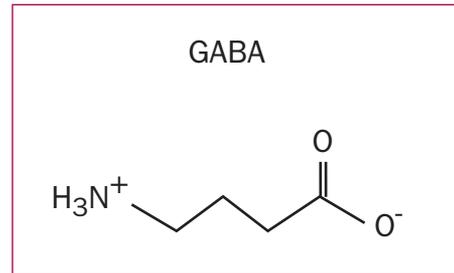


Gamma-Aminobutyric Acid (GABA)



Introduction

Gamma-aminobutyric acid (GABA) is a major neurotransmitter widely distributed throughout the central nervous system (CNS). Because too much excitation can lead to irritability, restlessness, insomnia, seizures, and movement disorders, it must be balanced with inhibition. GABA – the most important inhibitory neurotransmitter in the brain – provides this inhibition, acting like a “brake” during times of runaway stress. Medications for anxiety, such as benzodiazepines, stimulate GABA receptors and induce relaxation. Either low GABA levels or decreased GABA function in the brain is associated with several psychiatric and neurological disorders, including anxiety, depression, insomnia, and epilepsy. Studies indicate GABA can improve relaxation and enhance sleep.

Both synthetic and natural GABA are available as dietary supplements in the United States. Natural GABA is produced 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.

Biochemistry and Pharmacokinetics

Within the brain, glutamic acid is converted to GABA via the enzyme glutamate decarboxylase and its cofactor pyridoxal 5' phosphate (P5P; active vitamin B6). GABA is metabolized by gamma-aminobutyrate transaminase, also a P5P-dependent enzyme, forming an intermediate metabolite succinate semialdehyde. This metabolite can then be reduced to gamma-hydroxybutyrate, or oxidized to succinate and eventually converted to CO₂ and water via the citric acid cycle.

When plasma membrane depolarization induces the release of GABA from nerve terminals, GABA binds to GABA receptors – such as the GABA_A and GABA_B receptors – that are distributed on post-synaptic cell membranes. The actions of GABA are terminated by its reuptake by glial cells or pre-synaptic neurons via specific high-affinity transporters. This appears to be the primary mechanism by which GABA concentrations are reduced in the brain extracellular fluid.

Mechanisms of Action

GABA mediates pre-synaptic inhibition of primary afferent fibers in the motor neuron system. It regulates brain excitability via GABA_A receptors, which are classified into three major groups (alpha, beta, and gamma) with subunits that determine its pharmacological activity. For instance, certain benzodiazepines have a strong binding affinity for the alpha1 subunit, while others bind to other alpha subunits.¹

In addition to neurological effects, GABA appears to exert effects on the endocrine system. It was shown to produce a significant increase in plasma growth hormone levels after a single, high-dose administration of 5 g.¹ GABA, found in high concentrations in pancreatic islet cells, resulted in increased plasma levels of immunoreactive insulin, C-peptide, and glucagon without affecting plasma glucose concentration, in 12 normal subjects given single oral doses of 5 or 10 g.² The clinical significance of these endocrine effects is unclear.

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Deficiency States

Low GABA levels are associated with several psychiatric and neurological disorders, including anxiety, depression, insomnia, and epilepsy.³⁻⁸ Because of the association between low GABA levels and these conditions, many anti-anxiety and sleep-enhancing drugs have been developed that interact primarily with GABA receptors. These include the benzodiazepine drugs – alprazolam (Xanax[®]), diazepam (Valium[®]), flurazepam (Dalmane[®]), quazepam (Doral[®]), temazepam (Restoril[®]), and triazolam (Halcion[®]) – and zolpidem tartrate (Ambien[®]) and baclofen (Kemstro[®] and Liore-sal[®]). Olfactory and gustatory hallucinations have been associated with low brain GABA levels. Treatment that reversed the hallucinations resulted in increased GABA in the CNS.⁹

