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REVIEW

Coupling between Neuronal and Glial Cells via Glutamate Metabolism in Brain of Healthy Persons and Patients with Mental Disorders

I. S. Boksha

Mental Health Research Center, Russian Academy of Medical Sciences, Zagorodnoe Shosse 2/2, Moscow 117152, Russia; fax: (7-095) 952-8940; E-mail: boksha_irina@yahoo.co.uk

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Abstract—This review summarizes general considerations on glutamate metabolism in human brain. Biochemical coupling between neurons and glia is discussed with respect to glutamate metabolism and its compartmentation. Glutamate recycling and the role of key glutamate-metabolizing enzymes are viewed. Alterations in components of glutamatergic system and glutamate metabolizing enzymes are considered with reference to mental disorders such as senile dementia of Alzheimer's type and schizophrenia.

Key words: glutamate metabolism, human brain, mental disorders

METABOLIC INTERACTION BETWEEN NEURONS AND ASTROCYTES. HYPOTHESES ON SEPARATION OF NEUROTRANSMITTER AND METABOLIC GLUTAMATE POOLS

During the past century, an idea was explicating that neurons and glia are metabolically coupled in the brain. In line with the present view, glutamate is an excitatory neurotransmitter in the nervous system (in all main afferent fibers ascending to the brain cortex and in the excitatory nerves) [1]. Moreover, the glutamate conversion pathways are important in brain energy metabolism [2, 3]. A hypothesis on separation of neurotransmitter and metabolic pools of glutamate has been put forward [4-7]. The separation is necessary to avoid the effect of non-transmitting glutamate on the signal/noise ratio during glutamatergic neurotransmission. This is realized through the compartmentation of distinct biochemical transformations. This compartmentation is a complex system comprising the following components.

1. The blood–brain barrier allows autonomous synthesis and utilization of glutamate in the brain.

2. The glutamatergic synapse is surrounded by glial cells, which can uptake glutamate more effectively in comparison with neurons.

3. The glutamate/glutamine cycle is operating between neurons and glial cells. Expression of glutamine synthetase (the key enzyme converting glutamate into glutamine) is restricted by glial cells (glutamine does not possess neurotransmitting activity and, when released into the intercellular space, passes through and returns to neurons as a source for glutamate formation).

4. The expression of key enzymes (pyruvate carboxylase and cytosolic malate dehydrogenase) which build *de novo* the carbon skeleton of glutamate from glucose is confined to glial cells, and "excessive" glutamate returns to the glucose oxidative pathway.

Due to these characteristics of brain tissue, neurons constantly need substrates newly supplied by glial cells for maintenance of the neuronal tricarboxylic acid cycle. As soon as the store becomes exhausted, neurons stop their neurotransmitter glutamate production with their oxidative metabolism impaired. Taking into account the tight connection between neurons and glia, brain functioning may be concerned as a series of interactions between neuronal and glial cells.

Let us consider the above listed points of coupling between the neuronal and glial cells. The existence of all these coupling points is confirmed at present by direct *in vivo* studies of human brain and by experiments with animal brain *in vivo* and *in vitro*.

Abbreviations: AAT) aspartate aminotransferase; DAT) dementia of Alzheimer's type; GDH) glutamate dehydrogenase; PAG) phosphate-activated glutaminase; α-KG) α-ketoglutarate; MSOX) L-methionine sulfoximine.

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The first link of the system separating glutamate pools is the blood–brain barrier, which is impenetrable to glutamate [8].

Glial cells actively uptake the extracellular glutamate including its neurotransmitter pool, and many data confirm the second "point" coupling neurons and glia [9]. The understanding that glial cells (astrocytes) are responsible for the absorption and metabolism of the major part of glutamate in the brain and it is this cell type that removes glutamate released by neurons into the synaptic cleft began from the study of cell cultures *in vitro*. The fact that the extracellular glutamate is absorbed more actively by an astrocyte culture than by a neuronal cell culture was reported at the end of the 1970s [10].

Experimental data were accumulated later indicating the interaction of glutamatergic neurons and glial cells *in vivo*. First of all, these are the data on the *structural organization* of glutamatergic *synapses*. Astrocytes enriched by glutamate transporters and glutamine synthetase (a key glutamate metabolizing enzyme) are co-localized with glutamatergic neurons. That means the astrocytes take posts in the synaptic apparatus enabling them to effectively fulfill the function of absorption and metabolism of glutamate released by neurons [11-13]. Glial glutamate transporters, such as GLT and GLAST, have been shown to be concentrated at the astrocyte processes surrounding presynaptic neuronal terminals [14].

At the level of glial cells, the co-localization of glial glutamate transporter (GLAST) and glutamine synthetase was discovered in glial cell processes surrounding glutamatergic synapses. This is evidence for association of glutamate uptake with its conversion inside the glial cells [15].

Data have accumulated suggesting the tight functional coupling of glutamatergic neurons with glial cells via glutamate. These data have been obtained using physiological and histochemical methods on cell cultures, surviving sections, tissue cultures, and on animals. Glial glutamate transporters localized at the membrane surface exposed to the synaptic cleft are activated by glutamate released into the synaptic cleft. Moreover, glutamate uptake by astrocytes from the synaptic cleft has been detected during this process [16, 17]. Also, the sodium ion flow associated with glutamate uptake in astrocytes reflects the release of the neurotransmitter glutamate by neurons [18]. The physiological importance of the consumption of glutamate by astrocytes *in vivo* has been proved by experiments on genetically modified animals (knock-out models) using intact brain of mice deficient in astrocytic glutamate transporter [19]. Histochemical studies provide additional support that the main portion of glutamate released by neurons is absorbed by astrocytes [20, 21].

Thus, glutamine/glutamate exchange proceeds between neurons and glia. This mutual exchange (cycle) represents a biochemical coupling point between glutamatergic neurons and glia. Although the cycle was first described more than 30 years ago [22], its existence *in vivo* has been directly proved by *in vivo* NMR measurements only during recent years [23-25].

The synthesis of glutamine from glutamate in glial cells is an important part of this cycle. It is catalyzed by glutamine synthetase localized in glia (previously it was considered as a marker for astrocytes, but later it was found in oligodendrocytes as well [26-28]). The functional role of the glutamine/glutamate cycle and glutamine synthetase was evaluated from experiments on glutamine synthetase inhibition in animals by the selective inhibitor L-methionine S-sulfoximine (MSOX) [29]. Being administered at toxic concentration, MSOX induces in animals misses in orientation, changes in behavior, and convulsions up to death, whereas an injection of MSOX or its application into a distinct area of the central nervous system results in the loss of function of this area. For example, an application of MSOX solution onto some area of the reticulum induces temporary blindness and the loss of ability to react to light [30], whereas glutamine synthetase inactivation in corpus striatum interferes with the memory process [31]. Both blindness and impairment of memory are reversible by the application of exogenous glutamine. This is additional evidence for functional alterations induced by MSOX due to the inhibition of glutamine synthetase. These facts provide a basis for the opinion that glutamine synthetase plays a significant role in memory processes [32].

