GABA – ESSENTIAL BIOACTIVE COMPONENT OF GABA-ENRICHED TEAS

What is GABA?

Gamma-aminobutyric acid (GABA) occurs naturally in Camellia sinensis tea and its natural level can be enhanced further by anerobic fermentation. Although GABA has been recognized as a plant metabolite since the mid 19th century, its key role in brain functon was not demonstrated until 1957 (1). GABA, a non-protein amino acid, is an inhibitory neurotransmitter in your brain. It reduces a nerve cell's ability to send and receive chemical messages throughout the central nervous system in both the brain and spinal cord. Specifically it slows down your brain by blocking specific signals in your central nervous system.

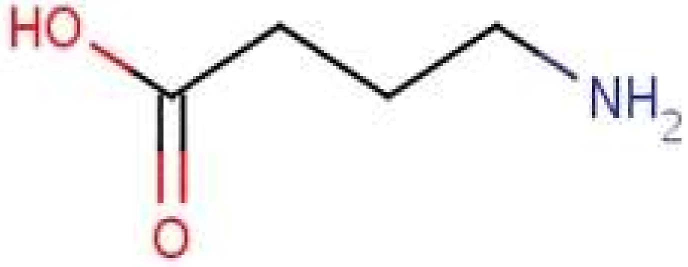

Figure 1. Chemical Structure of GABA

GABA, one of the most abundant neurotransmitters in mammals, is distributed in most areas of the brain and participates in 40% of the inhibitory synapses of adult vertebrates (2).

GABA is synthesized in the cytoplasm of the presynaptic neuron from the precursor glutamate by the enzyme glutamate decarboxylase, an enzyme which uses vitamin B6 as a cofactor. After synthesis, it is loaded into synaptic vesicles by the vesicular inhibitory amino acid transporter. It is predominantly released by local interneurons in the cerebral cortex to particular subcellular domains of the target cells (3).

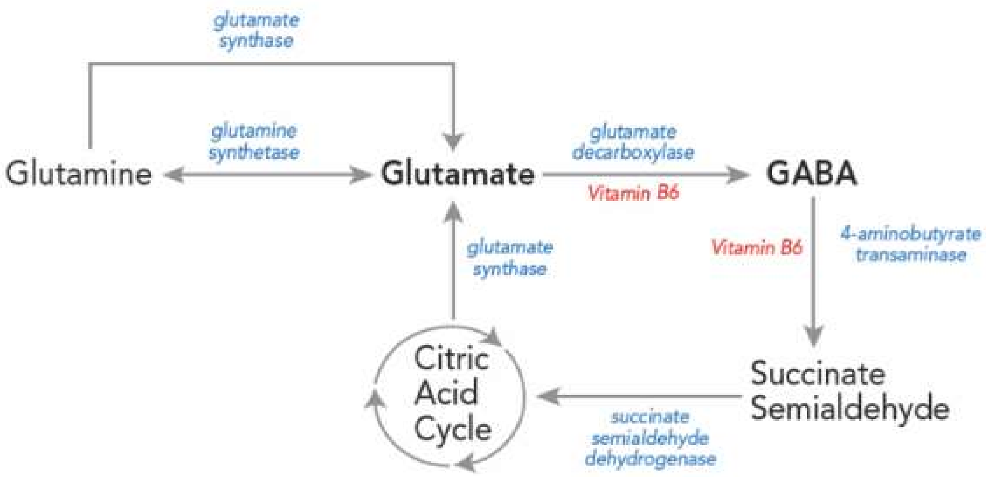

Figure 2. The synthesis of GABA in the body

In mammals, apart from the brain, GABA is also found in the spinal cord. The dorsal horn of spinal cord contains the highest concentration of GABA, followed by ventral gray matter and white matter. GABA plays an important role within the spinal cord controlling the levels of motoneuronal output and sensory input via modulation of primary afferent transmitter release, as well as direct postsynaptic inhibition of motoneurones (2).

Diseases caused by GABA deficiency and disorders in GABA synthesis in the body will be mentioned under the sub-title "Health Benefits of GABA" below.

In addition to humans and animals, GABA is produced by plants and microorganisms and performs a range of functions depending on the producing organism. While GABA is a well-known inhibitory neurotransmitter in the central nervous system (CNS) of animals, it is synthesized in plants and microorganisms mainly as a protective mechanism against stress (4).

