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Human brain glycogen content and metabolism: implications on its role in brain energy metabolism

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Öz G, Seaquist ER, Kumar A, Criego AB, Benedict LE, Rao JP, Henry PG, Van De Moortele PF, Gruetter R. Human brain glycogen content and metabolism: implications on its role in brain energy metabolism. *Am J Physiol Endocrinol Metab* 292: E946–E951, 2007. First published November 28, 2006; doi:10.1152/ajpendo.00424.2006.—The adult brain relies on glucose for its energy needs and stores it in the form of glycogen, primarily in astrocytes. Animal and culture studies indicate that brain glycogen may support neuronal function when the glucose supply from the blood is inadequate and/or during neuronal activation. However, the concentration of glycogen and rates of its metabolism in the human brain are unknown. We used in vivo localized ^{13}C-NMR spectroscopy to measure glycogen content and turnover in the human brain. Nine healthy volunteers received intravenous infusions of [1-^{13}C]glucose for durations ranging from 6 to 50 h, and brain glycogen labeling and washout were measured in the occipital lobe for up to 84 h. The labeling kinetics suggest that turnover is the main mechanism of label incorporation into brain glycogen. Upon fitting a model of glycogen metabolism to the time courses of newly synthesized glycogen, human brain glycogen content was estimated at ~3.5 μmol/g, i.e., three- to fourfold higher than free glucose at euglycemia. Turnover of bulk brain glycogen occurred at a rate of 0.16 $\mu mol \cdot g^{-1} \cdot h^{-1}$, implying that complete turnover requires 3–5 days. Twenty minutes of visual stimulation ($n = 5$) did not result in detectable glycogen utilization in the visual cortex, as judged from similar [^{13}C]glycogen levels before and after stimulation. We conclude that the brain stores a substantial amount of glycogen relative to free glucose and metabolizes this store very slowly under normal physiology.

glucose; ^{13}C nuclear magnetic resonance spectroscopy; visual stimulation

ENERGY METABOLISM IN THE BRAIN is compartmentalized between neurons and glia. Both cells metabolize glucose, the primary fuel for the adult brain. Although neurons utilize the majority of energy (16, 25), glial cells appear to support neurotransmission by increasing glycolysis as well as oxidative metabolism (25). Interestingly, in the adult brain the glucose storage molecule glycogen is primarily localized to astrocytes (37), the most abundant glial cells in the central nervous system. Glycogen content in astrocyte cultures and brain slices is regulated by numerous factors, including glucose, hormones, and neurotransmitters, indicating its involvement in the metabolic response to glycemic/hormonal state and brain activation (11, 17, 22). In vivo, glycogen content has been shown to be affected by glucose and insulin, among other factors (6, 23). On the basis of cell culture and animal model studies, astrocytic glycogen may support axonal function under normal physiology by responding to sudden increases in energy demand during neurotransmission (33) and/or provide neuroprotection primarily under glucose deprivation (32, 36), such as during hypoglycemia (6). To support neuronal function, astrocytes are thought to break down glycogen to lactate, or potentially to glucose (15), which is then exported to neurons as fuel (4, 10). Alternatively, astrocytes may utilize glycogen, sparing glucose for neurons (31). Despite significant progress, the primary role of brain glycogen has not been firmly established to date, and in vivo investigations designed to elucidate the circumstances under which glycogen is mobilized have been few.

Until recently, no methods have been available to study the function and regulation of glycogen in vivo in the human brain. Based on extensive work in rat brain (7), we recently developed a localized ^{13}C NMR method to measure human brain glycogen metabolism in the occipital lobe. This method involves administration of [^{13}C]glucose and measures its incorporation into brain glycogen with negligible contamination from subcutaneous muscle glycogen (26, 27). [1-^{13}C]glucose has been the substrate of choice, as the NMR resonance of [1-^{13}C]glucose in glycogen is well resolved from those of free [1-^{13}C]glucose as well as other glucosyl positions. In initial studies using this method, we observed very slow label incorporation into brain glycogen upon intravenous (iv) infusions of [1-^{13}C]glucose for up to ~6 h, with turnover rates that suggested that much longer infusion times were necessary to achieve complete isotopic turnover of cerebral glycogen (26). Therefore, the aims of the current study were *1*) to measure human brain glycogen content and turnover by continuously infusing [1-^{13}C]glucose for extended time periods, *2*) to determine the minimum duration of glucose infusion that would enable a reliable assessment of brain glycogen content and metabolism, and *3*) to test the hypothesis that glycogen provides fuel to the brain during neuronal activation.

