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/m2; duration of diabetes 15±8 yrs; HbA1c 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 1H volume coil and a circularly polarized 13C surface coil insert. 13C MR spectra were acquired from a voxel of ~125 mL in the occipital cortex with a sequential ISIS-DEPT sequence [2] using WALTZ-16 1H-decoupling (72 scans, TR=2s, duration=2.5 min). Acquisition of 13C 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.

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 13C 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 13C MRS under hypoglycemic conditions 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.


![Fig. 1 Summation of all 13C MR spectra acquired in a T1DM patient during euglycemic (top) and hypoglycemic (bottom) clamps.](image)

![Fig. 2 $V_{TCA}$ for T1DM patients and healthy subjects. (* P=0.014)](image)