Production of gamma amino butyric acid (GABA) through fermentation: From useful microorganisms to improve health

Hananeh Yazdanbakhsh
Student Research Committee, Kermanshah, University of Medical Sciences, Kermanshah, Iran
Elnaz Shamsi
Student Research Committee, Kermanshah, University of Medical Sciences, Kermanshah, Iran
Delara Moradi Mirhesari
Student Research Committee, Kermanshah, University of Medical Sciences, Kermanshah, Iran
Maryam Saki
Student Research Committee, Kermanshah, University of Medical Sciences, Kermanshah, Iran
Mahshid Bahraminejad*
Student Research Committee, Kermanshah, University of Medical Sciences, Kermanshah, Iran

Abstract

Gamma-aminobutyric acid (GABA) is a non-protein amino acid that, as a neurotransmitter, provides an important function in the central nervous system. It regulates brain activity, reduces stress, has a positive effect on sleep quality, and has therapeutic benefits for conditions such as anxiety, hypertension, epilepsy, and Parkinson's disease. Natural production of GABA can be caused by acid excretion of glutamic acid by glycolysis. Microbial fermentation is one of the best ways to make it. Lactic acid bacteria, such as Streptococcus plantus and Lactobacillus brevis, are often used in controlled environments to change glutamate to GABA. Different foods, such as milk, brown rice, soybeans, and green tea, can naturally contain or can be enriched with. Recent studies have emphasized the role of intestinal microbiota in GABA synthesis and its effect on neurological well-being. By studying the properties of germs and improving fermentation techniques, we can increase GABA production which can be used in practical foods and medical treatments. The survey offers a thorough study of GABA production, its biological importance, and its prospective role in health and disease management.

Keywords: GABA, Fermentation, GABA products, and GABA therapeutic

Introduction

Gamma aminobutric acid (GABA) is a non-protein amino acid that is very important for the proper functioning of different organs, especially the central nervous system[١]. It acts as an inhibitory neurotransmitter in this system. GABA is primarily synthesized by L-glutamic acid decarboxylase [٢,٣]. One effective method for producing GABA is through fermentation, where certain lactic acid bacteria and other beneficial microorganisms convert glutamate into GABA via decarboxylation [٤,٥]. The fermentation process begins with the selection of suitable raw materials, which should be rich in L-glutamic acid [٦,٨]. Common choices include brown rice, soybeans, dairy products, and seafood like shrimp. After that, bacteria that make GABA, like Lactobacillus brevis and Streptococcus plantarum, are used to help turn glutamate into GABA [٩,١٠]. To optimize GABA production, it is essential to control fermentation conditions: the pH should be maintained between ٥ and ٦ for a slightly acidic environment, the temperature should be kept between ٣٠ and ٤٠ degrees Celsius, and the fermentation duration can range from several hours to several days, depending on the specific product [٣,١١,١٢]. Furthermore, it is important to adjust the salt concentration, as excessive salt can encourage the growth of harmful bacteria during fermentation. The process of glutamate being changed into GABA works like this: a bacterial cell takes in glutamate, and an enzyme called glutamate decarboxylase (GAD) takes away a carboxyl group from it. This makes GABA, which is then released into the environment [١٣,١٤]. After fermentation, GABA can be extracted from the liquid medium using techniques such as filtration, centrifugation, and ion exchange chromatography [١٥]. This article aims to provide a comprehensive explanation of the production process of GABA through fermentation and its importance in bodily function and overall health improvement.

١. GABA production cycle

The GABA production cycle (gamma-aminobutyric acid) contains several stages; glutamate, known as the main precursor of GABA, is obtained by decomposing proteins or carbohydrates [١٦]. The GABA-T (GABA Transaminase) enzyme changes glutamate and makes it release carbon dioxide. The amino group is then added to glutamate, and it changes into gamma (figure ١) [١٧,١٨]. GABA can also be produced through fermentation; of course, the production of GABA by fermentation should be controlled in the environment, where microorganisms such as lactobacillus can produce GABA at the appropriate temperature and pH [٦]. After production, GABA is stored in the Noren and released if needed, which can help stimulate or inhibit adjacent neurons [١٩]. GABA connects to GABA receptors (GABA-A and GABA-B), and in target neurons, it has inhibited effects on their electrical activity, which can help regulate neurological activity and maintain chemical balance in the brain [٢٠]. Finally, GABA can be reconverted to glutamate or metabolized to other compounds. Finally, GABA can be reconverted to glutamate or to other compounds that specific enzymes such as GABA-T are involved in the above processes [٢١].

