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Gamma-aminobutyric acid as a bioactive compound in foods: a review

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ABSTRACT

Gamma-aminobutyric acid (GABA) is a non-protein amino acid, considered a potent bioactive compound. GABA has been widely studied because of its numerous physiological functions and positive effects on many metabolic disorders. One the most important of these is the hypotensive effect that has been demonstrated in animals and in human intervention trials. The biosynthesis of GABA and its optimization, without affecting sensory characteristics, are the key in obtaining GABA-enriched food products that have health benefits. Lactic acid bacteria (LAB) are the main GABA-producers and therefore there are a wide range of GABA-enriched fermented food products, in which GABA is natural, safe and eco-friendly. Increasing knowledge of bioactive components in food has opened avenues for the development of new, naturally occurring functional food with added value for health.

1. Introduction

Although GABA has been widely studied in medical and pharmaceutical fields, this article focuses on enhanced GABA levels in food products, its biosynthesis and physiological function, mainly when it is consumed, its optimization, and future beneficial effects in the food industry.

GABA is a four-carbon free amino acid that is widely present in bacteria, plants and vertebrates. In plants and bacteria it plays a metabolic role in the Krebs cycle, and in vertebrates it acts as a potent neural signal transmitter. GABA is primarily formed by the irreversible α-decarboxylation reaction of L-glutamic acid or its salts, catalysed by glutamic acid decarboxylase enzyme (GAD; EC 4.1.1.15) (Fig. 1) (Satya Narayan & Nair, 1990) whose biochemical properties have been characterized (Nomura, Nakajima, Fujita, & Kobayashi, 1999). This enzyme has been found in bacteria such as LAB (Bertoldi, Carbone, & Borri-Voltattorni, 1999), *Escherichia* (Rice, Johnson, Dunnigan, & Reasoner, 1993), *Streptococcus*, *Aspergillus* (Kato, Furukawa, & Hara, 2002) and *Neurospora* (Kubicek, Hampel, & Rohr, 1979); in plants such as tea (Zhao et al., 2011), tomato (Yoshimura et al., 2010), soybean (Serraj et al., 1998), mulberry leaf (Yang, Jhou, & Tseng, 2012), germinated brown rice (Dai-xin, Lu, Lan, Li-te, & Yong-Qiang, 2008) and petunia (Johnson, Narendra, Joe, Cherry, & Robert, 1997); and in mammalian animal brain (Nathan et al., 1994). GABA is also found in insects such as cockroach, grasshopper, moth, honeybee and fly (Anthony, Harrisson, & Sattelle, 1993). However, studies have mostly focused on GABA-producing microorganisms rather than GABA in isolation. LAB (Maras, Sweeney, Barra, Bossa, & John, 1992) and yeast (Hao & Schmit, 1993) are the most important GABA producers, because they are commercially useful as starters in fermented foods.

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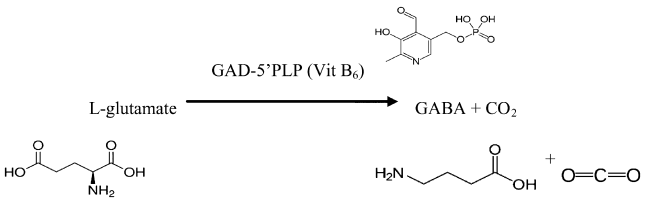

Fig. 1 – Decarboxylation reaction of L-glutamate to GABA catalysed by glutamate decarboxylase (GAD), which is dependent on the cofactor pyridoxal-5′-phosphate or vitamin B_6.

1.1. *Physiological functions*

There is considerable knowledge about the multiple physiological functions of GABA. As a result, the development of functional foods containing GABA has been actively pursued (Saikusa, Horino, & Mori, 1994). In animals, GABA is found at high concentrations in the brain and plays a fundamental role in inhibitory neurotransmission in several of its routes within the central nervous system, and also in peripheral tissues (DeFeudis, 1981). Alterations in GABAergic circuits are associated with Huntington's disease, Parkinson's disease, senile dementia, seizures, Alzheimer's disease, stiff person syndrome and schizophrenia (Wong, Bottiglieri, & Snead, 2003), because the GAD substrate (L-glutamate) acts as an excitant of human neurons and its product (GABA) acts as an inhibitor (Battaglioli, Liu, & Martin, 2003). One alteration can be caused by very low GABA content in the brain, which is observed in patients with Alzheimer's disease (Seidl, Cairns, Singewald, Kaehler, & Lubec, 2001). Okada et al. (2000) demonstrated that a daily oral administration of rice germ containing 26.4 mg GABA was effective in treating these neurological disorders. Indeed, the practice of yoga *asana* sessions increases GABA levels in the brain, and is a potential treatment for some autonomic disorders that are commonly observed in menopausal and presenium periods (Streeter et al., 2007).

