Supporting Text

1. Derivation of the flux ratios (V_{cyc}/V_{TCAn} based on steady-state labeling from [2-^{13}C]acetate

The metabolism of [2-^{13}C]acetate is depicted in Fig. 5. [2-^{13}C]Acetate is metabolized exclusively in glial cells to $AcCo_aC2$, followed by its oxidation in the glial TCA cycle leading to ^{13}C labeling of α-ketoglutarate. The ^{13}C label is transferred into cytosolic glutamate-C4 after exchange with mitochondrial α-ketoglutarate-C4 and converted to glutamine-C4 by glutamine synthetase. Glutamine-C4 is released by astroglia and metabolized by neurons to glutamate-C4 (Fig. 5*A*). In GABAergic neurons, glutamate-C4 is decarboxylated to GABA-C2 (Fig. 5*B*). Glutamine-C2/C3 and glutamate-C2/C3 carbons are labeled during subsequent turns of the TCA cycle.

A. Derivation of $V_{cyc(Glu/Gln)}]/V_{TCA(Glu)}$ for glutamatergic neurons

The dynamic ^{13}C labeling of Gln and Glu in astroglia and glutamatergic neurons can be described by the following equations:

$$d[Gln_{Glu4}^{*}]/dt = V_{cyc(Gln/Glu)}\, Gln_{a4} - V_{cyc(Gln/Glu)}\, Gln_{Glu4} \qquad [\mathbf{1}]$$

$$d[Glu_{Glu4}^{*}]/dt = V_{cyc(Gln/Glu)}\, Gln_{Glu\text{-}4} - (V_{cyc(Glu/Gln)} + V_{TCA(Glu)})\, Glu_{Glu4}, \qquad [\mathbf{2}]$$

where Glx_{i4} represents percent ^{13}C enrichment of glutamate or glutamine at carbon 4 in glutamatergic neurons (Glu) or astroglia (a), and $V_{cyc(Glu/Gln)} = V_{cyc(Gln/Glu)}$.

At isotopic steady state, Eq. **1** becomes

$$V_{cyc(Glu/Gln)}\, Gln_{a4} - V_{cyc(Gln/Glu)}\, Gln_{Glu4 = 0}$$

which leads to $Gln_{Glu4 =} Gln_{a4}$. [**3**]

Similarly, at isotopic steady state, Eq. **2** becomes

$$V_{cyc(Gln/Glu)}\, Gln_{Glu4 -} (V_{cyc(Glu/Gln)} + V_{TCA(Glu)})\, Glu_{Glu4} = 0.$$

For $V_{cyc(Glu/Gln)} = V_{cyc(Gln/Glu)}$,

it leads to

$$V_{cyc(Glu/Gln)}/V_{TCA(Glu)} = Glu_{Glu4}/(Gln_{Glu4} - Glu_{Glu4}). \qquad [\mathbf{4}]$$

Substituting the value of Gln_{Glu4} from Eq. **3** gives

$$V_{cyc(Glu/Gln)}/V_{TCA(Glu)} = Glu_{Glu4}/(Gln_{a4} - Glu_{Glu4}). \qquad [\mathbf{5}]$$

B. Derivation of $V_{cyc(GABA/Gln)}/V_{TCA(GABA)}$ for GABAergic neurons

The dynamic ^{13}C labeling of Gln and Glu in GABAergic neurons can be described by the following equations:

$d[Glu_{Gaba4}^{*}]/dt = V_{cyc(Gln/Gaba)}\ Gln_{a4} - (V_{TCA(Gaba)Net} + V_{GAD})\ Glu_{Gaba4}$, [**6**]

where $Gln_{Gaba4} = Gln_{a4}$ from Eq. **3** for glutamatergic neurons.

$d[GABA_{Gaba2}^{*}]/dt = V_{GAD}\ Glu_{Gaba4} - (V_{cyc(Gaba/Gln)} + V_{shunt})\ GABA_{Gaba2}$, [**7**]

where $V_{TCA(Gaba)} = V_{TCA(Gaba)Net} + V_{shunt}$ [**8**]

and $V_{GAD} = V_{cyc(Gaba/Gln)} + V_{shunt}$, [**9**]

and where Glu_{Gaba4} and $GABA_{Gaba2}$ represents the percent ^{13}C enrichment of glutamate-C4 and GABA-C2 in GABAergic neurons, and $V_{cyc(Gaba/Gln)} = V_{cyc(Gln/Gaba)}$.

