

Measurement of Brain Glycogen Metabolism by Localized ^{13}C MR Spectroscopy in Humans

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Brain glycogen was detected in three conscious humans with ^{13}C MR spectroscopy after infusion of $[1-^{13}\text{C}]$ glucose. The signal was localized by the use of a non-echo, outer volume suppression method that reduced the signals from outside the voxel by more than 100-fold, thereby minimizing contamination from the higher concentrated muscle glycogen. Based on the rate of ^{13}C label incorporation into glycogen and the isotopic enrichment of plasma glucose, the flux through glycogen synthase was estimated at $0.17 \pm 0.05 \mu\text{mol/g/h}$ indicating that brain glycogen metabolism is very slow in the conscious human brain.

Introduction

Virtually nothing is known about human brain glycogen metabolism since no method to noninvasively detect it in the conscious human has been available. The measurement of brain glycogen by NMR is challenging due to the requirement to eliminate the signal from the much more concentrated muscle glycogen (1). A recent study reported detection of a glycogen NMR signal in ~1000 scans at 3 Tesla from the head of a subject following subtraction of a pre-infusion spectrum in conjunction with use of surface dephasing gradients (2). However, considering the potential contribution of non-cerebral muscle glycogen to the NMR signal, use of three-dimensional localization methods is of paramount importance in establishing the cerebral origin of the signal. The feasibility of applying a non-echo localization method to human brain was recently established (3). The aim of the current study was to detect the fully localized ^{13}C NMR signal of glycogen in the human brain and to provide an estimate of the rate of label incorporation into glycogen from $[1-^{13}\text{C}]$ glucose.

Methods and Subjects

All measurements were performed on a 4 Tesla/90 cm magnet (Oxford/Varian). A quadrature 14 cm ^1H surface coil with a 9 cm diameter linear ^{13}C coil was used (4). The localization was achieved by outer volume suppression (OVS) in three dimensions combined with 1D ISIS as described previously (1, 3). Quantitation of the ^{13}C label in the C1 position of glycogen was done by the external referencing method (5).

Three healthy males were studied after an overnight fast by administering a total of 80g of $[1-^{13}\text{C}]$ glucose designed to maintain the isotopic ^{13}C enrichment (measured by GCMS) of plasma glucose above 50% for the first 4.5 hours of the study.

Results and Discussion

Two hours after the start of the administration of ^{13}C labeled glucose the ^{13}C NMR signal of glycogen C1 was detected at 100.5 ppm in all three subjects, along with the C1 resonances of β - and α -glucose (Fig. 1). The localization method suppressed the signals from outside the voxel by more than 100-fold in each subject as assessed by the suppression of the extra-cerebral lipid signals (3).

In order to estimate the rate of label incorporation into glycogen, the amount of ^{13}C label was quantified as a function of time (Fig.2). Linear regression of all data points between 2.5 - 4.5 hours resulted in a rate of label incorporation of $0.11 \pm 0.04 \mu\text{mol/g/h}$ ($R = 0.76$, $p = 0.01$) with a y-intercept not significantly different from 0. Since the average isotopic enrichment of the precursor glucose over this period was 64 %, the flux through the glycogen synthesis pathway was estimated at $0.17 \pm 0.05 \mu\text{mol/g/h}$, indicating very slow metabolism of bulk brain glycogen in the conscious human brain.

References

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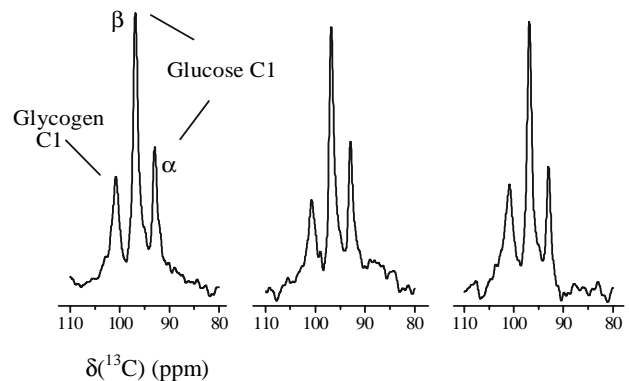


Fig. 1. Localized ^{13}C NMR spectra of glycogen and glucose C1 resonances averaged over 75 minutes in 3 subjects (VOI=210 ml in occipital lobe, TR=0.3s).

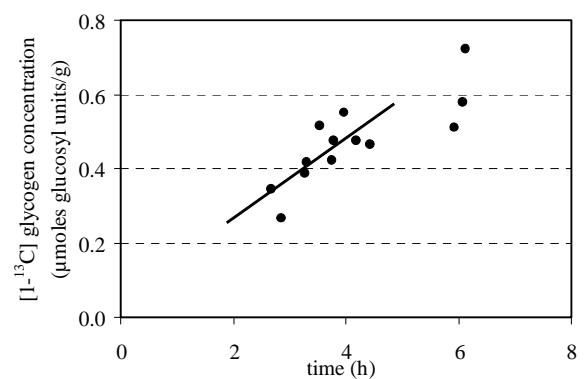


Fig.2. Quantification of ^{13}C label ($\mu\text{mol/g}$) incorporation into glycogen C1 over time. Administration of labeled glucose was begun at time zero. For each data point, NMR spectra were averaged over 25 minutes.