ORYZA OIL & FAT CHEMICAL CO., LTD.

Evaluation of the effects of rice germ enriched with γ-aminobutyric acid (GABA) on insomnia, depression, and autonomic disturbances in humans: A double-blind cross-over study in climacteric and presenile subjects

*Dr. O. Kajimoto **Dr. A. Miyamoto ***Dr. Y. Tanaka

**Center for Health Care Osaka University of Foreign Studies.*
***Department and Neurology Osaka University School of Medicine.*
****Department of Psychosomatic Medicine, Shirai Hospital*

ORYZA OIL & FAT CHEMICAL CO.,LTD.
1 Numata Kitagata-cho Ichinomiya-city Aichi-pref.
493-8001 Japan
TEL:＋81(0)586-86-5141
FAX:＋81(0)586-86-6191
URL/http://www.oryza.co.jp/
E-mail:info@ oryza.co.jp

Evaluation of the effects of rice germ enriched with γ-aminobutyric acid (GABA) on insomnia, depression, and autonomic disturbances in humans: A double-blind cross-over study in climacteric and presenile subjects

[Purpose]

The effects of a food enriched with GABA extracted from rice germ on insomnia, depression, impatience, and autonomic disturbances were evaluated by the double-blind cross-over scheme using placebo in climacteric and presenile subjects.

[Subjects]

The subjects were 20 women who consulted the department of psychosomatic medicine or the department of psychoneurology due to complaints including autonomic disturbances such as climacteric syndrome and presenile mental disorders such as insomnia. They were aged 49.4±11.7 years.

[Methods]

Test preparation

A test preparation containing 292 mg of GABA per 100 g was prepared. Rice powder was used as placebo, and they were packaged identically so that distinction between the test preparation and placebo would be impossible by either doctors or subjects.

Administration method

The subjects were divided into 2 groups (Group A, 15 subjects; Group B, 5 subjects) in advance by the controller. Group A was administered the test preparation first, and Group B was administered placebo first, until the crossover after 8 weeks. Nine grams of each preparation was administered daily between meals 3 times a day.

The administration was performed after confirmation of the stabilization of the symptoms during a 2-week observation period before the study. The study was carried out by sufficiently explaining the intention of the study to the subjects and obtaining their consent.

Evaluation method

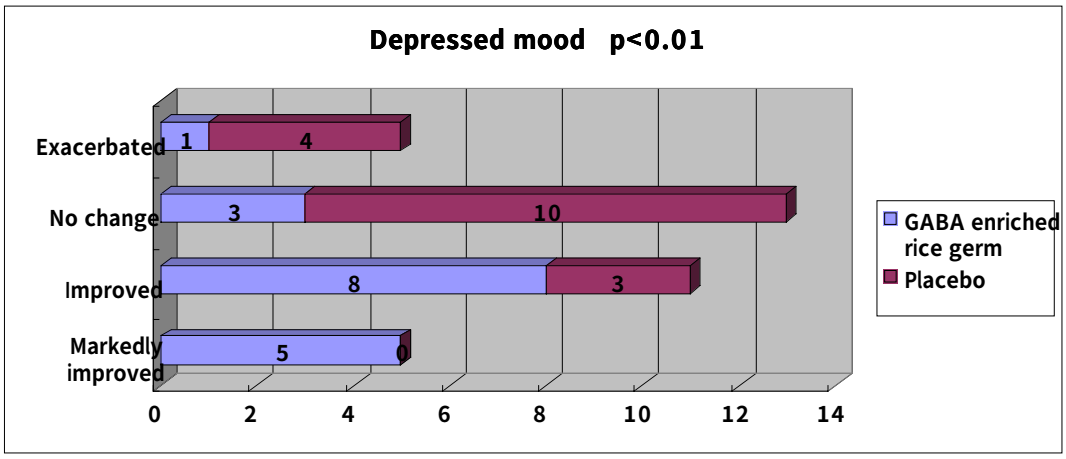
The severity of symptoms was evaluated using a 4-point scale concerning 13 items including Kupperman's scale of climacteric index. Evaluation was made 5 times, i.e. before the beginning of the administration of the first preparation, 4 weeks after the beginning of the first preparation, at the exchange of the preparations, during the administration of the second preparation, and at the end of the administration, in principle. To prevent variation of evaluation among physicians, an interview manual was prepared in advance, and each patient was evaluated by the same physician throughout the study.

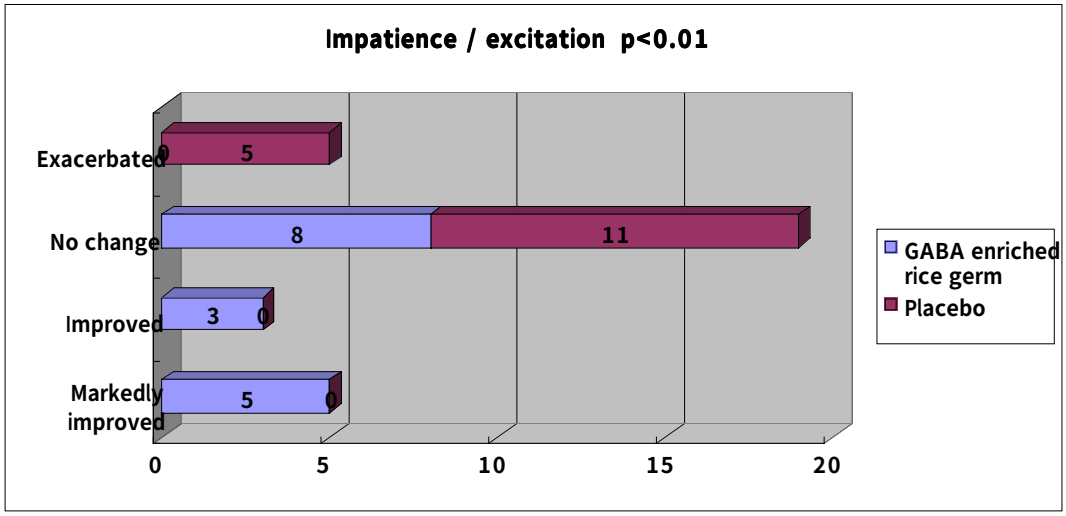
Non-parametric procedures were used for all statistical analyses.