MATERIALS AND METHODS

Participants and study design. Nine healthy volunteers (6 M/3 F, age 33 ± 14 yr, BMI 25 ± 4 kg/m^2, mean ± SD) were studied after giving informed consent using procedures approved by the Institutional Review Board: Human Subjects Committee. On the morning of the study, subjects reported between 6 and 7 AM to the General Clinical Research Center in the fasting state. Intravenous catheters placed antegrade in contralateral arms were used for [^{13}C]glucose infusion and blood sampling. A total of 80–615 g of [1-^{13}C]glucose (Isotec, Miamisburg, OH and Cambridge Isotope Laboratories, Andover, MA; prepared as 20% wt/vol D-glucose in water with 50 or

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99% isotopic enrichment) was administered into the arm vein. An initial bolus to rapidly raise blood glucose enrichment was followed by continuous infusion using a peristaltic pump. The infusion rate was adjusted to maintain blood glucose at 25% above basal levels, based on measurements done on an automatic glucose meter (OneTouch SureStep; Lifescan, Milpitas, CA) to minimize endogenous hepatic glucose production and achieve stable glucose enrichments, since postprandial insulin levels are known to suppress hepatic glucose output (2). Additional blood samples were immediately frozen for the later determination of isotopic enrichment of plasma glucose by gas chromatography-mass spectroscopy, as described previously (16). The volunteers received [1-^{13}C]glucose infusions for 6 ($n = 2$), 11 ($n = 2$), 22 ($n = 2$), and 46 ± 5 (SD) h ($n = 3$). Additionally, 5 of the volunteers who received infusions for 11–46 h (4 M/1 F, age 29 ± 13 yr, BMI 24 ± 4 kg/m^2) participated in visual stimulation studies conducted after plasma glucose isotopic enrichment was reduced to negligible levels.

NMR spectroscopy. All measurements were performed on a 4-Tesla, 90-cm bore magnet (Oxford Magnet Technology, Oxford, UK) with an INOVA console (Varian, Palo Alto, CA) as described previously (26, 27). A quadrature 14-cm ^{1}H coil combined with a 9-cm-diameter linearly polarized ^{13}C coil was utilized (1). Subjects were scanned every 2–10 h for up to 84 h after the start of the glucose infusion, and each scan lasted for 1–1.5 h except for those where glycogen utilization during visual activation was studied (see below). Those scans lasted for 2.5 h. These scan times included power and shim adjustments, imaging, and spectral acquisition. Each spectrum/data point presented here was averaged over 25–32 min.

The localized [1-^{13}C]glycogen NMR signal was acquired and processed and the amount of ^{13}C label in the C1 position of glycogen quantified as described previously (26, 27). Voxel dimensions were $7 \times 5 \times 6$ cm^3 for glycogen turnover studies and $3 \times 2.5 \times 3$ cm^3 for visual activation studies. Data were acquired in blocks of 1,024 scans (5–8 min), each of which was stored separately on disk prior to summation of 4–5 of these blocks for each data point.

Modeling glycogen turnover. 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. A model of glycogen metabolism (Fig. 1) was fitted to the time courses of the newly synthesized glycogen from the four subject groups (6-, 11-, 22-, and 46-h infusion groups) using the software SAAM II (SAAM Institute, Seattle, WA). To test whether the labeling kinetics primarily represented turnover or net synthesis, the model was built as a turnover model such that a good fit of the data to the model would indicate lack of significant net synthesis. Therefore, glycogen synthase (V_{syn}) and phosphorylase (V_{phos}) rates were set to be equal, and brain glycogen concentration was set to be constant. Thus, the fitted variables were total glycogen concentration [Glyc] and turnover rate $V_{syn} = V_{phos}$. The cerebral metabolic rate of glucose (CMR_{Glc}) in the human brain was assumed to be 0.4 μmol·g^{-1}·min^{-1} = 24 μmol·g^{-1}·h^{-1} (16) and the glucose 6-phosphate (G-6-*P*) concentration 0.1 μmol/g (35). Sensitivity analysis indicated that the results were not affected over large ranges of both of these variables (18–30 μmol·g^{-1}·h^{-1} for CMR_{Glc} and up to 1 μmol/g for G-6-*P* concentration). Concentration and rate estimates are reported as mean values ± standard deviations.

