Glutamine Metabolism: Nutritional and Clinical Significance

In Vivo Nuclear Magnetic Resonance Studies of Glutamate-γ-Aminobutyric Acid-Glutamine Cycling in Rodent and Human Cortex: the Central Role of Glutamine

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ABSTRACT It has been recognized for many years that the metabolism of brain glutamate and γ-aminobutyric acid (GABA), the major excitatory and inhibitory neurotransmitters, is linked to a substrate cycle between neurons and astrocytes involving glutamine. However, the quantitative significance of these fluxes in vivo was not known. Recent in vivo 13C and 15N NMR studies in rodents and 13C NMR in humans indicate that glutamine synthesis is substantial and that the total glutamate-GABA-glutamine cycling flux, necessary to replenish neurotransmitter glutamate and GABA, accounts for >80% of net glutamine synthesis. In studies of the rodent cortex, a linear relationship exists between the rate of glucose oxidation and total glutamate-GABA-glutamine cycling flux over a large range of cortical electrical activity. The molar stoichiometric relationship (~1:1) found between these fluxes suggests that they share a common mechanism and that the glutamate-GABA-glutamine cycle is coupled to a major fraction of cortical glucose utilization. Thus, glutamine appears to play a central role in the normal functional energetics of the cerebral cortex.


KEY WORDS: • glutamine • glutamate-glutamine cycle • neuron • astrocyte trafficking • NMR
• cerebral glucose utilization

In the central nervous system, glutamine synthesis occurs exclusively in the astroglia from glutamate and ammonia. Glutamine plays major roles in nitrogen and carbon homeostasis, in detoxification of ammonia and as a precursor for the synthesis of neurotransmitter glutamate and γ-aminobutyric acid (GABA) in specialized excitatory and inhibitory neurons. The existence of carbon cycles involving glutamate, GABA and glutamine have been recognized for nearly 30 years, although the quantitative significance of these pathways in relation to glucose metabolism and neuronal energetics is not known.


Until recently, the contribution of glutamate and GABA neurotransmitter cycling to glutamine synthesis was thought to represent a smaller fraction of its total synthesis, with the majority associated with ammonia detoxification. However, measurements of the fluxes of glutamine synthesis, glutamate-glutamine cycling and glucose oxidation in vivo using 13C NMR have revealed the glutamate-glutamine cycle to constitute a large flux, far greater than that associated with detoxification under physiologic conditions. Perhaps of greater significance, these studies provide evidence that the glutamate-glutamine neurotransmitter cycle and glucose utilization are functionally coupled. The new findings both support and extend a recent proposal in which glutamate release and its sodium-dependent uptake by astrocytes couples astroglial glucose utilization to glutamatergic neuronal activity (Pellerin and Magistretti 1994).

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Abbreviations used: CMRglu(ox), cerebral metabolic rate of glucose oxidation; EAAC, excitatory amino acid carrier; EAAT, excitatory amino acid transporter; EEG, electroencephalogram; GABA, γ-aminobutyric acid; GABA-T, GABA transaminase; GAT, GABA transporter; GDH, glutamate dehydrogenase; GLT, glutamate transporter; GS, glutamine synthetase; NMR, nuclear magnetic resonance; PAG, phosphate-activated glutaminase; PC, pyruvate carboxylase; PDH, pyruvate dehydrogenase; TCA, tricarboxylic acid cycle; Vco2, carbon dioxide fixation flux; Vcyclo, glutamate-glutamine cycle flux; Vglu, glutamine synthesis flux; VTCA, TCA cycle flux; Vamn, net ammonia transported out of the brain; Vamnt, glutamine synthesis flux; XEm, net ammonia transported into the brain.

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The present article describes the biochemical and molecular basis for the glutamate-GABA-glutamine cycle and evidence from recent in vivo $^{13}$C and $^{15}$N NMR studies conducted in our laboratory that this cycle plays a central role in brain glucose metabolism.

