Journal of Traditional and Complementary Medicine 6 (2016) 66–71

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Journal of Traditional and Complementary Medicine

journal homepage: http://www.elsevier.com/locate/jtcme

Original article

Effects of white rice containing enriched gamma-aminobutyric acid on blood pressure

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ARTICLE INFO

Article history:
Received 7 August 2014
Received in revised form
3 September 2014
Accepted 28 September 2014
Available online 8 January 2015

Keywords:
gamma-aminobutyric acid
gamma-aminobutyric acid-enriched white rice
home blood pressure
morning blood pressure
white rice

ABSTRACT

Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter with beneficial effects including antihypertension and antistress properties. In this study, we examined the effects of GABA-enriched white rice (GABA rice) on blood pressure (BP) in 39 mildly hypertensive adults in a randomized, double-blind, placebo-controlled study. The participants were divided into a test group ($n = 22$) who consumed rice with 11.2 mg GABA/100 g of rice and a placebo group ($n = 17$) who consumed rice with 2.7 mg GABA/100 g of rice. For 8 weeks, the participants took 150 g of either the GABA rice or the placebo rice. Hematological examinations were performed on both groups at 0, 4, and 8 weeks after the start of rice consumption. Home BP was self-measured two times daily, morning and evening, from 1 weeks before to 2 weeks after the intervention. Although the hospital BP and evening BP measurements of the participants showed no significant change, consumption of the GABA rice improved the morning BP compared with the placebo rice after the 1st week and during the 6th and 8th weeks. These results showed the possibility that the GABA rice improves morning hypertension.

1. Introduction

An increase in average blood pressure (BP), that is, hypertension, is a major cause of cardiovascular disease, and it can result in an increased risk of cardiovascular mortality. Several studies have shown that variations in BP are linked to the progression of organ damage and can trigger vascular events.[1] Similar to hypertension, the combined effects of smoking, dyslipidemia, diabetes, and other lifestyle-related disorders contribute to the early onset of severe diseases such as coronary atherosclerosis, angina pectoris, myocardial infarction, coronary artery disease, cardiac failure, and arrhythmia.[2]

Functional foods that can reduce the occurrence of hypertension are being extensively studied and developed. For example, several fish-derived peptides were found to be effective in reducing BP in rats by inhibiting the activity of angiotensin-converting enzyme.[3] Glycoside extracts of *Eucommia* leaf was reported to induce an antihypertensive effect by relaxing vascular smooth muscles through a direct action on the parasympathetic nervous system.[4] Various functional foods that can effectively reduce hypertension using gamma-aminobutyric acid (GABA) as the principle active component are also being developed.[5,6]

GABA is an amino acid that is present in high concentrations in mammalian brains, and it is also known to be present in plants. GABA is biosynthesized from glutamic acid by the action of glutamic acid decarboxylase (GAD), and it is metabolized by transamination by the catalyzing effects of GABA transaminase to yield succinic semialdehyde or succinic acid, which then enters the citric acid pathway.[7] GABA has been demonstrated to be a typical inhibitory neurotransmitter in the central nervous system. However, it is also active and found in the peripheral nerve or tissues. GABA receptors have also been found in heart muscles.[8] In addition, GABA is found to have antistress effects.[9] However, GABA does not pass through the blood–brain barrier,[10] and because the peak concentration of GABA in blood lasts only for approximately 30–60

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Peer review under responsibility of The Center for Food and Biomolecules, National Taiwan University.

http://dx.doi.org/10.1016/j.jtcme.2014.11.022

minutes, after which it is rapidly metabolized, its mechanism of action following oral ingestion is not fully understood.

