Does Brain Glycogen Supply Fuel for Neuronal Activation?

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Introduction

The role of brain glycogen, the main glucose reservoir in this tissue, has been elusive. Cell culture and rodent studies have led to two schools of thought about the role of brain glycogen: 1) support of axonal function under normal physiology by responding to sudden increases in energy demand during neurotransmission, and 2) neuroprotection under glucose deprivation, such as during hypoglycemia. Until recently no methods were available to study the function and regulation of glycogen in vivo in the human brain. We developed an OVS-based, non-echo localization method to measure human brain glycogen metabolism after incorporation of ^{13}C-glucose into the molecule (1, 2). Using this method we observed significant glycogen content (3-4 µmol/g) in the human brain that turns over very slowly (time constant for turnover ~ 1 day) (3). The aim of the current study was to test the first hypothesis about glycogen's role in the brain, namely that glycogen provides fuel to brain during neuronal activation.

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 (2). Five healthy volunteers (4 M/1F, 29 ± 13 years old) were studied after administering i.v. a total of 200-615 g of [1-^{13}C]glucose over 13-50 h to pre-label glycogen. The isotopic enrichment of plasma glucose was determined by GCMS. Following the infusion, when plasma glucose was no longer enriched (7-12 h after cessation of glucose infusion), [1-^{13}C]glycogen signal localized to the visual cortex (3×2.5×3 cm^3) was acquired before and after 20 minutes of continuous visual stimulation with a radial checkerboard pattern flickering at 8 Hz. To compare the pre- and post-stimulus intensity, the ^{13}C-glycogen signal was integrated using built-in spectrometer software. Attention control assured the subjects' compliance with the long stimulus. To ensure optimal voxel placement, BOLD activation maps were recorded prior to the glucose infusion using spin-echo blipped echo-planar imaging and a block paradigm of alternating intervals of 30 seconds with and without stimulation.

Results and Discussion

The study was designed to detect a reduction in [1-^{13}C]glycogen signal intensity after a strong visual stimulus if glycogen breakdown/turnover was increased significantly with neuronal activation. Thus, the experiment was performed when plasma glucose enrichment was negligible such that any ^{13}C-glucose removed from glycogen would not be replenished by plasma ^{13}C-glucose if glycogen turnover increased with neuronal activation. However, no significant difference was observed between [1-^{13}C]glycogen intensity before and after visual stimulation (Fig.), indicating no detectable increase in glycogen breakdown/turnover upon visual stimulation. Our method has the sensitivity to detect a signal change of ~20% in individuals; hence glycogen turnover/breakdown rates comparable to glucose utilization in the human brain (0.4 µmol/g/min, ref. 4) would have been easily detectable. Nevertheless, mobilization of a small fraction of the large glycogen molecule or increased glycogen utilization in a small fraction of the VOI cannot be ruled out.

Together with a very slow turnover of bulk brain glycogen (3), this observation lends support to the hypothesis that brain glycogen is primarily utilized when glucose supply from the blood is inadequate, rather than being continuously and extensively utilized under normal physiological conditions.

References

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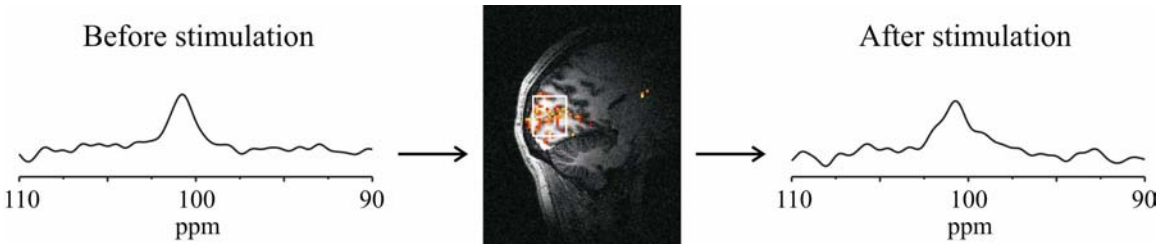

Fig. Localized [1-^{13}C]glycogen spectra (TR = 0.3 s, NEX=5120, VOI = 22.5 ml) acquired from the visual cortex before and after 20 minutes of visual stimulation in one volunteer. The voxel position was based on the BOLD activation map obtained in a separate scanning session prior to the [1-^{13}C]glucose infusion.