Longer T2 relaxation time is a marker of hypothalamic gliosis in mice with diet-induced obesity

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Lee D, Thaler JP, Berkseth KE, Melhorn SJ, Schwartz MW, Schur EA. Longer T2 relaxation time is a marker of hypothalamic gliosis in mice with diet-induced obesity. Am J Physiol Endocrinol Metab 304: E1245–E1250, 2013. First published April 2, 2013; doi:10.1152/ajpendo.00020.2013.—A hallmark of brain injury from infection, vascular, neurodegenerative, and other disorders is the development of gliosis, which can be detected by magnetic resonance imaging (MRI). In rodent models of diet-induced obesity (DIO), high-fat diet (HFD) consumption rapidly induces inflammation and gliosis in energy-regulating regions of the mediobasal hypothalamus (MBH), and recently we reported MRI findings suggestive of MBH gliosis in obese humans. Thus, noninvasive imaging may obviate the need to assess MBH gliosis using histopathological end points, an obvious limitation to human studies. To investigate whether quantitative MRI is a valid tool with which to measure MBH gliosis, we performed analyses, including measurement of T2 relaxation time from high-field MR imaging of mice fed HFD and chow-fed controls. Mean bilateral T2 relaxation time was prolonged significantly in the MBH, but not in the thalamus or cortex, of HFD-fed mice compared with Chow-fed controls. Histological analysis confirmed evidence of increased astrocytosis and microglial accumulation in the MBH of HFD-fed mice compared with controls, and T2 relaxation times in the right MBH correlated positively with mean intensity of gliarial fibrillary acidic protein staining (a marker of astrocytes) in HFD-fed animals. Our findings indicate that T2 relaxation time obtained from high-field MRI is a useful noninvasive measurement of HFD-induced gliosis in the mouse hypothalamus with potential for translation to human studies.

gliosis is a well-characterized neural tissue response to injury from ischemic, infectious, or inflammatory insults. At the microscopic level, gliosis involves three components: infiltration of the tissue by microglia (brain macrophages), activation of microglia and astrocytes, and increased cross-linking of astrocytes to each other and surrounding neurons. We (19) and others (6, 8, 23, 25) have reported that consuming a high fat diet (HFD) induces inflammation associated with gliosis in key body weight-regulating areas of the hypothalamus in rats and mice. Of particular interest is reactive gliosis noted in the arcuate nucleus (ARC), a critical hypothalamic region for regulation of total body energy stores (14). The ARC houses two distinct neuronal cell populations marked by their expres-

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MATERIALS AND METHODS

Animals. Animals were maintained in a temperature- and humidity-controlled room on a 12:12-h light-dark cycle and were housed and cared for in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. All protocols, animal handling, and treatment were approved by the Institutional Animal Care and Use Committee of the University of Washington. Group-housed male C57BL/6 mice (8–10 wk) were assigned to HFD (60% of kilocalories from fat, D12492; Research Diets) or standard laboratory chow (12% of kilocalories from fat; LabDiet 5001). Mice were given ad libitum access to their assigned diet (HFD, n = 8; control, n = 8) for 21 wk, and body weight was recorded weekly. During weeks 20 and 21, mice underwent body composition analysis, MRI imaging, and a terminal perfusion, each separated by ≥2 days.

Body composition analysis. In vivo analysis of body lean mass, fat mass, and water content was performed in conscious, immobilized mice by quantitative magnetic resonance (EchoMRI 3-in-1 Animal Tissue Composition Analyzer; Echo MRI, Houston, TX) (20).

MRI procedures. Mice underwent isoflurane anesthesia in an induction chamber. Once in an appropriate plane of anesthesia, eye lubricant was applied, the mice were placed on a bite bar, and their heads were placed into a radiofrequency coil and secured to a cradle created specifically for the MRI system. The coil was then inserted vertically into a scanner heated to maintain thermoneutrality (32°C). The coil is equipped with an adjustable anesthetic flow and vacuum system to maintain sedation throughout the experiment. Total scan time was 1–1.5 h, during which respiration was monitored through a respiration sensor under the abdomen (SA Instruments, Stony Brook, NY) and anesthesia titrated to ensure appropriate sedation. Following the imaging paradigm (described below), mice were removed from the