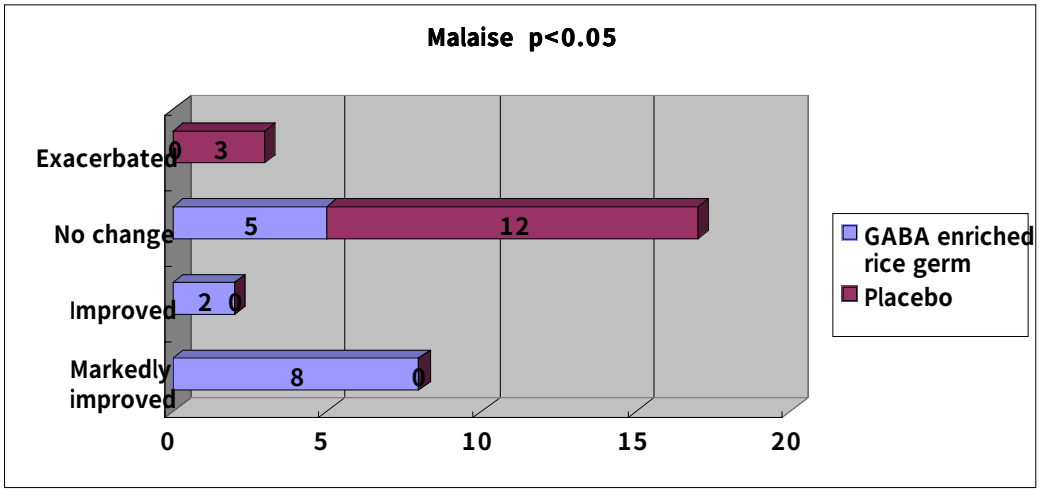
[Results]

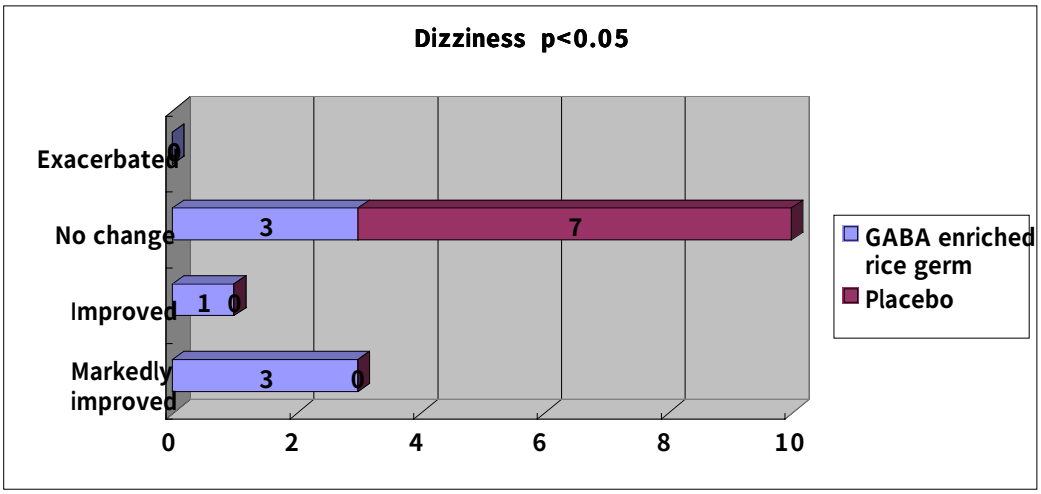
Percent improvement

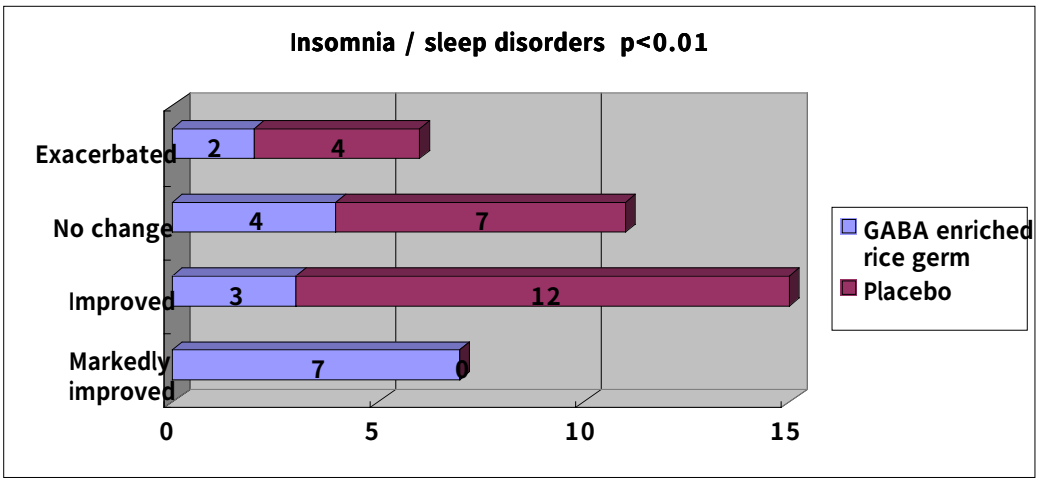
Percent improvements in major symptoms are shown below (Excepts. Statistics: Fisher's test)

