^{13}C MR Measurement of Glycogen Content in the Human Brain

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Introduction

The role of glycogen in the brain has been elusive. Until recently no methods were available to study its content and metabolism in vivo in the human brain. We have reported detection of human brain glycogen by ^{13}C NMR utilizing an OVS-based, non-echo localization method (1). Using this method we observed a low amount of ^{13}C label incorporation into glycogen after 6 hours of ^{13}C-glucose infusion and a very slow label washout, indicating a slow synthesis rate and turnover, respectively (2). The aim of the current study was **(a)** to determine if label incorporation from [1-^{13}C]glucose into human brain glycogen represents primarily turnover or net synthesis and **(b)** to estimate human brain glycogen content using a model of brain glycogen metabolism.

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 (1). Six healthy volunteers (4 males, 2 females, 39 ± 13 years old) were studied after an overnight fast by administering i.v. a total of 80-615g of [1-^{13}C]glucose using three experimental protocols: (A) 99% enriched glucose was administered for 6 h (n=2), (B) for 22 h (n=2) or (C) 50% enriched glucose was administered for 44 h (n=2). The blood glucose levels were maintained at 38 ± 10% above fasting baseline glucose. The isotopic enrichment of plasma glucose was determined by GCMS. The subjects were scanned every 2-10 h during and following the infusion for up to 84 h after the start of the glucose administration. The [1-^{13}C]glycogen signal in the occipital lobe was quantified using the external referencing method (1). The [1-^{13}C]glycogen concentrations were divided by the plasma glucose enrichments to correct for differences in isotopic enrichment between subjects.

A model of glycogen metabolism (Fig. 1) was fitted to the time courses of the newly synthesized glycogen from the 3 subject groups simultaneously using the software SAAM II (The SAAM Institute, Seattle, WA), assuming $V_{phos} = V_{syn}$, a constant brain glycogen concentration and that complete [1-^{13}C]glucose washout from blood was achieved within 2-6 hours.

Results and Discussion

^{13}C labeled brain glycogen levels continued to increase for 44h of [1-^{13}C]glucose infusion without reaching an apparent plateau (Fig. 2). Furthermore, the label washout rate increased with increasing labeling of glycogen indicating that the label incorporation kinetics primarily represent turnover rather than net synthesis (Fig. 2), ie. $V_{phos} = V_{syn}$ (Fig. 1). Indeed, when fitting the model (Fig. 1) to the data from all 3 experimental groups, an excellent fit was obtained with $V_{syn} = V_{phos} = 0.15 \pm 0.01$ µmol/g/h. The total glycogen content was estimated at 3.6 ± 0.1 µmol/g. The determination of V_{syn} and total glycogen concentration did not vary substantially when fitting the 3 experimental groups individually. Together these results indicate a time constant for glycogen turnover of ~ 24h, *i.e.* it takes ~3-5 days to completely turnover human brain glycogen, in agreement with our previous estimates (2). In addition, the combined data permit a robust estimation of human cortical brain glycogen content.

References

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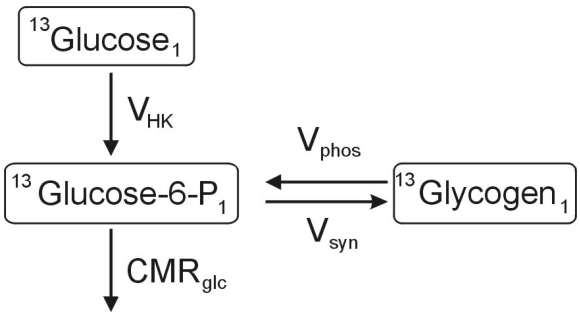

Fig. 1. Model of glycogen metabolism. The superscript 13 indicates ^{13}C labeled pools and the subscript 1 the label position C1. Abbreviations: V_{phos}, glycogen phosphorylase rate; V_{syn}, glycogen synthase rate; CMR_{glc}, cerebral metabolic rate of glucose utilization; V_{HK}, hexokinase rate. A previous estimate of CMR_{glc} in the human brain was used (0.4 µmol/g/min = 24 µmol/g/h, ref. 3)

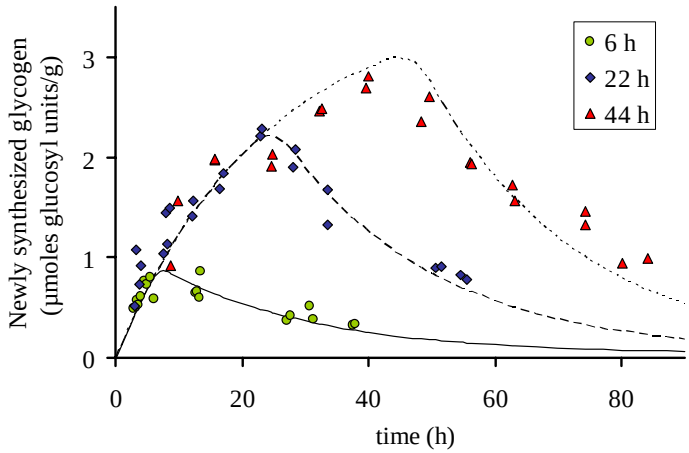

Fig. 2. ^{13}C label incorporation into and wash-out from glycogen C1 over time. [1-^{13}C]Glucose was administered for 6h (n=2), 22h (n=2) and 44h (n=2). The 3 subject groups are shown with different symbols. Each data point represents 25-32 min averaging (VOI=210ml in the occipital lobe) and was corrected for the isotopic enrichment of plasma glucose. The lines represent the best fit of the model in Fig. 1 fitted to all subject groups simultaneously.