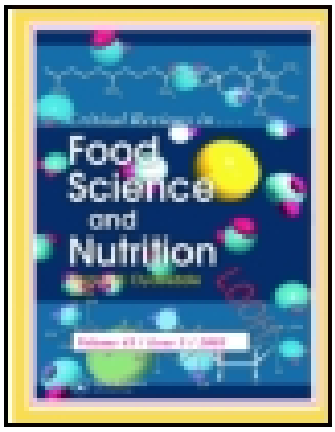

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EFFECTS OF AMINO ACID DERIVATIVES ON PHYSICAL, MENTAL AND PHYSIOLOGICAL ACTIVITIES

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Nutritional ergogenic aids have been in use for a long time to enhance exercise and sports performance. Dietary components that exhibit ergogenic activity are numerous and their consumption is common and popular among athletes. They often come under scrutiny by legal authorities for their claimed benefits and safety concerns. Amino acid derivatives are propagated as being effective aids to enhance physical and mental performance in many ways, even though studies have pointed out that individuals who are deficient are more likely to benefit from dietary supplementation of amino acid derivatives than normal humans. In this review, some of the most common and widely used amino acids derivatives in sports and athletics namely creatine, tyrosine, carnitine, HMB and taurine have been discussed for their effects on exercise performance, mental activity as well as body strength and composition. Creatine, carnitine, HMB and taurine are reported to delay the onset of fatigue, improve exercise performance and body strength. HMB helps in increasing fat free mass and reduce exercise induced muscle injury. Taurine has been found to reduce oxidative stress during exercise and also act as an antihypertensive agent. Although, studies have not been able to find any favourable effect of

tyrosine administration on exercise performance, it has been proved to be very effective in fighting stress, improving mood and cognitive performance particularly in sleep deprived subjects. While available data from published studies and findings are equivocal about the efficacy of creatine, tyrosine and HMB; more comprehensive researches on carnitine and taurine are necessary to provide evidence for the theoretical basis of their ergogenic role in nutritional modification and supplementation.

Key words Nutritional ergogenic aids, creatine, tyrosine, carnitine, HMB, taurine, amino acid derivatives.

INTRODUCTION

Ergogenic means to increase the capacity of the body or mind to perform a task. Ergogenic aids are substances, devices, or practices used to improve exercise and athletic performance. They work mainly by enhancing energy utilization and delaying the onset of fatigue. Ergogenic aids can be of several types like physical, mechanical, physiological, psychological and nutritional (Bucci, 1993; Sobal and Marquart; 1994; Thein et al., 1995). Nutritional ergogenic aids are dietary substances such as food or drugs that are consumed before, during or after the exercise to enhance physical performance (Bucci, 1993). They enhance performance by either stimulating the central or peripheral nervous system, increasing energy production during exercise (by increasing the concentration of substrates that supply fuel or inhibiting substances that interfere with energy productions) or, by reducing muscle damage and enhancing recovery (Ivy, 1994). Nutritional ergogenic aids can be broadly classified into three categories;

- Macronutrients such as water, carbohydrates, proteins and lipids.
- Micronutrients like minerals, vitamins and metabolic intermediates.
- Non-essential dietary substances like bicarbonates, caffeine etc.

The most important and effective of all nutritional ergogenic agents is water as water repletion and hydration by electrolyte solutions compensates for sweat loss during exercise and provides instant relief from fatigue and tiredness (Maughan and Noaks, 1991). Amino acids and amino acid derivatives have been commercially used as ergogenic supplements. They influence the secretion of anabolic hormones, supply of fuel during exercise, mental performance during stress related tasks and prevent exercise induced muscle damage (Williams, 2005). Hence, they are recognised to be beneficial as ergogenic dietary substances. There are many amino acids and their derivatives that have been claimed to confer ergogenic effects such as arginine, tryptophan, aspartate, tyrosine, branched chain amino acids (luecine, isoluecine, and valine), taurine, ornithine, glucosamine, creatine, carnitine, beta-hydroxy beta-methylbuyrate etc. This review will discuss in depth the ergogenic effects of the most extensively used amino acid derivates - creatine, tyrosine, carnitine, beta-hydroxy beta-methylbuyrate and taurine. These have generated huge interest among the athletes and active individuals, which has prompted many researchers to carry out studies to examine their claimed benefits and assess potential risks associated with their long term use. Table 1 shows ergogenic action of the five amino acid derivatives and their recommended dosage.

SYNTHESIS AND ROLE IN METABOLSIM

Creatine has been in use as an effective performance enhancing aid in many sports especially in track and field athletics for the past few decades. Since no harmful side effects have been found even at very large doses, its use is not prohibited by the governing bodies of sport (Maughan, 1999).

In mammals, creatine is synthesised naturally in the body from the amino acids, L-arginine and glycine. In the kidney, the amino acids undergo L-arginine:glycine amidinotransferase catalyzed reaction to give L-ornithine and guanidinoacetic acid. Guanidinoacetate is transported through the blood to liver where it is methylated to creatine in the presence of the enzyme *S*-adenosyl-L-methionine:*N*-guanidinoacetate methyltransferase. Creatine is then, supplied to creatine requiring tissues such as muscle and brain by the blood through an active transport system. In the muscles creatine and phosphocreatine are converted to creatinine which is excreted by the kidneys into the urine (Wyss and Kaddurah-Daouk, 2000).

Approximately 94% of creatine is found in muscle tissue. Creatine stored in free and phosphorylated forms in skeletal muscles, is important in maintaining a high ATP:ADP ratio during high intensity exercise. Intense short duration exercise results in phosphocreatine depletion from skeletal muscles. Inability to supply energy to rephosphorylate ADP to ATP, consequently leads to fatigue development and decline in physical performance (Greenhaff, 1997; Benzi, 2001; Hultman and Greenhaff, 1991; Sahlin et al., 1998, Chanutin, 1926). Creatine supplementation increases creatine and phosphocreatine concentrations in muscles, resulting in increased rate of ATP resynthesis and enhanced performance during high intensity short duration exercise (Benzi, 2001; Sahlin et al., 1998).

