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Panorama of L-glutaminase: Biological role and application

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Abstract: Glutaminase is one of the most important commercially produced industrial enzyme. Among its industrial applications it is used in dairy, fermentaed sauce production, vitamin B6 production, biosencer. The role of glutaminase as antileukamic and as food flavoring agent is established. The list of both the industrial and therapeutic uses of glutaminase is increasing continuously. Glutaminase has shown its profound effect an antiviral activity and HIV associated dementia and multiple sclerosis. The present review discusses some of important proven uses and some yet to be commercially established application of glutaminase.

Key words: L-glutaminase, food flavor, Glutamine, Glutamic acid, Antileukamic, anti HIV.

I. INTRODUCTION

Glutaminases (EC 3.5.1.2.) 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 (2Brown 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 (Watford, 1993; Curthoys and Watford, 1995). Liver type glutaminase have high level of expression in stressed and non-stressed condition due to tumor suppressor protein p53. 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 (*13*). 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 etl al., 1998). It is abundant amino acid in both intracellular (2 mM to 20 mM) and extracellular (0.7 mM) compartments (Cori et al., 2005). Change in intracellular glutamine concentration could affect glutamine-utilizing enzymes through other mechanisms involving glutamine sensing and signaling (Donadio et al., 1999)). 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, 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., 2009;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 subcellular 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

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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. Glutamine and glutamate regulates key metabolic pathways such as maintainance, 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). 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 catalysis only hydrolysis reaction for example – Microcococcus luteus K-3 (Morguchi et al., 1994), Pseudomonas putrefaciens (Holeenberg et al., 1973), glutaminase from mammalian origine etc. Second, hydrolysis prior to transfer reaction with some acceptors such as glutaminase from Pseudomonas aeruginosa (Soda et al., 1973) and E. Coli (Prushiner et al., 1976). Third, transfer reaction prior to and fourth, only transfer reaction the example for third and fourth is Pseudomonas nitroreducens (Tachiki et al., 1998). 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). Glutamate (also known as amino nitrogen), serves as the precursor of ϒ-aminobutyric acid (GABA) and glutathione (Brown, 2008). 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. Biological role: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.

II. BIOLOGICAL ROLES AND INDUCTRIAL APPLICATIONS

Metabolic role in intestine: 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, 1996). In the study on effect of starvation on intestinal glutaminase activity Kong et al, (Koong 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, 1996). 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., 1994).

Role in cancer: The level of glutamine in blood is approximately constant but in pathological condition, such as metabolic acidosis or cancer, interorgan 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 (Pan et al., 2015). Oncogene transcription factor C-Myc, induces the expression of Kidney type glutaminase and glutaminolysis through the repression of miR-23.This promotes tumor cell proliferation in human P-493 B lymphoma and PC3 prostate cancer cells (Erickson and Cerione, 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 (Erickson and Cerione, 2010). Antisense mRNA decreases growth and tumourigenicity of tumour cells by Inhibition of glutaminase expression (Lobo et al, 2000).

Glutaminase in Body defence: 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

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capable of rapidly converting the abundant extracellular amino acid glutamine into excitetoxic levels of glutamate in an energetically favorable process. HIV-1-infected patients have significantly higher concentrations of glutamate in their plasma and cerebrospinal fluid as compared to uninfected controls. 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 (Erdman et al., 2009). The glutamate excess is possibily immunosuppressive but short term glutamine deficiency is specifically immunosuppressive whereas asparagine deficiency is not (Ollenschlager, 1988).

Role 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).

Metabolism in Brain: Glutaminase is the only brain enzyme 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 simontaniously as neuroprotector and in neurotoxicity associated with various neurodegenerative diseases in the central nervous system (CNS) (Thomas et al., 2014).

Glutaminase inhibitor: 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). 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. Dibenzophenanthridines also works as inhibitors of Glutaminase and Cancer Cell Proliferation. 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).