At isotopic steady state, Eq. **6** becomes:

$V_{cyc(Gln/Gaba)}\ Gln_{a4} - (V_{TCA(Gaba)Net} + V_{GAD})\ Glu_{Gaba4} = 0$.

Therefore, $Glu_{Gaba4} = V_{cyc(Gln/Gaba)}\ Gln_{a4}/(V_{TCA(Gaba)Net} + V_{GAD})$. [**10**]

Similarly, at isotopic steady state, Eq. **7** becomes:

$V_{GAD}\ Glu_{Gaba4} - (V_{cyc(Gaba/Gln)} + V_{shunt})\ GABA_{Gaba2} = 0$.

Substituting $V_{cyc(Gaba/Gln)} + V_{shunt}$ and Glu_{Gaba4} from Eqs. **8** and **9**, respectively, gives:

$V_{GAD}\ V_{cyc(Gln/Gaba)}\ Gln_{a4}/(V_{TCA(Gaba)Net} + V_{GAD}) - V_{GAD}\ GABA_{Gaba2} = 0$,

which is equivalent to

$V_{cyc(Gln/Gaba)}\ Gln_{a4} = (V_{TCA(Gaba)Net} + V_{GAD})\ GABA_{Gaba2}$.

Substituting $V_{TCA(Gaba)Net}$ and V_{GAD} from Eqs. **8** and **9**, respectively,

$V_{cyc(Gaba/Gln)}\ Gln_{a4} = (V_{TCA(Gaba)} - V_{shunt} + V_{cyc(Gaba/Gln)} + V_{shunt})\ Gaba_{Gaba2}$,

which after rearrangement gives

$V_{cyc(Gaba/Gln)}/V_{TCA(Gaba)} = Gaba_{Gaba2}/(Gln_{a4} - Gaba_{Gaba2})$. [**11**]

2. Differential equations describing the three-compartment metabolic model (Fig. 1)

Mass balance equations

$d[Glc_{brain}]/dt = Vmax_{in}\ Glc_{blood}/(Km_{in} + Glc_{blood}) - Vmax_{out}\ Glc_{brain}/(Km_{out} + Glc_{brain}) - CMR_{glc} = 0$

$d[L]/dt = 2\ CMR_{glc} + V_{dilLac(influx)} - (V_{PC} + V_{dilLac(eflux)} + V_{pdh(a)} + V_{pdh(Gaba)} + V_{pdh(Glu)}) = 0$

$d[Asp_{a}]/dt = V_{xa(OAA/Asp)} - V_{xa(Asp/OAA)} = 0$

$d[Glu_{a}]/dt = V_{cyc(Glu/Gln)} + V_{xa(KG/Glu)} + V_{cyc(Gaba/Gln)} - (V_{Gln} + V_{xa(Glu/KG)}) = 0$

$d[KG_a]/dt = V_{pdh(a)} + V_{xa(Glu/KG)} + V_{dil(a)} – (V_{TCA(a)Net} + V_{xa(KG/Glu)} + V_{cyc(Gaba/Gln)}) = 0$

$d[OAA_a]/dt = V_{TCA(a)Net} + V_{xa(Asp/OAA)} + V_{PC} + V_{cyc(Gaba/Gln)} – (V_{xa(OAA/Asp)} + V_{TCA(a)}) = 0$

$d[Gln]/dt = V_{Gln} + V_{dilGln} – (V_{Gln(efflux)} + V_{cyc(Glu/Gln)} + V_{cyc(Gaba/Gln)}) = 0$

$d[Asp_{Gaba}]/dt = V_{xaGaba(OAA/Asp)} – V_{xGaba(Asp/OAA)} = 0$

$d[GABA_{Gaba}]/dt = V_{GAD} – (V_{shunt} + V_{cyc(Gln/Gaba)}) = 0$

$d[Glu_{Gaba}]/dt = V_{cyc(Gln/Gaba)} + V_{xGaba(KG/Glu)} – (V_{GAD} + V_{xGaba(Glu/KG)}) = 0$