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MRI protocol. High-resolution MRI acquisitions were performed on a 14T Avance 600 MHz/89-mm wide-bore vertical MR spectrometer (Bruker BioSpin, Billerica, MA) using a 25-mm inner diameter 1H birdcage coil. The 14T MR system was equipped with actively shielded gradient coils (maximum gradient strength of 100 G/cm) and a Paravision (version 5.1) console interface. A rapid acquisition with refocused echoes (RARE) sequence was used to acquire two-dimensional (2D) multislice cross-sectional images covering the entire mouse brain. We focused on the hypothalamus in the acquired 2D multislice RARE images to obtain high-resolution 2D multislice RARE images. The slice of interest was matched across animals. The slice was selected to include the midregion of the ARC, located in the mediobasal hypothalamus (MBH), and its selection was guided by the Paxinos and Franklin mouse brain atlas (between −1.46 and −1.82 mm from bregma) (16). Once the optimal slice was identified, a transverse relaxation time $T_2$ was acquired using a single-slice, multiecho sequence. A $T_2$ map was created by calculating $T_2$ values using an exponential fit function, $t_s = S_0 \times e^{-t/T_2}$. An echo planar imaging-based diffusion tensor imaging (DTI-EPI) sequence was used to measure values of diffusion tensor trace and fractional anisotropy (FA) with a built-in DTI reconstruction tool of the Paravision software, an MRI signal $S = S_0 \times e^{-t/T_2}$. The diffusion tensor trace $Tr(D)$ and fractional anisotropy FA are defined as the following:

$$Tr(D) = D_{xx} + D_{yy} + D_{zz} = 3D_{av}$$

and

$$FA = \frac{\sqrt{3[D_{xx} - D_{av}]^2 + [D_{yy} - D_{av}]^2 + [D_{zz} - D_{av}]^2}}{\sqrt{2[D_{xx}^2 + D_{yy}^2 + D_{zz}^2]}}$$

where $D_{ij}$ and $D_{av}$ are diffusion tensor components for the laboratory fixed specimen and the tissue frame of reference, respectively. Acquisition parameters for all sequences are provided in Table 1.

MR image analysis. All images were analyzed using Paravision 5.1 software. The MBH slice of interest was determined at the time of acquisition for $T_2$ maps based on a high-resolution multislice, multiecho sequence (see Table 1 and the description above). DTI slice of interest was selected at the time of analysis to be of a similar plane and orientation to the slice selected for the $T_2$ map-scanning sequence. Regions of interest (ROIs) were placed in the bilateral MBH, thalamus, and cortex (Fig. 1) (16). For DTI and $T_2$ relaxation time, ROIs were first placed on a signal intensity display for best identification of anatomy. Then, image parameters were switched to the $T_2$ relaxation time, fractional anisotropy, and tensor trace maps without the ROIs being moved from their original placement. ROI shape and size was maintained between animals. Unilateral 2D ROI areas for $T_2$ relaxation time were 0.20 mm$^2$ for the MBH, 0.49 mm$^2$ for the thalamus, and 0.22 mm$^2$ for the cortex. For DTI analysis, ROI areas were $\sim0.28$ mm$^2$ for the MBH, 0.62 mm$^2$ for the thalamus, and 0.32 mm$^2$ for cortex. Mean ROI values and standard deviations were recorded for each parameter. One of the eight mice from the chow-fed group was excluded from the DTI analyses (fractional anisotropy and tensor trace) due to an image artifact present in ROIs.

Immunohistochemistry. After imaging was completed, mice were perfused with 4% paraformaldehyde-PBS, and 14-μm-thick frozen sections in the coronal plane through the mouse hypothalamus were obtained on a cryostat and processed for glial fibrillary acidic protein (GFAP) and ionized calcium binding adaptor molecule 1 (Iba1) immunoreactivity using standard immunohistochemical procedures. Sections blocked in 5% normal goat serum (Jackson ImmunoResearch Laboratories) were incubated overnight at 4°C with mouse Cy3-conjugated anti-GFAP (1:10,000; Sigma-Aldrich) and rabbit anti-Iba1 (1:1,000) (Wako Pure Chemicals). Immunofluorescence was performed by adding Alexa Fluor 488-labeled anti-rabbit secondary antibody (1:500; Invitrogen). GFAP and Iba1 antibodies have been widely validated in the literature as markers for astrocytes and microglia, respectively (19).

Images were captured on an Eclipse E600 upright microscope equipped with a color digital camera (Nikon). Quantification and ROI placement within the ARC of the MBH were performed in a blinded fashion on ×20 immunofluorescence images. Both sides of bilateral structures were examined on two adjacent sections per animal, and replicate values from each animal were averaged individually before group means were determined (n = 8/group). To quantify astrocytosis, mean GFAP immunostaining intensity was calculated for individual ROIs using Image J (http://rsbweb.nih.gov/ij/). For microglial counts, Iba1 immunostaining allowed identification of discrete cells that were counted manually within the prespecified ROIs. Total microglial count was determined by summing right and left sides and then averaging this value from the two sections examined. For microglial density, thresholding was performed in Image J, followed by densitometric quantification.

