

# Role of brain glutamic acid metabolism changes in neurodegenerative pathologies

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## ABSTRACT

Glutamic acid is an essential participant of brain metabolism. It is known that the glutamate is a neurotransmitter in a numerous part of the brain synapses and acts through various ionotropic or metabotropic receptors. Multiple alterations of the brain glutamate system are observed in both acute and chronic brain injures. Glutamate metabolism changes take place in many neurodegenerative pathologies, such as brain ischemia, Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis etc. These disruptions may be related to changes of glutamate metabolism enzyme activities, alterations of the main energy formation reactions in mitochondria, and shifts of oxidation/redox balance in cells. Potential targets for therapy of neurodegenerative diseases, especially in chronic treatment, can include the drugs for recovery of glutamate metabolism system.

**Key words:** glutamic acid, glutamate metabolism, neurodegenerative pathologies, enzymes of glutamate metabolism, brain ischemia.

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**INTRODUCTION**

Due to many different roles associated with brain glutamate, it is not surprising that the glutamate system is probably the most versatile and complex signalling system in the brain. Glutamic acid is an essential participant of brain metabolism, as well as a main excitatory neurotransmitter in the brain, therefore changes in this process can be observed when studying most cases of neurodegenerative diseases [1-9]. It is known that the glutamate is a neurotransmitter in a numerous part of the brain synapses and acts through various ionotropic or metabotropic receptors (Fig. 1) [3, 8, 10, 11].

Another peculiarity of brain glutamate metabolism is its close relation to the citrate cycle and to energy metabolism [10-12]. Metabolism of glucose in the brain depends on glutamate to a great extent. Glucose and glycogen are essential sources of energy not only for maintaining glutamate homeostasis but also for glutamatergic neurotransmission [13]. Brain glutamate comes from 2-oxoglutarate by means of direct amine incorporation by glutamate dehydrogenase (GDH) or through reamine incorporation by transaminases [8]. These processes help to support levels of citrate cycle metabolites for sufficient energy formation and redox equivalents supply to neuron mitochondria.

Third peculiarity of brain glutamate metabolism is the fact that some of its steps take place in certain types of cells - in neurons or in glial cells, therefore a close and accurate interrelation between neurons and glia is necessary [14]. An injection of radioactively labeled main precursors of glutamate, such as glucose and acetate, showed their participation in the glutamate synthesis through two different citrate cycles in the brain tissue. It seems that glucose is metabolized in neurons [10, 11], whereas acetate is processed in astroglial cells [11], which display a higher glutamine synthase activity [12, 14, 15]. Apart from that, neurons must catch glutamine from glial cells for maintaining the transmitter role of the glutamate, and for maintaining energy metabolism, too. Glutamine is a transport form of glutamate transfer from glial cells into neurons. Since carboxylation of pyruvate to oxaloacetate occurs in astrocytes, net synthesis of 2-oxoglutarate in the TCA cycle can also take place in these cells.

At least a certain rate of glutamate synthesis is

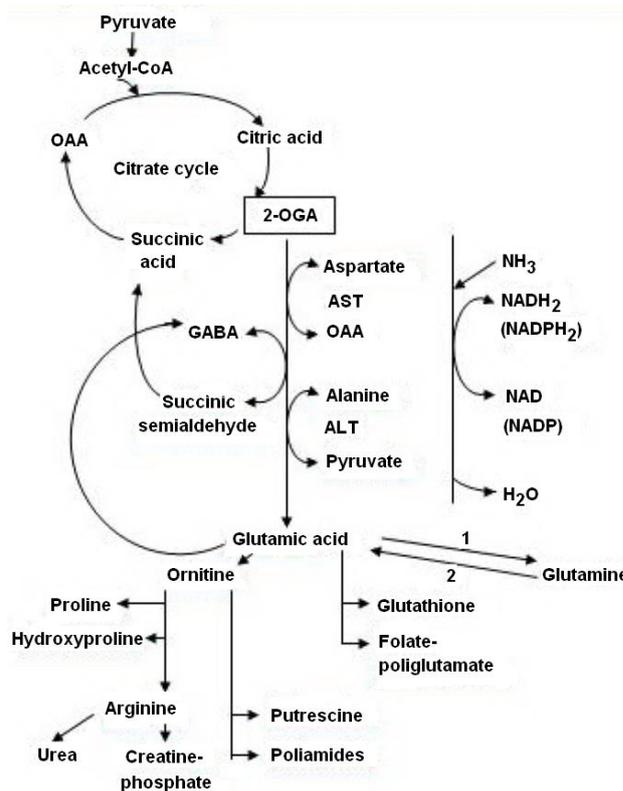


Fig. 1. Some ways for metabolism of glutamate in nervous tissue and its relation to citric acid cycle.