$d[KG_{Gaba}]/dt = V_{pdh(Gaba)} + V_{xGaba(Glu/KG)} + V_{dil(Gaba)} – (V_{TCA(Gaba)Net} + V_{xGaba(KG/Glu)}) = 0$

$d[OAA_{Gaba}]/dt = V_{TCA(Gaba)Net} + V_{shunt} + V_{xGaba(Asp/OAA)} – (V_{TCA(Gaba)} + V_{xGaba(OAA/Asp)}) = 0$

$d[Asp_{Glu}]/dt = V_{xGlu(OAA/Asp)} – V_{xGlu(Asp/OAA)} = 0$

$d[Glu_{Glu}]/dt = V_{cyc(Glu/Gln)} + V_{xGlu(KG/Glu)} – (V_{cyc(Glu/Gln)} + V_{xGlu(Glu/KG)}) = 0$

$d[KG_{Glu}]/dt = V_{xGlu(Glu/KG)} + V_{dil(Glu)} + V_{pdh(Glu)} – (V_{xGlu(KG/Glu)} + V_{TCA(Glu)}) = 0$

$d[OAA_{Glu}]/dt = V_{xGlu(Asp/OAA)} + V_{TCA(Glu)} – (V_{xGlu(OAA/Asp)} + V_{TCA(Glu)}) = 0$

Isotope balance equations

$d[Glc_{brain,16}^*]/dt = Vmax_{in}\ Glc_{blood,16}/(Km_{in} + Glc_{blood}) – Vmax_{out}\ Glc_{brain,16}/(Km_{out} + Glc_{brain}) – CMR_{glc}\ (Glc_{brain,16}/Glc_{brain})$

$d[L_3^*]/dt = CMR_{glc}\ (Glc_{brain,16}/Glc_{brain}) + V_{dilLac(influx)}\ (0) – (V_{PC} + V_{dilLac(efflux)} + V_{pdh(a)} + V_{pdh(Gaba)} + V_{pdh(Glu)})\ (L_3/L)$

$d[Asp_{a2}^*]/dt = V_{xa(OAA/Asp)}\ (OAA_{a2}^* /OAA_a) – V_{xa(Asp/OAA)}\ (Asp_{a2}^* /Asp_a)$

$d[Asp_{a3}^*]/dt = V_{xa(OAA/Asp)}\ (OAA_{a3}^* /OAA_a) – V_{xa(Asp/OAA)}\ (Asp_{a3}^* /Asp_a)$

$d[Glu_{a3}^*]/dt = V_{xa(KG/Glu)}\ (KG_{a3}^* / KG_a) + V_{cyc(Glu/Gln)}\ (Glu_{Glu3}^* /Glu_{Glu}) + V_{cyc(Gaba/Gln)}\ (KG_{a3}^*/KG_a) – (V_{Gln} + V_{xa(Glu/KG)})\ (Glu_{a3}^* /Glu_a)$

$d[Glu_{a4}^*]/dt = V_{cyc(Glu/Gln)}\ (Glu^*_{Glu4}/Glu_{Glu}) + V_{xa(KG/Glu)}\ (KG_{a4}^* /KG_a) + V_{cyc(Gaba/Gln)}\ (KG^*_{a4}/KG_a) – (V_{Gln} + V_{xa(Glu/KG)})\ (Glu^*_{a4}/Glu_a)$

$d[KG_{a3}^*]/dt = V_{xa(Glu/KG)}\ (Glu_{a3}^* /Glu_a) + V_{TCA(a)}\ (OAA_{a2}^* /OAA_a) - (V_{TCA(a)Net} + V_{xa(KG/Glu)} + V_{cyc(Gaba/Gln)})\ (KG_{a3}^* /KG_a)$

$d[KG_{a4}^{*}]/dt = V_{pdh(a)} (L_3^{*} / L) + V_{xa(Glu/KG)} (Glu^{*}_{a4}/Glu_a) + V_{dil(a)} (0) – (V_{TCA(a)Net} + V_{xa(KG/Glu)} + V_{cyc(Gaba/Gln)}) (KG^{*}_{a4}/KG_a)$

