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Effects of Oral Supplementation with Cystine and Theanine on the Immune Function of Athletes in Endurance Exercise: Randomized, Double-Blind, Placebo-Controlled Trial

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Athletes become increasingly susceptible to infection with intense training that results in immune suppression. The immune state was investigated after administering cystine/theanine (CT), which has been reported to have an immune reinforcement effect, to athletes before training involving a prolonged period of intense exercise. Fifteen long-distance runners were each allocated to the CT or placebo group, and the test food was ingested for 10 d prior to the start of training. Clinical examinations were performed before and after the training. The results indicate a significant increase in the high-sensitivity C-reactive protein (hs-CRP) and neutrophil count in the blood, as well as a decreasing tendency for lymphocytes in the placebo group, but not the CT group. These observations suggest that the ingestion of CT contributed to suppressing the change in inflammatory response, prevented a decrease in the immune function, and prevented infection and reduced symptoms when infected associated with continuous intense exercise.

Key words: cystine; theanine; exercise; immune function; inflammatory

We have been engaged in studies on the actions and effects of amino acids (including BCAA, arginine, and glutamine) on athletes[1–3] to supplement the many of has studies.[4–6]

Cystine, a dipeptide of the sulfur amino acid, cysteine, is a precursor of glutathione (GSH) that is responsible for the antioxidative response inside the body, and its supply is limited in the synthesis of GSH.[7] On the other hand, theanine is an amino acid abundant in green tea and is known to be metabolized to glutamic acid and ethylamine within the intestinal tract, liver, *etc.*[8,9] A recent experiment on mice has indicated that an oral administration of cystine and theanine (cystine/theanine) reinforced GSH synthesis and the humoral immune response after antigen stimulation, and as a result reinforced the antigen-specific antibody production.[10] In addition, a clinical study on humans reported by Miyagawa *et al.* indicated that an oral administration of cystine/theanine improved antibody production in the elderly with a lowered immune function at the time of flu vaccination.[11] However, the actions and effects of cystine/theanine on athletes have not previously been reported.

It has been reported that athletes often experience an overtraining syndrome by which they are unable to sufficiently recover their physical condition after a certain period of intense, strenuous exercise.[12,13] This is due to lowered immunity, increasing the likeliness of infectious diseases (diarrhea, fever, pharyngitis, and symptoms of the common cold, *etc.*) and causing a prolonged period of fatigue and reduced physical performance. As the mechanism underlying this phenomenon, it has been reported that such prolonged periods of intense endurance exercise are accompanied by an increase in inflammatory cytokine concentration, causing an immunosuppressive effect.[14,15] This immunosuppressive effect has also been reported to cause athletes to be more susceptible to infectious diseases of the respiratory system due to viral infection after intense exercise.[16–19]

We, therefore, analyzed the effects of cystine/theanine on the immune state and inflammatory response of long-distance runners before and after participation in training, by which intense prolonged endurance exercise could be expected to lower the athletes' immune function.

Materials and Methods

Procedures. This experiment was performed in accordance with the principles of the Declaration of Helsinki, and with the approval of the institutional review board (IRB) of Juntendo University School of Health & Sports Science as a randomized, double-blind, placebo-controlled, parallel-group study.

Subjects. The subjects were 15 male long-distance runners, members of the Juntendo University Track and Field team, attending a summer training camp held in Shibetsu City, Hokkaido, Japan. Each subject signed a voluntary informed consent form, which was reviewed and approved by IRB and supplied by the investigator and doctor in attendance for this experiment when registering for the study, as well as receiving a detailed explanation regarding the contents of the study. The 15 subjects were distributed evenly between two groups considering their age and personal best time for the 5,000 m run. Eight

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subjects were assigned to the cystine/theanine (CT) group and 7 subjects were assigned to the placebo (P) control group (average age, 20.7 ± 0.3; average weight, 57.3 ± 0.8 kg; personal best time for 5,000 m run, 13 min 36 s 51 ms to 14 min 40 s 26 ms; average, 14 min 18 s 64 ms ± 5 s 01 ms). The subjects all stayed in a dormitory close to the campus and their lifestyle, including meals and exercise before and during the training camp, was the same among all subjects.

Dosage and method. With reference to the previous report by Miyakawa *et al.*,[11] the active ingredients included in CT food consisted of 700 mg of cystine and 280 mg of theanine per pack (per day), and was in granular form. P food was also in granular form and contained 950 mg of crystalline cellulose and 50 mg of monosodium glutamate. The subjects ingested the CT or P food from 5–14 September 2007 for 10 d after dinner every day before the summer training camp. The subjects were prohibited from taking other amino acids, proteins, or creatine 5 d before the starting date until the end of the study.

