Increased Brain Lactate Concentrations without Increased Lactate Oxidation during Hypoglycemia in Type 1 Diabetic Individuals with Hypoglycemia Unawareness

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Introduction

Previous studies have reported that brain metabolism of acetate is increased more than two-fold in type 1 diabetic subjects with hypoglycemia unawareness. These data support the hypothesis that upregulation of blood-brain barrier monocarboxylic acid (MCA) transport may contribute to the maintenance of brain energetics during hypoglycemia in subjects with hypoglycemia unawareness. Plasma lactate concentrations are approximately ten-fold higher than acetate concentrations, making lactate the most likely alternative MCA to act as brain fuel. We therefore examined transport of [3-^{13}C]-lactate across the blood-brain barrier and its metabolism in brain of type 1 diabetic patients with hypoglycemia unawareness and non-diabetic control subjects during a hypoglycemic clamp using ^{13}C magnetic resonance spectroscopy (MRS).

Materials and methods

Five healthy type I diabetic patients with a history of hypoglycemia unawareness (Age: 34±5 yrs, BMI: 23.0±1.5 kg/m^2) and six healthy control subjects matched for BMI (Age:24±1 yrs, BMI:23.5±0.9 kg/m^2) were recruited. The type I diabetic subjects all showed well to moderate glycemic control (Hb_{A1C}: 7.6±0.9 %) and had a self-reported history of hypoglycemia unawareness. ^{13}C MR spectra were acquired during 90-120 min infusion of [3-^{13}C]-lactate (10 μmol/(kg-min) which started after establishing steady low plasma glucose levels of 3-3.5 mM. The degree of symptoms experienced by the subjects during the study was assessed using a standard questionnaire [1] before and during the induction of hypoglycemia (20 and 80 min following [3-^{13}C]-lactate infusion). MR 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 ^{13}C coil for acquisition and two quadrature ^{1}H surface coils for imaging, shimming, polarization transfer and decoupling. Following scout imaging, shimming was performed using the FASTERMAP [2] procedure and decoupling power was calibrated. ^{13}C 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 90 ml voxel located in the occipital-parietal lobe [3]. Blood samples were collected every 5-10 minutes for determination of plasma glucose and lactate concentration and fractional ^{13}C enrichments. MR spectra were fitted using an LC model approach with in-house written software. Concentrations of ^{13}C lactate, glutamate (Glu) and glutamine (Gln) were calculated using the averaged NAA C3 and C6 peak amplitudes and assumed concentration for NAA of 11 μmol/g. Fractional ^{13}C enrichment of Glu C4 and Gln C4 were determined assuming concentrations for Glu (9.8 μmol/g) and Gln (4.2 μmol/g). Brain lactate concentrations were determined from the measured ^{13}C concentration of lactate C3 by assuming that at steady state the fractional ^{13}C enrichment of C3 lactate was similar to that of Glu C4. Data are presented as mean ± SEM

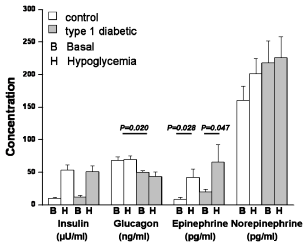

Figure 1. Plasma hormone concentrations measured during basal conditions (B) and hypoglycemia (H). Bars represent mean ± SEM.

Results

Following the start of the [3-^{13}C]-lactate infusion, plasma lactate concentrations quickly increased to 1.77±0.40 mM in control subjects and 1.33±0.21 mM in type 1 diabetes subjects (*P=0.05*). The average ^{13}C fractional enrichment of plasma lactate was 26.2±4.0% in control and 31.6±6.7% in type 1 diabetic subjects (*P=0.13*). Upon inducing hypoglycemia, only plasma epinephrine concentrations increased from baseline concentrations (*P<0.05* for both groups), and this increase was similar in the two groups (Fig.1). Scoring of symptoms normally associated with hypoglycemia did not reveal a difference between the groups. Figure 2 shows examples of ^{13}C MR spectra averaged over the last 30 minutes of [3-^{13}C]-lactate infusion from a control and a type 1 diabetic subject, respectively. Glu C4 ^{13}C fractional enrichment increased quickly following the infusion of [3-^{13}C]-lactate reaching similar steady state levels (corrected for 1.1% natural abundance) of 2.80±0.30% in control and 2.68±0.18% in type 1 diabetic subjects (*P=0.40*). GlnC4 ^{13}C fractional enrichment was 1.89±0.46% in control and 1.99±0.37% in type 1 diabetic subjects (*P=0.77*). The calculated brain lactate concentrations were increased by more than fivefold in the type 1 diabetic subjects (1.65±0.60 μmol/g) compared to the control subjects (0.32±0.16 μmol/g, *P<0.05*)

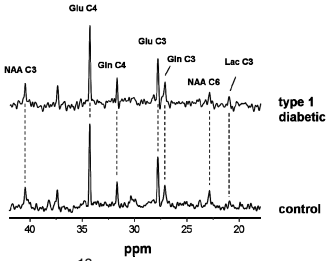

Figure 2. ^{13}C MR spectra of a type 1 diabetic (top) and control subject (bottom) averaged over the last 30 min of [3-^{13}C]-lactate infusion.

Discussion

Administration of lactate during hypoglycemia resulted in pronounced blunting of the counter-regulatory response in control subjects as evidenced by an almost identical hormone profile as seen in the hypoglycemia unaware type 1 diabetes subjects (Fig.1). In support of increased MCA transport capacity in the type 1 diabetic subjects we found elevated concentrations of lactate in the brain during the infusion of [3-^{13}C]-lactate. Surprisingly, despite the several-fold higher brain lactate levels in the diabetic subjects, the fractional entry of blood-borne lactate into the brain lactate pool did not appear any different from control subjects, given similar Glu C4 fractional enrichments. These data suggest that in addition to increased MCA transport at the blood-brain barrier there may be other metabolic adaptations, most likely increased glucose metabolism, that contribute to hypoglycemia unawareness in patients with type 1 diabetes.

References

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