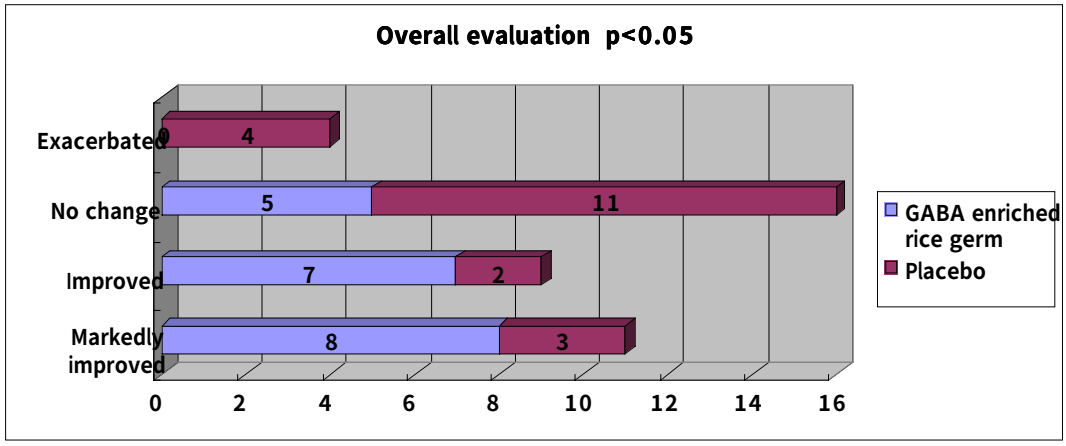





Malaise p<0.05
Exacerbated
No change
Improved
Markedly improved
0
3
5
12
2
0
8
0
0
5
10
15
20
GABA enriched rice germ
Placebo


Dizziness p<0.05
Exacerbated
No change
Improved
Markedly improved
0
3
7
1
0
3
0
0
2
4
6
8
10
GABA enriched rice germ
Placebo

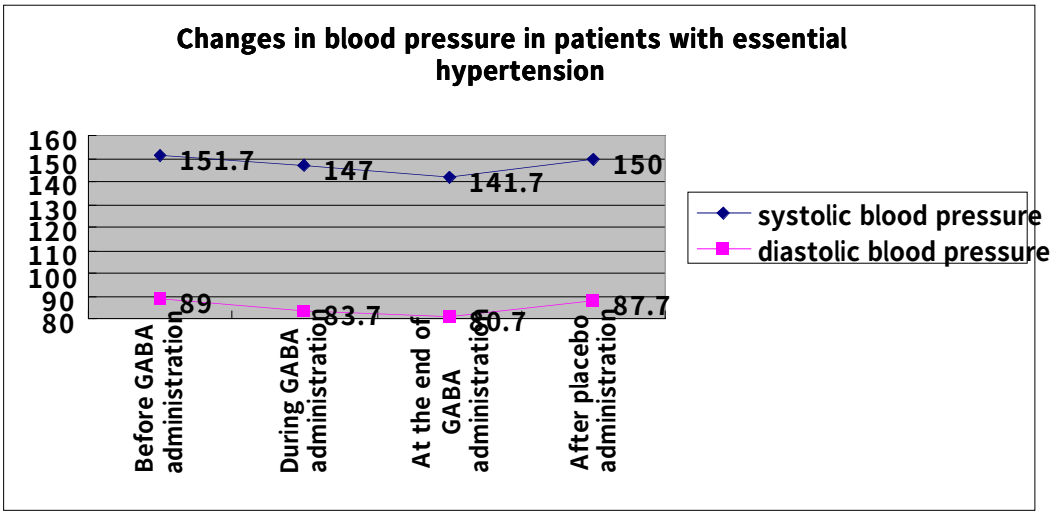

Insomnia / sleep disorders p<0.01
Exacerbated
No change
Improved
Markedly improved
2
4
4
7
3
12
7
0
0
5
10
15
GABA enriched rice germ
Placebo



Clearly greater improvements were observed in the above symptoms in the GABA group than in the placebo group during the administration period. Significant improvements in symptoms were observed already 4 weeks after the beginning of the administration, and even greater improvements were observed after 8 weeks. Therefore, GABA is considered to have sustained effects over a prolonged period.

Changes in blood pressure

Changes in the blood pressure in 6 subjects with essential hypertension are shown below.



Slight decreases ($p<0.05$) of 152→142 in the systolic pressure and 89→81 in the diastolic pressure were observed.

However, no decrease in the blood pressure was observed in the subjects who showed normal baseline blood pressures so that GABA was suggested to control the blood pressure in the normal range.

Safety

No exacerbation of symptoms considered to be an adverse effect of the preparation was noted in either group. No abnormal changes were observed in the results of blood tests, and decreases in the triglyceride level (TG) of 523→309 and 375→259, suggesting improvements in hyperlipidemia, were observed after 8-week treatment in 2 patients with a high baseline TG level.

Usefulness

The overall condition was considered to have improved in 75% of all patients, and the test preparation was judged to be “clearly more useful than placebo” in 65% of all patients after exclusion of the placebo effect by the authorized mental health physicians who carried out the administration.

[Discussion]

A preparation enriched with GABA extracted from rice germ was shown to be extremely useful for the treatment of various symptoms observed in the climacteric and presenile periods such as depression, insomnia, and impatience. Although GABA has been reported to stabilize and regulate nerve functions by a number of investigators, its effects at a dose contained in the preparation used in this study suggest that GABA is promising as a food supplement for the prevention and treatment of climacteric syndrome and presenile mental symptoms such as insomnia, impatience, and autonomic disturbances. In addition, its extreme safety and beneficial effects on hypertension and liver functions demonstrated by studies to date, GABA is considered to be of great value as a functional food to be eaten daily. The physicians also favorably evaluated its utility by commenting, “Adverse effects such as sleepiness and tiredness are observed less frequently than tranquilizers, and the patients can use it with a greater sense of security and less hesitation.”