Amount of exercise. The 15 subjects took part in practice sessions at Juntendo University School of Health & Sports Science for 10 d from 5–14 September 2007, and at the training camp in Shibetsu City, Hokkaido, Japan, for 11 d from 15–25 September 2007; all 15 subjects had approximately the same workload. Generally, morning practice and main practice took place every day both before and during the training. The total distance run by the subjects for the 10 d before the training camp was an average of 152.2 km (an average of 15.2 km/d), and for the 11 d during the training camp was an average of 198.7 km (an average of 18.1 km/d). The main program of exercise before the training camp was as follows: 10 September, 60-min cross-country run; 11 September, 1,000-m interval runs 10 times; 12 September, 90-min cross-country run; 13 September, 12,000-m paced running. The main program of exercise during the training was as follows: 15 September, 20-km run; 16 September, 22-km run; 18 September, 80-min cross-country run; 19 September, 22 km run in the morning and 25-km run in the afternoon; 22 September, 35-km run.

Test schedule and analysis parameters. The test food was ingested for only 10 d prior to the training camp, and blood and saliva samples were collected on 13 and 29 September 2007 immediately before and after the training camp. The blood and saliva samples were collected at 06:00 after waking up and before the subjects had eaten anything or engaged in any form of exercise. The parameters measured from the blood samples were 12 items as part of a general peripheral blood test: red blood cells (RBC), hemoglobin (Hgb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelets, white blood cells (WBC), eosinophils, neutrophils, lymphocytes, and monocytes. In addition, 25 items were included in the general biochemical examination: total protein (TP), albumin (Alb), urea nitrogen (UN), creatinine (Cre), total cholesterol (T-Cho), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), cholinesterase (ChE), γ-glutamyl transpeptidase (γ-GTP), creatine phosphokinase (CPK), sodium (Na), chlorine (Cl), potassium (K), calcium (Ca), magnesium (Mg), iron (Fe), total iron-binding capacity (TIBC), unsaturated iron-binding capacity (UIBC), myoglobin (Mb), and ferritin. Four items were measured in the inflammatory reaction/immunological function test: high-sensitivity C-reactive protein (hs-CRP), interleukin (IL)-6, IL-8, and natural killer (NK) cell activity. Two items were examined in tests using saliva: cortisol and immunoglobulin A (IgA). Thus, a total of 43 items were measured. During the period of 21 d before and during the training camp, we surveyed the subjects' temperature, pulse rate, and general health status every day on waking. The survey consisted of 13 items: sleeping condition, general malaise, sore throat, symptoms of a cold, muscle ache or joint pain, appetite, diarrhea, constipation, general feeling, weight gain or loss, fever, nausea or vomiting and headache, and the subjects were asked to self-evaluate each symptom with a score between 1 and 5, with 1 indicating no symptom. The analyses were performed by referring to a study of the rate of infection with a cold,[20,21] and poor physical condition was defined as follows: standard 1, body temperature above 37.0°C and at least one day where more than 2 items scored above 2; standard 2, at least one day where more than 3 items scored above 2. Based on this definition, the frequency of poor physical condition was calculated for both the CT and P groups.

Statistical analysis. Each value is shown as the mean ± SEM. The pre- and post-training camp data for each group were compared for statistical significance by using the paired *t*-test or Wilcoxon's signed rank test. Comparisons between the groups on the days blood and saliva samples were collected were performed by using the *t*-test or Mann-Whitney rank sum test. A statistical analysis of differences in the frequency of poor health conditions between the two groups based on the survey was performed by using Fisher's exact test. All statistical analyses were performed by using SigmaStat3.1 software (Systat Software, Inc., Richmond, CA), and $P < 0.05$ is taken to indicate significance.

Results

The blood test results shown in Fig. 1A and B indicate significant increases in the neutrophil count and hs-CRP after the training camp in the P group ($P = 0.018$ and $P = 0.047$, respectively), but not in the CT group ($P = 0.460$ and $P = 0.688$, respectively). A decreasing trend in lymphocyte count after the training camp was observed only in the P group ($P = 0.087$) (Fig. 1C). Table 1 shows the results from all other blood and saliva tests performed in this study. In the general peripheral blood test, Hct and MCV had decreased significantly

