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L-Ornithine supplementation attenuates physical fatigue in healthy volunteers by modulating lipid and amino acid metabolism

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Abstract

We examined the effects of L-ornithine administration on physical fatigue. In a double-blind, placebo-controlled, 2-way crossover study, 17 healthy volunteers were randomized to L-ornithine (2000 mg/d for 7 days and 6000 mg/d for 1 day as L-ornithine hydrochloride) or placebo for 8 days. The fatigue-inducing physical task consisted of workload trials on a cycle ergometer at fixed workloads for 2 hours on 2 occasions. We found that oral L-ornithine administration promoted lipid metabolism and activated the urea cycle from serum triacylglycerol, ketone bodies, free fatty acids, and blood ammonia level changing. L-ornithine significantly attenuated the subjective feeling of fatigue (measured by visual analog scale at postrecovery) compared with postload ($P < .01$). Moreover, in female subjects, the subjective feeling of fatigue was significantly lower compared with the placebo group ($P < .05$). In the physical performance test in female subjects, the decrease in mean speed for 10 seconds maximum pedaling from 0.5- to 3.5-hour trials in the group receiving L-ornithine was smaller than that in the group receiving placebo ($P < .05$). These results suggest that L-ornithine has an antifatigue effect by increasing the efficiency of energy consumption and promoting the excretion of ammonia. L-ornithine is a free amino acid and is not rich in meats or fish, so it is difficult to obtain amounts of L-ornithine from ordinary meals that would be sufficient to promote the antifatigue effect. We recommend L-ornithine intake as a nutritional supplement in cases of physical fatigue.

Keywords: Humans; L-ornithine; Lipid metabolism; Ammonia; Performance; Visual analog scale
Abbreviations: BCAA, branched chain amino acid; BUN, blood urea nitrogen; CPK, creatine phosphokinase; TG, triacylglycerol; VAS, visual analog scale

1. Introduction

Fatigue is a common symptom both in sickness and in health [1-3]. Chronic or accumulated fatigue can affect an individual's performance. In addition, long-term accumulated fatigue can lead to *karoshi* (death as a result of overwork). Recently, there has been a great increase in the use of over-the-counter supplements and naturally occurring nutraceuticals for the attenuation of fatigue. However, there are no established treatment recommendation for fatigue. One reason for this has been the lack of standardized fatigue-inducing tasks or appropriate methods for objective quantification of fatigue.

Fatigue is best defined as difficulty in initiating or sustaining voluntary activities [4]. It can be subdivided into physical and mental fatigue. Recently, we succeeded in establishing physical fatigue-inducing tests and in developing some methods for evaluating physical fatigue [5,6]. By using those, we sought to evaluate the effects of a candidate antifatigue substance on physical fatigue.

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Muscular exercise causes rapid adenosine triphosphate consumption, and energy deficiency is an important factor in fatigue [7]. Thus, exogenous dietary substances that can lead to adenosine triphosphate production are considered to be candidate antiphysical fatigue materials.

In addition, physical exercise inducing fatigue elevates blood ammonia level [8], and cerebral ammonia uptake and accumulation during exercise provoke the subjective feeling of fatigue [9].

L-Ornithine is a free amino acid that is not coded for by DNA or involved in protein synthesis. L-Ornithine promotes growth hormone release by stimulating the pituitary gland [10]. Growth hormone promotes the metabolism of carbohydrates, proteins, and lipids [11]. In addition, L-ornithine is one of the products of the action of the enzyme arginase on L-arginine, creating urea. Therefore, L-ornithine is a central part of the urea cycle, which allows for the disposal of excess nitrogen [12]. Therefore, L-ornithine is considered to inhibit the increase in blood ammonia level caused by physical load. L-Ornithine is expected to improve the efficiency of energy production to promote the ammonia detoxification. For these reasons, we investigated the effects of L-ornithine administration on physical fatigue in healthy volunteers.