Legend:

- 1 - glutamine synthetase,
- 2 - glutaminase,
- 2-OGA - 2-oxoglutaric acid,
- AST - aspartate transaminase,
- ALT - alanine transaminase,
- OAA - oxaloacetic acid.

necessary for maintaining glutamate level in synaptic vesicles. New molecules of glutamate and GABA are mainly formed from glucose [8, 11, 13]. Oxaloacetic acid is predominantly formed from pyruvate within astrocytes, therefore main synthesis of 2-oxoglutaric acid for the Krebs cycle takes place within astrocyte cells.

Fourth peculiarity of brain glutamate metabolism is its close relation to ammonia metabolism. The urea cycle reactions are considerably slower in the brain tissue, and the main way of binding excessive ammonia ions in the brain is through formation of glutamine. The ammonia ions enter brain by diffusing through the blood-brain barrier or are formed within brain [16]. Excessive levels of ammonia ions are toxic for brain, therefore amount of ammonia is kept low with the help of high activity of the glutamine synthetase.

The influx of glutamate from plasma across the blood-brain barrier is much lower than its efflux from

brain [17, 18], therefore brain metabolism of glutamate plays an important role in the maintenance of normal brain tissue function.

Depolarization of glutamatergic presynaptic nerve endings leads to excretion of glutamate from vesicles by Ca-dependent exocytosis into synaptic cleft (Fig. 2). During excitation glutamate concentration may peak at around 1 mM in the synaptic cleft, but it is then immediately decreased to 1-2  $\mu$ M. Glutamate acts on ionotropic receptors (i-glu-R, bound with ion channels) or metabotropic ones (m-glu-R, bound with second messengers), after that it is removed from the synaptic cleft by reuptake into nerve endings, or by diffusion and uptake into glial cells by glutamate transporters [9, 19, 20]. Excitatory amino acid transporter EAAT-2 is one of the major glutamate transporters expressed predominantly in astroglial cells and is responsible for 90% of total glutamate uptake. Glutamate transporters tightly regulate glutamate concentration in the synaptic cleft [21].

Within presynaptic nerve endings glutamate enters specialized vesicles with the help of specific vesicular transporter. Amount of glutamate that can be excreted from nerve ending depends on the activity of the transporter. Glutamate is removed from a synaptic cleft by reuptake transporters which are located in neuronal and glial membranes. The transporters carry inside one molecule of glutamate together with one sodium ion and one proton, and transfer outside one potassium ion.

Glutamate inside astrocytes is turned into glutamine by glutamine synthetase. One of the primary roles of astrocytes is to protect neurons from excitotoxicity by taking up excess ammonia and glutamate and converting them into glutamine with the help of enzyme glutamine synthetase [5, 14]. After that glutamine is transferred into neurons where it is transformed into glutamate by glutaminase. Then glutamate is preserved within vesicles. Part of resulting glutamate may be immediately transferred to presynaptic nerve ending by special membrane transporter.

Disruption of glutamate removal from synaptic cleft results in glutamate excitotoxicity [3, 9, 20]. In cases of energy shortage (e.g. during ischemia), glutamate level in the synaptic cleft may remain unusually high for a long time which will initiate a cascade of excitotoxic reactions. Excitotoxicity is caused by excessive activation of excitatory amino acid receptors which leads to an uncontrolled