Tyrosine is a non-essential amino acid found in protein rich food. In the body it is synthesised from phenylalanine by the enzyme phenylalanine hydroxylase. Tyrosine is a precursor for several catecholamine neurotransmitters of the brain including dopamine, norephinephrin and epinephrine that are reported to effect human behaviour (Wurtman et al.,1974; Wurtman et al., 1980; Liebermann et al., 1985; Joh and Hwang, 1987; Fernstorm, 2007). Administration of tyrosine before exposure to physical or environmental stressors can maintain optimum physical performance and behaviour (Liebermann et al., 2005)

Carnitine plays an indispensable role in fatty acid metabolism in cardiac and skeletal muscles. It helps in the translocation of fatty acids across the inner memberane of mitochondria. Long chain fatty acids are esterified to acylcarntines with carnitine in the cytoplasm with the help of enzyme carnitine palmitoyl transferase I. Acylcarnitine are easily transferred across the mitochondrial membrane by the action of acylcarnitine transferase. Acylcarnitine are then converted to back to fatty acyl-CoA, which then, get metabolised to generate ATP by β-oxidation pathway. Carnitine also helps in the removal of fatty acids such as acyl CoA that build up in the mitochondria and thus, regulate the acyl-CoA: free CoA ratio in the mitochondria. (Bremer, 1983; Rebouche, 1986, 1992; Moffatt and Chilland, 2004; Lee et al., 2006). Since carnitine promotes fat oxidation and utilization, resulting in greater energy production, it was assumed that carnitine supplementation can enhance performance by prolonging endurance exercise and delaying fatigue and maintain the level of plasma and muscle carnitine concentration during exercise; and based on this rationale there is widespread use of L-carnitine as an ergogenic aid by athletes around the world.

Beta-hydroxy beta-methylbutyrate (HMB) is a derivative of the essential amino acid leucine and is produced endogenously in muscle and liver. Biosynthesis of HMB involves two steps. Leucine is converted to α-ketoisocaproate by transamination reaction in the muscle. Some of the α-ketoisocaproate produced (about 5%) is then oxidized to HMB in liver. (Sabourin and Bieber, 1982, 1983; Van Koevering and Nissen ,1992) HMB is converted to HMB-CoA which is then used for the synthesis of cholesterol in muscle cells (Nissen and Abumrad, 1997). Cholesterol is needed for the growth, repair and stabilization of cellular membranes during exercise (Chen, 1984). HMB also helps to reduce protein breakdown in skeletal muscles, possibly by inhibiting the activity of proteolytic enzymes such as cathepsin and calpain (Jank et al., 2001; Holecek et al., 2009).

Taurine is a non-essential amino acid produced primarily in the liver. It is synthesised endogenously from cystein by two different pathways. Sulphur oxidation of cystein in the presence of cystein oxidase yields cystien sulphinic acid, which then undergoes a decarboxylation reaction catalysed by enzyme cystein sulphinate decarboxylase to give hypotaurine. Hypotaurine gets oxidised to taurine in the presence of hypotaurine oxidase. Cystein sulphinic acid may get oxidised to cystiec acid in the presence of cystein sulphinic oxidase and further reaction in the presence of cystiec acid decarboxylase gives rise to taurine. An alternate pathway for the synthesis of taurine is conversion of cystein to cystamine by the enzyme cystein decarboxylase, which is then oxidised to hypotaurine through a cysteamine oxygenase catalysed reaction (Meister, 1957; Yamaguchi et al., 1973; Bender, 1975).

In the liver, taurine in conjugation with cholic acid gives taurocholic acid which is excreted in urine. Bacterial action on taurine in the intestine yields a sulphate form, which gets

excreted in urine (Struman et al., 1975). Taurine intake is reported to be effective in regulating blood pressure in hypertensive patients (Kohashi et al., 1983; Fujita et al., 1987), lowering body weight and serum lipid level in obese or overweight individuals (Zhang et al., 2004), treatment of congestive heart failure (Azuma et al., 1983; 1985; 1992; Xu et al., 2008) and in controlling diabetes induced cell apoptosis and platelet aggregation (Wu et al., 1999; Franconi, 1995). Taurine in recent years has been widely used as a performance enhancing ingredient in energy drinks, although, not many research works have investigated its potential ergogenic benefits on humans.

Biosynthesis, dietary sources and biological role of creatine, tyrosine, carnitine, HMB and taurine have been shown in Table 2. These five amino acid derivatives have been found to affect the physical, mental and physiological activities on dietary supplementation and thus, confer many ergogenic benefits which have been discussed below in the review.

EFFECT ON PHYSICAL ACTIVITY

The primary and the most common use of ergogenic aids is to improve exercise performance, muscle strength and delay the onset fatigue. Researchers have been interested to find scientific evidences for the ability of these supplements to aid and enhance physical activities. Creatine perhaps has been most extensively studied in this regard when compared to the other amino acid derivatives.

Creatine and exercise performance

Numerous studies have evaluated the effect of creatine supplementation on exercise performance. Majority of the studies have proved that creatine supplementation can increase fatigue resistance and exercise performance. For example, Bosco et al. (1997) studied the effect of creatine monohydrate ingestion (20g/day for 5 days) on jumping and all-out treadmill running performance. Results showed that creatine supplementation was helpful in maintaining the maximal rate of power output for a prolong time period. Some of the studies reported in literature on the exercise performance enhancement effect of creatine supplementation are shown in Table 3.

However, some studies, though few in number have found that creatine supplementation did not confer any significant ergogenic effects on exercise performance. For example, Kinugasa et al. (2004) reported that 5 day creatine supplementation of 4x (5 g Cr monohydrate + 2.5 g maltodextrin)/day did not influence short duration repetitive sprint cycling performance. Hickner et al. (2010) and Finn et al. (2001) also found no improvement in sprint performance during cycling exercises. Mendes et al. (2004) found no significant improvement in swimming performance of competitive swimmers after supplementation with creatine. Nevertheless, creatine remains to be widely used by athletes and sportsmen for its claimed enhancement of exercise performance and fatigue resistance.