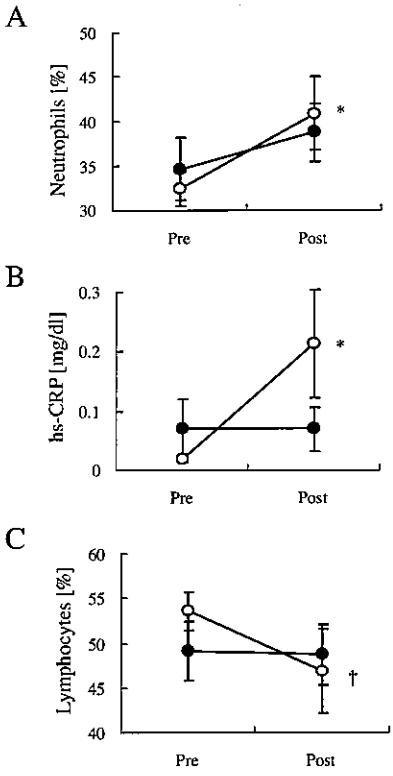

Fig. 1. Effects of CT Supplementation on the Neutrophil, hs-CRP, and Lymphocyte Levels in the Subjects Pre- and Post-Training.

The placebo group (unfilled circles) shows significant increases in neutrophils (A) and hs-CRP (B) after the training, although no significant changes were apparent in the CT group (filled circles). The lymphocyte number (C) tended to have decreased in the placebo group after training, although no significant change was apparent in the CT group. Each value represents the mean ± SEM. $^*P < 0.05$ and $^\dagger P < 0.1$ compared with pre-training.

Table 1. Effects of CT Supplementation on Parameters in the Subjects Pre- and Post-Training

			Placebo		Cystine/Theanine	
			Pre	Post	Pre	Post
Hematological parameters	RBC	[$\times 10^6$/μl]	5.01 ± 0.08	4.96 ± 0.12	4.99 ± 0.08	4.91 ± 0.09
	Hgb	[g/dl]	14.63 ± 0.22	14.60 ± 0.33	15.09 ± 0.26	14.61 ± 0.33
	Hct	[%]	45.31 ± 0.45	43.97 ± 0.82*	46.79 ± 0.63	44.24 ± 0.84**
	MCV	[fl]	90.43 ± 1.13	88.57 ± 1.38*	94.00 ± 1.00#	90.25 ± 1.03***,##
	MCH	[pg]	29.24 ± 0.43	29.43 ± 0.36	30.26 ± 0.24#	29.75 ± 0.33*,#
	MCHC	[%]	32.29 ± 0.24	33.20 ± 0.24*	32.24 ± 0.25	33.01 ± 0.24**,##
	Platelets	[$\times 10^4$/μl]	21.83 ± 1.75	21.23 ± 1.49	23.49 ± 0.90	23.13 ± 0.89
	WBC	[$\times 10^3$/μl]	5.17 ± 0.29	5.50 ± 0.43	5.99 ± 0.39	6.10 ± 0.33
	Eosinophils	[%]	4.00 ± 1.05	3.29 ± 0.75	6.25 ± 1.25	5.50 ± 1.21
	Neutrophils	[%]	34.00 ± 1.95	43.14 ± 4.46*	37.25 ± 3.35	40.13 ± 3.39
	Lymphocytes	[%]	53.57 ± 2.05	46.86 ± 4.72	49.13 ± 3.32	48.75 ± 3.40
	Monocytes	[%]	7.57 ± 0.48	6.29 ± 0.99	6.38 ± 0.89	5.25 ± 0.65
Biochemical parameters	TP	[g/dl]	6.96 ± 0.13	7.03 ± 0.13	6.83 ± 0.14	6.86 ± 0.11
	Alb	[g/dl]	4.56 ± 0.07	4.46 ± 0.06	4.38 ± 0.05	4.33 ± 0.05
	UN	[mg/dl]	14.29 ± 1.15	15.14 ± 0.60	13.75 ± 0.98	16.38 ± 0.53**,##
	Cre	[mg/dl]	0.82 ± 0.05	0.77 ± 0.03*	0.80 ± 0.03	0.77 ± 0.03
