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REVIEW

Glutamic acid as anticancer agent: An overview



Satyajit Dutta ^a, Supratim Ray ^{b,*}, K. Nagarajan ^c

^a Department of Pharmaceutical Chemistry, IIMT College of Medical Sciences, Meerut 250001, Uttar Pradesh, India

^b Department of Pharmaceutical Chemistry, Dr. B.C. Roy College of Pharmacy and AHS, Durgapur 713206, West Bengal, India

^c Department of Pharmaceutical Chemistry, KIET School of Pharmacy, Muradnagar, Ghaziabad 201206, Uttar Pradesh, India

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Abstract The objective of the article is to highlight various roles of glutamic acid like endogenic anticancer agent, conjugates to anticancer agents, and derivatives of glutamic acid as possible anticancer agents. Besides these emphases are given especially for two endogenous derivatives of glutamic acid such as glutamine and glutamate. Glutamine is a derivative of glutamic acid and is formed in the body from glutamic acid and ammonia in an energy requiring reaction catalyzed by glutamine synthase. It also possesses anticancer activity. So the transportation and metabolism of glutamine are also discussed for better understanding the role of glutamic acid. Glutamates are the carboxylate anions and salts of glutamic acid. Here the roles of various enzymes required for the metabolism of glutamates are also discussed.

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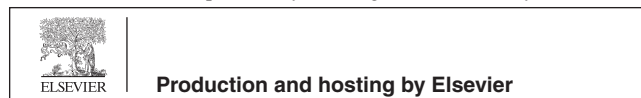
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* Corresponding author. Tel.: +91 9434443946; fax: +91 3432532679.

E-mail address: supratimray_in@yahoo.co.in (S. Ray).

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1. Introduction

In Cancer mostly there is depletion of glutamine, as cancer cells consume glutamine at large scale that is why there is lack of glutamine in the skeletal muscle (Kulkarni et al., 2005). Glutamine plays very important roles in tumor cell. Firstly it acts as a nitrogen donor in the nucleotide and amino acid biosynthesis, secondly glutamine helps in the uptake of essential amino acid and it maintains the activation of TOR kinase (Wise and Thompson, 2010). In many cancer cells, glutamine is the primary mitochondrial substrate and it maintains mitochondrial membrane potential and integrity. It provides support for the NADPH production needed for redox control and macromolecular synthesis. Glutamine is the respiratory fuel of tumor cells. Glutamic acid and glutamine both are interconvertible. Glutamic acid comes under the major group of neurotransmitters. It is the major work horse neurotransmitter of the brain. It increases the brain function and mental activity. It detoxifies the brain from ammonia by attaching itself to nitrogen atoms in the brain and also helps in the transportation of potassium across the blood–brain barrier. It is conjectured that glutamate is involved in cognitive functions like learning and memory in the brain, though excessive amounts may cause neuronal damage associated with diseases like amyotrophic lateral sclerosis, lathyrism and Alzheimer's disease (Dutta et al., 2011).

2. Glutamic acid as anticancer agent

L-Glutamic acid is converted into L-glutamine by L-glutamine synthetase. L-glutamine biosynthesize purines and pyrimidines

by contributing 3- and 9-nitrogen groups of purine bases, 2-amino group of guanine, 3-nitrogen group and amino group of cytosine which are the bases of DNA and RNA (Dewald and Moore, 1958). L-Glutamine cannot be synthesized in neoplastic cells due to the lower reactivity of L-glutamine synthetase. Thus an antagonist of this enzyme can interfere with the metabolic process of L-glutamine and act as anticancer agents (Luzzio et al., 2000). Patients of cancer often develop glutamine depletion in the muscles due to uptake by tumors and chronic protein metabolism. On the basis of these, it can be assumed that structural variants of glutamine might possess possible antitumor activity.