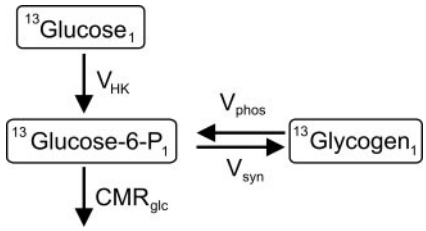

Fig. 1. Model of glycogen metabolism. Superscript 13 indicates ^{13}C-labeled pools, subscript 1 the label position C1. V_{phos}, glycogen phosphorylase rate; V_{syn}, glycogen synthase rate; CMR_{glc}, cerebral metabolic rate of glucose utilization; V_{HK}, hexokinase rate.

Glycogen utilization with visual stimulation. This experiment 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. Therefore, it was performed after plasma glucose enrichment had returned to natural abundance (7–12 h after cessation of glucose infusion) such that any [1-^{13}C]glucose removed from glycogen would not be replenished by plasma [1-^{13}C]glucose if glycogen turnover increased with neuronal activation. To assess glycogen utilization with neuronal activation, [1-^{13}C]glycogen concentration in the visual cortex was determined before and after visual stimulation for 20 min with a radial checkerboard pattern alternating between red and black colors at a frequency of 8 Hz. The visual stimulus was retroprojected onto a screen and visualized by subjects using a 45° mirror. The visual field was 36° wide and 29° high. A small cross at the center of the screen was rotated at random times and served as a fixation point for attention control. Subjects were instructed to keep their eyes open and focused on the cross at all times and to press a mouse button whenever the cross rotated. Answers were recorded, and the percentage of correct answers was above 90% in all subjects. Both the generation of the stimulus and the recording of answers from the subjects were performed using Matlab with the Psychophysics Toolbox extensions (3).

Visual activation maps were recorded during a separate session before the [^{13}C]glucose infusion. Spin-echo blipped echo-planar images [sagittal orientation, field of view 32×20 cm, matrix 128×80, echo time (TE) = 25 ms, repetition time (TR) = 6 s, 20 slices, slice thickness = 2.5 mm] were acquired. A block paradigm was used by alternating intervals of 30 s without stimulation and 30 s with stimulation for a total of 270 s. The experiment was repeated twice in each subject. Time courses of functional images were analyzed in Stimulate (30), using a cross-correlation with a hemodynamic response function (14). Activated pixels ($P > 0.3$, 3-D cluster, $n = 22$) were overlaid with an anatomic T_1 image.

RESULTS

Glycogen labeling kinetics: turnover vs. net synthesis. Steady ^{13}C enrichments were achieved in blood glucose over the long infusion periods by maintaining blood glucose levels slightly above euglycemia, using infusions of [1-^{13}C]glucose over increasing periods of up to 2 days (Fig. 2). The average blood glucose level during the infusions in all studies was 108 ± 8 (SD between volunteers) mg/dl (6.0 ± 0.4 mM), and average blood glucose isotopic enrichment was 47 ± 2% when 50% enriched glucose was infused and 74 ± 11% when 99% enriched glucose was infused. After cessation of glucose infusion, the isotopic enrichment of plasma glucose dropped rapidly, whereas the washout of ^{13}C label from cerebral glycogen lasted several days (Fig. 2).

Label incorporation into glycogen was very reproducible between the four groups (see overlap of data points from different groups during [^{13}C]glucose infusion in Fig. 3). ^{13}C-labeled brain glycogen levels continued to increase for 46 h of [1-^{13}C]glucose infusion without reaching an apparent plateau, indicating that complete turnover of all glucosyl moieties was not achieved in 2 days (Fig. 3). The label washout rate increased with increasing labeling of glycogen, as estimated by linear regression of the first 24 h of data after cessation of glucose infusion [0.01 ± 0.01 (SE) μmol·g^{-1}·h^{-1} for the 6-h group, 0.03 ± 0.01 μmol·g^{-1}·h^{-1} for the 11-h group, 0.07 ± 0.02 μmol·g^{-1}·h^{-1} for the 22-h group, and 0.07 ± 0.02 μmol·g^{-1}·h^{-1} for the 46-h group]. Additionally, the initial label

