IARJSET

ISSN (Online) 2393-8021
ISSN (Print) 2394-1588

International Advanced Research Journal in Science, Engineering and Technology

ISO 3297:2007 Certified

Vol. 3, Issue 8, August 2016

Glutaminase: Clinical Concerns and Prospects

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Abstract: Hydrolytic enzyme, L-glutaminase (EC3.5.1.2) converts glutaminase into glutamate and ammonia. It is a multifunctional enzyme which contributes majorly in food, pharmaceutical and chemical industry. The enzyme has been subject of some reviews on types, distribution, biochemical and immunological properties. Glutaminase is a ubiquitous enzyme and catalyzes the hydrolysis of γ-amido bond of L-glutamine. Due to having structurally and folding pattern similarity, it belongs to serine-dependent β-lactamases and penicillin binding proteins. Glutamase enhance the flavor of food that why it is used as a food enhance in food industry. It also known for major source for energy and nitrogen in the cell biosynthesis and promoting cancer. Directly and indirectly involvement of glutaminase in main metabolic process has made its great importance in biological system.

Key words: L-glutaminase, Glutamine, Glutamic acid, Monosodium Glutamate, Cancer.

I. INTRODUCTION

About 50-60 years before glutaminase was identified as primary and ubiquitous enzyme by researchers. Involvement of glutaminase in tumor metabolism was discovered in 1950s. Uncontrolled highly proliferative cells generally run out of energy and this has opened one more way to treat cancer. The participation of Glutaminase is in every core metabolic task has made it therapeutically useful. The other name is amidohydrolase (EC 3.5.1.2), in the reaction it cleaves amide group and replaces with hydroxyl group in glutamine. It is true hydrolytic enzyme because the ammonium and acyl acceptor is water (Rosa et al., 2009). Glutaminases belong to the large superfamily of serine-dependent β-lactamases and penicillin binding proteins which have a common evolutionary origin and share the protein fold, structural motifs, and catalytic mechanism (Brown et al., 2008). A multifunctional enzyme glutaminase involves in various metabolism i.e. energy metabolism, ammonia trafficking and regeneration of neurotransmitter glutamate (Bae et al., 2013). It is a mitochondrial enzyme and localized in outer face of the inner mitochondrial membrane (McCouley et al., 1999). Phosphate-activated glutaminase (PAG) exists in mitochondria in two forms, an inner membrane-bound and a soluble form. They present differential kinetic profiles and sensitivity to inhibitors and activators; the membrane-bound form seems to be the active form of the enzyme (Bak et al., 2008). The two isoform glutaminase encoding genes are present in different chromosomes in human. One is Kidney type (70kDa) isozyme located in chromosome 2q32–q34 and commonly referred as Gls1. It is abundant in kidney, brain, intestine, fetal liver, lymphocytes, and transformed cells, where the resulting ammonia is released without further metabolism (Bae et al., 2013). Second, liver-type isozyme (58 kDa) is located on chromosome 12q13 (Aledo et al., 2000, Bae et al., 2013) and referred as Gls2. It is mainly expressed in liver and couples effectively ammonia production with urea synthesis (Curthoys and Watford, 1995; Watford, 1993). Liver type glutaminase have high level of expression in stressed and non-stressed condition due to tumor suppressor protein p53. Antioxidant defense function is also regulated by Liver type glutaminase by increased level of reduced glutathione (GSH) and minimizes the reactive oxygen species (ROS) levels, which protects cells from oxidative stress (e.g. H2O2)-induced apoptosis (Hua et al., 2010, Dayea et al., 2012). Liver type glutaminase regulates cellular energy metabolism by increasing glutamate and α-ketoglutarate level to enhance mitochondrial respiration and ATP generation (Hua et al., 2010). Induction of Liver type glutaminase expression leads to increased mitochondrial oxidative phosphorylation and energy production from glutaminolysis. Initiation of Liver type glutaminase was suggested to contribute to p53-dependent tumor suppression. The cancerous liver tissues have hyperpolarized glutamate production, which is the result of a higher rate of transport rather than a higher expression of glutaminase (Cabella et al., 2013).

