Importance and Microbial Production of Gamma (Ɣ)-Aminobutyric Acid (GABA) in Food Systems

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Abstract

Gamma-aminobutyric acid (GABA) is a non-protein amino acid that is widely present in organisms. In particular, lactic acid bacteria (LAB) stand out in this regard. The biosynthesis of GABA in microorganisms is mainly regulated by pH, which usually has the most pronounced effect on a fermentation process. Also, GABA production, affects media composition, fermentation time, and fermentation temperature. GABA has important positive functions on human health. In particular, it is known that GABA is effective in the development of neural diseases such as schizophrenia, alzheimer's disease, parkinson's disease, hormone regulation, and antihypertensive activity. In the present study, concepts related to GABA such as GABA-producing microorganisms, biosynthesis mechanism of GABA, and factors affecting GABA synthesis, and different approaches to increase GABA production and GABA content, especially in the food industry, will be emphasized.

Keywords: Gamma (Ɣ)-aminobutyric acid, Bioactive Compound, Microbial Metabolites, Biosynthesis, Functional Microorganisms

Gama (Ɣ)-Aminobütirik Asitin (GABA) Gıda Sistemlerindeki Önemi ve Mikrobiyai Üretimi

Öz

Gama-aminobütirik asit (GABA), organizmalar arasında yaygın olarak bulunan ve protein olmayan bir amino asittir. Özellikle laktik asit bakterileri (LAB) GABA üreticisi olarak ön çıkmaktadır. GABA’nın mikroorganizmalarında biyosentezinde en etkili faktör pH değeridir. Ayrıca, GABA üretimi ortam bileşimi fermantasyon süresi ve fermantasyon sıcaklığı etkiler, GABA’nın insan sağlığı üzerinde önemli pozitif etkileri vardır. Özellikle, GABA’nın şizofreni, alzheimer hastalığı, parkinson hastalığı, hormon regülasyonu ve antihipertansif aktivite gibi nöral hastalıkların gelişiminde etkili olduğu bilinmektedir. Bu çalışmada, GABA üreten mikroorganizmalar, GABA’nın biyosentez mekanizması ve GABA sentezini etkileyen faktörler gibi GABA ile ilgili kavramlar, özellikle gıda endüstrisinde GABA üretimi ve GABA içeriğinin artırılmasına yönelik farklı yaklaşımlar üzerinde durulacaktır.

Anahtar Kelimeler: Gama (Ɣ)-aminobütirik asit, Biyoaktif Bileşik, Mikrobiyai Metabolitler, Biyosentez, Fonksiyonel Mikroorganizma

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1. Introduction

GABA (γ-aminobutyric acid) is a non-protein amino acid. It is produced from L-glutamic acid by glutamate decarboxylase enzyme (GAD) which is dependent on the cofactor pyridoxal-5'-phosphate or vitamin B6 (Cui et al., 2020). It is known to widely present in microorganisms, plants, and animals. Although GABA has been widely studied in medical and pharmaceutical fields, studies on its effect in the field of food have been very limited.

GABA is known to have multiple many functional features, such as neurotransmission, induction of hypotension, and diuretic and tranquiliser effects (Ribeiro et al., 2018). Besides, it has been beneficial in alcoholism treatment, depression and stimulation of immune cells (Diana et al., 2014).

The GABA content of most of the available GABA-containing foods is not at a sufficient level for people to benefit from the functional effects of GABA. Therefore, the use of this bioactive ingredient by the human body can be achieved, either as a nutraceutical product or through a new or modified functional food. The best, fastest, least costly way to do this is microbial biosynthesis. It is known that many microorganisms are able to synthesize GABA until now (Kook & Cho, 2013; Li & Cao, 2010).

In the present study, concepts related to GABA such as GABA-producing microorganisms, biosynthesis mechanism of GABA, and the factors affecting GABA synthesis, and different approaches to increase GABA production and GABA content, especially in the food industry, will be emphasized.

2. Gaba-Producing Microorganisms

Microorganisms are an important source of GABA. It is known that many types of microorganisms have the ability to synthesize GABA, including yeast, fungi, and bacteria (Cui et al., 2020).

Among bacteria, there are several studies on the GABA-producing ability of especially lactic acid bacteria (LAB) (Tamura et al., 2010; Q. Wang et al., 2018). Since LAB has GRAS (generally regarded as safe) status, its use in foods as a GABA-producer or source of GABA is also prominent. Besides, GABA production capacity varies between different types of LAB. As far as is known, mainly, GABA producing LAB species can be specified as Levilactobacillus brevis, Lactobacillus buchneri, and Enterococcus avium according to high efficiency production (Park & Oh, 2007; Tamura et al., 2010). Other LAB species (Pediococcus, Weissella, Streptococcus, Leuconostoc, etc.) and its production quantities are given in Table 1. According to the studies identified in the literature, Lactobacillus brevis NCL912 isolated from Paocai, a type of Chinese pickle, is the strain with the highest yield with 205 g/L GABA content when compared to other samples.

