

Table 1. Summary of research studies on creatine supplementation in exercising, trained or untrained individual, published 1996–2000 (n=35)

Study	*Subjects*	*Study type*[(a)]	*Creatine dose- trial*	*Event/Exercise test*	*Effect*	*Comments*
High intensity ergometer protocols						
Barnett et al. 1996 (13)	17M (active males)	RDBPC	20 g/day–4 days	Cycling (7 x 10 sec sprints)	No	No effect on multiple cycle performance
Burke et al. 1996 (14)	32M/F (elite swimmers)	RDBPC	20 g/day–5 days	Leg ergometry (2 x 10 sec sprints)	No	No significant effect on leg ergometry performance
Casey et al. 1996 (23)	9M (healthy males)	SGRM	20 g/day–5 days	Cycling (2 x 30 sec sprints)	Yes	Increase in total work (1%) and peak power (4%)
Cooke & Barnes, 1997 (18)	80M	RPC	20 g/day–5 days	Cycling (30, 60, 90, 120 sec of recovery)	No	No effect on maximum power or peak power output
Kirksey et al. 1997 (25)	36M/F (track/field athletes)	RDBPC	0.3 g/kg/day–42 days	Cycling (Wingate test)	Yes	Increase in mean peak power (13%)
Odland et al. 1997 (19)	9M (active but untrained)	SGRM	20 g/day–3 days	Cycling (30 sec Wingate test)	No	No effect on any recorded exercise measures
Prevost et al. 1997 (26)	18M/F (college students)	RPC	18.75 g/day–5 days 2.25 g/day–7 days	Cycling (time exhaustion at 150% $VO_{2\ max}$)	Yes	Significant increase was found for all work measures
Schneider et al. 1997 (24)	9M (untrained males)	RSBPC	25 g/day–7 days	Cycling (5 x 15sec)	Yes	Improved total work (6.5%) during bout of maximal cycling
Smith et al. 1998 (27)	15M/F (untrained)	RDBPC	20 g/day–5 days	Cycling (4 maximal bouts-ergonometer)	Yes	Improved time to exhaustion at shorter, higher-intensity exercise
Vandenbuerie et al. 1998 (28)	12M (amateur cyclists)	RDBPC	25 g/day–4 days	Cycling (progressive to exhaustion)	Yes	Improved power output for the maximal sprints
Kamber et al. 1999 (29)	10M (trained sport students)	DBPCX	20 g/day–5 d (28 days trial)	Cycling (10 x 6 sec, 30 sec rest)	Yes	Supplementation improved short-term performance, increased body mass
Isokinetic protocols						
Vandenberghe et al. 1996a (16)	20F	RDBPC	20 g/day–4 days	Isokinetic (5 x 30 max arm)	No	No ergogenic effect
Hamilton-Ward et al. 1997 (21)	20F (athletes)	RDBPC	25 g/day–7 days	Isokinetic (elbow flexion torque)	No	No ergogenic effect was found
Van Leemputte et al. 1999 (43)	16M (untrained)	DBPC	20 g/day–5 days	Maximal isometric elbow-flexions on isokinetic dymometer	Yes	Relaxation time reduced following creatine
Isometric, isotonic and resistance exercise protocols						
Vandenberghe et al. 1996b (12)	9M (healthy males)	RDBPCX	40 g/day–6 days	Isometric and isokinetic (3 x max)	Yes	Increase in torque production, but no effect for isometric
Becque et al. 1997 (44)	23M (weight-lifters)	DBPC	20 g/day–7 days	Isotonic (bicep curl 1-repetition max)	Yes	Increase in bicep curl (28%)
Kurosawa et al. 1997 (45)	5M/F (healthy)	SGRM	5 g/day–14 days	Isometric (high intensity)	Yes	Ergogenic effect (20% untrained arm, 35% trained arm)
Vandenberghe et al. 1997a (46)	19F (healthy sedentary)	DBPC	20 g and 5 g/day–10 weeks	Resistance training (3 hrs/week)	Yes	Long-term supplementation enhances progress of muscle strength
Volek et al. 1997 (47)	14M (healthy active)	RDBPC	25 g/day–7 days	Isotonic (jump squad 5 x 10 repetition max)	Yes	Significant increase in repititions to exhaustion and peak power for squats. Increase in body mass