The most important plant-based natural sources of GABA are tea, cruciferous vegetables, soybean, spinach, mushrooms, brown rice, chestnuts, potato, broccoli, cabbage. In addition, some fermented foods and beverages such as yogurt, mulberry beer, and fermented soybeans are rich in GABA (5,6).

Lactobacillus species are the most widely used probiotic microorganisms in the production of GABA-enriched food. Dhakal et al. reported that the amount of GABA isolated from fermented products such as yogurt, cheese and kimchi varies between 36 mg/kg and 31,145.3 mg/l depending on the culture medium and isolation source (7).

Recently, GABA has been manufactured and widely used as a dietary supplement because of its health benefits.

GABA Contents of Tea Types

The main types of tea produced from the Camellia sinensis tea plant are black tea, oolong tea, green tea, white tea and dark tea. All of these teas contain modest amounts of GABA as normally processed, and relatively unprocessed white tea contains the highest levels. On the other hand whilst the anaerobically processed GABA-enriched tea, also known as Gabaron tea, has the highest GABA content, the tea with the lowest content is the dark tea pu-erh.

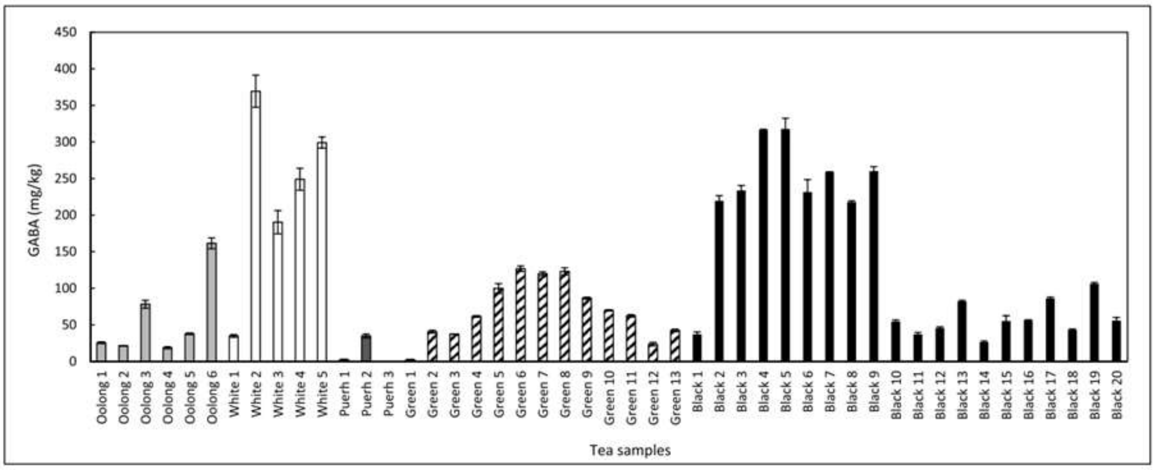

Figure 3. Concentrations of GABA (mg/kg) found in various white, oolong, green, black and pu-erh tea samples (Yılmaz et al.2020).

Yilmaz et al (2020) determined the GABA contents of white tea, oolong tea, green tea, black tea and pu-erh tea samples and the results of the study are illustrated in Figure 3. The GABA contents of the samples were 18.-161.5 mg/kg of oolong tea, 34.9 - 369.3 mg/kg of white tea, 0.1-34.9 mg/kg of pu-erh tea, 2.4 -126.8 mg/kg of green tea, and 26.5 -317.9 mg/kg of black tea. According to the results of the analysis, the highest and lowest GABA concentrations were determined in white tea and pu-erh tea, respectively (8).

In a similar study, Zhao et al. (2011) determined and compared the GABA contents of different tea types. This study showed that white tea was the tea with the highest GABA content, and Puerh tea had the lowest content, except for the GABA-enriched teas. In addition, it determined that the GABA content of puerh tea decreased with increased ripening time. Data related to the study are summarized in Table-1 (9).