Kidney-type glutaminase (Gls1) and liver-type glutaminase (Gls2) have antagonistic effects in tumor formation. Oncogene transcription factor myc, induces the expression of Kidney-type glutaminase; while p53 induces the expression of liver-type glutaminase. Increase in Kidney-type glutaminase shows oncogenic transformation and cancer cell proliferation while overexpression of liver-type glutaminase is tumor suppressive (Daye et al., 2012). The Kidney type is activated by high phosphate levels and strongly inhibited by the end-product glutamate, whereas Liver type glutaminase is activated by low phosphate levels and not inhibited by glutamate. Therefore, these two glutaminase isoforms may have different impacts upon the fine regulation of energy metabolism and antioxidant defense (Hua et al., 2010). The two isoenzymes of glutaminase are known to have different structural, kinetic, immunologic, and molecular characteristics that are subject to different regulatory mechanisms, and exhibit different tissue-specific expression (Daye et al., 2012; Curthoys and Watford, 1995; Hua et al., 2010). One of the

IARJSET
ISSN (Online) 2393-8021
ISSN (Print) 2394-1588
International Advanced Research Journal in Science, Engineering and Technology
ISO 3297:2007 Certified
Vol. 3, Issue 8, August 2016

important functions of glutamine metabolism is to provide precursors for glutathione production, which helps to maintain the oxidative status of cells. Indeed, glutaminase has been directly linked to redox balance in cancer cells (Katt and Cerione, 2014).

II. CHEMICAL CHARACTERISTICS AND ROLE OF GLUTAMINE AND GLUTAMIC ACID

Glutamine and glutamate are non-essential amino acid in mammals, as mammal body has a metabolic capacity to synthesize these amino acids when necessary. L-Glutamine is an amide of glutamic acid with amine as the functional group. The contribution of molecular weight 146.15 KDa is by C = 41.09 %, H = 6.90 %, O = 32.84 %, and N = 19.17 %. In water, the solubility is 3.6% at 18°C (Archibald, 1945). It is a non-toxic vehicle for the transport of nitrogen and carbon-skeleton between different tissues where this amino acid fulfills many different physiological functions (Aledo et al., 1998). It is abundant amino acid in both intracellular (2 mM to 20 mM) and extracellular (0.7 mM) compartments (Curi et al., 2005). Change in intracellular glutamine concentration could affect glutamine-utilizing enzymes through other mechanisms involving glutamine sensing and signaling (Donadio et al., 2008). Physiological functions and required for number of cellular functions such as in cellular metabolism by supplying nitrogen required for the biosynthesis of various nitrogenous metabolic intermediates between organs as well (Calderon et al., 1999, Szeliga et al., 2009). Few peptides, purines, pyrimidines, nucleic acids amino sugars, and other nitrogenous compounds in the cells use it as a precursor. Glutamine synthesis and glutamine hydrolysis occurs in many tissues, but primary sites of glutamine synthesis are skeletal muscle, lung, brain, adipose tissue, and under certain conditions, the liver (Watford, 1993). The major sites of glutamine utilization are the small intestine and active cells such as thymocytes, macrophages, lymphocytes and actively dividing enterocytes (Chang et al., 1999; Curi et al., 1999). Other major sites of glutamine utilization are the kidneys during metabolic acidosis, the mammary gland during lactation, and many tumor cells (Watford, 1993). In certain condition such as trauma, surgery and sepsis glutamine is essential to body as alternate source of energy. So it is considered as a ‘conditionally essential’ or ‘‘semi-essential’’ amino acid (Takahashi et al., 2011).Glutamine and glutamate plays a key role in the synthesis of glutathione which is a major mammalian endogenous antioxidant in cell. Several metabolic products derived from glutamine also include neurotransmitter, proline and hexosamines. Tumor cell can depend on glucose and the glutamine for viability and growth (Heuvel et al., 2012) Thus, it is essential for the growth of cultured cells, both normal and malignant. In Poly Morphonuclear neutrophils by inhibiting Glutaminase, Glutamine metabolism causes a significant decrease in superoxide production. Therefore, the sub-cellular location of glutamine appears to be important for glutamine dependent superoxide production by Poly Morphonuclear neutrophils (Castell et al., 2004). In vitro and in vivo, study suggested that Poly Morphonuclear neutrophils may benefit from exogenous glutamine, which repletes the decrease in the blood concentration observed after stress (Castell et al., 2004). Glutamine metabolism regulates of autophagy. Ammonia, generated from Glutamine deamination in mitochondria, functions as an autocrine- and/or paracrine-acting stimulator of autophagic flux (Eng and Abraham, 2010). Glutamine and glutamate regulates key metabolic pathways such as maintenance, growth, reproduction and immunity (Takahashi et al., 2011). They act as substrate in the ureagenesis in liver and gluconeogenesis in liver and kidney. The glutamine precursor’s or glutamine uptake in athletes resulted in decrease illness, particularly for upper respiratory tract infections (URTI) (Castell et al., 2004).