Japanese food is well-known worldwide for being healthy and of high nutritional value, and in 2013, Japanese food was designated as an intangible cultural heritage by the United Nations Educational, Scientific and Cultural Organization.[11] Because of its high nutritional value, rice is considered the most important item in Japanese food. Previous research has demonstrated the unique properties of rice in preventing lifestyle-related diseases.[12] Sprouted brown rice in particular has been shown to contain high amounts of vitamins, and it is also rich in GABA.[13]

With the addition of water to brown rice, GAD and glutamic acid (which are both present in brown rice) will react with each other to produce large amounts of GABA rapidly. Taking advantage of this fact, Satake Co., Ltd. (Hiroshima, Japan) developed a new variety of white rice enriched with GABA (GABA rice).[14,15] The GABA rice was developed to retain all of the nutritional content that is already present in the white rice, and in addition, its GABA content was enriched than the ordinary white rice. The GABA rice can be consumed easily on a daily basis for prolonged periods. Considering such merits, daily consumption of the GABA rice can lead to a high GABA intake, resulting in overall health benefits.

In this clinical study, we tested the effects of rice containing enriched GABA content on BP (GABA rice), and found that the GABA rice improved the morning BP of study participants who ate it every day.

2. Methods

2.1. Study participants

Forty-six volunteers (age, 40–64 years) were recruited. None of the participants had any history of recent gastrointestinal disorders, pregnancy, significant diseases, surgery, severe allergic reaction to food, or current use of any medication including antihypertensive medication. The mean values of the participants' characteristics and body composition are presented in Table 1.

The clinical intervention was carried out as a randomized, double-blind, placebo-controlled trial. At randomization, the 46 participants were randomly and blindly assigned to two groups evenly distributed according to the sex ratio, average age, and systolic BP (SBP). As shown in Table 2, the test rice was rich in GABA (containing 11.2 mg GABA per 100 g of rice) and the placebo rice had a lower concentration of GABA (containing 2.7 mg GABA per 100 g of rice). For 8 weeks, the participants took 150 g of either the GABA rice or the placebo rice. Hematological examinations were performed at baseline (Week 0), Week 4, and Week 8 during the intervention. The schedule of this clinical study is shown in Fig. 1.

Hematological examinations were consigned to Sapporo Clinical Laboratory Inc. (Sapporo, Japan). The body composition and hospital and home BPs were measured using InBody (Biospace Co., Tokyo, Japan) and OMRON digital BP monitors (OMRON Healthcare, Kyoto, Japan), respectively.

All participants provided written informed consent before undergoing any study-related tests, and the protocol was approved by the Ethics Committee of Hokkaido Information University (Certificate No. 2013-04). The study protocol conformed to the Helsinki Declaration.

Table 1
Characteristics of the placebo group and the test group participants.

Characteristics	Placebo	Test
Number of participants	$n = 17$	$n = 22$
Number of males (%)	7 (41.2%)	12 (54.6%)
Age (y)	54.35 ± 5.9	52.5 ± 6.8
Height (cm)	160.6 ± 7.1	166.0 ± 9.1
Body weight (kg)	62.5 ± 10.8	67.3 ± 12.5
Body fat rate (%)	28.8 ± 7.2	25.4 ± 8.2
Body mass index (kg/m^2)	24.2 ± 3.7	24.3 ± 3.3
Systolic blood pressure (mmHg)	135.5 ± 15.3	138.0 ± 14.8
Diastolic blood pressure (mmHg)	82.0 ± 10.0	85.4 ± 10.5

Values are presented as mean ± standard error. Statistical analysis was performed by one-way analysis of variance with age, height, body weight, and body mass index, and by Chi-square test for sex.

Table 2
Components of the GABA-enriched white rice (GABA rice) and the placebo rice.

Component	Placebo rice (per 100 g)	GABA rice (per 100 g)
Calories (kcal)	341	342
Water (g)	15.6	15.5
Proteins (g)	6.1	6.2
Lipids (g)	0.9	1.1
Carbohydrates (g)	77.1	76.8
Ash (g)	0.3	0.4
Sodium (mg)	–	–
Potassium (mg)	56.3	98.8
GABA (mg)	2.7	11.2

GABA = gamma-aminobutyric acid.

2.2. Test meal preparation

A nonglutinous rice (brand name: Yumepirika) cultivated in Hokkaido, Japan was used a test meal in this study. The GABA rice was produced by an air heating and humidifying process developed by Mizuno et al.[14,15] The temperature and humidity of grain were controlled using testing equipment (LGB03; Satake) scaled down of actual equipment to increase the quantity of GABA, and then the product (grain) was hulled and milled. The quantity of GABA was analyzed by the automatic amino acid analysis method, based on the procedure described by Ohisa et al[16] but with some modifications. The production and the packing of rice were carried out at Satake Corporation in a quality-controlled manufacturing plant in compliance with the Food Sanitation Act (the Ministry of Health, Labor, and Welfare of Japan). The quality and safety of the test samples were thoroughly examined by Satake Co., Ltd.