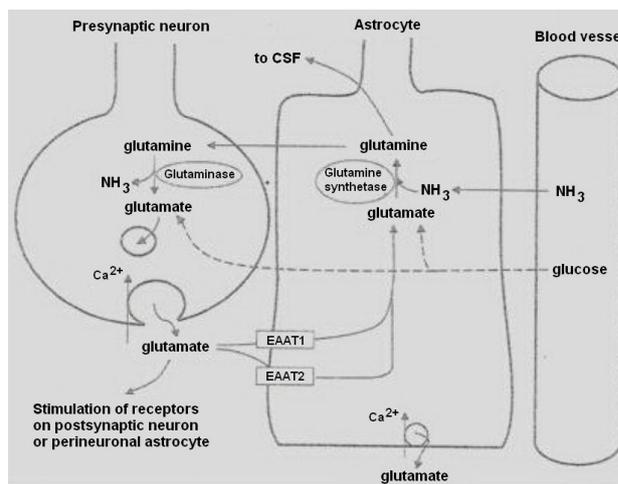


Fig. 2. Schematic representation of the synthesis, metabolism and intracellular transport of glutamate into the brain (based on Vaquero J, Butterworth RF, 2006). EAAT-1, EAAT-2 - high-affinity glutamate transporters localized on astrocytes.

increase of sodium and potassium ion levels in the cell resulting in cell death [21].

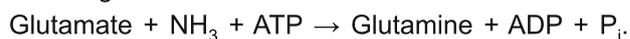
Exposure of brain tissue to very high concentrations of potassium (above 20 mM) leads to membrane depolarization and depolarization-dependent increase of free potassium in synaptosomes, neurons and astrocytes. This facilitates removal of glutamate (and GABA) from neurons and CO<sub>2</sub> accumulation within astrocytes. As the result, metabolic exchange between neurons and glial cells is intensified therefore stimulating synthesis of neurotransmitter precursors inside neurons [22-24].

## REVIEW

### Glutamate metabolism enzymes

#### Glutamine synthetase (EC 6.3.1.2)

Glutamine synthetase acts as a catalyst in the following reaction:



The enzyme from mammalian brain has two important functions: assimilation of ammonia and biosynthesis of glutamine. It catalyzes the direct and reverse reactions with rate approximately 10:1 (with sufficient level of ATP in a tissue) [25, 26]. Glutamine synthetase is composed of eight identical subunits (44-50 kDa). Distribution of glutamine synthetase is uneven in the central nervous system: the highest activity is observed in the structures where the quantity of glutamatergic neurones is the

highest [14, 15, 18, 30], and the enzyme takes place in cytosole [26, 27, 31]. Induction of the glutamine synthetase expression is the way for protection of neurons against increase of extracellular glutamate concentration, whereas decrease of the expression may lead to disruption of metabolic interrelations between neurons and glia during hyperammonemia [31, 32, 33].

Changes in glutamine synthetase expression may reflect changes in astroglial function, which can affect neuronal functions, especially in astrocytes located in glutamatergic areas. Hyperammonemia is an important factor responsible of hepatic encephalopathy and causes astroglial swelling [1]. The induction of glutamine synthetase expression in these specific areas would balance the increased ammonia and glutamate uptake and protect against neuronal degeneration, whereas decrease of its expression in non-glutamatergic areas could disrupt the neuron-glial metabolic interactions as a consequence of hyperammonemia [18, 34, 35].

In glutamatergic areas, the distribution of both glial glutamate receptors and glial glutamate transporters parallels the glutamine synthetase location, suggesting a functional coupling between glutamate reuptake and glutamine synthase to attenuate brain injury in these areas.

In hyperammonemia, the astroglial cells located in proximity to blood capillars in glutamatergic areas show increased glutamine synthase protein content in their perivascular tissue. Since ammonia freely crosses the blood-brain barrier and astrocytes are responsible for maintaining the blood-brain barrier, the presence of glutamine synthase in the perivascular tissue could produce a rapid glutamine synthesis to be released into blood, and glutamine synthase could play an important role in removal of ammonia from the brain. Glutamine synthetase is not working at maximum rate in brain and its activity may be increased by blocking i-glu (NMDA) receptors [36, 37]. The activation of glutamate receptors may also favour nitric oxide (NO) formation by activation of NO-synthase (NOS), and NO has been implicated in the pathogenesis of several CNS diseases [36]. Glial cells have carboanhydrase which catalyzes conversion of CO<sub>2</sub> into H<sub>2</sub>CO<sub>3</sub>, too. Consequently, glial cells take part in a regulation of oxidation-reduction balance and of metabolism of glutamate-related amino acids in the CNS. The glutamine synthetase is activated by 2-oxoglutarate in a liver but not in a brain [25, 30, 35]. Glutamine synthetase is irreversibly inhibited by

methionine sulfoximine. And this inhibition significantly impairs glutamate uptake and glutamine release [38].