Glutamate is the recognized neurotransmitter of several clinically important pathways, including cortical association fibers, corticofugal pathways such as the pyramidal tract, and hippocampal, cerebellar, and spinal cord pathways (Ebling, 1996; Timothy, 1986). Glutamate (also known as amino nitrogen), serves as the precursor of ϒ-aminobutyric acid (GABA) and glutathione (Bae et al., 2013). In Ultra organizational studies validated the presence of glutamate in presynaptic terminals within the suprachiasmatic nucleus of the hypothalamus. (Ebling, 1996). Glutamate is indicative of human neurodegenerative disorders also because it has excitotoxic and neurotoxic properties. Abnormally enhanced glutamatergic neurotransmission may cause excitotoxic cell damage and lead to the neuronal death associated with olivopontocerebellar atrophy, Huntington's disease, status epilepticus, hypoxia/ischemia, and hypoglycemia.

Amidohydrolase family that deaminates the glutamine content has two classes. One is glutaminase (3.5.1.5) which is very specific for its substrate glutamine and the other is glutaminase-asparaginase (3.5.1.38) that can catalyze both glutamine and asparaginase as substrate with similar efficiency. The glutaminase to asparginase activity was 1.5:1.0 in the enzyme from Pseudomonas boreopolis. The glutaminase and glutaminase-asparaginase has aproximately same deamidation mechanism (Nandkumar et al., 2003). Hartman suggested the categorization of glutaminase and ϒ-glutamyltransferase (EC 2.3.2.2) based on catalysis. The first, which catalyses only hydrolysis reaction for example – Micrococcus luteus K-3 (Moriguchi et al., 1994), P. putrefaciens (Holcenberg et al., 1973), glutaminase from mammalian origine etc. Second, hydrolysis prior to transfer reaction with some acceptors such as glutaminase from P. aeruginosa (Soda et al., 1972) and E. Coli (Prusiner, et al., 1976). Third, transfer reaction prior to and fourth, only transfer reaction the example for third and fourth is P. nitroreducens (Tachiki et al., 1998). The metabolism of both L and D form of glutaminase are summarized in Figure 1.

IARJSET
ISSN (Online) 2393-8021
ISSN (Print) 2394-1588
International Advanced Research Journal in Science, Engineering and Technology
ISO 3297:2007 Certified
Vol. 3, Issue 8, August 2016

