Relieving Occupational Fatigue by Consumption of a Beverage Containing γ-Amino Butyric Acid

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Summary To elucidate the effect of γ-aminobutyric acid (GABA) on both psychological and physical fatigue and on the performance advances for task solving, we assigned an arithmetic task for the Uchida-Kraepelin Psychodiagnostic Test (UKT) to 30 healthy Japanese subjects, 9 of whom were diagnosed as having chronic fatigue. The subjects were administered 250 mL of a test beverage containing GABA at the dose of 0, 25, and 50 mg before assigning the task for the UKT. Psychological fatigue assessed by the Visual Analogue Scale (VAS) was significantly lower in the group administrated the beverage containing 50 mg GABA than in the control group (p<0.05). The results of the Profile of Mood States (POMS) also indicated that psychological fatigue was significantly reduced in the 50-mg-GABA group. The salivary secretion levels of chromogranin A and cortisol—markers of physical fatigue—in both 25-mg and 50-mg-GABA groups were significantly lower than those in the control group. The 50-mg-GABA group also showed higher score on UKT by solving the arithmetic task more accurately than the control group (p<0.01). The results suggest that intake of GABA-containing beverages, especially those containing 50 mg of GABA, may help reduce both psychological and physical fatigue and improve task-solving ability.

Key Words GABA, psychological fatigue, cortisol, chromogranin A, concentration

In recent years, the number of individuals being subjected to various stresses at workplaces, schools, homes, etc., has been increasing. An epidemiological study conducted between 1999 and 2004 by the Fatigue Study Group in the Ministry of Education, Culture, Sports, Science and Technology reported on the domestic economic loss associated with chronic fatigue and estimated that those populations would reach around 1.2 trillion JPY per year (1).

According to another epidemiological survey conducted in Japan in 1999 by the Study Group on Fatigue in the Ministry of the Health, Labour and Welfare, about 60% of working individuals experienced fatigue, and of these, more than 50% had experienced long-term chronic fatigue lasting for at least 6 mo (1).

Most of the individuals with subjective symptoms of fatigue feel they are producing poorer activities than in their previous state and experiencing lowered working ability (1), and about 0.3% of these individuals were diagnosed as having chronic fatigue syndrome.

According to the National Institute of Health, fatigue can be a normal and important response to physical exertion, emotional stress, boredom, or lack of sleep. However, it can also be a nonspecific sign of a serious psychological or physical disorder. Individuals with chronic fatigue who remain untreated are at a higher risk of developing diseases such as depression, eating disorders, and sleep disorders. Reducing fatigue and maintaining a balanced and healthy diet is desirable to ensure productivity in daily life.

γ-Aminobutyric acid (GABA), converted from glutamic acid, was found in the mammalian brain (2). GABA is one of the major inhibitory neurotransmitters in the central nervous system and has been found in several peripheral tissues (3, 4). In addition, GABA is known to mediate presynaptic inhibition of primary afferent fibers in the motor system and may be involved in postsynaptic forms of motor neuron inhibition (5). Amino acid neurotransmitters are critical for the proper functioning of the central nervous system (CNS): this is because they exert fast actions, produce responses within a few milliseconds, and play an important role in brain functions and neurological diseases (6). GABA not only regulates cardiovascular (7–10) and pituitary functions and modulates renal function (11) but also inhibits metastasis of cancer cells (12).

Several studies have reported the effects of GABA on relaxation and stress reduction. Abdou et al. found that oral administration of GABA significantly (i) increased α-waves and decreased β-waves in the brain and (ii) maintained salivary immunoglobulin A (IgA) levels.
when subjects were subjected to stress conditions such as crossing a suspended bridge (13). Their study indicated that GABA could induce relaxation by diminishing anxiety while enhancing immunity under stress conditions.

Cortisol is the main glucocorticoid hormone that is produced in the adrenal cortex and is released in response to various mental and physical stresses via the hypothalamic-pituitary-adrenal axis (15). Several studies have reported that psychological stress affects the secretion of salivary cortisol in response to anticipation of negative events such as academic examinations (16–19). The salivary cortisol levels in women awaiting surgery, i.e., fine-needle aspiration for the diagnosis of a lump in the breast, were found to be higher than those in the control subjects who were physically examined (20).

CgA that is released with catecholamine is the major acid-soluble protein in catecholamine-storage vehicles of the adrenal medulla (21–24) and sympathetic nerve (25, 26). CgA is ubiquitously secreted in many kinds of tissues (27) and has been recently found to be present in human submandibular glands and saliva (28).