#### **Glutaminase (EC 3.5.1.2)**

Glutaminase catalyzes reaction of glutamine catabolism to glutamate and ammonia. Its activity can be observed both in neurones and astroglial cells [39], but glutaminase is more active in neurons, predominantly in mitochondria [40, 41]. Mitochondria from pig brain have two main isoforms of the enzyme. One of them is soluble and resides in matrix, while the other is membrane-bound and remains on inner mitochondria membrane. Both isoforms are activated by phosphate [39].

Soluble glutaminase is a dimer of rather low specific activity which easily aggregates into a more active form following incubation in presence of phosphate [39, 42]. It seems that soluble and membrane-bound forms of the enzyme have different functions in brain. Km for glutamine is equal 0.8-1.4 mM and 3.4-9.7 mM. One of the products, glutamate, inhibits glutaminase to a great extent while the other product, ammonia, inhibits the enzyme very weakly. Activity of glutaminase in brain is low. The enzyme becomes free from inhibitory influence of glutamate only when the concentration of glutamic acid falls below normal values [43].

#### **Glutamate dehydrogenase (EC 1.4.1.2-4, GDH)**

Glutamate dehydrogenase catalyzes a reversible reaction:  
L-glutamic acid + H<sub>2</sub>O + NAD(P) ↔ 2-oxoglutarate + NH<sub>3</sub> + NAD(P)H.

GDH is an enzyme central to the metabolism of glutamate. It is encoded by a single gene (GLUD1 in humans) which occurs widely. Humans and other primates also possess a second gene, GLUD2, which encodes a highly homologous GDH isoenzyme (hGDH2) expressed predominantly in retina, brain and testis. hGDH2 localizes mainly to mitochondria and to a lesser extent to the endoplasmic reticulum of these cells [44].

The GDH reaction is reversible but equilibrium is shifted closer to direct reaction (i.e. to synthesis of glutamic acid) [9, 42, 43, 44]. Consequently, GDH in brain takes part in synthesis of glutamate from 2-oxoglutaric acid more than in oxidation of the amino acid. This is the way for continuous maintenance for changing of a free ammonia into amino nitrogen of amino acids. On the other hand,

this leads to a loss of 2-oxoglutarate from the pool of citrate cycle intermediates inside mitochondria and to decrease of rate of glucose oxidation which is a main energy source for brain cells. On the contrary, reversion of the GDH reaction is one of the ways for restoration of cytrate cycle intermediate pool. Only optimal ratio of direct and reverse reactions may guarantee normal work of brain cells.

GDH may exist in one of three forms. Each of them can contain NAD/NADH (EC 1.4.1.2), or NADP/NADPH (EC 1.4.1.4), or both the cofactors (EC 1.4.1.3). Neuronal GDH (EC 1.4.1.3) may possess both cofactors but NAD is more effective than NADP [9, 11]. The direction of preferable reaction depends on the balance between NAD(P)/NAD(P)H in the tissue.

Two forms of GDH are present in brain, soluble and insoluble. They differ by their kinetic parameters, stability to heat denaturation, and allosteric properties. Oxidative deamination of glutamate takes place if glucose is absent. In the presence of glucose, redox amination of 2-oxoglutaric acid prevails [9, 11]. GDH from a bull brain can utilise both NAD and NADP cofactors. It has molecular mass of 332 kDa and consists from 6 identical subunits.  $V_{max}$  of GDH in synaptic mitochondria from a rat brain is 20-40% lower than  $V_{max}$  of aspartic acid transaminase (AST) but 4-5 times higher than the activity of phosphate-dependent glutaminase [43].

#### **Aspartate transaminase (AST, or glutamate oxaloacetate transaminase, EC 2.6.1.1)**

Aspartate transaminase catalyzes reversible transfer of amino group to 2-oxoglutarate, as a result oxaloacetate and glutamate are formed. This is the most active transaminase in a brain. Rat brain AST activity is 2.5-10 times higher than activity of GDH [8]. 90% of glutamate is transaminated to aspartic acid within brain mitochondria.

