Steady-state in Vivo Glutamate Dehydrogenase Activity in Rat Brain Measured by $^{15}$N NMR*

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The in vivo activity of glutamate dehydrogenase (GDH) in the direction of reductive amination was measured in rat brain at steady-state concentrations of brain ammonia and glutamate after intravenous infusion of the substrate $^{15}$NH$_4$$. The in vivo rate was determined from the steady-state fractional $^{15}$N enrichment of brain ammonia, measured by selective observation of $^{15}$NH$_4$ protons in brain extract by $^1$H-$^{15}$N heteronuclear multiple-quantum coherence transfer NMR, and the rate of increase of brain $^{[15]}$N-glutamate and $[2-{^{15}}N]$glutamine measured by $^{15}$N NMR. The in vivo GDH activity was 0.76–1.17 $\mu$/mol/h/g at a brain ammonia concentration of 0.87 ± 0.18 $\mu$/mol/g, and 1.1–1.2 $\mu$/mol/h/g at 1.0 ± 0.17 $\mu$/mol/g. Comparison of the observed in vivo GDH activity with the in vitro rates of glutamine synthesis and of phosphate-activated glutaminase suggests that, under mild hyperammonemia, GDH-catalyzed de novo synthesis can provide a minimum of 15% of the glutamate pool that is recycled from neurons to astrocytes through the glutamate-glutamine cycle.

Glutamate dehydrogenase (GDH)$^3$ catalyzes the reversible reaction below.

$$\text{NH}_3 + 2\text{-oxoglutarate} + \text{NAD}(P)H \rightleftharpoons \text{glutamate} + \text{NAD}(P)$$

**REACTION 1**

This mitochondrial enzyme is present at a high level in rat brain, with an in vitro activity of 900 $\mu$/mol/h/g (1). GDH is believed to contribute to the synthesis of the metabolic and neurotransmitter pools of glutamate. While glutamine is also an important precursor of the neurotransmitter glutamate (2-4), there is evidence to suggest that the glutamate-glutamine cycle is not operating in a stoichiometric manner (5), and some de novo synthesis of glutamate from glucose is required to maintain the neurotransmitter pool (5, 6). GDH is a likely candidate for this role, since the equilibrium of the reaction favors the formation of glutamate.

While GDH activities measured in cultured astrocytes and synaptosomal preparations have provided useful information (7-9), it is also important to measure the activity in intact brain, because the distribution of this enzyme according to cell type is controversial. Biochemical and histochemical studies show higher GDH levels in neurons (10–12), while immunocytochemical studies show highest GDH immunoreactivity in astrocytes (13) with only 15% reactivity in neurons (14). Moreover, a recent review of glutamate metabolism in mammalian brain (6) suggests that the rapid labeling of brain glutamate after intravenous injection of $^{15}$NH$_4$Cl (15, 16) and the slow labeling of brain glutamate after short term $^{15}$NH$_4$ or $^{13}$NH$_4$ infusion (17, 18) give conflicting pictures of the role of GDH in glutamate synthesis. The classical study by Berl et al. (17) on the $^{15}$N labeling of brain glutamate and glutamine in $^{13}$NH$_4$-infused cat led to the important concept of compartmentation of brain glutamate metabolism. A subsequent $^{15}$N study in normal rat brain (18) confirmed the labeling pattern. However, these short term (10–25 min) labeling experiments did not yield a rate for GDH-catalyzed glutamate synthesis. To our knowledge, measurement of steady-state in vivo GDH activity in mammalian brain has not been reported. We report here measurement of in vivo GDH activity in the direction of reductive amination at steady-state concentrations of brain ammonia and glutamate in rats given $^{15}$NH$_4$ infusion for 1–6 h, using $^{15}$N NMR in combination with biochemical techniques. $^{15}$N NMR was previously used for noninvasive monitoring of $^{15}$N-metabolites to determine in vivo glutamine synthetase (GS) (19) and phosphate-activated glutaminase (20) activities in rat brain. In the present study, after $^{15}$N enrichment in vivo, brain $^{[15]}$N-glutamate and $[2-{^{15}}N]$glutamine were quantified in vitro for better spectral resolution. The results are discussed in relation to the role of GDH in glutamate replenishment. An explanation is offered for the apparent discrepancy between results obtained with labeled glucose and ammonia on the role of GDH in glutamate synthesis.

