Cerebral glucose metabolism during euglycemia and hypoglycemia in patients with type 1 diabetes

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Introduction: As result of insulin treatment, patients with type 1 diabetes mellitus (T1DM) frequently experience hypoglycemic events. Recently, it has been shown in healthy subjects that brain glucose metabolism as reflected by the tricarboxylic acid cycle flux (V_{TCA}) was similar during euglycemia and hypoglycemia [1]. However, whether these findings can be extrapolated to patients with T1DM is unknown.
Target audience: Researchers and clinicians interested in diabetes, hypoglycemia or brain metabolism in general.
Purpose: To investigate the effect of hypoglycemia on brain glucose metabolism in patients with uncomplicated T1DM.

Methods: Hyperinsulinemic euglycemic and hypoglycemic clamps using [1-^{13}C]glucose were applied to 10 T1DM patients (4M/6F; age 31.2±7.8 yrs; BMI 22.9±3.1 kg/m^2; duration of diabetes 15±8 yrs; HbA_{1C} 7.6±1.4%; mean±SD). Six patients completed both clamps (on separate days), two only a euglycemic clamp, and two others only a hypoglycemic clamp. During the clamps arterial blood was sampled each 5 min. to determine plasma concentrations and enrichments of glucose and lactate and less frequently to measure plasma insulin and counterregulatory hormones.
MR experiments were conducted as described in [1] on a 3T MR system (Magnetom Trio, Siemens, Erlangen, Germany) equipped with a home-built ^{1}H volume coil and a circularly polarized ^{13}C surface coil insert. ^{13}C MR spectra were acquired from a voxel of ~125 mL in the occipital cortex with a sequential ISIS-DEPT sequence [2] using WALTZ-16 ^{1}H-decoupling (72 scans, TR=2s, duration=2.5 min). Acquisition of ^{13}C MR spectra started 20 minutes before [1-^{13}C]glucose infusion to obtain 8 reference spectra, and continued throughout the entire clamp of 2 hrs.
During post-processing FIDs were summed in running averages of 15 min. and the averaged reference spectra were subtracted to remove natural abundance signals and residual lipid signals. Signals of Glu4 and Glu3 were quantified by the AMARES algorithm in jMRUI.
Modeling was performed with a one-compartment model using plasma concentration and enrichment of both glucose and lactate as input functions [1]. The time courses of the formation of Glu4 and Glu3 were fitted, resulting in the metabolic flux values representing the TCA cycle (V_{TCA}), loss of label upon exchange with unlabeled glutamine (Vefflux), and the exchange of intracellular lactate with plasma lactate (Vdil). Data previously obtained on healthy volunteers were reanalyzed using the exact lactate concentration input-curves, rather than approximations as done before [1].

Results: Plasma glucose levels stabilized at 5.0 ± 0.2 (euglycemia) and 2.9 ± 0.2 mmol/L (hypoglycemia). During hypoglycemia, plasma adrenaline, noradrenaline, cortisol and growth hormone levels increased, but there was no glucagon response, as expected in patients with longstanding T1DM.. During both glycemic conditions ^{13}C MR spectra of good quality were obtained (Figure 1). Calculated values for V_{TCA} were not different under euglycemic or hypoglycemic conditions (0.59±0.19 versus 0.62±0.15 μmol/g/min, P=0.72, figure 2). Compared to results obtained in healthy volunteers [1], V_{TCA} in T1DM patients was significantly higher under hypoglycemic conditions (0.62±0.15 versus 0.43±0.08 μmol/g/min, P=0.014, Figure 2). There were no significant differences in Vdil or Vefflux between glycemic states or in comparison with healthy subjects.

Discussion: The unique aspect of our study is that we could measure brain glucose metabolism with ^{13}C MRS under hypoglycemic conditions *in vivo* in a relevant population at high risk of recurrent hypoglycemia. Limitations of our study comprise assumptions on several cerebral metabolite concentrations and fluxes related to the model, which we assumed to be equal for both groups and to remain unaltered during hypoglycemia. The higher V_{TCA} during hypoglycemia in T1DM patients compared to healthy controls suggests cerebral adaptations in the patients, presumably to recurrent antecedent hypoglycemic episodes.

Conclusions: Hypoglycemia does not affect brain glucose metabolism in patients with longstanding, uncomplicated T1DM, suggesting that alternative sources of energy, such as lactate, may be utilized by the brain when glucose delivery falls. A higher TCA cycle flux in T1DM patients versus healthy volunteers during hypoglycemia may indicate cerebral adaptations in these patients.

References: **[1]** Van de Ven KCC, de Galan, BE, van der Graaf M, et al. Effect of acute hypoglycemia on human cerebral glucose metabolism, measured by 13C magnetic resonance spectroscopy, *Diabetes* 2011; 60:1467-1473; **[2]** Klomp DW, Kentgens AP, and Heerschap A. Polarization transfer for sensitivity-enhanced MRS using a single radio frequency transmit channel. *NMR Biomed*.208; 21:444-452.

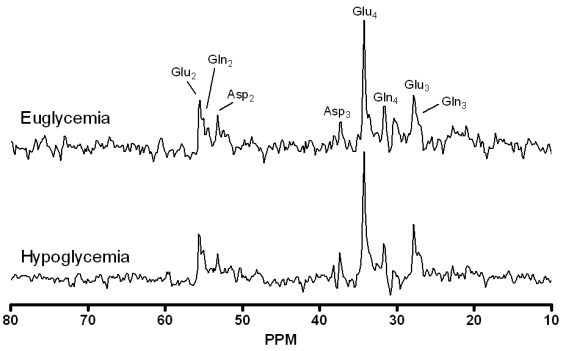

Fig. 1 Summation of all ^{13}C MR spectra acquired in a T1DM patient during euglycemic (top) and hypoglycemic (bottom) clamps.

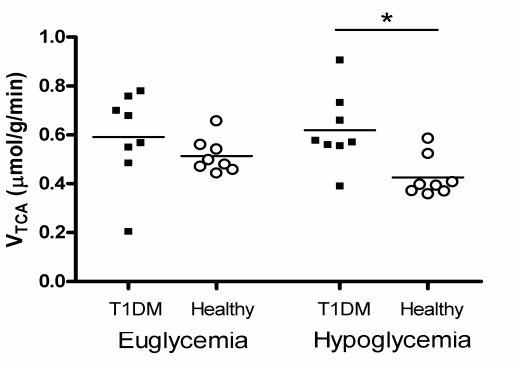

Fig. 2 V_{TCA} for T1DM patients and healthy subjects. (* P=0.014)