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ORIGINAL PAPER

Glutamate Dehydrogenase as a Neuroprotective Target Against Neurodegeneration

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Abstract

Regulation of glutamate metabolism via glutamate dehydrogenase (GDH) might be the promising therapeutic approach for treating neurodegenerative disorders. In the central nervous system, glutamate functions both as a major excitatory neurotransmitter and as a key intermediate metabolite for neurons. GDH converts glutamate to α-ketoglutarate, which serves as a TCA cycle intermediate. Dysregulated GDH activity in the central nervous system is highly correlated with neurological disorders. Indeed, studies conducted with mutant mice and allosteric drugs have shown that deficient or overexpressed GDH activity in the brain can regulate whole body energy metabolism and affect early onset of Parkinson's disease, Alzheimer's disease, temporal lobe epilepsy, and spinocerebellar atrophy. Moreover, in strokes with excitotoxicity as the main pathophysiology, mice that overexpressed GDH exhibited smaller ischemic lesion than mice with normal GDH expression. In additions, GDH activators improve lesions in vivo by increasing α-ketoglutarate levels. In neurons exposed to an insult in vitro, enhanced GDH activity increases ATP levels. Thus, in an energy crisis, neuronal mitochondrial activity is improved and excitotoxic risk is reduced. Consequently, modulating GDH activity in energy-depleted conditions could be a sound strategy for maintaining the mitochondrial factory in neurons, and thus, protect against metabolic failure.

Keywords Glutamate dehydrogenase · Energy metabolism · Neuroprotection · Neurodegenerative disorders

Regulation of glutamate dehydrogenase (GDH) activity in the human brain could be a promising therapeutic approach for treating neurodegenerative diseases [1–4]. This concept arose from evolutionary studies of the human GLUD2 gene [5–7]. The acquisition of the human GLUD2 gene in pyramidal cortical neurons enhanced the capacity for glutamate metabolism in the brain, which is thought to increase the excitatory transmission that contributes to locomotion and higher cognitive functions [5, 6]. GDH catalyzes the reversible interconversion of glutamate to α-ketoglutarate (α-KG). This conversion requires cofactors, NADP(H) and NAD(H), for oxidative deamination of glutamate to α-KG and reductive amination of α-KG to glutamate [8]. The direction of the reaction may be determined by conditions at the moment [9]. In addition to conversion by GDH, neuronal glutamate can be metabolized to α-KG by transamination; aminotransferases target specific amino acid; thus glutamate can be metabolized by aspartate, alanine, and branched aminotransferases [10, 11]. Among them, aspartate aminotransferase (AAT) has been well-studied for glutamate metabolism in astrocytes though AAT in neurons rather participates in highly active malate-aspartate shuttle [10, 12, 13]. The contribution of GDH and AAT in glutamate metabolism requires further investigation.

GDH1 functions as an energy switch, because its activity can fuel the TCA cycle, depending on energy status. Elevated GTP acts as an allosteric inhibitor and ADP is an activator of GDH1 [14]. Thus, the activity of GDH1 is tightly regulated by these metabolic intermediates. In the brain, both GDH1 and GDH2 are mainly expressed in the astrocytes. Compared to GDH1, GDH2 localized in cortical neurons has little basal catalytic activity and a lower optimal pH; moreover it is resistant to inhibition by GTP, highly responsive to activation by ADP and/or leucine, and more thermolabile than GDH1 [7, 15, 16]. The characteristics of GDH2 might provide metabolic advantages, due to the uniquely high metabolic demand for neurotransmission,

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furthermore it might be possible to use the modulatory potential of GDH activity for addressing human neurodegenerative processes.

GDH has been classified as both membrane-bound and soluble, although mammalian GDH is mainly localized in the mitochondrial matrix [17, 18]. Extramitochondrial GDH functions as a serine protease or an ATP-dependent tubulin-binding protein [19, 20]. Moreover, GDH with hexameric structures, which include multiple regulatory binding sites, can participate in transient heteroenzyme complexes. These so-called 'metabolons' can alter enzymatic kinetics and ultimately influence metabolism [21]. Thus, although modifications of GDH activity, including allosteric regulation of GDH, have been studied, the regulatory roles of GDH activity are likely to be extensive.

In the brain, the delicate regulation of glutamate metabolism via GDH is important both for energy homeostasis and for excitatory transmission [2, 7, 22]. In conditions of adequate energy status, with low ADP levels, high GTP levels, and sufficient supply of glucose, GDH is inactive [7]. However, in conditions of increased energy demand, with high ADP levels and low GTP levels, GDH metabolizes glutamate to α-KG [7], which fuels the TCA cycle to produce energy. This was shown in mice with a CNS-specific GDH knockout (CnsGlud1$^{-/-}$). The respiration fueled by glutamate in CnsGlud1$^{-/-}$ mice was significantly lower than that fueled in wild type mice [23]. With the ablation of GDH-dependent glutamate oxidation, CnsGlud1$^{-/-}$ mice exhibited fasting-like central energy deprivation and activated energy sensor, including elevations in hypothalamic ADP/ATP ratio and AMPK phosphorylation [24]. This study showed that central GDH played roles in the regulation of whole-body energy homeostasis.