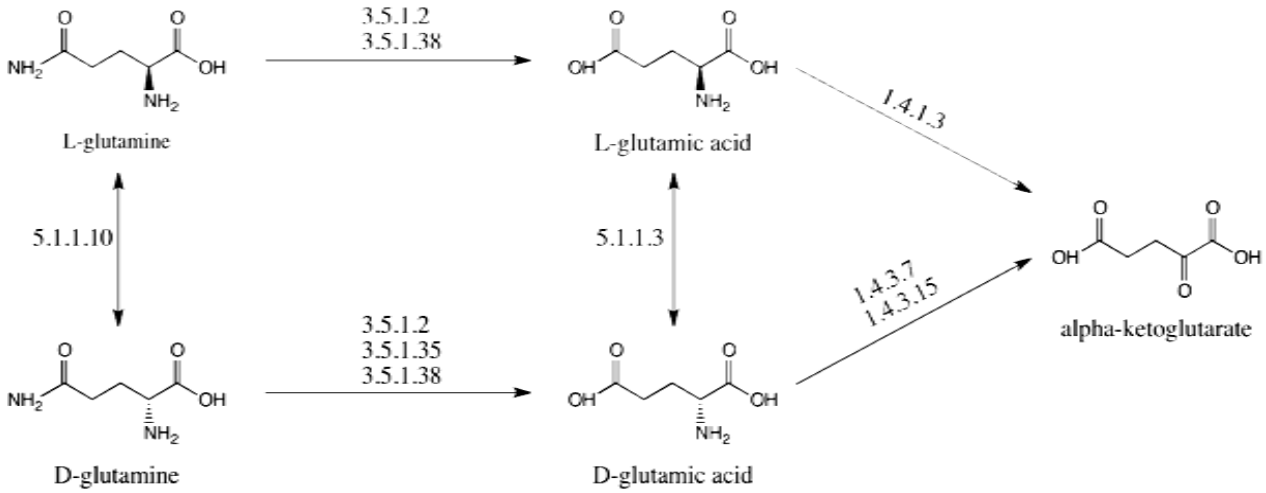

Figure 1. Metabolism of L-glutamine and D-glutamine. List of involved enzymes: 1.4.1.3: glutamate dehydrogenase, 1.4.3.7: D-glutamate oxidase, 1.4.3.15: D-glutamate(D-aspartate) oxidase, 3.5.1.2: glutaminase, 3.5.1.35: D-glutaminase, 3.5.1.38: glutamin-(asparagin-)ase, 5.1.1.3: Glutamate racemase, 5.1.1.10: amino-acid racemase. (Kubala, 2013)

III. BIOLOGICAL ROLE L- GLUTAMINASE

Glutaminase uses glutamine as substrate to form glutamate and ammonia. In a healthy cell, glutaminase is main supporting enzyme in TCA for ATP production in absence of glucose. This is intriguing, suggesting perhaps that glucose-depleted cells become more dependent on glutamine via glutaminase.

A. Glutaminase as cancer suppresser: The hallmark of cancer is uncontrolled cell division; metabolic deregulation and/or altered energy balance (Heuvel et al., 2012). Uncontrolled cell division of cancer cell leads to metabolic deregulation which further leads to altered energy balance. Removing glutamine from culture medium promotes tumor cell differentiation and decreases proliferation; inversely, addition of glutamine protects cells from apoptosis and induces proliferation (Medina et al., 1992; Tapiero et al., 2002). The level of glutamine in blood is approximately constant but in pathological condition, such as metabolic acidosis or cancer, inter organ glutamine metabolism is extremely altered. An uncontrolled proliferative cell of tumor competes for circulating glutamine and essential amino acids in host (Aledo et al., 1998**).** Glutamate is a major source for energy and nitrogen for biosynthesis, and a carbon substrate for anabolic processes in cancer. Oncogene transcription factor C-Myc, induces the expression of Kidney type glutaminase and glutaminolysis through the repression of miR-23 (Pan et al., 2015). This promotes tumor cell proliferation in human P-493 B lymphoma and PC3 prostate cancer cells (Pan et al., 2015; Hua et al, 2010; Erickson et al., 2010). Due to critical function of glutaminase in cancer cell survival, it is a target of interest for therapy. It's inhibitor such as BPTES interferes with the cellular metabolism. Cellular metabolism is incredibly dynamic and appears to compensate for changes in intermediary metabolism. So there is a probability that glutaminolysis inhibition may be not work as single arm therapy (Pan et al., 2015). Antisense mRNA decreases growth and tumourigenicity of tumour cells by Inhibition of glutaminase expression (Lobo et al., 2000).

B. Glutaminase in intestinal health: Glutaminase has a crucial role in intestinal metabolism because the product of glutaminase can be transaminated, catabolized to yield energy or act as precursor for nucleotide synthesis (McCouley et al., 1999). In the study on effect of starvation on intestinal glutaminase activity Kong et al, (2000) has observed that the starvation does not alter the distribution of glutaminase in intestinal mucosa. Starvation decreases the total intestinal activity per centimeter of glutaminase. More importantly, the results indicate that the intestine adapts to starvation by accumulating glutaminase mRNA. This process prepares the intestine for a restoration of intake.