The glutamate-glutamine cycle: biochemical and molecular considerations

The metabolism of neurotransmitter glutamate and GABA is linked to a substrate cycle between neurons and astrocytes involving glutamate, GABA and glutamine (Martin 1995, Schousboe et al. 1993, Van den Berg 1972). The efficient functioning of the glutamate-glutamine cycle is made possible by the physical segregation of specific enzymes between neurons and glia and the presence of specialized amino acid transporter proteins. Glutamate and GABA released into the synapse in response to nerve terminal depolarization, bind to their respective receptors and are cleared from the interstitium by uptake into astroglia. Within astroglia, glutamate (and GABA through an indirect process) is converted to glutamine by the astroglia-specific enzyme, glutamine synthetase (GS) (Martinez-Hernandez et al. 1977). Glutamine is transported from astroglia into neurons and is hydrolyzed to glutamate by the mitochondrial enzyme, phosphate-activated glutaminase (PAG) (Kanamori and Ross 1995, Kvenmme and Lenda 1982). Thus, this pathway results in a cyclic flow of carbon between nerve terminals and glia, i.e., a glutamate-GABA-glutamine cycle. Some of the key molecular components required for the operation of this cycle are described below.

Specialized transporters clear interstitial glutamate and GABA during synaptic activity

Glutamate transport. The rapid clearance of transmitter glutamate from the synapse is accomplished by the $\mathrm{Na}^+\cdot\mathrm{K}^+\cdot\mathrm{Cl}^-$ dependent, high affinity, glutamate transporter proteins. Three glutamate transporters (GLT) have been identified in the cerebrum, the astroglial transporters, glutamate-aspartate transporter and GLT1 [or their human homologs, excitatory amino acid transporters (EAAT)1 and EAAT2, respectively], and the neuronal transporter, excitatory amino acid carrier (EAAC)1/EAAAT3 (Chaudhry et al. 1995, Kanai and Hediger 1992, Rothstein et al. 1994 and 1996). Two other neuronal transporters, EAAT4 and EAAT5, are expressed on cerebellar GABAergic Purkinje cells and in the retina, respectively, and appear to differ from their cortical counterparts in gating Cl$^-$ ions (Arriza et al. 1997, Fairman et al. 1995, Yamada et al. 1996). Although the functions of the neuronal transporters are not yet clear, one of them (EAAC1) is expressed on some GABAergic nerve terminals (Kanai and Hediger 1992, Rothstein et al. 1994 and 1996) where it may have a role in the supply of precursor glutamate for GABA synthesis (Sepkuty et al. 2000).

Evidence from molecular (Rothstein et al. 1996 and 1994) and electrophysiologic studies (Bergles and Jahr 1997 and 1998) indicates that the astroglial transporters clear the majority of glutamate from the synaptic cleft. As discussed subsequently, the molecular findings are consistent with in vivo NMR study results showing that glutamate uptake into astroglia and its conversion to glutamine is the predominant path for recycling of neuronal glutamate in vivo (Rothman et al. 1999).

Glutamate transport is electrogenic and driven by the electrochemical potential gradients of $\mathrm{Na}^+$, $\mathrm{K}^+$ and $\mathrm{H}^+$. Studies of the stoichiometry of GLT1 show glutamate uptake to be coupled to cotransport of 3 $\mathrm{Na}^+$ and 1 $\mathrm{H}^+$ and countertransport of 1 $\mathrm{K}^+$ (Levy et al. 1998). The cotransport of $\mathrm{Na}^+$ with glutamate has been reported to stimulate $\mathrm{Na}^+/\mathrm{K}^+$-ATPase and glucose utilization in cultured astrocytes (Pellerin and Magistretti 1994, Sokoloff et al. 1996). As explained below, an extension of this molecular mechanism has been proposed to explain the 1:1 flux stoichiometry discovered between cortical glucose oxidation and glutamate-glutamine cycling.

