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NUTS AND BOLTS

A pathway map of glutamate metabolism

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Abstract Glutamate metabolism plays a vital role in biosynthesis of nucleic acids and proteins. It is also associated with a number of different stress responses. Deficiency of enzymes involved in glutamate metabolism is associated with various disorders including gyrate atrophy, hyperammonemia, hemolytic anemia, γ-hydoxybutyric aciduria and 5-oxoprolinuria. Here, we present a pathway map of glutamate metabolism representing metabolic intermediates in the pathway, 107 regulator molecules, 9 interactors and 3 types of post-translational modifications. This pathway map provides detailed information about enzyme regulation, protein-enzyme interactions, post-translational modifications of enzymes and disorders due to enzyme deficiency. The information included in the map was based on published experimental evidence reported from mammalian systems.

Keywords Activators · Feedback regulation · Glutamine and inhibitors

Abbreviations

PTMs	Post-translational modifications
ChEBI	Chemical Entities of Biological Interest

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Introduction

Glutamate is a non-essential amino acid that can be synthesized in the body through distinct metabolic pathways. It is an excitatory neurotransmitter in the central nervous system of mammals (Watkins and Evans 1981) and functions as both substrate and product in many distinct reactions. It serves as a precursor molecule for the synthesis of various metabolites including N-acetyl-L-glutamate, δ-1-Pyrroline-5-carboxylate, β-citrylglutamate, L-γ-glutamyl-L-cysteine (Sonoda and Tatibana 1983; Wakabayashi et al. 1991b; Collard et al. 2010; Tu and Anders 1998; Battaglioli et al. 2003). Glutamate is synthesized from glutamine, α-ketoglutarate and 5-oxoproline (Hu et al. 2010; Cho et al. 2001; Chen et al. 1998). Besides its role in the synthesis of metabolites, glutamate also serves as a precursor for the biosynthesis of amino acids such as L-proline and L-arginine (Wakabayashi et al. 1991a; Murphy et al. 1996). In addition, the excitatory neurotransmitter, N-acetyl-L-aspartyl-L-glutamate, the inhibitory neurotransmitter, γ –aminobutyrate, and the antioxidant, glutathione are also synthesized from glutamate (Ffrench-Mullen et al. 1985; Schafer and Jones 1982; Dringen and Hirrlinger 2003). Thus, glutamate is of immense interest as it is involved in different metabolic pathways.

Glutamate metabolism comprises of several reversible and irreversible reactions. These reactions are catalyzed by enzymes that are regulated by activators and inhibitors. For instance, conversion of L-glutamate to N-acetyl-L-glutamate in presence of N-acetylglutamate synthase (NAGS) is activated by L-arginine and inhibited by succinate, coenzyme A, N-acetyl-L-aspartate and N-acetyl-L-glutamate (Shigesada and Tatibana 1978). Similarly, glutamine to glutamate conversion is catalyzed by enzymes, which include glutaminase (GLS/GLS2), phosphoribosyl pyrophosphate amidotransferase (PPAT) and glutamine-fructose-6-phosphate transaminase (GFPT1 and GFPT2) (Hu et al. 2010; Holmes et al. 1973; Chang et al. 2000). GLS/GLS2 is regulated by inorganic phosphate (Pi), and ammonia while PPAT is regulated by AMP, GMP and Pi (McGivan and Bradford 1983; Wang et al. 2010; Wood and Seegmiller 1973). GFPT is regulated by members of protein kinases (Li et al. 2007). Apart from glutamate being involved in metabolic pathways, it also regulates various signaling pathways by interacting with a class of membrane-bound, inotropic glutamate receptors such as AMPA and NMDA (Szczurowska and Mares 2013; Dingledine et al. 1999). The downstream signaling includes MEK/ERK/ELK and calcium/calmodulin-dependent protein kinase II signaling pathways (Choe and McGinty 2001; Hosokawa et al. 2006).