Glutamine synthetase may exercise a protective function as demonstrated in model experiments. An excessive glutamate release is likely to be the main cause of neurodegeneration induced by an injury of the central nervous system. Glial cells prevent excessive accumulation of released glutamate in synapses under normal conditions. However, a supposition has been put forward [33] that in central nervous system injury the glial cells cannot neutralize neurotoxicity of glutamate because of insufficient activity of glutamine synthetase. It was shown experimentally with retinal injury that induction of glutamine synthetase gene expression in glial cells by glucocorticoids could protect neurons from degeneration [34]. The purified glutamine synthetase applied on the retina cell culture can also protect neurons from death in a dose-dependent manner. Thus glutamine synthetase may be an effective neuroprotector, and the enhancement of glutamine synthetase expression in glial cells is probably an endogenous mechanism protecting neurons from toxic action of excessive glutamate in extra-cellular fluid (for instance, in trauma, stroke, or ischemia).

These findings may possibly provide a new approach to the treatment of neurodegenerative disorders in the future.

Schematic presentation of glutamate metabolism. Compartmentation of glutamate metabolism is characteristic of glutamate conversion in nervous tissue. One

can distinguish three levels of glutamate pool separation: in the whole organism (due to the blood–brain barrier), in nervous tissue (between neurons and glial cells), and inside the cell (in cytoplasm and mitochondria).

Since glutamate does not pass the blood–brain barrier, the glutamate in central nervous system is formed from glucose within the system, wherein this process is essentially supported by the synthesis *de novo* of components of the tricarboxylic acid cycle [35]. Hertz with coworkers [5, 6] has elaborated a hypothetical scheme. According to the scheme, the pathways of glucose conversion through the tricarboxylic acid cycle to glutamate in neurons and in astrocytes and neuronal biosynthesis of glutamate (a "shuttle" between cytoplasm and mitochondria in neurons) are interconnected as presented in Figs. 1-3. An intracellular pathway of metabolic degradation of glucose to glutamate through the tricarboxylic acid cycle regulates the neurotransmitter glutamate pool providing glutamatergic neurotransmission (Figs. 1 and 2).

A biochemical "shuttle" between mitochondria and cytoplasm is involved in glutamate synthesis in neurons (Fig. 3).

GLUTAMATE SYNTHESIS IN NEURONS (A "SHUTTLE" BETWEEN CYTOPLASM AND MITOCHONDRIA)

Glutamine synthesized by glutamine synthetase in astrocytes and entering through the intercellular space into neurons is converted to glutamate by neuronal phosphate-activated glutaminase (PAG) [1, 36, 37]. However, the synthesis of neurotransmitter glutamate from glutamine is more complex than direct conversion of glutamine.

Glutamine synthesized by astrocytes is transferred through the cytoplasm and outer mitochondrial membrane of neurons. Then PAG (which is localized between the outer and inner mitochondrial membranes) hydrolyzes it to glutamate. For further transformations, glutamate is transferred into the mitochondrial matrix through the inner mitochondrial membrane by the transporter (*1*) in exchange for aspartate and then undergoes transamination to α-ketoglutarate (α-KG) by mitochondrial aspartate aminotransferase (AAT_m) localized inside the mitochondria. The α-KG formed in this way is transferred by the dicarboxylic acid transporter (*2*) through both mitochondrial membranes into the cytoplasm in exchange for malate. Then the cytoplasmic AAT_c transaminates α-KG to glutamate accumulated in synaptic vesicles with subsequent release via a calcium-dependent mechanism. Transamination of aspartate in cytoplasm results in release of oxaloacetate followed by NADH-dependent reduction of oxaloacetate to malate, which is transported into mitochondria by the transporter (*2*).

Alternatively, α-KG (possibly transferred from astrocytes, Fig. 1) may be accumulated in cytoplasm and transaminated into glutamate using another amino acid (such as alanine or other branched-chain amino acid), but no transfer across the mitochondrial membrane happens during this process.

ALTERNATIVE PATHWAYS FOR GLUTAMATE SYNTHESIS

Glutamate can be synthesized from α-KG via amino group transfer from alanine (Figs. 1 and 2), leucine, isoleucine, or valine in a reaction catalyzed by corresponding transaminase (Fig. 2) [1, 38].

While the export of alanine and tricarboxylic acid cycle intermediates from astrocytes may be considered as proven [39-41], the opinion is not uniform whether α-KG is transferred from astrocytes into neurons and the transamination goes on there or, alternatively, α-KG conversion through glutamate into glutamine by glutamine synthetase occurs within astrocytes, and the produced glutamine is released and accumulates in neurons as a precursor of glutamate (Figs. 1 and 2). Various views on this question were regarded in detail earlier [5].

Glutamate dehydrogenase (GDH) is an enzyme joining the carbon and nitrogen metabolic pathways and possibly participating in glutamate biosynthesis in the brain (Figs. 1 and 2) [42].

From thermodynamic parameters, the equilibrium of GDH reaction *in vitro* is shifted to the glutamate synthesis, but the direction of the GDH reaction *in vivo* probably depends on both the local substrate concentrations and pH. Particularly, the changes in pH (tissue acidosis) can determine the direction of glutamate/glutamine metabolic reaction [43].

The role and localization of GDH compared with aspartate aminotransferase (AAT) are regarded in the studies of McKenna with coauthors [7]. Both enzymes catalyze a reversible conversion of glutamate to α-KG, but via different mechanisms.

Intracellular compartmentation is important to specify the direction of the reversible AAT reaction. Association of the enzyme into a complex and/or its activation via attachment to the inner mitochondrial membrane may provide a mechanism controlling the enzymatic activity *in vivo*, wherein metabolites can modulate the enzymatic activity *in vivo* through their effect on the binding of AAT to the membrane [44]. Although these data were obtained from experiments on non-neuronal tissue, one may anticipate that these fundamentals are common for different tissue types.

