WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 2, Issue 3, 731-739. Review Article ISSN 2277– 7105

AMINO ACID GLUTAMIC ACID ITS ANTICANCER PROPERTIES AND PHARMACOLOGY (A REVIEW)

[1]*Nazir Ahmad Wani and [2]Mukhtar Ahmad Wani

[1]*Govt. Degree College Boys Anantnag Jammu & Kashmir (India).

[2]Department of Chemistry, IGNOU New Delhi (India).

Article Received on
20 Feb. 2013,

Revised on 10 March. 2013,
Accepted on 30 March. 2013

DOI: 10.20959/wjpr20133-7924

***Corresponding Author**
Nazir Ahmad Wani
Govt. Degree College Boys Anantnag Jammu & Kashmir (India).
waninazir03@yahoo.com

ABSTRACT

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.

KEYWORDS: anticancer activity, glutamine synthase, glutamic acid.

INTRODUCTION

Glutamate is a key compound in cellular metabolism. In humans, dietary proteins are broken down by digestion into amino acids, which serve as metabolic fuel for other functional roles in the body. A key process in amino acid degradation is transamination, in which the amino group of an amino acid is transferred to an α-ketoacid, typically catalysed by a transaminase.[1-4] 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.[5-7] 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 inter convertible.

L-Glutamic acid-γ-(4-hydroxyanilide) is isolated from mushroom *Agaricus bisporous*. 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 *Justica 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 in hippocampal long-term potentiation and memory. Glutamic acid, a glutamate receptor agonist enhances retention of memory (Cui et al., 2009).[8-11] 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).

Hanahan and Weinberg have argued that in order for a cell to become cancerous, it must acquire six unique traits as a result of altered cell physiology.[12-13] These defining traits of cancer cells are: (1) the ability to generate their own growth signals or respond to weak growth signals that are ignored by healthy cells; (2) insensitivity to antiproliferative signals; (3) resistance to cellular suicide mechanisms that normally cause aberrant cells to die by apoptosis; (4) the capacity for limitless replication; (5) the ability to stimulate new blood vessel development in order to allow for tumour growth; and (6) the capacity to invade tissues, at first locally and later to spread or metastasize throughout the body. Although localized cancers can often be successfully treated by surgery and/or radiation therapy, chemotherapy remains the usual treatment of choice for advanced or metastatic disease.[5] However, the use of conventional chemotherapeutic agents that typically target rapidly dividing cancer cells is often associated with deleterious side-effects caused by inadvertent

drug-induced damage to healthy cells and tissues.[14-15] Moreover, cancer cells that are quiescent or slowly proliferating are refractory to the cytotoxic effect of chemotherapeutic drugs that act at the level of DNA synthesis. Cancer cells also frequently become resistant to chemotherapy as a consequence of cellular changes that include increased expression of drug-detoxifying enzymes and drug transporters, altered interactions between the drug and its target, an increased ability to repair DNA damage and defects in the cellular machinery that mediate apoptosis.[16-17]

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

Glutamic acid derivatives as anti-cancer drugs

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).

Chemically methotrexate is *N*-[4-[[(2,4-diamino-6-pteridinyl) 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)[18-21] 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).

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).

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.

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 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).

Pharmacology of Glutamic acid

The drug phencyclidine (more commonly known as PCP) antagonizes glutamic acid non-competitively at the NMDA receptor. For the same

reasons, dextromethorphan and ketamine also have strong dissociative and hallucinogenic effects. Acute infusion of the drug LY354740 (also known as eglumegad, an agonist of the metabotropic glutamate receptors 2 and 3) resulted in a marked diminution of yohimbine-induced stress response in bonnet macaques (Macaca radiata); chronic oral administration of LY354740 in those animals led to markedly reduced baseline cortisol levels (approximately 50 percent) in comparison to untreated control subjects.[21] LY354740 has also been demonstrated to act on the metabotropic glutamate receptor 3 (GRM3) of human adrenocortical cells, downregulating aldosterone synthase, CYP11B1 and the production of adrenal steroids (i.e. aldosterone and cortisol).[22] Glutamate does not easily pass the blood brain barrier, but, instead, is transported by a high-affinity transport system.[23][24] It can also be converted into glutamine.