Evaluation of usefulness of rice germ enriched with γ-aminobutyric acid (GABA) for the treatment of climacteric syndrome and senile mental disorders in humans.

[Introduction]

γ-Aminobutyric acid (GABA), an amino acid widely distributed in animals and plants, is a suppressive neurotransmitter present in the mammalian brain and spinal cord. It has long been used as a drug with a product name of Gammaron (Daiichi Pharmaceutical Co., Ltd.) for the treatment of headache, tinnitus, and hypobulia as sequelae of stroke and head trauma or cerebral arterial disorders because it improves the blood flow in the brain, increases the oxygen supply to the brain, and enhances brain metabolism.

GABA also reduces the blood pressure by acting on the vasomotor center in the medulla oblongata and by suppressing the secretion of the antidiuretic hormone vasopressin and dilating blood vessels. Furthermore, Omori et al. reported that GABA increases the renal blood flow and enhances the renal function on the basis of the results of an experiment using spontaneously hypertensive rats. In a series of experiments in which GABA was administered to rats, it was also shown to have excellent effects such as improving liver functions, reducing triglyceride, and suppressing body weight gains.

The greatest advantage of GABA, which is attracting attention from the medical field as a drug or a physiologically active agent, is that it is present naturally and intrinsically in foods. Nutritional investigations to date have established that GABA is contained at high levels in rice retaining germ and green tea. However, the quantity of GABA ingested as natural foods is limited despite its wide distribution, and its intake from foods in a quantity sufficient for it to produce its pharmacological effects has been difficult. **The Chugoku National Agriculture Research Experimental Station of the Ministry of Agriculture, Forestry, and Fishery** and **Oryza Oil & Fat Chemical Co., Ltd**. together succeeded in developing a food in which GABA is enriched by converting glutamic acid to GABA using enzymes contained intrinsically in rice retaining germ. This development has made intake of GABA at a quantity expected to produce its physiological effects possible by overcoming the

quantitative limitation of its oral intake from natural foods.

In this study, we evaluated the usefulness of GABA-enriched rice germ as a functional food for alleviating climacteric and presenile symptoms such as insomnia, depression, and autonomic disturbances, against which GABA has been reported to be effective.

[Subjects]

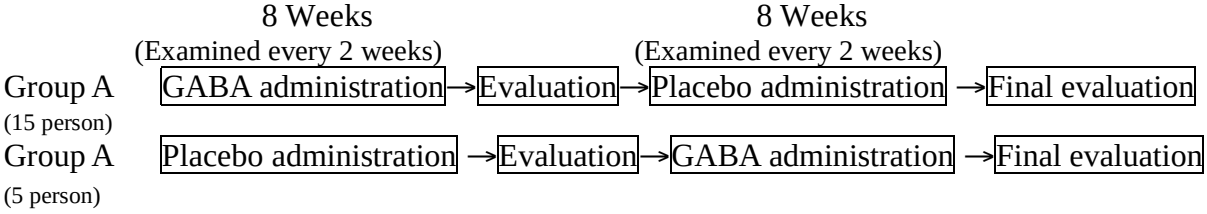
The subjects were 20 women who consulted the outpatient clinics of the department of psychosomatic medicine and the department of psychiatry due to various symptoms of mental disorders or autonomic disturbances observed in the climacteric or presenile period. Their mean age was 49.4±11.7 years. Their profiles including the diagnosis and severity of symptoms are shown in the table. The study was carried out after confirming that none of the patients had used tranquilizers, antipsychotic drugs, or other drugs that might affect the mental state on their own or by prescriptions of other physicians within 8 weeks before the beginning of the study. Prior to the study, the purpose of this study was sufficiently explained to the subjects, and their written consent was obtained according to the spirit of Helsinki Declaration.

[Methods]

The study was carried out by the double-blind cross-over scheme using placebo. The test preparation contained 292 mg of GABA in 100 g of powder made from rice germ. Placebo was a 100% rice powder identical in appearance to the test preparation. The identities of the test preparation and placebo were coded on their packages so that neither the subjects nor the physicians who administered them would not distinguish them.

Both the GABA-containing test preparation and placebo were administered orally over 8 weeks. The administration scheme is shown below. The 20 subjects were divided in advance into 15 (Group A) and 5 (Group B) at random by the controller (Osami Kajimoto). Group A was administered the GABA-containing preparation for the first 8 weeks and placebo for the next 8 weeks while Group B was administered placebo first and the GABA-containing preparation next.

Powdery products developed by Oryza Oil & Fat Chemical Co., Ltd. were used as the GABA-containing preparation (product name: **ORYZA GABA GERM**) and placebo. They were administered at 3 g per administration 3 times a day.



GABA: Powdered rice germ containing 292mg of GABA per 100g
(Daily GABA intake: 26.4 mg)

Placebo: Rice powder identical in appearance and packaging to the GABA-containing preparation

[Evaluation method]

Group A was evaluated 5 times, i.e. before the beginning of administration, during GABA administration, at switching from GABA to placebo, during placebo administration, and at the end of placebo administration, in principle. Group B was evaluated 5 times, i.e. before the beginning of administration, during placebo administration, at switching from placebo to GABA, during GABA administration, and at the end of GABA administration, in principle. The data of subjects who could not visit the outpatient clinic for examination were regarded as statistically valid if there were data before and after the administration of each preparation. For evaluation, an interview manual was prepared in advance to avoid variation between physicians, and each subject was evaluated by the same physician before, during, and after the administration of each preparation throughout the study to increase the reliability of evaluation.

Items of Kupperman's climacteric index, which are typical evaluation criteria for climacteric syndrome, were adopted for evaluation, and each item was rated using a 4-point scale of "no symptom" (0), mild (1), moderate (2), and severe (3).

Items of Kupperman's climacteric index are shown in a table. The evaluation criteria

were unified by determining specific anchor points to prevent variation among physicians.