In this study, we determined the effect of a GABA-containing beverage on the feelings of individuals with chronic fatigue after task performance.

**MATERIALS AND METHODS**

Being a non-invasive procedure, measurement of salivary CgA is now being used as an indicator of stress. Many studies have been performed to measure a variety of stressors in humans: stress-relief effects of spa bathing (29), effects of laughter (30), and effects of administration of certain amino acids (31).

**Test samples.** GABA was obtained from Pharma Foods International Co., Ltd. (Kyoto, Japan; Product name: PharmaGABA™). It is produced by a fermentation process using a strain of lactic acid bacteria, Lactobacillus hilgardii K-3. A basic formulation of the test sample was a common type of hypotonic beverage consisting of invert sugar, a flavoring agent, citrate, and an alternative sweetener. GABA was added to the test sample so that the final concentration was 25 mg GABA: 50 mg sample. The effective dose of GABA used in our study was around 20–50 mg, because several reports have suggested that 26.4 mg GABA (32), 30 mg GABA (33), and 25–50 mg GABA (34) were effective.

The nutritional constituents of the test beverage are shown in Table 1.

**Screening of the subjects.** In all, 30 healthy Japanese individuals (16 males and 14 females; age range, 24–43 y; average age, 31.7 y) who volunteered to participate in this study were included. None of the subjects had a history of behavioral disturbance, drug or alcohol abuse, diabetes, or other pre-existing medical conditions. The participants were forbidden to eat, drink, or use any form of tobacco 2 h before the start of the experiment.

In order to screen the subjects who had chronic fatigue, the health and psychological statuses of the participants were assessed by using the following 3 validated methods: the Profile of Mood States (POMS), the checklist for the degree of fatigue by self-diagnosis, and the Visual Analogue Scale (VAS). The POMS has 6 subscales: confusion, fatigue, vigor, depression-dejection, anger-hostility, and tension-anxiety. Japanese version #850 of the POMS (Kaneko Shobo Co., Ltd., Tokyo, Japan), consisting of 65 questions regarding the current mood states scored at 5 levels from 0 (not at all) to 4 (extremely), was used. Level scale was calculated and converted to T-scores according to the conversion table provided in the instructions.

The checklist for the degree of fatigue by self-diagnosis consists of 20 questions regarding the psychosomatic state. Each question is scored at 5 levels from 0 (not at all) to 4 (very strong).

The subjects were also evaluated for the intensity of fatigue by using a 100-mm VAS scale (from 0 = no symptoms to 100 = contented with life), as per a previous method (35).

The inclusion criteria for the study subjects were as follows: more than 75 points on the POMS score (without vigor score); more than 50 mm on the VAS scale; and more than 9.6 points on the degree of fatigue by self-diagnosis. All 3 measurements were conducted on a weekly basis over a 4-wk period. Before the start of the study, on the day of examination at 9:00 a.m., the subjects were asked to fill out the questionnaires in a quiet air-conditioned room. Individuals who met one of the above-mentioned criteria each time throughout the study period were selected as subjects who experienced chronic fatigue on a daily basis.

The study was approved by the Ethics Committee of the Pharma Foods International Co., Ltd., which follows the code of the Declaration of Helsinki.

**The self-diagnostic questionnaires.** The self-diagnostic questionnaires (36) consist of 30 questions. Questionnaires on self-diagnostic fatigue are divided into 3 categories: “Drowsiness and lassitude,” “Difficulty of attention concentration,” and “Localized physical discomfort,” which are evaluated simultaneously. The subjects filled out the self-diagnostic questionnaires by marking ○ or × on the basis of the level of fatigue experienced at the time of the test. The total number of ○ was counted while analyzing the responses to the questionnaire. Furthermore, we asked the subjects about their condition.

**Task load study.** The study was conducted as a single...
blind, crossover trial throughout the 3 wk. The Uchida-Kraepelin Psychodiagnostic Test (UKT) (37, 38), an arithmetic task to induce mental stress, was used to assess the effects of GABA on the subjects. VAS was conducted 3 times, i.e., before intake of the test beverage, at the midpoint of the task, and after the completion of the task. The POMS was measured twice, i.e., before and after task performance. After the subjects filled out the forms for POMS and VAS, they were administered 3 different types of beverages: control (containing no GABA), 25 mg GABA, or 50 mg GABA dissolved in 250 mg of beverage. After 15 min, subjects performed the UKT for 15 min (first half). At a 5-min interval, the remaining half of the task was completed. Differences in the POMS T-scores between before and after the UKT were calculated. Differences in the VAS scores before and after the UKT were also calculated as follows: differences before and after the first half, before and after the second half, and before the first half and after the second half.

