Mathematical model of glial metabolism assessed using C1-labeled acetate

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Introduction:

The two dominant techniques for cerebral labeling studies in vivo are nowadays NMR and PET, using respectively stable or radioactive isotopes as label. A current very challenging subject in biomedical imaging is the possible combination of the PET and NMR technologies in a single experimental setup. To compare brain metabolism measurements, an approach based on a consistent mathematical formulation is of advantage. The aim of the present study was to develop a metabolic model of neuro-glial metabolism suitable to assess metabolic rates resulting from acetate labeled at the C1 position and to apply this model to experimental radiotracer time courses following ^{11}C[1]-acetate infusion.

Materials and methods:

The acetate infusion model was based on a recently described approach to simplify the mathematical expressions allowing to gain substantial insight into metabolic relationships in brain [1,2]. Briefly, only significantly large pools labeled by the biochemical pathway of C1-labeled acetate were considered and steady-state was assumed (constant metabolic rates and pool sizes). The mathematical expressions are independent of the fact whether C1 is labeled by 13C or by 11C. Tissue radioactivity following 11C acetate infusion was measured using the beta-probe approach placed in the striatum [3,4]. Total blood radioactivity was continuously recorded using an arterio-venous shunt and a coincidence counter [5] to obtain the arterial input function simultaneously. While 13C NMR allows to distinguish label in different positions of the molecule, the positron emission measures total tissue activity, and the measured curve was fitted to the sum of the different chemical pools. A best fit was obtained by fitting the apparent Krebs-cycle rate Vgt and the apparent rate of neurotransmission Vnt.

Results and Discussion:

1. Our model of neuro-glial metabolism after labeled acetate infusion used the approach introduced recently for labeled glucose infusion [1,2]: Briefly, the concentrations of the intermediary chemical pools in the TCA cycle, whose concentrations are too low to be detected in NMR, were eliminated from the equations leading to a simplified model of glutamate labeling with the composite flux Vgt; glutamate labeling due to TCA cycle activity. We investigated the model by using a step function for the acetate precursor enrichment from which is was shown that the glial and neuronal glutamine pool could be described by one single kinetic pool (Fig.1). As a result, labeling of Glu, Gln from C1 acetate was described by only 6 differential equations.

2. Using a constant enrichment of acetate as precursor, the back flux of tracers from the neuronal compartments to the glia affects glial glutamate labeling in a significant extent only after ~1000s (Fig.2) depending on the apparent neurotransmission rate, Vnt.

3. The application of our model to PET data shows excellent fit (Fig.3). We obtained metabolic rates for Vnt and glial Vgt in good concordance with the literature [6]. In contrast to NMR measurements, the input function is a bolus when administering PET tracers. In this case, the fractional enrichment (FE) of the neuronal glutamate remained low during all the experiment due to its large pool size. In addition to Vnt, the apparent glial TCA cycle flux Vgt was reliably estimated from the best fit. The low specific activity of the neuronal pools explained the observation that the neuronal TCA fluxes have insignificant influence on the derived Vgt and Vnt.

We conclude that adapted metabolic model approaches originally designed for NMR studies can be used to fit the positron measurements made with the beta-probe by summing all the significantly labeled pools, implicating a common approach to labeling studies using combined MR and PET in the same animal.

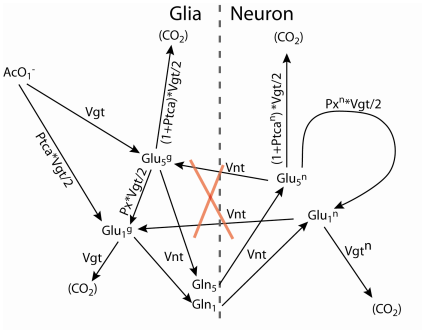

Fig.1: *possible fusion of the glutamine neuronal and glial pools for some infusion protocols. For short experiment times (~20min) the backflux of tracers can be neglected (red cross).*

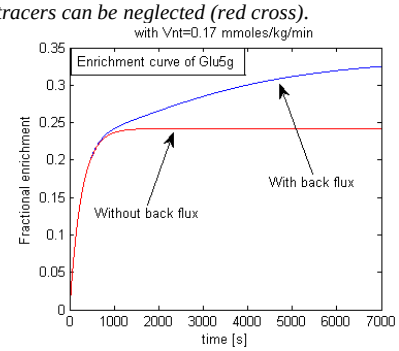

Fig.2: *influence of the labeling of neuronal pools on glial glutamate pool C5.*

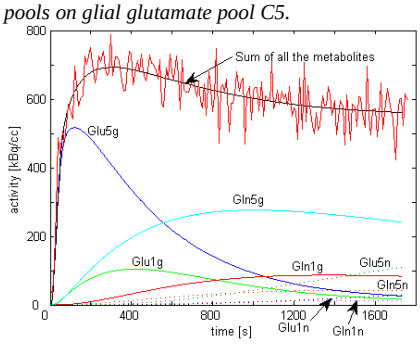

Fig.3: *fit of brain positron emission measurement with the biochemical labeling model. From this fit we can exctract the glial Vgt and Vnt.*

Vgt	0.14±0.02
Vnt	0.077±0.01

Table 1: *Metabolic fluxes in mmoles/kg/min obtained by the fit of fig.3.*

References:

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