Glutamate plays a significant role in neuronal excitability, synaptic plasticity, immunity and behavioural mechanisms such as learning and memory in the central nervous system (Dutta et al. 2013). Glutamine, which serves as a precursor of glutamate is known to protect the body from nutrient depletion, oxidative stress and tumor stress (Shanware et al. 2011). Several glutamate metabolizing enzymes such as glutamate dehydrogenases (GLUD1/GLUD2), glutamate-ammonia ligase (GLUL) and glutaminase (GLS) have been reported to be significantly associated with Alzheimer's disease (Burbaeva et al. 2005). Alterations in glutamate metabolism have been implicated in coronary heart disease (Qi et al. 2013). hyperinsulinism/hyperammonemia syndrome (Stanley et al. 2000) and pyridoxine-dependent seizures (Bennett et al. 2005). Recent reports have shown that ammonia released from glutamine by the action of glutaminases regulates autophagy in cancer cells through a process known as glutaminolysis (Eng et al. 2010). In cancer cells, glutaminolysis serves as a fuel for cell growth and proliferation through the synthesis of fatty acids, nucleotides and amino acids (Benjamin et al. 2012). Expression of glutaminase is regulated by the transcription factor, c-Myc, which in turn regulates cell proliferation and cell death in human prostate cancer cells (Gao et al. 2009). In brain tumors such as gliomas, it has been shown that glioma cells may release excess glutamate into the extracellular space resulting in tumor-related epilepsy or seizures (Simon and von Lehe 2011). Accumulating evidence also suggests that glutamate release promotes cell proliferation, cell invasion and tumor necrosis in glioblastoma (Schunemann et al. 2010; Lyons et al. 2007; Noch and Khalili 2009). The diverse functions of glutamate metabolism and their role in cancers and other metabolic disorders prompted us to manually curate glutamate metabolic pathway with a special focus on regulators, interactors, isozymes and post-translational modifications (PTMs) of catalytically active enzymes. Although canonical metabolic pathway networks are available in different databases, information pertaining to regulators, disorders, interactors and PTMs of enzymes is missing. In this study, for the first time a comprehensive map was developed representing 107 regulators, 9 interactors and 3 types of PTMs.

Materials and methods

We began by searching for reactions along with their corresponding enzymes and cofactors in review articles and prepared a basic skeleton on glutamate metabolism. Subsequently, we carried out literature search in PubMed by giving terms such as "glutamate metabolism" or "glutamate" and specific searches with metabolite, reaction or corresponding enzyme was performed. The search furnished us the information with respect to cofactors, interactors, regulators, reaction reversibility, PTMs, isozymes, enzyme subunits and disorders. The information documented was based on experimental evidence from literature. The enzyme and its corresponding interactors were mapped to Entrez gene identifiers. The metabolites in glutamate metabolic pathway were

mapped to ChEBI identifiers and disorders to OMIM identifiers. In case of unavailability of ChEBI identifiers for certain metabolites, PubChem, HMDB or ChemSpider identifiers were provided. The structures were manually drawn from ChEBI, PubChem or ChemSpider databases. The stoichiometry of chemical reactions was maintained based on the information obtained from literature, IUBMB or Rhea databases.

Results and discussion

Over 1500 research articles were screened, of which 200 articles had information on experimental evidence for the reactions and enzymes reported in the context of glutamate metabolic pathway. From these articles, we curated 89 metabolites pertaining to 34 reactions catalyzed by 37 enzymes including isozymes. In addition, 107 regulators were also documented for 31 enzymes that catalyze 25 reactions in this metabolic network. Of these, 26 were activators, 65 were inhibitors and 16 were both activators and inhibitors. Further, 6 cofactors for 19 enzymes were also represented in the map. Of 34 reactions assembled in the pathway, 11 were reversible and 23 were irreversible reactions. Fifteen reactions and 19 enzymes including isozymes were known to be involved in feedback regulation. These reactions have been reported to be regulated by 16 feedback inhibitors. In addition, a total of 10 reactions and 8 enzymes were represented in this map that has not been depicted previously in glutamate metabolic pathway. The complete pathway map representing all the enzymes, reactions, regulators and interactors is shown in Fig. 1.