2. Methods and materials

2.1. Subjects

Seventeen healthy volunteers (40.9 ± 11.8 years of age; 9 women and 8 men; height, 163.6 ± 8.1 cm; body weight, 58.2 ± 9.8 kg; body mass index, 21.7 ± 3.1 kg/m^2 [mean ± SD]) were enrolled in this double-blind, randomized, placebo-controlled, 2-way crossover trial. The participants were recruited using an advertisement. Subjects taking chronic medication, supplemental vitamins, or amino acids; subjects with a body weight less than 40 kg; and subjects who had a blood hemoglobin level less than 12.0 g/dL were excluded. The participants' health status was assessed through physical examination and laboratory examinations, including an electrocardiogram, chest x-ray, blood chemistry panel (glucose, hemoglobin A1c, creatinine, blood urea nitrogen, sodium, potassium, chloride, uric acid, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, and creatine phosphokinase [CPK]), lipid profile (total cholesterol and triacylglycerol [TG]), complete blood count, and urinalysis. The protocol was approved by the Ethics Committee of Soiken Inc. and Soiken Clinic; all subjects gave their written informed consent.

2.2. Experimental design

This study was conducted at Soiken Clinic. After enrollment, the subjects were randomized into 2 groups to receive the following treatments twice a day for 1 week before the experimental day in a double-blind fashion: 2 capsules of 500 mg of L-ornithine hydrochloride (Kyowa Hakko Kogyo Co, Ltd, Tokyo, Japan) or a placebo consisting of 270 mg of crystalline cellulose (JRS Pharma GmbH & Co KG, Rosenberg, Germany). The dose of L-ornithine was based on previous human studies [13,14]. The day before each test day, the subjects finished the same dinner at the designed dinning room by 8:00 PM and then fasted overnight. At 7:15 AM the following morning, the participants were asked to subjectively rate their fatigue level; blood pressure and heart rate were measured; and blood samples were collected. Thereafter, the subjects had breakfast (glucose solution; TRELAN-G 75, Shimizu Pharma, Shizuoka, Japan) for the energy intake and 6 capsules of placebo or L-ornithine. The fatigue-inducing physical task consisted of workload trials on a cycle ergometer (Aerobike 75XL2 ME; Combi Wellness Co, Tokyo, Japan) at fixed workloads to reach 80% of the heart rate at the anaerobic threshold for 2 hours, as described previously [5,15]. This task was repeated twice in each (placebo or L-ornithine) arm of the study. The physical load began at 8:10 AM. Just after the end of the first task section (2-hour load), participants were asked to subjectively rate their fatigue, had their blood pressure and heart rate measured; and had 6 capsules of placebo or L-ornithine. After the end of the last task section (4-hour load), participants were again asked to subjectively rate their fatigue; blood pressure and heart rate were measured; and blood samples were collected. At 1:30 PM, the subjects had the same lunch. After lunch, to recover from fatigue, the subjects read books or magazines, listened to music, or talked until 4:30 PM. After the end of the recovery period, the subjects were again asked to subjectively rate their fatigue; blood pressure and heart rate were measured; and blood samples were collected. During the experiment, the subjects could only consume water and the specified meals. All participants had the same dinner before the test day and the same lunch on the test day. The tests were conducted in a quiet temperature- and humidity-controlled environment. For 1 week before each test, subjects refrained from strenuous physical activity and followed their normal diets,