Tyrosine and exercise performance

Avraham et al. (2001) reported that tyrosine (100 mg/kg/d) improved appetite and exercise tolerance in rats fed on restricted diet (2h/day). Studies on humans have not shown any

favourable effect of tyrosine on exercise performance. For example, in a study conducted by Chinevere et al. (2002), it was found that tyrosine ingestion (25 mg/kg body wt) with or without carbohydrate supplementation did not enhance performance during a cycling time trial after 90 minutes of steady-state exercise. Strüder et al. (1998) also reported that 20 g tyrosine supplementation in 10 male subjects did not affect physical performance in cycling exercise although plasma tyrosine level increased after 30 minutes of exercise. Sutton et al. (2005) reported that tyrosine supplementation (150 milligrams/kilogram body weight) did not affect endurance, muscle strength, or anaerobic power in healthy men subjected to a various physical performance tests. However, in a study conducted by Ratamess et al. (2003), seventeen resistance trained men ingested a total of 0.4 g/kg body weight of an amino acid supplement per day (containing 0.7g/100g L-tyrosine) or placebo and underwent 4 weeks of total-body resistance training. Results showed significant increase in muscle strength and power in tyrosine group in comparison to placebo group. Further studies are needed to provide evidence for the enhancement of exercise performance by tyrosine supplementation.

Carnitine and exercise performance

Human studies on the potential use of carnitine as an ergogenic aid have shown conflicting results. Some studies have reported positive effect of carnitine supplementation on exercise performance. For instance, Chun et al. (2011) administered various dosage of L-carnitine (2-6g/day) to elite athletes for a period of 4 weeks. The carnitine and placebo group were subjected to physical training programme. The VO_2max level and respiratory coefficient increased in carnitine group after the training period. Blood lactate concentration associated with

recovery from fatigue showed significant decrease on carnitine supplementation. In another study, Vecchiet et al. (1990) administered 2 g of L-carnitine to 10 moderately trained young men and subjected them to cycle ergometer testing. Results indicated that L-carnitine supplementation significantly increased both maximal oxygen uptake and power output and reduced pulmonary ventilation and plasma lactate. Gorostiaga et al. (1989) found that L- carnitine supplementation (2 g/day for 28 days) reduced respiratory quotient during submaximal exercise (45 minutes of cycling at 66% of VO2max) in endurance-trained humans. Cerretelli and Marconi (1990) found that carnitine supplementation (4g/d for 14 days) increased peak aerobic power in six healthy subjects. However, many studies have reported that carnitine supplementation did not confer any favourable changes in exercise performance. Trappe et al. (1994) did not find any ergogenic benefit of carnitine intake (2 grams L-carnitine in a citrus drink taken two times a day for 7 days) in highly trained swimmers during repeated bouts of high-intensity anaerobic exercise. Stuessi et al. (2005) reported that 2 g L –carnitine supplementation in twelve subjects did not enhance performance in endurance cycling test. In a double-blind cross-over trails study by Greig et al. (1987), healthy, untrained subjects were administered 2g/day L-carnitine. Maximum and submaximum exercise capacity were assessed by cycle ergometer exercise test. . The results showed no significant changes in maximum oxygen uptake (VO2max) upon carnitine supplementation. Colombani et al. (1996) investigated the effects of acute L-carnitine supplementation (2 g L-carnitine, 2 h before the start and after 20km of the run) on performance of seven endurance-trained male athletes during and after a marathon run. No significant changes were observed in marathon running time and in respiratory exchange ratio determined before and at the end of the run.

HMB and endurance exercise performance

Vukovich and Dreifort (2001) studied the effect of HMB (3g/day) and leucine (3g/day) separately on endurance-trained cyclists subjected to 2 week supplementation period followed by two week washout period. Cycle ergometry test showed that HMB significantly increased the time taken to reach VO2 peak and the onset of blood lactate accumulation when compared to leucine and control groups. Lamboley et al. (2007) reported that HMB supplementation (3 g/d) during 5 week interval training on treadmill (3 times a week) improved aerobic performance by increasing the maximal oxygen consumption measured using a respiratory-gas analyzer in active college students.

Taurine and exercise performance

Several studies modelled on rat examined the effect of taurine on exercise. For example, Miyazaki et al. (2004) reported that taurine administration between 100 to 500 mg/ kg/ day for two weeks increased running time to exhaustion on treadmill , as compared to placebo and taurine dosage of less than 100mg.Taurine supplementation in Sprague-Dawley rats protected muscle function during high-frequency in vitro stimulation (Goodman et al., 2009). Imagawa et al. (2009) studied the combined effect of caffeine and taurine on endurance performance in mice. They found that 2 weeks of caffeine and taurine intake enhanced endurance exercise performance and taurine reduced lactate accumulation during exercise.

Studies on the effect of taurine supplementation in humans during exercise have been carried out in recent years. Although, these studies are few in number and mostly focussing on

the combined effects of taurine with other supplements, they supported the use of taurine as an ergogenic dietary aid. For instance, Hoffman et al. (2008) found that taurine supplementation along with branched chain amino acids, creatine, caffeine and glucuronolactone to trained men 10 minutes before resistance exercise increased growth hormone and insulin concentration and increased the number of repetitions performed. Supplementation of caffeine, taurine, glucuronolactone, creatine, β-alanine, and the amino acids; leucine, isoleucine, valine, glutamine and arginine in trained college men, enhanced power performance and increased training volume during a multi-joint resistance training session (Gonzalez et al., 2011). Red bull is a commercially sold energy drink that contains taurine along with caffeine and taurine as main ingredients. In double-blind, randomized, crossover design study (Ivy et al., 2009) 6 male and 6 female trained cyclists were given 500 ml of placebo or Red Bull Energy Drink and after 40 minutes tested for cycle time trial performance. Improvement in endurance performance was seen in test group over placebo group. However, Candow et al. (2009) and Astorino et al. (2011) found no beneficial effect of Red Bull on exercise performance.