As for other microorganism types, their number is more limited (Table 1). For example, it was determined that Monascus purpureus and Monascus sanguineus species of the non-pathogenic a fungus Monascus spp. produced 7.453 and 0.015 g/L GABA, respectively, albeit in small quantities (Dikshit & Tallapragada, 2015). The strain isolated from Paocai, a type of Chinese pickle, is the strain with the highest yield with 205 g/L GABA content when compared to other samples.

Table 1. Some GABA-producing microorganisms and their GABA production amounts (Cui et al., 2020)

| Microorganism                | GABA (g/L) | References               |
|------------------------------|------------|--------------------------|
| **Lactic acid bacteria**     |            |                          |
| Levilactobacillus brevis NCL912 | 205.80     | (Q. Wang et al., 2018)   |
| Lactobacillus buchneri WPZ001 | 129.00     | (Zhuang et al., 2018)    |
| Enterococcus avium G-15      | 115.70     | (Tamura et al., 2010)    |
| Lactiplantibacillus plantarum CGMCC 1.2437 | 74.37     | (Zhao et al., 2015)     |
| Lactobacillus sakei B2-16    | 68.05      | (Seo et al., 2012)      |
| Levilactobacillus brevis RK03 | 62.52      | (Wu et al., 2018)        |
| Levilactobacillus brevis TCCC13007 | 61.00    | (Zhang et al., 2012)    |
| Levilactobacillus brevis K203 | 44.40      | (Binh et al., 2014)      |
| Enterococcus faecium G22     | 41.87      | (Wang et al., 2016)      |
| Levilactobacillus brevis NCL912 | 35.66     | (Li et al., 2010)        |
| Levilactobacillus brevis DPC6108 | 32.32     | (Barrett et al., 2012)  |
| Lactobacillus paracasei NFR1 7415 | 31.14    | (Komatsuzaki et al., 2005) |
| Lactobacillus rhamnosus YS9  | 19.28      | (Lin, 2013)             |
| Streptococcus thermophilus fmb5 | 9.66      | (Chen et al., 2018)     |
| Pediococcus pentosaceus IN8  | 9.06       | (Ratanaburee et al., 2013) |
| Weissella hellenica SB 105   | 7.69       | (Kim et al., 2007)      |
| Leuconostoc citreum SC-10    | 0.50       | (Demirbaş et al., 2017) |

| **The other microorganism** | GABA (g/L) | References               |
|-----------------------------|------------|--------------------------|
| Monascus purpureus          | 7.45       | (J. J. Wang et al., 2003) |
| Monascus sanguineus         | 0.02       | (Dikshit & Tallapragada, 2015) |
| Pichia anomala MR-1         | 1.20       | (Masuda et al., 2008)    |
| Rhizopus microsporus var. oligosporus IFO 32002 | 17.40 | (Aoki et al., 2003)    |
| Rhizopus microsporus var. oligosporus IFO 32003 | 15.00 | (Aoki et al., 2003)    |
determined that two isolates that belong *Rhizopus microspores* var. *oligosporus*, a fungus, produced 17.40 and 15.00 g/L GABA (Aoki et al., 2003). Despite all this information, the leading microorganisms in GABA production is LAB.

3. Biosynthesis of GABA

The biosynthesis of GABA by microorganisms is carried out by the glutamic acid decarboxylase (GAD) system. This system consists of GAD enzyme and glutamate/GABA antiporter GadC. This is shown in Figure 1.

Firstly, L-glutamate is transported a cell through the antiporter GadC. Subsequently, the decarboxylation of L-glutamate to GABA catalyzed by GAD. This leads to the formation of GABA and release of CO2 as by product. Finally, GABA is exported to the extracellular matrix by antiporter GadC. In this reaction, pyridoxal-5'-phosphate (PLP) (Vit B6) takes part as a cofactor.

GAD is an intracellular enzyme (Huang et al., 2007). The GAD enzyme is encoded by gad genes. Generally, LAB species have gadB gene (gadB2), but most *Levilactobacillus brevis* strains contain two distinct gad genes (gadA and gadB). However, *Enterococcus avium* 352 has three gad genes (gadB1, gadB2 and gadB3) (Lyu et al., 2018; Yu et al., 2019). Besides, antiporter GadC transports GABA/Glu generally under acidic conditions (Kook & Cho, 2013). Furthermore GADs from LAB are specific for L-glutamic acid.