2.3. Measurement and analysis of home BP

Home BP was self-measured by the participants two times a day, in the morning (between urination and breakfast) and in the evening (before going to bed). At each measurement, after taking a 5-

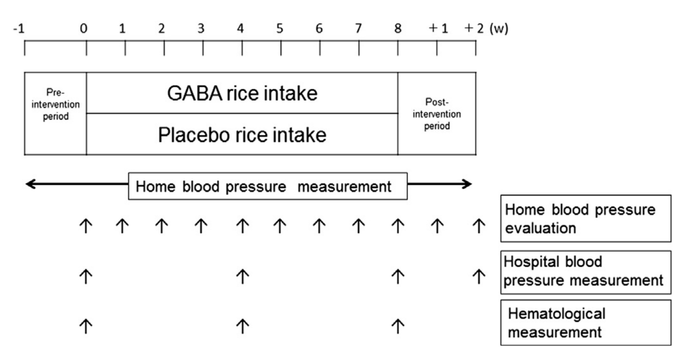

Fig. 1. Schedule (in weeks) for this clinical study. Home blood pressure was recorded two times daily (morning and evening) and was evaluated one time per week until the 2nd week after the intervention. Hospital blood pressure was recorded at baseline (0 weeks), the 4th week, the 8th week, and 2nd week after the intervention. Hematological measurements were obtained at baseline (0 weeks), the 4th week, and the 8th week.

minute rest, the participants measured their BPs three times in a relaxed position using the nondominant arm. We used the average value of two consistent measurements with an approximate value.

2.4. Statistical analysis

The average and standard error of age and other parameters were calculated for each group. Statistical analyses were performed using SPSS Statistic 20 (IBM, Armonk, NY, USA). The home BP values were analyzed using the mean of 5 days' data in each 7-day period. A two-way analysis of variance (ANOVA) with the *post hoc* Dunnett test was used to compare the results at each time point with respect to home and hospital BP values. When the variance ratio (F) was significant between groups, the mean values were compared by Student t test. Except for the home and hospital BP data, the Student t test was used to compare the change in values between the placebo group and the test group from baseline to each evaluation point. P-values less than 0.05 were considered significant.

3. Results

3.1. Effect of GABA-enriched white rice on hospital BP

Initially, 46 volunteers agreed to participate in this study, but seven were excluded from the data analysis due to one or more of the following reasons: irregular ingestion amounts of the test/placebo meal, low SBP (<120 mmHg) values at the beginning of the study, the initiation of antihypertensive treatment, or the lack of home BP records. Thus, 39 participants completed the study. There were no significant differences in the participants' ages, body weights, heights, or body mass index values between the test and placebo groups (Table 1). We first measured and analyzed all of the participants' hospital BP values, and found no significant differences in these values between the groups (Fig. 2).

3.2. Effect of GABA-enriched white rice on home BP

Fig. 3 shows the home SBP and diastolic BP (DBP) values recorded in the morning and evening by the participants from both groups. We first examined the results by conducting a two-way ANOVA with repeated measures, and the results did not indicate any significant effect of the test meal compared with the placebo meal. We then used nonpaired t tests to analyze the change in home BP levels from baseline to each evaluation point. Significant decreases in the morning SBP at the 6^{th} and 8^{th} week of consumption of the GABA rice and 1 week after the intervention were observed compared with the placebo rice intake. In addition, the morning DBP at the 1^{st} week after the intervention was found to be improved (Fig. 3).

3.3. Effect of GABA-enriched white rice on noradrenaline

Although the mechanism underlying the hypotensive action of GABA intake has not been fully elucidated, it is suspected that this action may be due to GABA's ability to inhibit noradrenaline release from sympathetic nerve fibers.[17] Fig. 4 shows the results of the participants' serum noradrenaline levels before and after the intake of a test/placebo meal. There was no significant difference between the two groups.