Unlike AAT, an opinion is not generally held on the direction of the GDH reaction *in vivo* (whether biosynthesis or degradation of glutamate prevails). GDH and AAT may be regarded therewith as complimenting each other in

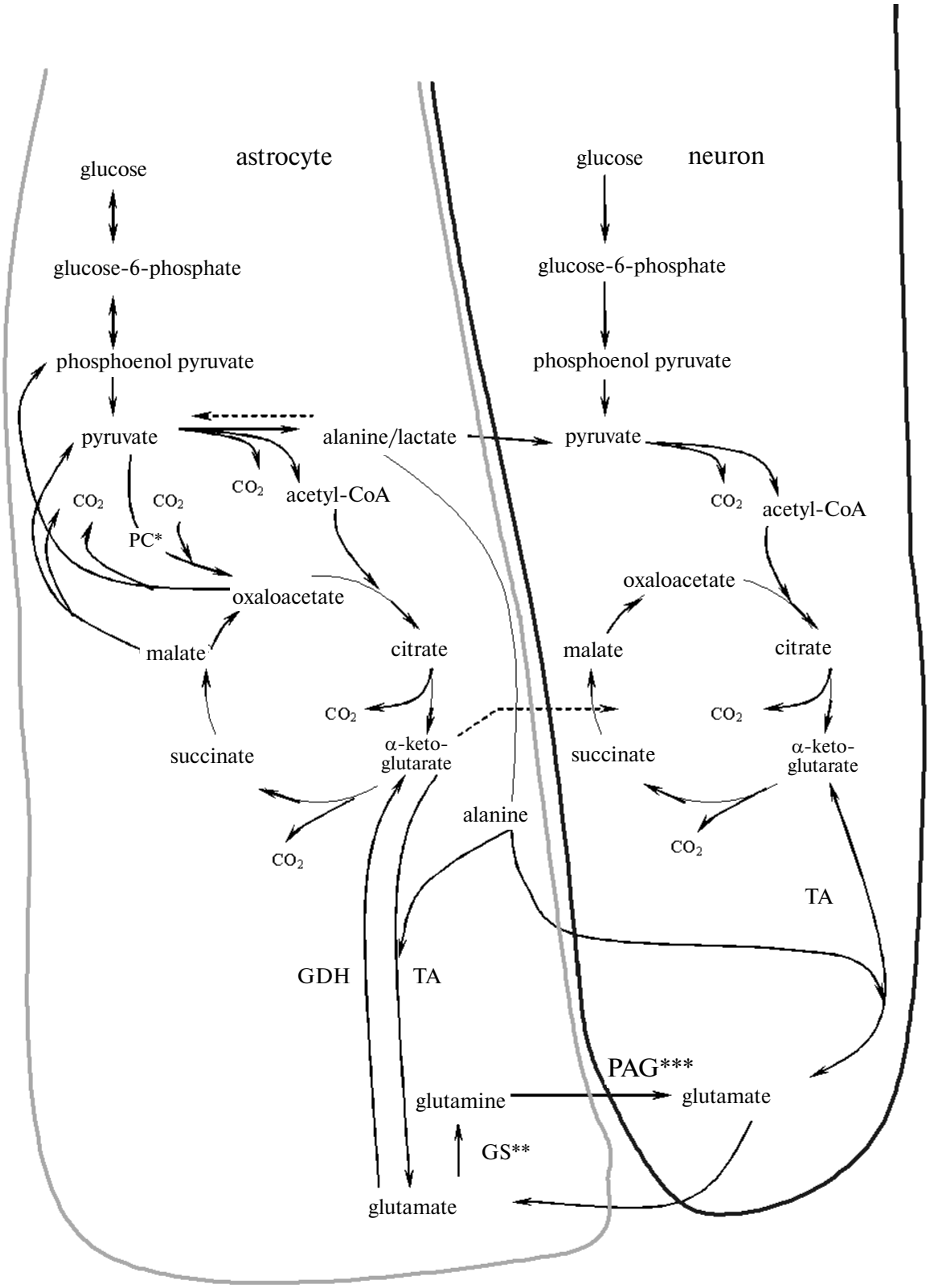

Fig. 1. Metabolism of glucose to glutamate via the tricarboxylic acid cycle in neural and glial cell [5, 6]. Abbreviations: PC*, pyruvate carboxylase, astrocytic enzyme; TA, transaminases; GDH, glutamate dehydrogenase; GS**, glutamine synthetase, glial enzyme; PAG***, phosphate-activated glutaminase, neuronal enzyme.

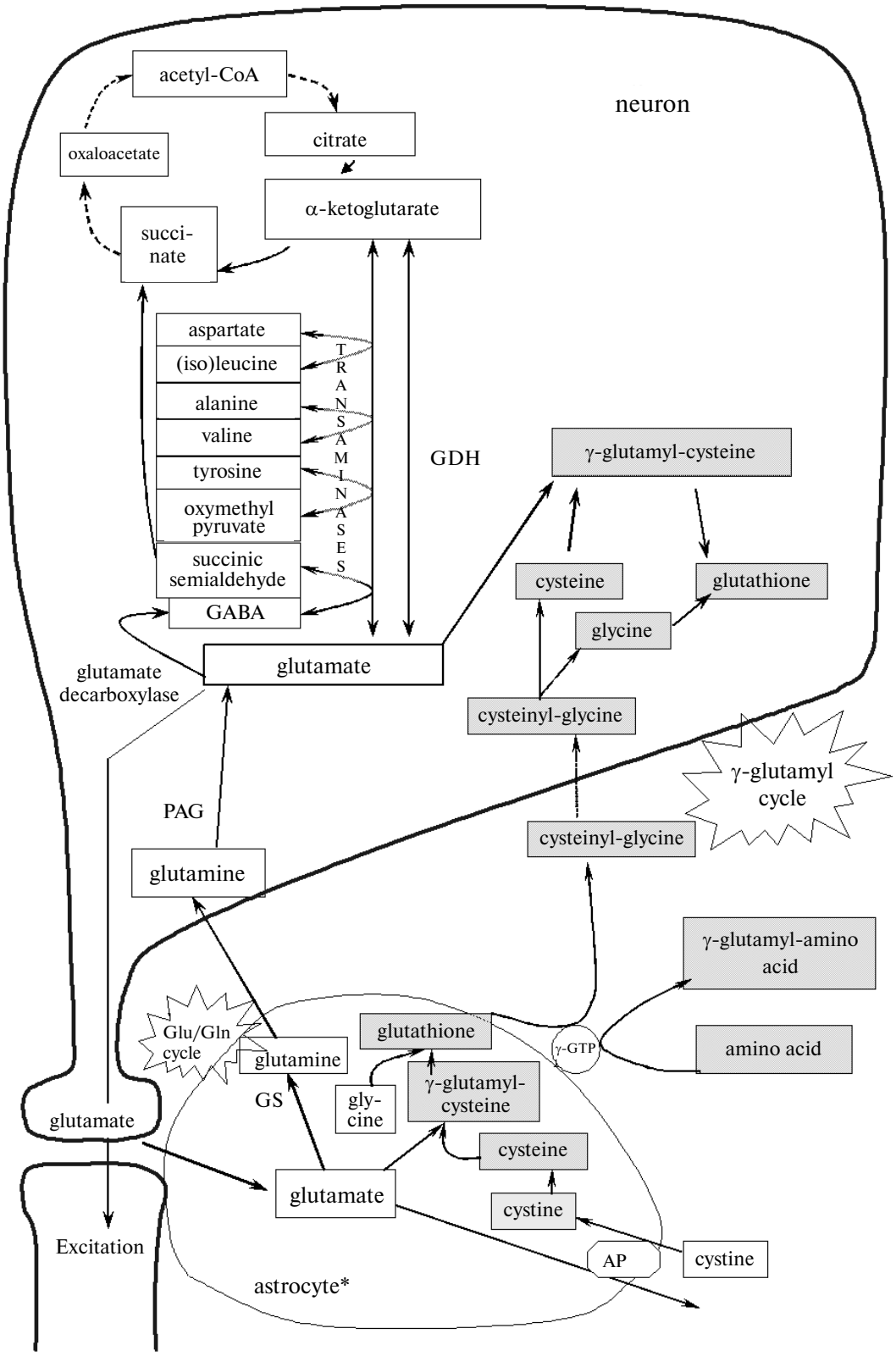

Fig. 2. The main metabolic pathways of glutamate in nervous tissue (astrocytic–neuronal glutamate/glutamine cycle and γ-glutamyl cycle) [94]. Abbreviations: GS, glutamine synthetase; GDH, glutamate dehydrogenase (localization, see text); PAG, phosphate-activated glutaminase, neuronal enzyme; GABA, γ-aminobutyric acid; γ-GTP, γ-glutamyl transpeptidase; AP, glutamate–cystine antiporter. Astrocyte*, glutamine synthetase has been revealed in oligodendrocytes as well (see text).