Statistical analysis. Group means ± SE were determined for body composition variables. Right and left values were averaged together for each animal to provide a total measurement for each region and are

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Table 1. High-resolution MRI protocol for quantitative assessment of gliosis in mouse MBH

<table>
<thead>
<tr>
<th>Method</th>
<th>Sequence Type</th>
<th>TR/TE, ms</th>
<th>FOV, mm</th>
<th>Acquisition/Reconstruction Resolutions</th>
<th>Acquisition Time</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scout imaging</td>
<td>GRE</td>
<td>30/1.3</td>
<td>30</td>
<td>~10 s</td>
<td></td>
<td>3 orthogonal images used for animal positioning</td>
</tr>
<tr>
<td>Image planning</td>
<td>Multislice RARE</td>
<td>668/4.5, 15 slices</td>
<td>20</td>
<td>~1 min</td>
<td></td>
<td>Slice position and orientation selected</td>
</tr>
<tr>
<td>$T_2w$</td>
<td>Multislice RARE</td>
<td>4,000/10, 15 slices (slice thickness: 200 μm), $\theta = 90^\circ$</td>
<td>17</td>
<td>66 × 66 μm</td>
<td>8 min</td>
<td>To cover MBH and determine a slice of interest</td>
</tr>
<tr>
<td>$T_2$ map</td>
<td>Single-slice, multiecho</td>
<td>4,000/6-75, 12 echoes, 1 slice (slice thickness: 200 μm), $\theta = 90^\circ$</td>
<td>17</td>
<td>66 × 133/66 × 66 μm</td>
<td>12 min</td>
<td>Fast $T_2$ maps to observe $T_2$ changes between high fat diet- and chow-fed mice</td>
</tr>
<tr>
<td>Diffusion</td>
<td>DTI-EPI</td>
<td>4,000/18 ms, 4 shot EPI, 30 diffusion directions, multislice 2D, $b = 1,000$ s/mm$^2$ (slice thickness: 500 μm), $\theta = 90^\circ$</td>
<td>19</td>
<td>150 × 150 μm</td>
<td>9 min</td>
<td>FA and diffusion tensor trace maps to monitor changes in brain microstructural integrity</td>
</tr>
</tbody>
</table>

TR, recycle delay; TE, echo time; FOV, field of view; GRE, gradient echo; $\theta$, flip angle; SE, spin echo; RARE, rapid acquisition with refocused echoes; $T_2w$, $T_2$ weighted; DTI-EPI, diffusion tensor imaging-echo planar imaging; 2D, two-dimensional; FA, fractional anisotropy; MBH, mediobasal hypothalamus.
reported as such unless otherwise indicated. Unpaired t-tests were used to test for group differences in body weight, body composition, and histopathological measurements. Two-way analysis of variance was used for analyses that examined the effect of diet (HFD vs. chow) and region (thalamus, cortex, MBH) on MR-derived outcomes and the interaction of those factors or that assessed laterality within a specific ROI. Pearson’s correlation coefficients were determined, and linear regression models were used to determine significant associations among MR, body composition, and histological measures. Results were considered significant at \( P < 0.05 \). All statistical analyses were performed with GraphPad Prism (La Jolla, CA) version 5.04.

**RESULTS**

**Body composition.** At the time of imaging (21 wk of diet), HFD-fed mice were slightly heavier than chow-fed mice (31.9 ± 0.75 vs. 30.0 ± 0.39 g; \( t_{14} = 2.21, P = 0.04 \)) but had a substantially higher percentage of fat mass (12.8 ± 1.9 vs. 7.76 ± 0.5%; \( t_{14} = 2.55, P = 0.02 \)) and lower percentage of lean body mass (82.8 ± 1.6 vs. 87.8 ± 0.9%; \( t_{14} = 2.73, P = 0.02 \)).