L-Glutamic acid- γ -(4-hydroxyanilide) is isolated from mushroom *Agaricus bisporus*. It acts as a growth regulatory substance for inhibiting the B16 melanoma cells in culture (Srikanth et al., 2002). Azaserine and 6-diaza-5-oxo-L-norleucine antagonized the metabolic process involving L-glutamine and exhibited antitumor activity in animal models (Vishwanathan et al., 2008). An aryl amide derivative of L-threo- γ -hydroxy glutamic acid which is isolated from *Justicia ghiesbreghtiana* is active against various tumors (Nishiyama et al., 2001). The synthetic amides of L-glutamic acid exhibit activity against Ehrlich ascites carcinoma (Vila et al., 1990). Four *N*-(benzenesulfonyl)-L-glutamic acid bis(*p*-substituted phenylhydrazides) have anticancer activity against PC-3 prostate cancer and in COLO-205 colon cancer. L-Glutamic acid- γ -monohydroxamate (GAH) demonstrated complete cytotoxicity against L-1210 cells in the culture and marked antitumoral activity *in vivo* against L-1210 leukemia and B-16 melanoma (Xu et al., 2005). Glutamate receptor is another important player

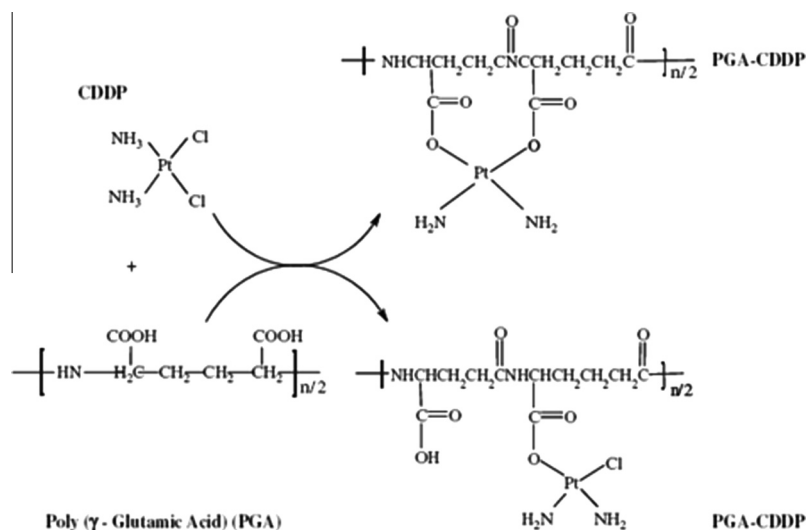


Figure 1 Chemical structures of CDDP, γ -PGA, and PGA-CDDP conjugates.

in hippocampal long-term potentiation and memory. Glutamic acid, a glutamate receptor agonist enhances retention of memory (Cui et al., 2009). Glutamic acid is also useful in lowering blood pressure. According to a study by the Imperial College of London, people who consume more glutamic acid have low blood pressure than those who consume less (Stamler et al., 2009). When the glutamine importer SLC1A5 is impaired then the uptake of essential amino acids is also impaired and without the aid of essential amino acids rapamycin-sensitive mTORC1 is not activated. mTORC1 is responsible for the regulation of cell growth, protein translation and plays an important role in inhibiting macro autophagy (Nicklin et al., 2009). That means if mTORC1 is inactivated then there will be no cell growth and no protein translation. In glioblastoma cells, metabolism of glutamine provides the bulk of oxaloacetic acid (OAA) cellular pool (DeBerardinis et al., 2007). This OAA is one of the substrates in mitochondria that leads to the synthesis of many essential biological macromolecules like cholesterol (Hatzivassiliou et al., 2005). Hence glutamine is the primary substrate in cancer cells that provides precursor molecules to mitochondria for anaplerosis (replenishment of the carbon pool). c-MYC (Myc), a DNA transcription factor regulates three out of the five steps of purine and pyrimidine synthesis at oncogenic level. It also promotes glutaminolysis and this catabolism of glutamine leads to the larger amount of carbon in the cell, which allows the cell to produce more NADPH (Wise and Thompson, 2010). Since cancer cells depend on glutamine lack of glutamine can lead to the death of cancer cells. But as it is also required for some other essential functions in the body such as in the brain therefore that treatment should be adopted which can reduce the ability of the cell to uptake glutamine by targeting Myc and other proteins that are responsible for transporting glutamine into the cell. L- γ -Glutamyl-p-nitroanilide (GPNA) which inhibits SLC1A5 (Esslinger et al., 2005) and BCH (2-aminobicyclo-(2,2,1)heptanes carboxylic acid) which blocks mTORC1 (Nicklin et al., 2009) and that treatment which reprograms the mitochondria so that it no longer depends on glutamine can also be effective, e.g. amino-oxyacetic acid (AOA) is used be-

cause it is a transaminase inhibitor (Moreadith and Lehninger, 1984).