EFFECT ON MENTAL ACTIVITY

Stressful physical conditions such as extreme heat, cold and physiological stressors such as sleep deprivation, fear and loneliness deplete brain catecholamine concentration and disrupt behaviour (Banderet and Lieberman, 1989). Under stressful situations catecholamines become more active and the availability of tyrosine is rate limiting for the synthesis of neurotransmitters. Several studies have demonstrated that administration of tyrosine can accelerate catecholamine

concentration and turnover in brain. Sved et al. (1979) found that tyrosine dosage of 50mg/kg in rats increases norepinephrin levels in brain. Oral tyrosine feeding of 7.5 g/day increased brain norepinephrin activity and reduced plasma norepinephrin concentration (Benedict et al., 1983). Strüder et al. (1998) found that 20g of tyrosine ingestion in 10 male subjects increased plasma tyrosine levels, norepinephrin and epinephrine levels after 30 minutes of cycling exercise. Wurtman et al. (1974) estimated brain catechole synthesis on tyrosine administration and found that dopamine levels were increased on tyrosine administration. A study by Agharanya et al. (1981) also indicated that tyrosine administration can raise catecholamine synthesis in humans.

As these studies suggest, administration of tyrosine before exposure to physical or environmental stressors can help to enhance physical performance and behaviour (Liebermann et al., 2005). Several studies in this regard have been carried out with favourable outcomes.

Tyrosine and stress resistance

Administration of tyrosine has been found to reduce stress in animals. Lehnert et al. (1984) reported that tyrosine enriched diet protected rats from behavioural depression by stress when subjected to tail shock. Lieberman et al. (2005) studied the effects of tyrosine (400 mg/kg) on rats exposed to heat stress. It was found that tyrosine protects against the adverse effects of heat, as norepinephrin release was sustained and coping behaviour was not impaired. In another study, Sved et al. (1979) reported that tyrosine injection of 50mg/kg reduced blood pressure in hypertensive rats.

Though human studies are numbered, evidences show that tyrosine administration may mitigate the acute effects of stress on human behaviour. Deijen and Orlebeke. (1994) reported

that tyrosine ingestion of 100 mg/kg in 16 healthy individuals decreased diastolic blood pressure, 15 min after ingestion, when subjected to stress sensitive tasks while 1 hour after ingestion diastolic blood pressure was the same with tyrosine and placebo. In a study conducted by Banderet and Lieberman (1989), it was found that tyrosine (100 mg/kg) reduced environmental stress in humans exposed to cold (15 ^{o}C) and hypobaric hypoxia (4200 and 4700 m) when tested by standard behavioural tests of mood and mental performance. It has been suggested that tyrosine has potential use as a dietary aid to stress resistance and improving mood and performance among military troops (Salter, 1989; Owasoyo et al., 1992). In this context, Deijen et al. (1999) reported that tyrosine ingestion reduced blood pressure in cadets after one week of a combat training course.

Tyrosine and cognitive performance

Avraham et al. (2001) studied the effect of tyrosine administration on the cognitive and neurochemical alterations caused by diet restriction in mice. Injections of tyrosine (100 mg/kg/day) reversed the altercations caused by diet restriction without an increase in body weight, suggesting possible implications for the treatment of patients with anorexia nervosa. Shukitt-Hale et al. (1996) reported that tyrosine administration (400 mg/kg) prevents hypoxia-induced decrements in male Fischer 344 rats when exposed to simulated altitude of 5950 m for 8 hours. Studies on human subjects have shown that tyrosine administration is useful in improving cognitive functioning during stressful and multitasking environments (Table 4).

Tyrosine supplementation in phenylketonurics

In patients suffering from phenylketonuria, there is severe accumulation of phenylalanine in blood due to non-functioning of enzyme phenylalanine hydroxylase which breaks down phenylalanine to tyrosine. Such individuals are restricted from the dietary intake of phenylalanine. This leads to deficiency of tyrosine and development of mental retardation and other neuropsychological problems (Poustie and Rutherford, 2009; Gonzalez and Willis, 2010; Scriver et al., 1995; Smith et al., 1998). Limited numbers of studies have been carried out to examine the effect of tyrosine supplementation on phenylketonuria. One such study by Lou et al. (1987) found that tyrosine addition at160 mg/kg/day dosage to phenylalanine restricted diet increases vigilance and dopamine synthesis. Smith et al. (1998) tested the efficacy of tyrosine supplementation (100 mg/kg body weight/d of L-tyrosine) on the neurophysiologic performance in 21 phenylketonuria patients. The results indicated that although dietary tyrosine supplementation increased plasma concentrations of tyrosine, no significant changes in neuropsychological test performance were observed between the test and placebo groups. There is not enough evidence to show the effects of dietary tyrosine supplementation in people with phenylketonuria. More studies however, are necessary to determine the effect of tyrosine administration in phenylketonuria.

Among the five amino acid derivatives, tyrosine has most successfully shown to aid mental activity especially in fighting stress and improving cognitive performance under stressful conditions, because of its direct role in increasing the catecholamine synthesis in brain. Although, some random studies on creatine, carnitine and taurine have also suggested improvement in mental performance, more evidences are required to claim any such effects on consuming these drugs. For example, Ando et al. (2001) reported that chronic administration of

acetyl L- carnitine (100 mg/kg for 3 months) increased cholinergic synaptic transmission and enhanced learning capacity in aging rats. No studies have been conducted on humans to provide any evidence that carnitine supplementation may increase cognitive functions.

Rawson et al. in 2008 found that six weeks of creatine supplementation (0.3g/kg/day) did not improve cognitive function in non-sleep deprived young adults. A previous study (McMorris et al., 2007) had reported that creatine monohydrate supplementation (5g/day for 7 days) improved central executive functioning after 36 hours of sleep deprivation. Horne and Reyner (2001) reported that Lane drifting and reaction time was significantly improved in sleep deprived drivers after consuming taurine containing energy drink, Red Bull. A study by Seidl et al. (2000) showed that Red bull improves mental performance and mood. More studies to assess the effect of these supplements on mental performance can validate the results of the above mentioned studies.