interrelated metabolic pathways. There are many evidences for co-localization of these enzymes: their consequent work in an "assembly" facilitates the conversion (synthesis or degradation) of amino acids. So, during amino acid synthesis GDH attaches NH_3 to α-KG to produce glutamate, and AAT transfers an amino group from glutamate to oxaloacetate to form a new amino acid (aspartate) (Fig. 3). These processes reverse upon amino acid degradation.

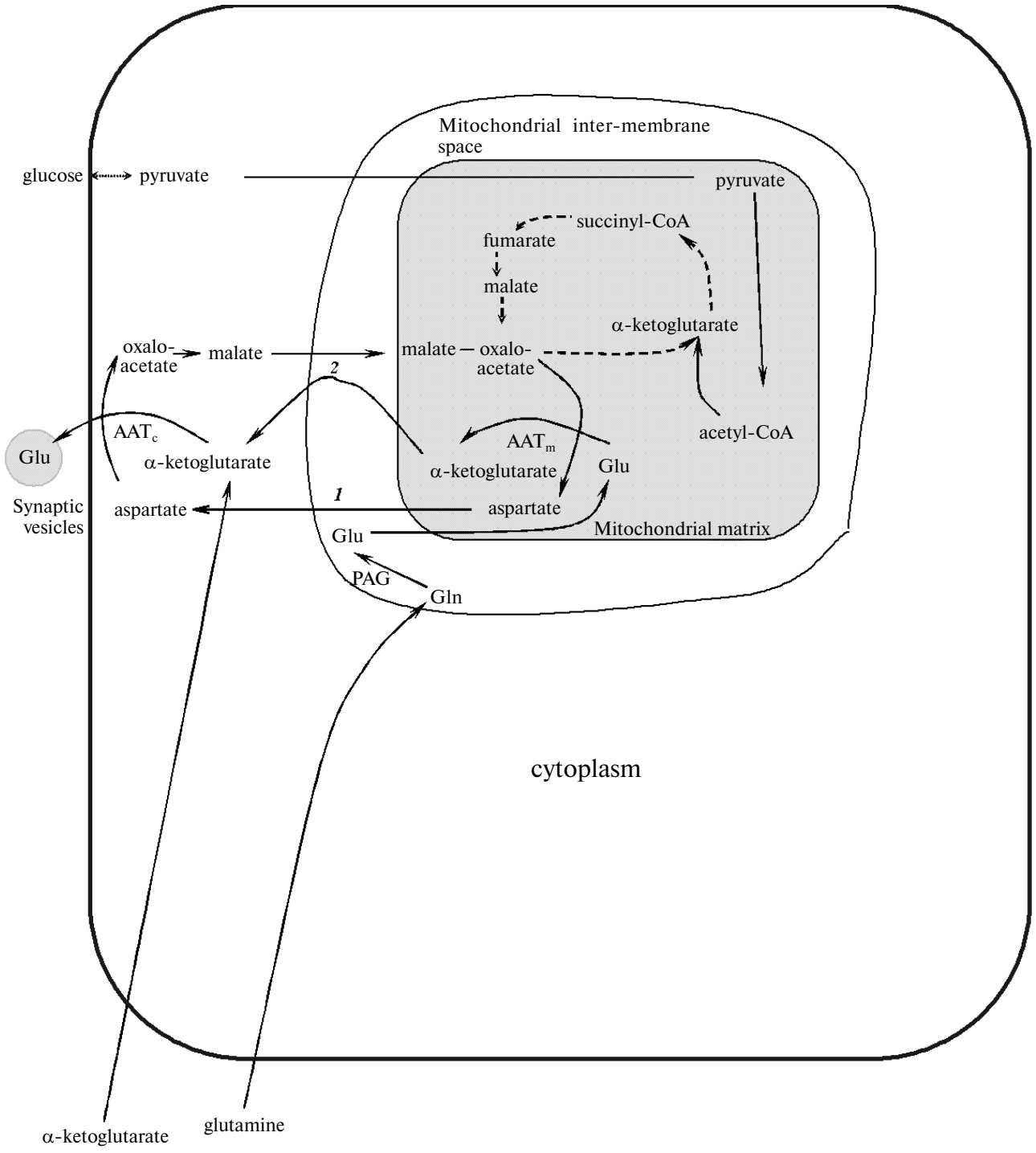

Fig. 3. Cytoplasmic and mitochondrial reactions involved in biosynthesis of neurotransmitter glutamate in neurons. Abbreviations: PAG, phosphate-activated glutaminase; AAT_c, cytoplasmic aspartate aminotransferase; AAT_m, mitochondrial aspartate aminotransferase; *1*) glutamate transporter; *2*) dicarboxylic acid transporter.

The data are conflicting on the participation of GDH in the conversion of neurotransmitter glutamate and on the intracellular GDH localization in human or animal nervous tissue. Earlier biochemical data suggested the presence of GDH activity both in neuronal and glial cells [45, 46]. Immunocytochemical studies have shown that GDH is preferentially localized in astrocytes [47, 48] and oligodendrocytes [49]. Molecular biology data suggested a prominent expression of the GDH gene in neurons (as judged from the GDH mRNA level) [50]. Some researchers anticipate that GDH participates preferentially in oxidative deamination of glutamate to α-KG in astrocytes [51, 52]. McKenna with coauthors [7] presumes that this opinion is based on the fact that GDH is found chiefly in astrocytic but not neuronal mitochondria (by immunocytochemical methods). However, the authors who found GDH in glia noted its presence in neurons as well [48].