Previously mentioned, decreased GDH activity in CnsGlud1$^{-/-}$ mice modified the metabolic handling of glutamate; however, it did not alter synaptic transmission [25]. On the other hand, transgenic (Tg) mice that overexpressed Glud1 in CNS neurons showed moderately elevated glutamate release in the CNS, which consequently induced neuronal loss in select brain areas [26]. In addition, transcriptomic analysis showed age-associated neuronal loss in Tg mice, although the expression of genes associated with neuronal growth and synaptic formation increased [27]. Glud1 overexpression appeared to cause premature brain aging, based on the hippocampus transcriptome; this finding suggested that glutamate dysregulation in the brain might contribute to aging or neurodegenerative disease [28].

The machinery of GDH in astrocytes is well established [12, 29]. Astrocytes take up and metabolize most of the extracellular glutamate released from presynaptic neurons, which efficiently removes excess glutamate from synaptic clefts [30]. GDH is enriched in the regions of dense glutamatergic innervation; thus, a GDH deficiency in astrocytes impairs the removal of glutamate from synaptic clefts, and, excessive extracellular glutamate accumulation leads to excitotoxic neuronal degeneration [31]. Astroglial glutamate transporters, GLT-1 and GLAST, can take up about 90% of synaptic glutamate [32]; these transporters are coupled to many energy-generating systems, including the Na^+/K^+-ATPase, the Na^+/Ca^{2+}-exchanger, glycogen metabolizing enzymes, glycolytic enzymes and mitochondria. These mechanisms provide fuel for removing extracellular glutamate [33]. A loss-of-function study showed that GDH mainly worked in the direction of oxidative deamination, not reductive amination [34]. The GDH-deficient astrocytes with siRNA-mediated knock down up-regulated the compensatory metabolic pathways for the reduced oxidative metabolism, which involved in maintaining the amount of TCA cycle intermediates such as pyruvate carboxylation as well as utilizing alternative substrates such as branched chain amino acids [35]. In addition, astrocytes in human GDH2 expressing transgenic mice increased capacity for uptake and oxidative metabolism of glutamate, particularly during augmented workload and aglycemia [36]. GDH plays roles to maintain energy metabolism and spare glucose metabolism during intense glutamatergic activity. Therefore, in astrocyte, GDH serves important roles in proper neurotransmission in synapse and replenishment of TCA cycle intermediates in metabolism.

GDH dysfunction plays various roles in human neurodegenerative disorders [4, 18, 37–39]. In 1950s, GDH deficiency in patients with olivopontocerebellar atrophy (OPCA, multisystemic neurological disorders) was characterized by juvenile parkinsonism, bulbar palsy, cerebellar ataxia, amyotrophy and peripheral neuropathy. However, the activities of other dehydrogenases were not altered significantly [40]. In addition, a human GDH2 gain-of -function hastened the onset of hemizygous Parkinson's disease [41]. Alterations in either the expression or activity of GDH are found in many neurologic disorders, including Alzheimer's disease, schizophrenia and temporal lobe epilepsy [37, 38, 42, 43]. A GDH gain-of function mutation was correlated with familial hyperinsulinism and hyperammomia syndrome, which has a seizure phenotype [44]. In epilepsy, GDH overactivity might alter the GABA concentration and sustain neuronal depolarization, due to a malfunction in the ATP-sensitive potassium channels [45]. Thus, GDH is an important regulator of neuronal excitability [45, 46]. Therefore, modulation of GDH activity can be a potential target in metabolic treatment of epilepsy and in the development of new anti-epileptic drugs [3, 47, 48].

Cancer cells require high aerobic glycolytic activity to support more active mitosis rates. In these cells, which are highly dependent on glutamine metabolism, GDH has atypical characteristics [49, 50]. Glutamine is initially deamidated to glutamate and ammonia by glutaminase,

and then, the glutamate is converted to α-KG via GDH [51, 52]. Downregulation of GDH activity results in decreased glutamine catabolism, which render cancer cells more dependent on glycolysis and vulnerable to stress condition [53]. In human cancers, GDH is commonly upregulated; this upregulation is important for redox homeostasis in cancer cells, because it allows control of α-KG level [54]. Thus, GDH regulation is important in the bioenergetic homeostasis of cancer cells [55].

