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PharmaGABA: Natural Support for Stress, Anxiety and Insomnia

INTRODUCTION

Gamma-aminobutyric acid (GABA) is a major neurotransmitter that is abundantly and widely distributed throughout the central nervous system (CNS). Within the brain, GABA is formed in neuronal cells by the α-decarboxylation of glutamic acid and further metabolized by GABA-α-keto-glutarate transaminase and then returned to the tricarboxylic acid cycle (TCA) cycle. Plasma membrane depolarization induces the release of GABA from the nerve terminals and GABA binds to GABA receptors, such as the $GABA_A$ receptor and the $GABA_B$ receptor, which are distributed on the post-synaptic cell membranes. Among other effects, GABA is known to mediate pre-synaptic inhibition of primary afferent fibres in the motor system and may also be involved in post-synaptic forms of motor neuron inhibition.

The neurotransmitter actions of GABA in the synaptic cleft are terminated by its reuptake by either pre-synaptic neurons or nearby glial cells via specific and high-affinity transporters that are believed to be the major mechanism for reducing its concentration in the extracellular fluid within the brain.

GABA LEVELS IN HUMAN DISEASE

Low levels or decreased GABA function in the brain is associated with several psychiatric and neurological disorders, but most primarily anxiety, depression, insomnia, and epilepsy.[1-6] Currently, many popular anti-anxiety drugs – the sedative-hypnotics – interact primarily with GABA receptors. These drugs include the benzodiazepine drugs like alprazolam (Alprazolam, Xanax) and diazepam (Valium); as well as drugs like flurazepam (Dalmane); quazepam (Doral); temazepam (Restoril); triazolam (Halcion); zolpidem tartrate (Ambien); and baclofen (Kemstro, Lioresal). All of these drugs mimic the effects of GABA in a much distorted manner and are associated with significant risks and side effects. Problems with these drugs include the fact that they are highly addictive and are very poor candidates for long term use. Common side effects include dizziness, drowsiness, and impaired coordination, it is important not to drive or engage in any potentially dangerous activities while on these drugs. Alcohol should never be consumed with these drugs as it could be fatal.

Recently, there has been renewed interest in studying the role of GABA in depression as preclinical studies have suggested that GABA levels are decreased in patients suffering from depression.[3-5] The role of GABAergic dysfunction in mood disorders was first proposed 20 years ago. Now various antidepressant drugs have been shown to be effective in unipolar and bipolar patients not only by affecting monoaminergic and serotonergic activity, but also by increasing brain GABAergic activity. GABA is also being investigated for its potential antihypertensive effects.

PHARMAGABA: AN IMPROVED FORM OF SUPPLEMENTAL GABA

GABA has been available as a dietary supplement in the United States for decades. However, there is a new form of GABA that is considerably more effective than other forms. This new form, PharmaGABA, is naturally manufactured via a fermentation process that utilizes *Lactobacillus hilgardii* – the bacteria used to ferment vegetables in the preparation of the traditional Korean dish known as kimchi. In contrast, the synthetic form of GABA is produced from pyrrolidinone – a compound not allowed for use in Japan as it is listed as a dangerous substance. The GABA content of synthetic GABA is about 99.6%, the remaining amount consisting of pyrrolidinone.

PharmaGABA has been shown to produce relaxation as evidenced by changes in brain wave patterns, diameter of the pupil, and heart rate as well as reduce markers of stress including salivary cortisol and chromagranin A levels. In a head-to-head double blind trial with PharmaGABA, the synthetic GABA was not shown to produce these effects.[7] It is possible that synthetic GABA, unlike natural forms of GABA, is not able to bind to GABA receptors.

Once ingested, it appears that the PharmaGABA is absorbed easily and binds to GABA receptors in the peripheral nervous system leading to activation of the parasympathetic nervous system. This arm of the autonomic nervous system is responsible for producing what is referred to as the "relaxation response," a physiological response that is in direct contrast to the stress or "fight or flight" response. This activation of the parasympathetic nervous system by PharmaGABA is measurable within 5 to 30 minutes after ingestion.