EFFECT ON PHYSIOLOGICAL ACTIVITY

Amino acid derivatives in question have found to improve body strength, muscular endurance, reduce exercise induced muscle damage and effect body composition. HMB supplementation has shown to greatly influence the body strength and composition and also prevent muscle injury during exercise and improve muscle endurance. Taurine helps to reduce oxidative stress during exercise and also regulates blood pressure and inhibits cholesterol accumulation in the body. Such effects on physiological activities have been broadly discussed below.

Creatine Supplementation and muscular performance

Volek et al. (1997) reported that creatine monohydrate supplementation improved muscular performance during high intensity resistance exercise. Kerksick et al. (2007) also reported that Protein- creatine supplementation enhanced muscular endurance and anaerobic sprint capacity during 12 weeks resistance training. Some studies evaluated the effect of creatine supplementation on muscle strength and endurance in older adults. For example; Stout et al. (2007) determined the effect of 14 day creatine supplementation (20g/day for first week and 10g/day for second week) on elderly men and women (64-68 years). Results showed a significant increase in grip strength, physical working capacity at fatigue threshold and lower body muscle endurance. Similar results were seen in a study reported by Brose et al. (2003), where creatine monohydrate supplementation in healthy men and women over the age of 65 improved several indices of isometric muscle strength.

HMB and physiological functioning

Various studies have been conducted to determine the ergogenic effect of HMB in physiological functioning. Ostaszewski et al. (1998) studied the effect of HMB supplementation in rabbits. After nine weeks of supplementation body weight increased, and after slaughtering, carcass fat, kidney fat, and cholesterol content was determined and found to reduce. Nissen et al. (1994) reported that HMB (0.01% of diet) fed to broiler chicken in combination with an antibiotic and coccidiostat increased body weight, carcass yield and breast meat yield. Moore et al. (2005) found that HMB supplementation (0.1% of diet) increased body weight in young

turkey. Buyse et al. (2009) reported increase in weight in chickens supplemented with 300 mg HMB/ kg feed. In another study (Henning, 2010), HMB was found to increase lean body mass and muscle mass under normal training and reduce loss of strength and muscle under catabolic conditions in C57BL/6 male mice.

Effect on body strength and composition

A number of studies on human subjects have shown that HMB supplementation confers favourable effects on body composition and strength. For example, Gallagher et al. (2000a) found that HMB supplementation of 38 mg/kg/day in untrained men increase body strength, as seen by increments in peak isometric and various isokinetic torque values and increased free fat mass. Thomson et al. (2009) administered 3 g/day of HMB or corn starch placebo to 22 trained men subjected to resistance training for 9 weeks. Results showed that lower body strength increased as assessed by 1-repetition maximum method for leg extension in HMB group in comparison to placebo group. Panton et al. (2000) studied the effect of 3g/day HMB supplementation on 39 men and 36 women in 4 week resistance training period. They found that upper body strength and fat free weight increased and fat percentage decreased due to HMB supplementation regardless of gender. Hung et al. (2010) reported that 3g/day HMB supplementation for 3 days decreased body weight and body fat percentage in well-trained female judo athletes. HMB supplementation was found to be helpful in improving body composition and body strength in elderly people as reported in two studies. Vukovich et al. (2001b) supplemented 3g/day Ca-HMB to elderly men and women in an eight week double blind study to find out whether 70 year old adults responded similarly to HMB supplementation as

young adults. Computerized tomography (CT) and Dual X-ray Absorptiometry (DXA) scans were taken before and after the training programme. An increase in fat free mass and body fat loss percentage was seen at the end of the training period in HMB group. CT scans results showed a significant decrease in the percentage of body fat due to HMB. Flakoll et al. (2004) studied the effect of daily supplementation of 2 g HMB, 5 g arginine, and 1.5 g lysine in elderly women for 12 weeks and found increase in leg strength, handgrip strength and in fat-free mass. Jówko et al. (2001) studied the combined effect of creatine and HMB on lean body mass and muscle strength in humans subjected to progressive resistance-exercise training for 3 weeks. Increase in lean body mass and muscle strength was seen in creatine group, HMB group and combination of creatine and HMB (creatine/HMB) group. Creatine/HMB group showed greatest increase in these indices. However, O'Connor and Crowe (2003, 2007) reported that 6 weeks of Creatine/HMB supplementation (3 g/ day) showed no significant effect on muscular strength, endurance and body composition of trained athletes during a series of exercise performance tests.

Effect on muscle damage

Studies evaluating the effect of HMB on muscle damage during exercise have found that there was a decrease in the indirect markers of muscle damage such as muscle creatine phosphokinase, lactate dehydrogenase and muscle proteolysis. Nissen et al. (1996) reported subjects given either 1.5 or 3 g HMB/day prior to weightlifting showed significant decrease in both exercise-induced rise in muscle proteolysis as measured by urine 3-methylhistidine and plasma creatine phosphokinase, whereas placebo group showed no such effects. In another study, Knitter et al. (2000) supplemented 3g/day HMB to individuals undergoing 6 weeks of daily

training. At the end of training period, effect of HMB on muscle damage was measured after a 20 km prolong run. Results showed decrease in lactate dehydrogenase and creatine phosphokinase activity in muscles in test group. In a crossover design study by Wilson et al. (2009), subjects were given 3g of HMB either before or after performing an eccentric knee exercise bout. Subjects who were administered HMB before exercise showed no significant increase in serum lactate dehydrogenase level whereas, muscle soreness was reduced. Byrd et al. (1999) had previously found similar results in subjects exposed to downhill running.

