

L-theanine: A promising substance in tumor research

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Received 30 April 2012, accepted 20 January 2013.

Abstract

Malignant tumor which can proliferate abnormally and transfer rapidly to other tissues, holds high mortality rate and is difficult to cure. Herewith it is responsible for great loss in economy. L-theanine, the specific amino acid in tea, performed a significant anti-tumor potential, it works via various methods, such as exert antitumor effect by itself; increase antitumor drugs concentration in tumor cells, inhibit tumor cell invasion and so on. Here, the authors elucidate and discuss these mechanisms comprehensively.

Key words: L-theanine, antitumor drug, malignant tumor, tea.

Introduction

In a variety of carcinogenic factors, a certain cell of local tissue loses the regulatory functions of normal growth in the level of gene. It causes activation of oncogenes, deletion and mutation of tumor suppressor gene, which leads to abnormal proliferation of oncogenes. In this case, the tumor is generated. According to growth properties, tumor cells with abnormal morphology, metabolism and function are divided into benign and malignant tumors. Based on the character of infiltration and metastasis, malignant tumor cannot only grow in the primary site, but proliferates to other parts of the body through various means. As a result, it cannot be completely exterminated by oversimplified excision. Malignant tumor often makes blood vessel blockage and oppression and destructs the structure and function of organs, eventually leading to deaths. Therefore, the study of tumor suppressor has significant prospect.

Theanine (Fig.1A) is an amino acid found specifically in tea plant and contained at 1% to 2% of the dry weight of tea leaves. Through extraction and identification, it was first discovered as a constituent of green tea ¹. As a derivative of glutamate that is

synthesized from glutamic and ethylamine in the roots of tea plant and then is transported to tea leaves, theanine exists only in the free (non-protein) form in the nature, determined to be γ -ethylamino-L-glutamic acid ². Physical properties of theanine are pretty stable with melting point of 217-218°C and specific rotation of +8.57. It is easily soluble in water, the aqueous solution being slightly acidic, and insoluble in anhydrous ether. Because of its distinctive chemical structure, there are many important physiological functions for theanine, such as protecting nerves, improving memory, sedation and anti-tumor ³⁻⁸. In this paper, the mechanism of anti-tumor is discussed and summarized.

Anti-tumor mechanism of L-theanine: L-theanine has a direct effect on the inhibition of tumor and tumor invasion ⁹. As the competitor of glutamine (Fig.1B), L-theanine can interfere with glutamine metabolism in tumor cell, thereby inhibiting the growth of tumor cell ¹⁰. In addition, it can affect the transfer of glutamate, intracellular glutathione synthesis, glutathione and doxorubicin (GS-DOX) conjugation, as well as suppress the extracellular transport of GS-DOX by the multidrug resistance associated protein/glutathione with anticarcinogen S-conjugate export pump (MRP/GS-X), thus maintaining the concentration of DOX (Fig. 1C) in tumor cells and indirectly suppressing the tumor ^{11, 12}. Furthermore, the side effects can be reduced when L-theanine and anticarcinogen are used simultaneously for anti-tumor treatment ¹³⁻¹⁶.

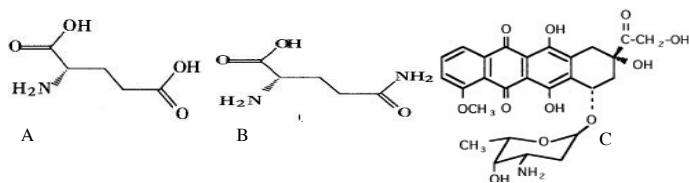


Figure 1. A: L-theanine; B: L-glutamine; C: Doxorubicin (DOX).

Anti-tumor effect: The main reason of anti-tumor effect of L-theanine is that L-theanine is similar to its derivative glutamine in molecular structure. L-theanine has the ability against tumor on normal cells and tumor cells. In tumor cells, L-theanine inhibits uptake and metabolism of glutamate, thereby metabolism of tumor cell cannot be conducted and tumor cell is suppressed to death. In normal cells, L-theanine can be regarded as a precursor of glutathione and does not affect the glutamate transfer; as a result, the quantity of glutathione synthesized in cell and its antioxidant effects are increased¹⁷. L-theanine can induce proliferation of $\gamma\delta$ T cells and interferon gamma (IFN- γ) secretion which improve the immunocompetence and play an important role in anti-tumor^{9,18}. After 14 days feeding with 2% green tea powder or casein with 0.1% L-theanine for hepatoma-bearing rats, volume and weight of tumor are decreased with prolonged feeding¹⁹. Fujii *et al.*²⁰ studied the toxicity of L-theanine and suggested that both of volume and weight of L-theanine are decreased when L-theanine was orally administered at a concentration of 0–5% of the diet to B6C3F1 mice for 13 weeks in subacute test and 78 weeks in chronic toxicity test. These studies are strongly proved that L-theanine has great anti-tumor ability.

Enhancement in the anti-tumor ability of anticarcinogen: L-theanine can improve efficiently the anti-tumor efficacy of anticarcinogen - DOX, IDA and CPT-1, and the mechanism is that concentration of anticarcinogen in tumor cells is increased by L-theanine²¹. We take DOX - an anticarcinogen - for example. Firstly, as analogue of glutamine, L-theanine reduces the concentration of glutamate in tumor cells by competitively binding glutamate transporter; secondly, as precursors of glutathione, reduction of glutamate reduces the synthesis of glutathione in tumor cells and the conjugates of GSH and anticancer drugs. It reduces the exclusion of cancer drugs caused by multidrug resistance associated protein (MRP)/GS-X pump. As a result, concentration of anticancer drugs in cells is maintained⁹⁻¹¹. Thus, L-theanine has the anti-tumor efficacy by increasing the concentration of anticancer drugs in tumor cells (Fig. 2)¹⁷.