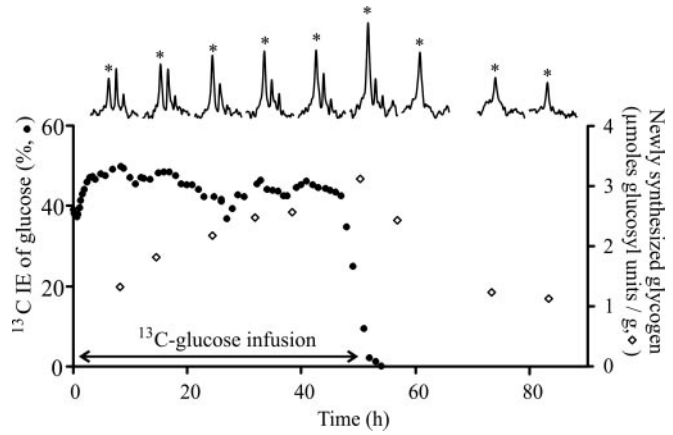

Fig. 2. ^{13}C isotopic enrichment (IE) of plasma glucose and newly synthesized glycogen concentrations (corrected for IE of plasma glucose) obtained in 1 participant. [1-^{13}C]glucose (50% enriched) was administered intravenously for 50 h. Proton-decoupled ^{13}C-NMR spectra are shown at the corresponding time points. *C1 peak of glycogen at 100.5 ppm; the other 2 peaks originate from α- and β-glucose. Each glycogen data point and spectrum represents 4,096 transients with a repetition time (TR) of 0.45 s. Volume of interest was 210 ml ($7 \times 5 \times 6$ cm^3) in the occipital lobe.

washout rate (0.07 ± 0.05 μmol·g^{-1}·h^{-1} for the 46-h group, estimated using the first 10 h of data after cessation of glucose infusion) approached the initial label incorporation rate (0.13 ± 0.02 μmol·g^{-1}·h^{-1}, estimated using the first 10-h data during glucose infusion from all groups) as steady-state levels of [1-^{13}C]glycogen were approached. Neglecting glycogen cycling to and from glucose 1-phosphate (21), the initial label incorporation rate is representative of glycogen synthase and the initial label washout rate representative of glycogen phosphorylase flux. In a pure turnover situation, where synthase (V_{syn}) and phosphorylase (V_{phos}) rates are equal, initial rates of label incorporation and washout (after complete turnover) are expected to be equal as long as the isotopic enrichment of the precursor glucose pool is changed in a step function, which was reasonably approached in the persent study (Fig. 2). Therefore, the observed ^{13}C labeling kinetics of glycogen indicated that label incorporation occurred primarily through turnover rather than net synthesis.

Modeling glycogen turnover. To further investigate whether [1-^{13}C]glucose was incorporated into glycogen through turnover, we utilized a mathematical model of glycogen turnover (Fig. 1). When the model was fitted to the data from all four experimental groups (Fig. 3*A*), an excellent fit was obtained with $V_{syn} = V_{phos} = 0.16 \pm 0.01$ μmol·g^{-1}·h^{-1}. The total glycogen content was estimated at 3.5 ± 0.1 μmol/g. These results did not vary substantially when the data were fitted from each of the four groups separately (Fig. 3*B*: $V_{syn} = 0.16 \pm 0.02$ μmol·g^{-1}·h^{-1}, [Glyc] $= 3.7 \pm 0.2$ μmol/g) or each individual participant ($V_{syn} = 0.16 \pm 0.03$ μmol·g^{-1}·h^{-1}, [Glyc] $= 3.6 \pm 0.4$ μmol/g). Table 1 shows that no trends for turnover rates were observed with decreasing infusion times, although glycogen content might be somewhat overestimated with shorter durations of infusion (6–11 h). By dividing the glycogen concentration with the turnover rate, a time constant for glycogen turnover of ~22–23 h was derived.

Glycogen utilization during visual stimulation. After the glucose infusion had been stopped and blood glucose ^{13}C enrichment dropped to negligible levels, the [1-^{13}C]glycogen signal localized to the visual cortex (based on BOLD activation maps recorded prior to the glucose infusion) was acquired before and after 20 min of continuous visual stimulation (Fig. 4). This stimulus is known to increase glucose utilization by ~25% (24) and therefore could potentially trigger glycogen utilization or increased turnover, either of which would result in a decrease in [1-^{13}C]glycogen because [^{13}C]glucosyl units removed from glycogen would be replaced by unlabeled glucose from the blood. However, no significant difference was observed between the [1-^{13}C]glycogen intensity before and after stimulation ([^{13}C]glycogen level after stimulus relative to before was $103 \pm 11\%$, $P = 0.93$), indicating no detectable increase in glycogen breakdown/turnover with this visual stimulation paradigm.