3. Glutamic acid as conjugates with anticancer drug

Glutamic acid is used as a conjugate because it increases the efficacy of anticancer drug and decreases its toxicity toward normal cells. Polyglutamic acid is biodegradable, edible and nontoxic toward humans (Shih et al., 2004).

3.1. Conjugate with All-trans retinoic acid (ATRA)

ATRA is an active metabolite of vitamin A. It is used in the treatment of acute promyelocytic leukemia and myelodysplastic syndrome. It has a slow dissolution rate and low bioavailability. Therefore to obtain ATRA with better solubility, transportation and bioavailability, derivatives of ATRA containing glutamic acid or its sodium salt were synthesized. The two derivatives of ATRA, RAE and RAENA, exhibited improved aqueous solubility and were more effective in mice bearing S(180) tumors (Cui et al., 2009).

3.2. Conjugate with paclitaxel

Conjugation of paclitaxel and the water-soluble polyglutamate is known as poly (L-glutamic acid)-paclitaxel (PG-TXL). Observations showed that PG-TXL has more antitumor activity than free paclitaxel. PG-TXL exerts its anticancer activity by the continuous release of free paclitaxel into cells (Oldham et al., 2000).

3.3. Conjugate with cisplatin

Cisplatin [*cis*-dichlorodiammineplatinum (II), CDDP] is combined with γ -poly(α ,L-glutamic acid) (γ -PGA) to form γ -poly(α ,L-glutamic acid)-*cis*-dichlorodiammineplatinum (γ -PGA-CDDP) which is water soluble. γ -PGA-cisplatin conjugate effectively inhibits human breast tumor cells xenografted into nude mice. It also reduces the toxic side effects associated with

the use of free CDDP and also produced desirable pharmacokinetics and enhanced antitumor activity (Ye et al., 2006) (Figure 1).

3.4. Conjugate with curcumin

Curcumin [diferuloylmethane; 1,7-bis-(4-hydroxyl-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is the major pigmentary component of turmeric (*Curcuma longa*). Curcumin with nphthaloyl-glutamoylchloride forms 4,40-(di-o-glutamoyl)-curcumin. According to a study curcumindiglutamoyl derivative was found to be more potent against cancer cell lines, HeLa (cervical cancer) and KB (oral cancer), than other derivatives. It is due to the activation of caspases which is facilitated due to accumulation and better stability of diglutamiccurcumin (Dubey et al., 2008).

3.5. Conjugate with 20(s)-camptothecin (CPT)

Due to the instability of active lactone the therapeutic efficacy of 20(s)-camptothecin (CPT) is limited in humans. By binding one molecule of a drug via the γ -carboxylic acid of each monomeric subunit of poly-(L-glutamic acid) (PGA) it leads to the stability of lactone. Linking of CPT to a high molecular weight anionic polymer that is PGA enhances solubility and improves distribution to the tumor through enhanced permeability and retention (EPR effect) (Singer et al., 2001).

3.6. Conjugate with N-(4-hydroxyphenyl)retinamide (4HPR)

Several studies have indicated that N-(4-hydroxyphenyl)retinamide (4HPR) treatment is associated with the inhibition of angiogenesis and a decreased vascular response *in vitro* and *in vivo*. 4HPR was bound to a synthetic polyamino acid, poly(L-glutamic acid) (PG). PG-4HPR was evaluated for its release kinetics and *in vitro* anti-proliferative and *in vivo* antitumor activities against ovarian cancer cell lines. It was confirmed that treatments with both 4HPR and PG-4HPR decreased the expression of pre-angiogenic factor VEGF in SKOV3 tumors. *In-vivo*, PG-4HPR demonstrated significantly enhanced antitumor activities compared to 4HPR in both early treatment and later treatment protocols. Treatments with PG-4HPR suppressed the expression of VEGF and reduced blood flow into the tumor (Zou et al., 2007).