٢. Importance of GABA and its therapeutic properties

GABA is an essential molecule in the body that has several therapeutic properties that help improve general health and nervous system function. This amino acid acts as a neurotransmitter in the central nervous system and plays an important role in regulating brain activity [٧,٢٢]. GABA helps maintain a balance between stimulation and inhibition in the brain, which can lead to reduced brain activity, thereby reducing stress and causing a sense of relaxation [٧,٢٣]. In addition, GABA serves as an effective agent for improving sleep. This amino acid can facilitate deeper sleep and prevent sudden awakenings during the night,

which is particularly important for individuals suffering from sleep disorders [١٥,١٦]. Research has shown that GABA can help reduce symptoms of depression and anxiety, alongside enhancing mood. GABA is also influential in regulating blood pressure and can assist in controlling diastolic and systolic blood pressure in patients with hypertension. Furthermore, this amino acid has been recognized as a potential treatment for neurological disorders such as epilepsy and Parkinson's disease. GABA may also help stimulate insulin secretion and play a role in regulating blood sugar levels. Other therapeutic properties of GABA include its role in inhibiting tumor growth and reducing carcinoma migration, which can help prevent cancer occurrence [٦,٩]. Overall, GABA is recognized as an effective substance for enhancing both physical and mental health and can be utilized as a beneficial therapeutic supplement in many diseases and disorders [٢٤,٢٥].

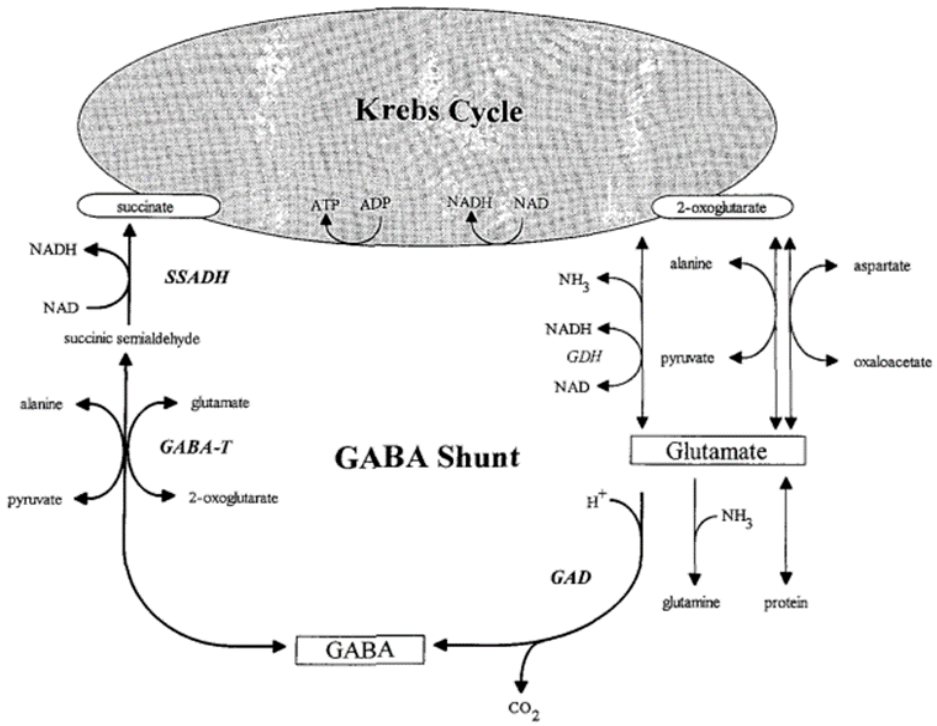

Figure ۱. The GABA shunt and its relationship to other metabolic pathways. Enzymes are indicated in italics; those associated exclusively with the GABA shunt are in boldface. SSADH, succinic semialdehyde dehydrogenase; GABA-T, GABA transaminase; GDH, L-glutamate dehydrogenase [۲۶].

