GABA

Structure/Function Claim Substantiation Report
For GABA on behalf of Verb Biotics

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Improving health through microbiome innovation

Contents

Executive Summary of Findings

GABA satisfies the definition of a dietary supplement, and it has a presumed safety profile equal to that of a food or other dietary ingredients. GABA was affirmed GRAS by scientific procedures. Lactic acid bacteria (LAB) have been shown to produce GABA. GABA is bioavailable and can exert an effect within 30 minutes. The literature reviewed supports the following structure/function claims (see Table 1).

- Supports/promotes relaxation
- Supports a healthy mood
- Supports a healthy reaction to stress
- Supports healthy stress response
- Supports healthy sleep
- Enhances sleep quality

The dose to support these claims is a minimum of 100 mg per day.

Table 1: Supported Structure/ Function Claims

Supported Claims		Reference (100 mg)
Supports/promotes relaxation **Supports a healthy mood/mood state**	• **50–100 mg / day** of GABA showed positive benefits on measures of relaxation and mood in clinical studies.	1–3
Supports a healthy reaction to stress/ stress response **Supports stress management** **Supports mental outlook during stress**	• A systematic review of 14 RCTs support moderate improvements in stress. • Significant decrease in mental stress task 30 to 60 min after intake of 100 mg of GABA.	4–5
Supports healthy sleep **Aids in falling asleep/falling asleep faster** **Enhances sleep quality**	• **100 mg** GABA taken for 1 week significantly shortened sleep latency and increased the total non-rapid eye movement (non-REM) sleep time. • Questionnaires showed subjects receiving GABA felt their sleep was improved compared to placebo. • Oral administration of GABA **(100 mg)** had beneficial effects on sleep. GABA shortened sleep latency by 5.3 minutes.	6–7
Supports exercise recovery **Supports muscle gains with exercise**	• An increase in growth hormone following GABA administration. • After 12 weeks, the group receiving 10g whey protein (WP) + 100 mg GABA exhibited significantly greater increase in whole body fat-free mass than the 10g WP group.	8–9
Fast acting **Rapid absorbing**	• It is rapidly absorbed demonstrating an effect 30 minutes after ingestion.	3, 7
GABA can be given (taken) with or without food	• GABA supplementation can be given with or without food.	10

RECENT HUMAN SAFETY DATA

The United States Pharmacopeia published a comprehensive safety evaluation of GABA noting "Clinical data from 16 studies that examined the effect of GABA in different matrices (fermented milk or soy) on mild hypertension, insomnia, and stress and as an ergogenic substance at doses of 120 mg of GABA/day for 12 weeks reported that ingestion of GABA was not associated with any serious adverse effects." However, it should be noted that the review found no clinical studies specifically designed to study the safety of GABA in healthy individuals. Three short-duration clinical studies (a one-time 5 g dose, 18 g for 4 days, and 5 g or 10 g daily for 5 days) administered up to 18 g of GABA, and in all three studies, only a few participants reported a slight burning sensation in the throat immediately after taking GABA which ceased shortly thereafter. In some cases, the burning sensation was accompanied by brief shortness of breath. Additionally, intake of 5 or 10 g daily for 4–5 days resulted in increases in immunoreactive insulin and glucagon, although no change in blood glucose level was observed.[11] Taken together, no serious side effects were associated with the administration of pure GABA at doses of up to 18 g daily for 4 days.[12]

The USP concluded no serious adverse event concerns within the above noted confines. Based on this review, the USP Dietary Supplements Admission Committee admitted GABA for USP monograph development.[12]

The USP also surmised the following as related to its safety review of GABA; "Because some studies showed that GABA was associated with decreases in blood pressure, it is conceivable that concurrent use of GABA with anti-hypertensive medications could increase risk of hypotension. Caution is advised for pregnant and lactating women since GABA can affect neurotransmitters and the endocrine system, i.e., increases in growth hormone and prolactin levels."[12]

As a dietary supplement that is compliant with DSHEA 1994 (GABA), the ingredient has a presumed safety profile equal to that of a food or other dietary ingredients.[13]

Further regulatory affirmation of GABA's status, is the Environmental Protection Agency (EPA) notation of GABA as GRAS. The EPA further affirms GABA's human

safety as noting “toxicity tests in animals and humans showed no adverse effects from GABA.”[14]

Safety of GABA as a dietary ingredient is further supported by Health Canada (The Canadian equivalent of the FDA). **Health Canada regulates GABA as an approved safe Natural Health Product (NHP). Health Canada recommends for doses greater than 300 mg GABA per day** and when used for four or more consecutives weeks, one should consult a healthcare practitioner.[15]

Ingredient Review

MECHANISM OF ACTION

Gamma-aminobutyric acid (GABA) is a non-protein amino acid that is widely distributed in nature.[16] It is present in high concentrations in the brain. GABA and its receptors are also detected in the peripheral system, endocrine, and several non-neural tissues where it plays a role in oxidative metabolism.[17] It is found in various foods such as green tea, soybean, germinated brown rice, kimchi, cabbage pickles, and yogurt. GABA is well known as the major inhibitory neurotransmitter in the mammalian central nervous system. It modulates synaptic transmission, promotes neuronal development and relaxation, and prevents sleeplessness and depression.[18,19] 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.[20] It has been shown to effect the early stages of sleep at a dose of **100 mg**.[7]

Rodent studies have suggested that GABA plays a role in the release of growth hormone.[21,22] The findings were supported by human studies.[8,23] This suggests a potential role for GABA in exercise recovery and protein synthesis via an increase in growth hormone by GABA administration.