This proposed mechanism of action is based upon an animal study[8] showing that the blood pressure lowering effect of GABA is due to binding to peripheral GABA receptors as well as the results from a human study.[9] Using a double blind, crossover design, 12 males (aged 21.7± 0.8yr) consumed a placebo or PharmaGABA-containing capsules (30 mg per meal) after an overnight fast. Parasympathetic nervous system activity was evaluated by means of heart rate variability power spectral analysis before and after administration for 30 and 60 minutes. There were significant increases in overall autonomic and parasympathetic nervous system activities after PharmaGABA ingestion indicating that PharmaGABA may induce relaxation effects by modulating autonomic nervous system activity.

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PharmaGABA is approved for use in Japan as an aid to conquer stress and promote relaxation. It is a very popular ingredient in function foods and beverages as well as dietary supplements designed to produce mental and physical relaxation, without inducing drowsiness. The most popular applications of PharmaGABA at present is in chocolate and coffee beverages. It is particularly helpful in counteracting the effects of caffeine.

PHARMAGABA: EFFECTS ON EEG

Electroencephalogram (EEG) is a well known measure of brain waves activity. The four major brain waves are classified according to their frequency: alpha (less than 8–13 Hz), beta (more than 13 Hz), theta (less than 4–8 Hz), and delta waves (less than 4 Hz). Each wave's type is associated with a certain mental status. Delta and theta occur during deep sleep and early stages of sleep, respectively. Alpha is generated in relaxed and effortless alertness, while beta is seen in highly stressful situations and where there is difficulty in mental concentration. Therefore, the ratio of alpha to beta waves has been used as indices of relaxation, arousal, anti-stress, and better concentration. The greater the alpha to beta ratio, in general, the more relaxed and alert a person is.

Research has shown that PharmaGABA quickly (i.e. within 5 minutes) and efficiently increases the alpha to beta brain waves ratio – a state often achieved by meditation and characterized by being relaxed with greater mental focus and mental alertness. In one study conducted at the University of Shizuoka, 13 healthy Japanese volunteers, 7 males and 6 females, aged from 21 to 35 years, were enrolled. Two hours before the study they were forbidden to eat, drink or use any form of tobacco. EEG tracings were recorded before and after each of three administrations. The order of testing for each volunteer administered 200 mL of distilled water was as follows: (i) only distilled water; (ii) containing 100 mg of PharmaGABA ; and (iii) containing 200 mg L-theanine (an amino acid from green tea known to increase alpha brain waves). Tests of the 3 administrations were separated by 7-day

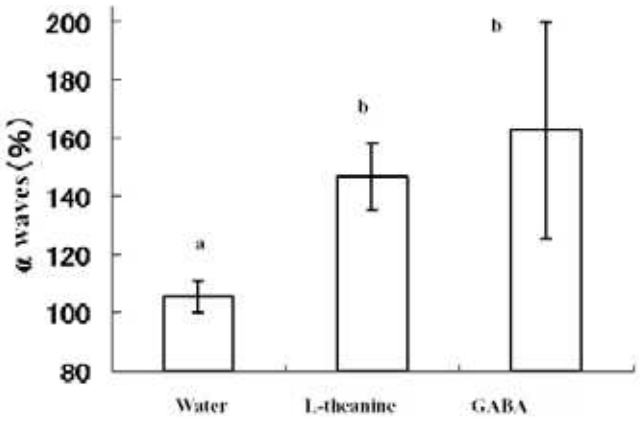

Figure 1 **Changes of alpha waves generation ratios after administration of water (control), L-theanine, and PharmaGABA measured by electroencephalogram (EEG).** Values are means ± SEM of waves ratios of 3 measurements (at 0, 30 and 60 minutes after each administration). Values with different letters are significantly different at P <0.05.[10]