The apparent discrepancy in the results of GDH studies may reflect the heterogeneity of GDH in nervous tissue. In fact, several GDH isoforms have been described in nervous tissue of mammals including humans [53-58]. Multiple GDH genes were found in the human genome [59-61], and at least two of them are functionally active [62]. The mRNA transcript of the *GLUD1* gene is found in various tissues and is supposed to be a template for "housekeeping" GDH form [63]. Synthesis of mRNA from the *GLUD2* gene sequence is specific for nervous tissue and testes, and the protein product of *GLUD2* participates in a synthesis of neurotransmitter glutamate [64]. Activities of GDH isoforms encoded by *GLUD1* and *GLUD2* are regulated in different ways [54]. The study of mutation phenotype for human GDH genes could possibly elucidate functions of these GDH isoenzymes [65-67]. The physiological importance of GDH in neutralization of glutamate toxicity was discussed earlier [68]. With GDH as an example (as well as with other key enzymes of energy and glutamate metabolism), the importance of inter- and intracellular compartmentation is obviously providing various isoenzymes to fulfill different functions [7].

Heterogeneity (multiplicity of genes and their products – various isoenzymes) is typical of GDH and other enzymes metabolizing glutamate in nervous tissue, such as glutamate decarboxylase, glutamine synthetase, AAT, and PAG [1, 36, 69-76]. One may suppose that molecular heterogeneity of key metabolic enzymes is a fundamental property of nervous tissue underlying basic mechanisms of neuroplasticity [70, 77].

GLUTAMATE UTILIZATION IN NERVOUS TISSUE

Since glutamate produced in central nervous system cannot easily leave it, a mechanism exists providing utilization of glutamate. This is kept by the following processes. Astrocytic glutamine synthetase converts glutamate to glutamine, which returns into neurons in the glutamate/glutamine cycle (glutamine synthetase is a key enzyme of the cycle – see above). Other reaction types and corresponding enzymes are functioning as well. Decarboxylation of glutamate by glutamate decarboxylase results in the formation of the neurotransmitter γ-aminobutyric acid. Oxidative deamination (GDH) or transamination (AAT) of glutamate gives α-KG, which is then involved in energy metabolism [78] through succinyl-CoA, malate, and (involving malate dehydrogenase) oxaloacetate, the latter being included in the astrocytic tricarboxylic acid cycle. Otherwise, oxidation of malate gives pyruvate, which is either oxidized through acetyl-CoA in astrocytes or released (mainly after its conversion into lactate) into intercellular space from which it can be taken up by neurons and included in their metabolism. During glucogenesis, pyruvate is converted into phosphoenol pyruvate through oxaloacetate by pyruvate carboxylase (glial enzyme). Phosphoenol pyruvate can be utilized for glycogen synthesis (in astrocytes) and glucose, which is oxidized again (both in neurons and astrocytes) (Fig. 1).

It has long been known that isolated brain cells, particularly glial cells in culture, can oxidize glutamate and glutamine, and later the oxidation of these amino acids has been shown in normal brain *in vivo* [79, 80]. Oxidative catabolism of glutamate is important for the removal of its "excess" from the central nervous system. Yet the process allows a partial conservation of energy released from the process of glucose transformation to glutamate [81], and an "excess" of glutamine can be metabolized after its conversion to glutamate as well [82].

The first step on the pathway of glutamine oxidation for neuronal energy demands is a conversion of glutamine into glutamate. Enzymes possessing glutaminase activity can catalyze this reaction. Along with PAG, the glutamine transaminase producing α-KG from glutamine [83] and maleate-activated glutaminase activity ("phosphate-independent glutaminase"), which can be attributed to γ-glutamyl-transferase [84], are known, although the role of γ-glutamyl-transferase in glutamine conversion is questionable [1]. The role of glutaminase activity in glia remains still unclear (the role of glutaminase in astrocytes is discussed by Laake with coworkers [1]).

In terms of the concept of McKenna with coworkers [7] on GDH and AAT functions in intracellular compartmentation of glutamate metabolism, the conversions of "endogenous" and "exogenous" glutamate are spatially separated. In fact, many authors have shown differences between metabolic pathways for exo- and endogenous glutamate [85-87]. Exogenous glutamate taken up by cells from the synaptic cleft is transferred into mitochondria by glutamate/aspartate antiporter and utilized for energy production. In the first step, this glutamate is con-

verted by GDH (ADP-activated under low energy conditions). Contrariwise, the conversion of endogenous glutamate produced from glutamine (by neuronal PAG or possibly by other glutaminases, see above) begins from the aspartate aminotransferase step [87, 88].

INCLUSION OF GLUTAMATE INTO PEPTIDES AND ITS CLEAVAGE FROM PEPTIDES

Yet another point of neuron-glia coupling of metabolic pathways of glutamate in the brain is the inclusion of glutamate in (poly)peptides and its cleavage from them.

The N-acetyl-L-aspartate–N-acetyl-aspartyl-glutamate cycle. The N-acetyl-L-aspartate–N-acetyl-aspartyl-glutamate cycle is known wherein three cell types (oligodendrocytes, astrocytes, and neurons) participate in the conversions [89, 90]. Compartmentation of metabolism (coupling of catabolism and anabolism) for N-acetyl-aspartyl-glutamate and N-acetyl-aspartate is presented in Fig. 4. The synthesis of N-acetyl-aspartyl-glutamate from N-acetyl-aspartate and glutamate by N-acetyl-aspartyl-glutamate synthase occurs in neurons, and hydrolysis of N-acetyl-aspartyl-glutamate by the N-acetyl-aspartyl-glutamate peptidase (on the astrocytic surface) results in glutamate release. N-Acetyl-aspartyl-glutamate possibly possesses a neurotransmitter activity, because it can activate glutamate receptors of N-methyl-D-aspartate (NMDA) type, moreover it is a selective agonist for metabotropic glutamate receptors (mGluR3) and regulates the expression of receptor subunits for γ-aminobutyric acid (GABA) and suppresses its release from cortical neurons [90].

The γ-glutamyl cycle. Another example of metabolic coupling between astrocytes and neurons associated with glutamine and glutamate translocation is the synthesis of glutathione, a glutamate-containing tripeptide (Fig. 2).