GABA transport. Astroglia and neurons possess a high capacity for the transport of GABA (Henn and Hamburger 1971, Hertz et al. 1978, Ryan and Roskoski 1977). Molecular cloning studies have identified four high affinity, $\mathrm{Na}^+$ and $\mathrm{Cl}^-$-dependent, GABA transporters (GAT) in the brain (GAT1, GAT2, GAT3, GAT4/BGT-1). With the exception of GAT-3, which is expressed on astrocytes, the other GAT subtypes are expressed on both neurons and astrocytes (Minelli et al. 1995 and 1996, Ribak et al. 1996). The functional roles of the different GABA transporter subtypes in the clearance of GABA from synaptic, and possibly extrasynaptic sites remain to be elucidated. Rapid metabolism of GABA in astrocytes via an active GABA-transaminase (Chan-Palay et al. 1979, Larsen and Schousboe 1990) maintains GABA at a low level in these cells, resulting in a large concentration gradient between GABAergic neurons and the surrounding transporter-rich astroglia. GABA synthesis depends on glutamine for its supply of glutamate precursors in vitro and in vivo (Balazs et al. 1973, Patel et al. 2000, Sonnewald et al. 1993, Van den Berg 1972) indicating that some fraction of GABA released from GABAergic neurons is not recycled directly back into the terminal. Thus, it appears likely that astroglial uptake could be as important for GABA as it is for glutamate.

Astroglial metabolism of extracellular glutamate and GABA stimulates glutamine synthesis. Glutamine synthesis in astroglia is generally considered the major net metabolic pathway for the metabolism of extracellular glutamate (Wainerski and Martin 1986). GABA metabolism in astroglia can also lead to glutamine synthesis. Unlike glutamate, however, GABA must be further processed in the astroglial tricarboxylic acid (TCA) cycle, a two-step reaction involving $\alpha$-ketoglutarate and NAD$^+$ that converts GABA to succinic acid via GABA-transaminase (GABA-T) and succinic semialdehyde dehydrogenase. The initial transamination between GABA and $\alpha$-ketoglutarate catalyzed by GABA-T produces gluta- mate, which may then proceed to formation of glutamine.

Glutamine is not the only pathway for the metabolism of extracellular glutamate in astroglia. Significant oxidation of extracellular glutamate was reported by Yu et al. (1982) in cultured astrocytes although McKenna et al. (1996) showed this process to be dependent on the concentration of extracellular glutamate. Net oxidation of glutamate and GABA can occur in astrocytes through the pyruvate recycling pathway, which involves malic enzyme (Cruz et al. 1998, Haberg et al. 1998, McKenna et al. 1995). In the study of McKenna et al. (1996), oxidation was significant for extracellular glutamate levels above $\sim 100$ $\mu$mol/L, which is far greater than estimated normal levels (Levy et al. 1998), and within the range considered to be excitotoxic (Choi et al. 1987). Thus, glutamate oxidation may be of pathophysiologic significance when neuronal release exceeds uptake (e.g., ischemia or epileptic seizures). Evidence for oxidation of glutamate and GABA after transient ischemia in vivo has been reported (Pasqual et al. 1991). Pyruvate recycling and malic enzyme may play an important role in the generation of NADPH to maintain reduced glutathione (Vogel et al. 1999), which is highly concentrated in astroglia. Glutathione has been shown to protect glia against free radical damage associated with...
Glutamine transporters mediate the flow of glutamine from astrocytes to neurons

Glutamine produced from exogenous glutamate is readily released by cultured astrocytes (Wanienski and Martin 1986) where it serves as a major precursor of the releasable pool of glutamate and GABA in nerve terminal preparations (Sonnewald et al. 1993, Szerb and O’Regan 1983). Until recently, little was known specifically about glutamine transport in neurons and glia. Cloning studies have begun to reveal the molecular properties of the major glutamine transporters expressed in brain cells. Specific Na+- and H+-dependent astroglial [SN1; (Chaudhry et al. 1999) and ASC1T2; (Broer et al. 1999)] and neuronal [GlnT/SAT1 and SAT2; (Varoqui et al. 2000), (Yao et al. 2000)] glutamine transporters have been described with differing substrate dependencies. Differences reported in the kinetic properties between the specific glutamine transporters favor the efflux of glutamine from astroglia and its influx into neurons, providing for efficient operation of the glutamate-glutamine cycle.

