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The effect of histidine on mental fatigue and cognitive performance in subjects with high fatigue and sleep disruption scores

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HIGHLIGHTS

- Histidine decreased the POMS fatigue score in men feeling fatigue and drowsiness.
- Histidine shortened reaction times on a cognitive function battery test.
- Histidine increased sensations of clear thinking and of attentiveness.

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ABSTRACT

Our previous study reported that a dried bonito broth known in Japan as 'dashi' improved or ameliorated mood states, including fatigue, during the daily lives of human subjects. Histidine is an amino acid that is present in dried bonito broth, and we sought to evaluate whether histidine would affect feelings of fatigue in humans. We investigated the effects of histidine intake on the feeling of fatigue, mood states and mental task performance by performing a placebo-controlled, double-blind crossover trial. Twenty subjects with high fatigue and sleep disruption scores were asked to ingest histidine or a placebo every day for two weeks. The subjects' mood states were evaluated using the Profile of Mood States (POMS) scale and a visual analog scale (VAS) for eight feelings (fatigue, depression, carelessness, drowsiness, clear thinking, motivation, attentiveness and concentration). We also measured subjects' cognitive performance using the CogHealth test battery. The fatigue T-scores on the POMS test decreased significantly following histidine ingestion compared to placebo ingestion ($p < 0.05$). After two weeks of histidine ingestion, the reaction time for the working memory task in the CogHealth test battery was significantly shorten compared to placebo ingestion. The VAS scores for clear thinking and for attentiveness were increased significantly following histidine ingestion compared to placebo ingestion ($p < 0.05$). These results suggest that daily ingestion of histidine may ameliorate feelings of fatigue, increase performance during working memory tasks, and improve the clear thinking and attentiveness.

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1. Introduction

Fatigue is a common sensation that is caused by a variety of activities associated with daily life, although fatigue is also associated with psychiatric and other medical conditions [1]. Fatigue is associated with reduced physical activity, drowsiness, and a desire to rest and is caused by mental and physical workloads [2]. Mental fatigue is defined as a psychobiological state caused by a prolonged period of demanding cognitive activity [3], and it is measured as a reduction in the ability to perform mental tasks. Working on cognitively demanding tasks for a considerable amount of time often leads to mental fatigue, which can impact task performance [4]. Several studies have reported that sleep disruptions, which may induce mental fatigue [5,6], decrease cognitive functioning and psychomotor vigilance task (PVT) performance [7,8]. Although mental fatigue is a very common phenomenon in modern, everyday life, very little is known about the psychophysiological mechanisms underlying mental fatigue [9]. Moreover, despite the many studies on fatigue, it is remarkably difficult to understand mental fatigue and the cognitive processes underlying its behavioral manifestations [4].

In Japan, bonito (skipjack tuna; *Katsuwonus pelamis*) is among the most commonly consumed fish, and dried bonito broth is used more frequently than beef or chicken bouillon for soup stock [10,11]. Dried bonito is called katsuobushi, and its broth is called dashi; both ingredients are commonly used in traditional Japanese meals [12]. Several studies have reported improvements in or amelioration of mood states,

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including feelings of fatigue in daily life, and in mental task performance following ingestion of dried bonito broth (DBB) [10,11,12,13,14]. In particular, ingestion of DBB has been shown to improve scores for the six mood factors, including the feeling of fatigue and the total mood disturbance, on the Profile of Mood States (POMS) questionnaire in young women [11]. DBB ingestion also improved the scores for the feeling of fatigue and for total mood disturbance among middle-aged subjects with a high fatigue score, as shown by poorer mental task performance (Uchida-Kraepelin psychodiagnostic test score) [10]. DBB contains abundant quantities of histidine, as histidine makes up approximately 10% of its dry matter [15], and histidine is the precursor of histamine, which functions as a neurotransmitter in the brain.

Neuronal histamine has been implicated in a variety of brain functions. Central histaminergic neurons are located exclusively in the tuberomammillary nucleus of the posterior hypothalamus, and they project extensively throughout the brain [16,17]. Neural histamine acts as a neurotransmitter through four types of histamine receptors. Histamine H1 receptors moderate a variety of physiological functions, including wakefulness, appetite, cognition and emotion [18]. Indeed, object recognition and Barnes maze performance were found to be significantly impaired in both H1 receptor knockout and H2 receptor knockout mice [19]. The nucleus accumbens is the brain region that controls motivation, and the striatum is the region that controls psychomotor function [18,20,21]; stress alters the turnover of histamine in the brain, and acute stress increases the levels of histamine and histamine-degrading enzymes in the diencephalon, nucleus accumbens and striatum [22]. Furthermore, chronic restraint stress has been shown to increase the levels of histamine-degrading enzymes in the nucleus accumbens and striatum in Fischer rats [23]. It is also known that chronic stress often results in depression and chronic fatigue syndrome in humans [1,24,25], and both of these conditions promote low motivation and body-dragging [1,24].