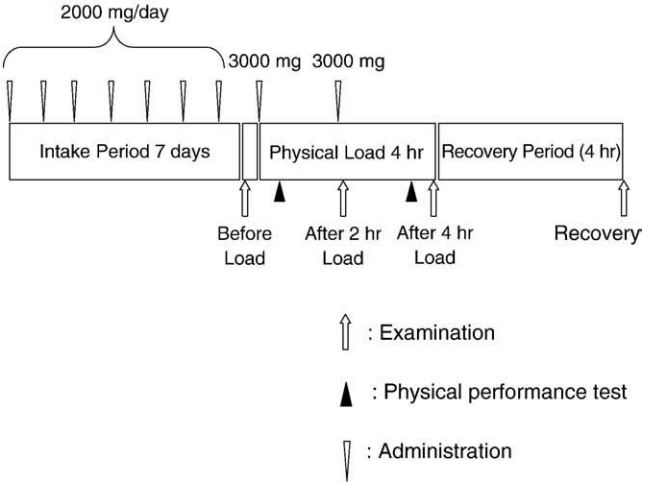

Fig. 1. Study design (effect of L-ornithine on physical fatigue).

as well as their normal drinking and sleeping patterns. The time interval between each test was set at 4 weeks to take into account the female subjects' menstrual cycles. The study design is summarized in Fig. 1.

2.3. Visual analog scale

The subjects were asked to subjectively rate their fatigue level on a visual analog scale (VAS) from 0 (no fatigue) to 100 (total exhaustion) before, during, and after physical exertion and after the recovery period. The VAS was originally developed for measuring pain level [16] and has been used for fatigue level [17].

2.4. Blood sample analyses

Blood samples were collected from the brachial vein; the volume was 30 mL each time. To assess serum blood urea nitrogen (BUN) by an urease–glutamate dehydrogenase method, CPK by a UV method, TG by an enzymatic method, free fatty acids by an enzymatic method, and ketone bodies (acetoacetic acid, 3-hydroxybutyric acid) by a UV method, the blood samples were centrifuged at 1700 × *g* for 10 minutes at 4°C. The blood samples used to determine the plasma glucose levels by a hexonase–glucose-6-phosphate dehydrogenase method were collected in a fluorosodium-containing tube and centrifuged at 1700 × *g* for 10 minutes at 4°C. The blood samples used to determine blood lactate by an enzymatic method and ammonia by a colorimetric method were collected in a 0.8 N perchloric acid-containing tube or phosphotungstic acid and sodium sulfate–containing tube individually and kept on ice until centrifuged at 1700 × *g* for 5 minutes at 4°C. All of the supernatants were stored at −80°C until analyzed. Assays of serum BUN, CPK, TG, free fatty acids, ketone bodies, plasma glucose, and blood lactate and ammonia levels were performed at Sakai Bio-clinical Laboratory, Inc (Osaka, Japan). The blood samples used to determine plasma amino acids and related substances (glycine, alanine, valine, isoleucine, leucine, arginine, tryptophan, proline, urea, citrulline, and ornithine) and were collected in a heparin-containing tube and kept on ice until centrifuged at 1700 × *g* for 10 minutes at 4°C. The plasma sample was deproteinized with 5% sulfosalicylic acid for 30 minutes on ice and centrifuged at 7500 × *g* for 10 minutes at 4°C, and the supernatant was stored at −80°C until analyzed. The concentration of amino acids in the supernatant was measured using HPLC (high performance liquid chromatography) at SRL, Inc (Tokyo, Japan).

Table 1
Effects of L-ornithine on physiological parameters

	Before load	After 2-h load	After 4-h load	Recovery
Heart rate (beat/min)				
L-Ornithine	70 ± 11	76 ± 12	77 ± 12	81 ± 9 [a]
Placebo	69 ± 10	74 ± 10	77 ± 8	78 ± 9
Systolic blood pressure (mm Hg)				
L-Ornithine	111 ± 13	111 ± 9	111 ± 15	113 ± 10
Placebo	114 ± 15	110 ± 12	112 ± 12	112 ± 15
Diastolic blood pressure (mm Hg)				
L-Ornithine	67 ± 8	67 ± 10	62 ± 8	63 ± 11
Placebo	65 ± 10	65 ± 10	63 ± 9	62 ± 8

Values are means ± SD (N = 17).
[a] Value is significantly different ($P < .05$) from the placebo group for each variable, using paired *t* test.

