Neuronal-glial glucose oxidation and glutamatergic-GABAergic function revealed by ^{13}C MRS studies

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INTRODUCTION

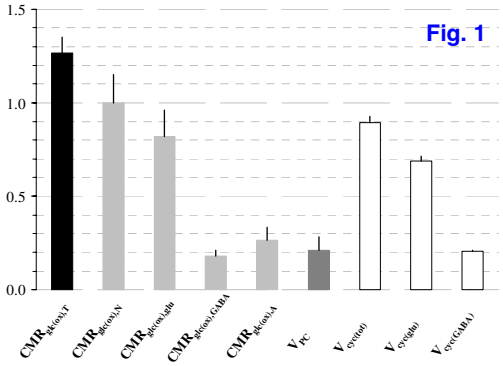
Previous ^{13}C MRS measurement of *in vivo* rates of total glutamate-glutamine cycling ($V_{cyc(tot)}$) and neuronal glucose oxidation ($CMR_{glc(ox),N}$) revealed a linear relationship between ΔV_{cyc} and $\Delta CMR_{glc(ox)N}$ above iso-electricity, with a slope of ~1. These findings together with and *in vitro* results were consolidated into a model for coupling of neuronal activity with cerebral glucose metabolism: recycling of one molecule of neurotransmitter between glia and neurons was associated with oxidation of one glucose molecule in neurons. In this model glucose was taken up *only* by glia and *all* the lactate generated by glial glycolysis was transferred to neurons for oxidation. The model excluded the energetics of glia and GABAergic neurons because quantitative values for flux through these pathways were not available. Here we have revised this model based on the recent data available from the ^{13}C and ^{14}C isotope studies to include energetics of astroglia and GABAergic neurons.

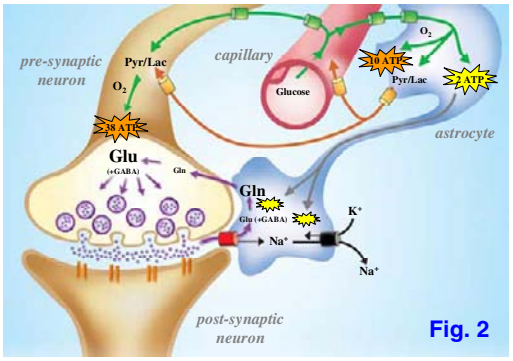
METHODS

A close review of recent metabolic fluxes measured by *in vivo* ^{13}C MRS [1-5] indicated the following relations. For the contribution of glutamate and GABA neurotransmission to total neuronal energy consumption: $V_{cyc(tot)}/CMR_{glc(ox)N} \cong 0.89$; $V_{cyc(GABA)}/CMR_{glc(ox)N} \cong 0.21$; $V_{cyc(Glu)}/CMR_{glc(ox)N} \cong 0.68$. Similarly the contribution of GABAergic and glutamatergic cell type to total neuronal energy consumption: $CMR_{glc(ox)GABA}/CMR_{glc(ox)N} \cong 0.18$ and $CMR_{glc(ox)Glu}/CMR_{glc(ox)N} \cong 0.82$, respectively [5]. More recent ^{13}C MRS data for glial flux measurement for the contribution for the pyruvate carboxylase and pyruvate dehydrogenase pathways indicated following relationship: $V_{PC}/CMR_{glc(ox)N} \cong 0.21$ and $CMR_{glc(ox)A}/CMR_{glc(ox)N} \cong 0.21$ [4,6-8]. For comparison purposes, cerebral metabolic fluxes are standardized relative to neuronal glucose oxidation values.

RESULTS AND DISCUSSION

Standardized relationships for contributions of different pathways to cerebral energetics are shown in Fig. 1. Contribution of astrocytes to total glucose oxidation is ~21% (0.27/1.27) and rest (~79%) is oxidized by neurons (glutamate + GABA). The total neurotransmitter cycling is 89% of glucose oxidized in neurons, with contributions of ~68% and ~21%, respectively, for glutamatergic and GABA neurons. The proposed revise model is shown in Fig. 2. The novel features of the model are derived from the measured values of glial oxidation. In the revised model glucose uptake and oxidation occur in both glia and neurons, but not all of glial lactate (or pyruvate) is transported to neurons and a slight excess being lost to the blood. For the measured cycling fluxes of glutamate and GABA, the amount of Na^+ entering the glia would be ~2.7 μmol/g/min (0.68×4) and ~0.4 μmol/g/min (0.21×2) respectively, or ~3.1 μmol/g/min due to their combined cycling. With the 3:1 stoichiometry of Na^+:ATP for the ATP-dependent Na^+ pump, ~1 μmol/g/min of ATP production would be sufficient to re-establish the Na^+ ion gradient. An additional ~0.89 μmol/g/min of ATP would be required for the synthesis of glutamine. Thus combined cycling of glutamate and GABA together would require a total of ~1.89 μmol/g/min of ATP, which could be supplied by glycolysis of ~0.94 μmol/g/min of glucose in glia. In total, ~0.27 μmol/g/min glucose is oxidized in the glial tri-carboxylic acid cycle to produce ~10 ATP in glia. The remaining glucose consisting of lactate is transported to neurons (~0.61 μmol/g/min), which is consistent with the previous model. An additional ~0.39 μmol/g/min (=1.00-0.61) of glucose is phosphorylated and metabolized in neurons, thereby reaching neuronal glucose oxidation of 1.00 μmol/g/min. Thus the oxygen to glucose index (OGI) for this standardized condition would be ~5.4, which is very close to the OGI observed under resting awake conditions. The inclusion of glial oxidative fluxes into the revised model rectifies simplification made previously. Thus to achieve the full oxidative metabolism in neurons required by the 1:1 stoichiometry, ~40% of pyruvate generation would come from neuronal glycolysis. The revised model predicts 30%:70% partitioning of glucose into neurons and astroglia.





REFERENCES [1] Sibson et al (1998) *Proc Natl Acd Sci USA* **95:**316; [2] Degraaf et al (2004) *Proc Natl Acd Sci USA* **101**:12700; [3] Patel et al (2004) *J cereb Blood Flow Metab* **24**:972; [4] Oz et al (2004) *J Neurosci* **24**:11273; [5] Patel et al (2005) *Proc Natl Acd Sci USA* **102**:5588; [6] Sibson et al (2001) *J Neurochem* **76**:975. [7] Patel et al (2005) *J Neurosci Res* 79:128; [8] Lebon et al (2002) *J Neurosci* **22** :1523.

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