Table 1. GABA Contents of Different Tea Types

Tea Type	GABA Content (mg/100g)	Number of Sample
Green Tea	3.9 - 40.1	13
Oolong Tea	7.2 – 32.0	8
Black Tea	8.8 – 44.4	8
White Tea	36.8 – 50.5	3
Puerh Tea (6 month stored)	2.4 – 15.4	15
Puerh Tea (7 year stored)	0.7 – 3.2	16
GABA Tea	168.5 – 404.9	3

(Zhao et al. 2011)

Processing Methods of GABA-enriched Teas

Gabaron tea is the special tea enriched GABA by anaerobic treatment of fresh tea leaves during processing (10). The process was discovered accidentally in Japan in 1984.

In one study, fresh tea leaves were processed into both traditional green tea and GABA-enriched tea. For processing the GABA-enriched tea, fresh tea leaves were collected and placed in a nitrogen-filled chamber for 8 hours and then continuously shaken under aerobic conditions for 3-4 hours. These two steps were repeated twice (ie, for a total of 22-24 hours). The leaves were then subjected to anaerobic fermentation for 8 hours and finally processed into green tea by the traditional green tea processing method. Thus, a sample of green tea enriched with GABA was prepared. On the other hand, a control sample of green tea was produced from the same age tea leaves by the traditional method. Then, GABA-enriched green tea and traditionally processed green tea samples were compared and it was observed that the GABA content of GABA-enriched tea increased from 16.94 mg/100g to 180.97 mg/100g. It was determined that the amounts of aspartic acid and glutamic acid decreased significantly during GABA tea processing (11).

Liao et al. determined that the concentration of GABA in leaves subjected to anoxia (oxygen-free) treatment increased 20 times compared to fresh tea leaves. The reason for this is due to the increase in glutamate decarboxylase and diamine oxidase activities. For the anoxia treatment, tea leaves were first aerated at room temperature for 1 hour and then put under vacuum for 0, 3,4, 7, 8 or 11 hours at 25 °C, 70% humidity and dark environment. The best results are obtained from 11 hours of anoxia treatment (Figure 4). Researchers infer that about one-quarter of GABA formed in tea leaves under anoxia comes from the polyamine degradation pathway, opening the possibility of producing GABA tea through the regulation of metabolism (12).