Table 2
Effects of L-ornithine on biochemical parameters

	Before load	After 4-h load	Recovery
BUN (mg/dL)			
L-Ornithine	13.2 ± 3.6	13.1 ± 3.2 [a]	13.0 ± 3.3 [a]
Placebo	12.3 ± 2.7	11.0 ± 2.4	11.4 ± 2.5
CPK (IU/L)			
L-Ornithine	83 ± 23	110 ± 37	121 ± 74
Placebo	85 ± 26	106 ± 34	110 ± 42
Glucose (mg/dL)			
L-Ornithine	99 ± 8	89 ± 7	107 ± 19
Placebo	100 ± 7	86 ± 5	113 ± 17
Lactate (mg/dL)			
L-Ornithine	8.7 ± 3.5	6.9 ± 1.5	8.9 ± 3.1
Placebo	9.1 ± 3.6	7.5 ± 2.2	10.0 ± 2.9
TG (mg/dL)			
L-Ornithine	66 ± 26 [a]	70 ± 29	48 ± 24 [b]
Placebo	79 ± 28	78 ± 37	56 ± 29
FFA (mEq/L)			
L-Ornithine	0.40 ± 0.19 [b]	1.30 ± 0.38	0.06 ± 0.06
Placebo	0.30 ± 0.12	1.31 ± 0.35	0.04 ± 0.04
KB (μmol/L)			
L-Ornithine	74 ± 81 [b]	682 ± 187	15 ± 9
Placebo	32 ± 13	638 ± 221	14 ± 6
AA (μmol/L)			
L-Ornithine	16 ± 10 [a]	100 ± 43	8 ± 4
Placebo	9 ± 4	104 ± 63	9 ± 4
3-OHBA (μmol/L)			
L-Ornithine	57 ± 72 [b]	581 ± 161	7 ± 6
Placebo	23 ± 10	534 ± 175	6 ± 2

Abbreviations: FFA, free fatty acid; KB, ketone body.
Values are means ± SD (N = 17). AA indicates acetoacetic acid; 3-OHBA, 3-hydroxybutyric acid.
[a] Value is significantly different ($P < .01$) from the placebo group for each variable, using paired *t* test.
[b] Value is significantly different ($P < .05$) from the placebo group for each variable, using paired *t* test.

2.5. Physical performance test

The physical performance test is a primary end point for evaluating the antifatigue effect. During the physical performance test, the subjects were asked to perform 10 seconds of maximum pedaling using a cycle ergometer at 0.5 hour after the start of the load (0.5-hour trial) and 0.5 hour before the end of the load (3.5-hour trial). The torque of each subject was calculated as 8.5% of body weight for male subjects and 7.5% of body weight for female subjects. We evaluated fatigue levels by the decrease in pedaling speed from 0.5 to 3.5-hour trials.

2.6. Statistical analyses

The values are shown as mean ± SD. Paired *t* tests were used to evaluate the significance of differences between the

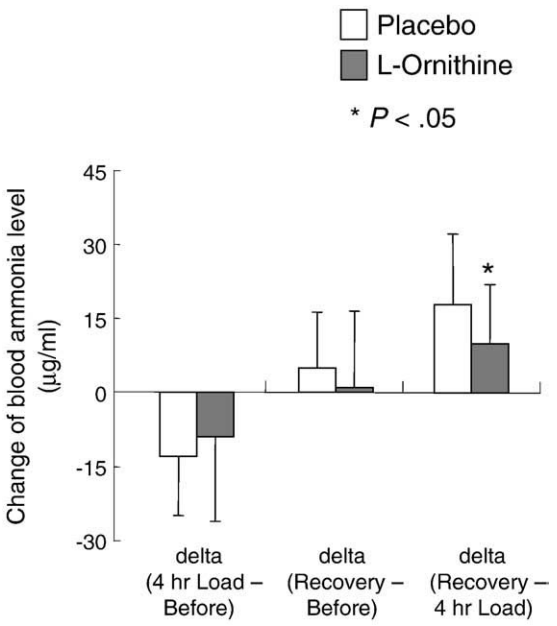

Fig. 2. Effect of L-ornithine administration on blood ammonia level.

