Brain energy metabolism measured by ^{13}C MRS *in vivo* upon infusion of [3-^{13}C]lactate

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TARGET AUDIENCE – Scientists interested in brain energy metabolism and applications of ^{13}C MRS.

PURPOSE – Previous MRS studies revealed similar peak patterns in ^{13}C spectra after infusion of ^{13}C-glucose and ^{13}C-lactate, contrasting with spectra obtained after infusing glial-specific ^{13}C-acetate [1]. ^{13}C MRS studies *in vivo* allow non-invasive estimation of fluxes through biochemical pathways of oxidative metabolism in both neurons and astrocytes [2], and can be employed to further estimate the relative contribution of ^{13}C enriched substrates to mitochondrial oxidation within the neuronal and astrocytic compartments [3]. The aim of the present study was to test the hypothesis that exogenously provided [3-^{13}C]lactate is preferentially oxidised in neurons rather than glial cells, thus leading to differential fractional enrichment of the respective pyruvate pools.

METHODS – MRS experiments in the rat brain (n=5) were performed on a 14.1 T/26 cm horizontal bore magnet with a surface coil as detailed previously [4], during infusion of [3-^{13}C]lactate under α-chloralose anaesthesia. ^{13}C spectra were acquired from a volume of 320 µL in the rat brain semi-adiabatic distortionless enhancement by polarization transfer (DEPT) combined with 3D-ISIS for ^{1}H localization [5]. LCModel was used for analysis of ^{13}C spectra [6]. The scaling of ^{13}C fractional enrichment (FE) curves was based on MRS of brain extracts [4]. A two-compartment model was used to analyse the time courses of aliphatic carbons of glutamate and glutamine, and variance of parameters was determined by Monte-Carlo analyses [4]. For modelling of [3-^{13}C]lactate metabolism, the following constraints were applied [4]: the flux of the glial TCA cycle (V_{TCA}^{g}) was 38% of total pyruvate oxidation; the flux through pyruvate carboxylation (V_{PC}) was 25% of V_{TCA}^{g}; and the transmitochondrial 2-oxoglutarate/glutamate exchange flux in the glia (V_X^{g}) was equal to V_g that denotes the fraction of flux through glial pyruvate dehydrogenase corresponding to the complete oxidation of pyruvate.

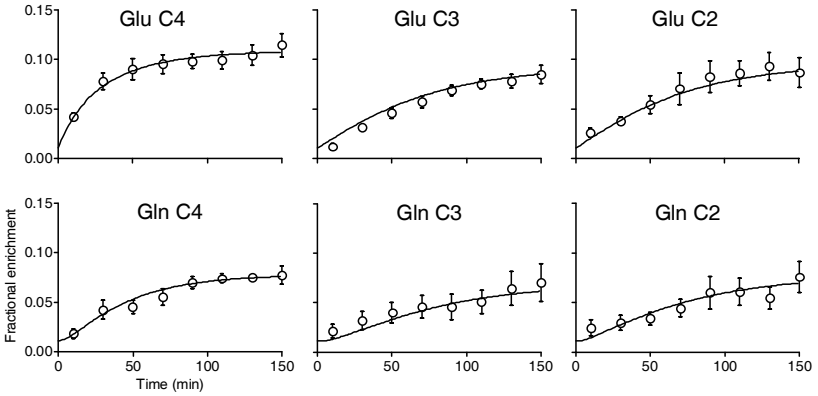

Figure 1. FE in carbons of glutamate (Glu) and glutamine (Gln) *in vivo* (mean±SEM, n=5) and best fit of the two-compartment model of brain energy metabolism.

RESULTS – The two-compartment model of brain metabolism described well the labelling of carbons in glutamate and glutamine (fig.1) with fluxes in the glial compartment constrained based on the relative rates measured upon administration of [1,6-^{13}C]glucose [4]. Variation of these constraints within reasonable limits had minor effects on modelling results. This resulted in estimated metabolic fluxes that were similar to those previously determined upon infusion of [1,6-^{13}C]glucose (fig.2). FE of neuronal pyruvate C3 was 0.13±0.01. In the glial compartment, FE was 0.062±0.013 for pyruvate C3 and 0.049±0.013 for acetyl-CoA C2. Based on the FE achieved in these experiments (31%), we estimate that plasma lactate at supra-physiological levels (~5 mM) contributed to 43% of neuronal pyruvate and to 20% and 17% of glial pyruvate and acetyl-CoA, respectively.

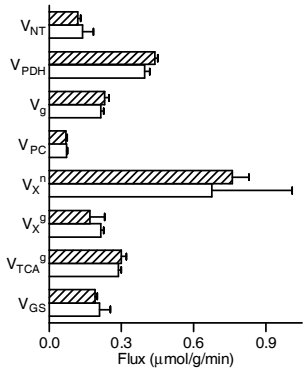

Figure 2. Measured metabolic fluxes (±SD) with [3-^{13}C]lactate (open bars) or [1,6-^{13}C]glucose (dashed bars, from [4]).

DISCUSSION/CONCLUSION – Blood-born [3-^{13}C]lactate was more diluted in astrocytes than neurons, leading to pyruvate enrichment of 6% and 13%. This suggests preferential utilisation of unlabelled substrates within the glial compartment. Thus, given the low enrichment in glutamine, experiments with [3-^{13}C]lactate did not allow to accurately determine glial metabolic fluxes. We conclude that extra-cerebral lactate can be used as fuel by the brain under normoglycaemia conditions leading mostly to production of pyruvate for neuronal oxidation.

REFERENCES – [1] Bouzier *et al*. (2000) J Neurochem 75(2):480. [2] Lanz *et al*. (2013) Front Endocrinol 4:156. [3] Jeffrey *et al.* (2013) JCBFM 33(8):1160. [4] Duarte *et al*. (2011) Front Neuroenergetics 3:3. [5] Henry *et al*. (2003) MRM 50:684. [6] Henry *et al*. (2003) NMR Biomed 16:400.

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