Glycogen Utilization during Hypoglycemia in the Human Brain

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Introduction

The role of brain glycogen, the main glucose reservoir in this tissue, has been elusive. Studies in rat brain have suggested a neuroprotective role for brain glycogen under glucose deprivation, such as during hypoglycemia (1). However, until our recent development of an OVS-based, non-echo localization technique to measure human brain glycogen metabolism after incorporation of ^{13}C-glucose into the molecule (2, 3), no methods were available to study the function and regulation of glycogen in vivo in the human brain. Using this method we observed significant glycogen content (3-4 µmol/g) in the human brain that turns over slowly (time constant for turnover ~ 1 day) (4). The aim of the current study was to test the hypothesis that glycogen provides fuel to the brain during hypoglycemia in humans.

Methods and Subjects

All measurements were performed on a 4 T / 90 cm magnet (Oxford/Varian). A quadrature 14 cm ^{1}H surface coil with a 9 cm diameter linear ^{13}C coil was used. Localization was achieved by 3D outer volume suppression (OVS) combined with 1D ISIS (3). Four healthy volunteers (3 M / 1 F, 41 ± 14 (SD) years old) received IV a total of 186 g of 99% enriched [1-^{13}C]glucose over 11 ± 1 (SD) h to pre-label glycogen. During the infusion, average blood glucose levels were 133 ± 17 mg/dL and average isotopic enrichment of plasma glucose 70 ± 10 % (determined by GC-MS). Following the ^{13}C-glucose infusion, unlabeled glucose was infused for 1-2.5 h to facilitate label wash-out from blood glucose. 5 ± 1 h after cessation of the ^{13}C-glucose infusion each participant underwent a 2 h long hyperinsulinemic, euglycemic (average blood glucose 96 ± 3 (SD between subjects) mg/dL) and hyperinsulinemic, hypoglycemic (average blood glucose 53 ± 5 mg/dL) clamp on separate occasions, hence each served as their own control. During the clamps the [1-^{13}C]glycogen signal localized to the occipital lobe (7 × 5 × 6 cm^3) was measured and quantified using the external referencing method (2). The [1-^{13}C]glycogen concentrations were divided by the plasma glucose enrichments to correct for differences in isotopic enrichments between subjects and to determine the newly synthesized glycogen concentrations. During each clamp, 4 glycogen spectra were acquired, each over 0.5 h.

Results and Discussion

The study was designed to determine if the rate of label wash-out from [1-^{13}C]glycogen is higher during hypoglycemia than during euglycemia, which would indicate glycogen utilization in the brain under glucose deprivation. We have indeed detected a significantly higher rate of ^{13}C wash-out during hypoglycemia (0.12 ± 0.05 µmol/g/h) than during euglycemia (0.01 ± 0.05 µmol/g/h, $p = 0.02$). The glycogen signal was stable during the euglycemic clamps while it decreased during the hypoglycemic clamps (Figs. 1 and 2). A paired comparison of the normalized integrals of the second, third and fourth glycogen spectra during eu- vs. hypoglycemic clamps of all participants also revealed a highly significant difference ($p < 0.001$).

These data represent the first evidence for glycogen utilization in the human brain during hypoglycemia. Together with our previous results regarding very slow turnover of bulk brain glycogen under normal physiology (4), they support the hypothesis that brain glycogen is utilized to support energy metabolism when glucose supply from the blood is inadequate.

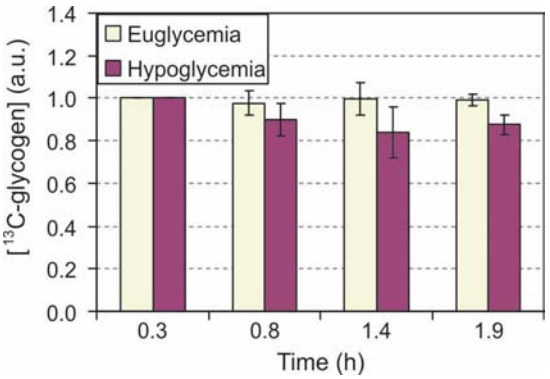

Fig 1. Change in [1-^{13}C]glycogen signal during eu- and hypoglycemic clamps. Error bars indicate SD between subjects. Glycogen integrals were normalized to the spectrum acquired during the first half hour of the clamp.

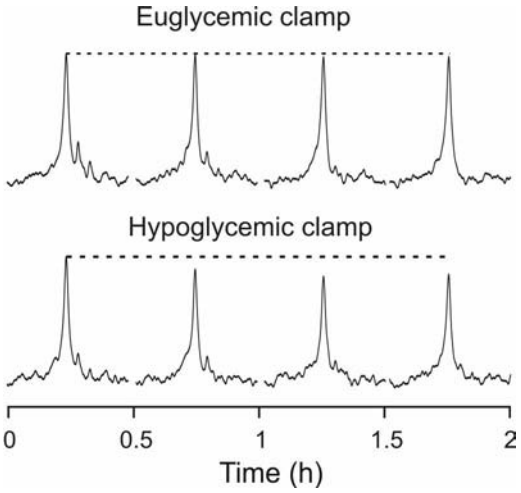

Fig 2. Localized [1-^{13}C]glycogen spectra (TR = 0.45 s, NEX = 4096 x 4, VOI = 210 ml) acquired from the occipital lobe during eu- and hypoglycemia clamps. Spectra were averaged over 4 volunteers and normalized with respect to the first 0.5 h spectrum.

References

1. Choi et al, *J Neurosci Res*, 72:25, 2003. **2.** Öz G et al, *Neurochem Int,* 43: 323, 2003. **3.** Öz G et al, *Appl Magn Reson,* 29: 159, 2005. **4.** Öz G et al, *Proc ISMRM*, 13: 208, 2005.

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