placebo and L-ornithine groups with statistical software (SPSS Ver. 11.5). Analysis of variance for repeated measurements with Bonferroni post test was used to evaluate the significance of differences between each examination point in individual groups. All P values were 2-tailed; P values less than .05 were considered to be statistically significant.

3. Results

3.1. Physiological examination

Physiological parameters after L-ornithine administration are summarized in Table 1. Systolic blood pressure and diastolic blood pressure did not differ among the 2 groups at any examination points. Heart rate in the L-ornithine group was higher than in the placebo group.

3.2. Visual analog scale

The VAS score for 'fatigue feeling' in the L-ornithine group was not changed compared with that in the placebo group at any examination points. In females, however, the increase in fatigue feeling from preload to postrecovery was smaller in the L-ornithine group (1.89 ± 2.95) compared with the placebo group (3.62 ± 2.83) ($P < .05$). In the L-ornithine group, fatigue feeling at postrecovery (7.46 ± 1.42) was significantly lower compared with at postload (6.32 ± 1.99) ($P < .01$), but in the placebo group, the difference was not observed between the examination points.

3.3. Blood biochemistry

Biochemical and metabolic parameters after L-ornithine administration are summarized in Table 2. The 2 groups did not differ with respect to serum CPK, plasma glucose, or blood lactate levels at any examination points. However, at preload after 7-day administration, serum TG was lower and serum free fatty acid and ketone bodies were higher in the L-ornithine group than in the placebo group. In addition, serum BUN was higher at postload and postrecovery. The change of blood ammonia level from postload to postrecovery was lower in the L-ornithine group than in the placebo group, as shown in Fig. 2.

Plasma amino acids after L-ornithine administration are summarized in Table 3. Plasma ornithine was higher in the L-ornithine group than in the placebo group at all examination points. Plasma glycine level was lower at preload and postload, alanine level was higher and tryptophan was lower at postrecovery, branched chain amino acid (BCAA; valine, isoleucine, leucine) levels were higher at postload, proline was lower at preload and higher at post-load, and urea was higher at preload and postload in the L-ornithine group compared with values in the placebo group.