$d[OAA_{a2}^{*}]/dt = 0.5\ V_{TCA(a)Net} ((KG_{a4}^{*} /KG_a) + (KG_{a3}^{*} /KG_a)) + V_{xa(Asp/OAA)} (Asp_{a2}^{*} /Asp_a) + 0.5\ V_{PC} (L_3^{*} /L) + V_{cyc(Gaba/Gln)} (GABA_{Gaba2}/GABA_{Gaba}) – (V_{xa(OAA/Asp)} + V_{TCA(a)}) (OAA_{a2}^{*} /OAA_a)$

$d[OAA_{a3}^{*}]/dt = V_{cyc(Gaba/Gln)} (GABA_{Gaba3}^{*}/GABA_{Gaba}) + V_{xa(Asp/OAA)} (Asp_{a3}^{*} /Asp_a) + 0.5\ V_{PC} (L_3^{*} /L) + 0.5\ V_{TCA(a)Net} ((KG_{a4}^{*} /KG_a) + (KG_{a3}^{*} /KG_a)) – (V_{xa(OAA/Asp)} + V_{TCA(a)}) (OAA_{a3}^{*}/OAA_a)$

$d[Gln_3^{*}]/dt = V_{Gln} (Glu_{a3}^{*} /Glu_a) + V_{dilGln} (0) – (V_{Gln(efflux)} + V_{cyc(Glu/Gln)} + V_{cyc(Gaba/Gln)}) (Gln_3^{*}/Gln)$

$d[Gln_4^{*}]/dt = V_{Gln} (Glu^{*}_{a4}/Glu_a) + V_{dilGln} (0) – (V_{Gln(efflux)} + V_{cyc(Glu/Gln)} + V_{cyc(Gaba/Gln)}) (Gln_4^{*}/Gln)$

$d[Asp_{Gaba2}^{*}]/dt = V_{xGaba\ (OAA/Asp)} (OAA_{Gaba2}^{*} /OAA_{Gaba}) – V_{xGaba\ (Asp/OAA)} (Asp_{Gaba2}^{*} /Asp_{Gaba})$

$d[Asp_{Gaba3}^{*}]/dt = V_{xGaba\ (OAA/Asp)} (OAA_{Gaba3}^{*} /OAA_{Gaba}) – V_{xGaba(Asp/OAA)} (Asp_{Gaba3}^{*} /Asp_{Gaba})$

$d[GABA_{Gaba2}^{*}]/dt = V_{GAD} (Glu_{Gaba4}^{*} /Glu_{Gaba}) – (V_{shunt} + V_{cyc(Gaba/Gln)}) (GABA_{Gaba2}^{*}/GABA_{Gaba})$

$d[GABA_{Gaba3}^{*}]/dt = V_{GAD} (Glu_{Gaba3}^{*}/Glu_{Gaba}) – (V_{shunt} + V_{cyc(Gaba/Gln)}) (GABA_{Gaba3}/GABA_{Gaba})$

$d[Glu_{Gaba3}^{*}]/dt = V_{cyc(Gln/Gaba)} (Gln_3^{*} /Gln) + V_{xGaba(KG/Glu)} (KG_{Gaba3}^{*} /KG_{Gaba}) – (V_{GAD} + V_{xGaba(Glu/KG)}) (Glu_{Gaba3}^{*} /Glu_{Gaba})$

$d[Glu_{Gaba4}^{*}]/dt = V_{cyc(Gln/Gaba)} (Gln_4^{*}/Gln) + V_{xGaba(KG/Glu)} (KG_{Gaba4}^{*} /KG_{Gaba}) – (V_{GAD} + V_{xGaba(Glu/KG)}) (Glu^{*}_{Gaba4}/Glu_{Gaba})$

$d[KG_{Gaba3}^{*}]/dt = V_{xGaba(Glu/KG)} (Glu_{Gaba3}^{*} /Glu_{Gaba}) + V_{TCA(Gaba)} (OAA_{Gaba3}^{*} /OAA_{Gaba}) – (V_{TCA(Gaba)Net} + V_{xGaba(KG/Glu)}) (KG_{Gaba3}^{*} /KG_{Gaba})$

$d[KG_{Gaba4}^{*}]/dt = V_{pdh(Gaba)} (L_3^{*} / L) + V_{xGaba(Glu/KG)} (Glu_{Gaba4}^{*} /Glu_{Gaba}) + V_{dil(Gaba)} (0) – (V_{TCA(Gaba)Net} + V_{xGaba(KG/Glu)}) (KG_{Gaba4}^{*} /KG_{Gaba})$