ABSORPTION AND METABOLISM

GABA derived from food has been shown to be bioavailable.[24] GABA supplementation can be given with or without food.[10] It is rapidly absorbed demonstrating a pharmacokinetic effect 30 minutes after ingestion.[5,7]

The Figure below demonstrates the rapid absorption of oral GABA, occurring by the 30-minute post ingestion period. The elevation above baseline levels remained at the 60-minute mark (1 hr.).[7]

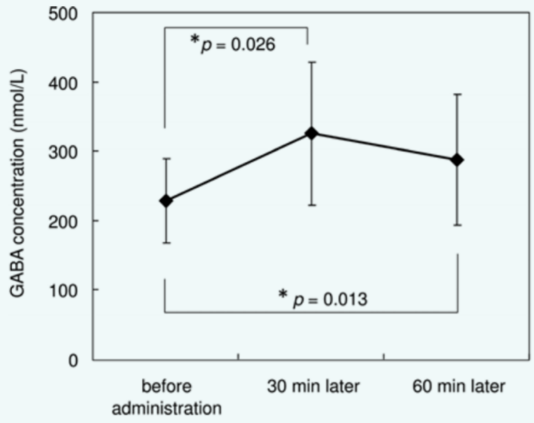

Fig. 4. Plasma GABA concentration before, 30 min after, and 60 min after GABA administration. Values are the mean±SD. *indicates a significant difference compared with the value before administration (p<0.05).[7]

A separate study detailed the rapid absorption of oral GABA at 30 minutes, further described with a half-life of 5 hours.[25] The study found that the time to maximum blood concentration of GABA after dosing was 1.5 hours, and that whether a single dose or repeat dosing was used (12 hours later), the half-life remained at ~5 hours (see Table 1 in the referenced document). 12 hours after dosing with GABA, the blood values were returning towards baseline, but were not yet baseline, consistent with the determined half-life. This data suggests no apparent pharmacokinetic benefit to dosing more than once per day.[25]

Biosynthesis

Lactic acid bacteria (LAB) are able to produce GABA though the production of GABA varies among various strains of LAB and various types of fermentation.[26]
Several LAB strains with the ability to produce GABA have been isolated from fermented foods such as cheese, kimchi, yogurt, and fermented soy beans.[27]
The biosynthesis of GABA by microorganisms is conducted by the glutamic acid decarboxylase (GAD, EC 4.1.1.15) system, which is composed of the GAD enzyme (encoded by *gadA* or *gadB*) and glutamate/GABA antiporter GadC.[28] LAB strains with the GAD gene are able to synthesize GABA.[27] Conditions of the fermentation such as pH, nitrogen source, and temperature optimize the amount of GABA produced by impacting GAD activity.[27,29]

CLINICAL STUDIES

50–100 mg / day of GABA showed positive benefits on measures of relaxation and mood in clinical studies.[1–3]

A systematic review was conducted to assess scientific evidence supporting the beneficial effects of oral GABA (natural or biosynthetic) intake on stress, sleep, and related psychophysiological measures. Only placebo-controlled human trials that assessed stress, sleep, and related psychophysiological outcomes as a response to natural GABA (i.e., GABA that is present naturally in foods) or biosynthetic GABA (i.e., GABA that is produced via fermentation) intake were included. Fourteen studies met the criteria and were included in the systematic review. The authors concluded that there was low to moderate evidence for GABA's stress benefits (due to the fact that there are more studies with positive results) and low evidence for GABA's sleep

benefits especially in the studies that measured a one-time dose. They stated that GABAs effects on sleep are most likely recognized after at least 1 week of intake. The most commonly used dose across the studies was 100 mg.[4] Below is the table summarizing studies used in the systematic review:

TABLE 1 | Continued

References	Participants (*N* and characteristics)	Intervention (I) vs. control (C)	Duration of intervention	Design	Dependent measures	Time measures taken
Yamatsu et al. (2016)	10 (6 males, age range: 24–57, poor sleepers: PSQI >6)	I: 100 mg GABA + 4.7 mg Glutamic acid, 2.3 mg other amino acids, 3.4 mg minerals and 1.6 mg water (112 mg)—capsule C: 112 mg dextrin	1 week	Single-blind, controlled, crossover	PSQI Total, VAS for sleep satisfaction, easiness to fall asleep, and feelings upon awakening, EEG for sleep latency, sleep efficiency, Non-REM sleep latency, REM sleep time, Non-REM sleep time, Light Non-REM sleep time, Deep Non-REM sleep time, Awakening frequency, Delta wave	Pre-ingestion and post-ingestion, exact timelines are not clear
Yamatsu et al. (2015)	16 (7 males, age range: 27–45, poor sleepers: PSQI >6)	I: 100 mg GABA + 50 mg dextrin (capsule) I: 100 mg GABA + 50 mg AVLE (capsule) I: 50 mg AVLE + 100 mg dextrin (capsule) C: 150 mg dextrin (capsule)	1 week	Single-blind, controlled, crossover	PSQI Total, VAS for sleep satisfaction, easiness to fall asleep, and feelings upon awakening, EEG for sleep latency, Non-REM sleep latency, REM sleep time, Non-REM sleep time, Awakening frequency, Delta wave	Pre-ingestion and post-ingestion, exact timelines are not clear
Yoto et al. (2012)	63 (28 males, age range: 20–28, healthy)	I: 100 mg GABA (capsule) C: 100 mg dextrin (capsule)	Single dose*	Single-blind, controlled, crossover	POMS-tension/anxiety, VAS for arousal and relaxation, EEG-alpha and beta wave	Pre-ingestion, 10, 40, and 70 min post-ingestion
Abdou et al. (2006)	*Experiment 1* 13 (7 males, age range: 21–35, healthy)	*Experiment 1* I: 100 mg GABA + 200 ml water I: 200 mg theanine + 200 ml water C: 200 ml water	*Experiment 1* Single dose	*Experiment 1* Controlled, crossover	*Experiment 1* EEG for alpha and beta wave	*Experiment 1* Pre-ingestion, at the time of ingestion, 30 and 60 min post-ingestion
	Experiment 2 8 (5 males, age range: 25–30, acrophobic)	*Experiment 2* I: 100 mg GABA + 200 ml water C: 200 ml water	*Experiment 2* Single dose*	*Experiment 2* Controlled, parallel	*Experiment 2* IgA	*Experiment 2* Before crossing, at middle, and at the end of the bridge
Byun et al. (2018)	40 (10 males, age range: 30–64, poor sleepers: PSQI >5 and ISI >8)	I: 300 mg GABA + maltodextrin (tablet) C: Maltodextrin (tablet)	4 weeks	Double-blind, controlled, parallel	ISI, PSQI for total score, sleep quality, sleep latency, total sleep time, sleep efficiency, PSG for total sleep time, N1, N2, N3, REM, WASO, Arousal Index, AHI, RDI, REM sleep latency, sleep latency, sleep efficiency	Pre-intervention and at the end of Week 4
Yamatsu et al. (2013)	38 (14 males, age range: 71–92, healthy)	I: 100 mg GABA in 6.8 g chocolate C: Dextrin in 6.8 g chocolate	4 weeks	Double-blind, controlled, parallel	Cortisol, OSA sleep inventory	Pre-ingestion, 30 and 60 min after ingestion

A randomized, single-blind, placebo-controlled crossover-designed study was conducted to evaluate the effect of GABA on sleep in 10 healthy adults with self-reported sleep issues. 100 mg GABA taken for 1 week significantly shortened sleep latency and increased the total non-rapid eye movement (non-REM) sleep time. Questionnaires showed that subjects receiving GABA realized its effects on sleep. In addition, the blood level of GABA after administration was investigated, and the absorption and metabolism rates of GABA were determined. GABA was

quickly absorbed, and the blood level of GABA was the highest 30 min after oral administration, with a subsequent decrease in concentration.[7]

The effects GABA produced by natural fermentation on the improvement of sleep were investigated in humans. The electroencephalogram (EEG) test revealed that oral administration of GABA (100 mg) had beneficial effects on sleep. GABA shortened sleep latency by 5.3 min.[6]

A single blind, cross-over, randomized, placebo-controlled study assessed the effects of GABA (100 mg or placebo with 250ml of water) each day intake on CNS activities in 63 healthy people under mental task stress loads by measuring electroencephalography (EEG) and Profile of Mood States (POMS). EEG activities including alpha band and beta band brain waves decreased from 30 to 60 min after intake indicating that the mental stress tasks used in the study might have reduced the overall brain activities from alpha band to beta band during the rest periods. At 30 minutes after GABA intake, this decrease diminished significantly more than it did for the placebo condition. This action was supported by the POMS V score which showed that vigor-activity significantly decreased after each mental stress task.[5]

A randomized, double-blind study was conducted to examine the effects of oral GABA plus whey protein supplementation on muscular hypertrophy in men after progressive resistance training. Twenty-one healthy men (26 - 48 years) were randomized to receive whey protein isolate (WP; 10 g) or whey protein isolate + GABA (WP + GABA; 10 g + 100 mg) daily for 12 weeks. Both groups performed resistance training twice per week (three sets of 12 repetitions at 60% of maximal strength; leg press, leg extension, leg curl, chest press, and pull down). In the WP + GABA group, resting plasma growth hormone concentrations were significantly elevated at 4 and 8 weeks, compared to baseline. However, resting plasma growth hormone concentrations in the WP group were only significantly elevated at 8 weeks. After 12 weeks, the WP + GABA group exhibited significantly greater increase in whole body fat-free mass than the WP group.[9]

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