Dynamic Metabolic Modeling of Glucose Transport and Utilization in the Human Brain

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Introduction

Glucose is the primary fuel for cerebral function. Therefore, quantifying the kinetics of its transport into and eventual utilization in the brain is critical for assessing cerebral energy metabolism. The kinetic parameters of cerebral glucose transport have so far been obtained by fitting steady-state models to brain glucose as a function of plasma glucose concentrations (1, 2). This way, K_M for transport (K_M^{tr}) and the ratio of V_{max} for transport (V_{max}^{tr}) to cerebral metabolic rate of glucose (CMR_{glc}) were obtained and, assuming a constant CMR_{glc} from prior work, V_{max}^{tr} was calculated (1, 2). Recently, a new method was proposed to determine all four kinetic parameters for transport and utilization (K_M^{tr}, V_{max}^{tr}, K_M^{ut}, V_{max}^{ut}) independently by fitting both dynamic and steady-state data (3). The goal of the current study was to apply the same methodology to obtain the kinetic parameters for glucose transport and utilization in the human brain.

Methods and Subjects

All measurements were performed on a 4 T / 90 cm magnet (Oxford/Varian). A quadrature 14 cm ^{1}H surface coil was used. Localization was achieved with STEAM (TE = 5 ms, TR = 4.5 s) as described previously (4). Five healthy volunteers (3 M / 2 F, 31 ± 16 (SD) years old) participated in the study. Upon placement in the scanner, a baseline spectrum was obtained from the occipital lobe (22-27 ml VOI, 10 min acquisition). Then the volunteers received IV a 40-60 mL glucose bolus (50% dextrose) over 1-2 min followed by continuous infusion of glucose (20% dextrose) as necessary to maintain the plasma concentration at ~17 mmol/l for ~2h. Blood samples were obtained every 5 min for determination of plasma glucose concentration. Additional samples were obtained every 20 min for later determination of serum insulin concentrations. During the infusion, ^{1}H MR spectra were continuously obtained in single scan mode from the occipital lobe. Spectra were frequency and phase corrected and summed over 32 scans to provide 2.5 min resolution. Spectra were quantified with LCModel (5) using unsuppressed water as reference as described before (4).

The kinetic parameters for glucose transport and utilization were obtained with a reversible, non-steady-state Michaelis-Menten model (Fig. 1). First, the model was fitted to $[Glc]_{brain}$ as a function of $[Glc]_{plasma}$ at steady-state from literature (1, 2) to extract the parameters K_M for transport and utilization (Fig. 2). These K_M values were then used to fit the time courses of $[Glc]_{brain}$ obtained in the current study using $[Glc]_{plasma}$ as input function (Fig. 3). Minimization was performed using BFGS, Simplex or Levenberg-Marquart algorithms.

Results and Discussion

Fitted values for transport and utilization kinetics were: $V_{max}^{tr} = 0.94 \pm 0.21$ µmol/g/min and $K_M^{tr} = 2.6 \pm 1.9$ mM for glucose transport through the BBB and $V_{max}^{ut} = 0.48 \pm 0.12$ µmol/g/min with $K_M^{ut} = 0.1 \pm 0.2$ mM for cerebral glucose utilization. Therefore, maximum transport capacity for glucose through the BBB was nearly two-fold higher than maximum cerebral glucose utilization rate. The steady-state CMR_{glc} at euglycemia (5 mM plasma glucose) was 0.41 ± 0.11 µmol/g/min (mean ± SD; n = 5), while a ~10% increase in CMR_{glc} at 17 mM plasma glucose was observed. Numerical simulations with the fitted parameters also predicted a ~12% decrease in CMR_{glc} during hypoglycemia (3 mM plasma glucose) compared to euglycemia.

The glucose transport parameters were consistent with previously published values for human brain (1, 2). In addition, inclusion of glucose phosphorylation in the reversible MM model allowed fitting of the steady-state and dynamic data adequately. At high plasma glucose concentrations (~10 mM and above), glucose metabolism is rate-limited after entry of glucose into the brain (at hexokinase level) rather than at the BBB, while at hypoglycemia transport through BBB may influence the glucose utilization rate and could be rate-limiting especially for activated states.

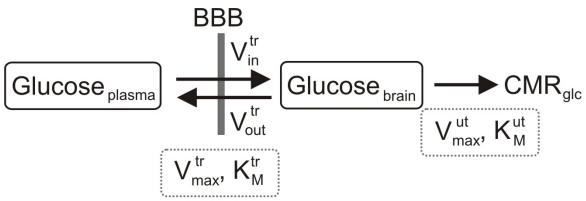

Fig. 1. The reversible glucose transport and utilization model. The extracted kinetic parameters are shown in dotted boxes.

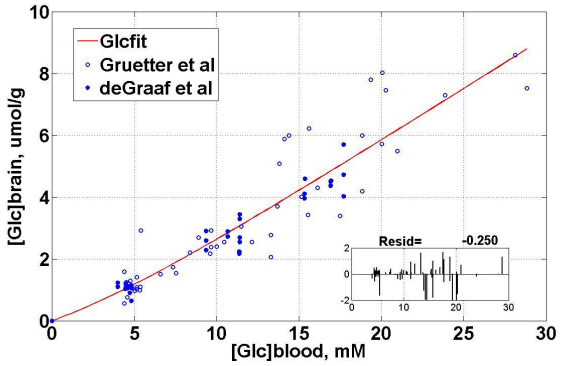

Fig. 2. Fit of the reversible MM model to the steady state data from literature (1, 2). The residuals are shown in the inset.

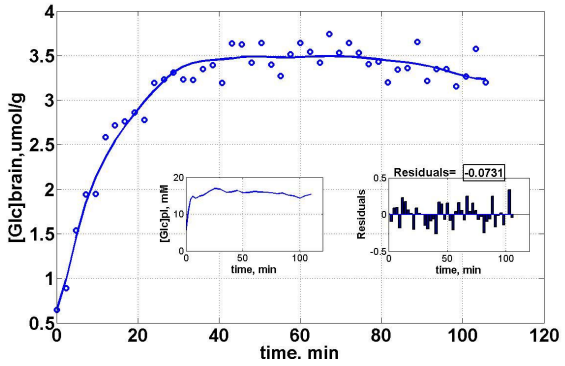

Fig. 3. Fit of the non-steady-state, reversible MM model to non-steady state data from one volunteer. The input function (plasma glucose concentrations) and the residuals are shown in the insets.

References

1. Gruetter et al, *J Neurochem*, 70: 397, 1998. **2**. de Graaf et al, *JCBFM*, 21: 483, 2001. **3.** Deelchand et al, *J Neurochem*, 109: 46, 2009. **4.** Tkac et al, *Magn Reson Med*, 62: 868, 2009. **5.** Provencher SW, *Magn Reson Med*, 30: 672, 1993.

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