Branched-Chain Amino Acids in Exercise

Amino Acid Mixture Improves Training Efficiency in Athletes[1,2]

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ABSTRACT   This review discusses some of the beneficial effects of a dietary amino acid supplement on muscle function, fatigue, and recovery in exercising athletes. The supplement, a mixture of amino acids that included the branched-chain amino acids, arginine and glutamine, was studied chronically at several daily dose levels for extended periods of time (10, 30, and 90 d). Outcome variables included physical measures of muscle strength, fatigue and damage, and blood indices of muscle damage and oxygen-carrying capacity. One beneficial effect of the amino acid supplement was a quicker recovery from the muscle fatigue that followed eccentric exercise training. A dose-response study of the amino acid mixture at 2.2, 4.4, and 6.6 g/d for 1 mo showed that at the highest dose, indices of blood oxygen-carrying capacity were increased and those of muscle damage were decreased at the end of the trial. When the amino acid mixture was given for 90 d to elite rugby players during training at a dose of 7.2 g/d, a blood-component analysis indicated improvements in the oxygen-carrying capacity of the blood. Together, the studies suggest that the amino acid supplement contributed to an improvement in training efficiency through positive effects on muscle integrity and hematopoiesis.   J. Nutr. 136: 538S–543S, 2006.

KEY WORDS: • *amino acids* • *blood-component analysis* • *athletic training*
 • *creatine phosphokinase* • *hematopoiesis*

Athletes have long experimented with nutritional supplements to improve physical performance. To assess whether a nutritional approach might actually benefit performance, exercise physiologists and biochemists have devoted considerable effort to the study of nutrient needs and stores of the athlete, and the usefulness of ergogenic supplements (1). Nutritional ergogenic aids are classified into 4 categories: *1)* substances that promote anabolism and improved body composition (e.g., dietary amino acids), *2)* substances that provide quickly utilizable energy (e.g., dietary carbohydrates), *3)* substances that facilitate recovery from physical exhaustion (e.g., dietary antioxidants), and *4)* substances that fill other critical roles in exercise physiology (e.g., vitamins, sodium bicarbonate) (2).

This article focuses on the use of dietary amino acids in sports nutrition, in particular, on their collective effects during and after training. Whereas amino acids are the building blocks of muscle protein, they also serve as an energy source for skeletal muscle. For example, the BCAAs leucine, isoleucine, and valine are transaminated in muscle to their respective α-keto acids, which are then utilized for gluconeogenesis in the liver. During endurance exercise, the BCAA pool is maintained through muscle protein breakdown. However, the oxidation of BCAAs in skeletal muscle often exceeds their supply from protein during prolonged endurance exercise. As a result, BCAA concentrations decline in the blood, an effect that is thought by some to cause the unexpected consequence of promoting tryptophan uptake across the blood–brain barrier, and increasing serotonin formation in brain (3). One consequence of this effect may be central fatigue. In this regard, it is of interest that the ingestion of a BCAA solution by rats blocks the rise in serotonin that occurs during exercise (4). Another amino acid, arginine, may also serve useful functions during exercise. Its ingestion promotes the secretion of hormones that exert important actions during exercise (5,6), and also facilitates ammonia removal through the urea cycle, which may reduce peripheral fatigue associated with exercise. The arginine derivative, nitric oxide, a potent endogenous vasodilator, may also enhance athletic performance (7,8). As a final example, glutamine is also central to muscle function. The concentration of free glutamine in muscle is about 20 mmol/L, making it by far the amino acid present in the highest concentrations in the free amino acid pool of skeletal muscle (60% of the total free amino acid pool) (9). A negative arterio-venous difference in the plasma glutamine concentration occurs across muscle and becomes particularly pronounced after prolonged exercise (10). In slow-twitch muscle, the intracellular concentration of

glutamine is 3-fold higher than in fast-twitch muscle (11), suggesting a greater demand for glutamine in the muscle fibers most associated with endurance training. In prolonged and high-intensity exercise, plasma glutamine rises during exercise and then falls during the postexercise recovery period (12). This decline in glutamine following exercise has been implicated in the onset of acidosis (13), and in diminished immune response, particularly in the case of overtraining (14).