In humans, neural histamine modulates a variety of physiological functions, such as wakefulness, learning and memory, and emotions [18]. Depressed patients show decreased brain histamine H1 receptor binding, and this decrease correlates with the severity of depression symptoms [25]. A histamine H1 receptor blocker induces drowsiness and decreases psychomotor performance [26]. Antihistamines prolong the braking reaction time when subjects experience dual-task interference while driving [27] and are known to increase tiredness and impair cognitive functions [18,26,27].

Oral amino acids are absorbed into the blood from the small intestine, and histidine has been reported to cross the blood–brain barrier in mammals [28,29,30]. These findings suggest that ingesting histidine, the precursor of histamine, may increase brain histamine levels and reduce mental fatigue in humans.

Based on the results of these previous studies, we hypothesized that histidine intake could ameliorate the feeling of fatigue and improve mental task performance in subjects with a feeling of fatigue or mental fatigue. In the present study, we examined the effects of daily histidine ingestion on the feeling of fatigue and on mental task performance using a placebo-controlled, double-blind study of middle-aged subjects who had high fatigue scores on the Japanese version of the POMS questionnaire [31] and high sleep disorder scores on the Pittsburgh sleep quality index (PSQI) [32]. We evaluated subjects' feelings of fatigue using the POMS questionnaire and measured their performances of mental tasks using simple card game tests called the CogHealth test battery. We also measured some mental states that could be accompanied by activation of histaminergic neurons using the visual analog scale (VAS).

2. Materials and methods

2.1. Participants

The subjects included 20 healthy adult men (45 to 65 years old) with high fatigue scores on the POMS questionnaire (over 16 points) and the PSQI (over 5 points). A fatigue score greater than 16 points on the POMS questionnaire indicates that the study subject had greater feelings of fatigue than normal Japanese individuals, and a PSQI score greater than 5 points indicates that the study subject sleeps poorly and frequently experiences mental fatigue [5,6]. We excluded people with a history of a chronic disease that is correlated with fatigue, smokers, those who regularly consumed energy drinks, and those who regularly consumed fish containing high concentrations of free histidine. No study subject had sleep apnea. This study was approved by the Ethics Review Committee of the Shinkokai C'est La Vie Shinbashi Clinic Medical Corporation. After the purpose, procedures and schedule of the study were explained, informed consent was obtained from all subjects, in accordance with the Helsinki Declaration. Twenty men were enrolled as study subjects and randomly divided into two groups, group A and group B. The baseline data regarding age, physical characteristics, mood factors, and sleep-state scores for the study subjects are shown in Table 1.

2.2. Test samples

The test samples were prepared as follows. A 1.65-g quantity of L-histidine (Ajinomoto Co., Inc., Tokyo, Japan) was compressed into 5 hard gelatin capsules. To prepare the placebo, an equal volume of cellulose (1.00 g) was compressed into 5 capsules. Both sample types were packaged in identical aluminum pouches; the L-histidine samples and the placebo samples were indistinguishable. The study subjects ingested capsules containing either the test substance or the placebo once daily, in the morning. We hypothesized that the optimal time for treatment with histidine would be in the morning because histaminergic neuronal activity shows a clear circadian rhythm, with high levels during the active period [20].

2.3. Study protocol

The subjects were randomly divided into two groups, groups A and B. During the first experimental period, subjects in group A ingested one package of the test sample per day, in the morning after their regular breakfasts, for 2 weeks, and those in group B ingested the placebo samples. A 2-week washout period was followed by a second experimental period, in which the groups were reversed. To ensure that the subjects actually took the capsules, we required them to record their intake daily and to submit their records with all empty capsule packages and spares. The POMS test, the VAS and the cognitive assessment task were administered before and after both experimental periods. All assessments were performed at the same time on Saturday mornings (from 7:30 to 11:30 AM). All measurements were performed in a

Table 1
Baseline data for the study subjects.

	Group A	Group B	*p* value	All subjects
	Mean + SD	Mean + SD		Mean + SD
Parameter				
Number	10	10		20
Age	51.9 ± 4.8	51.0 ± 4.5	0.671	51.5 ± 4.6
Height (cm)	172.2 ± 6.3	171.8 ± 4.6	0.857	172.0 ± 5.4
Weight (kg)	77.2 ± 7.4	73.3 ± 11.9	0.388	75.3 ± 9.9
BMI	26.0 ± 2.2	24.9 ± 4.2	0.448	25.5 ± 3.3
POMS				
Tension–anxiety	20.90 ± 6.31	17.80 ± 5.85	0.254	19.35 ± 6.13
Depression–dejection	30.50 ± 16.13	21.90 ± 7.71	0.271	26.20 ± 13.07
Anger–hostility	29.00 ± 11.25	19.90 ± 6.87	0.059	24.45 ± 10.21
Vigor	9.90 ± 4.48	7.50 ± 4.97	0.222	8.70 ± 4.77
Fatigue	20.50 ± 3.84	19.50 ± 4.14	0.616	20.00 ± 3.92
Confusion	18.10 ± 5.57	15.00 ± 5.16	0.224	16.55 ± 5.46
PSQI	8.50 ± 1.96	8.60 ± 2.95	0.930	8.55 ± 2.44

p value; comparisons between groups were made with unpaired Student's t-tests.

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