Oxaloacetate is quickly transformed into malic acid which enters from cytoplasma into mitochondria. In this way the aspartate-malate bypath for transfer redox equivalents from a cytosol into mitochondria is formed. This bypath is the main way for transfer redox equivalents into mitochondria in neurons. Influx of aspartate through mitochondria membrane is bound with efflux of a glutamate. In such a way influx of a malate is bound with efflux of 2-oxoglutarate, too.

Mammals have two isoforms of the enzyme -

cytoplasmic and mitochondrial. Both forms are dimers containing subunits in 45 and 2 kDa [8, 42]. Functional roles of these forms are different. The mitochondrial form is related to citrate cycle functioning whereas the cytoplasmic form determines gluconeogenesis activity.

Another transaminase, **alanine transaminase (ALT, EC 2.6.1.2)**, transfers an amino group from alanine to 2-oxoglutarate with forming pyruvate and glutamate. It has cytoplasmic and mitochondrial isoforms.

Macroergic substances play an important role in the regulation of balance between dehydrogenase and transaminase ways of metabolism, which compete for one substrate. Under normal conditions, citrate cycle utilises transaminase way products while dehydrogenase path of glutamate oxidation is suppressed. If the level of macroergic compounds decreases (for example, after addition of 2,4-dinitrophenol which divides oxidative phosphorylation), the transamination way is suppressed but the dehydrogenase path of glutamate oxidation increases to a great extent.

Systemic introduction of ammonia salts cause seizures and increase of glutamine content in a brain [16, 18]. Synthesis of adequate content of glutamate must precede glutamine synthesis because the amount of glutamate received from blood flow may be insufficient if level of ammonia in blood is high. Since 2-oxoglutarate is a direct precursor of glutamate, formation of glutamine from glutamic acid and ammonia may cause rapid decrease of levels of the Krebs cycle intermediates if they are not replenished by transformation of pyruvate into oxaloacetate accompanied with  $CO_2$  fixation. Indeed, significant inclusion of  $CO_2$  into amino acids is observed in brain tissue after possible metabolism of  $CO_2$  in the Krebs cycle. After an injection of ammonia, additional quantity of oxaloacetate goes to a synthesis of glutamine (through a 2-oxoglutarate step). Activation of AST may help with protection from toxic effects of ammonia [1, 8, 33].

#### **Glutamic acid decarboxylase (EC 4.1.1.15, GAD)**

Glutamic acid decarboxylase catalyzes separation of a carboxylic group from glutamate with forming of gamma-amino butyric acid (GABA). Cofactor in the reaction is a pyridoxal phosphate, as in AST and ALT. The enzyme has high specificity for substrate, and its activity is found predominantly in

brain tissue. When GAD acts on glutamate which has excitatory influence on neurons, then GABA is formed which is a main inhibitory neurotransmitter in the brain. It is known that the degree of a brain tissue damage depends not only on the level of glutamate, but also on the ratio of excitatory and inhibitory processes, that is on balance between levels of glutamate and aspartate and levels of GABA and glycine [42, 45]. Increase of excitatory/inhibitory index during reperfusion is shown in the regions susceptible to ischemic injury, and the rise correlates with an increasing of a glycine level.

### **Disruptions of glutamate metabolism in the brain**

Glutamate-induced excitotoxicity is responsible for neuronal death in acute neurological conditions as well as in chronic neurodegeneration. The underlying mechanisms through which glutamate excitotoxicity affects neurodegeneration still needs further investigation. Glutamate excitotoxicity has been linked to neurodegenerative disorders such as amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, brain ischemia and reperfusion and others [7-10, 46, 47]. Maintenance of a low level (1-3  $\mu\text{M}$ ) of extracellular glutamate is a necessary condition for normal functioning of brain as this restricts excessive stimulation of receptors and excessive formation of ammonia by GDH. These effects of extracellular glutamate may lead to neuron death. Glutamate neurotoxicity may be prevented by glutamate antagonists and weakened by addition of antagonists following exposure to glutamate. Excessive activation of glutamate receptors by excitatory amino acids leads to a number of deleterious consequences, including impairment of calcium buffering, generation of free radicals, activation of the mitochondrial permeability transition and secondary excitotoxicity [48-53].