DISCUSSION

We report the first noninvasive measurement of brain glycogen content and turnover over extended periods of time in the healthy human brain. We have estimated the metabolically active glycogen content in the human brain to be 3–4 μmol/g. This compares with a glycogen concentration in the muscle of ~80 μmol/g (20) and in the liver of 200–400 μmol/g (28). However, it is still severalfold higher than the free glucose concentrations in the brain at euglycemia and therefore represents a significant energy reservoir. We also found that brain

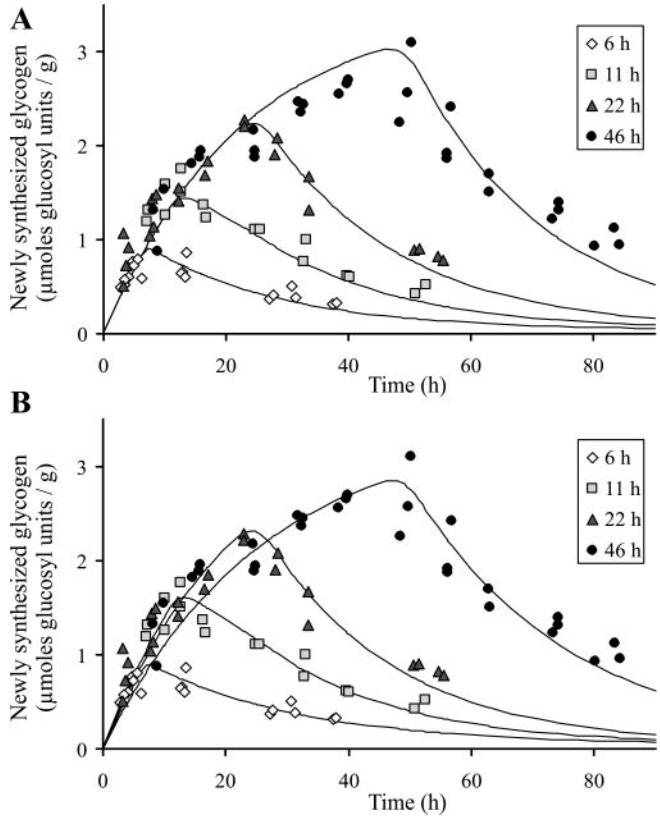

Fig. 3. ^{13}C incorporation into and washout from glycogen C1 over time. [1-^{13}C]glucose was administered for 6 h ($n = 2$), 11 h ($n = 2$), 22 h ($n = 2$), and 46 ± 5 h ($n = 3$). The 4 subject groups are shown with different symbols. Each data point represents 25–32 min averaging (volume of interest = 210 ml in the occipital lobe) and was corrected for the isotopic enrichment of plasma glucose. Lines represent the best fit of the model in Fig. 1 fitted to all subject groups simultaneously (*A*) or each group individually (*B*).

Table 1. *Total glycogen concentration and turnover rates obtained in the 4 participant groups*

	6-h Group (n = 2)	11-h Group (n = 2)	22-h Group (n = 2)	46-h Group (n = 3)
[Glyc], μmol/g	3.9	3.9	3.5	3.4
$V_{syn} = V_{phos}$, μmol·g^{-1}·h^{-1}	0.15	0.18	0.17	0.14

[Glyc], Glycogen concentration; V_{syn}, glycogen synthase rate; V_{phos}, glycogen phosphorylase rate.

glycogen turnover is very slow and that the complete turnover of human brain glycogen requires 3–5 days, based on a time constant for turnover of ~1 day. Interestingly, we did not find a change in glycogen content measured before and after a period of prolonged visual stimulation.