**Measurement of salivary CgA and cortisol levels.** Concentration of salivary CgA and cortisol was measured at 3 points: before the intake of the test beverage, at the midpoint of the task, and after the completion of the task. The salivary samples were collected using a specific saliva-sampling device, the Salivette® (SARSTEDT, Nümbrecht, Germany). Each subject was asked to chew a cotton roll for 45 s. Each cotton roll soaked with the saliva was placed in a container and sealed with a plastic stopper, centrifuged at 1,000 × g for 5 min, and stored at −20°C until analysis. Some precautions were taken to reduce the factors that affect saliva sampling: subjects were asked to refrain from eating 60 min before sample collection, avoid alcohol intake for 24 h, maintain good oral health, and avoid teeth brushing or oral abrasion. Concentrations of CgA were measured by using a Human Chromogranin A Enzyme Immunoassay (EIA) kit (Yanaihara Institute Inc., Shizuoka, Japan). Cortisol levels were assayed by using the Expanded Range High Sensitivity Salivary Cortisol Enzyme Immunoassay kit (Salimetrics LLC, State College, PA).

**Statistical analysis.** All values are presented as means±SE. Significant differences between the means in the control group and those in the 25-mg and 50-mg-GABA groups (POMS, VAS, CgA, Cortisol, Subjective symptoms, and UKT) were evaluated using Dunnett’s test. A probability value of less than 5% was considered to indicate a significant difference. Data were analyzed by KaleidaGraph® version 4.0 (Synergy Software, Reading, PA, USA).

**RESULTS**

**Changes in mood measured on VAS and POMS**

Figure 1 shows the changes in VAS scores of the 9 subjects who were selected as having chronic fatigue by prior screening. In the first half, difference in the fatigue scores before and after the UKT task were lower in the 50-mg-GABA group, whereas the differences were higher in the control group or the 25-mg-GABA group.

![](images/fig1.png)

Fig. 1. Change in VAS scores after administration of the UKT. We analyzed the differences before the UKT and after the first half of the test (First half), after the first half of the UKT and after the second half of the test (Second half), and before the UKT and after the second half of the test (Total). Control, 25 mg GABA, 50 mg GABA. Mean (SE); n=9. *Significant vs. the control group (p<0.01).

The changes in the values of the 50-mg-GABA group were significantly different from those of the control (p<0.05). In the 50-mg-GABA group, the range of decrease in the difference in the VAS score before and after the UKT task in the second half was greater than that in the first half, and the range of decrease in the values throughout the first and second halves was additively enhanced in total. In the case of both the values for the second half and the total score, the differences in the VAS scores of the 50-mg-GABA group were significantly different from those of the control group (p<0.01). Meanwhile, there was no apparent decrease in the scores for the control or the 25-mg-GABA group.

Table 2 shows the change in the POMS scores of the 9 subjects. Differences in the fatigue T-scores before and after the UKT task decreased in the 50-mg-GABA group, whereas the differences increased in the control or the 25-mg-GABA group. The change in the difference in the values of the 50-mg-GABA group was significantly different from that of the control group (p<0.01).

**Change in salivary CgA and cortisol levels**

Changes in the salivary CgA levels are shown in Fig. 2i. Salivary samples from the control group showed significant increase in the levels of CgA both in the first and second half of the UKT task compared to those before the UKT task. In other words, salivary samples from 25-mg-GABA group showed significantly lower CgA levels than those of the control group (after the first half of the UKT task, p<0.01; after the second half, p<0.05). This tendency was more pronounced in the 50-mg-GABA group (after the first half, p<0.01; after the second half, p<0.05).

Changes in salivary cortisol levels are shown in Fig. 2ii. Similar results were obtained to those for the CgA levels. Cortisol levels in the salivary samples of the 25-
Table 2. Change in the Profile of Mood States (POMS) T-scores before and after the administration of the UKT.