Dysfunction of EAAT2 and accumulation of excessive extracellular glutamate are among the causes of development of several neurodegenerative diseases including Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis [21].

Presence of increased level of extracellular glutamate during neurodegenerative diseases (including diseases with brain hypoxia/ischemia) was described in many articles. Excessive extracellular glutamate accumulation during hypoxia

may be related to activation of Ca-independent mechanism disrupting glutamate transport into neurons [22, 30, 52, 53]. This increase of extracellular glutamate acts predominantly on postsynaptic structures and leads to increase of intracellular calcium concentration, resulting in cell death.

Mechanisms for increase of glutamate level during neurodegenerative diseases have not been fully studied. Increase of extracellular glutamate levels may be caused by inhibition of GDH activity (e.g. in Parkinson's disease) [49, 54] or because of a reduction of Na-dependent glutamate transporters (in lateral amyotrophic sclerosis, Huntington's disease) [55-59].

In Alzheimer's disease death of cells may be caused by excessive synthesis or excretion of glutamate, or insufficiently active reuptake, weakened degradation or decreased inhibition of excitatory neurons. Each of these processes, particularly in the beginning of a disease, may promote local increase of glutamate level and therefore initiate slowly progressing neurodegeneration and probable death of a neuron [45, 50, 51].

Postmortal study of brains of patients with Alzheimer's disease showed lower glutamate content in frontal and parietal lobes, but level of free glutamate in cerebrospinal fluid was significantly higher than in samples taken from control group [45, 59].

In Huntington's disease glutamate and GABA contents are lower in brain basal ganglia but not in the frontal lobes. This decline may be caused by disruption of glutamate reuptake from a synaptic cleft but not by lowered secretion as significant decrease of the high-affinity sites for glutamate binding is observed in autopsy tissue of basal ganglia of patients with Parkinson's disease [59]. High concentration of glutamate in synaptic cleft causes damage of neurons. Excess glutamate enters into liquor, and level of the amino acid in the basal ganglia is decreased. Altered glutamatergic neurotransmission and neuronal metabolic dysfunction appear to be central to the pathophysiology of Parkinson's disease [9].

Decline of an activity of the mitochondrial respiratory chain complex I in substantia nigra was found at Parkinson's disease [56]. Failure of complexes II and IV was observed in biopsy muscle tissue in patients with Parkinson's disease, as well

as decreased activity of GDH but not of pyruvate dehydrogenase complex. Intake of redox equivalents (NADH) into respiratory chain takes place at the complex I level, therefore its decrease may cause inhibition of GDH caused by feedback mechanism, which in turn would result aggravation of glutamate excitotoxicity through NMDA-receptors at dopaminergic nerve endings within corpus striatum and contribute to degeneration of neurons.

Amyotrophic lateral sclerosis is characterized by neuron degeneration in motor cortex, brain stem and spinal cord. It seems that change of glutamate transporter function presented within astrocytes [57] is the main reason of such neurodegeneration, but weakening of glutamate uptake is not accompanied by decrease of expression of the transporter synthesis, so data on gene mutations of the synthesis of the protein is absent. Studies have shown an important role of free radicals and disruptions of superoxide dismutase function in development of an amyotrophic lateral sclerosis. It is possible that these changes cause injuries to glutamate transporters. It was shown that changes of glutamate level in amyotrophic lateral sclerosis, and these disruptions were associated to glutathione decrease in the brain [60].

Now we have strong proof for the important role of changes of glutamate transport in development of ischemic injuries in brain tissue. In the first minutes of ischemia slow shift of pH to acid side accompanied with slow increase of extracellular concentration of a potassium and following decrease of extracellular levels of calcium and sodium is observed. The elevation of potassium level leads to depolarization of surrounding cells by -20 mV (anoxic depolarization) and release of glutamate [24, 42]. Explanations for the disruptions of glutamate release mechanisms are rather contradictory. On the one hand, there is evidence that this release is Ca-dependent (i.e. glutamate excreted from vesicles), but on the other hand we know that the release does not depend on Ca. Latter information supports the suggestion of an important role that is played by glutamate reuptake disruption [42]. It was shown that increased level of glutamate release induces apoptotic cell death in the 11 vessel occlusion ischemic model [61].