**EXPERIMENTAL PROCEDURES**

Animal Preparation and Ammonia Infusion—Male Wistar rats (250–300 g) were anesthetized by the intraperitoneal injection of sodium pentobarbital (Nembutal; 40 mg/kg body weight), and prepared for ammonia infusion through the femoral vein (21). Two infusion protocols were used to achieve different steady-state brain ammonia concentrations for measurement of in vivo GDH activities. One group of rats (Group I) was given infusion of $^{15}$NH$_4$Cl (Cambridge Isotopes; $\geq$97% enriched in $^{15}$N in 1 m aqueous solution at pH 7.4) at a rate of 2.3 ± 0.04 $mmol/h/kg$ body weight. The infusion was continued (a) for the time indicated up to 6 h, or (b) for a fixed period of 3.1 ± 0.18 h, followed by $^{15}$NH$_4$Cl infusion at the same rate for ≤3.2 h (chase period). In Group II, $^{13}$NH$_4$Cl (2×) was infused at a rate of 3.3 ± 0.07 $mmol/h/kg$ for ≤6 h. In this group, ammonia concentration was increased to 2× to keep the infusion volume below 1 ml/h.

NMR—In vivo and in vitro $^{15}$N NMR spectra were obtained on a General Electric CSI-II spectrometer operating at 20.25 MHz for $^{15}$N, as described previously (19, 20). $^{13}$N chemical shifts are reported in ppm from nitromethane, with the negative sign indicating an upfield shift.
For in vitro study, the rat was sacrificed at the time indicated after \( ^{15} \text{NH}_4 \) infusion or \( ^{14} \text{NH}_4 \) chase. With the anesthetized rat still breathing, the cranium was opened by scissor dissection and the brain was removed in toto and rapidly frozen in liquid nitrogen for preparation of a perchloric acid extract, as described previously (21). This procedure takes \(<30 \text{ s}\) and is as fast as similar dissection-freezing methods (22, 23) because it has been shown to yield brain ammonia, glutamate, and glutamine concentrations that are in good agreement with those obtained by freeze-blowing (24). \( ^{15} \text{NH}_4 \) glutamate, \( ^{2-15} \text{N} \) glutamine, and \( ^{5-15} \text{N} \) glutamine in the brain extract were identified by \( ^{15} \text{N} \) NMR and quantified from the observed peak intensity (measured as integrated peak area) by comparison with those of standards, as described previously (20). The \( ^{15} \text{NH}_4 \) concentration in brain extract was measured by selective observation of the \( ^{15} \text{NH}_4 \) protons by \( ^1 \text{H} - ^{15} \text{N} \) heteronuclear multiple quantum coherence NMR at 200 MHz for \( ^1 \text{H} \) as described previously (20, 25), with the following modification. A sample volume of 3.7 ml was used to accommodate the entire brain extract (\(-4 \text{ ml}\) brain). To quantify brain \( ^{15} \text{NH}_4 \), a new standard curve was constructed by measuring the \( ^1 \text{H} \) peak intensities for 300, 500, and 700 nmol of \( ^{15} \text{NH}_4 \text{Cl} \) dissolved in 3.7 ml of unlabeled brain extract at pH 3.3. For quantification of brain \( ^{14} \text{NH}_4 \) and \( ^{2-15} \text{N} \) glutamate + glutamine, the brain extract prepared from a single rat was used in each experiment, for the number of rats indicated in Table I. For resolution of \( ^{15} \text{N} \) glutamate (\( ^{15} \text{N} \) Glu) and \( ^{2-15} \text{N} \) glutamate (\( ^{2-15} \text{N} \) Glu) at pH 9.1, the brain extract for each NMR experiment was prepared from a single rat (Group I), or pooled from 2 or 3 rats that were infused at the same rate for the same duration, to increase sensitivity (Group I). In the latter case, the number of separate experiments is shown in parentheses in Table I. The concentrations of total \( ^{14} \text{N} + ^{15} \text{N} \) ammonia, glutamate, and -glutamine in the brain extracts were measured enzymatically according to published procedures (26–28).