3.4. Levels of biomarkers of liver and renal functions and lipid and glucose metabolism after the ingestion of GABA-enriched white rice

We examined the levels of several biomarkers of liver function and renal function. Minimal changes were seen in the parameters

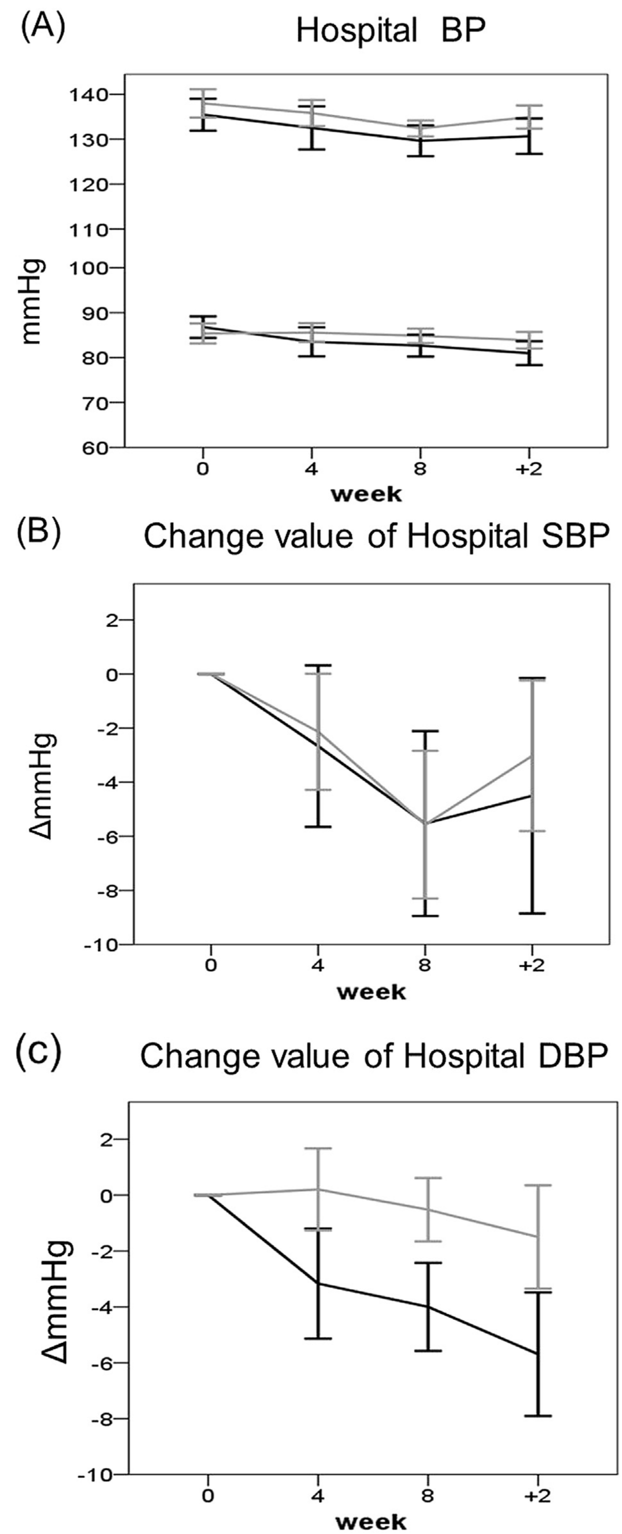

Fig. 2. Hospital blood pressure values during the clinical trial for the gamma-aminobutyric acid (GABA)-enriched white rice compared with the placebo rice. Gray bar represents the test group. Black bar represents the placebo group. (A) Hospital blood pressure values. (B) Rate of change in systolic blood pressure (SBP). (C) Rate of change in diastolic blood pressure (DBP). Values are means ± standard error. *$p < 0.05$, Student t test.