	T-Cho	[mg/dl]	172.29 ± 6.76	177.71 ± 11.41	164.13 ± 5.45	183.75 ± 11.26
	LDL-C	[mg/dl]	85.14 ± 6.76	86.43 ± 8.73	88.50 ± 2.56	99.13 ± 9.47
	HDL-C	[mg/dl]	75.00 ± 4.70	76.43 ± 4.66	60.13 ± 4.60#	65.00 ± 4.54*,#
	TG	[mg/dl]	59.57 ± 3.79	78.71 ± 8.65	81.50 ± 11.83	120.75 ± 23.02
	GOT	[IU/l]	24.43 ± 1.13	31.86 ± 4.83	23.88 ± 2.54	32.75 ± 5.04*
	GPT	[IU/l]	17.00 ± 1.09	25.29 ± 3.15*	21.88 ± 1.87#	34.38 ± 5.21*,#
	ALP	[IU/l]	257.29 ± 20.85	290.14 ± 29.46*	276.88 ± 21.97	300.75 ± 26.25
	LDH	[IU/l]	195.43 ± 9.87	204.00 ± 12.18	200.13 ± 14.24	208.38 ± 26.97
	ChE	[$\times 10^3$ IU/l]	4.75 ± 0.02	4.63 ± 0.03	4.35 ± 0.02	4.40 ± 0.02
	-GTP	[IU/l]	19.43 ± 2.05	19.86 ± 2.21	23.13 ± 2.45	24.63 ± 3.08
	CPK	[IU/l]	280.43 ± 31.88	383.43 ± 111.94	270.63 ± 43.66	408.75 ± 75.21
	Na	[mEq/l]	141.00 ± 0.22	141.71 ± 0.29	140.38 ± 0.57	141.25 ± 0.41
	Cl	[mEq/l]	104.43 ± 0.43	104.00 ± 0.54	104.38 ± 0.57	103.88 ± 0.48
	K	[mEq/l]	4.20 ± 0.06	4.14 ± 0.07	4.25 ± 0.11	4.33 ± 0.10
	Ca	[mg/dl]	9.99 ± 0.10	9.66 ± 0.07*	9.60 ± 0.11#	9.45 ± 0.07
	Mg	[mg/dl]	2.37 ± 0.04	2.27 ± 0.04	2.30 ± 0.04	4.99 ± 2.72
	Fe	[μg/dl]	103.29 ± 17.54	55.86 ± 7.66*	68.38 ± 4.85	52.88 ± 7.01
	TIBC	[μg/dl]	303.14 ± 8.28	312.57 ± 10.87	298.63 ± 11.95	317.25 ± 8.13*,#
	UIBC	[μg/dl]	199.86 ± 18.68	256.71 ± 15.02*	230.25 ± 14.08	264.38 ± 11.86**,##
	Mb	[ng/dl]	32.14 ± 2.39	31.86 ± 3.34	30.63 ± 3.34	29.00 ± 2.94
	Ferritin	[ng/dl]	65.14 ± 12.36	53.86 ± 11.39*	62.38 ± 7.42	44.63 ± 6.84*,#
Inflammatory and immune parameters	hs-CRP	[mg/dl]	0.02 ± 0.01	0.21 ± 0.09*	0.07 ± 0.05	0.07 ± 0.04
	IL-6	[pg/ml]	1.19 ± 0.40	1.21 ± 0.40	1.40 ± 0.43	0.86 ± 0.13
	IL-8	[pg/ml]	8.17 ± 0.17	8.53 ± 0.53	8.00 ± 0.00	8.00 ± 0.00
	NK cell activity	[%]	18.57 ± 3.76	30.57 ± 3.19*	34.13 ± 3.56#	44.38 ± 3.02*,##
Salivary parameters	Cortisol	[μg/dl]	0.40 ± 0.06	0.42 ± 0.10	0.41 ± 0.06	0.42 ± 0.06
	IgA	[μg/ml]	210.13 ± 17.40	211.81 ± 28.25	250.50 ± 37.71	227.97 ± 20.29