RESULTS

Rate of Increase of Brain \( ^{2-15} \text{N} \) Glu + Gln—Fig. 1A shows an in vivo \( ^{15} \text{N} \) NMR spectrum obtained from the head of an anesthetized rat after \( 3 \text{ h}\) of \( ^{15} \text{NH}_4 \) infusion at the rate of 2.3 mmol/h/kg weight. We have previously shown that the peaks for \( ^{5-15} \text{N} \) glutamine (\(-271 \text{ ppm}\)) and \( ^{2-15} \text{N} \) glutamate/glutamine (\(-342.1 \text{ ppm}\)) arise exclusively from the brain (29). Fig. 1B shows an \( ^{15} \text{N} \) NMR spectrum of the perchloric acid extract of the brain of a rat after \( 4.2 \text{ h}\) of \( ^{15} \text{NH}_4 \) infusion at the rate of 3.3 mmol/h/kg weight, and Fig. 1C shows the spectrum of an extract after \( 2.9 \text{ h}\) of infusion at the rate of 2.3 mmol/h/kg. In vivo and in extracts, at pH 7, the \( ^{15} \text{N} \) glutamate peak overlaps the \( ^{2-15} \text{N} \) glutamine peak at \(-342.1 \text{ ppm}\). The two peaks can be well resolved at pH 9.1, as described previously (20), and will be shown later in this work. However, for measurement of in vivo GDH activity, we need to monitor the increase, not only of brain \( ^{15} \text{N} \) glutamate but also of \( ^{2-15} \text{N} \) glutamine, because a substantial portion of the \( ^{15} \text{N} \) glutamate pool is subsequently converted to \( ^{2-15} \text{N} \) glutamine by GS. Hence, the concentrations of brain \( ^{2-15} \text{N} \) glutamate + \( ^{2-15} \text{N} \) glutamine (abbreviated hereafter to \( ^{2-15} \text{N} \) Glx) was determined from the observed peak intensity at \(-342.1 \text{ ppm}\) at various time points during the \( ^{15} \text{NH}_4 \) infusion. \( ^{15} \text{N} \) Aspartate (\(-343.5 \text{ ppm}\)) was easily resolved from \( ^{2-15} \text{N} \) Glx at pH 7 (20), was not detected.

Fig. 2 shows the progressive increase in the cerebral concentration of \( ^{2-15} \text{N} \) Glx in rats infused with \( ^{15} \text{NH}_4 \) at the rates of 2.3 and 3.3 mmol/h/kg weight (Groups I and II) for \(-6 \text{ h}\). Brain \( ^{2-15} \text{N} \) Glx increased linearly with time in both groups. From the slope of the least-squares line through the plots, the rate of increase was determined to be \( 0.295 \mu \text{mol/h per g}\) of brain for Group I and \( 0.50 \mu \text{mol/h per g}\) for Group II.

\( ^{15} \text{N} \) Enrichment of Brain Ammonia—Table I shows the concentration and the \( ^{15} \text{N} \) enrichment of brain ammonia and the concentration of brain glutamate \( ^{2-15} \text{N} + ^{15} \text{N} \) after \( 0.9, 2.4, \) and \( 4.3 \text{ h}\) of \( ^{15} \text{NH}_4 \) infusion for Group I. Clearly, during the observation period, the concentration and the \( ^{15} \text{N} \) enrichment of the substrate ammonia and the concentration of product glutamate were at steady state. The cerebral concentration of 2-oxoglutarate yields a positive nuclear Overhauser effect for these \( ^{15} \text{N} \) nuclei. A, an in vivo spectrum obtained from the head of an anesthetized rat after \( 3 \text{ h}\) of \( ^{15} \text{NH}_4 \) infusion at the rate of 2.3 mmol/h/kg weight. The peaks for \( ^{5-15} \text{N} \) glutamine (\(-271 \text{ ppm}\)) and \( ^{2-15} \text{N} \) glutamate/glutamine (\(-342.1 \text{ ppm}\)) arise exclusively from the brain (29).
through glutamine 5-N (catalyzed by GS) when 15N is chased by [2-14N]glutamate/glutamine. At brain glutamine levels observed in these rats, the effluxing metabolites consisted mainly of endogenous transamination from [15N]glutamate. However, the maximum activity in the direction of reductive amination in the brain was unaffected by acute or chronic hyperammonemia (30, 31), because deprotonation of -NH3+ to -NH2+ causes a 8 ppm upfield shift and pKw values differ for glutamate (9.6) and glutamine (8.9). From the concentrations of [15N]glutamate and [2-15N]glutamine determined by NMR and the total [14N]+[15N]glutamate and glutamine levels measured enzymatically, the 14N enrichments of brain glutamate and glutamine 2-N in Groups I and II were calculated and are listed in Table I. It was previously shown that total brain glutamine reaches steady-state levels of 8.5 ± 0.96 (Group I) and 9.8 ± 0.86 μmol/g (Group II) after 3–4 h of ammonia infusion (32). It is interesting that, after 3–4 h of 15NH4+ infusion, the 15N enrichment of brain glutamate is higher than that of glutamine 2-N.

