Measuring the glutamate-glutamine cycle rate in the brain: simulated comparison between [1-^{13}C]glucose and [2-^{13}C]acetate

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Introduction

^{13}C MRS is a powerful tool to measure quantitative metabolic fluxes in the brain *in vivo*. With the two-compartment neuronal-glial metabolic models, this approach has allowed non-invasive measurements of the glutamate-glutamine cycle rate (V_{NT}) between neurons and astrocytes. This flux may directly reflect glutamatergic neurotransmission. However, we have recently showed that the determination of the V_{NT} flux is not very precise when using either [1-^{13}C] or [1,6-$^{13}C_2$]glucose as a substrate [1]. The goal of this work was to determine whether dynamic metabolic modeling using a glial-specific substrate (such as [2-^{13}C]acetate) leads to improved precision on the quantitative determination of V_{NT}.

Methods

All simulations were performed in Matlab (The Mathworks Inc). The metabolic model used in this study was essentially identical to previously published two-compartment metabolic models [2,3]. This model contains 6 free parameters: $V_{TCA(N)}$, $V_{TCA(G)}$, V_{NT}, V_{PC}, V_X, V_{OUT}. Differential equations describing the metabolic model were solved (using Runge-Kutta algorithm) to yield simulated ^{13}C turnover curves for glutamate and glutamine. Monte-Carlo simulations were performed with the following conditions: 20 points per turnover curve, tmax = 150 min, noise level $\sigma = 0.2$ $\mu mol.g^{-1}$. Fitting was carried out using BFGS or Simplex algorithms. At least 500 fits were performed with different noise realizations to estimate the standard deviation of fitted metabolic fluxes.

Results

Simulated ^{13}C turnover curves for glutamate and glutamine were found to be more sensitive to the value of V_{NT} when using [2-^{13}C]acetate than when using [1-^{13}C]glucose as a substrate (Figure 1). When infusing [1-^{13}C]glucose, the turnover curves for glutamate and glutamine C4 remained almost unchanged when V_{NT} was varied by ±50%. In contrast, with [2-^{13}C]acetate, the turnover curves for both glutamate and glutamine C4 changed noticeably. This suggests that the determination of V_{NT} would be more reliable when infusing [2-^{13}C]acetate compared to [1-^{13}]glucose. Monte-Carlo simulations confirmed that V_{NT} is indeed much more precise when using [2-^{13}C]acetate: the standard deviation on V_{NT} was 670 % for [1-^{13}C]glucose and only 12% for [2-^{13}C]acetate.

Discussion

Our simulations show that dynamic metabolic modeling using [2-^{13}C]acetate should lead to improved precision on the determination of the glutamate-glutamine cycle rate V_{NT} compared to [1-^{13}C]glucose (or [1,6-$^{13}C_2$]glucose). Most dynamic metabolic modeling studies have used [1-^{13}C]glucose or [1,6-^{13}C2]glucose as a substrate. A few studies have used [2-^{13}C]acetate [4-6]. Two studies have used analysis of ^{13}C label at isotopic steady-state to determine the ratio $V_{NT}/V_{TCA(N)}$ [5,6], but this approach does not allow absolute measurement of V_{NT} unless an additional [1-^{13}C]glucose experiment is performed.

To the best of our knowledge, dynamic metabolic modeling of ^{13}C turnover curves obtained during [2-^{13}C]acetate infusion in order to measure the glutamate-glutamine cycle rate has not been reported. Such modeling has been hampered by the fact that acetate transport into brain tissue is not well characterized. In addition, infusion of acetate may alter brain metabolism (e.g. pyruvate recycling [7]).These issues will need to be further investigated. Nonetheless, we expect that dynamic metabolic modeling using [2-^{13}C]acetate will allow more precise measurements of V_{NT} than has been possible so far using [1-^{13}C] or [1,6-$^{13}C_2$]glucose.

Conclusion

We conclude that dynamic metabolic modeling using [2-^{13}C]acetate as a substrate has the potential to improve the determination of the glutamate-glutamine cycle rate V_{NT} compared to using [1-^{13}C] or [1,6-$^{13}C_2$] glucose.

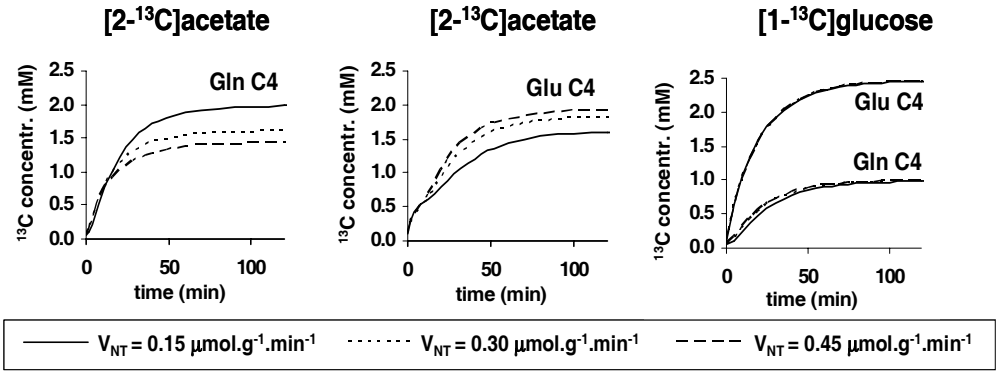

Figure 1. Sensitivity of glutamate and glutamine ^{13}C turnover curves to the value of the glutamate-glutamine cycle rate V_{NT} when using (a) [1-^{13}C]glucose and (b) [2-^{13}C]acetate. Turnover curves were more sensitive to the value of V_{NT} with [2-^{13}C]acetate than with [1-^{13}C]glucose.

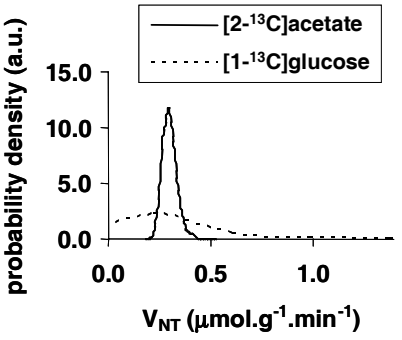

Figure 2. Probability distribution of V_{NT} determined by Monte-Carlo simulations. Estimation of V_{NT} was more precise with [2-^{13}C]acetate than with [1-^{13}C]glucose.

References

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