Development of a regulatory network map for glutamate metabolic pathway

Glutamate metabolic pathway was developed using PathVisio (van Iersel et al. 2008). a publicly available tool for depicting biological pathways. All linear and circular reactions in the pathway map were represented with the arrows directing the metabolites as either forward or backward reactions. Reversible reactions catalyzed by single enzyme were clearly represented using double-headed arrows and by placing the enzyme on one of the sides of the reaction. Similarly, the reverse reactions catalyzed by two different enzymes each of which acting on forward and backward directions were depicted by connecting the substrate and product with different reaction lines. Co-reactants, which include metabolites and small molecules, were represented on the reaction edges. PubMed identifiers for all the reactions, enzymes, regulators and cofactors were appended in the pathway map, to provide further information to the users. Enzyme commission number, common name and IUBMB nomenclature was also listed, which are made available upon mouse-hover option over the enzymes, in the HTML version of the pathway map. The number of subunits for every enzyme has also been provided as a subscript inside the enzyme box. Further, isozymes for a given enzyme were also assembled in a box. Enzymes with more interactors were demarcated from individual interactors by assembling them in a box as intact entities. Regulators such as activators and inhibitors were distinguished with plus and minus symbols, respectively, on a dotted arrow. Enzyme regulation by substrates at high/low concentrations were clearly demarcated from regulation at normal concentrations using different colored arrows. PTMs regulating the enzyme activities were shown with information on site of PTM and modified amino acid residue in the protein sequence along with enzyme responsible for the PTM. Different types of PTMs were clearly demarcated with different colors. Disorders due to increased or decreased enzyme activities were also listed. OMIM identifiers for the disorders were provided as mouse hover function. The metabolites leaving or entering other metabolic pathways have also been depicted in the map. The pathway map of glutamate metabolism is made available at http://www.netpath.org/metabolic_pathways/glutamate_map.html.

Regulation of glutamate metabolic pathway

Glutamate metabolic enzymes in the pathway are tightly controlled by regulators. The reversible reactions involved in the conversion of L-glutamate to α-ketoglutarate is catalyzed by a number of enzymes including GLUD1, GLUD2 (Kuo et al. 1994). glutamic-pyruvate transaminases (GPT, GPT2) (Glinghammar et al. 2009) and glutamic-oxaloacetic transaminases (GOT1 and GOT2) (Rej 1978). Each of these enzymes has been reported to be regulated by different activators and inhibitors. Enzymes such as L-glutamate gamma-semialdehyde dehydrogenase (ALDH4A1) (Forte-McRobbie and Pietruszko 1989), GOT1, GOT2 (Henson and Cleland 1964). GPT1, GPT2 (Bergmeyer et al. 1978). GLS (Krebs 1935) and carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase (CAD) (Meek et al. 1987) are subject to regulation via feedback inhibition by the product, L-glutamate. Similarly, γ -aminobutyrate aminotransferase (ABAT) is inhibited by γ -aminobutyrate through feedback regulation (van der Laan et al. 1979). In addition to product inhibition, substrate inhibition at different concentrations were also documented in glutamate metabolic pathway. α-ketoglutarate is the substrate inhibitor of GOT2, which inhibits the enzyme at high concentration (Henson and Cleland 1964). Succinic semialdehyde as a substrate inhibits NAD(+)-dependent succinic semialdehyde dehydrogenase (ALDH5A1) and succinic semialdehyde reductase (AKR7A2) at high concentration (van der Laan et al. 1979; Cash et al. 1979). Succinic semialdehyde can either enter into