۳. Products obtained from GABA

As mentioned, GABA is a neurotransmitter in the brain that plays an important role in reducing neuronal excitability and promoting relaxation. GABA-containing products can be produced in either natural or synthetic forms and are found in certain foods and beverages. In the following, we will review some GABA-containing products. For example, according to research by Kittibunchakul et al. (۲۰۲۱), milk naturally contains GABA and can be considered a beneficial source of this neurotransmitter. GABA in milk acts as a nutrient and can help reduce stress and anxiety. Consuming milk, especially at night, can aid in better sleep and increased relaxation. Additionally, milk is a beneficial source of protein and calcium, which are important for overall body health [۲,۲۷]. Also, in other studies conducted by Angelino et al. (۲۰۲۰), GABA probiotic drinks, both plain and lychee-flavored, have similar nutritional values. The energy in these drinks mainly comes from their carbohydrate content. Additionally, the protein content of both drinks is higher than that of other fermented and non-fermented plant-based beverages [۲۷,۲۸]. Oketch-Rabah et al. (۲۰۲۱) concluded that the production of GABA-containing probiotic drinks uses brown rice as a key raw material. This drink has high levels of GABA and a large number of probiotic cells. Additionally, brown rice adds value to this drink, as it typically has a low price. Furthermore, this drink can serve as a suitable option for individuals who are lactose intolerant or adhere to plant-based diets, as it is a non-dairy product [۲۵]. Green tea is another food that contains GABA; green tea is another food that contains GABA [۲۹]. Soy can also be a GABA-containing food; for example, according to YEE research in ۲۰۲٤, GABA (gamma-aminobutyric acid) is

recognized as a natural compound in soy that has gained attention for its health and nutritional properties. Soy, as a rich source of plant-based protein and fiber, can help increase GABA levels in the body [١١,٣٠]. Research has shown that consuming soy products can contribute to improving mental health, reducing anxiety and stress, and enhancing sleep quality. Furthermore, the GABA present in soy may play a role in lowering blood pressure and improving heart health. Therefore, consuming soy as a rich dietary source of GABA can be considered a healthy and beneficial option in the diet [٣١].

٤. GABA Microbial Properties

Microbiological tests related to this focus on the ability of microorganisms, especially probiotic bacteria such as Lactobacillus and Bifidobacterium, to produce this compound [١٤,٢٧]. In these tests, microorganisms are identified and described from various sources, and their GABA production levels are measured in appropriate crop media. In addition, the effects of variables such as pH, temperature, and fermentation time on GABA production have been investigated to identify optimal conditions [٧,٣٢]. The results of these tests can help us learn more about GABA's role in human health and make probiotic products that contain more of this compound [٣٣,٣٤]. Therefore, GABA plays a vital role in the communication between the gut microbiota and the brain as an inhibitory neurotransmitter [٤,٢١,٣٥]. The production of GABA by gut microorganisms, particularly Bacteroides and lactic acid bacteria, can impact gut integrity and GABAergic signaling pathways. Alterations in gut microbiota are associated with diseases like Alzheimer's and may lead to changes in GABA production [٢٧,٣٦,٣٧]. These changes could improve neurological conditions and may be explored as a treatment for neurological disorders. Overall, studying microbial GABA can provide an important understanding of how the microbiota affects brain health and the nervous system [٤,٣٧].