$d[OAA_{Gaba2}^{*}]/dt = 0.5\ V_{TCA(Gaba)Net} ((KG_{Gaba3}^{*} /KG_{Gaba}) + (KG_{Gaba4}^{*} /KG_{Gaba})) + 0.5\ V_{shunt} ((GABA_{Gaba2}/GABA_{Gaba}) + (GABA_{Gaba3}^{*}/GABA_{Gaba})) + V_{xGaba(Asp/OAA)} (Asp_{Gaba2}^{*}/Asp_{Gaba}) – (V_{TCA(Gaba)} + V_{xGaba\ (OAA/Asp)}) (OAA_{Gaba2}^{*}/OAA_{Gaba})$

$d[OAA_{Gaba3}^{*}]/dt = 0.5\ V_{TCA(Gaba)Net} ((KG_{Gaba4}^{*} /KG_{Gaba}) + (KG_{Gaba3}^{*}/KG_{Gaba})) + 0.5\ V_{shunt} ((GABA_{Gaba2}/GABA_{Gaba}) + (GABA_{Gaba3}/GABA_{Gaba})) + V_{xGaba(Asp/OAA)} (Asp_{Gaba3}^{*}/Asp_{Gaba}) – (V_{TCA(Gaba)} + V_{xGaba\ (OAA/Asp)}) (OAA_{Gaba3}^{*}/OAA_{Gaba})$

$d[Asp_{Glu2}^{*}]/dt = V_{xGlu(OAA/Asp)} (OAA_{Glu2}^{*} /OAA_{Glu}) – V_{xGlu(Asp/OAA)} (Asp_{Glu2}^{*} /Asp_{Glu})$

$d[Asp_{Glu3}^{*}]/dt = V_{xGlu(OAA/Asp)} (OAA_{Glu3}^{*} /OAA_{Glu}) – V_{xGlu(Asp/OAA)} (Asp_{Glu3}^{*} /Asp_{Glu})$

$d[Glu_{Glu3}^{*}]/dt = V_{cyc(Gln/Glu)} (Gln_3^{*} /Gln) + V_{xGlu(KG/Glu)} (KG_{Glu3}^{*} /KG_{Glu}) - (V_{cyc(Glu/Gln)} + V_{xGlu(Glu/KG)}) (Glu_{Glu3}^{*} /Glu_{Glu})$

$d[Glu_{Glu4}^{*}]/dt = V_{cyc(Gln/Glu)} (Gln_4^{*}/Gln) + V_{xGlu(KG/Glu)} (KG_{Glu4}^{*} /KG_{Glu}) – (V_{cyc(Glu/Gln)} + V_{xGlu(Glu/KG)}) (Glu_{Glu4}^{*}/Glu_{Glu})$

$d[KG_{Glu3}^{*}]/dt = V_{xGlu(Glu/KG)} (Glu_{Glu3}^{*} /Glu_{Glu}) + V_{TCA(Glu)} (OAA_{Glu2}^{*} /OAA_{Glu}) – (V_{xGlu(KG/Glu)} + V_{TCA(Glu)}) (KG_{Glu3}^{*} /KG_{Glu})$

$d[KG_{Glu4}^{*}]/dt = V_{xGlu(Glu/KG)} (Glu_{Glu4}^{*}/Glu_{Glu}) + V_{dil(Glu)} (0) + V_{pdh(Glu)} (L_3^{*} /L) - (V_{xGlu(KG/Glu)} + V_{TCA(Glu)}) (KG_{Glu4}^{*}/KG_{Glu})$

$d[OAA_{Glu2}^{*}]/dt = V_{xGlu(Asp/OAA)} (Asp_{Glu2}^{*} /Asp_{Glu}) + 0.5 V_{TCA(Glu)} ((KG_{Glu4}^{*} /KG_{Glu}) + (KG_{Glu3}^{*} / KG_{Glu})) – (V_{xGlu(Asp/OAA)} + V_{TCA(Glu)}) (OAA_{Glu2}^{*} /OAA_{Glu})$

$d[OAA_{Glu3}^{*}]/dt = V_{xGlu(Asp/OAA)} (Asp_{Glu3}^{*} / Asp_{Glu}) + 0.5V_{TCA(Glu)} ((KG_{Glu3}^{*} /KG_{Glu}) + (KG_{Glu4}^{*} / KG_{Glu})) – (V_{xGlu(OAA/Asp)} + V_{TCA(Glu)}) (OAA_{Glu3}^{*} /OAA_{Glu})$

Values of parameters

$CMR_{glc} = (V_{pdh(a)} + V_{pdh(Glu)} + V_{pdh(Gaba)} + V_{PC})/2$

Km_{in} = 13.9 mM; Michaelis–Menten half-saturation constant for blood-to-brain glucose

transport (1).