AST which metabolizes glutamate into citric cycle intermediates may be useful to harness excess neurotoxic extracellular glutamate during brain ischemia. And delivery of AST minimized

lesion volume, whereas AST knockdown worsened stroke outcomes [62]. Superfusate aspartate, glutamate, phosphoethanolamine, taurine, and GABA were significantly elevated by cerebral ischemia, then declined during reperfusion. The ischemia-evoked accumulations of aspartate, glutamate, taurine and GABA were all significantly depressed by glucose, while phosphoethanolamine levels were elevated [63].

Glutamate toxicity and cellular calcium overload are thought to be pathophysiological key factors not only in gray matter but also in white matter during ischemia and reperfusion [45, 51]. Glutamate, aspartate, GABA, and taurine are increased in gray matter but not in white. Deleterious processes such as glutamate accumulation and cellular  $Ca^{2+}$  influx occur in gray matter only.

Glutamate excitotoxicity is closely bound with energy metabolism disruptions and changes of antioxidant activity in the brain tissue. Oxidative stress and unbalanced cellular energy homeostasis are key aspects in many neurodegenerative pathologies [13, 64].

Free radicals decrease activity of the reactions of transamination in the brain that exacerbate disruptions of energy-dependent transport of ions, inhibit glutamine synthetase, and activate synthesis of glutamate in GDH reaction [4, 34].

Brain lacks a complete urea cycle and glutamine represents a temporary storage form of excess ammonia which is neurotoxic. Hyperammonemia results in increased formation of glutamine directly in astrocytes, thereby generating an osmotic stress in these cells, which in turn leads to neuronal dysfunction. Syndromes which result in increased level of ammonia (e.g. liver failure, inborn defects of an urea cycle, Reye disease) lead to astrocyte damage. Harm is done directly by increased glutamine synthesis inside astrocytes and also induced by osmotic stress.

Chronic treatment of rats with the anti-epileptic drug sodium valproate leads to dose-dependent increase in glutamate uptake capacity in hippocamp, but not in hemispheres or cerebellum, by increasing of the levels of glutamate transporters EAAT1 and EAAT2 [11]. And this effect is the result of inhibition of phosphate-activated glutaminase. It seems that valproate may have a role in the treatment of excitotoxic effects of glutamate in the hippocampus.

Immediately following the hypoxic stroke there

was a rapid transient elevation of glutamate level in neonatal rat brain followed by a fall. Glutamine content and glutamine synthetase activity were decreased immediately after hypoxia and returned to normal values within 6 hours [12].

Changes in astrocytes glutamine synthetase in some regions of postischemic rat brain were correlated with regional neuronal vulnerability or resistance of the regions to ischemia. Immediately after ischemia activity of glutamine synthetase was increased in cortex, striatum and hippocampus but not in other brain regions [13]. These changes may be important in normalizing extracellular glutamate following ischemia and protecting brain from neurotoxic effects of the amino acid. Brain glutamine and glutamate loss is correlated with deteriorated social functioning and gray matter losses in schizophrenia, consistent with neurodegeneration [65]. Glutamatergic neurotransmission has also been implicated in mechanisms of alcohol-induced neurodegeneration and cognitive impairment [66].

Changes in glutamate levels as well as correlation between glutamate and glutamine in the whole brain of newborn rats were not found despite 2-fold decrease of glutamine synthetase activity. This fact testifies that significant changes in glutamate metabolism take place only in separate important brain structures [45].

## CONCLUSIONS

Multiple alterations of the brain glutamate system are observed in both acute and chronic brain injuries. Glutamate metabolism changes take place in many neurodegenerative pathologies, such as brain ischemia, Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis etc. These disruptions may be related to changes of glutamate metabolism enzyme activities, alterations of the main energy formation reactions in mitochondria, and shifts of oxidation/redox balance in cells. Potential targets for therapy of neurodegenerative diseases, especially in chronic treatment, can include the drugs for recovery of glutamate metabolism system.

## TRANSPARENCY DECLARATION

The author declare no conflicts of interest.

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