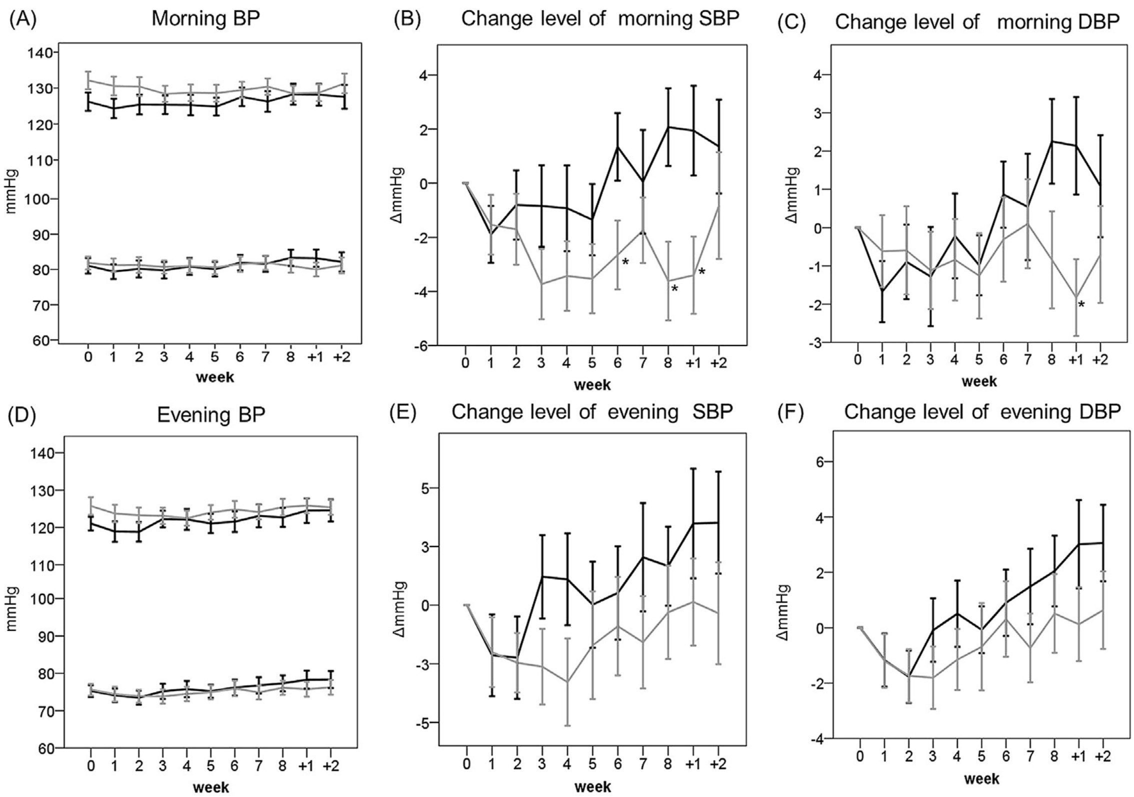

Fig. 3. Home blood pressure values during the clinical trial for the gamma-aminobutyric acid (GABA)-enriched white rice compared with the placebo rice. Gray bar represents the test group. Black bar represents the placebo group. (A) Morning blood pressure values (upper, systolic blood pressure; lower, diastolic blood pressure). (B) Rate of change in morning systolic blood pressure (SBP). (C) Rate of change in morning diastolic blood pressure (DBP). (D) Evening blood pressure (upper, SBP; lower, DBP). (E) Rate of change in evening SBP. (F) Rate of change in evening DBP. Values are means ± standard error. $^{*}p < 0.05$, Student t test.

of liver function (aspartate aminotransferase, alkaline phosphatase, and glutamyl transpeptidase), in the parameters of renal function (blood urea nitrogen and creatinine), in the parameters of glucose metabolism (fasting plasma glucose and hemoglobin A1c), and in the parameters of lipid metabolism (total cholesterol, triglyceride, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol), and body composition after the participants consumed the test meal (GABA rice), suggesting that the GABA rice has no or minimal unfavorable effects on the liver, kidney, lipid, and glucose metabolism even at the dose of 150 g/day (Tables 3 and 4).