Clinical Applications

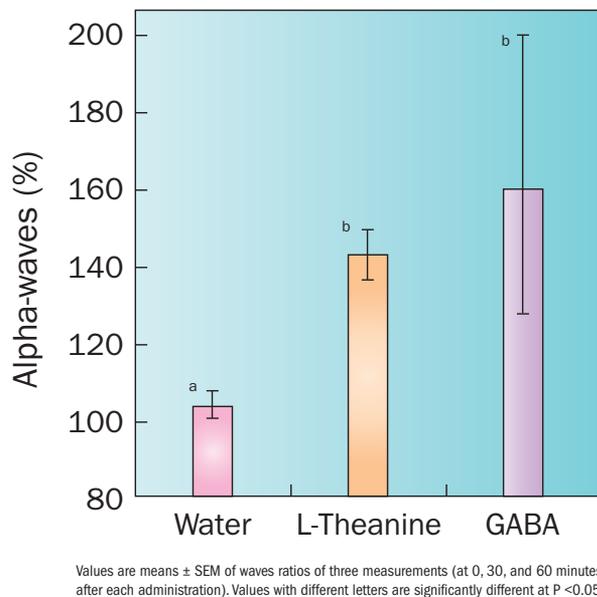
Clinical studies on GABA supplementation are limited. Rather, studies have primarily focused on patentable synthetic GABA analogues, such as gabapentin, or other drugs that bind to GABA receptors. Thus, much of the suggested clinical application of GABA is theoretical, based on anecdotal clinical experience, or extrapolated from drug studies. Large-scale clinical studies on a wide array of psycho-neurological conditions are warranted.

Stress/Anxiety

Because inadequate GABA brain activity or low levels of GABA have been associated with anxiety, many anti-anxiety drugs, some in use for more than 40 years, target the GABA_A receptor.¹⁰ A small preliminary study of six subjects found gabapentin (structurally similar to GABA; increases brain GABA levels) to be effective for panic disorder.¹¹ Natural therapies that produce relaxation also act, at least in part, by enhancing GABA levels. A controlled pilot study found brain GABA levels were significantly increased after a single 60-minute yoga session compared to a 60-minute reading session.¹² Another study found valerianic acid, an active component of valerian, modulates GABA_A receptors.¹³

In an unpublished, double-blind comparison trial, a natural-source GABA (PharmaGABA[®]), but not synthetic GABA, was shown to produce relaxation as evidenced by changes in brain wave patterns, diameter

Figure 1. Changes in Alpha-wave Generation after Administration of Water, L-Theanine, or Natural GABA



of the pupil, and heart rate, as well as reduction of stress markers salivary cortisol and chromogranin A (a marker of adrenal stress).¹⁴

An electroencephalogram (EEG) is a measure of brain-wave activity. Alpha waves are generated in a relaxed state, whereas beta waves are seen in stressful situations that make mental concentration difficult. Therefore, the ratio of alpha-to-beta waves has been used as an indication of relaxation and better concentration. In general, the greater the alpha-to-beta ratio, the more relaxed and alert is the person.

A small pilot study conducted at the University of Shizuoka in Japan enrolled 13 healthy volunteers, seven males and six females ages 21-35. Two hours prior to commencement of the study, subjects were not allowed to eat, drink, or use any form of tobacco. EEG tracings were recorded before and after each of three administrations of 200 mL distilled water: (1) only distilled water; (2) distilled water containing 100 mg natural GABA (PharmaGABA); and (3) distilled water containing 200 mg L-theanine (an amino acid from green tea known to increase alpha-brain waves). Tests of the three administrations were separated by seven-day intervals.