Moreover, “irregular menstruation” and “gastrointestinal symptoms such as constipation”, which are often observed in the climacteric period and were complained of by many subjects, were included as additional evaluation items and were rated using the same scale.

[Statistical procedures]

Using the above 4-point scale, an improvement of 2 or more points after the administration compared with the state before the administration or complete disappearance of the symptom (0) was rated as “markedly improved”, an improvement of 1 point as “improved”, no change as “no change”, exacerbation of 1 point as “exacerbated, and exacerbation of 2 or more points or exacerbation of the symptom to “severe” (3) as “markedly exacerbated”.

All statistical analyses were performed as non-parametric procedures.

[Results]

The results are shown in the following pages.

Results are the percent improvements in various symptoms for the test preparation and placebo. As a result of the χ^2-test and Fisher's test, significant differences were observed in the percent improvement in 5 items, i.e. insomnia/sleep disorders, emotional disturbances such as nervousness/impatience/excitation, depressed mood, dizziness, and malaise, of the 13 items examined between the GABA group and placebo group. The percent improvement in overall symptoms was also significantly different between the two groups. These results suggest that GABA is effective for the treatment of symptoms of the climacteric and presenile periods such as insomnia, depression, and impatience.

Results are changes in the severity of various symptoms in the group administered GABA for the first 8 weeks and placebo in the next 8 weeks (n=15). Clear effects were observed in nearly all symptoms, particularly, insomnia, impatience, and depressed mood, already 4 weeks after the beginning of GABA administration, and these effects tended to be further enhanced after 8 weeks. From these results, the effects of GABA are considered to appear relatively rapidly, or within 4 weeks after the beginning of the administration, and to be maintained or enhanced further to the 8th week of administration.

Results 3 show overall usefulness evaluation of GABA or placebo by the authorized mental health physicians who administered the drugs. In this double-blind cross-over study, whether the preparation being administered was GABA or placebo was concealed to the two authorized mental health physicians who were in charge of the administration, and the usefulness evaluation was performed according only to the code number indicated on the package. Placebo was considered to be better than GABA in none of the 20 subjects, GABA was considered to be markedly better than placebo in 4, and GABA was considered to be better than placebo in 9; the usefulness rating was higher for GABA than for placebo in 65% of the subjects.

As mentioned above, the overall percent improvement was high at 75%, and the physicians who actually used the drugs judged that GABA was "useful" in 65% of the

subjects even after exclusion of improvements presumably due to placebo effect. These results indicate that GABA-enriched rice germ has extremely high utility. In fact, as the percent improvements achieved with tranquilizers or drugs for autonomic disturbances are similar to those achieved by GABA, GABA-enriched rice germ is considered to be of great value as a food supplement for daily intake.

Subjects' Profiles

	Patient's name	Age	Sex	Diagnosis	Severity
Group A	H.T	56	F	Climacteric disturbance	Moderate
	T.T	64	F	Presenile dementia	Moderate
	I.C	49	F	Climacteric disturbance	Moderate
	Y.M	41	F	Climacteric disturbance	Moderate
	A.A	61	F	Presenile depression	Severe
	O.S	33	F	Neurosis	Severe
	H.K	23	F	Autonomic disturbance	Mild
	T.H	51	F	Climacteric disturbance	Mild
	I.T	53	F	Climacteric disturbance	Moderate
	A.Y	49	F	Climacteric disturbance	Moderate
	I.M	48	F	Depression	Moderate
	H.M	43	F	Autonomic disturbance	Mild
	N.H	26	F	Autonomic disturbance	Moderate
	T.T	52	F	Manic-depressive psychosis	Severe
	N.F	48	F	Climacteric disturbance	Mild
Group B	I.K	64	F	Presenile depression	Moderate
	N.K	50	F	Presenile dementia	Moderate
	S.H	65	F	Presenile depression	Mild
	K.F	52	F	Climacteric disturbance	Moderate
	T.F	60	F	Climacteric disturbance	Moderate
Mean		49.4 ± 11.7			

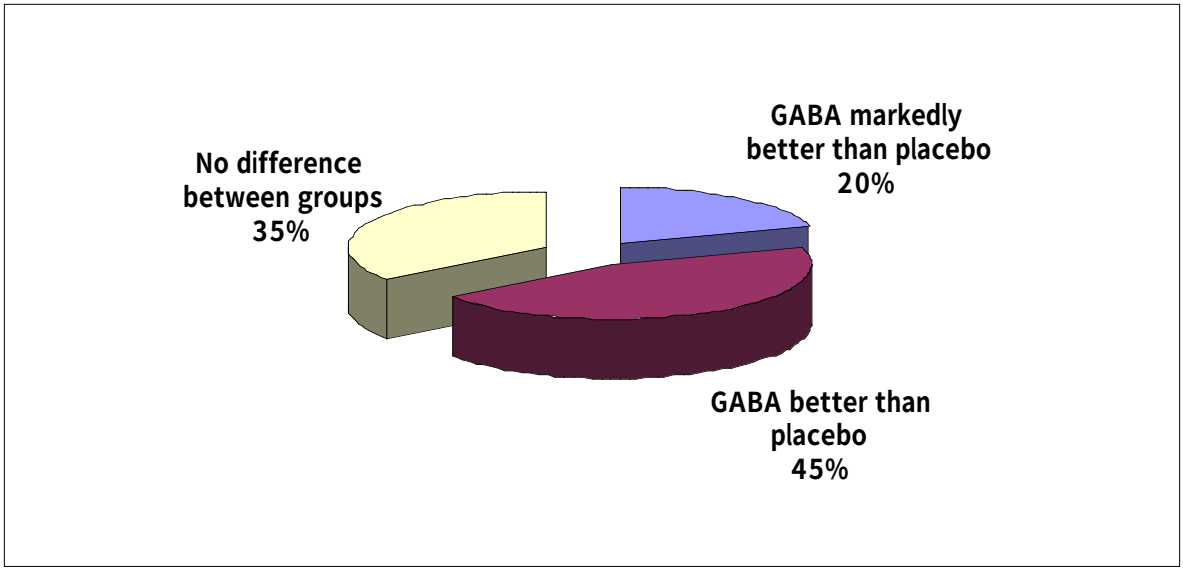
Items of **Kupperman's Climacteric Index**