Role in viral infection: In Human Cytomegalovirus Infection (HCMV) infection, infected cells become dependent upon glutamine for ATP production and viral production. It was observed that glutaminase and glutamate dehydrogenase gets increased within 24 h of infection, glutamine becomes main substrate for ATP production and this increases significantly by 48 h post infection. The inhibition of glutamine uptake or glutaminolysis may be an effective antiviral therapy for Human Cytomegalovirus Infection (Chambers et al., 2010).
HIV infected macrophages are glutamine dependent. It's main cellular energy source is extracellular glutamate (Jeong et al. 2009). HIV infected patients have significantly higher concentrations of glutamate in plasma (Droge et al. 1987; Ollenschlager et al. 1988) which induces neuronal damage (Olney 1971; McCall et al.1979; Choi 1988; Newcomb et al. 1997). So the inhibition of glutaminase can reduce the problem.
Glutaminase has central role in the generation of excitotoxic glutamate in central nervous system disorders such as HIV-associated dementia and multiple sclerosis. Glutaminase is responsible the generation of glutamate which is a key excitatory neurotransmitter in the CNS. Excessively activated macrophages and microglia releases elevated level of glutamate which correlates with upregulated glutaminase contribute to neuroinflammation, a hallmark of several neurodegenerative diseases.Two methods, glutaminase siRNA and glutaminase inhibition have been shown to be effective in in-vitro models of cancer and HIV-associated dementia, suggesting a potential role for small molecule glutaminase inhibitors. However, there are no potent, selective inhibitors of glutaminase currently available. The two prototypical glutaminase inhibitors, BPTES (bis-2-(5-phenylacetimido-1,2,4-thiadiazol- 2-yl)ethyl sulfide) and DON (6-diazo-5-oxo-Lnorleucine), are either insoluble or non-specific. It was reported ebselen, chelerythrine and apomorphine appear to be significantly more efficient than either DON or BPTES (bis-2-(5-phenylacetimido-1, 2, 4-thiadiazol- 2-yl) ethyl sulfide) for glutaminase inhibition (Thomas et al., 2014).

Application in food processing: There are four classic taste: sweet, salty, sour and bitter. The fifth taste discovered by K. Ikeda in 1908 (umami taste) appears to be the natural taste of the foods available to early man such as human milk, fish, chicken, sea-foods, sea weeds, all rich in glutamate proving the glutamate taste (Takahashi et al., 2011). Glutaminase converts glutamine into glutamate. The 'umami' taste includes 'delicious', 'umami' and 'brothy' tastes.

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Glutamate is most important amino acids and the main active component that improve the taste of meat (Kato & Nishimura 1987; Fujimura et al. 1996). Therefore, more the concentration of glutamate in meat gives better taste of meat. Free glutamate stimulates the salivation which is essential for mastication and swallowing. Glutamate evokes the cephalic phase of food digestion, such as an indication of pancreatic juice secretion (Takahashi et al., 2011). In fermented food, the concentration of glutamate increases and gives it palatable taste. By increasing the level of free glutamate in meat or tissues by feeding animals diets containing glutamate-rich feeds or by directly administration can rise the flavor of meat. Glutamate is not directly absorbed in many tissues because it is predominantly used as an energy source by intestinal cells (Reeds et al. 1996). It has reported that high protein diet in broiler chicks regulates muscular glutamate metabolism (Kobayashi et al., 2011).
Glutamate is present in some vegetarian food supplements as Soyabeans, beans, corn, green peas, tomato spinach, cabbage, mushroom, onion, sea-weeds, dried lever, kelp (konby) and some non-vegetarian food supplements as beef, fish, chicken, chees, human breast milk, sea foods, crabs, scallop etc. Food additives such as monosodium glutamate or hydrolyzed vegetable protein are also significant sources (Takahashi et al., 2011).

Use in dairy Industry: Glutamine and its counterpart Glutamic acid are most abundant in milk. Ruminents have low plasma glutamine level because of low glutamine synthatase capacity as compare to monogastic animals. Glutamine is limiting amino acid because of high metabolic stress of milk production the uptake of glutamine by mammary gland is 100 % (Meijer et al., 1993).