In the past, when dietary amino acids have been studied for their effects on physical performance, experiments were conducted using only a single amino acid, given at a pharmacological dose, and examined over a relatively short period of time. Relatively few reports are available that have examined the physical performance effects of ingesting amino acids chronically. And when chronic studies have been pursued, such as with the BCAA (15–17), arginine (18–20) or glutamine (21,22), few have focused on the physiological effects of these amino acids during and after athletic activities, on the dosage that would optimize observed beneficial effects (23–25), or on the effects of using these amino acids together. We therefore developed a working hypothesis, which we have examined over the past several years, that a dietary supplement that includes BCAA, glutamine, and arginine might collectively improve athletic performance. We discuss some of the results of our investigations below, which involved examining physiological and biochemical responses to an amino acid (AA)[4] mixture containing these amino acids during and after athletic activities in studies of short, intermediate, and long-term design.

Recovery from muscle fatigue by oral administration of an amino acid mixture

Muscle contraction is divided into 2 types: isometric and isotonic. Skeletal muscle contracts while maintaining its length in an isometric contraction, and contracts while resisting a constant applied load in an isotonic contraction. The isotonic contraction is further divided into concentric and eccentric contractions; the muscle shortens in a concentric contraction, and resists a constant pulling force in an eccentric contraction (26). The eccentric force generated is greater than either the concentric or isometric forces in flexor and extensor muscles during exercise sessions involving mechanical devices such as a dynamometer (27). Therefore, eccentric exercise training is considered more effective than isometric or concentric training for the purpose of increasing muscle strength (28).

However, eccentric exercise is likely to cause severe muscle soreness, the result of damage to muscle fibers, tendons, and other connective tissue. Indeed, structural damage in myoplasmic membranes (29,30) and sarcoplasmic reticulum (31) of muscle fibers are reported to result from eccentric exercise. When the structural integrity is compromised in this manner, calcium homeostasis is disturbed and induces unwanted protein degradation (32), as indicated by elevated creatine phosphokinase (CPK) levels in blood. Blood CPK measurements therefore serve as a useful indicator of muscle-fiber damage (33,34).

In recent years, we have studied the effects of oral AA mixtures during exercise on indices of muscle function, damage, and recovery (35–37). The results are discussed below. The objective of such studies (37) has been to determine if an oral AA mixture would facilitate the recovery from muscular fatigue that results from the damage to muscle infrastructure

occurring during eccentric exercise (38,39). In these studies, 3 types of muscular-strength measurements were made to assess the recovery from muscle fatigue following eccentric exercise: maximum isometric strength, maximum concentric strength, and maximum eccentric strength. Both elbow flexor and extensor muscles were tested.

One study employed male students, aged 19–21 y, with average heights and body weights of 172.0 ± 1.2 cm and 65.2 ± 1.8 kg, respectively. The AA mixture examined (35–37) contained L-glutamine (~14% by weight), L-arginine (~14% by weight), L-leucine, L-isoleucine, L-valine (total BCAA ~30% by weight), L-threonine, L-lysine, L-proline, L-methionine, L-histidine, L-phenylalanine, and L-tryptophan, altogether totaling 5.6 g in each dose, with vitamins and minerals. The placebo contained vitamins and minerals, as in the amino acid mixture, but an equicaloric amount of carbohydrate in place of amino acids. The experiment was a double-blind, crossover design, with subjects receiving the AA mixture and the placebo during 2 trials separated by 2 mo. In each trial, the subjects began with a 1-wk period during which they consumed a standardized meal plan prepared by a dietician. They then undertook a session of eccentric exercise training, after which they were allowed to recover for 10 d. During the recovery period, they received the AA mixture or the placebo 2/d. Muscle strength was measured the d before the exercise training session, immediately after this session, and then 1, 2, 3, 5, 6, and 10 d later. The measures of muscle strength employed were maximum isometric (ISO) strength, maximum concentric (CON) strength, and maximum eccentric (ECC) strength., shown in the figures as the relative peak torque, or the percentage of pretraining peak torque (**Figs. 1** and **2**).

For the elbow extensor muscle, in the placebo trial, the relative peak torque for the maximum ISO strength declined to 77% of the pretraining strength immediately after the training and to 68% 1 d after training. The maximum ISO strength reached the lowest value (66.5% of the pretraining strength) 2 d after the training, and then started to recover. The maximum CON strength reached the lowest value 1 d after the training before the onset of recovery. The maximum ECC strength reached the lowest value 2 d after the training before the onset of recovery. In the AA trial, the maximum ISO strength and the maximum ECC strength of the elbow extensor muscle showed a smaller decline 2 d after the training, relative to placebo, suggesting earlier recovery (Fig. 1, panels A and C). The differences in the maximum ISO strength between the amino acid treatment and the placebo were statistically significant ($P \leq 0.05$) on days 2, 3, and 6 (Fig. 1, panel A). The difference between the amino acid group and placebo group was statistically significant ($P \leq 0.05$). When the elbow flexor muscle was tested, no significant difference was noted between the placebo and AA trials for any of the measures (Fig. 2).