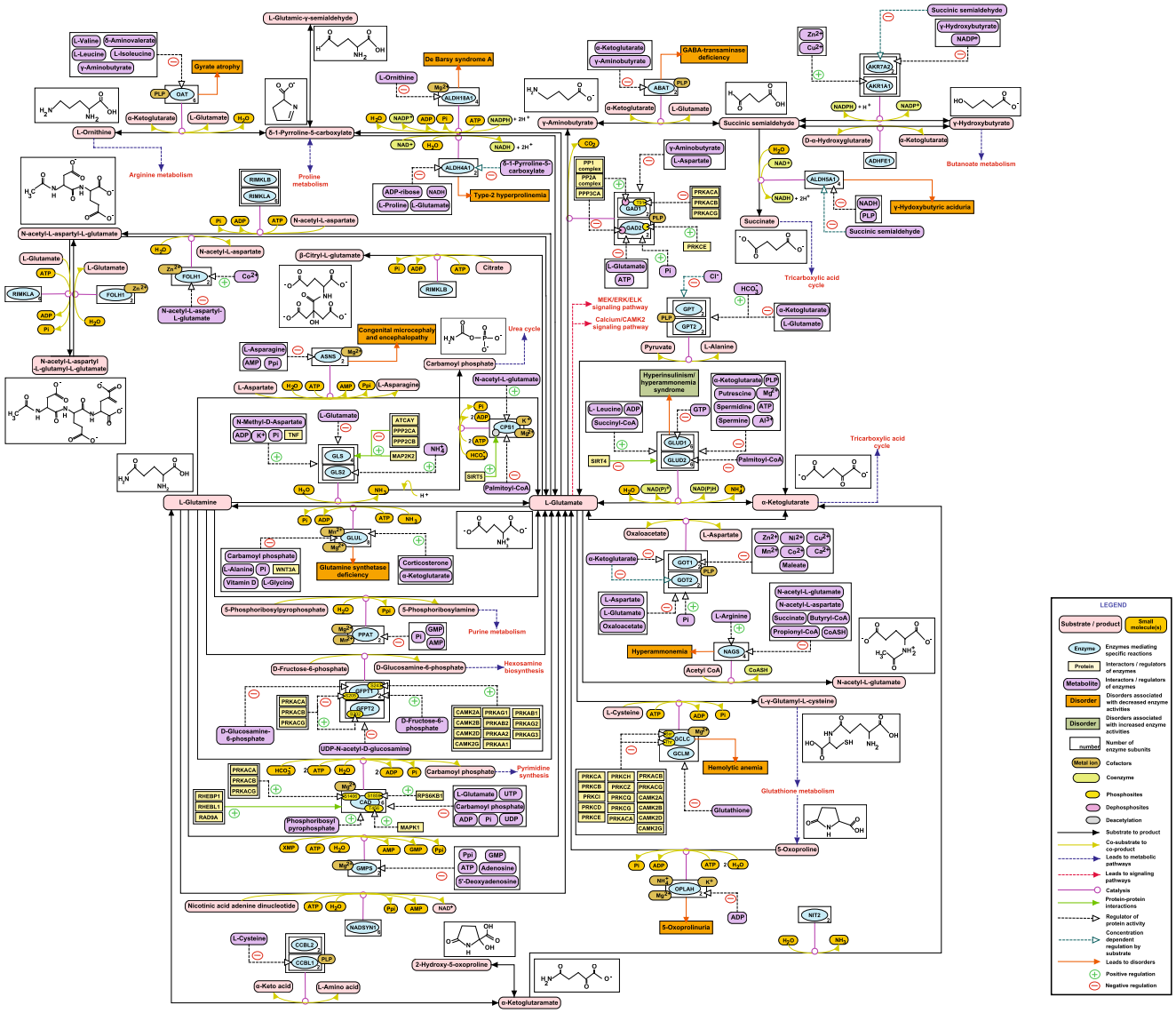

Fig. 1 Schematic representation of glutamate metabolism: The pathway represents metabolites, enzyme regulators and disorders in different colors as provided in the legend. Structures for the main metabolites are provided in boxes. Reversible and irreversible reactions are represented in the figure and inhibition and activation of these reactions by regulators is represented by (−) and (+) signs, respectively. Subunit information is indicated as subscript for the enzymes

tricarboxylic acid cycle through the synthesis of succinate in presence of ALDH5A1 or butanoate metabolism through γ-hydroxybutyrate in presence of the reversible enzymes - AKR7A2, hydroxyacid-oxoacid transhydrogenase, mitochondrial (ADHFE1) and aldo-keto reductase family 1 member A1 (AKR1A1). AKR7A2 is inhibited by the products γ-hydroxybutyrate and NADP+ in the forward direction (Hearl and Churchich 1985). Delta1-pyrroline-5-carboxlate synthetase (ALDH18A1) is a bi-functional enzyme and it has been suggested that L-γ-glutamyl phosphate, an intermediate of the reaction probably remains bound to the enzyme (Strecker 1957). The shorter isoform of ALDH18A1 has been reported to be inhibited by L-ornithine (Hu et al. 1999).