Glutamine is a precursor for the resynthesis of neuronal glutamate and GABA. Mature neurons do not contain the necessary anaplerotic enzymes to resynthesize glutamate and GABA lost during neurotransmission and depend on astrocytes to supply the needed carbon (Cooper and Plum 1987, Kaufman and Driscoll 1993, Martin 1995). Phosphate-activated glutaminase (PAG) is a mitochondrial enzyme, present mainly in neurons but also reported in glia (Hogstad et al. 1988, Wiesinger 1995), which converts glutamine to glutamate and ammonia. Highly enriched in glutamatergic and GABAergic neurons, PAG provides an important pathway to replenish neurotransmitter stores of glutamate and GABA in nerve terminal preparations (Sonnewald et al. 1993, Wanienski and Martin 1986, Ward et al. 1983). Application of 6-diazo-5-oxo-L-norleucine, a potent and selective inhibitor of PAG, to the rat cortex in vivo results in a rapid (<30 min) but reversible loss of glutamate immunostaining in pyramidal cell bodies and dendrites, which returns over the course of several days (Conti and Minelli 1994). In vitro studies have shown that in addition to glutamine, malate and α-ketoglutarate may serve as carbon sources for repletion of neuronal glutamate and GABA (Peng et al. 1993, Shank and Campbell 1984). However, as described subsequently, results of in vivo NMR studies of the rat and human cortex suggest that glutamine is the major precursor of neuronal glutamate and possibly GABA as well.

In vivo NMR studies of the role of glutamine in the glutamate-glutamine cycle

Although there is little disagreement about the existence of the glutamate-glutamine cycle, the significance of this cycle in relation to brain energetics and function has been controversial due mainly to the paucity of quantitative flux information. The development of quantitative noninvasive NMR techniques to measure the fluxes associated with brain glucose and glutamate metabolism has begun to fill this knowledge gap and in the process reveal new insights into the coupling between metabolism and function. As described subsequently, research findings from our laboratory using in vivo 13C and 15N NMR suggest that in the cerebral cortex, the glutamate-GABA-glutamine cycle is a major flux and it is tightly coupled to the oxidation of glucose.

Development of a quantitative approach to interpret glutamate metabolism in terms of glutamate neurotransmitter cycling and de novo (anaplerotic) synthesis

Glutamine synthesis in astroglia reflects the sum of the fluxes of glutamate (and GABA) neurotransmitter cycling and de novo glutamine synthesis to fix excess ammonia in the process of ammonia detoxification. As shown in a diagram depicting these flows (Fig. 1), unique determination of the glutamate-glutamine cycling flux requires knowledge of the rate of de novo glutamine synthesis, which is related to the anaplerotic flux. Employing a constrained kinetic model of glutamate-glutamine cycling (Shen et al. 1998, Silson et al. 1997 and 1998b) in which carbon and nitrogen are balanced.

**FIGURE 1** Schematic representation of the glutamate-glutamine cycle between neurons and astrocytes. (A) Depiction of glutamine synthesis from glutamate neurotransmitter cycling only. Glutamate is released from neurons and is transported into astrocytes at the rate, V cycle, and combines with ammonia to form glutamine at the rate, V gln. Glutamine is released from the astrocyte and transported into neurons at the rate, V cycle, and is hydrolyzed to glutamate completing the cycle. (B) Deposition of glutamine synthesis as the sum of glutamate neurotransmitter cycling and ammonia detoxification. Same as in (A) but now includes the rates of net ammonia transport into the astrocytes from blood (V ame) and anaplerotic glutamine synthesis (V anap) from glucose (Glc). Solution of the differential equations describing these flows at steady state constrained by mass and isotope balance as described in the text permits the individual fluxes to be determined. An alternate model involving the cycling of α-ketoglutarate (not shown) was found to be incompatible with enrichment time courses obtained from [2-13C]glucose (Sibson et al. 2001). [From Silson et al. (1998b), with permission from S. Karger AG, Basel, Switzerland.]
acetate in rats, a metabolic steady state can be achieved in the metabolic model. After a prolonged infusion of ammonium can be used to test the validity of relationships predicted by the appropriate experimental conditions, hyperammonemia brain during hyperammonemia (Cooper and Plum 1987). Untamine synthesis using [2-13C] glucose have confirmed the Waelsch et al. 1964).