The results of this study thus indicate that the ingestion of the AA mixture accelerated the rate of elbow extensor muscle recovery, compared with the placebo response. Furthermore, the AA mixture produced higher muscle strength throughout the recovery period. Most of the subjects reported less delayed muscle soreness when given the amino acid mixture. These results support the hypothesis that, collectively, amino acids protect skeletal muscle from a destructive aspect of the eccentric exercise training when administered orally as a mixture.

Other studies have also observed that muscular damage is moderated by dietary supplementation with an AA mixture in human subjects and in laboratory animals. In a human study the damage to elbow extensor muscle and muscle soreness were reduced (compared with the placebo) by the use of an AA mixture of the same composition (39). In a crossover study,

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[4] Abbreviations used: AA, amino acid; CPK, creatine phosphokinase; ISO, isometric.
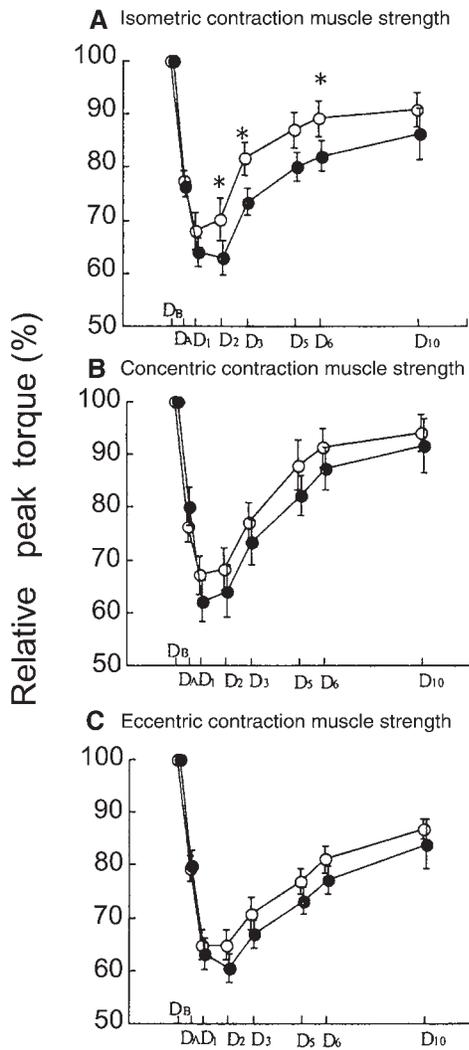
FIGURE 1 Isometric contraction muscle strength (*A*), concentric contraction muscle strength (*B*), and eccentric contraction muscle strength (*C*) of the elbow extensor muscle before, immediately after, and during the 10-d recovery period. Muscle strength was measured as the peak torque and expressed as relative peak torque when the peak torque value before the eccentric exercise training was defined as 100%. Open circles represent the amino acid mixture trial; closed circles are the placebo trial. Data are presented as means ± SEM ($n = 22$); *$P < 0.05$ vs. placebo on the same day; ANOVA; *t* test). Reproduced from Sugita et al. (37), with permission.