Flavor enhancing of Meat: Glutamine is claimed to increase muscle protein (Meijer et al., 1993). Increased concentration of Glutamate in meat improves the taste of meat. The free Glutamate content in pork and chicken meat is increased by aging for 6 or 2 days post-mortem, respectively (Nishimura et al., 1987). Because of dietary Glutamate is not directly absorbed in many tissues of body, so muscle free Glutamate content, which is an active taste component of meat, was significantly increased by short-term feeding of a short-term high-protein diet. Lysine α-ketoglutarate reductase and glutaminase appear to be involved in the increase in the muscle free Glutamate level (Kobayashi et al., 2011).

fermented foods: In addition to nutritional benefit, protein associated glutaminase gives texture and sensory properties to the foods. In dough softening in baking industry, enhancement of 'umami' taste in hydrolyzed vegetable protein and increase protein digestibility foods. Microorganisms are sources of glutaminase, Lactobacillus spp. are probiotic bacteria and used in the food fermentation industry for manufacturing cheeses, buttermilk, sauerkraut, and yogurt (Jeong et al., 2009).

Protein deamidation: Protein deamidation technology by glutaminase leads to production of protein containing foods with improved functional properties, especially protein solubility, and potentially decreased flavor fade problems associated with flavor-protein interactions, especially with carbonyl containing flavor compounds (Suppavorasatit *et al*., 2013). Protein-glutaminase converts glutaminyl residues into glutamyl residues which results in increase of negative charge in food proteins (milk casein, wheat gluten, rice glutelin etc.) due to increase in negative charge the isoelectric point of deamidated protein gets lowered and gives good solubility of product in acidic pH. Protein foldings gets changed by deamidation due to newly form negative charges and exposure of hydrophobic region, results in a protein with improved amphiphillic character. This character is responsible for making the protein an ideal emulsifier or foaming agent.
The value of broken and debris rice or by-product of rice starch can be significantly improved by this method. Moreover, the resource waste and environment pollution could be minimized. These new features of deamidated rice glutelin suggested that glutaminase could be a potential tool for enhancing the usability of rice protein in the food industry (Liu et al., 2011). Soy-protein isolates enzymatic deamidation by protein-glutaminase, increases functional properties of soy protein. That can be used for various purposes in the food industry, especially for use in acidic soy based beverages. However, studies on the conformational changes and other functional properties, such as impact on the flavor profile and flavor binding properties, are still needed (Suppavorasatit et al., 20113).

Production of soy-food: In Japanese soy sauce fermentation study Wakayama et al. (2005) studied that glutaminase from S. maltophilia has high ability for glutamic acid production as compare to other microorganism such as Aspergillus oryzae, Escherichia coli, Pseudomonas citronellolis, and Micrococcus luteus, indicating that this enzyme is suitable for application in Japanese soy sauce fermentation. The unique flavor of fermented soy sauce is credited mainly to glutamic acid (concentrations of 0.7 to 0.8% per total nitrogen) (Nandakumar et al., 2003). Under optimal conditions the partial deamidation of soymilk by protein-glutaminase, enhances protein solubility under acidic conditions (pH 5.0) and decreased the flavor binding potential of the protein to both vanillin and maltol. These could benefit soy protein and soy-food manufacturers who intend to reduce the flavor fade problem in aqueous food products containing soy proteins (Suppavorasatit et al., 2013).

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monosodium glutamate alike taste producer: The sodium salt of glutamic acid is monosodium glutamate. It has the nutrient property and salt substitute (Takahashi et al., 2011). Food industry has widely used monosodium glutamate as a flavor enhancer. However, monosodium glutamate shows negative side effects such as wheezing, heart-rate changes, and breathing difficulty in some people which is questionable on its safety (Jeong et al., 2009). It can induce hypothalamic lesions and leptin resistance, possibly influencing energy balance, leading to overweight (Takahashi et al., 2011).