4. Discussion

Morning BP is the most variable BP of the day, and high values are often displayed. The effects of any BP medication are often nullified during this period. According to the 2009 hypertension treatment guidelines issued by The Japanese Society of Hypertension (JSH2009), controlling hypertension on a 24-hour basis is recommended, and nighttime BP values are considered very important in treating hypertension. A recent study confirmed that home BP variability has an important role in the progression of organ damage, and it also recommended monitoring of home BP both in the morning and in the evening.[18]

In agreement with these reports, we evaluated the effects of rice containing enriched GABA on BP by analyzing home BP and hospital BP measurements in mildly hypertensive participants. We observed that the morning SBP was significantly decreased following the GABA rice intake compared with the placebo rice at the 6th and 8th week during the intervention and at the 1st week after the intervention. In addition, the participants' serum levels showed that the biomarkers of liver and renal function and those of glucose and lipid metabolism were almost unchanged after the 8-week study period. These results suggested that the 150 g/day consumption of the GABA rice (the GABA equivalent of 16.8 mg/day) has the potential effect of improving BP without causing any unfavorable effects on the health.

It was suggested that GABA exhibits an antihypertensive effect through the regulation of vascular nerves in the intestinal submucosa,[19] and that its function is mediated by the release of noradrenaline through the $GABA_B$ receptors.[17] However, in our study, GABA rice ingestion did not reduce the participants' serum noradrenaline levels. Noradrenaline values show diurnal variations,[20] and thus, the values obtained in this study may not be accurate enough. Moreover, noradrenaline values are related to other factors, such as angiotensin and vasopressin, that affect the BP. In this study, noradrenaline levels were not reduced throughout the study period, and this may be related to the hospital BP values, which were almost unchanged. However, the changes in the morning SBP values from baseline to 8 weeks and the baseline level of morning SBP were highly correlated in the test group (Pearson correlation; placebo group, $p = 0.074$; test group, $p = 0.014$), and these results indicate that GABA was more decreased in the hypertensive participants, and did not influence the healthy ones. A similar result was reported with fermented milk containing GABA.[21] Although a reduction of noradrenaline was not observed, the improvement in BP values following the ingestion of the test meal had a strong relation to GABA intake in our study.

The onset of morning hypertension is not fully understood, but it is thought to occur by the inducement of the α-receptors

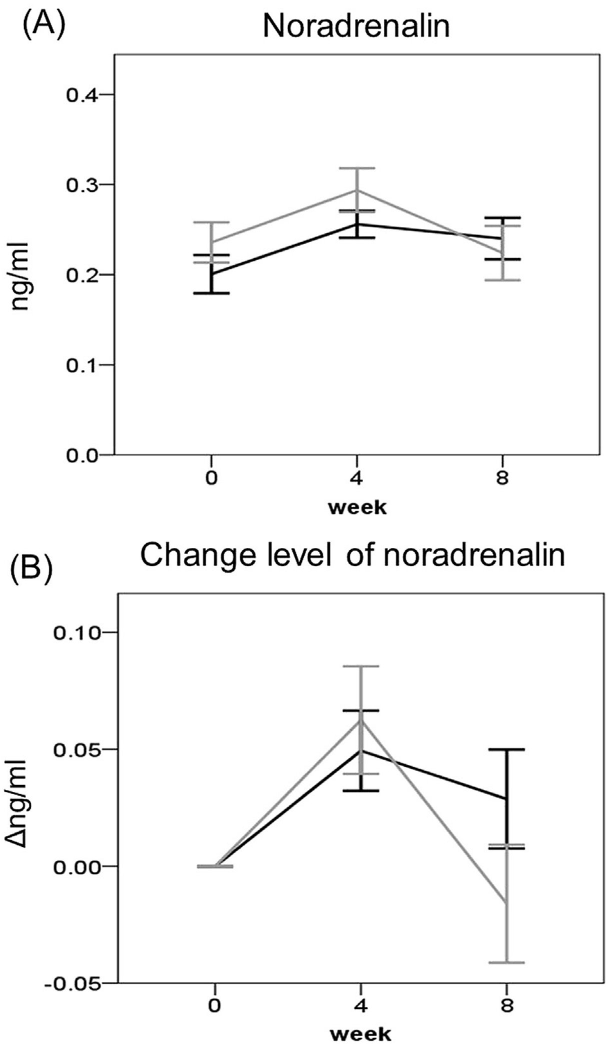

Fig. 4. Blood serum levels of noradrenaline during the study. Gray bar represents the test group. Black bar represents the placebo group. (A) Mean values. (B) Rate of change in noradrenaline levels. Values are means ± standard error. $^{*}p < 0.05$, Student t test.