Though majority of the studies showed evidences for the potential ergogenic effect of HMB, some studies did not find HMB to be useful in bringing about significant differences in body strength and composition or in protecting the muscle against exercise induced damage. For example, Slater et al. (2001) found that 3g/day HMB supplementation for 6 weeks in resistance-trained male athletes did not significantly change body mass and body composition, measured using dual energy X-Ray Absorptiometry. Ranson et al. (2003) administered HMB (3g/day) to collegiate football players during a 4 week strenuous exercise program and found no influence of HMB on muscular strength, body weight and body fat. In a series of test conducted on rugby players by Crowe et al. (2003) and O'Connor and Crowe (2003, 2007), HMB supplementation 3g/day for 6 weeks was not found to influence body composition, strength, aerobic or anaerobic capacity. Paddon-Jones et al. (2001) reported that HMB supplementation (40mg/kg bodyweight/day for 6 days) had no effect on swelling, muscle soreness, or torque in non-resistance trained subjects. Hoffman et al. (2004) and Nunan et al. (2010) also found no significant benefits of HMB supplementation on indices of muscle damage.

Rowlands and Thomson (2009) carried out a meta analysis on nine studies to summarise the effectiveness of HMB on strength, body composition, and muscle damage. They reported that based on the evaluation of data published in previous studies, HMB supplementation of 3g/day during resistance training improved average body strength in untrained individuals. However, HMB had little influence on the body strength and composition of trained athletes. Another meta analysis study carried out by Nissen and Sharp (2003) on the ergogenic effect of dietary supplements established that out of the six supplements studied, creatine and HMB clearly showed significant increase in lean body mass and strength. The meta analysis studies and the individual studies conducted support the use of HMB as an effective aid to increase body strength, body composition and to prevent muscle damage during resistance training.

Taurine supplementation and physiological effects

Antihypertensive and anti-oxidative effect

Animal studies investigating the effect of taurine on the body have found that taurine reduced oxidative stress and cholesterol accumulation and also exerted antihypertensive properties. Hong et al. (2003) reported that cholesterol level in serum and liver in swine was found to decrease after taurine administration (0.3 and 0.6% of feed). In another study, taurine supplementation helped to reduce oxidative stress and cholesterol accumulation in rabbits (Balkan et al., 2002). Other studies also reported to find evidences for antioxidant and cholesterol lowering effects of taurine (Hagar et al., 2006; Goodman et al., 2009; Mochizuki, 1998; Chahine et al., 2010).

Taurine has been reported to exert antihypertensive activity. Anuradha and Balakrishnan (1999) and Hu et al. (2009) found that 2 % taurine in drinking water administered to hypertensive rats and insulin fed rats respectively, prevented elevation in blood pressure. Similar result was reported by Chahine et al. (2010) from studies conducted on hypertensive rats. Hagar et al (2006) studied the effect of taurine treatment (1% in drinking water)) on rats injected with immunosuppressant Cyclosporine A. They found that taurine inhibited elevation in blood pressure induced by Cyclosporine A.

Taurine intake is reported to be effective in regulating blood pressure in hypertensive patients (Kohashi et al., 1983; Fujita et al., 1987), lowering body weight and serum lipid level in obese or overweight individuals (Zhang et al., 2004b), treatment of congestive heart failure (Azuma et al., 1983; 1985; 1992; Xu et al., 2008) and in controlling diabetes induced cell apoptosis and platelet aggregation (Wu, 1999; Franconi, 1995).

Effect on muscle strength

In a study (Dawson et al., 2002), Sprague-Dawley rats were supplemented with the drinking water with 3% taurine for one month and subjected to 90 minutes of downhill treadmill running. Taurine content in muscles increased, running performance was enhanced and supplementation also protected against exercised induced muscle injury. Eleven men were subjected to seven day taurine supplementation and underwent two identical bicycle ergometer exercises until exhaustion. Plasma thiobarbituric-acid reactive substance (TBARS) was reduced and VO_2max, exercise time to exhaustion and maximal workload increased during exercise after taurine supplementation (Zhang et al., 2004b). Rutherford et al. (2010) studied the effect of

intake of noncaloric sweetened beverage containing 1.66 g of taurine 1 hour before exercise in endurance-trained male cyclists. They reported an increase in fat oxidation during submaximal cycling in the test subjects when compared to control group. A study reported that consumption of Red Bull increased upper body muscle endurance measured by bench press test (Forbes, 2007). In contrast to the above studies, Galloway et al. (2008) found that 7 days of taurine supplementation does not increase skeletal muscle taurine content or inhibit fat oxidation during exercise.

Carnitine supplementation and body composition and functioning

Various studies have been carried out in recent years to evaluate the effects of carnitine supplementation in animals. For example, Xia et al. (2008) reported that L-carnitine supplementation resulted in significant reduction in the average swimming time, body weight and abdominal fat contents in Kunming mice. Yang et al. (2006) found that administration of genistein (the principal soy isoflavone) with carnitine exerts anti-obesity effects in C57Bl/6J mice fed a high-fat diet. Similar results were reported by Murosaki et al. (2007), who found that a combination of caffeine, arginine, soy isoflavones, and L-carnitine enhanced lipolysis and fatty acid oxidation in KK mice. In a study by Karanth and Jeevaratnam (2005), carnitine supplementation in male Wistar rats fed on diets containing either hydrogenated fat or peanut oil, was found to protect against lipid peroxidation due to exercise. The blood glutathione level was increased significantly in exercising rats. Carnitne supplementation helped in redistribution of glutathione from liver to blood and muscle.

Human studies have reported an increase in blood lactate and body strength upon carnitine administration. For example, Blood lactate concentration associated with recovery from fatigue showed significant decrease on carnitine supplementation (2-6g/day) to elite athletes for a period of 4 weeks (Chun et al., 2011). Marconi et al. (1985) studied the effects of L-carnitine ingestion (4 g/d for 2 weeks) on the aerobic and anaerobic performance of 6 long distance competitive walkers. Results showed significant increase in VO_2max, serum L-carnitine and blood lactate concentrations upon carnitine loading. In another study, Vecchiet et al. (1990) administered 2 g of L-carnitine to 10 moderately trained young men and subjected them to cycle ergometer testing. Results indicated that L-carnitine supplementation significantly increased both maximal oxygen uptake and power output and reduced pulmonary ventilation and plasma lactate. Gorostiaga et al. (1989) found that L- carnitine supplementation (2 g/day for 28 days) reduced respiratory quotient during submaximal exercise (45 minutes of cycling at 66% of VO2max) in endurance-trained humans. Cerretelli and Marconi (1990) found that carnitine supplementation (4g/d for 14 days) increased peak aerobic power in six healthy subjects. However, Soop et al. (1988) found that 5 days of 5g/day L-carnitine supplementation in seven moderately trained males did not affect O2 uptake and exercise-induced changes in arterial levels and turnover of FFA.