\[ V_{\text{ana}} = V_{\text{efflux}} = V_{\text{CO2}} = (0.5 \text{ to } 1) V_{\text{trans}} \quad (1) \]

\[ V_{\text{glu}} = V_{\text{cycle}} + [(0.5 \text{ to } 1) V_{\text{trans}} = V_{\text{ana}} = V_{\text{CO2}} = V_{\text{efflux}} \quad (2) \]

Thus, \( V_{\text{cycle}} \) can be derived from a measurement of glutamine synthesis if one of the other fluxes is either known or can be measured.

**Measurements of glutamine synthesis during hyper- and normoammonemia: experimental validation of a model of glutamate-glutamine cycling**

*In vivo 13C NMR measurements using [1-13C] and [2-13C]glucose.* Glutamine levels increase throughout the brain during hyperammonemia (Cooper and Plum 1987). Under appropriate experimental conditions, hyperammonemia can be used to test the validity of relationships predicted by the metabolic model. After a prolonged infusion of ammonium acetate in rats, a metabolic steady state can be achieved in which the glutamine level and rate of synthesis (\( V_{\text{glu}} \)), although elevated, remain constant. In the absence of changes in \( V_{\text{cycle}} \) the increase in \( V_{\text{glu}} \) with hyperammonemia would be predicted by Equation (2) to equal the increase in de novo (anaplerotic) glutamine synthesis (\( V_{\text{ana}} \)) and glutamine efflux (\( V_{\text{efflux}} \)).

Steady-state values of \( V_{\text{glu}} \) were determined for the cortex of hyperammonemic and control rats using 13C NMR (Sibson et al. 1997). The enrichment time courses of glutamate and glutamine labeling in the rat cortex during an intravenous infusion of [1-13C]glucose in anesthetized control and hyperammonemic rats. A steady-state hyperammonemic condition (constant and elevated levels of blood ammonia and brain glutamine) was established in the blood before the labeled isotope infusion began. (From Sibson et al. 1997, Copyright 1997 National Academy of Sciences, U.S.A., with permission.)

**FIGURE 2** In vivo 13C nuclear magnetic resonance (NMR) time courses of glutamate and glutamine labeling in the rat cortex during an intravenous infusion of [1-13C]glucose in anesthetized control and hyperammonemic rats. A steady-state hyperammonemic condition (constant and elevated levels of blood ammonia and brain glutamine) was established in the blood before the labeled isotope infusion began. (From Sibson et al. 1997, Copyright 1997 National Academy of Sciences, U.S.A., with permission.)

Measurements of the contribution of anaplerosis to glutamine synthesis using [2-13C] glucose have confirmed the essential features of the glutamate-glutamine cycling model. [2-13C] glucose is metabolized to [2-13C]pyruvate by the glycolytic pathway of neurons and astroglia. Entry of [2-13C] pyruvate into the TCA cycle via pyruvate dehydrogenase (PDH) leads to the labeling of glutamate C5 and loss of the label as CO2. In addition to PDH, astroglia possess an alternate pathway for the metabolism of pyruvate. In these cells [2-13C] pyruvate may enter the astroglial TCA cycle through CO2 fixation catalyzed by pyruvate carboxylase, resulting in labeling of C3, C2 and C1 of astroglial glutamate and glutamine. The steady-state rates of anaplerotic glutamine synthesis (\( V_{\text{ana}} \)) and glutamate-glutamine neurotransmitter cycling (\( V_{\text{cycle}} \)) during hyperammonemia were determined from the best fit of the metabolic model to the time courses of C3 and C2 isotopic labeling of glutamine and glutamate. The close correspondence between the predicted \([0.1 \mu mol/(g \cdot min)]\) and measured \([0.09 – 0.10 \mu mol/(g \cdot min)]\) values of \( V_{\text{ana}} \) and the measured values of \( V_{\text{cycle}} \) using either [1-13C]glucose or [2-13C]glucose (Sibson et al. 2001) lends strong support for the current metabolic model. During hyperammonemia, anaplerosis contributed ~32% of the glutamine synthesis flux but only 17–23% under physiologic conditions in the cortex of anesthetized adult rats (Sibson et al. 2001). Thus, \( V_{\text{cycle}} \) represents the larger component of glutamine synthesis. Quantitation of glutamate and glutamine fluxes in the conscious human occipital cortex after infusions of [1-13C]glucose (Shen et al. 1999) and more recently, [2-13C]glucose (Mason et al. 2000), indicates that \( V_{\text{cycle}} \) constitutes the major fraction (80–90%) of total glutamine synthesis. In contrast to the results cited above, Grutter et al. (1998) reported a somewhat higher value of anaplerosis in human brain, although \( V_{\text{cycle}} \)
still accounted for a majority (70–85%) of glutamine synthesis.