Table 3
Hematological data of the placebo rice group ($n = 17$) and the GABA rice group ($n = 22$).

Parameter	Group	0 wk	4 wk	8 wk
WBC ($\times 10^3/\mu L$)	Placebo rice	4.78 ± 1.00	5.32 ± 1.02	5.14 ± 1.00
	GABA rice	4.96 ± 1.15	5.01 ± 1.11	5.11 ± 1.27
RBC ($\times 10^4/\mu L$)	Placebo rice	474.00 ± 27.06	474.18 ± 25.29	475.71 ± 27.65
	GABA rice	469.23 ± 39.98	471.29 ± 44.01	473.09 ± 38.22
Hb (g/dL)	Placebo rice	13.62 ± 1.96	13.55 ± 1.90	13.69 ± 1.87
	GABA rice	13.91 ± 1.79	13.97 ± 2.07	14.11 ± 1.99
Ht (%)	Placebo rice	40.89 ± 4.62	40.76 ± 4.35	41.36 ± 4.05
	GABA rice	41.98 ± 4.47	42.05 ± 5.10	42.1 ± 4.98
Plt ($\times 10^4/\mu L$)	Placebo rice	25.68 ± 6.65	25.44 ± 6.70	25.68 ± 7.25
	GABA rice	24.51 ± 7.60	23.97 ± 7.91	24.62 ± 8.38
AST (U/L)	Placebo rice	23.53 ± 8.41	23.71 ± 6.84	25.18 ± 6.82
	GABA rice	23.82 ± 5.80	26.24 ± 7.68	25.45 ± 6.58
ALT (U/L)	Placebo rice	24.47 ± 14.06	26.76 ± 14.28	29.12 ± 15.33
	GABA rice	25.41 ± 13.30	29.52 ± 16.74	28.64 ± 15.99
γ-GTP (U/L)	Placebo rice	36.18 ± 22.72	43.88 ± 34.77	42.12 ± 27.47
	GABA rice	35.55 ± 21.61	34.76 ± 17.83	34.95 ± 18.37
Urea nitrogen (mg/dL)	Placebo rice	14.16 ± 3.09	14.76 ± 3.31	13.39 ± 3.40
	GABA rice	14.76 ± 4.08	14.68 ± 3.16	13.5 ± 2.98
Creatinine (mg/dL)	Placebo rice	0.73 ± 0.14	0.74 ± 0.12	0.75 ± 0.13
	GABA rice	0.82 ± 0.13	0.82 ± 0.16	0.82 ± 0.15
FPG (mg/dL)	Placebo rice	90.9 ± 6.2	91.5 ± 11.8	89.1 ± 9.7
	GABA rice	93.0 ± 9.7	92.1 ± 10.3	90.9 ± 9.8
HbA1c (%)	Placebo rice	5.42 ± 0.37	5.34 ± 0.36	5.41 ± 0.35
	GABA rice	5.41 ± 0.33	5.34 ± 0.32	5.37 ± 0.38

Values are mean ± standard deviation.
ALT = alkaline phosphatase; AST = aspartate aminotransferase; FPG = fasting plasma glucose; GABA = gamma-aminobutyric acid; Hb = hemoglobin; HbA1c = hemoglobin A1c; Ht = hematocrit; Plt = platelets; RBC = red blood cells; WBC = white blood cells; γ-GTP = glutamyl transpeptidase.

Table 4
Lipid metabolism parameters and body composition of the placebo rice group ($n = 17$) and the GABA rice group ($n = 22$).