Isometric, isotonic and resistance exercise protocols						
Maganaris & Maughan, 1998 (48)	10M (weight-trained)	RDBPCX	10 g/day–5days	Knee extension (maximal and exhaustion)	Yes	Increased maximum voluntary contraction, endurance capacity and body mass
Smith et al. 1999 (32)	9M/F (active-untrained)	SBPC	0.3 g/kg/day–5 days	Leg knee extension to exhaustion	No	Muscle ATP cost of contraction not affected
Stone et al. 1999 (49)	42M (college football players)	RDBPC	0.22 g/kg/day–7 weeks	Resistance exercise	Yes	Increased squat and bench press, static vertical jump power output. Increase in body mass and lean body mass
Urbanski et al. 1999 (50)	10M (active-untrained)	RDBPCX	20 g/day–5 days	Maximal & submaximal isometric knee estension and handgrip exercise	Yes	Increased maximal and submaximal knee-extension torque, handgrip exercise and time to fatigue. No significant increase in body mass
Volek et al. 1999 (51)	19M (resistance-trained)	RDBPC	25 g/day–1 week & 5 g/day–11 weeks	Resistance exercise (bench press, squat, strength/jump and muscular endurance)	Yes	Improved bench press and squat, increased muscle fibre cross-sectional areas. Increase in body mass and lean body mass
Burke et al. 2000 (52)	41M (university athletes)	RDBPC	7.7 g/day–21 days	Bench press until exhaustion, peak force and peak power	Yes	Increased total work and great improvements in force and power peak. Improved factors associated with short-duration, high-intensity activity
Sport performance protocols						
Mujika et al. 1996 (33)	20M/F (elite swimmers)	RDBPC	20 g/day–5 days	Swimming (25 m, 50 m and 100 m)	Yes	Increase in body mass but no significant performance changes
Redondo et al. 1996 (15)	18M/F (trained athletes)	RDBPC	25 g/day–7 days	Running (3 x 60 m sprint)	No	No significant difference between groups
Bosco et al. 1997 (53)	14M (sprinters & jumpers)	RBDPC	20 g/day–5 days	Jumping and running and treadmill run	Yes	Improved jumping performance of the jumping test and improved intensive running time exhaustion
Goldberg & Bechtel, 1997 (20)	34M (football/track athletes)	RDBPC	3 g/day–14 days	Isotonic (1 repetition max bench)	No	No ergogenic effect was found
Grindstaff et al. 1997 (54)	18M/F (junior swimmers)	RDBPC	21 g/day–9 days	Swimming (3 x 100 m freestyle sprint)	Yes	Improved swim time
Terrillion et al. 1997 (17)	12M (competitive runners)	RDBPC	20 g/day–5 days	Running (2 x maximal 700 m run)	No	No significant differences between placebo or supplemented
McNaughton et al. 1998 (55)	16 M (elite surf-ski / kayak)	RDBPCX	20 g/day–5 days	Kayaking (kayak ergonometer test)	Yes	Significant increase in work in all tests, increase in body mass
Peyrebrune et al. 1998 (56)	14M (elite swimmers)	RDBPC	9 g/day–5 days	Swimming (maximal swims)	Yes	Increased performance as there was a reduction in total sprint time
Leenders et al. 1999 (57)	32M/F (college swimmers)	RDBPC	20 g/day–6 days	Swimming	Yes	Mean overall swimming velocity improved. No change in body mass
Theodorou et al. 1999 (58)	22M/F (elite swimmers)	RPC	25 g/day–4 days	Swimming	Yes	Improvement (1.5%) in mean swim and interval set. Increase in body mass

(a) RDBPC: randomised double-blind placebo control, RPC: randomised placebo control, RSBPC: randomised single-blind placebo control, SGRM: single group repeated meaures; RDBPCX: randomised double-blind placebo control crossover.

force production and attenuate the decline in power during repetitive isokinetic exercise (6).

Isometric and resistance exercise protocols

Studies of the effect of creatine supplementation on isometric (knee extension, handgrip, elbow flexion) and resistance exercise tests (bench press, squat strength/jump, peak force and peak power) indicate changes in muscle ATP cost of contraction for isometric exercise (12,22). Only two of nine studies (12,22) failed to find this. Both studies used small sample sizes (nine subjects), and in one study the subjects differed in gender (six females and three males) and were not randomised (22). Also, because the sample size was small, it was possible that the study groups had different proportions of non-responders to creatine. Across studies there is evidence that the creatine-loading response varies between individuals, with approximately 30 % of individuals being 'non-responders' or failing to significantly increase muscle creatine stores (3,30). Ideally, studies employing large sample sizes and co-variant analysis should be used. This approach allows real changes to be detected and may also identify the characteristics of individuals that predict 'response' and 'non-response' (3). Measurement of creatine stores in muscle (e.g. using magnetic resonance spectroscopy, a non-invasive method) is another way to determine if a person has responded with increases in muscle creatine after supplementation (31,32).

Sport performance protocols

Five studies have investigated the effect of creatine supplementation on actual sport performance (sprint running and swimming in a field setting), using high-intensity, short-duration repetitive activities (14,15,20,33,34). The outcomes were unanimous—finding no effect of creatine supplementation on performance. In one study, an increase in body mass occurred but there were no significant performance changes (33). More investigations are needed concerning the use of creatine in sports events involving multiple high-intensity, intermittent exercise tasks, such as soccer. In two studies of running performance creatine supplementation failed to improve run time (15,17). However, Harris et al. (35) also tested creatine supplementation and running performance, and it was found that the group that received supplementation (30 g of creatine for six days), showed enhanced performance in the final run and best time over 300 M. The authors suggested the increased use of phosphocreatine during exercise may contribute to the buffering of hydrogen ions (35). As has been found in laboratory studies, creatine supplementation does not appear to enhance performance in field studies involving more prolonged high-intensity tasks. Four of five field studies involving swimming and running performance, all using a double-blind placebo design, reported negative findings concerning the efficacy of creatine supplementation (1).