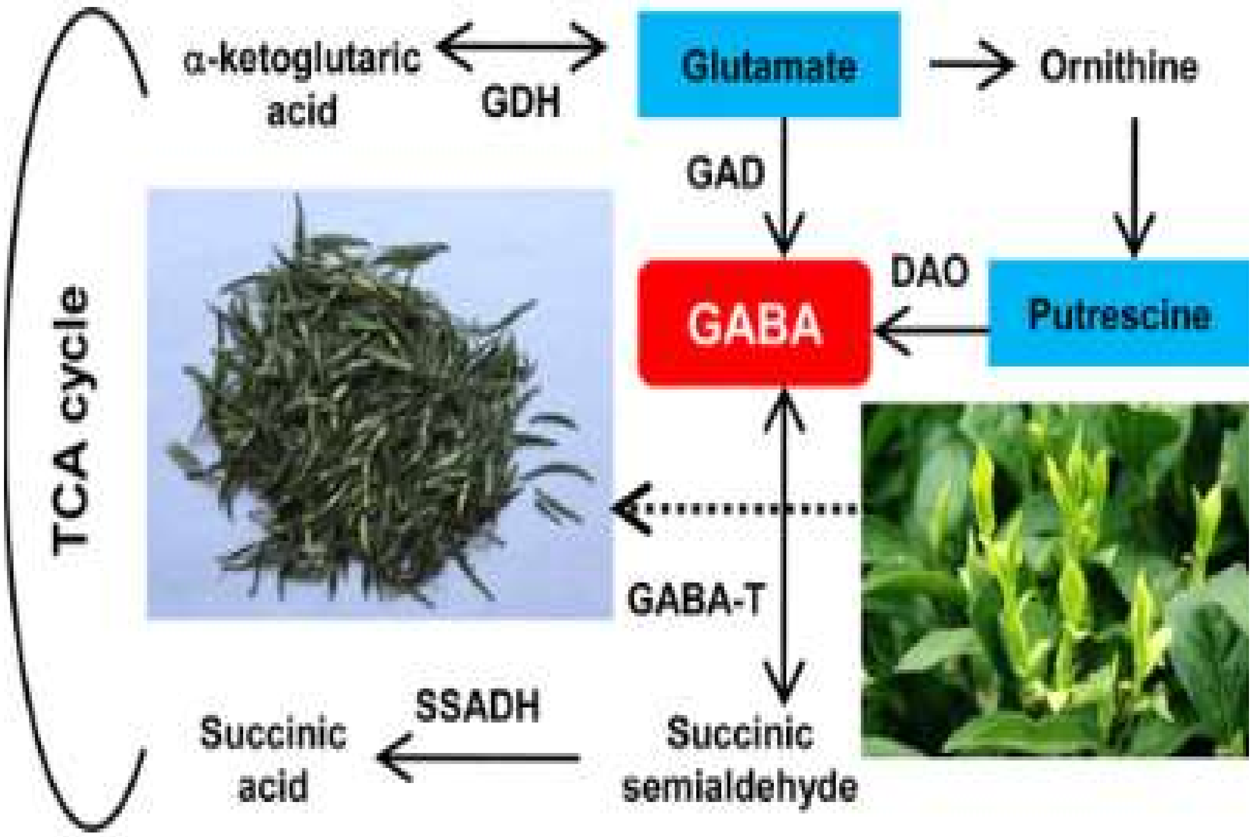

Figure 4. Biosynthesis and metabolism pathway of GABA in tea plant in relation to polyamines, and TCA cycle. GABA (γ-aminobutyric acid), GABA-T (GABA transaminase), GAD (glutamate decarboxylase), DAO (D-amino acid oxidase), GDH (glutamate dehydrogenase), SSADH (succinic semialdehyde dehydrogenase), TCA (Tricarboxylic acid) (Liao et al. 2017) .

In another study lactic acid fermentation and GABA-enriched green tea production trials were conducted using Lactobacillus spp. isolated from green tea, (Figure 5). Levilactobacillus brevis strain GTL 79 was determined as the most outstanding GABA producing strain by optimizing the fermentation conditions and was determined to be the most effective in increasing the lactic acid, acetic acid and GABA content in LFG by 522.20%, 238.72% and 232.52% respectively (13).

In the experiments of Hakamata (1990) on the determination of Gabaron tea production parameters, it was observed that when the tea leaves were incubated under nitrogen and CO_2 gases, the GABA contents were very high, and CO_2 was even more effective than nitrogen gas in the production of GABA (14).