٥. Conclusion

Gamma-aminobutyric acid (GABA) is an important non-protein amino acid that has significant consequences for mental and physical health. Its role as a neurotransmitter in the central nervous system is essential to maintaining the balance between stimulation and inhibition in the brain, thereby helping to reduce stress, improve sleep quality, and improve general mental health. GABA production through fermentation by useful microorganisms, such as Lactobacillus and Bifidobacterium, offers a promising street to increase GABA levels in various food products, including brown rice, soybeans, and dairy products. These enriched products can naturally be therapeutic options for managing conditions such as anxiety, depression, hypertension, and neurological disorders. In addition, understanding the interaction between intestinal microbiota and the production of GABA can pave the way for innovative treatments that use the intestinal axis to improve health results. Continuous research on GABA microbial potential has the potential to open new diets and practical foods that increase mental and physical health and emphasize the importance of GABA as a beneficial compound in nutrition and health.

References

١. Zhao Z, Liu H, Tang J, He B, Yu H, Xu X, et al. Pork preservation by antimicrobial films based on potato starch (PS) and polyvinyl alcohol (PVA) and incorporated with clove essential oil (CLO) Pickering emulsion. Food Control. ٢٠٢٣;١٥٤:١٠٩٩٨٨.

٢. Kittibunchakul S, Yuthaworawit N, Whanmek K, Suttisansanee U, Santivarangkna C. Health beneficial properties of a novel plant-based probiotic drink produced by fermentation of brown rice milk with GABA-producing Lactobacillus pentosus isolated from Thai pickled weed. Journal of Functional Foods. ٢٠٢١;٨٦:١٠٤٧١٠.

٣. Zhang C, Wang X, Su R, He J, Liu S, Huang Q, et al. Dietary gamma-aminobutyric acid (GABA) supplementation increases food intake, influences the expression of feeding-related genes and improves digestion and growth of Chinese mitten crab (Eriocheir sinensis). Aquaculture. ٢٠٢٢;٥٤٦:٧٣٧٣٣٢.

٤. Conn KA, Borsom EM, Cope EK. Implications of microbe-derived ɣ-aminobutyric acid (GABA) in gut and brain barrier integrity and GABAergic signaling in Alzheimer's disease. Gut microbes. ٢٠٢٤;١٦(١):٢٣٧١٩٥٠.

٥. Nakamura U, Nohmi T, Sagane R, Hai J, Ohbayashi K, Miyazaki M, et al. Dietary gamma-aminobutyric acid (GABA) induces satiation by enhancing the postprandial activation of vagal afferent nerves. Nutrients. ٢٠٢٢;١٤(١٢):٢٤٩٢.

٦. Pannerchelvan S, Rios-Solis L, Wong FWF, Zaidan UH, Wasoh H, Mohamed MS, et al. Strategies for improvement of gamma-aminobutyric acid (GABA) biosynthesis via lactic acid bacteria (LAB) fermentation. Food & Function. ٢٠٢٣;١٤(٩):٣٩٢٩-٤٨.

٧. https://doi.org/١٠,١٠٣٨/s٤١٥٣٨-٠٢٤-٠٠٢٥٣-٢. Gamma-aminobutyric acid as a potential postbiotic mediator in the gut–brain axis. ٢٠٢٤.

٨. Mallakpour S, Sirous F, Hussain CM. A journey to the world of fascinating ZnO nanocomposites made of chitosan, starch, cellulose, and other biopolymers: Progress in recent achievements in eco-friendly food packaging, biomedical, and water remediation technologies. International Journal of Biological Macromolecules. ٢٠٢١;١٧٠:٧٠١-١٦.

٩. Ramos IM, Poveda JM. Fermented sheep's milk enriched in gamma-amino butyric acid (GABA) by the addition of lactobacilli strains isolated from different food environments. Lwt. ٢٠٢٢;١٦٣:١١٣٥٨١.

١٠. Iorizzo M, Paventi G, Di Martino C. Biosynthesis of gamma-aminobutyric acid (GABA) by Lactiplantibacillus plantarum in fermented food production. Current Issues in Molecular Biology. ٢٠٢٣;٤٦(١):٢٠٠-٢٠.