Symptom categories	**Symptoms**
1) Vasomotor nerve disorders	Hot flushes
	Perspiration
	Cold sweat
	Shortness of breath
2) Dysesthesia-like symptoms	Numbness
	Reduced limb sensibility
3) Insomnia/sleep disorders	Difficulty of falling asleep
	Lightness of sleep
4) Nervousness	Increased excitability
	Impatience
5) Depressed mood	Worrying and regretting
	Feeling low
6) Dizziness	Dizziness
	Nausea
7) Malaise	Easy to get tired
	Slow to recover from fatigue
8) Arthralgia/myalgia	Stiffness of shoulders
	Low back pain
	Myalgia
	Limb pain
9) Headache	Headache
	Feeling heavy in the head
10) Palpitation	Palpitation
11) Formication	Formication

Results 3 Group-wise comparison of overall usefulness evaluation

GABA markedly better than placebo	4
GABA better than placebo	9
No significant difference between two groups	7
Placebo better than GABA	0
Placebo markedly better than GABA	0

Comparison of usefulness between groups



GABA was judged to be better than placebo in 65% of the subjects on the physicians' overall evaluation. (The identities of the preparations were concealed from the physicians by a coding system.)

[Percent improvements by the severity and disease]

The percent improvements by the pre-administration severity and disease are shown in the next page.

GABA was effective regardless of the severity of symptoms, suggesting that it is effective in a wide range of patients.

GABA was also effective in all symptoms of climacteric syndrome, autonomic disturbances, and presenile mental disorders such as insomnia, impatience, and depression.

The GABA level in the brain is reported to decrease when a person feels strong

anxiety and is mentally unstable. Decreases in GABA have also been reported in conditions including presenile dementia. Therefore, the brain GABA level is considered to be reduced in patients having severe symptoms such as insomnia, impatience, and depression and other indefinite complaints often observed in climacteric syndrome. GABA-enriched rice germ is considered to have alleviated these symptoms by supplementing GABA in the brain.

Improvements by the severity before administration

Severity before administration	Markedly improved	Considerably improved	Improved	No change	Exacerbated	Overall percent improvement
Severe	0	1	1	1	0	67%
Moderate	1	4	4	3	0	75%
Mild	1	1	2	1	0	80%

Overall percent improvement = Number of patients rated as “improved” or better/Number of all patients

Improvements by diseases

Disease name	Markedly improved	Considerably improved	Improved	No change	Exacerbated	Overall percent improvement
Climacteric disturbance	0	4	2	3	0	67%
Autonomic disturbance	0	0	2	1	0	67%
Presenile depression	1	1	0	1	0	67%
Presenile dementia	0	0	2	0	0	100%
Depression	1	0	0	0	0	100%
Manic-depressive psychosis	0	1	0	0	0	100%
Neurosis	0	0	1	0	0	100%

Overall percent improvement = Number of patients rated as “improved” or better/Number of all patients

Results

1) GABA-enriched rice germ was shown to be effective regardless of the pre-administration severity.

2) GABA-enriched rice germ was shown to be effective for all disorders that cause insomnia, irritation, and depressive mood according to the percent improvement in each disorder.

[Changes in the blood pressure in hypertensive patients]

In this study, changes in the blood pressure after GABA administration were examined in 6 patients diagnosed to have essential hypertension or borderline hypertension. The results are shown in the next page.

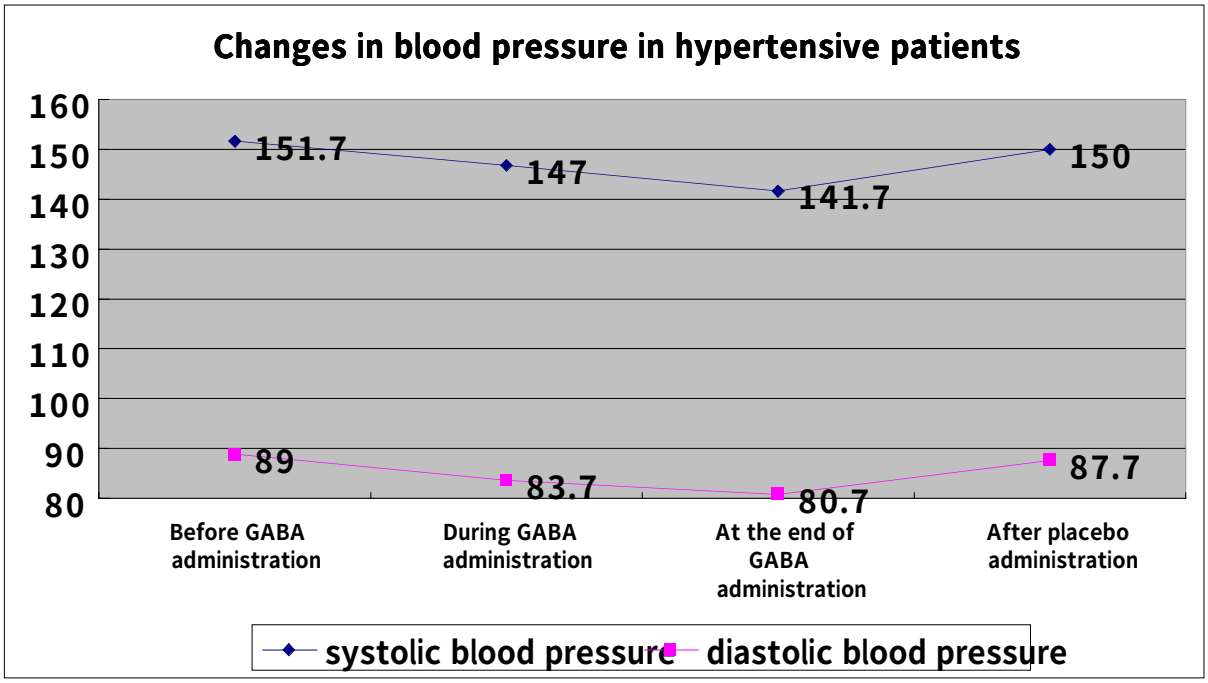
The blood pressure tended to decrease though not significantly after GABA administration for 4 weeks, and both the maximum and minimum blood pressures showed mild but significant decreases at the end of 8-week GABA administration ($p<0.05$: Wilcoxon test).