**DISCUSSION**

Our results show that in vivo GDH activity in the direction of reductive amination in rat brain is 0.76–1.17 μmol/h/g at steady-state brain ammonia level of 0.87 ± 0.18 μmol/g, and 1.1–1.2 μmol/h/g at 1.0 ± 0.17 μmol/g. The low in vivo activity compared to the reported in vitro activity measured at enzyme-saturating concentrations of the substrates, 900 μmol/h/g (1), is most probably the result of the low in situ concentrations of ammonia and 2-oxoglutarate (0.23 ± 0.05 mM) (30, 31) relative to the Km values of the enzyme, 10–18 mM for NH2+ and 0.2–1.5 mM for 2-oxoglutarate (33, 34).

Carbon Versus Nitrogen Labeling—It has been suggested that the rapid labeling of brain glutamate after intravenous injection of [14C]glucose (15, 16, 35) and the slow labeling of brain glutamate after 15NH4+ or 13NH4+ administration (17, 18) lead to conflicting conclusions on the role of GDH in glutamate synthesis (6). In reality, both carbon and nitrogen labeling experiments are correct, but use of labeled ammonia leads to measurement of GDH activity while use of labeled glucose yields the rate of 2-oxoglutarate-glutamate exchange, as shown by Mason et al. (36, 37) using in vivo 13C NMR. This exchange is catalyzed by transaminases, including aspartate aminotransferase, as well as by GDH. Aspartate aminotransferase is present in the brain at a much higher level than GDH and is near equilibrium (38). Baláz and Haslam (39) showed that the rapid 14C labeling of brain glutamate from labeled glucose mainly reflects aspartate aminotransferase-catalyzed isotopic exchange between 2-oxoglutarate and glutamate. After intravenous injection of [14C]glucose, formation of [14C]glutamate from [14C]-2-oxoglutarate and [14N]aspartate, concomitant with the conversion of unlabeled glutamate to 2-oxoglutarate, results in rapid labeling of the glutamate pool until isotopic

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equilibrium is reached, without net glutamate synthesis (39). Labeling with ammonia, on the other hand, permits measurement of the rate of GDH-catalyzed glutamate synthesis from 2-oxoglutarate and ammonia.

Garfinkel (40) combined data from 14C-glucose labeling (15, 35, 41) and 15NH4+ labeling experiments (17) to calculate the rates of 104 reactions involved in the tricarboxylic acid cycle and amino acid metabolism. The rates were adjusted to provide the best overall fit to the reported specific isotopic enrichments of the brain metabolites, using a two-compartment brain model. The calculated aspartate aminotransferase activity was very high, 27–240 μmol/h/g, while GDH activity (reductive amination) was 1.08 μmol/h/g for the large compartment and 7.8 μmol/h/g for the small compartment. The large compartment was thought to contain 4–10 times as much of the metabolites as the small compartment. On that assumption, GDH activity for the whole brain is expected to be about 1.7–2.8 μmol/h/g, which is only slightly higher than the rate reported here. These considerations, together with the experimental result reported here, strongly suggest that in vivo GDH activity in the direction of reductive amination in rat brain is of the order of 1 μmol/h/g of brain.