High value chemical production: Glutamic acid is a product of hydrolysis of glutamine by glutaminase. Theanine, which is a food additive and dietary supplement, can be synthesized efficiently by a ϒ-glutamyl transfer reaction using glutaminase. Generally, the production of theanine synthetase (EC 6.3.1.6) synthesizes theanine but Tachiki *et al.* (2010) have developed a method of producing theanine from glutamic acid and ethylamine using a combination reaction of bacterial glutamine synthetase with a sugar fermentation reaction of baker's yeast as an ATP- regenerating system (Moriguchi *et al.*, 2003). Another method for production of L-theanine was done using glutaminase encapsulated in carbon-coated mesoporous silica. Glutamine, glutamate and proline are the precursor for the synthesis of arginine in the intestinal-renal axis in human and most other mammals (Takahashi *et al.*, 2011). Pseudomonas nitroreductions IFO 12694 has been reported for the catalysis of ϒ-glutamyl transfer reaction and hydrolysis simontaniously in which the reaction mixture contains ϒ-glutamyl donor and ϒ-glutamyl acceptor (Tachiki *et al*., 1998).

Vitamin B6 Synthesis: Plants and microorganisms have the capacity to synthesize vitamins through De Novo biosynthesis but animals must have to obtain it from diet. Glutaminase involve in vitamin B6 synthesis. Vitamin B6 is vital metabolite for all living organisms and for various biochemical reactions, it works as cofactor. In eubacteria, deoxyxylulose 5-phosphate dependent and in archaea, fungi, plants, protista, and most eubacteria deoxyxylulose 5-phosphate independent two distinct and mutually exclusive de novo pathway are present. In these organisms, pyridoxal 5'-phosphate (PLP) formation is catalyzed by a single glutamine amidotransferase (PLP synthase) composed of a glutaminase domain, PDX2, and a synthase domain, PDX1 (Studart et al., 2007).

Application in Biosensors: In biosensor, for monitoring the glutamine level in mammalian and hybridoma cell cultures without the need of separate measurement for glutamic acids. Simultaneous measurement of L-glutamine and L-glutamate, Integrated thin film biosensors were developed for the microbial micro-flow cell. Due to a novel glutaminase with an activity optimum in the neutral pH range, direct monitoring of glutamine in a mammalian cell culture medium could be performed (Moser et al., 1995).

Glutamine biosensor system based on a conductance-surface acoustic wave (SAW) frequency response, in which a SAW resonator oscillating at 61 MHz and a biosensor was developed for the determination of glutamine. In biosensor kidney cortex tissue (porcine) or Escherichia coliform Glutaminase was used as a biocatalyst of the hydrolysis reaction of glutamine (Shouzhuo et al., 1995).

Use in research and development: Glutaminase catalyzes the hydrolysis of glutamine to glutamate and plays a central role in the proliferation of neoplastic cells via glutaminolysis. For understanding the role of glutaminase in cancer cell metabolism to identify therapeutic targets (Jang et al., 2013). It is used as analytical agent for the determination of glutamine and glutamate. Study of brain-specific BNIP-2-homology protein Caytaxin relocalises glutaminase to neurite terminals and reduces glutamate levels (Buschdorf et al., 2006). For L-glutaminase production partitioning studies has performed on Bacillus cereus MTCC 1305 in different PEG–salt/dextran (Singh and Banik, 2012) etc.

III. CONCLUSION

Structural, regulatory and biochemical understanding will be helped by glutaminase understanding at the gene level from different microorganisms. Application study will increase the thrust in this area and open-up new ways to simplify or improve living beings life. It is required for further improvement in production. Pharmacologic manipulation of the glutamatergic systems or inhibition of glutamate producing enzyme (glutaminase) may have great potential for the rational treatment of a variety of neurologic diseases (Timothy, 1986). Recent research on glutaminase has been focused on its biochemistry to understand the mechanism and the role in mammalian metabolism. The structural, molecular, biochemical and cell-based studies provide detailed insights into allosteric inhibition of human Kidney-type glutaminase by BPTES (Thangavelu *et al*., 2012).

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