GABA had been shown to reduce the blood pressure in animal experiments, but this study confirmed this effect in humans.

However, no significant decrease in the blood pressure was noted in the other normotensive subjects, so that GABA was suggested to normalize the blood pressure. Also, as the decreases in the mean systolic and diastolic blood pressures were 152→142 and 89→81, respectively, in the hypertensive patients, GABA is considered to induce mild changes in the blood pressure without straining the body or the brain. According to recent reports, drugs that force the blood pressure to decrease may induce attacks of cerebral ischemia such as cerebral infarction. With this respect, also, GABA-enriched rice germ is considered to be an excellent food supplement that prevents exacerbation of borderline hypertension for which medication is still premature.

Changes in the blood pressure in 6 hypertensive patients after administration of test drug

Patient's name	Before GABA administration		During GABA administration		At withdrawal of GABA		After placebo administration	
	Maximum blood pressure	Minimum blood pressure	Maximum blood pressure	Minimum blood pressure	Maximum blood pressure	Minimum blood pressure	Maximum blood pressure	Minimum blood pressure
T.T	158	84	152	80	148	78	152	86
I.C	148	102	156	98	140	92	152	102
A.A	148	88	142	80	140	80	152	82
I.K	152	88	146	80	142	80	148	86
N.K	146	84	138	78	136	72	138	82
S.H	158	88	148	86	144	82	158	88
Mean	151.7	89.0	147.0	83.7	141.7	80.7	150.0	87.7



Results of statistical analyses

1) The systolic blood pressures before and after GABA administration were significantly different ($p<0.05$), and GABA was shown to reduce the systolic blood pressure in hypertensive patients. (Wilcoxon test)

2) The diastolic blood pressures before, during, (4 week after the beginning of administration), and after GABA administration were significantly different ($p<0.05$), and GABA was shown to reduce the diastolic blood pressure in hypertensive patients. (Wilcoxon test)

Results of blood tests

Test Item	WBC		RBC		Hb		ALP	
Normal value	3500-9500		376-516		11.2-16.0		74-223	
Patient's name	Pre-administration	Post-administration	Pre-administration	Post-administration	Pre-administration	Post-administration	Pre-administration	Post-administration
H.T	7700	8000	402	420	13.8	13.8	142	130
Y.M	6780	7200	480	455	14.4	14.3	160	160
A.A	9600	6000	402	430	13.7	14.2	160	148
O.S	7000	5400	410	432	12.1	12.6		
T.H	7300	7100	461	451	13.3	13.8		
T.T	5800	6400	508	507	15.6	15.5		
I.K	6800	7000	420	430	14.2	14.6	158	170
S.H	7500	6800	370	385	13.2	13.7	123	143
T.F	10500	6800	420	434	14	14.2	180	165
Mean	7664	6744	430.3	438.2	13.8	14.1	153.8	152.7
Abnormal changes	No abnormal changes		No abnormal changes		No abnormal changes		No abnormal changes	

(Red letters indicate abnormal values.)

Test Item	GOT		GPT		Total cholesterol		Triglycerides	
Normal value	10-40		5-45		150-219		50-149	
Patient's name	Pre-administration	Post-administration	Pre-administration	Post-administration	Pre-administration	Post-administration	Pre-administration	Post-administration
H.T	24	22	32	28	168	170	124	128
Y.M	28	28	33	30	192	184	120	132
A.A	38	27	42	29	203	189	103	120
O.S	13	13	14	13	175	193	53	139
T.H	21	14	29	16	179	180	375	259
T.T	30	30	49	45	256	306	523	309
I.K	38	36	30	38	170	172	108	120
S.H	20	15	18	15	123	143	98	106
T.F	38	32	40	34	202	200	138	130
Mean	27.8	24.1	31.9	27.6	185.3	193.0	182.4	160.3
Abnormal changes	No abnormal changes		No abnormal changes		No abnormal changes		No abnormal changes	

(Red letters indicate abnormal values.)

Test Item	BUN		Crea		Na		K	
Normal value	8-20		0.6-1.0		135-145		3.5-5.0	
Patient's name	Pre-administration	Post-administration	Pre-administration	Post-administration	Pre-administration	Post-administration	Pre-administration	Post-administration
H.T	20	16	0.7	0.6	138	142	4	3.9
Y.M	10	12	0.4	0.4	138	138	4	3.8
A.A	12	15	0.6	0.6	140	140	4	4.2
O.S	7.4	9.5	0.6	0.5	142	143	4.5	4.4
T.H	8.7	8.7	0.7	0.8	142	143	3.8	3.8
T.T	12.6	11.6	0.7	0.8	142	143	3.9	4.5
I.K	18	16	0.8	0.7	140	137	3.9	3.8
S.H	12	13	0.3	0.4	140	142	3.7	3.8
T.F	15	14	0.9	0.7	138	142	4	3.9
Mean	12.86	12.87	0.63	0.61	140.0	141.1	3.98	4.01
Abnormal changes	No abnormal changes		No abnormal changes		No abnormal changes		No abnormal changes	

As observed above, no abnormal changes were observed in the blood components, liver function, kidney function, or electrolyte balance after GABA administration in the 9 subjects who underwent blood tests both before and after the administration. Concerning the patients who showed abnormal values before the administration, WBC returned to a normal level (9600→6000, 10500→6800). In T.T., GPT normalized, and the triglycerides improved (523→309). A similar improvement (375→259) was observed also in T.H.