Net Glutamate Synthesis by GDH—The GDH reaction is reversible and the whole-brain glutamate level is expected to be at steady state. It is important to consider whether (a) the observed GDH-catalyzed [15N]glutamate synthesis is offset by oxidative deamination of [14N]glutamate at an equal rate, resulting in no net GDH-catalyzed glutamate synthesis, or (b) there is net synthesis by GDH but glutamate is utilized by other pathways, such as GS (conversion to glutamine) and glutamate decarboxylase (conversion to GABA). The following considerations suggest that GDH-catalyzed glutamate catabolism is negligible in the brain. The equilibrium of GDH reaction favors glutamate formation, particularly in brain compartments with a low glutamate level such as astrocytes and GABAergic neurons (42). Glutamatergic neurons have a high glutamate level, but the highest concentration occurs in the presynaptic terminal where the transmitter glutamate pool is sequestered in vesicles (43). In neuronal perikarya, mitochondria do not show a gradient of glutamate-like reactivity over the cytoplasm (43). Neuronal GDH level, on the other hand, is highest in somatic zones and dendritic processes and lower in axon terminals (12). Hence, glutamate concentration at the site of GDH in mitochondria is probably not high enough to overcome the unfavorable equilibrium. Rat brain mitochondria incubated with 10 μM glutamate produced no detectable ammonia (44), while synaptosomal preparation incubated with [15N]glutamate produced 15NH4+ at the rate of only 0.2 mmol/mg protein in 30 min (9). In contrast, intact brain, 15NH4+ and 13NH4+ label GABA and glutamatergic ions (17, 18). These considerations strongly suggest that the GDH-catalyzed [15N]glutamate synthesis reported here reflects net synthesis, which can replenish the metabolic and neurotransmitter pools of glutamate.

Role of GDH in Glutamate Replenishment—The glutamate-glutamine cycle is not operating in a stoichiometric manner (5), and some de novo synthesis of glutamate from glucose is needed to maintain the neurotransmitter pool (5, 6). The relative contributions of glutamate synthesized de novo by GDH and of glutamine-derived glutamate to the pool can be estimated by comparing the observed in vivo GDH activity, 0.76–1.17 μmol/h/g, with the in vivo rate of glutamine synthesis and utilization, 3.3 ± 0.3 μmol/h/g, also measured under identical mildly hyperammonemic condition (32), and of phosphate-activated glutaminase, 1.1 ± 0.2 μmol/h/g (20). These in vivo rates show that glutamine is converted to glutamate in astrocytes at the rate of 3.3 ± 0.3 μmol/h/g. After migration to neurons, glutamine is reconverted to glutamate by phosphate-activated glutaminase at the rate of 1.1 ± 0.2 μmol/h/g. Amidotransfases involved in purine and pyrimidine synthesis also release glutamate from glutamine. The maximum possible rate of glutamate conversion to glutamine is the experimentally measured rate of total glutamine utilization, which, at steady state, is equal to the rate of glutamine synthesis (32). Hence the in vivo rate of glutamine conversion to glutamate is between 1.1 ± 0.2 μmol/h/g (phosphate-activated glutaminase) and 3.3 ± 0.3 μmol/h/g (total glutamine utilization rate). Comparison with the observed in vivo GDH activity shows that GDH-catalyzed de novo synthesis can provide at least 0.76/(0.76 + 3.3) × 100% = 19% of the glutamate pool that is recycled from neurons to astrocytes through the glutamate-glutamine cycle. Thus, the role of GDH in glutamate replenishment can be significant. The source of carbon for the GDH reaction is likely to be glucose, but the rate of net conversion of 2-oxoglutarate to glutamate cannot be significantly greater than that identified here for GDH.

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**TABLE I**

Tissue levels and 15N enrichments of brain metabolites and in vivo GDH activities in 15NH4+-infused rats

| NH4+ inf. rate | 15N (chase) | Ammonia | Glutamate | Glutamine | (2-15N)Glx/(5-15N)Gln | In vivo GDH activity |
|---------------|------------|---------|-----------|-----------|----------------------|---------------------|
|               | mmol/h/kg wt | h | h | μmol/g | % | μmol/g | % | μmol/g | % | 15N enrichment | % | 15N enrichment | % | 15N enrichment | % | % | μmol/h/g |
| 2.3           | 0.9        | 2.4 | 4.3 | 5.9 | 3.1 | 0 | 1.75 | 2.3 | 3.2 | 3.3 | 3.2 | 1.0 | ± 0.17 (3) | 43 ± 2 (2) | 9.0 | ± 0.21 (3) | 11 ± 1.6 (2) | 6.2 | ± 1 (2) | 8.8 | ± 0.1 (2) | 1.1–1.2 |
| 0.23(3)       | 39         | 43 | 37 | 4.3 | 3.3 | 0.12(4) | 43 | 9.0 | ± 0.21 (3) | 11 ± 1.6 (2) | 6.2 | ± 1 (2) | 8.8 | ± 0.1 (2) | 1.1–1.2 |

*The number of experiments is shown in parentheses (see “Experimental Procedures” for details).
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