Improving the precision of brain ^{13}C metabolic modeling using co-infusion of [1,2-$^{13}C_2$]acetate and [1,6-$^{13}C_2$]glucose

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Introduction

Dynamic metabolic modeling of ^{13}C MRS data is a powerful tool to measure compartmentalized metabolic fluxes in the brain. In particular, the use of two-compartment neuronal-glial models allows determination of metabolic rates such as the TCA cycle rate in both neurons (Vtca(n)) and glia (Vtca(g)) and the glutamate-glutamine cycle rate (Vnt) between neurons and astrocytes, which reflects glutamatergic neurotransmission. However we recently reported that using [1-^{13}C]glucose or [1,6-$^{13}C_2$]glucose as the infused substrate may not permit very precise determination of all metabolic fluxes in the model [1]. The goal of the present study was to determine whether the use of alternative substrates or combination of substrates leads to improved precision on fitted metabolic rates in the model using Monte-Carlo simulations.

Methods

The metabolic model used was based on a published two-compartment neuronal-glial model [2]. Solving the set of differential equations using a stiff Runge-Kutta algorithm yielded time courses for total positional enrichment in glutamate and glutamine at different carbon positions. Monte-Carlo simulations were performed to evaluate the precision of fitted free metabolic fluxes with the following conditions: 6 turnover curves (glutamate C4,C3,C2, and glutamine C4,C3,C2), 20 points per turnover curve, tmax=150min, noise σ=0.2 µmol/g. The acetate bioavailability parameter for glia was set as 90%. Fitting of synthetic turnover curves was repeated at least 500 times with a different noise realization to yield a statistical distribution for each of the six free parameters in model. Minimization was performed using BFGS or Simplex algorithms.

Results

The figure shows the statistical distribution of parameter estimation for Vtca(n) and Vnt obtained using either [1,6-$^{13}C_2$]glucose, [2-^{13}C]acetate or the combination of [1,2-$^{13}C_2$]acetate and [1,6-$^{13}C_2$]glucose. Each statistical distribution is centered around the nominal value used in the simulation (Vtca(n) = 1 µmol.g^{-1}.min^{-1} and Vnt = 0.3 µmol.g^{-1}.min^{-1}). Data are shown only for these two fluxes due to space limitation. Results demonstrate that using [2-^{13}C]acetate infusion leads to improved precision on the determination of Vnt compared to [1,6-$^{13}C_2$]glucose, but that the precision on Vtca(n) is degraded. This is consistent with the fact that [2-^{13}C]acetate is a glial specific substrate [3]. The relative standard deviation (SD) for Vnt was 65% for [1,6-$^{13}C_2$]glucose and improved to 12% with [2-^{13}C]acetate. In contrast the relative SD for Vtca(n) was 7% with [1,6-$^{13}C_2$]glucose but degraded to 37% with [2-^{13}C]acetate. The best results were obtained with co-infusion of [1,2-$^{13}C_2$]acetate and [1,6-$^{13}C_2$]glucose, for which the estimated SD was 5% for Vtca(n) and 12% for Vnt under the conditions of the simulation.

Conclusion

Co-infusion of glucose and acetate has been used in brain extracts [4,5] but to the best of our knowledge dynamic metabolic modeling has not been reported under these experimental conditions. The present study suggests that ^{13}C metabolic modeling using co-infusion of [1,2-$^{13}C_2$]acetate and [1,6-$^{13}C_2$]glucose provides superior results for the precise determination of metabolic rates using two-compartment metabolic modeling in the brain. This double infusion protocol can be expected to advantageously replace more commonly used approaches that utilize either ^{13}C-glucose or ^{13}C-acetate alone.

References

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