Introduction: Patients with type 1 diabetes (T1D) who experience recurrent hypoglycemia as a result of insulin treatment are at risk of developing hypoglycemia unawareness (HU), the syndrome where the first symptom of a low blood sugar is unconsciousness due to an impaired counter-regulatory hormonal response (e.g. epinephrine) to hypoglycemia. Fear of developing HU limits the ability of patients to achieve the level of glucose control known to reduce the risk of microvascular complications of diabetes. Although the mechanism for HU is not known, changes in neurotransmission and cerebral energy metabolism during hypoglycemia may be involved. A recent 1H MRS study found a decrease of the cortical glutamate (Glu) to creatine (Cr) ratio in response to hypoglycemia in healthy volunteers, but not in patients with T1D. The Glu reduction in healthy controls was thought to reflect reduced TCA cycle activity, leading to reduced Glu synthesis, and raised the possibility that maintenance of normal energy metabolism in T1D may contribute to the development of HU. The goal of this study was to determine whether the cortical Glu response is absent in HU by studying patients with T1D and HU and two control groups: patients with T1D who are hypoglycemia-aware and healthy volunteers. We used ultra-high field MRS to follow the time course of the Glu response to hypoglycemia in these three groups.

Methods: Five subjects with T1D and HU as assessed by a standardized questionnaire (T1D-HU, 1 male, age 48±10 years, BMI 25±5 kg/m²), 5 subjects with T1D who were aware of hypoglycemia (T1D-HA, 2 males, age 36±15 years, BMI 24±3 kg/m²), and 5 healthy controls (1 male, age 32±4 years, BMI 24±5 kg/m²) completed the study. Brain Glu was measured at euglycemia (target glucose 90 mg/dL) followed by a hyperinsulinemic-hypoglycemic clamp (target glucose 50 mg/dL) without removing the subject from the scanner. Blood was sampled to assess glucose and counter-regulatory hormone concentrations (including epinephrine). 1H MR spectra were measured from a 22 x 22 x 22 mm³ occipital cortex voxel at 7 T (Magnex/Siemens) with a quadrature half-volume transceiver using STEAM (TE = 8 ms, TR = 5 s, TM = 32 ms, NEX = 64) and water as a quantification reference. Single-shot data were frequency and phase corrected prior to summation. First- and second-order shims were adjusted using FASTMAP. Metabolites were quantified using LCModel and a typical basis set of neurochemicals. The change in brain Glu concentration from baseline to that measured after blood glucose reached 50 mg/dL was computed for each subject and used to calculate the post hypoglycemic ratio to baseline. ANOVA was used to analyze whether a drop in brain Glu concentration occurred in each group, and to account for blood glucose concentration during hypoglycemia as a covariate.

Results: The counter-regulatory hormonal response of the T1D-HU group to hypoglycemia was impaired (Table 1), as expected based on their HU history. A high spectral quality was consistently achieved (Fig. 1), such that Glu was detected reliably (CRLB ≤ 3%, correlation coefficients with other metabolites > -0.5) in all cases. The target blood glucose level for hypoglycemia was achieved in all groups (Fig. 2B). Contrary to prior findings, brain Glu levels dropped after initiation of hypoglycemia in all groups (p ≤ 0.02) (Fig. 2A). There was no change (p > 0.1) in the concentration of the major metabolites (NAA, Cr, Cho) during hypoglycemia in any group, confirming the specificity of the effect to Glu.

Conclusions: The spectral dispersion and sensitivity achieved at 7 T enabled measurement of a human brain time course of Glu in response to hypoglycemia. Cortical Glu levels decreased in response to hypoglycemia in patients with T1D-HU, as in the two control groups, indicating that the metabolic response to hypoglycemia is similar in hypoglycemia-aware and unaware patients with T1D to that in healthy volunteers. Note however that Glu appeared to drop slower and to a lesser extent in T1D-HU than both control groups (Fig. 2A), which could be attributed to a neurometabolic adaptation in HU. Future analysis and studies with control for confounding by the rate of drop in blood glucose and with larger sample sizes will be necessary to investigate a difference in the rate of change of Glu during hypoglycemia between these groups.


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