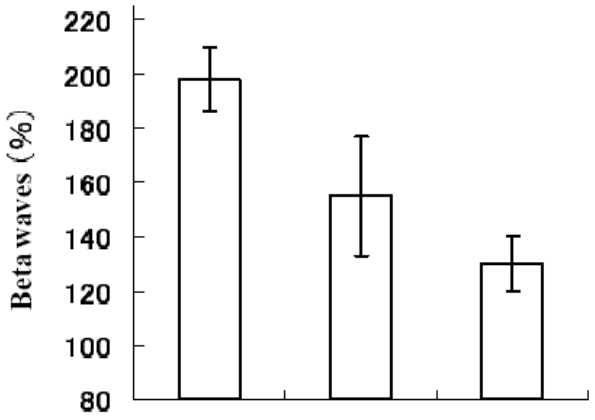

Figure 2 **Changes of beta waves generation ratios after administration of water (control), L-theanine, and PharmaGABA measured by EEG.** Values are means ± SEM of waves ratios of 3 measurements (at 0, 30 and 60 minutes after each administration).[10]

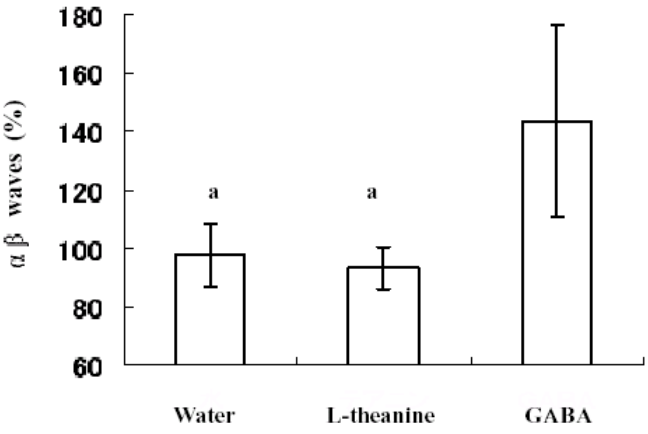

Figure 3 **Changes of alpha/beta waves ratio values after administration of water (control), L-theanine, and PharmaGABA measured by electroencephalogram (EEG).** Values are means ± SEM of alpha/beta ratio values of 3 measurements (at 0, 30 and 60 minutes after each administration). Values with different letters are significantly different at P < 0.05.[10]

intervals. EEG recordings were obtained with the subject resting quietly with closed eyes. EEG tracings were made before administration, then at 0, 30 and 60 minutes after each administration for 5 minute recording sessions. Alpha and beta waves were calculated as a percentage between pre- and post-administration values. Alpha/beta ratios have been calculated as a ratio between alpha and beta percentage values. As apparent in Figures 1 and 2,[10] PharmaGABA produced significant effects on both increasing alpha waves and decreasing beta waves. As a result there was a highly significant increase in the alpha to beta wave ratio (Figure 3).[10]

ADDITIONAL ANTI-STRESS EFFECTS OF PHARMAGABA

Additional clinical studies with PharmaGABA have yielded further support for an anti-stress agent. For example, one study had

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Illustration 1 **Walking across this suspension bridge is enough to give anyone a bit of anxiety.** This bridge at Nara Totsu River Village is Japan's longest pedestrian suspension bridge with a length of 1,000 feet, height of 150 feet, and a width of 6 feet. When subjects with a fear of heights were given PharmaGABA they actually experienced a relaxed state at the halfway point across the bridge.

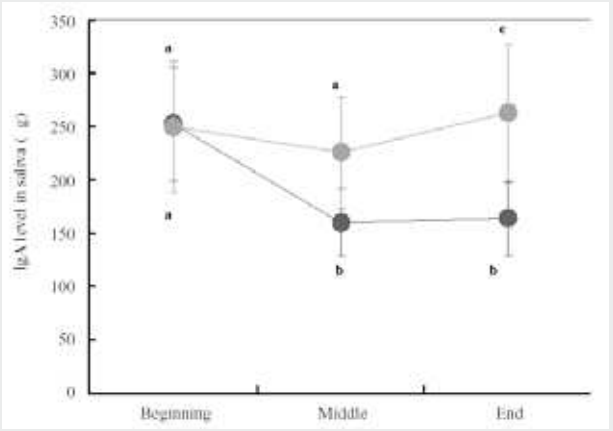

Figure 4 **Immunoglobulin A (IgA) levels in saliva of acrophobic volunteers crossing the suspended bridge as a tool of stress.** Values are means ± SEM of IgA levels in 8 volunteers at beginning, middle and end of the bridge alpha/beta ratio values of 3 measurements. Values with different letters are significantly different at $P < 0.05$.[10]