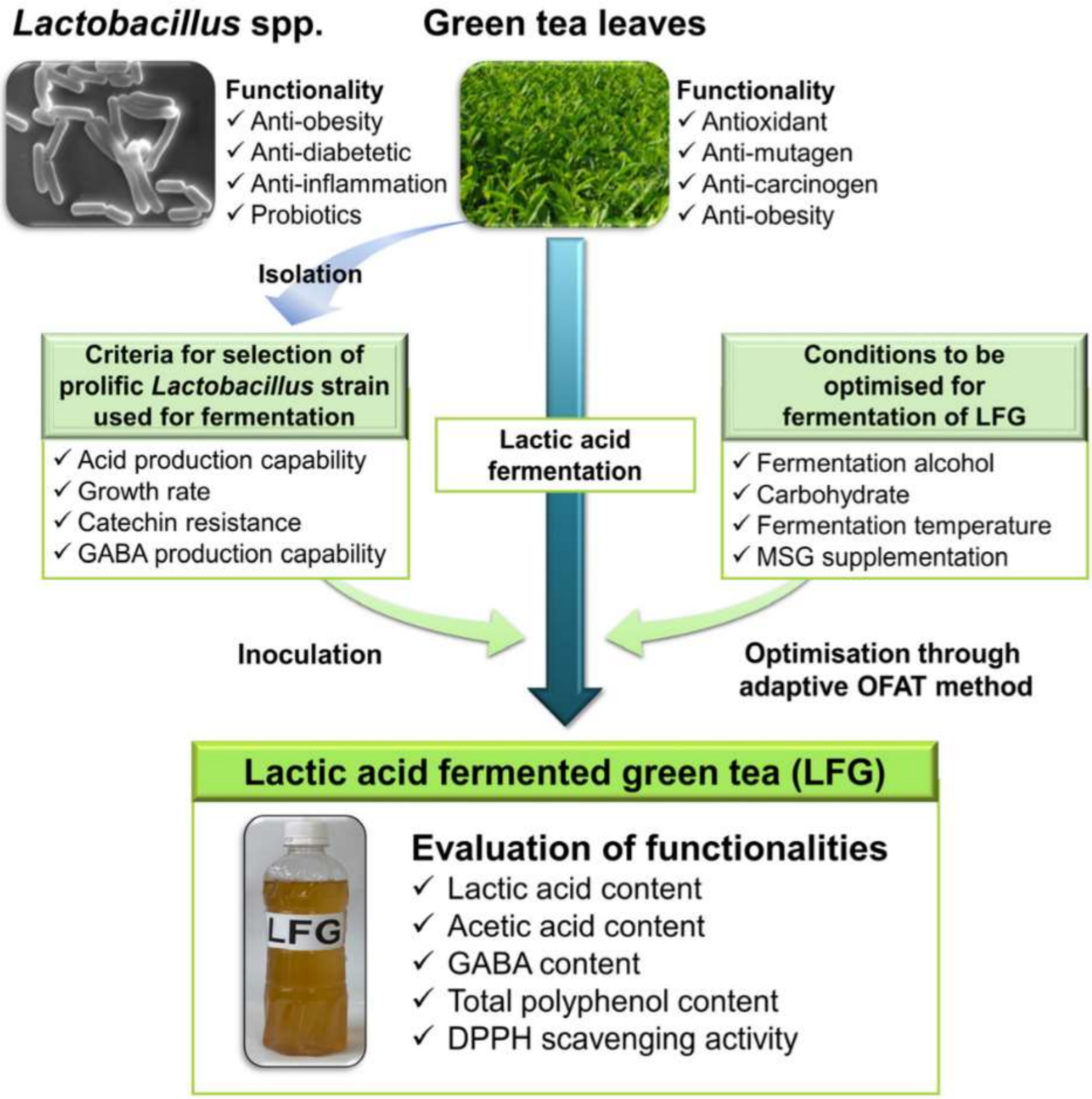

Figure 5. LFG fermentation with a GABA-producing Lactobacillus strain under optimised fermentation condition. LFG: Lactic acid fermented green tea, OFAT (One-Factor-at-a-Time), MSG (Monosodium Glutamate) (Jin et al. 2021)

Mechanism of Action of Dietary GABA

The earliest studies on the mechanism of action of dietary GABA in the body were concerned with whether GABA passes through the blood-brain barrier (BBB) (Figure 6). As a fundamental component of the central nervous system (CNS) the BBB protects the brain against toxins and ion abnormalities that find their way into vascular space through ingestion, infection, or other means. In other words, the BBB is important in keeping the brain safe from harmful substances (15).

However, this protective mechanism also severely limits the transmission of substances that may be beneficial to the individual, such as the neurotransmitter GABA, and drugs that treat central nervous system disorders (16).

Even though the earliest studies claimed that GABA did not pass or very little passed the blood-brain barrier, the discovery of GABA transporter systems and Cell-penetrating peptides (CPPs), which increase cell membrane permeability, strengthened the view that a significant amount of blood transported dietary GABA could cross the BBB (17, 18, 19,20).