2 groups of 24 untrained male students performed a session of endurance exercise with one arm, and were followed during a 4-d recovery period. Four weeks later, the trial was repeated using the other arm. The subjects were given either the AA mixture or placebo before and after the exercise session, and at night and in the morning for the next 4 days. When the subjects received the AA mixture, the increases in CPK activity and myoglobin concentration in plasma were effectively suppressed ($P \leq 0.05$), and muscle soreness with extension was lessened ($P \leq 0.05$) (N. Nosaka, M. Newton, P. Sacco, K. Mawatari, and H. Satou, unpublished). And in an animal study, the timing of the administration of the AA mixture was found to be critical in alleviating muscular damage. When mice were forced to jump in response to repeated electrical shocks, the AA mixture was found to be effective in suppressing the rise of plasma CPK only when given before and after the forced exercise (F. Ohta, K. Mawatari, and H. Satou, unpublished).
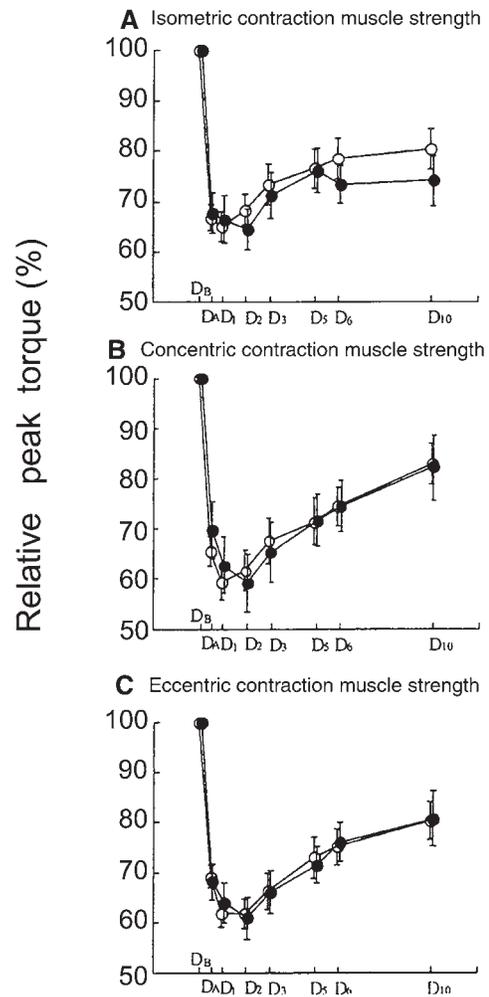
FIGURE 2 Isometric contraction muscle strength (*A*), concentric contraction muscle strength (*B*), and eccentric contraction muscle strength (*C*) of the elbow flexor muscle before, immediately after, and during the 10-d recovery period. Muscle strength was measured as the peak torque and expressed as relative peak torque when the peak torque value before the eccentric exercise training was defined as 100%. Open circles represent the amino acid mixture trial; closed circles are the placebo trial. Data are presented as means ± SEM ($n = 22$). Reproduced from Sugita et al. (37), with permission.

A dose-response study of the AA mixture: effects on blood markers of muscle damage in athletes training as middle- and long-distance runners

We also undertook a study to identify an effective-dose range for the AA mixture in reducing muscle damage during training (35). In this experiment, a group of athletes on a college track team ($n = 13$) engaged in sustained exercise for 2–3 h/d, 5 d/wk for 6 mo. The level of training was made constant for 6 mo by adjusting the distance and the exercise intensity. The combination of distance and exercise intensity was indexed to compute exercise load. At the time of study, the average subject age, weight, and height were 20.2 ± 0.4 y, 60.0 ± 0.9 kg, and 172.5 ± 0.4 cm, respectively. These middle- and long-distance runners maintained their body weight and level of exercise constant throughout the 6-mo study period. During the 6-mo period, subjects received three 1-mo treatments, separated by a washout month between each trial. The subject group was divided into 3 subgroups, and the 3 treatments were administered in a Latin-square design. The treatments were

3 doses of the oral AA mix: 2.2, 4.4, and 6.6 g/d (the AA mix was the same as that used in the above studies; the 2.2 g/d dose was administered as a single dose at dinner; the 4.4 g/d dose was administered as two 2.2 g doses at breakfast and dinner; the 6.6 g/d dose was given as three 2.2 g doses, one at each daily meal). Blood samples were drawn at the beginning and end of each trial, and assayed for indices of muscle damage and aerobic fitness.

The 2.2 g/d dose of the AA mix produced no significant effects on the blood measures of muscle damage and oxygen-carrying capacity. The 4.4 g/d dose produced a significant increase in serum albumin and significant reductions in serum iron and blood lactic acid concentrations ($P \leq 0.05$) [data not shown]. However, the 6.6 g/d dose produced notable changes in physical condition, blood measures of muscle damage, and oxygen-carrying capacity (see **Table 1**). The physical condition index, a self-assessment made by the athletes, improved significantly ($P \leq 0.05$) from 3.0 to 3.7. The most noteworthy chemical improvement was the reduced elevation of serum CPK activity ($P \leq 0.05$). Serum CPK is an indicator of muscle inflammation and is elevated maximally 12–24 h after a session of strenuous exercise involving heavy muscular load (40). The decline in serum CPK activity, such as was seen in this portion of the study, indicates an early recovery from muscle inflammation, which is considered favorable by athletes. In addition, serum glutamate-oxaloacetate aminotransferase activity declined and serum albumin concentration increased

($P \leq 0.05$). Three factors relating to hematopoiesis were also increased ($P \leq 0.05$): red blood cell count was elevated from $508 \times 10^4/\mu L$ to $528 \times 10^4/\mu L$, hemoglobin concentration from 15.2 g/dL to 15.8 g/dL, and hematocrit from 44.9 to 46.8% (**Fig 3**). Hence, the AA mixture at the daily dose of 6.6 g improved the self-assessment of the physical condition, reduced muscle damage, and enhanced hematopoiesis measures, which suggests improved oxygen-handling capacity.