subjects with acrophobia (fear of heights) transverse a long walking suspension bridge that spanned a 150 foot canyon. Halfway across the bridge a saliva sample was obtained. What the researchers were looking for in the saliva was the level of secretory IgA – an important antibody in saliva that helps fight infection. Typically, during times of stress saliva levels drop, sometimes quite precipitously. This event happened when the subjects were given a placebo, but when they were given PharmaGABA the secretory IgA levels in the saliva were maintained halfway across the bridge and actually increased upon completion of the crossing (Figure 4).[10]

A second study using the same suspension bridge and different subjects produced additional support on PharmaGABA's ability to reduce markers of stress as during GABA supplementation subjects experienced a 20% decrease in salivary chromogranin A, (an andrenal stress marker), at the halfway point across the bridge compared to starting values, while the control group had a 20% increase in chromogranin A.[7] In other words, although the subjects were under stress, when they took PharmaGABA their physiology responded as if it was experiencing a state of relaxation.

GABA agonist drugs are used as sedatives in the treatment of insomnia. While PharmaGABA has no real sedative effect per se, it has been shown to significantly improve sleep efficiency. Poor sleep quality is a major issue in North America and is associated with many common complaints including fatigue, depression, fibromyalgia and reduced productivity. PharmaGABA can help patients fall asleep faster as well as achieve deeper levels of sleep and to stay in this deep sleep for sufficient time. In the small pilot study, PharmaGABA reduced sleep latency by 20%, while increasing the time spent in deep sleep by 20%.[7]

DOSAGE RECOMMENDATIONS

PharmaGABA can be used for situational stress, more pervasive feelings of anxiety or as a sleep enhancer. The typical dosage is 100 to 200 mg up to three times daily. As a general guideline it is recommended to take no more than 1,000 mg within a 4 hour period and no more than 3,000 mg within a 24 hour period.

SIDE EFFECTS

While GABAergic drugs have numerous side effects and are highly addictive drugs not suitable for long term use, PharmaGABA is completely safe and can be very effective without side effects at recommended dosages. The difference in safety is probably a result of a limited capacity of the brain to retain excessive amounts of GABA as there is a very efficient efflux of GABA across the blood-brain barrier.[11] The transport of GABA into the CNS is limited and the efflux of GABA out of the brain is one of the primary routes of elimination of GABA. As a result, it is highly unlikely that oral PharmaGABA supplementation at recommended dosages would produce any significant effect.

High intake of synthetic GABA was shown to produce a significant increase in plasma growth hormone levels (single administration of 5,000 mg) and prolactin (daily administration of 18,000 mg for four days) in one human study, but the clinical significance of these observations is not clear.[12] In another study, 12 normal subjects given a single oral dose of 5 or 10 g GABA, as compared to placebo, caused a significant (p less than 0.01) and dose-dependent (p less than 0.01) increase of plasma levels of immunoreactive insulin, C peptide and glucagon, without affecting plasma glucose concentration.[13]

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SAFETY

PharmaGABA is exceptionally safe and has recently achieved Generally Recognized As Safe status (GRAS) in the United States. LD50 tests conducted on natural GABA in doses of 5,000 mg/kg in rats did not cause any mortality, confirming that LD50 is more than 5,000 mg/kg in rats.[7]

PREGNANCY AND LACTATION

Not recommended during pregnancy and lactation unless recommended by a health care practitioner.

CHILDREN

Not recommended for children under 6 years of age unless recommended by a health care practitioner.

DRUG INTERACTIONS

There are no known drug interactions at recommended levels.

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