Factors influencing creatine supplementation

Dietary background may have a significant effect in creatine supplementation studies. Co-ingestion of substantial amounts of carbohydrate (57 to 100 g) with creatine doses has been shown to enhance creatine accumulation (36,37). The amount of carbohydrate that induces alterations on creatine loading is still under investigation but researchers should ensure adequate carbohydrate when studying the effects of supplementary creatine. Vegetarians do not consume a source of creatine and may demonstrate reduced body creatine stores, suggesting they do not totally compensate for the lack of dietary intake (38). It has been hypothesised that a high dosage of caffeine (5 mg per kg per day) counteracts the ergogenic effect of creatine supplementation (12,39) but there is some evidence that caffeine (in the quantities commonly found in food and beverages) does not interfere with creatine loading (40). Supplementation with caffeine (5 mg per kg per day) does not alter creatine-induced improvements in repeated high-intensity exercise (41), maximal torque and contraction time in humans (42). A range of exercise activities may benefit from caffeine supplementation (3).

Summary

Creatine supplementation appears to be most effective in enhancing repetitive short-duration (≤ 30 seconds), high-intensity tasks such as cycle ergometry; strength, torque and force production; and jump performance in a laboratory setting. In general, creatine supplementation has not been shown consistently to enhance performance in exercise tasks dependent on the lactic acid energy system (anaerobic glycolysis). Additionally, creatine supplementation has not been shown to enhance performance in aerobic endurance exercise tasks. More research is indicated, particularly on the effect of chronic supplementation as an aid to improving performance in competitive sport and of lower intensity activity, such as those performed by non-athletes in daily gym activities.

Hydroxymethylbutyrate (HMB)

The leucine metabolite hydroxymethylbutyrate (HMB) is found in some foods in small amounts (catfish and some citrus fruits), it is found in breast milk, and it is used and produced by body tissues (8). It has recently become a popular dietary supplement purported to promote gains in fat free mass and strength during resistance training (9). The rationale is that leucine and its metabolite α-ketoisocaproate appear to inhibit protein degradation (59,60) and this anti-proteolytic effect may be mediated by HMB. Although it seems that HMB has some influence on protein metabolism, the mechanisms behind any effects are unknown. It may regulate protein synthesis either through hormonal receptor effects (cortisol, testosterone, GH, IGF-1, insulin) or by modulating the enzymes responsible for muscle tissue breakdown. Hydroxymethylbutyrate may have effects on the metabolism of leucine and glutamine and perhaps other anabolic and anticatabolic amino acids, or may decrease gluconeogenesis and the subsequent oxidation of amino acids in the intracellular amino acid pool and catabolism of skeletal muscle cellular protein (8). It appears to be nontoxic (61,62).

Table 2 summarises data collected from eight studies (from 1996 to 2000) in which humans were fed 0 g, 3 g and/or 6 g HMB per day. The studies were from three to eight weeks' duration, included both males and females and healthy athletes or/and exercising subjects.

Of the eight studies only one found that HMB supplementation did not affect catabolism or induce changes in body composition and strength (63). This trial was not placebo-controlled and of short duration (28 days) and this may explain the lack of effect. Seven other studies on

HMB supplementation have found significantly less exercise-induced proteolysis and muscle damage (64,65); increased strength and gains in fat free mass (64–66); or larger gains in muscle function and in resistance training (64,65). Only three studies (63,64) assessed exercise training in highly trained individuals and/or athletes. A recent study by Slater et al. (68) reported HMB supplementation did not change strength or body composition in resistance-trained male athletes. It may be that further studies with highly trained individuals will find the impact of the supplements on exercise outcome are different to the earlier studies with less trained individuals (9).

All studies reported in Table 2 supplemented with 3 g of HMB per day. In two studies, 1.5 g of HMB per day was tested and compared with the results obtained with 3 g per day. Less effect was found for increase in strength and decrease of the exercise-induced proteolysis (64,65). Some other studies have compared 6 g HMB per day with 3 g per day, but doses of HMB higher than 3 g a day do not promote strength or gains in fat free mass (63–69). The popular use of supplemental HMB at 3 g per day for periods of up to one month (in a healthy population) as an ergogenic aid for exercise appears to be well-tolerated and safe in humans (62).

Summary

Given the generally good quality design of most of these studies, and the consistency of proven effects, it can be concluded that there is reasonable evidence that HMB supplementation results in gains in strength and body mass associated with resistance training, on enhancement of loss of body fat and on recovery from exercise (3). Although HMB supplementation during training may enhance training adaptations in untrained individuals initiating training, it is less clear whether HMB supplementation reduces markers of catabolism or promotes greater gains in fat free mass and strength during resistance training in well-trained athletes.