Interestingly, although the gad gene is found, some LAB strains cannot produce GABA. In one study (Nomura et al., 2000), this situation was examined. It was determined that a LAB strain (*Lactococcus cremoris*) that had the Gad gene, but did not produce GABA had a mutation in the Gad gene. This mutation was determined to be a one-base deletion of adenine and a one-base insertion of thymine were detected. This indicated that the application of polymerase chain reaction (PCR)-based methods for the detection of GABA-producing LAB is quite difficult.

![Figure 1 The biosynthetic pathway of GABA by microbes (Kook & Cho, 2013; Cui et al., 2020)](image)

4. Factors Affecting GABA Synthesis

Different fermentation factors affect the rate of GABA production by microorganisms. The pH value of media,
temperature of media, cultivation time and media additives are among the prominent factors.

4.1. pH value

Since the biochemical properties of GAD differ between different microorganisms, the effective pH value for maximum GABA production depends on the species (Dhakal et al., 2012). Generally, in studies (Komatsuzaki et al., 2005; Siragusa et al., 2007; Choi et al., 2012) optimum pH values were determined as acidic values and values below pH 6.5.

Furthermore, the production of GABA is not only dependent on activating the activities of GAD but also on inhibiting the activities of GABA-decomposing enzymes. GABA can be converted to the succinic semi-aldehyde and subsequently to succinate. The enzymes played role in these reactions; have optimum pH value around 8-8.5 (Dhakal et al., 2012). Therefore, a value that can inhibit these enzymes in the fermentation medium and is also suitable for GAD activity is important.

4.2. Temperatures

The incubation temperature is important for GABA production. In general, a high GABA yield was obtained in the fermentation temperature range from 25°C to 40°C. For example, L. plantarum DSM19463 synthesized the highest amount of GABA at temperatures between 30°C and 35°C (Di Cagno et al., 2010). The optimum temperatures for some L. brevis strains were found to be as 30°C, 37°C, and 40°C, respectively (Huang et al., 2007; Ueno, 2000).

4.3. Fermentation Time

The time factor plays an important role in the fermentation. In a study (Di Cagno et al., 2010), L plantarum DSM19463 required 72 h of fermentation time to reach the highest production of GABA, respectively. In another study (Kim et al., 2009), L. brevis GABA-100 reached the highest level of GABA at the 12 th day. On the other hand, in a study in which a co-factor was added to the medium (Yang et al., 2008), it was determined that the higher amount of GABA was produced at 48 h.

4.4. Effect of Media Composition

Nutrient composition affect the GABA production by fermentation. For this, PLP (vit B6) as the coenzymes of GAD are the major factors (Komatsuzaki et al., 2005).

On the other hand, the concentrations and diversity of substrates are important for GABA yield. In particular, a nitrogen source is needed. Because l-glutamate is needed for GABA production. This amino acid must either be added to the medium from the outside, or the nutrients necessary for microorganisms capable of synthesizing this amino acid must be given to the medium.

L-glutamate is formed by the conversion of α-ketoglutarate by l-glutamate dehydrogenase. Alpha-ketoglutarate is synthesized from glucose via the glycolysis pathway and part of the tricarboxylic acid (TCA) cycle. Furthermore, it was known that the addition of sulfate ions increased the GAD activity (Dhakal et al., 2012).

5. Effect of GABA on Health

GABA as an effective compound with bio-functions can be used as a drug with significant pharmacological effects. Besides, it is effective as a component of health food as well (Diez-Gutiérrez et al., 2020).

GABA is an inhibitory neuro-transmitter. Neurotransmitters are small chemical conductors that enable the flow of information in nerve cells. Because of this feature, it is known that GABA can modulate mood (e.g. relaxation), sleep disorders, and temporal and spatial memory. Also, several studies have demonstrated the importance of GABA in the development of neural diseases such as schizophrenia, Alzheimer’s disease, Parkinson’s disease (Boonstra et al., 2015; Porges et al., 2017).

On the other hand, GABA has cardiovascular effect. Because GABA has the effect of reducing hypertension (Abd El-Fattah et al., 2018). Another effect of GABA is hormone regulator. It regulates progesterone, thyroid, and insulin hormones (Adeghate & Ponery, 2001; Wiens & Trudeau, 2006).

Furthermore, GABA has serum cholesterol-lowering effect (Ngo & Vo, 2019), control effect in asthma (Arnold et al., 2016). Some studies have shown that it also has an effect on cancer cells such as Delaying and/or inhibiting the proliferation of cancer cells and potent tumour suppression (Brzozowska et al., 2017; Wang et al., 2016).

6. Conclusions and Future Prospects

The GABA-producing ability could be of interest for the food industry. GABA has been evidenced as a powerful bioactive compound with numerous health-beneficial effects. Thus, the functional foods produced from GABA are believed to be able to prevent and/or treat different diseases, especially hypertension, diabetes, and neurological disorders. Whereby, the researches into large-scale production, biotechnological techniques, and high Gaba-producing strains will be increased in food industry.

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