Other Applications of Glutamic acid

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.[22] GA is an amphopteric substance that contains both acidic and basic functional groups and thus a natural buffer by itself. 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. 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.[23]

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.[24]

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.[25-27]

CONCLUSION

Sometimes 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 cisplastin. 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.

REFERENCES

1. Bannai S., Ishii T. A novel function of glutamine in cell culture: utilization of glutamine for the uptake of cystine in human fibroblast. J. Cell. Physiol. 1988; 137(2): 360–366.
2. Boehm K., Borrelli F., Ernst E., Habacher G., Hung S.K., Milazzo S., Horneber M. Green tea (*Camellia sinensis*) for the prevention of cancer. Cochrane Database Syst. Rev. 2009; (3): CD005004. doi: 10.1002/14651858.CD005004.pub2.
3. Boksha I.S., Tereshkina E.B., Burbayeva G.S. Isolation and some properties of glutamine synthetase from human brain. Biokhimiia (Mosc)., 1995; 60(10): 1697–1705. (Rus).
4. Cui C., Zhang Y., Wang L., Liu H., Cui G. Enhanced anticancer activity of glutamate prodrugs of all-trans retinoic acid. J. Pharm. Pharmacol. 2009; 61(10): 1353–1358.
5. DeBerardinis R.J., Mancuso A., Daikhin E., Nissim I., Yudkoff M., Wehrli S., Thompson C.B. Beyond aerobic glycolysis: transformed cells can engage in glutamine metabolism that exceeds the requirement for protein and nucleotide synthesis. Proc. Natl. Acad. Sci. 2007; 104(49): 19345–19350.

6. Dewald H.A., Moore A.M. 6-Diazo-5-oxo-L-norleucine, a new tumor-inhibitory substance. Preparation of L-, D- and DL-forms. J. Am. Chem. Soc. 1958; 80(15): 3941–3945.
7. Dubey S.K., Sharma A.K., Narain U., Misra K., Pati U. Design, synthesis and characterization of some bioactive conjugates of curcumin with glycine, glutamic acid, valine and demethylenated piperic acid and study of their antimicrobial and antiproliferative properties. Eur. J. Med. Chem. 2008; 43(9): 1837–1846.
8. Dutta S., Ray S., Nagarajan K. Glutamic acid analogues used as potent anticancer: a review. Der Pharm. Chem. 2011; 3(2): 263–272.
9. Esslinger C.S., Cybulski K.A., Rhoderick J.F. N_{γ}-Aryl glutamine analogues as probes of the ASCT2 neutral amino acid transporter binding site. Bioorg. Med. Chem. 2005; 13(4): 1111–1118.
10. Giovannucci E., Stampfer M.J., Colditz G.A., Hunter D.J., Fuchs C., Rosner B.A., Speizer F.E., Willett W.C. Multivitamin use, folate and colon cancer in women in the Nurses' health study. Ann. Intern. Med. 1998; 129(7): 517–524.
11. Hatzivassiliou G., Zhao F., Bauer D.E., Andreadis C., Shaw A.N., Dhanak D., Hingorani S.R., Tuveson D.A., Thompson C.B. ATP citrate lyase inhibition can suppress tumor cell growth. Cancer Cell. 2005; 8(4): 311–321.
12. Kelly A., Stanley C.A. Disorders of glutamate metabolism. Ment. Retard. Dev. Disabil. Res. Rev. 2001; 7(4): 287–295.
13. Kulkarni C., Kulkarni K.S., Hamsa B.R. L-Glutamic acid and glutamine: exciting molecules of clinical interest. Indian J. Pharmacol. 2005; 37(3): 148–154.
14. Luzzio F.A., Mayorov A.V., Figg W.D. Thalidomide metabolites. Part 1: derivatives of (+)-2-(*N*-phthalimido)-γ-hydroxyglutamic acid. Tetrahedron Lett. 2000; 41(14): 2275–2278.
15. McPhee S.J., Papadakis M.A., Rabow M.W. 50 ed. Lange Medical Books/McGraw-Hill; New York: 2011. Current Medical Diagnosis and Treatment 2011.
16. Medina M.A., Sanchez-Jimenez F., Marquez J., Quesada A.R., Castro I.N. Relevance of glutamine metabolism to tumour cell growth. Mol. Cell. Biochem. 1992; 113(1): 1–15.
17. Moreadith R.W., Lehninger A.L. The pathways of glutamate and glutamine oxidation by tumor cell mitochondria. Role of mitochondrial NAD(P)+-dependent malic enzyme. J. Biol. Chem. 1984; 259(10): 6121–6215.
18. Nicklin P., Bergman P., Zhang B., Triantafellow E., Wang H., Nyfeler B., Yang H., Hild M., Kung C., Wilson C., Myer V.E., MacKeigan J.P., Porter J.A., Wang Y.K., Cantley