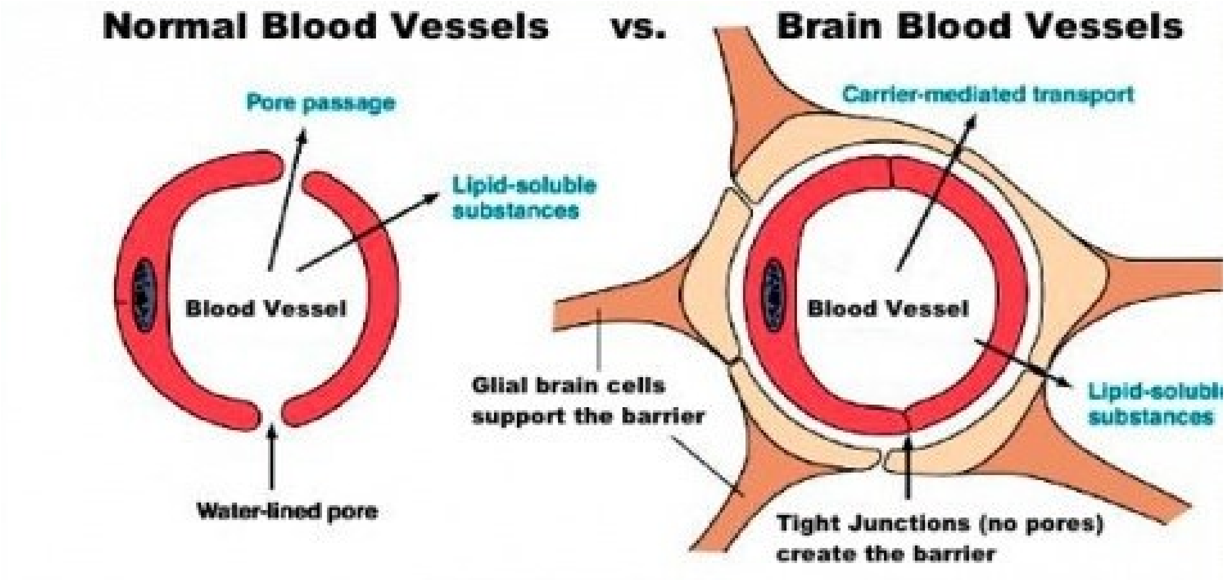

Figure 6. Differences between brain blood vessels and normal blood vessels: Unlike other vessels in the body, brain vessels have BBB

Studies conducted in recent years have revealed that dietary GABA also acts through the Enteric Nervous System (ENS), quite distinct from the CNS. The ENS is a group of neurons located on the wall of the gastrointestinal tract, that works independently from the central nervous system. However, there is a very strong connection and functional integration between the ENS and the brain.

Dietary GABA activates vagal afferent nerves in the ENS which can influence and regulate brain functions, for example inducing the satiety response (21). Vagal afferents are an important neuronal component of the gut–brain axis allowing bottom-up information flow from the viscera to the CNS. In addition to its role in ingestive behavior, vagal afferent signaling has been implicated modulating mood and affect, including distinct forms of anxiety and fear (22).

Thus, dietary GABA, whose ability to cross the BBB is still debated, may act independently through vagal afferent neural connections to the brain.

Health Benefits of GABA

The health effects of GABA have been researched for a long time, and many studies have proven the health benefits of GABA through in vitro and in vivo experiments.

In cases where GABA cannot be adequately synthesized in our body, this need must be met from external sources. GABA-containing foods and beverages including GABA-enriched tea, GABA supplements, and drugs are convenient external sources of GABA. So, besides being a very popular food additive in the food and beverage industry, GABA is also a very valuable supplement in pharmacy due to its health benefits.

By slowing certain brain functions, GABA is thought to be able to reduce stress and high blood pressure and improve sleep.

Effect of GABA on Stress

Stress is defined as a disruption of the body's homeostasis, which is a state of balance among all the body systems needed for the body to survive and function correctly. The body's ability to maintain homeostasis against continually changing environmental circumstances and stressors is controlled in part by the involuntary autonomic nervous system, which maintains a balance between the parasympathetic ("rest and digest") and sympathetic ("fight or flight)" responses of viscera, vasculature, the heart, skeletal muscle, and the control of energy metabolism. Stress results in sympathetic nervous system (SNS) activation in parallel wiith parasympathetic nervous system (PNS) withdrawal. Stressors may be psychological or physiological, or both.

There are some studies showing that tea (Camellia sinensis) reduces physiological stress and anxiety and causes relaxation. One of the reasons for this is the GABA content of tea, especially GABA-enriched teas, though tea's unique component L-theanine has a function in this as it stimulates GABA production in the brain.

Hinton et al determined that GABA-enriched oolong tea had a significant effect on acute stress level, according to the results of their trial on thirty healthy university students (11 males, 19 females) (23).

Effect of GABA on Insomnia

Insomnia is a common sleep disorder that can make it difficult to fall asleep, stay asleep, or cause you to wake up too early and not be able to get back to sleep. Insomnia reduces not only your energy level and mood, but also your health, work performance and quality of life. Because you start the new day feeling tired (24).

Although many people suggest emotional stress can cause their long-term inability to sleep (chronic insomnia), data show that almost half of all chronic insomnia results from emotional problems such as depression and anxiety or physical problems such as breathing problems, involuntary limb movements, side effects from certain medications, and disturbances with the body's internal clock (circadian rhythm).