Although our estimate of brain glycogen concentration agrees well with brain glycogen levels reported in most rodent studies (2–6 μmol/g) (Ref. 5 and references therein), it is lower than the concentrations observed recently in carefully handled rats (11–12 μmol/g) (8). Although this might represent a species difference, it is also possible that our methodology underestimated brain glycogen content. Glycogen exists in a tiered structure, and the inner layers of the glycogen molecule may not turn over. Watanabe and Passonneau studied the turnover of the outer vs. inner tiers of brain glycogen using [^{14}C]glucose and found that the turnover time of the inner layers (designated as limit dextrin), which contain about one-half the glucose molecules stored in glycogen, was only twice of that of total glycogen in the mouse brain (35). A similar relationship in the human brain would imply a turnover time constant of ~44 h for limit dextrin and ~5 h for the outer tier, based on our turnover time estimate for total glycogen. This would mean that all of the outer tier and ~70% of limit dextrin was turned over after 2 days of glucose infusion. Considering the outer tier and limit dextrin separately did not improve the modeling of our data, justifying the use of the model in Fig. 1. On the basis of these considerations, we expect that our estimate of glycogen content is accurate.

During glycogen turnover, some of the glucosyl units that are released from glycogen may, in principle, be reincorporated into glycogen, a process called "glycogen cycling" (21). Dynamic labeling experiments of glycogen such as those described here do not measure this process, and to that extent the true glycogen synthase and phosphorylase rates might be underestimated. However, if such futile glycogen cycling, i.e., [1-^{13}C]glycogen → [1-^{13}C]G-1-*P* → [1-^{13}C]glycogen (21), operates in the brain, our data would imply either a slow exchange between G-1-*P* and G-6-*P* or a compartmentalized G-6-*P* pool that is not in exchange with blood glucose. In the absence of a separate G-6-*P* pool, the fractional enrichment of brain G-6-*P* closely mimics that of plasma glucose due to the lack of substantial activity of the gluconeogenic pathway and due to fast circulation. In any case, the turnover reported here represents glycogen synthesis from glucosyl units that originate from free glucose in the brain and breakdown into glucosyl units that are involved in further metabolism.

In this study, [1-^{13}C]glucose was incorporated into glycogen primarily through turnover rather than net synthesis. This conclusion was based on the observation that the initial washout rates approached the initial label incorporation rate as complete turnover was approached (46-h data), as well as on the excellent fits of a glycogen turnover model to the data. When very similar techniques were utilized to measure glycogen metabolism in the rat brain, net glycogen synthesis occurred (7), likely because plasma glucose concentrations were maintained between 13 and 16 mM as opposed to 6 mM in the present human study. Indeed, using biochemical extraction methods, we (23) recently demonstrated that hyperglycemia and insulin promote glycogen synthesis in the rat brain. The moderate level of hyperglycemia and hyperinsulinemia in the present study did not appear to promote significant amounts of glycogen accumulation.

We were able to maintain stable ^{13}C enrichment levels in blood glucose during the infusions, which simplified modeling of the data. Due to the complicated and expensive nature of the studies our sample size was small; however, the glycogen labeling kinetics was reproducible among subjects (Fig. 3). In addition, we obtained similar glycogen concentrations and turnover rates when fitting data from individual groups, as well as individuals, compared with all groups together (Table 1), indicating that one to two day-long infusions are not necessary and 6- to 11-h infusions are sufficient for measurements of human brain glycogen content and metabolism.

The turnover time of human brain glycogen measured in this study was long, nevertheless in agreement with rodent findings compared with CMR_{Glc}. Thus, the turnover time constant for mouse brain glycogen was 4.4 h (35) and for rat brain glycogen 7–10 h (5). These translate to glycogen turnover rates of 0.6–0.9 μmol·g^{-1}·h^{-1} in the mouse (35) and ~0.5 μmol·g^{-1}·h^{-1} in the rat (7), compared with CMR_{glc} of ~40 μmol·g^{-1}·h^{-1} (34) and 21–54 μmol·g^{-1}·h^{-1} (18, 25), respectively. As such, the turnover rates of bulk brain glycogen are 1–2% of glucose utilization rates in both rodents and humans. The turnover rates we measured might have been affected by the mild hyperinsulinemia that occurred during the glucose infusion. However, a significant portion of the fitted