Inhibition of tumor infiltration: Tumor infiltration is that malignant tumor has the ability to infiltrate to surrounding normal tissue and can pass through blood and lymphatic vessels, resulting in secondary tumor or metastases in distant sites. The manifestations are enhancement of cell motility, cell adhesion decrease, release of soluble enzymes and production of toxic substances or membrane-bound organelles¹⁸. Tumor infiltration caused by enzyme can be inhibited by L-theanine and with the

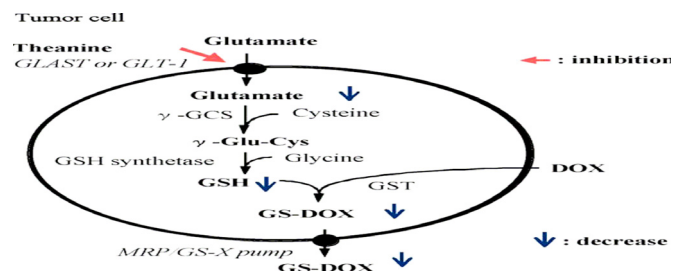


Figure 2. Mechanism of theanine in tumor cell. GLAST or GLT-1: Means of glutamate transferring; γ -GCS: Means of glutamate and cysteine synthesis; γ -Glu-Cys: Conjugation of glutamate and cysteine; GSH: glutathione; GST: Means of glutathione transferring; GS-DOX: Conjugation of glutathione and doxorubicin; GS-X: Transport pump of conjugation of glutathione and anticarcinogen.

increase of the concentration of L-theanine, the inhibition is enhanced⁹. As L-theanine can inhibit metabolism of tumor glutamate that may be the necessary material for the formation and release of lytic enzyme that cause infiltration, so it can inhibit the tumor infiltration. In addition, L-theanine can enhance the formation of relevant anti-cancer substances in serum and may stimulate proliferation of fibroblast to collagenation aiming to inhibit tumor infiltration^{5,13}.

Lower side effects of anticancer drugs: Nowadays it is hardly for the chemotherapeutics to completely focus on the tumor, therefore it is bound to affect normal cells by the side effects of the drugs. The side effects of anticancer drugs can be reduced by L-theanine¹¹. Sadzuka *et al.*¹⁰ indicated that L-theanine can reduce the inhibition of bone marrow caused by IDA, and significantly reverse the reduction of bone marrow cells and white blood cells IDA-induced. In addition, L-theanine can also reduce the side effects of DOX on normal tissues through alleviating DOX-induced cardiac toxicity and lessening lipid peroxide levels and glutathione peroxidase activity^{13-15,17}. In normal cells, L-theanine does not affect the glutamate transfer and can be rapidly used as the precursor of glutathione which can increase formation of glutathione and doxorubicin (GS-DOX) conjugation and as a result, the pumping of DOX is improved by MRP/GS-X pump^{21,22-28}. As Fig. 3²² shows, maintaining the concentration of glutathione in cells can inhibit the increase of lipid peroxidation and the activity of glutathione peroxidase caused by the transferring of anticancer drugs.

Discussion

The different mechanisms of action of L-theanine on normal and tumor cells is one of the important reasons for the anti-tumor ability of L-theanine which may be caused by the different expression of gene in cells.

With the conservation, restoration, sedation and other effects for nerve, L-theanine can indirectly achieve anti-tumor effects by improving the mentality of patients³⁻⁸. It has been confirmed that chemotherapy has a great impact on the body and brain. On the other hand, L-theanine can alleviate the effects of chemotherapy to brain with the functions to protect and repair the brain²⁹. While suffering from cancer, L-theanine can alleviate the anxiety and pain of patient which is conducive to ongoing treatment and rehabilitation.

L-theanine has many beneficial effects on human body, and it is a safe and non-toxic inhibitor of tumor according to the toxicology^{20,30}. The death rate of cancer is extremely high and hardly to cure. It is necessary to find a kind of anti-cancer drug through variety of

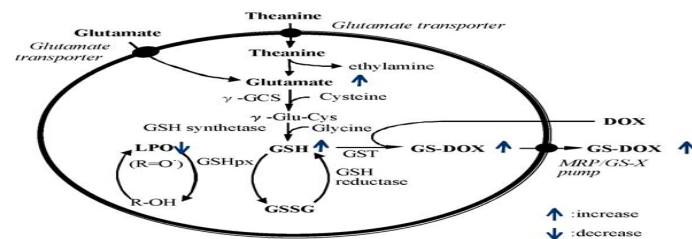


Figure 3. Mechanism of theanine in normal cell. γ -GCS: Means of glutamate and cysteine synthesis; γ -Glu-Cys: Conjugation of glutamate and cysteine; GSH: glutathione; GST: Means of glutathione transferring; GS-DOX: Conjugation of glutathione and doxorubicin; MRP/GS-X: pump/Transport pump of conjugation of multidrug resistance associated protein/ glutathione and anticarcinogen; LPO: Lipid peroxidation.

ways. Though L-theanine has distinctive effects on anti-tumor, the inhibition to tumor still requires abundant follow-up theoretical and experimental research.

Acknowledgements

Our profound admiration and respect go to researchers in this field and in our lab, whose dedication and hard work make it. This work was supported by the National Natural Science Foundation of China (31171654), Natural Science Foundation of Chong Qing (CSTC, 2010BB1134), Southwest University Basic Science Research Program (XDJK2010C075) and Southwest University Doctor Program (SWU111040).

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