Table 3
Effects of L-ornithine on plasma amino acids

	Before load	After 4-h load	Recovery
Glycine (nmol/mL)			
L-Ornithine	231.5 ± 44.0 [a]	186.9 ± 37.4 [a]	196.6 ± 32.7
Placebo	248.6 ± 38.2	204.3 ± 40.1	207.6 ± 38.9
Alanine (nmol/mL)			
L-Ornithine	349.1 ± 69.8	277.9 ± 65.6	309.2 ± 42.1 [a]
Placebo	390.3 ± 90.5	259.5 ± 76.1	289.6 ± 55.9
Valine (nmol/mL)			
L-Ornithine	217.1 ± 35.8	200.8 ± 35.2 [a]	174.8 ± 26.6
Placebo	210.7 ± 35.5	192.3 ± 28.5	169.3 ± 29.3
Isoleucine (nmol/mL)			
L-Ornithine	59.8 ± 11.8	61.7 ± 12.1 [a]	40.3 ± 5.8
Placebo	57.2 ± 10.0	56.6 ± 8.8	39.2 ± 7.7
Leucine (nmol/mL)			
L-Ornithine	117.0 ± 23.3	118.6 ± 22.9 [a]	75.8 ± 12.1
Placebo	110.4 ± 18.9	108.9 ± 17.1	72.1 ± 15.2
Arginine (nmol/mL)			
L-Ornithine	94.7 ± 19.5	82.4 ± 18.9	62.4 ± 11.6
Placebo	95.1 ± 16.1	82.1 ± 16.1	67.0 ± 12.3
Tryptophan (nmol/mL)			
L-Ornithine	49.0 ± 8.3	32.5 ± 4.2	43.7 ± 5.1 [a]
Placebo	50.4 ± 6.3	33.3 ± 5.5	47.5 ± 5.8
Proline (nmol/mL)			
L-Ornithine	138.5 ± 32.7 [a]	127.3 ± 29.1 [b]	107.1 ± 25.0
Placebo	152.5 ± 47.7	113.7 ± 35.9	105.6 ± 29.9
Urea (nmol/mL)			
L-Ornithine	4625.4 ± 1355.5	4662.3 ± 1217.1 [b]	4473.4 ± 1185.2 [a]
Placebo	4261.9 ± 967.6	3884.8 ± 788.2	4003.2 ± 879.8
Citrulline (nmol/mL)			
L-Ornithine	30.8 ± 5.4	30.9 ± 5.0	23.4 ± 4.5
Placebo	29.8 ± 5.9	30.0 ± 4.9	22.9 ± 3.4
Ornithine (nmol/mL)			
L-Ornithine	52.5 ± 9.5 [a]	168.4 ± 47.4 [b]	74.3 ± 11.9 [b]
Placebo	47.8 ± 8.8	40.6 ± 7.4	44.8 ± 8.6

Values are means ± SD (N = 17).

[a] Value is significantly different ($P < .05$) from the placebo group for each variable, using paired t test.

[b] Value is significantly different ($P < .01$) from the placebo group for each variable, using paired t test.

Table 4
Effects of L-ornithine on subjects' performance during physical load

	At 0.5-h trial	At 3.5-h trial	Decrease
Mean speed all subjects (rpm)			
L-Ornithine	54.0 ± 23.6	52.0 ± 23.6	−2.0 ± 8.1
Placebo	54.1 ± 21.6	49.5 ± 25.8	−4.6 ± 8.4
Mean speed male (rpm)			
L-Ornithine	72.5 ± 20.9	70.3 ± 20.7	−2.1 ± 11.3
Placebo	71.9 ± 17.7	67.8 ± 25.9	−4.1 ± 12.1
Mean speed female (rpm)			
L-Ornithine	37.6 ± 9.4	35.8 ± 10.3	−1.8 ± 4.4 [a]
Placebo	38.3 ± 8.0	33.2 ± 10.7	−5.1 ± 3.7

Values are means ± SD (N = 17). During the physical tests, subjects were asked to perform a 10-second maximum-pedaling trial using a cycle ergometer at 0.5 hour (0.5-hour trial) after the start of load and at 0.5 hour before the end of load (3.5-hour trial).

[a] Value is significantly different ($P < .05$) from the placebo group for each variable, using paired t test.

3.4. Physical performance test

The performance of the 2 groups during the physical tests is summarized in Table 4. The decrease in mean speed for 10 seconds of maximum pedaling from 0.5- to 3.5-hour trials in the female group receiving L-ornithine was smaller than that in the group receiving placebo, as shown in Table 4.

4. Discussion

Acute fatigue is a physiological phenomenon that disappears after a certain period of rest. In contrast, however, long-term fatigue sometimes causes irreversible damage, and the compensation mechanisms that function in recovery from acute fatigue are no longer effective. Therefore, the development of clinically proven antifatigue agents is very important.

To assess the effect of substances on physical fatigue, it is important to evaluate energy metabolism under the physical load, the subjects' performance, and the subjective feeling of fatigue, as was done in the current study. L-ornithine has the potential for activating the urea cycle and lipid metabolism, so it is a suitable candidate for an antifatigue agent. We investigated the effect of L-ornithine on physical fatigue in this study by physical performance, fatigue feeling, and biochemical parameter.