١١. Falah F, Vasiee A, Tabatabaei-Yazdi F, Moradi S, Sabahi S. Optimization of γ-aminobutyric acid (GABA) production by Lactobacillus spp. from agro-food waste. Biomass Conversion and Biorefinery. ٢٠٢٤;١٤(٣):٣٤٢٥-٣٧.

١٢. Liskiewicz A, Khalil A, Liskiewicz D, Novikoff A, Grandl G, Maity-Kumar G, et al. Glucose-dependent insulinotropic polypeptide regulates body weight and food intake via GABAergic neurons in mice. Nature Metabolism. ٢٠٢٣;٥(١٢):٢٠٧٥-٨٥.

١٣. Martin A, Mick GJ, Choat HM, Lunsford AA, Tse HM, McGwin Jr GG, McCormick KL. A randomized trial of oral gamma aminobutyric acid (GABA) or the combination of GABA with glutamic acid decarboxylase (GAD) on pancreatic islet endocrine function in children with newly diagnosed type ١ diabetes. Nature Communications. ٢٠٢٢;١٣(١):٧٩٢٨.

١٤. Lee X, Tan J, Cheng L. Gamma aminobutyric acid (GABA) enrichment in plant-based food–A mini review. Food Reviews International. ٢٠٢٣;٣٩(٨):٥٨٦٤-٨٥.

١٥. Utama GL, Sahab NRM, Nurmilah S, Yarlina VP, Subroto E, Balia RL. Unveiling microbial dynamics in terasi spontaneous fermentation: Insights into glutamate and GABA production. Current Research in Food Science. ٢٠٢٥;١٠:١٠٠٩٥٠.

١٦. Ochoa-de La Paz LD, Gulias-Cañizo R, Ruíz-Leyja ED, Sánchez-Castillo H, Parodí J. The role of GABA neurotransmitter in the human central nervous system, physiology, and pathophysiology. Revista mexicana de neurociencia. ٢٠٢١;٢٢(٢):٦٧-٧٦.

۱۷. Rehman A, Di Benedetto G, Bird JK, Dabene V, Vadakumchery L, May A, et al. Development of a workflow for the selection, identification and optimization of lactic acid bacteria with high γ-aminobutyric acid production. Scientific Reports. ۲۰۲۳;۱۳(۱):۱۳٦٦۳.

۱۸. Xue C, Ng I-S. Sustainable production of ٤-aminobutyric acid (GABA) and cultivation of Chlorella sorokiniana and Chlorella vulgaris as circular economy. Bioresource technology. ۲۰۲۲;۳٤۳:۱۲٦۰۸۹.

۱۹. Barrett E, Ross R, O'Toole PW, Fitzgerald GF, Stanton C. γ-Aminobutyric acid production by culturable bacteria from the human intestine. Journal of applied microbiology. ۲۰۱۲;۱۱۳(۲):٤۱۱-۷.

۲۰. Shelp BJ, Bown AW, McLean MD. Metabolism and functions of gamma-aminobutyric acid. Trends in plant science. ۱۹۹۹;٤(۱۱):٤٤٦-٥۲.

۲۱. Dabravolski SA, Isayenkov SV. The role of the γ-aminobutyric acid (GABA) in plant salt stress tolerance. Horticulturae. ۲۰۲۳;۹(۲):۲۳۰.

۲۲. Li Y, Fan Y, Ma Y, Zhang Z, Yue H, Wang L, et al. Effects of exogenous γ-aminobutyric acid (GABA) on photosynthesis and antioxidant system in pepper (Capsicum annuum L.) seedlings under low light stress. Journal of Plant Growth Regulation. ۲۰۱۷;۳٦:٤۳٦-٤۹.

۲۳. Wang H, Yin X, Li J, Sun Y, Cheng F, Zhu D. γ-aminobutyric acid (GABA) treatment improves disease resistance and preserves fresh-cut Mesembryanthemum crystallinum L. LWT. ۲۰۲٥:۱۱۷۳۹۸.

۲٤. Peerboom C, Wierenga CJ. The postnatal GABA shift: a developmental perspective. Neuroscience & Biobehavioral Reviews. ۲۰۲۱;۱۲٤:۱۷۹-۹۲.