EEG recordings were obtained with the subject resting quietly with closed eyes, and were made before administration, then at 0, 30, and 60 minutes after each administration for five-minute recording sessions. Alpha and beta waves were calculated as a percentage and pre- and post-administration values were compared. Alpha-to-beta ratios were calculated as a ratio between alpha and beta percentage values. GABA produced significant effects on both increasing alpha waves (Figure 1) and decreasing beta waves, resulting in a highly significant increase in the alpha-to-beta wave ratio.¹⁵

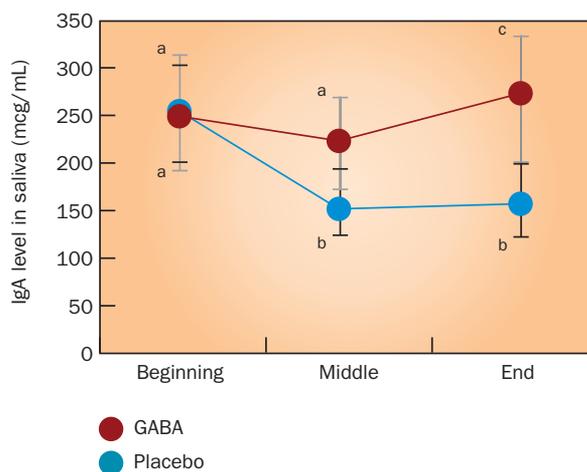
Another study yielded further evidence of natural GABA's anti-stress activity. In blinded fashion, eight subjects (ages 25-30) with acrophobia (fear of heights) were given 200 mg natural-source GABA (PharmaGABA) or placebo before traversing a long walking suspension bridge that spanned a 150-foot canyon.¹⁵ Salivary secretory immunoglobulin A (sIgA) was determined from samples taken before crossing, halfway across, and after crossing the bridge. Secretory IgA is an important antibody in saliva that helps fight infection. Relaxation results in significant ($p < 0.001$) increases in sIgA levels,¹⁶ while stress results in decreased salivary sIgA. In this study, sIgA levels decreased by approximately 35 percent in subjects in the control group; however, individuals in the GABA group maintained salivary sIgA levels at the halfway point on the bridge and actually demonstrated increased levels upon completion of the crossing (Figure 2). In order to offset the potential confounding effect of saliva quantity (stress can cause "dry mouth"), the absolute concentrations of sIgA were determined in mcg/mL.

A second unpublished study, using the same suspension bridge and different subjects ($n=13$), produced additional support for GABA's ability to reduce markers of stress. Subjects given 200 mg natural-source GABA experienced a 20-percent decrease in salivary levels of the adrenal stress marker chromogranin A at the halfway point across the bridge compared to starting values; the control group demonstrated a 20-percent increase in chromogranin A.¹⁴

Depression

Interest in studying the role of GABA for depression has been sparked by preclinical studies suggesting GABA levels are decreased in patients suffering

Figure 2. Salivary Immunoglobulin A Levels of Acrophobic Volunteers Crossing a Suspension Foot Bridge



Values are means \pm SEM of IgA levels in eight volunteers at beginning, middle, and end of the bridge. Values with different letters are significantly different at $p < 0.05$.

from depression.^{6,17,18} Since the role of GABAergic dysfunction in mood disorders was first proposed, various antidepressant drugs have been shown to be effective for depression by affecting not only monoamine and serotonin activity, but also by increasing brain GABA activity.

A 2006 study using magnetic resonance spectroscopy (MRS) found low occipital-lobe GABA levels during the postpartum period,¹⁹ suggesting a possible role of GABA for postpartum depression. A similar study using MRS found low occipital GABA levels in chronically depressed patients, even during medication- and depression-free periods. The authors concluded, "These changes could represent part of the neurobiological vulnerability to recurrent depressive episodes."²⁰

Although low GABA levels have been found in patients suffering from various forms of depression and GABAergic drugs offer an effective treatment for depression, to date no studies have been conducted to assess the effectiveness of GABA supplementation for depression.