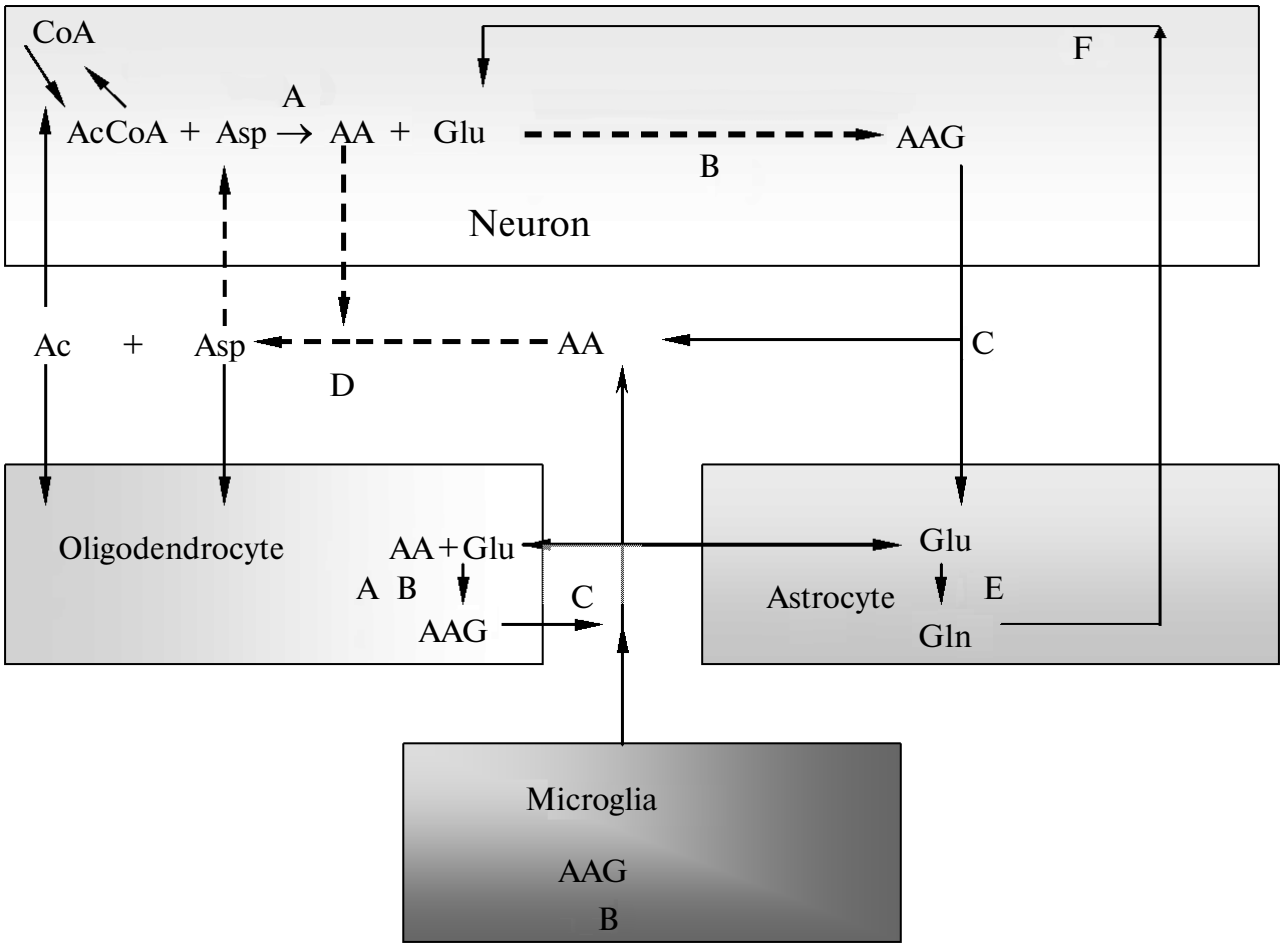

Fig. 4. The N-acetyl-L-aspartate–N-acetyl-aspartyl-glutamate cycle [89]. Abbreviations and notations: AA, N-acetyl-L-aspartate; AAG, N-acetyl-aspartyl-glutamate; A, synthase AA; B, AAG synthase; C, AAG peptidase; D, aspartate acylase; E, glutamine synthetase; F, glutaminase; Ac, acetate residue; AcCoA, acetyl coenzyme A; CoA, coenzyme A; Gln, glutamine; Glu, glutamate; Asp, aspartate.

Among the variety of brain cells astrocytes only are apparently endowed by the ability of cystine uptake (by means of cystine/glutamate antiporter), whereas neurons cannot consume cystine [91]. Cystine is reduced to cysteine in astrocytes, and afterwards it binds to a glutamate residue to form the dipeptide γ-glutamyl-cysteine. This synthesis is catalyzed by γ-glutamyl-cysteine synthetase in the reaction analogous to the glutamine synthetase reaction [92]. Besides, as mentioned above, γ-glutamyl-cysteine synthetase can express glutaminase activity [84]. γ-Glutamyl-cysteine synthetase is a two-subunit enzyme catalyzing the first step of glutathione biosynthesis [93]. Attachment of a glycine residue to γ-glutamyl-cysteine results in glutathione formation.

Glutathione released from astrocytes is a substrate for the astroglial γ-glutamyl transpeptidase localized on the astrocytic surface, and one of its products, dipeptide cysteinyl-glycine, is used by neurons as a precursor for neuronal glutathione [94]. It is unknown whether the hydrolysis of cysteinyl-glycine occurs in extracellular space by neuronal ectopeptidase or the dipeptide is hydrolyzed after its uptake by neurons in their cytoplasm. Glutamine is released by astrocytes and consumed by neurons as a glutamate precursor, which is used for glutathione synthesis. Glutamine and H_2O are the most probable acceptors for the γ-glutamyl residue transferred from glutathione by a transferase (see "amino acid" in Fig. 4) [94].

MSOX can inhibit glutamine synthetase, γ-glutamyl cysteine synthetase, γ-glutamyl transpeptidase, and glutamine synthetase-like protein acting in a yet unknown way in glutamate/glutamine metabolism [73]. It follows that toxic effects of MSOX *in vivo* may be due to the elevation of glutamate concentration because of glutamine synthetase inhibition, as well as impairment of glutathione biosyntheses and other metabolic processes.

GLUTAMATE UPTAKE BY GLIAL CELLS AND GLUTAMINE SYNTHESIS ARE ENERGY-DEPENDENT PROCESSES: ENERGY SOURCES SUPPORTING GLUTAMATE UPTAKE AND GLUTAMINE SYNTHESIS

Increased sensitivity of *in vivo* NMR techniques has enabled further evaluation of recycling rates for glutamate and relative rates for various metabolic pathways of glutamate in animals [95, 96] and humans [97, 98]. Correlation between the rates of glucose utilization and glutamine formation provided the basis for a hypothesis for the dependence of glutamate uptake followed by glutamine synthesis in astrocytes on the energy of glycolysis [96, 98, 99]. However, the hypothesis was in conflict with experimental data [100, 101] for independence of glutamate uptake by astrocytes and glutamine synthesis on glycolysis. In contrast, the experiments of Poitry [102] give evidence for glutamate uptake by Müller cells powered by the energy of glutamate oxidation.

Nonetheless, observations over the processes going on in animal brain subjected to ischemia–reperfusion suggest that glutamate uptake, when required, can be driven by the energy of glycolysis [5, 103].

INFLUENCE OF ENERGY DEFICIENCY ON GLUTAMATE METABOLISM IN THE BRAIN: ISCHEMIA

Energy deficiency in the central nervous system (exhaustion of oxygen and glucose storages) results in most cases from artery blockage leading to local ischemia. The blood flow decreases (sometimes drops to 20%) in an ischemic locus, wherein oxygen amount carried by the blood is below the level that is necessary for complete glucose oxidation. In contrast to neurons and oligodendrocytes, astrocytes can survive ischemia at the cost of the energy of glycolysis [103]. Hence, astrocytes surviving brain ischemia can longer fulfill some functions, such as glutamate uptake (in this case at the expense of glycolysis) [104]. In agreement with this, an enhancement of glutamate formation from glutamine by damaged glutamatergic neurons with subsequent release of this glutamate [107] rather than deficit of glutamate uptake is responsible for immediate increase in extracellular glutamate concentration under brain ischemia and associated neurotoxic effect of glutamate [105, 106]. Moreover, glutamate released in the first few minutes only represents neurotransmitter glutamate, whereas all the rest of the glutamate originates from other cytosolic pools due to reversion of processes of its consumption and utilization, impairment of membrane integrity under phospholipase action, or opening of anion channels induced by cell swelling.