A study by Byun et al (2018), was aimed to determine the effect of natural GABA intake on sleep. In the human experiment, 43 patients with insomnia symptoms were used. This placebo-controlled trial evaluated the efficacy and safety of natural GABA from fermented rice germ extract (RFE) at a daily dose of 300 mg. In this study, it was found that subjects receiving RFE-GABA had significantly reduced sleep delays compared to taking a placebo, that taking RFE-GABA improved subjective sleep quality, and it reduced symptom severity in people suffering from insomnia (25).

Effect of GABA on High Blood Pressure

Blood pressure regulation is perhaps the most important effect of GABA. Numerous studies have shown that GABA can reduce high blood pressure in animals and humans. In some of these studies, it has been reported that blood pressure decreases with the consumption of foods rich in GABA both in spontaneously hypertensive rats and hypertensive humans (26).

Another study reported that GABA-enriched green tea reduced blood pressure in young and old salt-sensitive rats. In the same study, it was reported that GABA-enriched tea not only lowered high blood pressure in rats fed a high-salt diet, but also prevented blood pressure elevation. (27).

In many countries where the habit of drinking tea is common, consuming tea enriched with GABA may be one of the supportive methods in reducing blood pressure in essential or primary hypertension.

Effect of GABA on Diabetes

Diabetes is a chronic disease that affects how your body turns food into energy. Your body breaks down most of the food you eat into sugar (glucose) and releases it into your bloodstream. When your blood sugar goes up, it signals your pancreas to release insulin.

Insulin signaling modulates neurotransmitter channel activity, including inhibitory receptors such as GABA and excitatory receptors such as glutamate. Thus, defects in brain insulin signaling can result in neuronal dysfunction and impaired cognitive performance (28).

It has been argued that GABA is released from cells in the body in an effort to *calm* and *prepare* cells for the next wave of insulin secretion, and the absence or reduction of GABA may increase the risk of dysfunction and inflammation associated with both type 1 and type 2 diabetes.

In one study, it was determined that GABA secretion occurs with a frequency similar to insulin secretion and regulates the insulin secretion interval. In the same study, it was also observed that GABA was released independently of glucose concentration (29).

Some neurological and mental disorders are thought to be related to conditions where the GABA concentration or signaling activity is out of balance and not working as it should. Some of these disorders and their relationship with GABA are given below.

Effect of GABA on Epilepsy

Epilepsy is one of the most common neurological diseases in which brain activity becomes abnormal, causing seizures or periods of unusual behavior, sensations and sometimes loss of awareness. There are data from a range of experimental and clinical sources supporting the role of GABA in the mechanism and treatment of epilepsy.

Although it has been predicted for years that a malfunction in the GABA neurotransmitter transmission pathway or GABA-A receptor causes epilepsy, confirmation has only come inthe last two decades. GABA-A, one of the two types of receptors that bind with GABA, is an ionotropic receptor that is selectively permeable to Cl^- ions (Figure 7).The first evidence of a relationship between GABA-A receptors and epilepsy was reported in 2001 by Baulac et al. (30).

The decrease in the inhibitory effect of GABA in neurons causes the removal of synaptic inhibition on epileptic neurons and causes seizures by creating epileptic discharges. In epileptic areas, GABA concentration decreased 10 times of normal. The reduction occurs at the level of both GABA and GABA receptors (31,32).