4. Derivatives of glutamic acid as anticancer agent

4.1. Aminopteroylglutamic acid or pteroyl-L-glutamic acid

Aminopterin (4-aminopteroic acid), a 4-amino analog of folic acid, is an antineoplastic drug with immunosuppressive properties used in chemotherapy (Oaks et al., 2010). Folate is involved in DNA synthesis and methylation which may reduce breast cancer risk, particularly among women with greater alcohol consumption. High intake of folate may reduce the risk of colon cancer (Giovannucci et al., 1998), but the dosage and duration relations and the impact of diet compared with supplementary sources are not well understood (Boehm et al., 2009). Folate intake decreased the risk of pancreatic cancer in women but not in men (Percival et al., 2008).

4.2. Methotrexate

Chemically methotrexate is N-[4-[[[(2,4-diamino-6-pteridiny] methyl] methylamino] benzoyl]-L-glutamic acid. Methotrexate tablets are used alone or in combination with other anticancer agents in the treatment of breast cancer, epidermoid cancers of the head and neck, advanced mycosis fungoides (cutaneous T-cell lymphoma), and lung cancer, particularly squamous cell and small cell types. Methotrexate tablets are also used in combination with other chemotherapeutic agents in the treatment of advanced stage non-Hodgkin's lymphomas. It reduces dihydrofolates to tetrahydrofolates by the help of enzyme dihydrofolic acid reductase which inhibits the synthesis of purines (Skeel, 2008).

4.3. L-Theanine

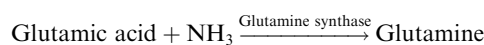
Chemically L-theanine is γ -ethylamino-L-glutamic acid. Limited studies evaluate the effects of L-theanine in the prevention of cancer. The observed anticancer effects are largely attributed to the catechins found in tea, while action on tumors may be due to an enhanced immune response (McPhee et al., 2011).

4.4. Thalidomide

It is a chemotherapeutic agent used against multiple myeloma, myelodysplastic syndrome, leprosy etc. It acts by inhibiting VEGF, TNF- α , GI growth factor, proliferation of NK cells and stimulation of T-cells.

5. Transportation and metabolism of glutamine

Glutamine is the most abundant amino acid present in the body. It is also known as levoglutamide, L-GA 5 amide, L-(+)-2-aminoglutamic acid. Glutamine is formed in the body from GA and ammonia in an energy requiring reaction catalyzed by glutamine synthase (Kulkarni et al., 2005).



Metabolism of glutamine takes place in the mitochondria. Glutamine is transferred from the extra cellular medium of mitochondria to the inner surface of mitochondria through the specific plasma membrane. Malignant cells transport glutamine across their plasma membranes at a faster rate than their non-malignant cells. Malignant cells show an uncontrolled rate

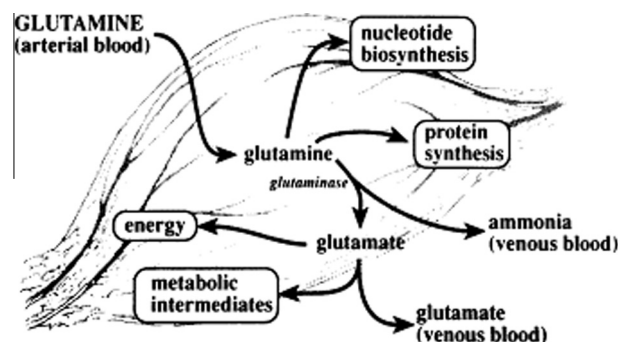


Figure 2 Transportation and metabolism of glutamine.

of cellular proliferation and therefore require increased supply of precursor amino acids for biosynthesis. Therefore they transport amino acids (glutamine) much faster than normal cells (Medina et al., 1992). It has been seen in human hepatoma cells which transport glutamine at a rate 10–20 times faster than normal hepatocytes (Bannai and Ishii, 1988). Cytoplasm is filled with excess of glutamine, and glutamine is transported to mitochondria. In the mitochondria, glutamine is acted upon by glutaminase, an enzyme requiring high phosphate concentrations to be fully active. The high concentrations of inorganic phosphate found in the mitochondria of tumor cells could explain the high activity of tumor glutaminase *in vivo*. For cellular metabolism it is essential to transport the amino acids through the plasma membrane. This transportation is mediated by proteins called carriers (Figure 2).