Glutamine

Glutamine provides nitrogen for the synthesis of nucleotides required in the formation of DNA and RNA during lymphocyte proliferation and macrophage activation (9). As glutamine is an important fuel for white blood cells, reductions in blood glutamine concentrations following intense exercise may contribute to immune suppression in overtrained athletes (70–73). Glutamine is utilised at a high rate by certain cells of the immune system (neutrophils, lymphocytes, and macrophages) and is essential for the viability and normal functioning of these cells (74,75). After prolonged intense exercise the number of lymphocytes in the blood is reduced, the function of natural killer cells is suppressed and secretory immunity is impaired (76). Glutamine has been demonstrated of benefit in trauma patients and individuals stressed by surgery (77,78). Although there are differences between exercising individuals and these patients, glutamine supplementation in athletes may be beneficial in increasing the anabolic drive (8). It has been theorised that a chronic glutamine debit may be responsible for the immunosuppression suffered by some athletes, and that supplementation may overcome the impaired immunity suffered by athletes undertaking repeated bouts of heavy training and overtraining (3). Regular runners are six times more likely to contract a cold virus in winter than nonparticipants (79). The few studies of increasing plasma glutamine concentrations with supplements have shown little or no effect on energy production or immune status (80,81). It is unclear whether long-term supplementation of glutamine affects protein synthesis, body composition, or the incidence of upper respiratory-tract infections during training (9).

The role of glutamine as an ergogenic aid has not been demonstrated in the scientific literature. Although there is evidence to support the requirement for exogenous glutamine in the maintenance of muscle protein mass and immune system function in the overtraining syndrome (77,78,82–84), little research has examined the use of glutamine for athletes (68). Blood glutamine concentrations may serve as a marker for determining whether athletes are overtraining (8,85). Studies have shown that decreased plasma glutamine concentrations are an objective, measurement of severe exercise stress and overtraining (86,87).

Summary

Few scientific data are available concerning potential benefits of glutamine supplementation for athletes. Further work is necessary to determine whether the benefits of exogenous glutamine supplementation shown in clinical situations apply in athletic populations. In those athletes demonstrating decreased plasma glutamine, supplements are indicated but this condition is uncommon.

Branched chain amino acids (BCAA)

The branched chain amino acids, valine, leucine and isoleucine, unlike most other amino acids, are oxidised by muscle cells, providing a source of cellular energy as ATP and phosphocreatine (7). There is a significant activation of BCAA metabolism with prolonged exercise, and studies indicate that this is more pronounced in endurance-trained subjects (88). Plasma concentrations of BCAAs are more affected by changes in energy, protein, fat, and carbohydrate intake in humans (89) than are the concentrations of other amino acids. Theoretically, BCAA supplementation (30% to 35% leucine) before and during endurance exercise may prevent or decrease the net rate of protein degradation, improve mental and physical performance and may have a sparing effect on muscle glycogen degradation and depletion of muscle glycogen stores (90). During intense training BCAA supplementation can help minimise protein degradation and thereby lead to greater gains in fat free mass (91–93), however, it can significantly increase plasma ammonia (toxic to the brain and muscle) (77) and lower physical performance in humans (94) and in rats (95). Reduced availability of BCAA has been theorised to contribute to central fatigue (79). During endurance exercise, BCAA are taken up by the muscles and the resultant decline in plasma BCAA can lead to an increase in the ratio of free tryptophan to BCAA, promoting the formation of the neurotransmitter 5-hydroxytryptamine (5-HT) in the brain. It has been shown to induce sleep, depress motor neuron excitability, influence autonomic and endocrine function, and suppress appetite in both humans and animals (93,96,97). An exercise-induced imbalance in the ratio of free tryptophan to BCAA has been implicated as a cause of acute physiological and psychological fatigue (the central fatigue) (93,96,97). The ingestion of carbohy-

Table 2. Summary of the research studies on β-hydroxy-β-methylbutyrate (HMB) supplementation in exercising (trained or untrained individuals), conducted from 1996–2000 (n = 8)

Study	*Subjects*	*Study type*	*HMB dose–duration trial*	*Effect*	*Comments*
Nissen et al. 1996a (65) (Endurance-exercise)	n = 41M) (healthy subjects	Placebo-controlled, Randomised	1.5 g or 3 g/day – 3 wk trial	Yes	HMB significantly decreased the exercise-induced proteolysis and increase strength.
Nissen et al. 1996a (65) (Resistance-training)	n = 28 (trained subjects)	Placebo-controlled, Single-blind, Randomised	3 g/day – 7 wk trial	Yes	HMB prevented proteolysis and muscle damage and results in larger gains in muscle function and in resistance-training.
Nissen et al. 1996b (64) (Resistance-training)	n = 40M	Placebo-controlled, Randomised	3 g/day – 4 wk trail	Yes	HMB supplementation increased bench press strength, fat free mass gain, but no effect on fat mass.
Kreider et al. 1999 (63) (Resistance-training)	n = 40M (athletes)	Double-blind, Randomised	3 g or 6 g/day – 28 days trial	No	28 d of HMB supplementation in athletes does not reduce catabolism or induce changes in body composition and strength.
Kreider et al. 1999 (63) (Resistance-training)	n = 41M (athletes)	Double-blind, Placebo-controlled, Randomised	3 g or 6 g/day – 4 wk trial	Yes	HMB supplementation promotes no gains in body mass, fat free mass or fat mass, but trend for increase work output on sprint test.
Knitter et al. 2000 (66) (Resistance-training)	n = 13 (5M 8F)	Double-blind, Placebo-controlled, Randomised	3 g/day – 8 wk trial	Yes	HMB helps prevent exercise-induced muscle damage.
Gallagher et al. 2000 (69) (Strength-training)	n = 37M	Double-blind, Placebo-controlled, Randomised	3 g or 6 g/day – 7 wk trial	Yes	Higher doses of HMB (> 3 g/d) do not promote strength or fat free mass gains, however 3 g appears to increase peak of isometric and isokinetic torque values and fat free mass gains.
Panton et al. 2000 (67) (Resistance-training)	n = 75 (39M 36F)	Double-blind, Placebo-controlled, Randomised	3 g/day – 4 wk trial	Yes	HMB supplementation may increase upper body strength and decrease muscle damage, regardless of gender and training status.