L.C., Finan P.M., Murphy L.O. Bidirectional transport of amino acids regulates mTOR and autophagy. Cell. 2009; 136(3): 521–534.

19. Nimmo G.A., Tipton K.F. The distribution of soluble and membrane-bound forms of glutaminase in pig brain. J. Neurochem. 1979; 33(5): 1083–1084.
20. Nishiyama N., Kato Y., Sugiyama Y., Kataoka K. Cisplatin-loaded polymer–metal complex micelle with time-modulated decaying property as a novel drug delivery system. Pharm. Res. 2001; 18(7): 1035–1041.
21. Oaks B.M., Dodd K.W., Meinhold C.L., Jiao L., Church T.R., Stolzenberg-Solomon R.Z. Folate intake, post-folic acid grain fortification and pancreatic cancer risk in the prostate, lung, colorectal and ovarian cancer screening trial. Am. J. Clin. Nutr. 2010; 91(2): 449–455.
22. Oldham E.A., Lic K.S., Wallace S., Huang P. Comparison of action of paclitaxel and poly(L-glutamic acid)–paclitaxel conjugate in human breast cancer cells. Indian J. Oncol. 2000; 16: 125–132.
23. Percival S.S., Bukowski J.F., Milner J. Bioactive food components that enhance $\gamma\delta$ T cell function may play a role in cancer prevention. J. Nutr. 2008; 138(1): 1–4.
24. Plaitakis A., Berl S., Yahr M.D. Neurological disorders associated with deficiency of glutamate dehydrogenase. Ann. Neurol. 1984; 15(2): 144–153.
25. Shih I.L., Van Y.T., Shen M.H. Biomedical applications of chemically and microbiologically synthesized poly(glutamic acid) and poly(lysine) Mini Rev. Med. Chem. 2004; 4(2): 179–188.
26. Singer J.W., Bhatt R., Tulinsky J., Buhler K.R., Heasley E., Klein P., de Vries.P. Water-soluble poly-(L-glutamic acid)-gly-camptothecin conjugates enhance camptothecin stability and efficacy *in vivo*. J. Controlled Release. 2001; 74(1–3): 243–247.
27. Skeel R.T. seventh ed. Lippincott, Williams & Wilkins; New York: 2008. Hand Book of Cancer Chemotherapy.
28. Srikanth K., Kumar C.A., Ghosh B., Jha T. Synthesis, screening and quantitative structure-activity relationship (QSAR) studies of some glutamine analogues for possible anticancer activity. Bioorg. Med. Chem. 2002; 10(7): 2119–2131.
29. Stamler J., Brown I.J., Daviglus M.L., Chan Q., Kesteloot H., Ueshima H., Zhao L., Elliott P. Glutamic acid—the main dietary amino acid and blood pressure: the INTERMAP study (international collaborative study of macronutrients, micronutrients and blood pressure) Circulation. 2009; 120(3): 221–228.