<table>
<thead>
<tr>
<th>Mood</th>
<th>Ingested sample</th>
<th>Before the UKT</th>
<th>After the UKT</th>
<th>Changed value</th>
<th>p value vs. Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tension-anxiety</td>
<td>Control</td>
<td>56.11 (4.76)</td>
<td>58.89 (5.11)</td>
<td>2.78 (3.90)</td>
<td>0.9247</td>
</tr>
<tr>
<td></td>
<td>25 mg GABA</td>
<td>53.56 (4.94)</td>
<td>54.89 (4.80)</td>
<td>1.33 (0.85)</td>
<td>0.7003</td>
</tr>
<tr>
<td></td>
<td>50 mg GABA</td>
<td>55.22 (4.67)</td>
<td>54.89 (4.78)</td>
<td>-0.33 (1.50)</td>
<td>0.7003</td>
</tr>
<tr>
<td>Depression-dejection</td>
<td>Control</td>
<td>56.89 (4.73)</td>
<td>60.11 (4.58)</td>
<td>3.22 (1.96)</td>
<td>0.9855</td>
</tr>
<tr>
<td></td>
<td>25 mg GABA</td>
<td>54.22 (5.06)</td>
<td>57.00 (4.59)</td>
<td>2.78 (1.79)</td>
<td>0.2463</td>
</tr>
<tr>
<td></td>
<td>50 mg GABA</td>
<td>56.89 (4.55)</td>
<td>55.56 (5.18)</td>
<td>-1.33 (1.41)</td>
<td>0.2463</td>
</tr>
<tr>
<td>Anger-hostility</td>
<td>Control</td>
<td>49.89 (4.13)</td>
<td>50.44 (4.34)</td>
<td>0.56 (0.82)</td>
<td>0.8611</td>
</tr>
<tr>
<td></td>
<td>25 mg GABA</td>
<td>50.67 (4.86)</td>
<td>50.44 (4.89)</td>
<td>-0.22 (0.95)</td>
<td>0.8164</td>
</tr>
<tr>
<td></td>
<td>50 mg GABA</td>
<td>52.22 (4.90)</td>
<td>51.11 (4.55)</td>
<td>-0.11 (0.79)</td>
<td>0.8164</td>
</tr>
<tr>
<td>Vigor</td>
<td>Control</td>
<td>42.56 (4.50)</td>
<td>45.33 (4.46)</td>
<td>2.78 (0.86)</td>
<td>0.6072</td>
</tr>
<tr>
<td></td>
<td>25 mg GABA</td>
<td>41.78 (4.58)</td>
<td>43.22 (4.55)</td>
<td>1.44 (0.47)</td>
<td>0.2693</td>
</tr>
<tr>
<td></td>
<td>50 mg GABA</td>
<td>41.89 (4.23)</td>
<td>42.44 (4.58)</td>
<td>0.56 (1.20)</td>
<td>0.2693</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Control</td>
<td>56.44 (4.91)</td>
<td>60.44 (4.46)</td>
<td>4.00 (1.34)</td>
<td>0.4746</td>
</tr>
<tr>
<td></td>
<td>25 mg GABA</td>
<td>57.78 (4.29)</td>
<td>60.33 (3.93)</td>
<td>2.56 (0.73)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>50 mg GABA</td>
<td>58.67 (4.07)</td>
<td>53.56 (4.33)</td>
<td>-5.11 (0.89)</td>
<td>0.6499</td>
</tr>
<tr>
<td>Confusion</td>
<td>Control</td>
<td>57.11 (5.26)</td>
<td>57.33 (5.34)</td>
<td>0.22 (1.35)</td>
<td>0.8958</td>
</tr>
<tr>
<td></td>
<td>25 mg GABA</td>
<td>55.67 (4.46)</td>
<td>54.33 (4.68)</td>
<td>-1.33 (0.99)</td>
<td>0.8958</td>
</tr>
<tr>
<td></td>
<td>50 mg GABA</td>
<td>58.11 (4.54)</td>
<td>59.11 (4.06)</td>
<td>1.00 (0.97)</td>
<td>0.8958</td>
</tr>
<tr>
<td>Total mood disturbance</td>
<td>Control</td>
<td>233.89 (22.57)</td>
<td>241.89 (21.60)</td>
<td>8.00 (6.89)</td>
<td>0.8504</td>
</tr>
<tr>
<td></td>
<td>25 mg GABA</td>
<td>230.11 (22.15)</td>
<td>233.78 (21.73)</td>
<td>3.67 (4.10)</td>
<td>0.1958</td>
</tr>
<tr>
<td></td>
<td>50 mg GABA</td>
<td>239.22 (20.96)</td>
<td>232.78 (21.71)</td>
<td>-6.44 (4.51)</td>
<td>0.1958</td>
</tr>
</tbody>
</table>

Mean (SE); n=9.

