Increased brain monocarboxylic acid transport and metabolism in T1DM patients with hypoglycemia unawareness

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Introduction
Repetitive mild hypoglycemic events in patients with Type 1 diabetes (T1DM) lead to brain adaptations that blunt the warning signals associated with low glucose levels (hypoglycemia unawareness) ¹. Increased capacity to oxidize alternative monocarboxylic acids (MCA) fuels (e.g. lactate and ketone bodies) associated with increased blood-brain barrier MCA transport via the MCA transporter 1 (MCT1), has been suggested as adaptations induced by repetitive hypoglycemia ². This hypothesis is based on our findings in well-controlled type 1 diabetes patients who showed increased metabolism of acetate, a molecule also transported over the blood-brain barrier via MCT1 ³. However, it is unclear whether these adaptations are related to the frequency and severity of hypoglycemic episodes or type 1 diabetes per se. We therefore investigated the relationship between CNS cortical metabolic adaptations and i) severity of antecedent hypoglycemia unawareness and ii) counterregulatory response to acute hypoglycemia using ¹³C magnetic resonance spectroscopy (MRS) and infusion of [²-¹³C]-acetate.

Materials and methods
Three groups of subjects were studied: 1) intensively-treated T1DM patients with a history of severe hypoglycemia and moderate-severe hypoglycemia unawareness as defined by the Ryan Hypoglycemia Score⁶ (n=7), 2) T1DM control patients with minimal or no hypoglycemia unawareness as defined by Ryan Hypoglycemia Score (n=4), and 3) non-diabetic control subjects matched for age, gender and BMI (n=10). ¹³C MR spectra were acquired before and during the 120 min infusion of [²-¹³C]-acetate which started after establishing steady state low plasma glucose levels of 3-3.5 mM. NMR spectra were acquired using a 4T whole body magnet equipped with a Bruker console (Bruker Instruments, Billerica, MA). The RF-coil setup was a combination of a circular ¹³C coil (Ø 8.5 cm) for acquisition and two quadrature ¹H surface coils for imaging, shimming, polarization transfer and decoupling. Following scout imaging, shimming was performed using the FASTERMAP procedure ⁴ and decoupling power was calibrated. ¹³C MR spectra were acquired using a polarization transfer sequence as described previously (TR=2500ms, 128 averages) in combination with 3D ISIS localization and outer volume suppression in a 900 ml voxel located in the occipital-parietal lobe ⁵. Blood samples were collected every 5-10 minutes for determination of plasma glucose and acetate concentration and fractional ¹³C enrichments. MR spectra were fitted using an LC model approach with in-house built software. Steady state ¹³C fractional enrichments were calculated from the last 30 min of [²-¹³C]-acetate infusion, based on the amplitude of N-Acetyl-Aspartate and the assumption the latter has a concentration of 10.1 mM.

Results
Ryan Hypoglycemia Score was 2145.7 (458-4315) and 118.3 (0-355) for T1DM and T1DM Control subjects, respectively, confirming the difference in severity of antecedent hypoglycemia and unawareness. The levels of counterregulatory hormones epinephrine and glucagon did not change in T1DM during hypoglycemia compared to the basal situation, in contrast to non-diabetic controls (Figure 1). Steady state fractional ¹³C enrichment of plasma glucose and acetate concentration and fractional ¹³C enrichments. MR spectra were fitted using an LC model approach with in-house built software. Steady state ¹³C fractional enrichments were calculated from the last 30 min of [²-¹³C]-acetate infusion, based on the amplitude of N-Acetyl-Aspartate and the assumption the latter has a concentration of 10.1 mM.

Discussion
The higher ¹³C fractional enrichment of GLN C4 in T1DM is consistent with increased transport of acetate across the blood brain barrier and metabolism of acetate within glial cells in the brain. Furthermore, these results support the hypothesis that increased transport and metabolism of MCAs may be a protective adaptation among T1DM individuals with hypoglycemia unawareness by providing alternative non-glucose fuels during episodes of acute glucose deprivation. GLN C4 labeling in the T1DM control group was comparable to the non-diabetic control group. This suggests that the significantly increased MCA transport and metabolism seen in the T1DM hypoglycemia unaware group is a function of recurrent hypoglycemia, rather than diabetes per se. The inverse relationship between the epinephrine response to acute hypoglycemia and CNS MCA transport and metabolism (as measured by GLN C4 labeling) across the entire study population suggests that the CNS cortical adaptation is an adaptation to recurrent hypoglycemia, independent of diabetes.

References

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