Table 3. Summary of research studies on branched chain amino acid (BCAA) supplementation in exercising, trained or untrained individuals, from 1991–2001 (n = 9)

Study	*Subjects*	*Study type*[a]	*Carnitine dose-trial*[b]	*Event/Exercise test*[c]	*Effect*	*Comments*
Soccer player protocols						
Blomstrand et al. 1991 (103)	6F (national standard soccer-field-players)	DBPCX	6%CHO+7.5 g BCAA or 6%CHO 40%val+35%leu+25%ile	Soccer match (2 games separated by one week) CWT given before (~2 h) and within the game	Yes	Improvement in CWT after game with CHO+BCAA. No such effect was found when subjects took the placebo drink (CHO).
Davis et al. 1999 (101)	8M and F (active)	PCX	CHO+7 g BCAA or CHO or placebo (before/during/after)	Running—intermittent shuttle run until exhaustion	No	No performance differences between (CHO or CHO+BCAA) trials. CHO and CHO+BCAA increased time to fatigue compared to placebo. No further enhancement with BCAA.

Runner protocols						
Blomstrand & Newsholme, 1992 (102)	26M (cross-country) 32M (marathon runners)	RPC	7.5 g BCAA (cross-country) or 12 g BCAA (marathon) 50%val+35%leu+15%ile or 5%CHO+BCAA (cross-country) 40%val+35%leu+25%ile or 6%CHO+BCAA (marathon)	Run - 30 km cross-country race or marathon Run time + CWT after cross-country run	Yes	CWT performance improved in BCAA trial after cross-country run. 'Slower runners' in BCAA group (marathon) ran faster but no significant effect on performance in the 'faster runners' group. BCAA ingested during exercise might decrease the net rate of protein degradation in human skeletal muscle during exercise.
Davis et al. 1999 (101)	8M and F (active)	PCX	CHO+7 g BCAA or CHO or placebo (before/during/after)	Running—intermittent shuttle run until exhaustion	No	No performance differences between (CHO or CHO+BCAA) trials. CHO and CHO+BCAA increased time to fatigue compared to placebo. No further enhancement with BCAA.
Krogh ergometer protocols						
MacLean et al. 1994 (104)	5M (healthy subjects)	RPC (own control)	77 mg/kg (~5.5 g, 2 x 38.5 mg/kg 45 min and 20 min before test) 30%val+44%leu+26%ile	Krogh ergometer modified for one-legged knee extensor. 60 min of dynamic knee extensor exercise ~71% of maximum work capacity	Yes	BCAA supplementation results in significantly greater muscle ammonia production during exercise. Increased results in decrease of muscle protein breakdown during exercise.
MacLean et al. 1996 (105)	5M (healthy subjects)	RPC (own control)	308 mg/kg (154, 77 mg/kg- 45 & 20 min prior to test and 77 mg/kg-5 min after starting the test ~22 g) 30%val+44%leu+26%ile	Krogh ergometer modified for one-legged knee extensor. 90 min of dynamic knee exercise ~64% of maximum workload	Yes	Long-term exercise+BCAA administration significantly increase muscle ammonia, alanine & glutamine production, as well as lower lactate production, than is observed without BCAA supplementation.
Cyclist protocols						
Madsen et al. 1996 (99)	9M (well-trained cyclists)	DBPCX	3.5 L @ 5% glucose or 5% glucose + 18 g BCAA: 50%val+35%leu+15% ile	Cycling 100 km time trial as fast as possible (own bikes) connected to a magnetic brake	No	No performance differences between trials. Plasma BCAA and ammonia levels higher with BCAA trial.
Blomstrand et al. 1997 (100)	7M (trained cyclists)	RDBPCX	90 mg/kg (~6.5 g), 40% val+35% leu+25% ile	Cycling 60 min @ ~70%$VO_{2\ max}$ + 20 min time trial. Stroop Colour Word Test after ride	No	No difference in physical performance between 2 trials (work done at the last 20 min maximal exercise), CWT improved after exercise-BCAA trial.
Mittleman et al. 1998 (106)	7M and 6F (13 subjects) (moderately trained)	DBPCX	9.4 g F and 15.8 g M 54% leu+19% ile+ 27% val	Cycling (ergometry) in the heat (34°C), time to exhaustion @ 40%VO_{2max}	Yes	Increased time to exhaustion with BCAA, increase in plasma BCAA and decrease tryptophan**:**BCAA. Trend to higher plasma ammonia. No difference between genders.
Blomstrand & Saltin, 2001 (107)	7M (recreational cyclists)	PC	100 mg/kg (~7 g) in 1.5 L 150 ml before and immediately before test, during and after test 30%val+45%leu+25%ile	Cycling 1 hour of ergometer cycle exercise and 2 hours of recovery period. Work rate ~164W ~75% VO_{2max}	Yes	BCAA have an anablic effect on muscle protein metabolism during recovery. Protein synthesis stimulated and/or protein degradation decreased as an effect of BCAA ingestion. However during exercise the data is too varioable to make any conclusion.