Glutamate metabolic enzymes that are known to be regulated by protein interactors have also been annotated. While most enzyme-regulator interactions are activating, a few of them are also inhibitory in nature. Nine interactors regulating the activity of 5 enzymes were curated for the first time in this study. Interactions between GLS enzyme and protein phosphatase 2, catalytic subunits (PPP2CA and PPP2CB) and ataxia, cerebellar, Cayman type (ATCAY), inhibit the catalytic activity of the enzyme (Thangavelu et al. 2012; Buschdorf et al. 2006). In contrast, mitogen-activated protein kinase kinase 2 (MAP2K2) and v-raf-1 murine leukemia viral oncogene homolog 1 (RAF1) interaction with GLS increases the catalytic activity of the enzyme (Thangavelu et al. 2012). Similarly, RAD9 homolog A (RAD9A), Ras-homolog

enriched in brain pseudogene 1 (RHEBP1), Ras homolog enriched in brain like 1 (RHEBL1) interaction with CAD, increases the catalytic activity of CAD (Lindsey-Boltz et al. 2004; Sato et al. 2015) and sirtuin 4 (SIRT4) interaction inhibits GLUD1 and GLUD2 (Haigis et al. 2006).

Signaling pathways regulating glutamate metabolism

Enzymes of glutamate metabolic pathway are also regulated by signaling molecules. We have represented 24 kinases, 3 phosphatases and 1 deacetylase for the first time in glutamate metabolic pathway. These kinases, phosphatase and deacetylases are known to regulate the catalytic activity of 7 enzymes. GLS is regulated by Raf-1/Mek2/ERK signaling module that mediates cell growth and proliferation (Thangavelu et al. 2012). Ribosomal protein S6 kinase, 70 kDa polypeptide 1 (RPS6KB1), activates by phosphorylating CAD at Ser1859 (Ben-Sahra et al. 2013). In addition, MAPK1 induces activation by phosphorylating CAD at Thr456 (Graves et al. 2000). Carbamoyl-phosphate synthase 1, mitochondrial (CPS1) is activated upon deacetylation by sirtuin 5 (SIRT5). This mechanism is known to facilitate the removal of large quantities of ammonia synthesized in the body (Nakagawa et al. 2009). Members of catalytic subunit of PKA (PRKACA, PRKACB, PRKACG) inhibits GFPT1 through phosphorylation at Ser205 (Chang et al. 2000) whereas phosphorylation at Ser243 by an AMP dependent protein kinase increased the enzyme activity (Eguchi et al. 2009). Interestingly, Ser202 in GFPT2, an isozyme of GFPT1, is activated by PKA (Hu et al. 2004). Glutamate decarboxylase 1 (GAD1) is inhibited upon phosphorylation at Thr91 residue by catalytic subunit of protein kinase A while glutamate decarboxylase 2 (GAD2), is activated on phosphorylation by protein kinase C, epsilon (PRKCE). Similarly, GAD1 and GAD2 are activated by protein phosphatases which include PP1, PP2A and PPP3CA (Wei et al. 2004).

Glutamate metabolic enzymes associated with disorders

Metabolic enzymes play an important role in regulation of gene expression (Hall et al. 2004). cell growth and proliferation (Thangavelu et al. 2012). energy metabolism and protection against antioxidants (Hu et al. 2010). Loss or gain of metabolic enzyme activities leads to diverse metabolic disorders and several enzymes of glutamate metabolism have also been implicated. For example, ALDH18A1 is associated with de Barsy syndrome A due to decreased enzyme activity (Fischer et al. 2014). Deficiency of ALDH5A1 is associated with γ-hydoxybutyric aciduria (Pearl et al. 2003). Other disorders including type-2 hyperprolinemia, gyrate atrophy, hemolytic anemia, 5-oxoprolinuria and hyperammonemia have been reported to manifest due to deficiency of distinct glutamate metabolic enzymes. Hyperinsulinism/hyperammonemia syndrome is known to occur due to increased activity of GLUD.

Conclusions

Glutamate serves as an important precursor or substrate for synthesis of various amino acids, nucleic acids, nucleotides and metabolites. Availability of a comprehensive pathway map of glutamate metabolism will enhance our understanding of the role of various molecules involved in regulation of this pathway. The pathway provides information regarding the enzyme interactors, regulators and disorders due to gain or loss of enzyme activity for most of the pathway reactions. Additionally, information of different types of post-translational modifications adds to the knowledge regarding the activity and regulation of the enzymes.

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Compliance with ethical standards

Conflict of interest No potential conflicts of interest were declared.

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