Glutamine is converted into glutamate and ammonia by phosphate dependent glutaminase. This is the first step in the series of reaction that generates the metabolic intermediate which is essential for cell growth. The high rate of intracellular glutaminolysis results in high release of ammonia. Glutamine is transported into cells mainly by sodium ion dependent systems A and ASC. After an excess of deposition of glutamine in the cell cytoplasm it is transferred to mitochondria otherwise it will be hydrolyzed by phosphate dependent glutaminase.

6. Glutamate and its metabolism enzymes

The carboxylate anions and salts of glutamic acid are known as glutamates. It is also important for metabolism.

6.1. Glutamine synthetase

It acts as a catalyst in this reaction



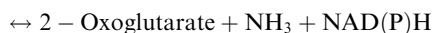
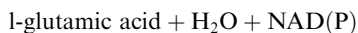
The enzyme from mammalian brain has two important functions: assimilation of ammonia and biosynthesis of glutamine (Boksha et al., 1995).

6.2. Glutaminase

Glutaminase catalyzes the reaction of glutamine catabolism to produce glutamate and ammonia. Its activity can be observed both in neurones and astroglial cells, but glutaminase is more active in neurones (Nimmo and Tipton, 1979), predominantly in mitochondria. The enzyme becomes free from the inhibitory influence of glutamate only when the concentration of glutamic acid falls below normal values (Plaitakis et al., 1984).

6.3. Glutamate dehydrogenase

Glutamate dehydrogenase (GDH) catalyzes a reversible reaction:



The GDH reaction is reversible but equilibrium is shifted closer to direct reaction (i.e. to synthesis of glutamic acid) (Zaganas et al., 2009). Consequently, GDH in brain takes part in

the synthesis of glutamate from 2-oxoglutaric acid, more than in oxidation of the amino acid. This is the way of continuous maintenance for changing of free ammonia into amino nitrogen of amino acids.

6.4. Aspartate transaminase or glutamate oxaloacetate transaminase

Aspartate transaminase catalyzes the reversible transfer of amino group to 2-oxoglutarate, as a result oxaloacetate and glutamate are formed. This is the most active transaminase in the brain (Kelly and Stanley, 2001). Oxaloacetate is quickly transformed into malic acid which enters from the cytoplasm into mitochondria. In this way the aspartate-malate bypath for transfer redox equivalents from the cytosol to mitochondria is formed. This bypath is the main way for transferring redox equivalents to mitochondria in neurones. Influx of aspartate through the mitochondrial membrane is bound with an efflux of a glutamate in such a way influx of a malate is bound with the efflux of 2-oxoglutarate, too.

6.5. Glutamic acid decarboxylase

Glutamic acid decarboxylase (GDA) catalyzes the separation of a carboxylic group from glutamate with the formation of gamma-aminobutyric acid (GABA). When GAD acts on glutamate which has an excitatory influence on neurones, then GABA is formed which is a main inhibitory neurotransmitter in the brain (Kelly and Stanley, 2001).

7. Applications

7.1. Pharmacological uses of glutamic acid

7.1.1. Fuel

Glutamic acid takes part in more metabolic reactions than any other amino acid. It is a source of glucose which is the chief source of fuel. It maintains the normal blood glucose level and also the acidity. It serves as a source of fuel for the intestinal epithelium. Glutamine increases the body's secretion of human growth hormone (HGH). It also plays a major role in removing excess ammonia from the bloodstream.

7.1.2. Muscle and other cell components

Glutamine is present in more than three-fifths of the human muscle tissue. It synthesizes both DNA and RNA and is essential for the synthesis of all proteins. By stimulating the release of the anabolic hormone HGH, it plays an indirect role in building the skeletal muscle. Glutamine also protects the integrity of the gastrointestinal tract when ulcers, chemotherapy agents or non-steroidal anti-inflammatory drugs are present.