Moffatt and Chilland (2004) stated in their review that most of the studies focussed on the blood or plasma levels of carnitine to evaluate the effect of carnitine supplementation on exercise performance. Since the action of carnitine is chiefly in the muscles, studies to determine the changes in muscle carnitine level will be more helpful and accurate. However, such studies, though few, found no changes in muscle carnitine level during exercise on supplementation of

subjects with carnitine. For example, Barnett et al. (1994) found no effect of 14 days L-carnitine supplementation (4g/day) on muscle carnitine level during high intensity sprint cycling in eight subjects. Similar results were observed in studies conducted by Janssen et al. (1989) and Decombaz et al. (1992).

Carnitine supplementation provides little benefits to trained individual as seen in most of the studies finding contradicting outcomes. Moreover, studies have shown that individuals who are deficient in carnitine are more likely to benefit from carnitine supplementation than normal humans. This is because supplementation will help to accumulate necessary carnitine content within the muscle in such individuals which will significantly affect exercise performance. Poorabbas et al. (2007) and Weigel et al. (2008) assessed serum free carnitine status in type II diabetic women and young patients with phenylketonuria respectively. They found that L-carnitine levels were low in such subjects and carnitine supplementation might be beneficial. Further research in this regard could provide more evidences.

TOXICOLOGICAL STUDIES

Adverse side effects and toxicity due to the consumption of ergogenic supplements is a cause for concern among researchers and several studies have been carried out to establish the health implications and optimum safe level for consuming these drugs. Table 5 shows the adverse effects encountered due to consumption of these supplements. Though some studies have raised concerns due to some negative findings, majority of the studies have found no

serious threat or side effects associated with consumption of any of the five amino acid derivatives.

Weight gain has been found to be the most common side effect of creatine supplementation reported in some studies. However, some recent studies found no increase in weight due to creatine supplementation. There have been concerns on the effect of long term use of creatine on renal function, particularly in humans with impaired renal function. Nevertheless, no adverse effects of creatine supplementation on renal function have been reported so far. More research on the effect of creatine supplementation on individuals who suffer from compromised renal capacity needs to be carried out. Benzi (2000) has recommended an intake of 2.5 – 3g/day of oral creatine in a healthy active individual and oral creatine administration of 5-6g/day for healthy athletes who undergo high intensity sprint or strength training. Shao and Hathcock (2006) determined the Observed Safe Level (OSL) of creatine monohydrate to be at 5g/day.

Since tyrosine is a normal constituent of food, it is not likely to confer any long term toxicity in humans. However, in patients suffering from tyrosinemia II, increased plasma tyrosine levels due to the deficiency of hepatic tyrosine aminotransferase is observed. This genetic disorder results in mental retardation and lesions of the eye and soles. Tyrosine supplementation in diet is not recommended for such individuals (Garlick, 2004).

No adverse or side effects have been reported due to carnitine or HMB intake. Hathcock and Shao (2006) OSL risk assessment method showed that chronic L-carntine intakes of less than or equal 2000 mg/day is safe. Nissen et al. (2000) analysed and compiled the results of 9 published studies that evaluated the safety of HMB. They summarised that intake of 3g/day of HMB did not cause any adverse side effects. No negative impact was seen on blood

haematology, blood chemistry or other indices of health. Nissen et al. (1996, 2000) and Gallagher et al. (2000b) recommend optimum dosage of 3g/day. HMB dosage of above 3g/day was not found to influence body strength and fat free mass (Gallagher et al., 2000a).

No adverse health effects in humans have been reported so for due to taurine intake. Extensive studies needs to be carried out to asses the safety aspects of taurine supplementation as there is little research on the risk assessment of taurine. Miyazaki et al. (2004) reported that the effective dose of taurine to prolong exercise performance in rat is between 100 to 500 mg. Shao and Hathcock (2008) identified the Observed Safe Level (OSL) for taurine in healthy adults as 3g/day. They mentioned that due to lack of evidence for systematic pattern of adverse effects in humans in response to taurine ingestion, a no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL) could not be established.

CONCLUSION

Application of dietary components as ergogenic aids has garnered public interest since a long time as they are relatively safer and adverse health effects on consumption are rare. Creatine, tyrosine, carnitine, HMB and taurine are among the most commonly used amino acid derivatives in sports and exercise for their ergogenic properties. Creatine amongst all is the most extensively used supplement by athletes for the past few decades. Numerous studies have successfully proved the performance enhancing benefits of oral creatine intake, which is chiefly due to its role in maintaining the ATP level in skeletal muscles during high intensity exercise. Since it is a natural component of the human body, adverse health effects on ingestion have not

been reported so far. Tyrosine, a precursor of neurotransmitters in the brain, has influence on cognitive performance and stress resistance. Some studies have also reported favourable effects of tyrosine in phenylketonuria patients. Carnitine derived from essential amino acids lysine and methionine has been popular among athletes as a performance enhancing agent. However, studies on its effectiveness in aiding exercise performance have produced mixed results. The ones showing positive effect reported that carnitine prolonged endurance exercise and delayed fatigue. Many studies reveal that carnitine supplementation is unnecessary as it is unlikely to confer any aid to exercise performance. However, favourable results found in some studies suggest that carnitine may be effective as a potential ergogenic aid. More researches on short term and long term supplementation of carnitine in humans are necessary

HMB, a derivative of leucine, prevents muscle damage and increases muscle strength by reducing exercise induced proteolysis in muscles and also helps in increasing lean body mass. Taurine is one of the main ingredients used in Red Bull, a widely popular energy drink, which has shown to favourably influence exercise performance and muscle endurance. Although, studies on taurine administration in animals and humans have confirmed its antihypertensive and cholesterol lowering activity; more extensive research needs to be carried out to examine the effect of taurine supplementation during exercise. It can be concluded that creatine and HMB have clearly shown to exhibit ergogenic properties; as results from a meta analysis mentioned before support their application in sports and exercise. Available data collected from the researches documented on tyrosine advocate its supplementation to improve cognitive function and performance in stress related tasks. In case of carnitine and taurine, more research in the future can provide more evidences to support their use as performance enhancing agents.