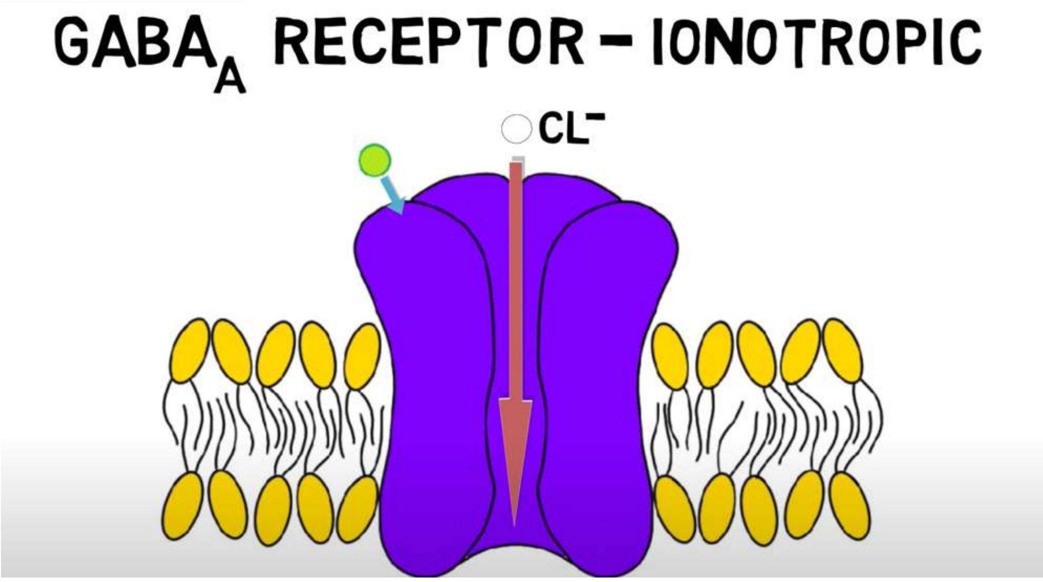

Figure 7. GABA-A receptor in brain

Effect of GABA on Anxiety

Anxiety disorders are the most common of mental disorders and affect nearly 30% of adults at some point in their lives. But anxiety disorders are treatable and a number of effective treatments are available. Treatment helps most people lead normal productive lives (33).

Anxiety is caused by the dysregulation of neurobiological systems. Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter that balances the effect of glutamate, the excitatory neurotransmitter. Anxiety occurs when glutamate has an over-stimulating effect, that is, if this balance is disturbed in favour of glutamate. GABA agonist drugs have been developed that eliminate anxiety symptoms by providing a balance between excitatory glutamate and inhibitory GABA, and these drugs generally act by binding to GABA receptors (34).

Effect of GABA on Stroke/cerebral ischemia

Stroke is the leading cause of death and long-term disability in adults worldwide. Recent studies have shown that the brain has a limited capacity to repair after stroke. Stroke/cerebral ischemia has been proven to be caused by the excess release of excitatory amino acid glutamate in the brain, and the inhibitory neurotransmitter GABA is considered to be the best choice to counteract the action of glutamate (35).

Effect of GABA on Schizophrenia

Schizophrenia is a serious mental disorder characterized by a wide variety of unusual behaviors, such as hallucinations and distorted or false perception, and often bizarre beliefs. Sufferers cannot distinguish between real and imaginary events. These unusual experiences seem real to the person.

The so-called GABA hypothesis claims that neuronal GABA concentration and neurotransmission are reduced in schizophrenia, resulting in cognitive impairments. Only a few in vivo studies have directly examined this hypothesis, however, in one of these studies, GABA levels were measured in 13 patients with schizophrenia and 13 healthy control subjects, using magnetic resonance spectroscopy (MRS). In these measurements, it was found that the GABA concentration of the schizophrenia group decreased by about 10% (36).

Effect of GABA on Alzheimer's disease

Alzheimer's disease (AD) is a brain disorder that slowly destroys memory and thinking skills and, eventually, the ability to carry out the simplest tasks. Symptoms of the disease usually appear in the mid-60s or later.

Initial studies applying postmortem human brains or animal models have shown that GABAergic neurons and receptors are more resistant to AD pathology.

Significantly lower levels of GABA and glutamate neurotransmitters were observed in the temporal cortex of AD patients' brains, indicating inadequate synaptic function and neuronal transmission in AD.

However, in recent years, a great deal of evidence has emerged to support the idea that the GABAergic signaling system undergoes pathological changes in AD patients (37).

In summary, GABA is an important bioactive component that may be used as a preventive and therapeutic in the diseases and disorders mentioned above. Additionally, GABA improves memory and alertness (38), alleviates alcohol withdrawal symptoms (39), increases sexual performance (40), improves skin elasticity and de-emphasizes wrinkles (41), promotes weight loss (42), increases energy levels and exercise endurance (43) and offers anti-aging properties(44).

As a conclusion, GABA is an essential bioactive component for maintaining human health, whether consumed as a food supplement, food additive or medicine, or biologically derived from dietary food and beverages, including all Camellia sinensis teas and particularly from GABA-enriched teas.

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