Sleep Enhancement

Due to its relaxation effects, GABA may be considered as a sleep aid. GABA_A receptors are highly expressed in the thalamus, a region of the brain involved

with sleep processes.²¹ GABA-agonist drugs, such as zolpidem (Ambien) and temazepam (Restoril), are sedatives used in the treatment of insomnia.^{22,23} The synthetic GABA-like drug gabapentin that increases brain GABA levels has been found to improve sleep disturbances associated with alcohol consumption.²⁴

In a small, unpublished study, 100 mg natural-source GABA reduced sleep latency by 20 percent, while increasing the time spent in deep sleep by 20 percent.¹⁴

Epilepsy

The mechanisms of most anti-epileptic drugs involve direct or indirect GABA enhancement.²⁵ The drugs act in a variety of ways by increasing GABAergic inhibition (benzodiazepines, phenobarbital, valproate), inhibiting GABA reuptake (tiagabine), increasing synaptic GABA concentration through inhibition of gamma-aminobutyrate transaminase (vigabatrin), and increasing brain synaptic GABA and decreasing neuronal influx of calcium ions (gabapentin).²⁶

The ketogenic diet, employed in particular for treatment of childhood epilepsy, is theorized to work via GABAergic mechanisms. Ketosis increases brain metabolism of acetate, which is converted to glutamine by glial cells. Glutamine is then taken up by GABAergic neurons and converted to GABA.²⁷ EEG tracings in healthy human subjects on a ketogenic diet yielded patterns consistent with increased GABA activity.²⁸

Research indicates oral GABA supplementation may be beneficial for epilepsy. Several animal and clinical studies have examined the effect of a combination of GABA and phosphatidylserine (PS) in the treatment of various types of seizure disorders.

A pilot study of 42 subjects with drug-resistant epilepsy (10 with absence seizures) found a combination of increasing doses of GABA (1,500/2,500 mg daily) and PS (300/500 mg daily) – in separate capsules – resulted in a significant, dose-dependent decrease in absence seizures, but not in simple or complex partial seizures.²⁹ A second, small pilot study examined the effect of a single acute dose of GABA and PS on nine epileptic patients with convulsions associated with intermittent photic stimulation (such as a strobe light). Neither 3 g GABA/600 mg PS nor 3 g GABA/1,200 mg PS resulted in improvement. The researchers suggested a one-time dose might not be sufficient to achieve positive results.³⁰

In animal studies, liposomes of phosphatidylserine and GABA were found to benefit both isoniazid-³¹ and penicillin-induced^{32,33} seizures. In the latter study, liposomes of GABA with phosphatidylcholine or phosphatidylethanolamine were not effective.³³

Movement Disorders: Tourette Syndrome, Parkinson's Disease, Tardive Dyskinesia

As the main inhibitory neurotransmitter, it is not surprising GABAergic pathways are involved in the pathophysiology of various movement disorders. Baclofen, a synthetic GABA analogue, exerts antispasmodic effects and has been found to benefit children with Tourette syndrome.^{34,35} The GABA-agonists zolpidem^{36,37} and gabapentin³⁸ have been found to benefit patients with Parkinson's disease, while the GABA-agonist vigabatrin (gamma-vinyl-GABA) provides benefit for tardive dyskinesia and other movement disorders.³⁹ While no clinical studies have been conducted on GABA for movement disorders, a trial of supplemental GABA seems prudent, considering the preponderance of evidence implicating faulty GABA-pathway signaling in the pathophysiology of these conditions.

Side Effects and Toxicity

Although synthetic GABA-agonist drugs can have significant side effects, ranging from drowsiness and dizziness to addiction, natural GABA supplementation is virtually without side effects. This difference in safety profiles may result from a limited capacity of the brain to retain excessive amounts of GABA, since there is an efficient efflux of GABA across the blood-brain barrier.⁴⁰ LD₅₀ tests conducted on natural GABA in doses of 5,000 mg/kg to rats did not cause any mortality, indicating an LD₅₀ >5,000 mg/kg in rats.¹⁴

Dosage

A typical dosage of GABA for anxiety or sleep disorders is 100-200 mg up to three times daily. Dosages of GABA found to benefit a subset of individuals with epilepsy ranged from 1,500-2,500 mg daily.

Warnings and Contraindications

GABA has not been tested for safety in pregnancy and, because of its effect on neurotransmitters, is not recommended during pregnancy or lactation.

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