Effects of the oral AA mixture in rugby players

In another study (36), we examined the effects of administering 7.2 g/d of the AA mix to rugby players for 3 months during a period of intensive physical training. Twenty-three members of an elite rugby team, which had won the championship in the Japan Football League for 7 consecutive years, participated in this study. The average age, height, body weight, and body fat percentage were 27.2 ± 0.4 y, 177.8 ± 1.6 cm,

TABLE 1

Effect of the 6.6 g/day dose of the amino acid mixture on physical parameters, hematology, and blood biochemistry in runners
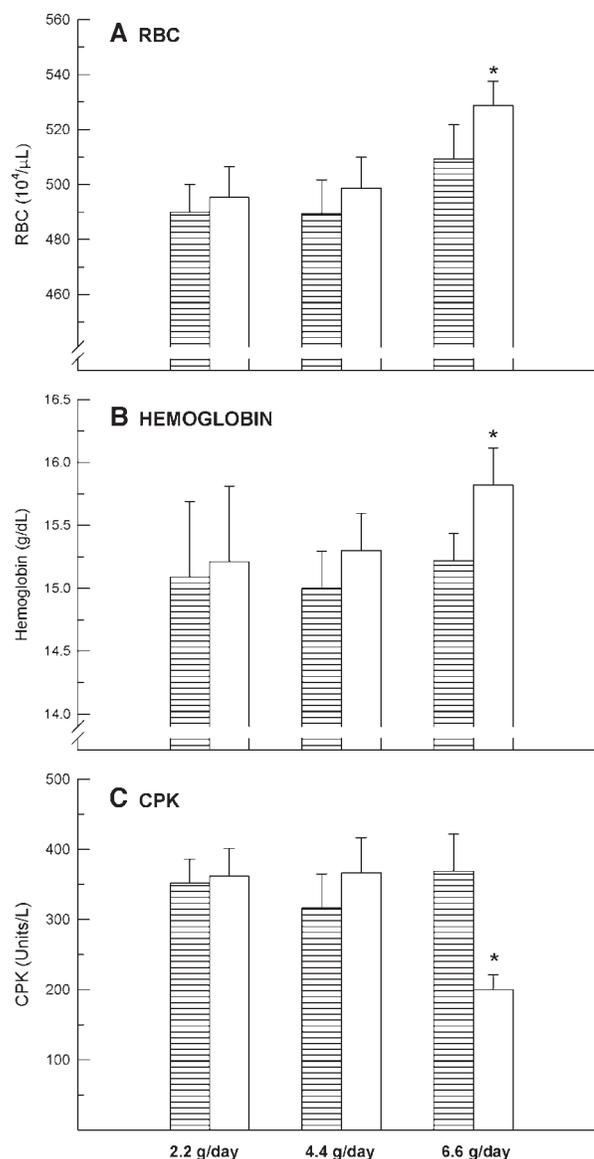
	Pre-test period	Post-test period
Body weight, *kg*	60.4 ± 0.9	59.4 ± 0.9
Exercise load, *% max*	80 ± 4	90 ± 3
Physical condition (score range 1–5)	3.0 ± 0.1	$3.7 \pm 0.2*$
Blood glucose, *mg/dL*	88 ± 1	$93 \pm 1*$
Blood ammonia, *μg/dL*	79 ± 3	82 ± 6
Blood lactate, *mmol/L*	1.2 ± 0.1	1.2 ± 0.1
Hematocrit, *%*	44.9 ± 0.8	$46.8 \pm 0.6*$
WBC, *μL^{-1}*	5300 ± 400	5400 ± 300
RBC, *$10^4/\mu L$*	508 ± 12	$528 \pm 9*$
Platelets, *$10^4/\mu L$*	20.3 ± 0.9	20.2 ± 0.8
Hemoglobin, *g/dL*	15.2 ± 0.2	$15.8 \pm 0.3*$
Serum HDL, *mg/dL*	65 ± 5	63 ± 4
Serum albumin, *g/dL*	5.0 ± 0.1	$5.2 \pm 0.1*$
Serum TC, *mg/dL*	168 ± 7	161 ± 7
BUN, *mg/dL*	17.2 ± 0.7	16.6 ± 0.8
Serum iron, *μg/L*	114 ± 15	99 ± 12
Serum ferritin, *μg/L*	40 ± 6	43 ± 7
Serum CPK, *U/L*	366 ± 52	$198 \pm 22*$
Serum GOT, *U/L*	32 ± 2	$24 \pm 1*$
Serum GPT, *U/L*	28 ± 3	27 ± 5
Serum LDH, *U/L*	365 ± 19	361 ± 16
Serum γ-GTP, *U/L*	25 ± 4	25 ± 3