7.1.3. Immune function

Glutamine is very essential for proper immune function. It is required for the proliferation of lymphocytes and cytokines. It increases the efficiency of macrophages, large immune cells which engulf and degrade foreign substances ranging from microbes to inorganic molecules. In many situations in which the immune function is compromised, for example, severe burns, sepsis or when athletes overexert themselves, gluta-

mine depletion is at least partly responsible for the immune suppression. The administration of glutamine to patients receiving bone marrow transplants results in a lower incidence of post-operative infections and a shorter stay in the hospital.

7.1.4. Neurotransmitter

It is an important excitatory neurotransmitter. It helps in the transportation of potassium across the blood-brain barrier. It also shows promise in the future treatment of neurological conditions, ulcers, hypoglycemic coma, muscular dystrophy, epilepsy, Parkinson's and mental retardation.

7.2. Other uses of glutamic acid

7.2.1. It is used as surfactants

It is hydrophilic by nature and can combine with hydrophobic fatty acids easily to form molecules with both water-soluble and water repelling portions that can be used as surfactants. There are many applications of GA derivatives as surfactants, especially due to its lack of harmful effects to skin and their general smooth appearance. It is very much favored by the cosmetic, moisture containing hair shampoo product manufacturers.

7.2.2. It is used as buffer

GA is an amphopteric substance that contains both acidic and basic functional groups and thus a natural buffer by itself.

7.2.3. It is used as Chelating agents

GA has two carboxylic groups, which can form chelates with many metal cations. Such chelating reaction is useful in the removal of heavy-metal contaminants in the wastewater treatment processes.

7.2.4. It is used as flavor enhancer

Monosodium glutamate (MSG), the single largest amino acid product, has been used as a flavor enhancer throughout the world for the past forty years. MSG is used worldwide in huge quantities as a flavor enhancer in foods. MSG is known to produce a unique taste sensation termed 'UMAMI' the fifth taste, *i.e.* savory or brothy taste present in tomatoes and cheese. Free glutamate content is said to increase during the process of natural ripening and brings about a fuller taste in many foods, the basis behind is not known.

7.2.5. It is used in culture medium

GA happens to be one of the main components in the cell wall of Gram-positive bacteria. It is also one of the most essential amino acids for other microorganisms to grow on. In most cases, it is often necessary to add GA into culture media to effect normal growth.

7.2.6. It is used in agriculture

GA is one of the major amino acids in plant proteins and plays a role of the major nitrogen storage for plants. That is why GA is often one of the more prominent ingredients in many plant growth supplements. Besides, GA is vital in the nitrogen metabolism in plants.

8. Overview and conclusion

The main objective of this article is to highlight the anticancer activity of glutamic acid. From the above discussion it has been concluded that glutamic acid is endogenic in nature hence will produce a fewer side effects. Some times it is seen that it increases the anticancer activity of that drug with which it is combined, as in the case of γ -poly (α ,L-glutamic acid)-cis-dichlorodiammineplatinum. This conjugate produces less side effect and increased anticancer activity when compared with cisplatin. Glutamine is the primary substrate in cancer cells that provide precursor molecules which allows the cell to produce more NADPH. Since cancer cells depend on glutamine, if glutamine synthesis and metabolism is blocked the anticancer activity can be produced. But as glutamine is required for several other functions of body like in the brain therefore blockage of glutamine is not a smart way to achieve anticancer activity. Rather the treatment should be done in such a way which can reduce the ability of the cell to uptake glutamine, such as by targeting Myc which is responsible for the synthesis of purine and pyrimidine at oncogenic level and other proteins that are responsible for transporting glutamine into the cell, or drugs which block mTORC1. It is also a source of glucose, essential for proper immune function. It also shows promise in the future treatment of neurological conditions, ulcers, hypoglycemic coma, muscular dystrophy, epilepsy, Parkinson's, and mental retardation. Hence it can be concluded that important therapeutic applications of glutamic acid are just waiting to be discovered and can be implicated in cancer treatment.

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