(a) RDBPCX: randomised double-blind placebo control crossover, RPC: randomised placebo control, DBPCX: double-blind placebo control, crossover, PC: placebo control, PCX: placebo control crossover.
(b) CHO: carbohydrate, BCAA: branched chain amino acids, Val: valine, Leu: leucine, Ile: isoleucine.
(c) VO_{2max}: maximal Oxygen consumption during exercise, CWT: Stroop Colour Word Test.

drate during exercise minimises the unfavourable change in the ratio of plasma free tryptophan:BCAA (3,98).

Table 3 shows the results of nine studies on the effect of BCAA supplementation (from 1991 to 2001). The studies were undertaken using placebo-controlled designs and subjects were supplemented with up to 22 g of BCAA. The trials were short-term studies from a few hours to a day. Healthy males and females were used, including both trained and untrained subjects. Three of nine studies failed to find any significant effect of BCAA supplementation on metabolism and/or performance (99–101).

Performance-based endpoints (fatigue, work performed and mental performance)

Of four studies in which performance was considered the main and/or only outcome, three failed to show any benefit of BCAA supplementation (99–101). The one study that reported an increase in performance of a 'slower runners' group (85) has been criticised for its methodology (11). Mental performance was measured in three of the nine studies using the Stroop Colour Word Test, and in all three improvements were found (100,102,103).

Metabolic-based endpoints

Metabolic endpoints (ammonia accumulation and production, the tryptophan:BCAA ratio, amino acids and lactate production, protein breakdown) were tested in four studies (104–107) and improvements were found in all. However in the study of Blomstrand and Saltin (107) the anabolic effect on muscle protein metabolism may be significant only during recovery. The results observed during exercise were too variable to form any conclusion.

Carbohydrate is not only an energy source during exercise but may also have positive effects on amino acid metabolism (108) and nitrogen balance (109–112). The positive effects are likely due to an insulin-mediated stimulation of protein synthesis and an attenuation of protein breakdown (3). Supplementation with carbohydrate during exercise suppresses the rise in free fatty acids concentrations, thereby attenuating the increase in free tryptophan concentrations (98) that is an effective strategy against both peripheral and central mechanisms of fatigue (3). Thus, several investigators emphasise the importance of dietary carbohydrate before, during and between repeated bouts of prolonged exercise to minimise central fatigue (81,97,98,113,114).

Summary

Research findings regarding the effects of BCAA supplementation on endurance performance in humans do not offer substantial proof. Most other reviewers evaluating the central fatigue hypothesis have concluded overall there is not convincing evidence that supplementation with BCAA prevents or stimulates central fatigue (108,115–118). Studies comparing the intake of BCAA and carbohydrate with the supplementation of carbohydrate alone are necessary to determine if BCAA exert an independent effect.

Carnitine

Carnitine in humans is derived from both dietary sources and endogenous biosynthesis. Meat and dairy products are major dietary sources of this compound (119). According to Brass, a number of specific mechanisms have been postulated for an effect of carnitine on exercise performance including: enhanced muscle fatty acid oxidation; decreased rate of muscle glycogen depletion; shifts in substrate utilisation in muscle from fatty acid to glucose; activation of pyruvate dehydrogenase via lowering of acetyl-CoA; improved muscle fatigue resistance; and replacement of carnitine lost during training (120). If carnitine administration increases muscle fatty acid oxidation, this might also delay the use of muscle glycogen and thus delay fatigue development (121).

Table 4 shows the results of 11 studies on the effect of carnitine supplementation (1988 to 2000). Most studies involved oral supplementation with carnitine at 0 to 6 g per day but two studies used intravenous carnitine administration (122,123). The duration of trials ranged from one to 28 days, they included only healthy males, and used untrained, moderately-trained or highly-trained subjects. Three of the 11 studies found a significant effect of carnitine supplementation on performance plasma concentration of lactate and pyruvate, time to exhaustion or maximal oxygen consumption during exercise (VO_{2max}) (124–126).