Glutamate increase in astrocytes *in vivo* under ischemia or combination of hypoxia and substrate limitation has been revealed by a number of researchers. This increase results from the relatively safe defense of glutamate uptake by astrocytes under ischemic conditions (in this case supported by the energy of glycolysis), whereas following glutamate oxidation is impaired owing to the lack of oxygen. Glutamate concentration is particularly elevated inside mitochondria [108]. As shown from experiments *in vivo* [109] and on surviving brain sections [110], a subsequent reperfusion or regain of tissue oxygen and energy supply can result in normalization of glutamate concentration in astrocytes, which is consistent with views on oxidative metabolism according to the pathways presented in Figs. 1 and 2. Experimental data on significant enhancement of glutamate oxidation in rat brain after hypoxia [111] are compatible with these observations as well.

Alterations in level of glutamine synthetase have been described under hypoxia of nervous tissue [112].

Redistribution of this enzyme in rat brain was found under prolonged portocaval anastomosis (the enzyme was determined immunohistochemically) with its decrease in some regions and increase in others [113].

IMPAIRMENT OF GLUTAMATE METABOLISM IN NERVOUS SYSTEM PATHOLOGIES

Pathologies of the nervous system can result from changes in the components of the glutamatergic system itself, such as amount and/or affinity of glutamate transporters and receptors as well as from dysregulation of inter- and intracellular glutamate metabolic pathways (represented in Figs. 1-3). This view is supported by both the studies of experimental ischemia or limitation of energy sources (simulation of stroke) and biochemical and genetic studies of patients with hyperammoniemia-hyperinsulinemia (displaying hepatic encephalopathy) [66, 67]. A bulk of evidence is known from the literature for anomalies of glutamatergic system components and glutamate metabolism under various neuropathological conditions, such as neurodegenerative disorders (olivopontocerebellar atrophy, spinocerebellar degenerations, and multiple system atrophy) [52, 114-117], multiple sclerosis [49], sporadic amyotrophic lateral sclerosis [49, 118], Down's syndrome, Parkinson's disease, and epilepsy [119, 120].

Functioning of the glutamatergic system and the interaction of neurons and astrocytes are impaired in mental disorders. Let us concern senile dementia of Alzheimer's type (DAT) and schizophrenia—the severe disorders impairing mental processes, cognitive functions, and memory.

SENILE DEMENTIA OF ALZHEIMER'S TYPE

At the end of the 1980s, a glutamatergic hypothesis had been put forward for pathogenesis of DAT [121]. In line with this hypothesis, glutamate concentration is elevated in the brain of patients, thus exerting toxic effect ("excitotoxicity") on neurons through the overstimulation of NMDA-type glutamate receptors [122] (indeed, excessive glutamate concentration is toxic for both neuronal and glial cells, particularly astrocytes, and induces their swelling and lysis) [123]. A good consensus exists among investigators at present that "dysfunction" or "overstimulation" of NMDA receptors is the central event in glutamatergic system dysfunction in DAT [124, 125]. However, the causes of glutamate level elevation in the brain are not clear. The level of glutamate depends on the balance between the processes of its capture/transport and production/conversion. The studies on glutamate transporters give evidence for their dysfunction in the brain of DAT patients with decrease in both total activity of glutamate transporters and the level of glial glutamate transporter (GLT1) [126, 127]. However, Beckstrom with coworkers failed to find any correlation between severity of dementia and amounts of GLT1, GLT2, and astrocyte-specific GLAST [128].

Thus, all of the components of the brain glutamatergic system are apparently impaired in dementia, and, because this system might be involved in memory processes (see above), this alteration is probably responsible for the memory loss [129].

On the other hand, alterations in the level of brain glutamate in DAT are indicative of the impairment of glutamate metabolic pathways [121, 126]. In particular, the amount of PAG drastically decreases in cortical neurons of demented patients [130], and the number of neurons expressing glutamate decarboxylase mRNA increases [131]. At first glance, these data would suggest a decrease in glutamate concentration, but the full pattern requires evidences for other enzymes involved in glutamate metabolism.

However, data on glutamine synthetase are only available from the literature. More than ten years ago a series of studies was carried out revealing a decrease in glutamine synthetase protein amount and activity in autopsied brain of patients with DAT [132, 133]. The investigators demonstrated that glutamine synthetase activity decreases in aged brain and, moreover, the activity is significantly lower in demented patients compared with a control group matched by age [132, 134, 135]. An inverse correlation was found in brain of patients between the level of glutamine synthetase (evaluated from immunoreactivity in brain extracts) and the count of beta-amyloid plaques [133]. A possible reason is that amyloid Abeta peptide (Abeta 1-40) induces inactivation of glutamine synthetase wherein peroxidation processes participate in the inactivation *in vitro* [136]. Yet another evidence for glutamine synthetase involvement in DAT pathology is alteration of its cellular localization confirmed immunocytochemically [137]. The level of glutamine synthetase immunostaining was found decreased in astrocytes of demented patients, and the enzyme was detected in a subpopulation of pyramidal neurons in all six autopsied brains of demented patients, whereas no glutamine synthetase was revealed in neurons of six control brains. This alteration in localization of the key enzyme is indicative of significant impairment of brain glutamate/glutamine cycle in DAT. Since glutamine synthetase appears in cerebrospinal fluid of demented patients (but was not detected in cerebrospinal fluid of healthy persons) and the level of glutamate is elevated with significant decrease in glutamine concentration [138], one can conclude that both glutamate metabolic pathways and glutamate/glutamine cycle are impaired in the brain of patients with DAT [139]. A decrease in glutamine synthetase activity in the brain of these patients

meets the hypothesis on elevated glutamate level in this pathology.

New approaches to the treatment of senile DAT are based on the recognition of the importance of glutamate toxicity mechanisms involved in the pathogenesis [140]. Views of the toxicity realized through glutamate receptors, particularly NMDA-receptors [125, 141], form the basis for the use of substances (pharmaceuticals) known as glutamate receptor ligands. Positive results of treatment trials have been reported for Memantine (Akatinol) and Dimebon. Memantine is an activator of (3)-H-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptors and antagonist of NMDA-receptors, and Dimebon is a low-affinity noncompetitive antagonist of NMDA-receptors. Psychiatrists have succeeded in significant and prominent improvement in the state of patients with Alzheimer's disease and those suffering from impairment of long-term and short-term memory, cognitive disorders, headache, and depression [140, 142, 143].