٢٥. Oketch-Rabah HA, Madden EF, Roe AL, Betz JM. United States Pharmacopeia (USP) safety review of gamma-aminobutyric acid (GABA). Nutrients. ٢٠٢١;١٣(٨):٢٧٤٢.

٢٦. Bown AW, Shelp BJ. The metabolism and functions of [gamma]-aminobutyric acid. Plant Physiology. ١٩٩٧;١١٥(١):١.

٢٧. Hou D, Tang J, Feng Q, Niu Z, Shen Q, Wang L, Zhou S. Gamma-aminobutyric acid (GABA): A comprehensive review of dietary sources, enrichment technologies, processing effects, health benefits, and its applications. Critical reviews in food science and nutrition. ٢٠٢٤;٦٤(٢٤):٨٨٥٢-٧٤.

٢٨. Angelino D, Rosi A, Vici G, Dello Russo M, Pellegrini N, Martini D, Group SYW. Nutritional quality of plant-based drinks sold in Italy: the Food Labelling of Italian Products (FLIP) study. Foods. ٢٠٢٠;٩(٥):٦٨٢.

٢٩. Ma C, Gao C, Li Y, Zhou X, Fan G, Tian D, et al. The Characteristic Aroma Compounds of GABA Sun-Dried Green Tea and Raw Pu-Erh Tea Determined by Headspace Solid-Phase Microextraction Gas Chromatography–Mass Spectrometry and Relative Odor Activity Value. Foods. ٢٠٢٣;١٢(٢٤):٤٥١٢.

٣٠. https://doi.org/١٠,١٠١٦/B٩٧٨-٠-٤٤٣-٢٣٦٣٤-١,٠٠٠٠٧-٥. ٧ - Gamma-aminobutyric acid: a bioactive compound in foods. ٢٠٢٥.

٣١. Yee CS, Ilham Z, Cheng A, Abd Rahim MH, Hajar-Azhari S, Yuswan MH, et al. Optimisation of fermentation conditions for the production of gamma-aminobutyric acid (GABA)-rich soy sauce. Heliyon. ٢٠٢٤;١٠(١٣).

۳۲. You W, Zhang J, Ru X, Xu F, Wu Z, Jin P, et al. CmCML۱۱ interacts with CmCAMTA۵ to enhance γ-aminobutyric acid (GABA) accumulation by regulating GABA shunt in fresh-cut cantaloupe. Plant Physiology and Biochemistry. ۲۰۲٤;۲۰٦:۱۰۸۲۱۷.

۳۳. Luo H, Liu Z, Xie F, Bilal M, Liu L, Yang R, Wang Z. Microbial production of gamma-aminobutyric acid: applications, state-of-the-art achievements, and future perspectives. Critical Reviews in Biotechnology. ۲۰۲۱;٤۱(٤):٤۹۱-٥۱۲.

۳٤. Gu X, Zhang R, Zhao J, Li C, Guo T, Yang S, et al. Fast-acidification promotes GABA synthesis in response to acid stress in Streptococcus thermophilus. LWT. ۲۰۲۲;۱٦٤:۱۱۳٦۷۱.

۳٥. Gao H, Wu S, Zeng Q, Li P, Guan W. Effects of exogenous γ-aminobutyric acid treatment on browning and food-borne pathogens in fresh-cut apples. Postharvest Biology and Technology. ۲۰۱۸;۱٤٦:۱–۸.

۳٦. Li Y, Wang T, Li S, Yin P, Sheng H, Wang T, et al. Influence of GABA-producing yeasts on cheese quality, GABA content, and the volatilome. LWT. ۲۰۲۲;۱٥٤:۱۱۲۷٦٦.

۳۷. Jena R, Choudhury PK. Lactic acid bacteria in fermented dairy foods: Gamma-aminobutyric acid (GABA) production and its therapeutic implications. Food Bioscience. ۲۰۲٤:۱۰٥۲۷٦.