Each value represents the mean ± SEM.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared with the pre-training figures in each group.
#$P < 0.05$, ##$P < 0.01$ compared with the placebo group in the pre- or post-training figures.

after the training camp in both groups, and MCHC had increased in both groups. There was a significant decrease in MCH after the training camp in the CT group only, but the MCH value in the CT group was significantly higher than that in the P group before the training camp. In the general biochemical tests, UN had increased significantly after the training camp only in the CT group, and Cre had decreased significantly after the training camp only in the P group. HDL-C was significantly lower in the CT group as compared to the P group before the training camp, and HDL-C had significantly increased only in the CT group after the training camp. GPT had increased significantly after the training camp in both groups, while ALP had increased significantly only in the P group, although an increasing trend was observed in the CT group. Ca and Fe had decreased significantly after the training camp only in the P group; however, the values for Ca and Fe were already significantly lower or tended to be lower in the P group than in the CT group before the training camp. TIBC and UIBC had both increased after the training camp in both groups. The ferritin level had decreased significantly after the training camp in both groups. In the inflammatory reaction/immunological function test, the NK cell activity had increased significantly after the training camp in both groups, and was significantly higher in the CT group than in the P group before and after the training camp. No changes were apparent in the items included in the saliva test.

The results of the survey indicate poor physical condition classified as standard 1 in 2 of the 7 subjects in the P group (28.6%) during the training camp and in 1

of the 8 subjects in the CT group (12.5%). Poor physical condition classified as standard 2 was seen in 2 of the 7 subjects in the P group (28.6%) and in 2 of the 8 subjects in the CT group (25.0%).

Discussion

The lymphocyte count and leukocyte fraction are commonly used indices to judge the immune state of healthy adult individuals including athletes.[22] After intense exercise, the lymphocyte count is known to decrease because of a lowered immune function, and the neutrophil count increases due to inflammation and infection, so the neutrophil fraction of leukocytes increases. In the present study, as shown in Fig. 1, a decreasing trend in lymphocyte count was observed only in the P group after the end of the training camp. The relationship between the GSH concentration and lymphocyte count and its function have been reported based on analyses using animal models.[23,24] This study also suggested the possible effect of CT ingestion in preventing the lymphocyte count reduction due to an increased GSH concentration in the body. In the mouse model, CT ingestion induced GSH synthesis and augmented humoral immunity.[10] Furthermore, CT ingestion increased the specific antibody production against influenza vaccination in elderly persons.[11] Including the present study, these results suggest that CT ingestion and induce increased B lymphocyte proliferation and improve the immune functions disrupted by aging or intense exercise. The neutrophil count and hs-CRP had both increased significantly after the training camp only in the P group. The neutrophil count is known to increase after intense exercise,[22] and the increase in hs-CRP is thought to be due to the inflammatory response after exercising. Inflammatory responses involving neutrophils have been reported to be regulated by GSH[25–27] and therefore the ingestion of CT is thought to suppress excessive growth or the infiltration of neutrophils as well as excessive inflammatory responses. Disruption of the skeletal muscles induced by intense exercise is partially due to excessive inflammatory responses and subsequent neutrophil infiltration into the tissue.[18] Therefore, CT ingestion may inhibit the inflammatory-induced disruption of skeletal muscles immediately after intense exercise.

As shown in Table 1, the Hct, MCV, MCHC, Fe, UIBC, and ferritin levels had increased or decreased significantly after the training camp in both groups. These changes were observed for both groups, and this appears to have been because of the mild anemia caused by the continued intense exercise during the training camp. MCH had significantly decreased after the training camp only in the CT group, but as there was no significant difference in the Hgb value, anemia appears not to have been induced by CT ingestion. The indices of hepatic function (GPT and ALP) showed significant increases after the training camp or an increasing trend in both groups. This was also likely to have been caused by the intense exercise, similarly to the indices related to anemia. UN had significantly increased after the training camp only in the CT group, and not in the P group. On the other hand, Cre showed a significant decrease after the training camp only in the P group. These observations indicate that CT ingestion did not affect the renal function, because both UN and Cre are indicators of this. Ca had significantly decreased after the training camp only in the P group, and not in the CT group. It has been reported that the blood Ca concentration was decreased by training with intense exercise.[28,29] These findings suggest that CT ingestion may contribute to the maintenance of calcium homeostasis. HDL-C had significantly increased after the training camp in the CT group. Including the effects on calcium homeostasis post mentioned, the working mechanism for CT is still unclear, although the results suggest that CT ingestion prevented the reduced immune function as well as improving the overall condition of the body, including the nutritional state. In the present study, the NK cell activity had significantly increased after the training camp in both groups, but the CT group had a higher value than the P group both before and after the training camp. The higher NK cell activity in the CT group compared with P group at the end of the training camp is thought to reflect the basal activity before training camp. The NK cell activity is known to decrease below the base level immediately after intense exercise.[22] We, therefore, were unable to observe the effects of CT on NK cell activity with the design of this experiment. There were no symptoms of physical deconditioning or low-performance in the CT group (data not shown), although some blood parameters (*e.g.*, HDL-C, GPT and NK cell activity) had significant changed in the CT group when compared with the P group before the training camp.

The results of this study also suggest that CT ingestion may be effective for preventing fever or poor physical condition, as well as for reducing the symptoms of infectious diseases. These observations agree with the results indicated by the clinical tests already discussed, and support the suggestion that CT ingestion prevented lowering of the immune function following the training camp. There were no harmful effects of ingesting CT in this study. In addition, a clinical study for the elderly by Miyagawa *et al.* has indicated that there were no adverse effects from 2 weeks of daily CT ingestion.[11] These findings suggest that CT would be a safe supplement for not only the elderly but also athletes.

These findings suggest that CT ingestion was safe and prevented changes in the inflammatory responses after prolonged, intense endurance exercise such as that in the present long-distance relay race training camp, as well as preventing lowering of the immune state, and contributed to the prevention of infectious diseases as well as reducing their symptoms.

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