Experimental result report shows that deprivation of glutamine in intestine induces intestinal atrophy. The enterocolitis which is induced by either radiation or methotrexate can also be lessening by supplementation of glutamine (McCouley et al., 1999). In vertebrates Glucocorticoid increases glutaminase expression which increases intestinal glutamine utilization by, an adaptive response that could provide more energy for mucosal cells in stress states (Rosa et al, 2009, Sarantos et al., 1992). Glutaminase catalyzes the rate-limiting step of glutamine degradation. Glutamine enriched parenteral nutrition accumulates the Kidney-type glutaminase mRNA which further results in increase of Kidney-type glutaminase activity in intestinal cells (Rosa et al, 2009, Kong et al., 2000).

DOI 10.17148/IARJSET.2016.3822

IARJSET
ISSN (Online) 2393-8021
ISSN (Print) 2394-1588
International Advanced Research Journal in Science, Engineering and Technology
ISO 3297:2007 Certified
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C. Immunity concerns of glutaminase: Initially Ardawi and Newsholme reported the importance of glutamine metabolism in cells belonging to the immune system. Clinically, depletion of glutamine below the physiological plasma concentration after surgery, major burns, sepsis or trauma shows weakening of immune response (Aledo et al., 1998). In HIV-1 infection glutamate production gets significantly increased and this process is dependent upon the glutamate-generating Liver-type glutaminase, not on Kideny-type glutaminase. Glutaminase is a mitochondrial protein, but during HIV-1 associated demencia (HAD) it was observed that it is released into the cytosol and extracellular space. Glutaminase inhibition was found to be significantly decreasing macrophage-mediated neurotoxicity. This released enzyme is capable of rapidly converting the abundant extracellular amino acid glutamine into excitetoxic levels of glutamate in an energetically favorable process (Erdmann et al., 2009). HIV-1-infected patients have significantly higher concentrations of glutamate in their plasma and cerebrospinal fluid as compared to uninfected controls (Ollenschlager et al. 1988) These findings support glutaminase as a potential element of the HAD pathogenic process and identify a possible therapeutic way for the treatment of neuroinflammatory states (Erdmann et al., 2009). The glutamate excess is possibly immunosuppressive but short term glutamine deficiency is specifically immunosuppressive whereas asparagine deficiency is not (Kafkewiz and Bendich, 1983). Microglia serves as local guards in brain and provides the necessary innate immune response against injury, infection and other adverse stimuli. In response to stimuli in vitro and in vivo, activated microglia produce pro-inflammatory cytokines (IFN-c, IL-1b, IL-6, IL-18, IP-10, PGE2, TNF-a), reactive oxygen species (NO, O_2, H_2O_2, OH, NOO) and excess glutamate that have been shown to injure CNS cells. But uncontrolled and excessively activated microglia contributes to neuroinflammation which is a hallmark of several neurodegenerative diseases (Thomas et al., 2014).

D. Glutaminase in brain health: Glutaminase is the only enzyme in brain known to hydrolyse glutamine to Glutamate (Robinson et al., 2007). Predominantly kidney-type glutaminase is present in the brain (Bae et al., 2013). In previous reported studies it was demonstrated that in cultured neurons the release of mitochondrial Kidney-type glutaminase from damaged neurons contributes to the delayed increase in extracellular glutamate and the amplification of excitotoxicity (Robinson et al., 2007).

The excitatory neurotransmitter glutamate is mainly synthesized by glutaminase enzyme which is finely regulated in the brain tissues because of harsh potential giving rise to excitotoxic damage (Rosa et al., 2009). Microglia plays two opposite role simultaneously as neuroprotector and in neurotoxicity associated with various neurodegenerative diseases in the central nervous system (CNS) (Thomas et al., 2014). In the meningitis the glutamate level increases in cerebro spinal fluid (Spranger et al., 1996). Microglia-mediated glutamate levels were significantly increased by tumor necrosis factor (TNF)-a, phorbol 12-myristate 13-acetate (PMA) and Toll-like receptor (TLR) ligands coincident with increased glutaminase activity (Thomas et al., 2014).