Subjects ($n = 13$) consumed the 6.6 g/d AA mixture for 30 d; blood samples were taken just before and after the 30-d period. Data are means $\pm$ SEM. *$P < 0.05$ vs. pre-test values. WBC, white blood cells; RBC, red blood cells; HDL, high density lipoproteins; TC, total cholesterol; BUN, blood urea nitrogen; GOT, glutamate-oxaloacetate aminotransferase; GPT, glutamate-pyruvate aminotransferase; LDH, lactate dehydrogenase; γ-GTP, γ-glutamyltranspeptidase. Reproduced from Ohtani et al. (35), with permission.

FIGURE 3 Changes in red blood cell count, hemoglobin, and serum CPK activity in subjects orally administered the AA mixture for 30 d at 2.2 g/d, 4.4 g/d, or 6.6 g/d. Asterisk indicates before-and-after difference ($P < 0.05$, paired *t* test). Reproduced from Ohtani et al. (35), with permission.

TABLE 2

Effect of ingesting the 6.6 g/d dose of the amino acid mixture for 90 d on physical parameters, hematology, and blood biochemistry in elite rugby players

	Sampling time[1]			Statistics[2]	
	Pre (A)	Post (B)	1-y Post (C)	A vs. B	B vs. C
Body weight, *kg*	93.6 ± 2.8	93.5 ± 2.7	93.2 ± 2.6		
BUN, *mg/dL*	16.4 ± 0.8	16.1 ± 0.6	17.7 ± 0.8		*
Creatine, *mg/dL*	1.09 ± 0.04	1.10 ± 0.03	1.14 ± 0.02		*
WBC, *mm³*	5900 ± 200	5400 ± 200	6500 ± 300		*
RBC, *10⁴/μL*	505 ± 7	516 ± 13	490 ± 6	*	*
Hematocrit, *%*	44.5 ± 0.6	46.2 ± 0.5	43.4 ± 0.5	*	*
Hemoglobin, *g/dL*	15.3 ± 0.2	15.6 ± 0.2	14.8 ± 0.2	*	*
Serum iron, *μg/dL*	101 ± 6	121 ± 7	109 ± 9	*	
Total protein, *g/dL*	7.1 ± 0.1	7.2 ± 0.1	7.1 ± 0.1		
Total cholesterol, *mg/L*	169 ± 5	191 ± 8	178 ± 6	*	*
High density lipoprotein, *mg/dL*	52 ± 2	52 ± 2	51 ± 1		
Low density lipoprotein, *mg/dL*	87 ± 6	109 ± 10	101 ± 8	*	
Triglyceride, *mg/dL*	148 ± 18	150 ± 12	129 ± 13		
GOT, *U/L*	28 ± 4	26 ± 2	28 ± 2		
GPT, *U/L*	23 ± 2	21 ± 2	27 ± 4		
γ-GTP, *U/L*	26 ± 2	29 ± 4	39 ± 6		*
Alkaline phosphatase, *U/L*	229 ± 16	171 ± 10	225 ± 22	*	*

[1] The 90-d study period occurred from June through August.
[2] An asterisk indicates a significant difference ($P < 0.05$). BUN, blood urea nitrogen; WBC, white blood cell count; RBC, red blood cell count; GOT, glutamate-oxalacetate aminotransferase; GPT, glutamate-pyruvate aminotransferase; γ-GTP, γ-glutamyl transpeptidase. From Ohtani et al. (36), with permission.

93.6 ± 2.8 kg, and 15.2 ± 0.7%, respectively. Athletes maintained a regular training schedule with their teammates before, during, and after the 90-d trial period. None had taken amino acid supplements in any form before this study.

The subjects were instructed to take a 3.6 g dose of the same AA mixture studied above after morning and evening meals every day for 90 days. Blood samples were collected at the beginning and the end of the 90-d period. A self-assessment of their physical condition was also made at the end of the treatment period. Blood samples were also collected 1 y later.

The results of blood analyses are presented in **Table 2**. Body weight stayed constant throughout the study. Comparing values at the beginning and end of the 90-d trial period, we found that the hematocrit and hemoglobin, iron, total cholesterol, and low-density lipoprotein concentrations were elevated at the end of the trial ($P \leq 0.05$), whereas alkaline phosphatase activity was reduced ($P \leq 0.05$). In addition, the RBC count was reduced ($P \leq 0.05$) 1 y after the withdrawal of the AA mixture administration. These results suggested that the long-term administration of the AA mixture may have increased the production of red blood cells, thereby perhaps enhancing the capacity of the blood to carry oxygen. In this study, rugby players in year-round training were used as experimental subjects. These highly trained athletes reported that the long-term intake of the AA mixture produced a favorable effect on their physical fitness.