Parameters	Group	0 wk	4 wk	8 wk
T-Cho (mg/dL)	Placebo rice	207.7 ± 27.5	216.4 ± 26.0	211.8 ± 23.3
	GABA rice	218.4 ± 35.4	223.2 ± 34.7	221.1 ± 38.7
TG (mg/dL)	Placebo rice	93.9 ± 41.1	103.2 ± 36.0	103.5 ± 54.3
	GABA rice	101.8 ± 61.0	133.7 ± 139.2	124.5 ± 81.5
LDL-Cho (mg/dL)	Placebo rice	131.0 ± 28.0	136.8 ± 26.0	134.2 ± 25.5
	GABA rice	135.7 ± 32.7	134.7 ± 32.4	136.5 ± 33.7
HDL-Cho (mg/dL)	Placebo rice	66.4 ± 17.1	65.2 ± 13.3	65.2 ± 14.8
	GABA rice	69.5 ± 18.7	68.8 ± 16.6	68.9 ± 20.9
Body weight (kg)	Placebo rice	62.5 ± 10.8	62.8 ± 10.9	62.8 ± 11.5
	GABA rice	67.3 ± 12.5	67.3 ± 12.8	67.7 ± 12.8
Body fat rate (%)	Placebo rice	28.8 ± 7.2	29.0 ± 7.3	29.1 ± 7.4
	GABA rice	25.4 ± 8.2	25.3 ± 8.1	25.6 ± 8.1
BMI (kg/m^2)	Placebo rice	24.2 ± 3.7	24.3 ± 3.7	24.3 ± 3.9
	GABA rice	24.3 ± 3.3	24.3 ± 3.4	24.4 ± 3.4

Values are mean ± standard deviation.
BMI = body mass index; Cho = cholesterol; GABA = gamma-aminobutyric acid; HDL-Cho = high-density lipoprotein-cholesterol; LDL-Cho = low-density lipoprotein-cholesterol; T-Cho = total cholesterol; TG = triglycerides.

of sympathetic nerves.[22] Thus, to counteract morning hypertension, drugs that can effectively block the action of sympathetic nerves are made.[23] However, sympathetic nerve activity, in which the renin–angiotensin–aldosterone system contributes to a reduction in nighttime BP and an increase in morning BP, was reported to be increased in some patients with morning hypertension.[24] The exact mechanism of BP reduction by GABA intake is as yet unknown, but in rats that ingested soy sauce enriched with GABA, sympathetic nerve activity was inhibited and sodium levels in urine were increased.[25] In our study, the findings of no reduction in noradrenaline and the significant improvement in morning BP indicate that GABA may have induced the increased excretion of sodium in urine. For Japanese people, who tend to ingest high-salt side dishes, a routine use of GABA rice in their diet could thus be very beneficial in improving overall health.

GABA receptor agonists act on appetite-controlling neurons located in the hypothalamus region, and they increase the feeling of hungriness.[26] The vesicular GABA transporter is widely distributed in the hypothalamic arcuate nucleus, which is the location of an appetite-controlling mechanism.[27] It is known that some of the neurons in the hypothalamic arcuate nucleus are located at the hypothalamus median eminence, which lacks the blood–brain barrier. These neurons respond to the direct activation of hormones such as GABA circulating in the blood, and they control the appetite.[28]

From these findings, we suspect that the ingestion of sufficient quantities of GABA can increase an individual's appetite and thereby promote obesity. However, in this study, we found no increase in the test group participants' lipid metabolism or body composition (Table 4). In our present clinical trial of GABA rice, the functions related to lipid metabolism did not worsen in the test group, and from these results, we can affirm that the GABA quantities were suitable during our study.

5. Conclusion

In the present study, a reduction in BP followed the participants' consumption of the GABA rice. We found that the GABA rice was effective at reducing hypertension, and we conclude that its ingestion can contribute to the delay or prevention of the early onset of high BP-related cardiovascular and cerebrovascular events.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Acknowledgments

We thank Mss Rina Kawamura, Tomoko Mino, Megumi Shibata, and Yoko Suwabe for their technical assistance with the data management and Mr Jungo Hayashi for his management of the clinical trial. Our special thanks to Dr Rahul Upadhye for his assistance with the preparation of the manuscript. This study was supported in part by the Hamanasu Foundation.

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