E. Glutaminase during pregnancy and lactation: During pregnancy it has been observed that most of the amino acids level in the fetus is generally increased and the concentration gets doubled in fetal plasma than mother. In physiological condition generally glutamate never passes hemochorial placenta. But the intravenous infusion of glutamate in large amounts leads to maternal concentration of glutamate more than 200 µmoles/dl (40 to 50 times fasting) and then some degree of transfer takes place (Pitkin et al. 1979). In late pregnancy liver appears to release glutamine but utilization of glutamine increases during peak lactation (Ardawi, 1987).

F. In viral infection: Human cytomegalovirus infected human fibroblast are more viable than uninfected cells during glucose starvation because virally infected cell uses an alternate carbon source glutamine more than glucose for energy production through TCA cycle. This allows glucose to be diverted for use in synthetic processes. However, the tumor cell and virally infected cells are glutamine dependent for energy but there is difference in their mechanism to achieve the anaplerotic utilization of glutamine (Chambers et al., 2010).

G. Glutaminase inhibitor: Inhibitor that target glutaminase activity in cancer is under development. Many efforts have been made to target glutaminase using glutamine analogs but they were unsuccessful. To target Kidney-Type glutaminase, predominantly 6-diazo-5-oxy-L-norleucine (DON) was used directly. DON acts as an irreversible glutamine-competitive inhibitor (Katt and Cerione, 2014). Then BPTES (bis-2-(5 phenylacetamido-1, 2, 4-thiadia-zol-2-yl) ethyl sulfide) has attracted much attention as a selective, nontoxic inhibitor of Kidney-type Glutaminase (Thangavelu et al., 2012). DON is not selective and has several verified targets (Katt and Cerione, 2014) but BPTES is specific to Kidney-type but not to Liver-type glutaminase (Robinson et al., 2007). It inhibits the enzymatic activity of Kidney-type glutaminase through (i) triggering a major conformational change on the key residues that would normally be involved in stabilizing the active sites and regulating its enzymatic activity; and (ii) forming a stable inactive tetrameric Kidney-type glutaminase form (Thangavelu et al., 2012). In glioma cells BPTES selectively suppresses the growth (Seltzer et al., 2010) and in animal model studies it inhibits the growth of lymphoma tumor growth (Le et al., 2012). Dibenzophenanthridines also works as inhibitors of Glutaminase and Cancer Cell Proliferation (Katt et al., 2012). Small molecule inhibitors such as DON, BPTES etc. and glutaminase siRNA have been shown to decrease excess glutamate to provide neuroprotection in multiple models of disease, including HIV-associated dementia (HAD), multiple sclerosis and ischemia (Thomas et al., 2014).

IARJSET
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ISSN (Print) 2394-1588
International Advanced Research Journal in Science, Engineering and Technology
ISO 3297:2007 Certified
Vol. 3, Issue 8, August 2016

H. Glutaminase interaction: glutaminase has attracted major attention in the area of its novel interacting partners. Subcellular locations which strongly suggest that they behave as multifunctional enzyme, besides their roles as classical metabolic enzyme (Martin-Rufian et al., 2012). Crystal structure reveals BPTES binding to an allosteric site at the dimer interface of Kidney-type glutaminase. It initiates a dramatic conformational change near the catalytic site and rendering it inactive (Thangavelu et al., 2012).

IV. CONCLUSION

Antileukamic role of glutaminase is proven along with this many industrial applications such as flavor enhancing agents has already received attention of the many workers. In spite of this several other clinical concerns like brain health, intestinal relation, pregnancy and lactation, connection with viral infection and immunity has now created scope on much more clinical application of glutaminase. The pathological and therapeutic application of glutaminase in these area is expected to be established in very near future.

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IARJSET
ISSN (Online) 2393-8021
ISSN (Print) 2394-1588
International Advanced Research Journal in Science, Engineering and Technology
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Vol. 3, Issue 8, August 2016

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