In summary, the results of all of our studies suggest that the recovery from muscular fatigue that occurs during exercise training is facilitated by the use of the orally administered AA mixture. Likewise, the AA mixture reduced the damage to muscular integrity that accompanies strenuous exercise. Additionally, the observation that the AA mixture produced favorable changes in indicators of hematopoiesis indicates that,

when used for extended periods, increases in the oxygen-carrying capacity of the blood may occur that further contribute to improved athletic performance.

LITERATURE CITED

1. Titchenal CA. Exercise and food intake: What is the relationship? Sports Med. 1988;6:135–45.

2. Williams MH. Nutritional ergogenics in athletics. J Sports Sci. 1995;13: S63–74.

3. Blomstrand E, Perrett D, Parry-Billings M, Newsholme EA. Effect of sustained exercise on plasma amino acid concentrations and on 5-hydroxytryp-tamine metabolism in six different brain regions in the rat. Acta Physiol Scand. 1989;136:473–81.

4. Smriga M, Kameishi M, Tanaka T, Kondoh T, Torii K. Preference for a solution of branched-chain amino acids plus glutamine and arginine correlates with free running activity in rat. Nutr Neurosci. 2002;5:189–99.

5. Van Haeften TW, Voetberg GA, Gerich JE, van der Veen EA. Dose-response characteristics for arginine-stimulated insulin secretion in man and influence of hyperglycemia. J Clin Endocrinol Metab. 1989;69:1059–64.

6. Maccario M, Procopio M, Loche S, Cappa M, Martina V, Camanni F, Ghigo E. Interaction of free fatty acids and arginine on growth hormone secretion in man. Metabolism. 1994;43:223–6.

7. Giugliano D, Marfella R, Verrazzo G, Acampora R, Coppola L, Cozzolino D. The vascular effects of L-arginine in humans. J Clin Invest. 1997;99:433–8.

8. Schaefer A, Piquard F, Geny B, Doutreleau S, Lampert E, Mettauer B, Lonsdorfer J. L-Arginine reduces exercise–induced increase in plasma lactate and ammonia. Int J Sports Med. 2002;23:403–7.

9. Bergström J, Furst P, Noree LO, Vinnars E. Intracellular free amino acid concentration in human muscle tissue. J Appl Physiol. 1974;36:693–7.

10. Graham TE, Turcotte LP, Kiens B, Richter EA. Training and muscle ammonia and amino acid metabolism in humans during prolonged exercise. J Appl Physiol. 1995;78:725–35.

11. Turinsky J, Long CL. Free amino acids in muscle: effect of muscle fiber population and denervation. Am J Physiol. 1990;258:E485–91.

12. Rowbottom DG, Keast D, Morton AR. The emerging role of glutamine as an indicator of exercise stress and overtraining. Sports Med. 1996;21:80–97.

13. Welbourne TC. Inter-organ glutamine flow in metabolic acidosis. Am J Physiol. 1987;253:F1069–76.

14. Castell LM. Glutamine supplementation in vitro and vivo, in exercise and in immunodepression. Sports Med. 2003;33:323–45.

15. Candeloro N, Bertini I, Melchiorri G, De Lorenzo A. Effects of prolonged administration of branched-chain amino acids on body composition and physical fitness. Minerva Endocrinol. 1995;20:217–23.

16. Freyssenet D, Berthon P, Denis C, Barthelemy JC, Guezennec CY, Chatard JC. Effect of a 6-week endurance training programme and branched-chain amino acid supplementation on histomorphometric characteristics of aged human muscle. Arch Physiol Biochem. 1996;104:157–62.

17. Mourier A, Bigard AX, de Kerviler E, Roger B, Legrand H, Guezennec CY. Combined effects of caloric restriction and branched-chain amino acid supplementation on body composition and exercise performance in elite wrestlers. Int J Sports Med. 1997;18:47–55.

18. Elam RP, Hardin DH, Sutton RAL, Hagen L. Effects of arginine and ornithine on strength, lean body mass and urinary hydroxyproline in adult males. J Sports Med Phys Fitness. 1989;29:52–6.