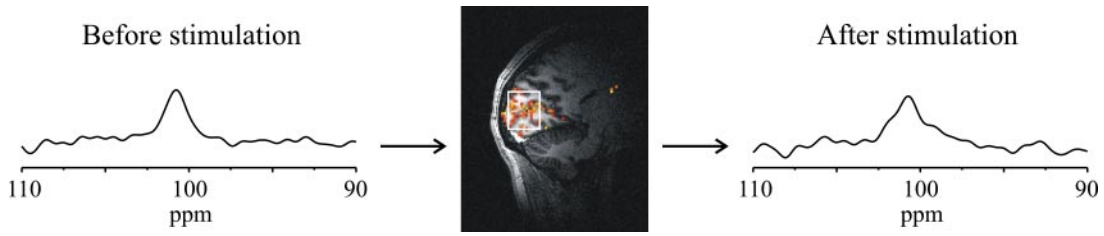

Fig. 4. Localized [1-^{13}C]glycogen spectra (TR = 0.3 s, 5,120 transients, volume of interest = 22.5 ml) acquired from the visual cortex before and after 20 min of visual stimulation in 1 volunteer. Voxel position was based on the BOLD activation map obtained in a separate scanning session prior to the [1-^{13}C]glucose infusion.

data was obtained during the label washout period after cessation of the infusion (Fig. 2). Therefore, our estimate was largely based on data acquired during normal physiology.

To more specifically evaluate the role of brain glycogen during neurotransmission, we assessed its utilization during a visual task. We were not able to detect any breakdown or increased turnover of glycogen in the visual cortex with an intense stimulus. However, mobilization of a small fraction of the large glycogen molecule, e.g., in the early stages of the stimulus prior to vasodilation, or increased glycogen utilization in a small fraction of the voxel cannot be ruled out. Although our voxel primarily contained gray matter, white matter that was unavoidably included in the voxel could also result in a partial volume effect if glycogen utilization increased only in gray matter. A recently proposed hypothesis (the "glycogen shunt") posits that a fraction of free glucose is cycled through cerebral glycogen and that this fraction increases with the degree of brain activation (29). This hypothesis was put forward to explain the decrease in oxygen-to-glucose index (OGI, CMR_{O_2}/CMR_{Glc}) observed with neuronal activation. According to this hypothesis, an OGI of 5.1 [average OGI observed in a variety of functional activation studies (29)] would necessitate one-third of the glucose molecules to be shuttled through glycogen. Because such OGI decreases were observed in volumes comparable with our volume of interest in the visual cortex (13), such glucose shuttling through glycogen would have decreased our signal by more than 70% with 20 min of stimulation (based on a basal CMR_{Glc} of 24 $\mu mol \cdot g^{-1} \cdot h^{-1}$). Our method has the sensitivity to detect a signal change of ~20% in individuals; hence, glycogen turnover rates predicted by the glycogen shunt hypothesis would have been easily detectable by our method.

Other investigators have detected a change in ^{14}C-glycogen levels with neuronal activation in awake rats using a pulse prelabeling of glycogen with ^{14}C combined with tissue extraction (8, 33). Although these studies utilized somatosensory, as opposed to visual, stimulation, it is unlikely that glycogen is utilized only with certain types of stimuli. As pulse labeling primarily labels the outer tier of glycogen, percent changes in [^{14}C]glycogen observed in these studies (e.g., ~20% in Ref. 33) are difficult to compare with our study, where a large fraction of the glycogen molecule was labeled with ^{13}C. Hence, a 20% change in [^{14}C]glycogen may represent a much smaller change in total glycogen that could be below our detection limit. Cruz and Dienel (8) also detected a reduction in total glycogen levels with sensory stimulation, although the inter-animal variability in glycogen concentrations in this study was high. It is possible that the brain mobilizes its glycogen stores after a low threshold for free glucose concentrations is reached. Thus, Swanson et al. (33) were able to detect glycogen mobilization only with longer (10–20 min) and not with shorter (2–5 min) stimuli, and the 20-min stimulus we utilized might have been too short considering much slower metabolic rates in humans. Also, glycogen mobilization during hypoglycemia was observed only when brain glucose concentrations approached 0 mg/dl (6). These observations are also in agreement with glucose being the main regulator of glycogen phosphorylase (12).

Together with a very slow turnover of bulk brain glycogen, the lack of a substantial increase in glycogen turnover with intense visual stimulation indicates that brain glycogen is not extensively utilized under normal physiology. However, since it stores three- to fourfold more glucose than is available from free glucose it may act as a buffer under physiological stressors such as hypoglycemia (6), hypoxia-ischemia (9), and sleep deprivation (19).

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