In vivo $^{15}$N NMR measurements of acute hyperammonemia. Nitrogen metabolism can be assessed directly in the brain using $^{15}$N-labeled substrates and $^{15}$N NMR in vitro and in vivo (Kanamori and Ross 1993 and 1995, Shen et al. 1998). Incorporation of $^{15}$N-labeled ammonia into glutamine $N_5$ is a direct measure of the flux through glutamine synthetase, whereas isotopic labeling of (glutamate $+\,$glutamine) $N_2$ reflects sequential flow through glutamate dehydrogenase (GDH) and GS. The flux of ammonia transported into the brain and fixed as glutamine ($V_{\text{trans}}$) was estimated from the sum of $^{15}$N labeling of $N_5$ (glutamine) and $N_2$ (glutamate $+\,$glutamine), which represented the major $^{15}$N-labeled resonances detected in the spectra (Fig. 3). The ammonia transport flux determined in the $^{15}$N NMR experiment, $V_{\text{trans}} = 0.13 \pm 0.02 \, \mu$mol/(g·min), may be related to anaplerotic glutamine synthesis through the 1:2 stoichiometric relationship of their fluxes (i.e., $\Delta V_{\text{trans}} = 0.5 \, \Delta V_{\text{trans}}$). The value reported for $V_{\text{trans}}$ of 0.065 $\mu$mol/(g·min) is somewhat lower than that given in the [2-$^{13}$C]glucose experiment and can be ascribed to the observed delay ($\sim 1$ h) in the labeling of glutamine $N_2$ compared with $N_5$ (Shen et al. 1998). This lag may reflect either a delay in the stimulation of anaplerosis and/or an inflow of unlabeled $N_2$ nitrogen from transamination with branched-chain amino acids (Yudkoff 1997). A close correspondence was found between the initial rate of glutamine synthesis (when anaplerosis flux is low) during acute hyperammonemia using $^{15}$N NMR ($0.20 \pm 0.06 \, \mu$mol/(g·min); Shen et al. 1998) and $^{13}$C NMR using [1-$^{13}$C]glucose [0.21 $\pm 0.04 \, \mu$mol/(g·min); Sibson et al. 1997]. Thus, the results of the nonsteady-state $^{15}$N NMR study indicate that even under conditions of acute hyperammonemia, anaplerosis represents a smaller fraction (in this case, approximately one third) of total glutamine synthesis with the larger fraction (approximately two thirds) contributed by glutamate neurotransmitter recycling. Under normal physiologic conditions in which blood ammonia levels are low, glutamate neurotransmitter recycling represents >80% of glutamine synthesis.

The rate of glutamine synthesis is proportional to electrical and metabolic activity supporting a direct link to function.