In stroke, a main cause of neuronal death is excitotoxicity, due to prolonged exposure to extracellular glutamate. To avoid excitotoxicity, the level of glutamate must be maintained at actually low concentration (0.5–5 μM) in the extracellular fluid, but at very high concentration (100 mM) in the synaptic vesicles [56, 57]. There is an ongoing debate about why sustained activation of extrasynaptic *N*-Methyl-D-aspartate acid receptors (NMDARs) signaling leads to neurotoxicity, but, stimulation of synaptic signaling through NDMARs can contribute to neuroprotection [58, 59]. Several studies have shown that, the concentration gradients of glutamate in both intracellular and extracellular space must be tightly regulated by potent transport systems and glutamate metabolism in neurons, astrocytes, and synaptic vesicles. In stoke models, redistribution of glutamate is observed after metabolic inhibition [1, 60–62]. Glutamate redistribution may occur by disrupting the glutamate uptake and release system, by enhancing glutamate catabolism, and by reducing glutamate synthesis from glucose [63, 64]. During the early phase of energy deprivation, vesicular release of glutamate is increased, which contributes to extracellular glutamate accumulation; simultaneously, net glutamate uptake via excitatory amino acid transporters is rapidly reduced [65–68]. With severe ATP depletion, synaptic vesicles spill their glutamate into the cytoplasm, and the vesicular glutamate release pathway malfunctions [60]. In these conditions, a large portion of glutamate release is probably due to the reversed operation of glutamate transporter in presynaptic terminals and in neuronal somata [60, 69, 70]. The cystine/glutamate antiporter might be a source of glutamate release during oxygen and glucose deprivation; indeed, inhibition of the antiporter attenuated anoxic depolarization and neuronal death [71]. In general, to reduce glutamate excitotoxicity, released glutamate must be promptly cleared from the extracellular space. Therefore, prompt glutamate removal from the synaptic cleft is a much-needed therapeutic approach for treating neurodegeneration [72].

Many studies have investigated methods for avoiding glutamate excitotoxicity to protect against stroke, including blocking glutamate receptor activation, enhancing the expression of glutamate transporters and their activities, enzymatic glutamate degradation, or regulating intracellular calcium [71, 73–77].

To reduce excitotoxicity, we suggest using GDH activators during acute neuronal injury conditions [1]. GDH activators improve the intracellular energy state, and ultimately, they protect against cerebral ischemia–reperfusion induced neuronal death. GDH activators increase the levels of intracellular α-KG for TCA cycling and subsequent ATP production, which results in neuronal survival [1]. In an in vitro neuronal culture model, we applied iodoacetate, a known glycolytic inhibitor, as a metabolic challenge. Iodoacetate effectively reduced the production of ATP and α-KG [1]. Although iodoacetate blocked energy generation at the glycolysis step with mitochondrial dysfunction, GDH activators, like 2-aminobicyclo-(2,2,1)-heptane-2-carboxylic acid (BCH) or β-lapachone (β-LA) could activate mitochondrial GDH to increase the influx of α-KG into a TCA cycle. In addition, GDH activation concomitantly reduced the level of extracellular glutamate [1]. In mice that over-expressed GDH, the lesions caused by infarction were smaller than those observed in wild-type mice [78]. Interestingly, a quantitative proteomics study showed that GDH expression increased after ischemia [79]. In our ischemia–reperfusion model, we showed that GDH activity increased during ischemia; however, its activity decreased during the following reperfusion episode, and at that time, the ATP level was completely depleted. This decline in GDH activity after reperfusion caused the cessation of further oxidative glutamate metabolism. In contrast, adding the GDH activators, BCH and β-LA, restored the decreased GDH activity and improved the intracellular ATP levels in brain. In the reperfusion phase, astrocytic TCA cycle metabolism significantly improved, and these cells could interact metabolically with adjacent neurons in the penumbra [80]. However, in the ischemic core, TCA cycle activity significantly declines in both neurons and astrocytes. Neuronal survival in the core was determined by mitochondrial activity and utilization of substrates provided by astrocytes [80]. Therefore, during a damage-mediated energy crisis, the GDH activator can increase tissue viability in the environment which ultimately reduces the size of the infarcted lesion [1]. Compared to astrocytes, neurons are more vulnerable to energy failure injury, probably due to their high energy-consumption and less ability to adapt to alternative energy production mechanisms. In high energy-demand condition, GDH-mediated glutamate oxidation occurs more in astrocytes than in neurons [31, 81]. However, neurons with low levels of GDH expression are vulnerable to stress conditions, because neuronal GDH activity is critical for increasing respiration when the energy demand is elevated [23, 82, 83]. Therefore, the abundance of glutamate in neurons for intracellular utilization through GDH activity has major clinical implications, particularly in emergency conditions, such as stroke [1].