Performance-based protocols

Some studies in which exercise capacity was tested with use of VO_{2max} and/or performance endpoints failed to show any benefit of carnitine supplementation (127,128). Similarly, studies searching for any ergogenic effect of carnitine supplementation during bouts of high-intensity anaerobic exercise in highly-trained subjects and during aerobic combined with anaerobic exercise failed to identify any improvement in metabolism, performance or lean body mass (122,129). However in one study, although no changes were found during exercise, an increase in fatty acid oxidation during recovery was observed (122).

Metabolic indices protocols

Most of the studies measuring metabolic indices of exercise (muscle fuel, muscle carnitine content, time to exhaustion, substrate utilisation, i.e. lipid or carbohydrate oxidation) failed to find any effect of carnitine administration (123,126,130–133). However Vecchiet et al. (128) found a decrease in lactate accumulation and/or production and Siliprandi et al. (125) reported a reduction in lactate and pyruvate. The latter study involved supplementation 60 or 90 minutes before exercise and it is difficult to discern if sufficient time elapsed for absorption and muscle uptake (125).

Although most studies demonstrate an increase in plasma carnitine concentrations following supplementation of 1 to 6 g carnitine per day, the effect on muscle carnitine content is less clear. The consensus is that there is no compelling evidence that the muscle content of carnitine is enhanced by supplementation (3,134,135). The few studies that report favourable metabolic outcomes, or an increase in exercise performance, are hard to explain. Hultman et al. (136) consider that it is unlikely that carnitine supplementation over a period of days to weeks will change total muscle carnitine content in humans. Available data confirm that muscle carnitine content is not increased by supplementation protocols similar to those described above (123,132,133), despite increases in plasma carnitine concentrations (120,122,123,129,132,133). Thus,

Table 4. Summary of research studies on carnitine supplementation in exercising, trained or untrained individuals, from 1988-2000 (n = 11)

Study	*Subjects*	*Study type*[a]	*Carnitine dose trial*	*Event/Exercise test*[b]	*Effect*	*Comments*
Soop et al. 1988 (130)	7M (moderately trained)	CX (own controls)	5 g/d (orally)–5 days	Cycling 120 min @ 50%VO_{2max}	No	No effect on muscle substrate utilisation during exercise and at rest.
Vecchiet et al. 1990 (124)	10M (moderately trained)	RDBPCX	2 g (orally) @ 1 h before exercise (acute administration)	Cycling ergometer until exhaustion, 72 hours rest and repeated exercise test	Yes	Increased time and work until exhaustion, decrease in lactate production and oxygen uptake.
Siliprandi et al. 1990 (125)	10M (moderately trained)	RDBPCX	2 g (orally) @ 1 h before exercise (acute administration)	Cycle to exhaustion (2 bouts of maximal ergometer) separated by a 3-day interval	Yes	Increased time to exhaustion. Post-exercise increase in plasma lactate and pyruvate was after maximal progressive work.
Decombaz et al. 1993 (131)	9M (untrained)	DBPCX	3 g/d (orally)–7 days	Cycling 20 min at 60%VO_{2max} + CHO depletion regime	No	No metabolic enhancement, substrate metabolism not affected during submaximal exercise. Performance was not measured.
Natali et al. 1993 (122)	12M (healthy active)	RPCX	3 g (intravenously)– 1 dose 40 min before	Cycling 40 min @ 60 w + 2 min anaerobic exercise (250W) + 50 min for recovery	No	No changes during exercise, but increased fatty acid oxidation during recovery.
Arenas et al. 1994 (126)	16M (well-trained long-distance runners)	RDBPC	2 g/day (orally)–28 days	Running 40–50%VO_{2max} 90 min/d for 5 days and 70–80%VO_{2max} 60 min/d for 2 days	Yes	Improvement in VO_{2max} based on biochemical findings and significant increase in the pyruvate dehydrogenase.
Barnett et al. 1994 (132)	8M (healthy males)	EP-2 controls	4 g/day (orally)–14 days	Sprint cycling 90%VO_{2max}/4 min, rest 20 min and 5 x 1 min ride at 115% VO_{2max}	No	No significant effect on muscle carnitine content and thus could not alter lactate accumulation.
Brass et al. 1994 (123)	14M (healthy males)	RDBPCX	92.5 mol/kg or 18.5 mol/kg (intravenously) administration–1 dose	Bicycle ergometer test (RQ, FFA glucose utilisation, $V0_2$ at fixed workload)	No	No effect on fuel metabolism during exercise in humans.
Trappe et al. 1994 (129)	20M (highly-trained swimmers)	RDBPC	4 g/day (orally)–7 days 2 g twice daily	Swimming bouts 5 x 91.4 m (100 yd) at supra-maximal intensity, 2 min rest each	No	No ergogenic benefit during repeated bouts of high-intensity anaerobic exercise in highly trained swimmers.
Vukovich et al. 1994 (133)	8M (healthy males)	R, C (1st trial) 3 trials	6 g/day (orally) 7–14 days	Submaximal exercise (cycled 60 min at 70% VO_{2max} - RQ, FFA glucose utilisation, VO_2)	No	No effect on lipid or carbohydrate oxidation during exercise.
Colombani et al. 1996 (127)	7M (endurance-trained athletes)	RDBPCX	4 g (orally) 2 g @ 2 h before run and 2 g @ 20 km mark	Marathon run + submaximal performance test day after marathon + post-race lactate	No	No changes in exercise metabolism or marathon running time, no change in recovery and submaximal test performance post race.