$Km_{out} = Km_{in} \times V_d$ = 10.7 μmol/g; Michaelis–Menten half-saturation constant for brain-to-blood glucose transport

$Vmax_{in} = 5.8 \times CMR_{glc}$, Michaelis–Menten maximum uptake rate for blood-to-brain glucose

transport (1).

$Vmax_{out} = Vmax_{in}$, Michaelis–Menten maximum uptake rate for brain-to-blood glucose transport.

V_d = 0.77 ml/g; brain water space (2)

$V_{Gln} = V_{cyc(Gln/Glu)} + V_{cyc(Gln/Gaba)} + V_{PC}$, glutamine synthesis flux.

$V_{PC} = 0.2 \times V_{Gln}$, anaplerotic flux (3).

$V_{TCA(Glu)}$, flux through glutamatergic TCA cycle (iterated).

$V_{cyc(Glu/Gln)} = V_{cyc(Gln/Glu)} = 0.45 \times V_{TCA(Glu)}$, glutamate/glutamine cycle flux, estimated using Eq. **5**.

$V_{TCA(Gaba)Net,}$ the net flux through the GABAergic TCA cycle (iterated).

V_{shunt}, flux through the GABA shunt (iterated).

$V_{TCA(Gaba)} = V_{TCA(Gaba)Net} + V_{shunt}$.

$V_{cyc(Gaba/Gln)} = V_{cyc(Gln/Gaba)} = 0.63 \times V_{TCA(Gaba)}$, GABA/glutamine cycle flux, estimated using Eq. **11**.

$V_{dil(a)}$, diluting inflow of astroglial lactate from blood (iterated).

$V_{dil(Gaba)}$, diluting inflow flux of GABA lactate from blood (iterated).

V_{dilGln}, diluting inflow flux of brain glutamine from blood glutamine (iterated).

V_{dilGlu}, diluting inflow flux of brain glutamate from blood lactate (iterated).

$V_{Gln(efflux)} = V_{PC} + V_{dilGln}$, glutamine efflux from brain.

$V_{GAD} = V_{shunt} + V_{cyc(Gaba/Gln)}$, GABA synthesis rate.

$V_{pdh(a)} = 0.176 \times V_{TCA(Glu)}$, astroglial pyruvate dehydrogenase flux (4)

$V_{TCA(a)Net} = V_{pdh(a)} + V_{dil(a)} - V_{PC} - V_{cyc(Gaba/Gln)}$, net flux through the astroglial TCA cycle.

$V_{pdh(Gaba)} = V_{TCA(Gaba)} - V_{dil(Gaba)}$, GABAergic pyruvate dehydrogenase flux.

$V_{pdh(Glu)} = V_{TCA(Glu)} - V_{dil(Glu),}$ glutamatergic pyruvate dehydrogenase flux.

$V_{TCA(a)} = V_{TCA(a)Net} + V_{PC} + V_{cyc(Gaba/Gln),}$ astroglial TCA cycle flux.

$V_{xa(OAA/Asp)} = V_{xa(Glu/KG),}$ mitochondrial/cytosolic OAA-to-Asp exchange rate in astroglia.

$V_{xa(Asp/OAA)} = V_{xa(Glu/KG),}$ cytosolic/mitochondrial Asp-to-OAA exchange rate in astroglia.

$V_{xa(KG/Glu)} = V_{xa(Glu/KG)} + V_{PC,}$ mitochondrial/cytosolic KG-to-Glu exchange rate in astroglia.

$V_{xa(Glu/KG)}$, cytosolic/mitochondrial Glu-to-KG exchange rate in astroglia.

$V_{xGaba(KG/Glu),}$ mitochondrial/cytosolic KG-to-Glu exchange rate in GABAergic neurons.