19. Palloshi A, Fragasso G, Piatti P, Monti LD, Setola E, Valsecchi G, Galluccio E, Chierchia SL, Margonato A. Effect of oral L-arginine on blood pressure and symptoms and endothelial function in patients with systemic hypertension, positive exercise tests, and normal coronary arteries. Am J Cardiol. 2004;93: 933–5.

20. Bednarz B, Jaxa-Chamiec T, Gebalska J, Herbaczynska-Cedro K, Ceremuzynski L. L-arginine supplementation prolongs exercise capacity in congestive heart failure. Kardiol Pol. 2004;60:348–53.

21. Lehmkuhl M, Malone M, Justice B, Trone G, Pistilli E, Vinci D, Haff EK, Kilgore JL, Haff GG. The effects of 8 weeks of creatine monohydrate and glutamine supplementation on body composition and performance measures. J Strength Cond Res. 2003;17:425–38.

22. Candow DG, Chilibeck PD, Bruke DG, Davison KS, Smith-Palmer T. Effect of glutamine supplementation combined with resistance training in young adults. Eur J Appl Physiol. 2001;86:142–9.

23. Ratamess NA, Kraemer WJ, Volek JS, Rubin MR, Gomez AL, French DN, Sharman MJ, McGuigan MM, Scheett T, et al. The effects of amino acid supplementation on muscular performance during resistance training overreaching. J Strength Cond Res. 2003;17:250–8.

24. Scognamiglio R, Negut C, Piccolotto R, Dioguardi FS, Tiengo A, Avogaro A. Effects of oral amino acid supplementation on myocardial function in patients with type 2 diabetes mellitus. Am Heart J. 2004;147:1106–12.

25. Scognamiglio R, Avogaro A, Negut C, Piccolotto R, de Kreutenberg SV, Tiengo A. The effects of oral amino acid intake on ambulatory capacity in elderly subjects. Aging Clin Exp Res. 2004;16:443–7.

26. Doss WS, Karpovich PV. A comparison of concentric, eccentric, and isometric strength of elbow flexors. J Appl Physiol. 1965;20:351–3.

27. Singh M, Karpovich PV. Isotonic and isometric forces of forearm flexors and extensors. J Appl Physiol. 1966;21:1435–7.

28. Komi PV, Buskirk ER. Effect of eccentric and concentric muscle conditioning on tension and electrical activity of human muscle. Ergonomics. 1972;15:417–34.

29. McNeil PL, Khakee R. Disruptions of muscle fiber plasma membranes. Am J Pathol. 1992;140:1097–109.

30. Warren GL, Lowe DA, Hayes DA, Farmer MA, Armstrong RB. Redistribution of cell membrane probes following contraction-induced injury of mouse soleus muscle. Cell Tissue Res. 1995;282:311–20.

31. Byrd SK. Alterations in the sarcoplasmic reticulum: a possible link to exercise-induced muscle damage. Med Sci Sports Exerc. 1992;24:531–6.

32. Armstrong RB, Warren GL, Warren JA. Mechanisms of exercise-induced muscle fibre injury. Sports Med. 1991;12:184–207.

33. Evans WJ, Cannon JG. The metabolic effects of exercise-induced muscle damage. Exerc Sport Sci Rev. 1991;19:99–125.

34. Nosaka K, Clarkson PM. Relationship between post-exercise plasma CPK elevation and muscle mass. Int J Sports Med. 1992;13:471–5.

35. Ohtani M, Maruyama K, Suzuki S, Sugita M, Kobayashi K. Changes in hematological parameters of athletes after receiving daily dose of a mixture of 12 amino acids for one month during the middle- and long-distance running training. Biosci Biotechnol Biochem. 2001;65:348–55.

36. Ohtani M, Maruyama K, Sugita M, Kobayashi K. Amino acid supplementation affects hematological and biochemical parameters in elite rugby players. Biosci Biotechnol Biochem. 2001;65:1970–6.

37. Sugita M, Ohtani M, Ishii N, Maruyama K, Kobayashi K. Effect of a selected amino acid mixture on the recovery from muscle fatigue during and after eccentric contraction exercise training. Biosci Biotechnol Biochem. 2003;67:372–5.

38. Ogilvie R, Armstrong RB, Baird KE, Bottoms C. Lesions in the rat soleus muscle following eccentrically biased exercise. Am J Anat. 1988;182:335–46.

39. Antonio J, Gonyea WJ. Skeletal muscle fiber hyperplasia. Med Sci Sports Exerc. 1993;25:1333–45.

40. Wheat MR, McCoy SL, Barton ED, Starcher BM, Schwane JA. Hydroxylysine excretion does not indicate collagen damage with downhill running in young men. Int J Sports Med. 1989;10:155–60.