(a) RDBPC: randomised double-blind placebo control, RDBPCX:randomised double-blind placebo control crossover, RPCX: randomised placebo control crossover, CX: crossover, DBPCX: double-blind placebo control, crossover, RC: randomised and control, EP: experimental protocol.

(b) VO_{2max}: maximal Oxygen consumption during exercise, VO_2: oxygen consumption, RQ: respiratory quotient, FFA: free fatty acids.

although it is possible that carnitine affects exercise physiology without modifying muscle carnitine pools, such a mechanism would clearly be distinct from the rationale usually made for supplementation. It is still possible that increases in muscle carnitine content might result from longer duration of therapy or/and muscle carnitine homeostasis (120).

Only three studies provide evidence for a distinct effect of carnitine, the studies by Arenas et al. (126,137) and Huertas et al. (138). They examined only athletes engaged in training programs for periods of one to six months. Under these conditions, carnitine supplementation prevented a training-associated decrease in muscle carnitine content and also increased muscle activity of key oxidative enzymes, including pyruvate dehydrogenase and electron transport chain enzymes. The physiological effect of these changes is unknown and further corroboration of these findings is needed.

Summary

The data available to date do not allow a definitive conclusion concerning the effect of carnitine on exercise metabolism and performance. Most studies have design limitations and further research using placebo-controlled trials, with bigger sample sizes, and examining other relevant endpoints is indicated.

Conclusions

Table 5 summarises the supplementation studies reviewed, evaluating the strength of the ergogenic effect and the conditions under which each supplement is ergogenic.

Creatine is the most studied of the amino acid supplements. Creatine supplementation appears to be an effective nutritional strategy to enhance high-intensity exercise performance and improve training adaptations in high-intensity, short-term (≤ 30 seconds) exercise tasks, with limited recovery time between repetitions. No significant improvement in aerobic endurance exercise tasks is demonstrated. Further research in field settings is needed to study effects on intermittent activity. The safety of long-term supplementation requires further study, particularly with regard to large doses that are associated with rapid loading and unconfirmed side effects such as cramps, muscle tears and pulls.

A small number of recent well-designed studies of supplementation with HMB indicate that it results in gains in strength and body mass associated with resistance training, as well as enhanced loss of body fat and recovery from exercise in the healthy population. Whether the same outcomes would be found for highly-trained individuals is not clear and more research is needed.

There is an abundance of clinical evidence supporting the need for exogenous glutamine in critically ill patients for the maintenance of muscle protein mass and immune system function. However, for healthy subjects the few scientific results available suggest that glutamine is only of benefit for athletes who show a true deficiency. The overtrained may have lower glutamine plasma concentrations but it remains unclear whether supplementation improves their condition.

Research findings regarding the effects of BCAA supplementation are equivocal. Most reviews evaluating the central fatigue hypothesis suggest that BCAA is not an effective ergogenic supplement. The few data available do not allow a conclusive position regarding the effect of BCAA supplementation on exercise metabolism and performance and more studies are needed.

Carnitine supplementation has been reported to increase exercise capacity in disease states. However, in healthy athletes carnitine fails to provide a significant ergogenic effect. Moreover, the few study trials that reported favourable outcomes or an increase in exercise performance suffer from design limitations.

Table 5. Summary of recent studies on supplementation with popular ergogenic aids and physical performance

Supplement type	*Evidence of efficacy*	*Condition for an ergogenic effect*	*Comments*	*Nº of examined trials*
Creatine	Clear evidence of efficacy	High-intensity, short-term exercise tasks (≤ 30 seconds), repeated exercise bouts and limited recovery time between repetitions.	No significant effect in aerobic endurance exercise tasks. Further research is needed (long-term studies, safety, side effects).	35
HMB[(a)]	Evidence of efficacy is limited	Gains in strength and body mass associated with resistance training, and recovery from exercise in healthy population.	Studies mainly positive for novice rather than well-trained athletes. Limited number of studies.	8
Glutamine		No ergogenic effect	Clinical evidence in the maintenance of muscle mass and immune system function in critically ill patients.	8
BCAA[(b)]		No ergogenic effect	No ergogenic effect, further study is needed.	9
Carnitine		No ergogenic effect	Study design limitations, further research is needed.	11

(a) HMB: hydroxymethylbutyrate.
(b) BCAA: branched chain amino acids.

Further research is still needed for better evaluation of the safety and efficacy of many of these supplements, especially focussing on their use in specific sporting situations. The marketing of sport supplements is an international, multimillion dollar business that preys upon the desires of athletes to be the best. The most appropriate advice to athletes may be to avoid using a specific sport supplement until the product has been evaluated for safety, efficacy, potency and legality. Athletes should discuss the use of any supplement with a qualified sports nutritionist, dietitian, or health professional. All users and creators of supplement information should consult the sport policy of the Australian Institute of Sport (www.ais.org.au/nutrition)—under supplements.

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