Measuring brain lactate with ^{1}H-MRS during hypoglycemia in humans; preliminary results

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Target audience: (Clinical) researchers interested in diabetes, hypoglycemia or brain metabolism in general.

Purpose: Iatrogenic hypoglycemia is the most frequent acute complication of insulin therapy in people with type 1 diabetes (T1DM). Recurrent hypoglycemia initiates a process of habituation, characterized by suppression of hypoglycemic symptoms and compromised hypoglycemic awareness, resulting in a high risk of severe hypoglycemia. Recent evidence suggests a pivotal role for increased brain lactate transport capacity as underlying mechanism.[1,2,3] The primary objective of this study is to investigate the effect of hypoglycemia on brain lactate content.

Methods: *Subjects and procedure:* After an overnight fast, 3 healthy volunteers (2 males, mean age: 23.6 ± 1.5 yrs, mean BMI: 22.8 ± 1.85 kg/m^2) underwent a stepped hyperinsulinemic (60 mU·m^2·m^{-1}) euglycemic-hypoglycemic glucose clamp, during which arterial plasma glucose levels were kept at 5.0 mmol/l for the euglycemic phase (30 min) and at 2.8 mmol/l for the hypoglycemic phase (45 min). Arterial plasma glucose levels and plasma lactate levels were determined every 5 minutes.

Brain lactate detection with ^{1}H-MRS: MR data were acquired at 3.0 T (Siemens, Trio) from a 31.25 cm^3 MRS voxel (2.5 x 5 x 2.5 cm), placed in the supraventricular cortex. ^{1}H-MR spectra were acquired with an interleaved J-editing semi-LASER sequence with TE 144 ms and TR 3000 ms and 32 averages. J-editing was performed with MEGA-pulses with a bandwidth of 7 Hz centered on the lactate quartet at 4.11 ppm. The power of the MEGA-pulse was switched on and off in an interleaved fashion, resulting in spectra where the lactate doublet at 1.33 ppm is negative (MEGA power off) or positive (MEGA power on). As a consequence, difference spectra contained only the (positive) lactate doublet, removing all other signals from the spectra.

Post-processing and quantification All spectra were zero-filled (from 1024 to 2048 points) and phase and frequency aligned with respect to the first recorded 'reference' spectrum. Alignment was done by maximizing the normalized scalar product between this reference spectrum and the other spectrum in Matlab (R2014a, the MathWorks). Apodized (5 Hz Lorentzian) difference spectra were created from every couple of spectra with the MEGA-pulse on and off, and subsequently two consecutive difference spectra were averaged to enable accurate measurement of the lactate doublet. The lactate signal was quantified using the AMARES algorithm in jMRUI[4] and the unsuppressed water signal, recorded with a shorter TE (30 ms), from the same voxel (sLASER, TR 5000 ms, 8 averages). The following assumptions were made for quantification of brain lactate levels: a T2-value of 240 ms for lactate[5] and 110 ms for water, 70% water content in the brain[6] and, regarding the used TRs, neglectable T1-effects. The amount of brain lactate measured during stable euglycemia and hypoglycemia was averaged. Data are presented as mean ± standard error of the mean. A paired sample t-test was performed to determine significant differences (p<0.05) between both glycemic conditions.

Results Plasma glucose levels stabilized at 4.68 ± 0.21 mmol/l and 2.90 ± 0.02 mmol/l during euglycemia and hypoglycemia, respectively. Plasma lactate levels increased significantly from 1.27 ± 0.23 mmol/l during euglycemia to 1.67 ± 0.17 mmol/l during hypoglycemia (mean change: 0.40±0.07 mmol/L, p=0.03).^{1}H-MRS was successful in detecting brain lactate as the lactate doublet was visible in all difference spectra. An example of a representative edited spectrum is shown in Fig. 1. We did not find changes in brain lactate levels between both glycemic conditions (euglycemia 0.39 ± 0.05 µmol/g, hypoglycemia 0.30 ± 0.02 µmol/g; mean change -0.09±0.03 µmol/g, p=0.12), as shown in Fig. 2.

Discussion and conclusion These preliminary data, obtained in healthy volunteers, suggest that increased plasma lactate levels during hypoglycemia are not accompanied by an increase in lactate content in the brain. Our data, which appear in line with those of Terpstra et al. 2014,[7] indicates either that excess lactate is not taken up by the brain, due to a relatively low amount of monocarboxyl-transporters (MCT),[8] or that lactate does not accumulate in the brain because it is immediately utilized. Further research, in both healthy subjects and (hypoglycemia unaware) T1DM patients, will determine the effect of hypoglycemia on brain lactate in these groups in more detail.

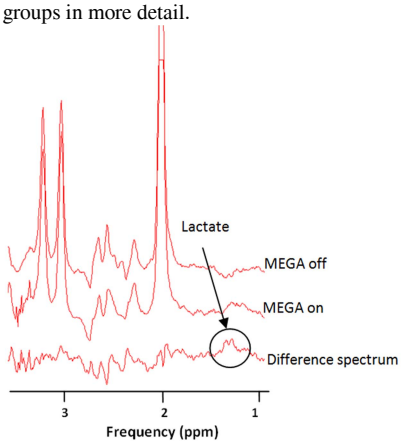

Fig. 1 MEGA off, MEGA on and difference spectrum. The lactate doublet is clearly visible at 1.33 ppm in the difference spectrum.

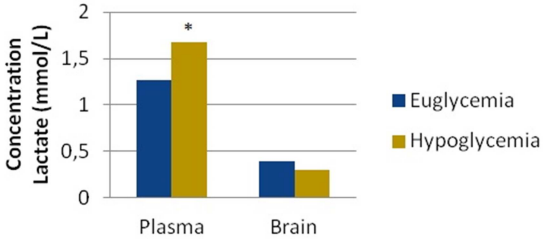

Fig. 2 Mean concentrations of lactate in the plasma and in the brain during euglycemia and hypoglycemia. The * determines a significant change in lactate concentration compared to euglycemia (p < 0.05).

References

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