Fig. 2. Changes in salivary hormone levels before, after the first half, and after the second half of the UKT. We compared the salivary levels of chromogranin A (i) and cortisol (ii) after the UKT with those of before the test. Control, 25 mg GABA, 50 mg GABA. Mean (SE); n=9. *Significant vs. the control group (p<0.01). **Significant vs. the control group (p<0.05).

Fig. 3. Change in the subjective symptom score after the administration of the UKT. We analyzed the differences in the subjective symptom scores before and after the administration of the UKT (Control, 25 mg GABA, 50 mg GABA. Mean (SE); n=9. *Significant vs. the control group (p<0.01).
The ingestion of 50 mg GABA significantly reduced the scores for nerve strain and tended to show decreased scores for psychological fatigue in a survey conducted using a self-diagnostic questionnaire in subjects with chronic fatigue. The scores for physical fatigue tended to be lower in the subjects with chronic fatigue but not in those without chronic fatigue. The reason for this difference is not clear. Further study is required to clarify the detailed mechanism underlying this finding.

The ingestion of 25 mg GABA did not affect the fatigue levels. On the basis of the results of this study, GABA was found to have considerable relieving effect on fatigue in the subjects with chronic fatigue, and a high dose of GABA (50 mg per dose) was found to relieve both psychological and physical stress. The ingestion of 50 mg GABA significantly increased the number of correct answers; this implies that GABA improves task performance by relieving stress and psychological and physical fatigue.

Yokogoshi reported the presence of radioisotope-labeled GABA in the liver, kidney, and urine, but not in the brain, of individuals who were administered GABA (39). Ingested GABA may probably not reach the brain by crossing the blood-brain barrier. Yokogoshi also reported that the serum levels of ingested GABA peaked between 30 and 60 min in rats (39). We assume that GABA does not exert its psychological and physical action directly in the brain but exerts it indirectly during the absorption in the alimentary tract, because ingested GABA is not detected in the brain (39).

This study revealed the efficacy of GABA on reducing stress and enhancing performance in subjects who are physically and emotionally stressed. GABA exerted a high level of stress relief in individuals who were exhausted, as well as showed as high level of efficiency-enhancing effect in stressed individuals compared with those who did not have any stress. Thus, individuals with chronic fatigue can be assumed to be deficient in GABA. In fact, GABA concentration in the cerebral fluid and blood of individuals with mood disorders such as depression has been reported to be lower (40–43).

Furthermore, reduction of subjective fatigue and enhanced performance suggest that orally administered GABA acts directly on the central nervous system. In fact, oral administration of GABA increases the frequency of α-waves (44), and some reports suggest improved cerebral blood flow with GABA ingestion (45); all these findings suggest the advantageous effect of GABA on the central nervous system.

Although further investigation is required to determine the mechanism underlying GABA action, our present findings show that ingestion of a hypotonic beverage containing 50 mg GABA could reduce not only psychological but also physical stress and relieve the feelings of chronic occupational fatigue, and conse-

**DISCUSSION**

Cortisol is the main glucocorticoid hormone that is produced in the adrenal cortex and is released in response to various mental and physical stresses via the hypothalamic-pituitary-adrenal axis (19). Several studies analyzed the relationship between salivary cortisol secretion and psychological stress. Salivary cortisol secretion was affected in response to anticipation of negative events such as academic examinations (20–23).

The ingestion of 50 mg GABA significantly decreased the scores for nerve strain and tended to show decreased scores for psychological fatigue in a survey conducted using a self-diagnostic questionnaire in subjects with chronic fatigue. The scores for physical fatigue tended to be lower in the subjects with chronic fatigue but not in those without chronic fatigue. The reason for this difference is not clear. Further study is required to clarify the detailed mechanism underlying this finding.

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Although further investigation is required to determine the mechanism underlying GABA action, our present findings show that ingestion of a hypotonic beverage containing 50 mg GABA could reduce not only psychological but also physical stress and relieve the feelings of chronic occupational fatigue, and conse-

**Table 3. Evaluation of performance on the UKT.** We analyzed the number of correct answers on the UKT and evaluated the performance of the subjects administered GABA.

<table>
<thead>
<tr>
<th>Ingested sample</th>
<th>Correct answers</th>
<th>p value vs. Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1979.8 (259.0)</td>
<td></td>
</tr>
<tr>
<td>25 mg GABA</td>
<td>1990.3 (260.9)</td>
<td>0.9557</td>
</tr>
<tr>
<td>50 mg GABA</td>
<td>2123.7 (267.6)</td>
<td>0.0033</td>
</tr>
</tbody>
</table>

Mean (SE); n=9.
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REFERENCES


