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1 Introduction

Glutamine is a nonessential amino acid which supports the function of the gut and the immune system. Several organs and tissues can both synthesise and degrade glutamine, dependent on the physiological condition. Skeletal muscle is considered to be the main glutamine producing tissue in man. Quantitative assessment of glutamine kinetics is required to understand its physiology and to diagnose pathology. Tracer dilution experiments with infusion of stable isotope amino acids are used to study *in vivo* transport and metabolic processes in human subjects. Experimental enrichment data are interpreted in context of (linear) compartment models to yield synthesis and degradation rates. Under steady-state assumption for both tracee and tracer the calculations reduce to algebraic equations only requiring measurement of the steady-state plateau enrichment. In literature experiments have been reported with tracer infusion periods of 8 [2] and 6 or 11 [3] hours. The obtained rates have caused controversy identifying skeletal muscle either as net producer or consumer of glutamine. In this paper it is shown that, based on non-steady-state identification of new data, the tracer steady-state assumption cannot be valid for the reported experiments.

2 Model

The tracee and tracer (*) are assumed to be homogenously mixed in two compartments: a blood plasma (p) and Whole-Body Free (WBF) pool (b). The mass balances of tracee and tracer have the same structure (2 sets of 2 differential equations):

$$\dot{\mathbf{x}} = \mathbf{A}\mathbf{x} + \mathbf{B}\mathbf{u} \qquad \dot{\mathbf{x}}^* = \mathbf{A}\mathbf{x}^* + \mathbf{B}\mathbf{u}^* \qquad (1)$$

with $\mathbf{x} = [[gln]_p,\ [gln]_b]^T$ and $\mathbf{x}^* = [[gln^*]_p,\ [gln^*]_b]^T$ [μmol·kg^{-1}]. Vector $\mathbf{u}^{(*)}$ [μmol·kg^{-1}·h^{-1}] contains the fluxes which are independent of the model states. Tracee inflow is assumed to be constant $\mathbf{u} = [r_{inflow},\ 0]$. The tracer infusion r_{infuse}^* is experimentally set: $\mathbf{u}^* = [r_{infuse},\ 0]$.
For the other fluxes a first–order exchange between the compartments is assumed, described by rate constants k_{ij} [h^{-1}], which are the same for tracer and tracee:

$$\mathbf{A} = \begin{bmatrix} -k_{12} - k_{10} & k_{21} \\ k_{12} & -k_{21} \end{bmatrix} \qquad \mathbf{B} = \begin{bmatrix} 1 & 1 \end{bmatrix}^T \qquad (2)$$

Stationarity constraints In tracer experiments it is usually assumed that the tracee pool concentrations remain constant throughout the experiment, i.e. $\dot{\mathbf{x}} = \mathbf{0}$. The tracee submodel reduces to a static representation and the plasma and WBF tracee concentrations become constants $\mathbf{V} = [V_1,\ V_2]$ [μmol·kg^{-1}]. The stationarity condition for the tracee yields a set of algebraic equations which set the values of V_1 and V_2, given a specific realisation for the parameters $\theta = [r_{inflow}, k_{10}, k_{12}, k_{21}]$:

$$\mathbf{A}(q)\mathbf{V} + \mathbf{B}\mathbf{u}(q) = \mathbf{0} \quad \Leftrightarrow \quad \mathbf{V} = -\mathbf{A}(q)^{-1}\mathbf{B}\mathbf{u}(q) \qquad (3)$$

To estimate the unknown parameters θ the remaining model states $\mathbf{x}^*$ need to be linked to experimental data. The model outputs $\mathbf{y}$ are the same quantities as experimentally accessible: plasma pool enrichment. $\mathbf{y} = \mathbf{C}\mathbf{x}^*$ with

$$\mathbf{C} = diag\left(\frac{1}{V_1} \quad 0\right) \qquad (4)$$

3 Identification

During 24 h a [5-^{15}N]-glutamine tracer was supplied to 7 healthy, male subjects by a continuous intravenous infusion in the arm, r_{infuse} = 0.68 [μmol·kg^{-1}·h^{-1}]. During 36 h 46 blood samples have been taken from the artery femoralis (leg) at non-equidistant times. Since the tracer infusion is started at t = 0, the initial values $\mathbf{x}_0^* = [0 \quad 0]^T$. For each subject the parameters $\theta \in \boldsymbol{R}^+$ have been estimated with a weighted least squares output error criterion using SAAM II (software for identification of compartment models based on tracer data [1], [4]) and Matlab. The datasets contained both the infusion (load) period and the wash-out curve (N=46). The average time constants of the 2 pools for the 7 subjects are $\boldsymbol{t}_1$ = 32±12 min and $\boldsymbol{t}_2$ = 18.1±2.2 hour. The stationarity condition of the tracee pools was verified.

4 Conclusion

The traditional calculations applied to tracer data are usually not based on time series data and system identification. The model realisation obtained here, shows that the required tracer steady-state is not reached during the reported experiments. Instead, an infusion of at least 90h is required to apply traditional calculations, which is hardly feasible with human subjects. The tracer steady-state calculations are not applicable.

References

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