Serum TG level decreased and serum free fatty acids and ketone bodies increased after a 7-day L-ornithine (2000 mg/d) administration. L-Ornithine is known to release growth hormone [18], which promotes lipid oxidation [19]. Therefore, these results suggest that L-ornithine promoted growth hormone release by stimulating the pituitary gland, and growth hormone is reported to activate the synthesis of free fatty acids and glycerol from fatty tissues [20]. Our findings suggest that L-ornithine plays an important role related to energy production. In addition, plasma ornithine and urea levels were higher in the L-ornithine group. It has been reported that L-ornithine activates the urea cycle in rat liver and the synthesis of urea by activating carbamoyl phosphate synthase [21]. These results show that L-ornithine administration promoted the urea cycle. However, levels of the other players in the urea cycle, arginine and citrulline, did not differ in the 2 groups. The turnovers of arginine and citrulline in the urea cycle were apparently so high that those changes were not detected. The change of blood ammonia level from postload to postrecovery was lower in the L-ornithine group than in the placebo group. L-ornithine administration suppresses the increase in blood ammonia level after exercise in rats [22] and activates the urea cycle with arginine in renal-insufficient rats [23]. This result suggests that L-ornithine administration in humans promoted the urea cycle and suppressed the increase in blood ammonia level after exercise. Moreover, in the L-ornithine group, plasma alanine and urea levels were higher, which were both final products of the ammonia detoxification process. Plasma BCAA levels increased in the L-ornithine group compared with the placebo group. The BCAA are major amino acids composing the muscle and are used as an energy source during exercise. L-Ornithine may suppress the BCAA decrease in muscle produced by exercise. Plasma tryptophan level decreased in the L-ornithine group. Tryptophan is a precursor of serotonin in the brain, and it is believed that brain serotonin level relates to the feeling of fatigue. It is known that blood BCAA and free tryptophan compete for transport through the blood–brain barrier because they are carried by the same transport system [24]. The plasma BCAA increase produced by L-ornithine administration may attenuate the feeling of fatigue. Plasma alanine levels increased after the recovery period in the L-ornithine group. L-ornithine administration may activate the glucose alanine cycle.

To evaluate the subjects' physical performance, we performed 10-second maximum-pedaling trials using a cycle ergometer during the fatigue-inducing physical tests. L-Ornithine improved physical performance during fatigue-inducing workload tests on a cycle ergometer in females. In terms of the subjective fatigue feeling, L-ornithine improved the VAS score during the recovery period in females. In this study, the effect of L-ornithine on physical fatigue was more remarkable in females than in males. In this study, plasma L-ornithine levels were higher in females than in males. If the plasma L-ornithine level remained higher, the effects might have been detected in males. Further studies, for example, study of higher dose or larger number volunteers, may be required.

We demonstrated that oral L-ornithine administration promoted lipid metabolism, activated the urea cycle, and in females improved fatigue feeling and physical performance. These findings suggest that L-ornithine has the potential of attenuating fatigue by promoting catabolism of lipids and proteins. The role of L-ornithine has not been reported, except with regard to the urea cycle. In this study, it was suggested that L-ornithine promoted lipid metabolism, improved energy production, and attenuated fatigue. To avoid long-term fatigue, it is important to develop effective strategies that

attenuate fatigue; L-ornithine use may prevent the unfavorable consequences of accumulated physical fatigue.

In conclusion, these results suggest that L-ornithine administration promotes lipid metabolism and activates the urea cycle. Moreover, in females, it decreases the impairment of performance caused by physical fatigue. L-Ornithine is contained in *Corbicula japonica* or dried *Lentinula edodes*, but it is not abundant in meats or fishes because of a free amino acid. It is difficult to obtain sufficient amounts of L-ornithine from ordinary meals for antifatigue. In this study, we used L-ornithine synthesized by the fermentation method. We recommend L-ornithine intake as a nutritional supplement in cases of fatigue.

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