Other physiological functions such as relaxation (Wong et al., 2003), sleeplessness and depression (Okada et al., 2000) have been treated with GABA. Very recently, Wu et al. (2014) showed the GABA content in a variety of tea and demonstrated the sleep-promoting effect of GABA. This bioactive compound could potentially protect against chronic kidney disease, ameliorate oxidative stress induced by nephrectomy (Sasaki et al., 2006), and activate liver and kidney function (Sun, 2004). GABA has been shown to naturally enhance immunity under stress conditions within one hour of its administration in humans (Abdou et al., 2006). GABA may also be useful for alcohol-related disease prevention and treatment (Oh, Soh, & Cha, 2003b). Furthermore, this amino acid contributes to increasing the concentration of growth hormone in plasma and the rate of protein synthesis in the brain (Tujioka et al., 2009). Recent studies also indicate that it is a potent secretor of insulin, and thus could help to prevent diabetes (Adeghate & Ponery, 2002). Other authors suggested that GABA tea ameliorates diabetic-induced cerebral autophagy and therefore may possess the potential on the therapy of diabetic encephalopathy (Huang et al., 2014).

GABA could delay or inhibit the invasion and metastasis of various types of cancer cells, such as mammary gland, colon and hepatic cancer cells (Kleinrok, Matuszek, Jesipowicz, Opolski, & Radzikowski, 1998; Minuk, 2000; Opolski, Mazurkiewicz, Wietrzyk, Kleinrok, & Radzikowski, 2000). Furthermore, consumption of GABA-enhanced brown rice can inhibit leukaemia cell proliferation and has a stimulatory action on cancer cell apoptosis (Oh & Oh, 2004). GABA has also been considered a potential tumour suppressor for small, airway-derived lung adenocarcinoma (Schuller, Al-Wadei, & Majidi, 2008). In addition, it has anti-inflammatory and fibroblast cell proliferation activities, which promote the healing of cutaneous wounds (Han, Kim, Lee, Shim, & Hahm, 2007). Besides, this amino acid is involved in maintaining cell volume homeostasis under UV radiation (Warskulat, Reinen, Grether-Beck, Krutmann, & Häussinger, 2004), in the synthesis of hyaluronic acid, and in enhancing the rate of dermal fibroblasts exposed to oxidative stress agents (Ito, Tanaka, Nishibe, Hasegawa, & Ueno, 2007), which makes GABA a potential novel application for dermatological purposes (Di Cagno et al., 2009). Kelly and Saravanan (2008) reported that GABA may reduce inflammation in rheumatoid arthritis and attenuate the metabolic response to ischemic incidents (Abel & McCandless, 1992). It also affects the control of asthma (Xu & Xia, 1999) and breathing (Kazemi & Hoop, 1991).

Several reports have referred to the link between GABA and mood disorders. Low GABA in plasma may be a biological marker of vulnerability to the development of various mood disorders. As Petty (1994) showed, plasma concentrations of GABA were significantly lower than control values in patients with major bipolar disorder and manic-depressive illness. Krystal et al. (2002) demonstrated that normal GABA levels may reflect effective antidepressant treatments and seizure control, and are a target for the treatment of bipolar disorder. Moreover, plasma GABA levels may correlate with aggressiveness in some patients with depression, mania and alcoholism (Bjork et al., 2001). There is a relationship between progesterone, GABA, and mood behaviour in women (Rapkin, 1999). Hormone secretion may also be regulated by GABA, as shown by Parkash and Kaur (2007). Furthermore, there is clinical evidence of the regulation of thyroid hormones and GABA systems. Thyroid dysfunction (i.e. hyperthyroidism or hypothyroidism) acts on the GABA system. It particularly affects enzyme activities that are responsible for the synthesis and degradation of GABA and GABA receptor expression and function. In the developing brain, hypothyroidism generally decreases enzyme activities and GABA levels, whereas in the adult brain, hypothyroidism tends to increase enzyme activities and GABA levels (Wiens & Trudeau, 2006). Furthermore, recently, Xie, Xia and Le (2014) demonstrated that GABA improves oxidative stress and functions of thyroids and thyroid hormones explaining lowered weight gains and suggesting GABA as a preventer of obesity. Other authors demonstrated GABA as a bioactive compound present in brown rice and germinated brown rice may mediate anti-obesity effects through the peroxisome proliferator-activated receptor gamma gene (Imam et al., 2014). Other studies have suggested that GABA could improve visual function in senescent animals (Leventhal, Wang, Pu, Zhou, & Ma, 2003) and even enhance memory (Kayahara & Sugiura, 2001). Finally, there is evidence of GABA acting as a signal between cell-to-cell