$V_{xGaba(Glu/KG)} = V_{xGaba(KG/Glu)} + V_{GAD} - V_{cyc(Gaba/Gln),}$ mitochondrial/cytosolic Glu-to-KG exchange rate in GABAergic neurons.

$V_{xGaba(OAA/Asp)} = V_{xGaba(KG/Glu)}$, mitochondrial/cytosolic OAA-to-Asp exchange rate in GABAergic neurons.

$V_{xGaba(Asp/OAA)} = V_{xGaba(OAA/Asp)}$, cytosolic/mitochondrial Asp-to-OAA exchange rate in GABAergic neurons.

$V_{xGlu(Asp/OAA)} = V_{xGlu(KG/Glu)}$, mitochondrial/cytosolic Asp-to-OAA exchange rate in glutamatergic neurons.

$V_{xGlu(OAA/Asp)} = V_{xGlu(KG/Glu)}$, mitochondrial/cytosolic OAA-to-Asp exchange rate in glutamatergic neurons.

$V_{xGlu(KG/Glu)}$, mitochondrial/cytosolic KG-to-Glu exchange rate in glutamatergic neurons.

$V_{xGlu(Glu/KG)} = V_{xGlu(KG/Glu)}$, cytosolic/mitochondrial Glu-to-KG exchange rate in glutamatergic neurons.

$X_1 = Vmax_{in} \times Glc_{blood}/(Km_{in} + Glc_{blood})$, value used to calculate the concentration of brain glucose.

$X_2 = X_1 - CMR_{glc}$, value used to calculate the concentration of brain glucose.

Concentrations of Metabolite Pools

$[Asp_T] = 4.2$ μmol/g, concentration of brain aspartate (measured).

*$[Asp_a] = 0.10 \times Asp_T = 0.42$ μmol/g, concentration of astroglial aspartate.

*$[Asp_{Glu}] = 0.45 \times Asp_T = 1.92$ μmol/g, concentration of aspartate in glutamatergic neurons.

*$[Asp_{Gaba}] = 0.45 \times Asp_T = 1.92$ μmol/g, concentration of aspartate in GABAergic neurons.

$[GABA_{Gaba}] = [GABA_T] = 1.75$ μmol/g, concentration of brain GABA (measured).

$[Glc_{brain}]$, concentration of brain glucose (calculated based on ref. 1).

$[Gln] = 6.83$ μmol/g, concentration of brain glutamine (measured).

$[Glu_a] = 0.10 \times Glu_T = 1.44$ μmol/g, concentration of glutamate in astroglia, 10% of total (5).

$[Glu_{Glu}] = 0.88 \times Glu_T = 12.65$ μmol/g, concentration of glutamate in glutamatergic neurons (5).

$[Glu_{Gaba}] = 0.02 \times Glu_T = 0.29$ μmol/g, concentration of glutamate in GABAergic neurons, 2% of total (6, 7)

†$[KG_a]$ = 0.020 μmol/g, concentration of α-ketoglutarate in astroglia.

†$[KG_{Gaba}]$ = 0.004 μmol/g, concentration of α-ketoglutarate in GABAergic neurons.

†$[KG_{Glu}]$ = 0.176 μmol/g, concentration of α-ketoglutarate in glutamatergic neurons.

[L]= 1.50 μmol/g, concentration of brain lactate (measured).

†$[OAA_a]$ = 0.020 μmol/g, concentration of oxaloacetate in astroglia.

†$[OAA_{Gaba}]$ = 0.004 μmol/g, concentration of oxaloacetate in GABAergic neurons.

†$[OAA_{Glu}]$ = 0.176 μmol/g, concentration of oxaloacetate in glutamatergic neurons.

*The distribution of tissue aspartate (Asp) among different cell types is unknown. In our analysis, the concentration ratio of astroglial-to-total aspartate was assumed to be the same as for glutamate, i.e. Asp_a is 10% of the total Asp pool. The remaining Asp (90%) was assumed to be equally distributed between glutamatergic (45%) and GABAergic neurons (45%).

†The cellular concentration distribution of KG_a:KG_{Gaba}:KG_{Glu} and OAA_a:OAA_{Gaba}:OAA_{Glu} was assumed to be the same as the cellular percentage distribution of glutamate, i.e. 10:2:88.

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