The glutamate-glutamine cycling flux in rat (Sibson et al. 1997 and 2001) and human (Grieter et al. 1998, Shen et al. 1999) cortex is comparable in magnitude (~80%) to the corresponding rate of neuronal glucose oxidation and between 60 and 80% of total cerebral glucose oxidation. Because oxygen and glucose utilization rates (Hyder et al. 1996, Siesjo 1978, Sokoloff 1993) depend on neuronal activity, it follows that the glutamine synthesis rate should also depend on glucose oxidation rate to the extent that the former reflects glutamate-glutamine neurotransmitter cycling. Employing various anesthetic agents to produce different states of cortical electroencephalogram (EEG) activity and metabolism, Sibson et al. (1998a) measured the rates of cortical glucose oxidation and glutamate-glutamine cycling using $^{13}$C NMR and [1-$^{13}$C]glucose. Glutamate and glutamine isotopic turnovers were strongly dependent on cortical activity as reflected in the EEG. A plot of $V_{\text{cycle}}$ against glucose oxidation [CMR$_{\text{glu(ox)}}$] reveals a linear relationship with slope ~1.0 and y-intercept (where $V_{\text{cycle}} = 0$ and the cortex is electrically silent) of 0.1 $\mu$mol/(g·min) (Fig. 4). The rate of glutamine synthesis (and $V_{\text{cycle}}$) during EEG silence induced by high dose pentobarbital approaches the calculated theoretical value of NH$_3$ transport into the brain [see discussion in Sibson et al. (1998b)]. The results suggest that >80% of neuronal glucose oxidation in the cerebral cortex is associated with the glutamate-glutamine cycle and neuronal activity.

A possible explanation for these findings comes from studies of glutamate transport in cultured astrocytes. Glutamate uptake in cultured astrocytes has been shown to stimulate glucose utilization and lactate release in conjunction with the Na$^+$-dependent activation of the plasma membrane Na$^+$/$\mathrm{K}^+$-ATPase (Pellerin and Magistretti 1994, Sokoloff et al. 1996, Tsacopoulos and Magistretti 1996). On the basis of this evidence, Magistretti and co-workers proposed that “functional” glutamate uptake occurs mainly in the astroglia in response to uptake of glutamate released from neurons and that lactic acid produced in the astroglia is transported to the neurons where it is oxidized. The flux stoichiometry between glucose oxidation...
produced by astroglial glycolysis fuels glutamate uptake. The model proposed by Magistretti and co-workers in which ATP strongly suggesting that these processes are coupled. The measurement of pentobarbital (120 mg/kg, isoelectric EEG), electroencephalogram (EEG) activities were determined under conditions of pentobarbital (120 mg/kg, isoelectric EEG), α-chloralose (90 mg/kg, large amplitude EEG with slow waves), and morphine (50 mg/kg, faster desynchronized EEG rhythm). [From Sibson et al. (1998a), Copyright 1998 National Academy of Sciences, U.S.A., with permission.]

The relationship between the rates of glutamate-glutamine cycling (Vcycle) and glucose oxidation (CMRglu) is linear over a wide range of electrocortic activity in the rat cortex in vivo. Fluxes and electrencephalogram (EEG) activities were determined under conditions of pentobarbital (120 mg/kg, isoelectric EEG), α-chloralose (90 mg/kg, large amplitude EEG with slow waves), and morphine (50 mg/kg, faster desynchronized EEG rhythm). [From Sibson et al. (1998a), Copyright 1998 National Academy of Sciences, U.S.A., with permission.]

Vcycle [μmol/(min·g)]

CMRglu(ox) (μmol/min/g) = 1.04(Vcycle) + 0.10

FIGURE 4 The relationship between the rates of glutamate-glutamine cycling (Vcycle) and glucose oxidation (CMRglu) is linear over a wide range of electrocortic activity in the rat cortex in vivo. Fluxes and electrencephalogram (EEG) activities were determined under conditions of pentobarbital (120 mg/kg, isoelectric EEG), α-chloralose (90 mg/kg, large amplitude EEG with slow waves), and morphine (50 mg/kg, faster desynchronized EEG rhythm). [From Sibson et al. (1998a), Copyright 1998 National Academy of Sciences, U.S.A., with permission.]