The illustration in Fig. 1 represents the metabolic pathway in cerebral ischemia and reperfusion. During

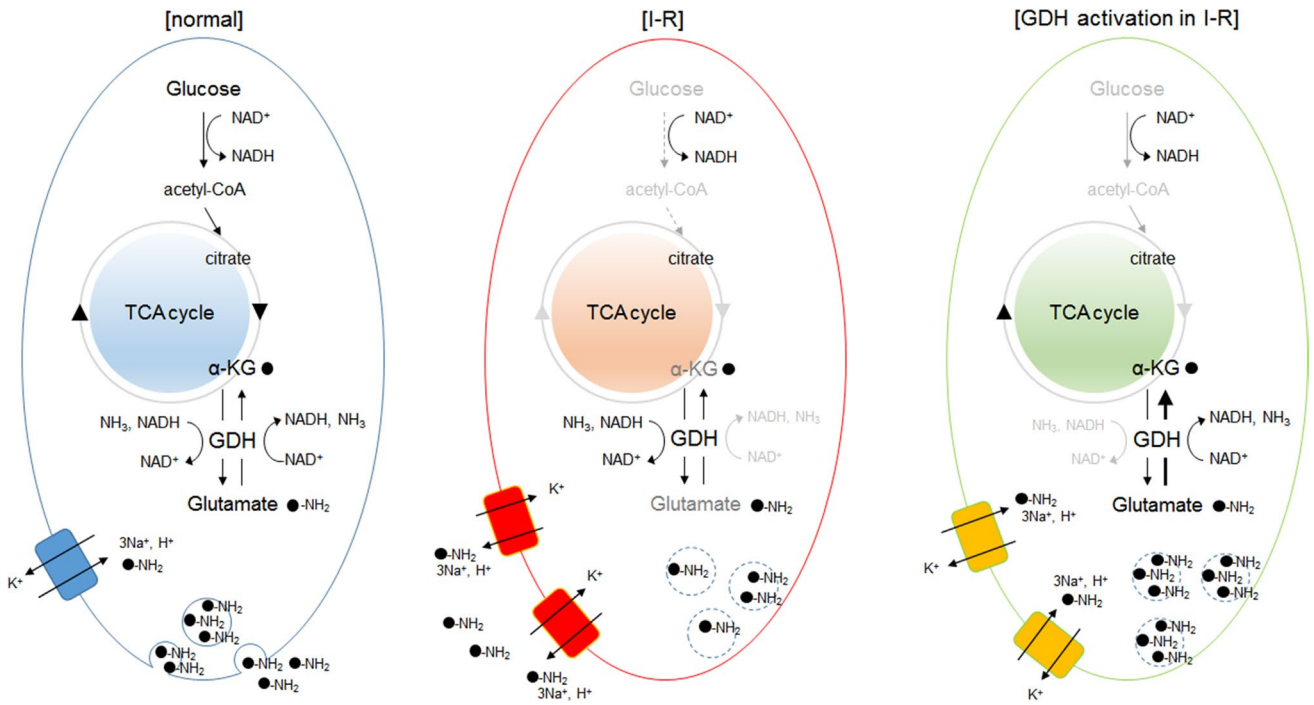

Fig. 1 Metabolic pathway in cerebral ischemia and reperfusion (I–R). During ischemia and reperfusion, when glucose availability is reduced, GDH cannot restore the depleted TCA cycle intermediates and ATP is reduced. Most glutamate in the cytoplasm is released by the glutamate transporter working in reverse mode. With GDH activators, glutamate metabolized to α-KG, which serves as an intermediate into the TCA cycle; simultaneously, extracellular glutamate release is reduced

reperfusion after ischemia, despite normal blood flow, glucose availability is reduced [84]. With energy depletion, the normal vesicular glutamate release is blocked, and glutamate is released from all over the cellular surface by glutamate-Na^+ co-transporter working in reverse mode [60]. Thus, intracellular glutamate is depleted, and extracellular glutamate is accumulated [1, 60]. The diminished intracellular glutamate cannot replenish the amount of TCA cycle intermediates by GDH-mediated conversion to α-KG. GDH activators can enhance the influx of glutamate into the TCA cycle, and can improve the intracellular energy production. These positive energy balance with glutamate catabolism can maintain the neuronal homeostasis with reducing extracellular glutamate release.

In conclusion, glutamate is an abundant, primary excitatory neurotransmitter in neurons. Glutamate also functions as an energy substrate via GDH in mitochondria. Dysregulation of glutamate metabolism is correlated with many neurological disorders. In energy-depleted conditions, enhanced GDH activation can rescue neurons from glutamate excitotoxicity and simultaneously maintain mitochondrial activity. Therefore, modulating GDH activity represents a promising therapeutic approach for protecting against neurodegeneration at least during acute stress crises.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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