[Adverse reactions and safety]

No exacerbation of symptoms considered to be due to adverse reactions was noted during the period of GABA or placebo administration.

On blood tests, which were carried out with consent of the subjects, blood components such as white blood cells, red blood cells, and hemoglobin, liver function markers such as ALP, GOT, and GPT, markers of hyperlipidemia such as total cholesterol and triglyceride, kidney function markers such as BUN and creatinine, and electrolytes such as Na and K were measured before and after GABA administration.

No abnormal changes were observed in the 9 patients who underwent these blood tests. The 1 patient who had liver dysfunction and hyperlipidemia before the administration showed clear improvements, i.e. normalization of GPT (49→45) and a decrease in triglyceride (523→309), after GABA administration.

These findings suggest that GABA has a very high level of safety. The incidence of adverse reactions to tranquilizers, antipsychotic drugs, and drugs for autonomic disturbances is generally reported to be about 10%, but the incidence of sleepiness and tiredness appears to be several times higher according to the impression of patients and physicians who observe them daily. In contrast, no adverse reaction to GABA-enriched rice germ was observed in this study despite its comparable efficacy to the above drugs, indicating the great value of this food.

[Conclusions]

GABA-enriched rice germ administered regularly over a sufficient period was shown to be effective for the treatment of autonomic disturbances and mental disorders of the climacteric or presenile period. Mental disorders such as insomnia and impatience often observed in the climacteric and presenile periods and autonomic disturbances are among the disorders that are the most difficult to treat in psychosomatic and psychiatric medicine. As they are called “a march of indefinite complaints”, they characteristically appear as a chain of different complaints. For example, tinnitus appears as dizziness improves, headache begins

as shoulder stiffness gets better, and lightheadedness occurs as difficulty of falling asleep is eased.

GABA has been studied extensively in the fields of neurology and psychiatry, and it has been known to stabilize neuronal excitation in the brain. In epileptic patients, it mitigates epileptic attacks by suppressing transmission of abnormal neural excitation. Also, easy excitability, i.e. emotional changes such as “becoming bad-tempered” and “becoming violent”, are occasionally observed in dementing disorders of the old age such as Alzheimer’s dementia, and decreases in the cerebral GABA level have been reported in these conditions. The GABA level of the brain is also reported to be reduced in mental disorders such as anxiety neurosis, in which patients suffer from unnecessary vague anxiety such as not being afraid to take a train or to meet people due to indefinite worries. Therefore, GABA present in the brain is considered to have the role of stabilizing the mental state.

Concerning the effects of orally administered GABA on the brain, drugs that have been sold for many decades demonstrate its effectiveness as mentioned in the Introduction. Therefore, at least part of the mental symptoms of the climacteric and presenile periods are considered to be caused by a decrease in the cerebral GABA level, and they are expected to be alleviated by oral supplementation of GABA.

This clinical study was carried out by using a preparation containing naturally occurring GABA extracted and enriched from rice germ rather than a synthetic drug. Although this preparation has a smaller GABA content than synthetic drugs, it is considered to have many advantages such as that it is extremely safe as it is prepared exclusively from rice germ, that it can be taken daily over a long period, and that it may be more digestible and absorbable than drugs.

As described in the results, overall improvements were observed in 75% of all patients orally administered this rice germ GABA. This percent improvement was significantly higher compared with placebo. According to the physicians’ evaluation, also, GABA was considered to be effective in at least 65% of the patients after exclusion of the cases in which improvements were suspected to be due to placebo effect. These results

suggest that refractory mental symptoms may be alleviated with a food containing GABA extracted from rice germ alone similarly to pharmaceutical preparations of GABA.

In addition, no exacerbation of symptoms considered to be adverse reaction was noted during the administration of rice germ GABA, and no gastrointestinal symptoms such as anorexia, constipation, and diarrhea, occasionally observed as adverse reactions to drugs, were noted. Gastrointestinal symptoms such as nausea, stomachache, and feeling of abdominal fullness tended to be alleviated during the administration of rice germ GABA, indicating a high safety level of naturally occurring GABA extracted and enriched from rice germ. The complete absence of abnormal changes in the results of blood tests and improvements in the liver function indicated by improvements in the triglyceride and GPT levels observed in some subjects further suggested its usefulness and safety.

GABA has been shown to improve hypertension and hyperlipidemia in animal experiments and has been regarded as a drug component useful for the prevention of adult diseases (lifestyle-related diseases). In this study, the systolic and diastolic blood pressures decreased mildly but significantly after 8 weeks of GABA administration in 6 patients diagnosed to have essential hypertension or borderline hypertension. However, no significant decrease in the blood pressure was noted in the 14 originally normotensive patients so that GABA was suggested to reduce the blood pressure only in hypertensive patients, or to control the blood pressure in the normal range. These observations suggest that GABA has blood-pressure-regulating actions different from those of so-called depressors such as calcium antagonists, ACE-inhibitors, and diuretics and that it is a useful food supplement for borderline hypertensive patients who do not yet need anti-hypertensive medication.

As GABA was shown to be useful for the treatment of mental changes associated with aging, i.e. climacteric syndrome, insomnia and impatience observed in the presenile period, and autonomic disturbances, it is considered to be a promising functional food effective for the prevention of age-related declines of mental as well as physical functions.