SCHIZOPHRENIA. INTERACTION BETWEEN NEUROTRANSMITTER SYSTEMS

The concept of the role of neurotransmitters and metabolic interrelations in the nervous system, which was substantially broadened in recent years, is especially important for understanding of the pathogenesis of schizophrenia [144]. Direct evidences have been obtained for the postulate on the dysfunction of dopamine neurotransmitter system in schizophrenic brain (only indirect data were counted in favor of the hypothesis for many years). Moreover, the interrelation between dopaminergic and other neurotransmitter systems has been found. Like other monoaminergic neurons, dopaminergic ones can be controlled either directly by glutaminergic neurons or indirectly via GABA-ergic interneurons acting as accelerators or inhibitors. Glutamate can inhibit dopamine release; in fact, a hypothesis has been confirmed that pulse-dependent mechanism of dopamine release is involved in the inhibitory effect of glutamate (mediated by ionotropic glutamate receptors) on dopamine nerve terminals [145].

The role of an impairment of the serotonergic neurotransmitter system in schizophrenia has long been accepted [146]. In this connection the facts suggesting the interaction between serotonergic and glutamatergic neurotransmitter systems are of interest. Serotonin directly influences the glutamatergic neuronal activity *in vitro* and in experiments on animals, and expression of the components of the glutamatergic system, AMPA-receptor subunits, is serotonin-regulated [147].

Thus, the hypothesis that systemic stabilization with the key task to achieve a balance between neurotransmitter systems should be the general therapeutic strategy in psychiatry and neurology became a concept to be verified in practice.

GLUTAMATERGIC HYPOTHESIS OF SCHIZOPHRENIA

The phencyclidine model of schizophrenia arose from the observation that phencyclidine and ketamine (noncompetitive antagonists of NMDA-type glutamate receptors) provoke schizophrenia-like symptoms, both positive (auditory hallucinations and delirium) and negative, in volunteers, whereas phencyclidine induces an acute state and psychoses in schizophrenia patients. Psychotomimetic properties of excitatory amino acid antagonists (such as phencyclidine, ketamine, and MK-801) have served as a basis for elaboration of the so-called "pharmacological glutamatergic" hypothesis of schizophrenia [148-150].

More than 20 years ago, Kim with coworkers [151] supposed that schizophrenia might arise from the dysfunction of the glutamatergic system in the brain. The recently accumulated data has enabled development of an updated neurochemical hypothesis that impairment of glutamate neurotransmission plays an important role in the pathogenesis of schizophrenia [152-157]. The hypothesis is based on the following dataset: strong NMDA receptor inhibitors induce the above symptoms in humans and disability to choose a correct behavior program in animals; expression of genes encoding the components of the glutamatergic system, such as receptors and glial glutamate transporters, is altered in brain of patients with schizophrenia; parameters of binding with agonists and antagonists are changed in glutamate receptors; glutamate level is decreased in the brain and cerebrospinal fluid of patients with schizophrenia, and glutamine level is increased in anterior cingulate cortex of first-episode schizophrenia patients before their treatment with neuroleptics [23, 158-165]. Recent data indicate the impairment of glutamate metabolism in schizophrenic brain. In particular, certain alterations were observed in activity and immunoreactivity of the enzymes involved in glutamate metabolism, such as glutamine synthetase [74, 166] and glutamate dehydrogenase [58, 167, 168]. Also, the alterations involve phosphate-activated glutaminase and glutamate decarboxylase; significant elevation in PAG and GAD enzymatic activities was found in thalamus and prefrontal cortex of subjects with schizophrenia [169-171]. The data on alterations in activity of glutamate-metabolizing enzymes enhance and broaden the glutamatergic hypothesis and offer great opportunities for the development of new approaches to the treatment of this mental disorder, for instance, the search for regulators controlling the function of glutamate-metabolism-related genes and/or the components of the glutamatergic system.

COMPARATIVE ROLE OF GLUTAMATERGIC SYSTEM IN ALZHEIMER'S TYPE DEMENTIA AND SCHIZOPHRENIA

Although we are far from the final discovery of events involved in pathogenesis resulting in senile DAT or schizophrenia, the recent neurochemical data have revealed a difference between alterations in the glutamatergic system in these pathologies of the central nervous system. The elevation of glutamate release from glutamatergic neurons is supposed to occur in DAT. So, the "background" concentration of glutamate is elevated in glutamatergic synapses, and excessive excitation of postsynaptic neurons occurs; as a result, NMDA receptors cannot properly fulfill the neurotransmitter signal transduction (that is, the signal does not transmit from presynaptic to postsynaptic neurons due to the high level of noise). Moreover, continuous hyperstimulation of NMDA receptors in glutamatergic neurons results in excessive elevation of intracellular calcium ion concentration with development of the abovementioned neurotoxicity. These alterations may be partly compensated by glutamate NMDA-receptor antagonists, thus providing the interpretation for the positive effect of Memantine (Akatinol) and Dimebon on the state of demented patients.

Unlike Alzheimer's disease, data are reported in the literature supporting either hypofunction [156, 172] or hyperfunction [153] of the glutamatergic system in schizophrenia. Several explanations may be supposed for these data [155]. The first, the regulation parameters of the glutamatergic system are more variable in schizophrenic patients compared to healthy persons (this explains, why some patients are hypoglutamatergic, whereas other ones are hyperglutamatergic). The second, some patients cannot effectively tune their glutamatergic system according to the changing conditions (for instance, stress). Hence, their status seems either hypo- or hyperglutamatergic depending on their current state.

The causes of insufficient functioning of glutamate receptors observed in schizophrenia (in particular, hypofunction of NMDA-receptors) are not still clear, nonetheless in the case of hypoglutamatergie a stimulation of the glutamatergic system activity seems to be a promising in treatment of schizophrenia [144, 173]. It is anticipated that both cognitive impairments and negative symptoms observed in schizophrenia might be alleviated by modulation of glutamate receptor function [141, 174, 175]. The effect of some typical and atypical neuroleptics employed in therapy of schizophrenia can (at least partly) result from their ability to modulate the NMDA-receptor activity through its glycine-binding site.

Since co-localization of NMDA- and AMPA-receptors in glutamatergic synapses formed by neocortical neurons has been proven [176], and a mechanism of their interaction is described in general [177, 178], employment of so-called "positive regulators" for AMPA-receptors ("ampakines") may be promising in the pharmacotherapy of schizophrenia.

Besides, some ventures have been made to alleviate negative symptoms with modulators of glutamate receptors, such as glycine, D-serine, D-cycloserine, and ampakine CX516 [178-181].

The "hypofunction" of NMDA-receptors may be compensated by medications (such as Lamotrigin and Riluzol) influencing glutamate transport [125].

Further studies on glutamate metabolism and its alterations in nervous and mental disorders and understanding of the role that the glutamatergic system plays (particularly in senile DAT and schizophrenia pathogeneses) should result in elaboration of new approaches to the treatment of these severe pathologies of the human central nervous system.

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