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Table 1. Ergogenic action, type of exercise performed and recommended dosage of the four amino acid derivatives

Supplements	Ergogenic action	Type of exercise	Recommended dosage
Creatine	Increased muscle mass, strength, fat free mass and fatigue resistance	Short term endurance exercise, resistance exercise, anaerobic exercise	20g/day – acute dose 3-5g/day- chronic dose
Tyrosine	Improved cognitive performance, accelerated neurotransmitter synthesis, stress resistance	Stress related tasks	Up to 100mg/kg body weight
Carnitine	Increased fat metabolism, energy production and fatigue resistance	Long term endurance exercise	2g/day
HMB	Increased body strength, fat free mass, muscle mass, body fat loss and reduced muscle damage	Resistance training, anaerobic exercise	3g/day
Taurine	Antihypertensive, increased maximal performance, reduced oxidative stress and body weight	Endurance exercise	3g/day

Table 2. Biosynthesis, dietary sources and biological role of the amino acid derivatives

Amino acid derivative	Biosynthesis	Dietary sources	Biological role
Creatine	In liver and kidney from L-arginine and glycine	Meat, fish and animal products	Converted to phosphocreatine in muscles and increases rate of ATP resynthesis
Tyrosine	Synthesised from phenylalanine by the enzyme phenylalanine hydroxylase	Protein rich food such as fish, chicken, almonds, peanuts, milk and dairy products	Converted to catecholamine neurotransmitters of the brain including dopamine, norephinephrin and epinephrine
Carnitine	Chiefly in the liver and kidney from lysine and methione.	Meat, fish, poultry and dairy products	Important for fatty acid metabolism in cardiac and skeletal muscles
HMB	In muscle and liver from leucine	Mainly from meat and meat products and in small amounts from some fruits and vegetables	Cholesterol synthesis and inhibition of protein breakdown
Taurine	Primarily in the liver from cystein	Meat, dairy products and sea food.	In conjugation with cholic acid forms bile salts,

			antihypertensive and antioxidant activity

Table 3. Effect of creatine intake on exercise performance

Exercise type	Effect	Researchers
Cycling	Improved performance in high intensity cycling exercise, cycle ergometric sprint test, maximal cycle pedalling	Prevost et al. (1997), Kreider et al. (1998), Wiroth et al. (2001), Tarnopolsky (2000)
Swimming	Increased swimming performance and decreased mean swimming time	Grindstaff et al. (1997), Vatani et al. (2011)
Sprint	Improved sprint performance, sprint velocity and decreased sprint time	Mujika et al. (2000), Skare et al. (2001), Faraji et al. (2010)

Table 4. Effect of tyrosine supplementation on cognitive functioning

Researchers	Dosage	Condition	Effect
Thomas et al. (1999)	150 mg/kg	Series of Multiple Task and a Simple Task battery	Sustain working memory in multitasking environment
Deijen and Orlebeke (1994)	100 mg/kg tyrosine	Exposure to stressor consisting of 90 dB noise	Improved cognitive performance
Neri et al. (1995), Magill et al. (2003)	150 mg/kg	Sleep deprivation for 24 hours	Counteracting decrements in cognitive performance such as visual scanning, running memory, logical reasoning, mathematical processing etc due to sleep loss
Deijen et al. (1999)	2 g tyrosine	Military combat training course.	Improvement in memory tasks

Table 5. Adverse effects and toxicological studies of amino acid derivatives

Ergogenic aid	Adverse effect/ toxicity	Dosage	Researcher
Creatine	Weight gain	>5g/day	Volek et al. (1997), Jowko et al. (2001), Kreider et al. (1998), Kerkisick et al. (2007) and Brose et al. (2003)
	Significant difference in body mass, fat free mass or fat mass	2.3g/day	Rawson et al. (2011)
	Creatine supplementation in Han:SPRD-cy rats increased cyst growth and worsened renal function	2g/kg of diet	Edmunds et al. (2001)
	No alterations in kidney function in aged patients with Parkinson's disease.	4g/day for 2 years	Bender et al. (2008)
	No adverse effect of creatine supplementation was found on renal function		Poortman and Francaux (1999)
Tyrosine	No adverse side effects, although catecholamines levels in blood increased	100 mg/kg	Melamed et al. (1980), Benedict et al. (1983), Rasmussen et al. (1983)

HMB	No adverse side effect in rats	3.49g/kg BW for males and 4.16g/kg BW for females (90 days)	Baxter et al. (2005)
	No adverse affects on hepatic enzyme, renal and immune system functioning in healthy males	76 mg/ kg/day	Gallagher et al. (2000b)
	No adverse effect due to supplementation of HMB in combination with arginine and glutamine.	3g/day	Rathmacher et al. (2004)
Taurine	Echocardiographic examinations performed before and after exercise on subjects who consumed Red Bull before exercise revealed a reduction in endsystolic diameter and volume influenced Stroke volume. An increase in the peak late diastolic inflow in the regeneration period, in comparison to pre exercise levels was also observed	Upto 1000 mg per serving	Baum and Weiss (2001)

	Consumption of energy drink containing taurine increased heart rate by 5-7 beats/min and fasted state, baseline blood pressure by 10 mm Hg in healthy adults.	Upto 1000 mg per serving	Steinke et al. (2009)
	No significant changes in cardiovascular and renal functions in humans upon Red Bull consumption.	Upto 1000 mg per serving	Ragsdale et al. (2010)