**T2 relaxation time.** ROIs and example images from the high-resolution 2D sequence, T2 parametric map, and DTI-EPI sequence are shown in Fig. 1. There was a significant effect of diet (\( F_{1,42} = 4.42, P = 0.04 \)), region (\( F_{2,42} = 8.09, P = 0.001 \)), and an interaction between diet and region for T2 relaxation time (\( F_{2,42} = 3.84, P = 0.03 \)), indicating that the effect of diet to significantly increase T2 relaxation times was dependent on the region (Fig. 2A). Region-by-region analyses confirmed that HFD-fed animals had modestly but significantly longer bilateral T2 relaxation times in the MBH (30.5 vs. 28.9 ms, \( t_{14} = 2.93, P = 0.01 \)) but not in the thalamus (28.3 vs. 28.4, \( t_{14} = 0.33, P = 0.75 \)) or cortex (29.5 vs. 29.2, \( t_{14} = 0.49, P = 0.63 \)).

The effect of HFD to lengthen T2 relaxation time in the MBH persisted when the left and right MBH were included separately in the model (\( F_{1,28} = 12.6, P = 0.001 \)). Laterality (right vs. left) had no effect (\( F_{1,28} = 0.68, P = 0.42 \)), nor was there evidence for an interaction between side and diet (\( F_{1,28} = 0.56, P = 0.46 \)).

**Diffusion imaging.** Using diffusion tensor imaging, values were compared for fractional anisotropy and tensor trace assessments. For fractional anisotropy (Fig. 2B), there was a significant effect of region (\( F_{2,39} = 3.28, P < 0.05 \)) but no effect of diet (\( F_{1,39} = 0.33, P = 0.57 \)). For tensor trace

**Fig. 1.** Regions of interest and representative images of scan parameters. A: high-resolution 2-dimensional rapid acquisition with refocused echoes image for a slice selected to include the midregion of the arcuate nucleus. B: T2 map generated from multiecho sequence. C and D: diffusion tensor imaging for fractional anisotropy (C) and tensor trace measurement (D). Regions indicate areas of analysis. R, right; L, left; MBH, mediobasal hypothalamus. Scale bar, 1 mm.

**Fig. 2.** Results of multiparametric imaging in high-fat diet (HFD)-fed mice and chow-fed controls. A: T2 relaxation time is higher in HFD-fed animals in the MBH (\( t_{14} = 2.93; *P = 0.01 \)) but not in the control regions of the thalamus and cortex (diet × region interaction: \( F_{2,42} = 3.84, P = 0.03 \)). B: there were no diet effects for fractional anisotropy, but there was an effect of region (\( F_{2,39} = 3.28, P < 0.05 \)). C: there were no group differences in tensor tracemeasurements; \( n = 8 \) for each group except in fractional anisotropy and tensor trace analyses, where \( n = 7 \) for HFD due to an image artifact.

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measurements (Fig. 2C), there was no effect of diet ($F_{1,39} = 0.83, P = 0.37$ or region ($F_{2,39} = 0.08, P = 0.92$).

Histopathological correlation. Animals fed a HFD had increased GFAP staining density in the MBH compared with chow-fed controls ($t_{14} = 2.68, P = 0.02$; Fig. 3, A, B, and E). Mean GFAP density from the MBH was negatively associated with percent lean mass ($r = -0.54, P = 0.03$) but was not as strongly associated with body weight or percent adipose mass ($r = 0.38$ and $P = 0.15$, $r = 0.37$ and $P = 0.16$, respectively). $T_2$ relaxation time in the right MBH was positively associated with mean GFAP density in this same region, although this trend did not achieve significance ($r = 0.48, P = 0.06$; data not shown). However, when stratified by diet, $T_2$ relaxation times in the right MBH were positively correlated with mean intensity in HFD-fed animals (Fig. 3F). No correlations were significant between intensity of GFAP staining and fractional anisotropy or tensor trace values (data not shown).

Total bilateral microglial number in the MBH was increased significantly in HFD- compared with chow-fed mice ($t_{14} = 2.58, P = 0.02$; Fig. 3, C, D, and G). Although not significant, microglial number tended to correlate with $T_2$ relaxation time ($r = 0.43, P = 0.09$). No group difference in total density of microglial staining was present ($3.22$ vs. $3.22, t_{14} = 3.24, P = 1.0$), nor was Iba1 staining density significantly correlated with $T_2$ relaxation time overall ($r = 0.1, P = 0.7$) or in stratified analyses considering HFD-fed mice only (data not shown).

DISCUSSION

Our findings add to growing evidence of MBH damage and gliosis induced by HFD feeding in mice and validate MR imaging as a tool for detecting and quantifying this effect in vivo. On high-field MR images, we found that $T_2$ relaxation time was selectively prolonged in the MBH but not in the thalamus or cortex of HFD- vs. chow-fed mice. These data are consistent with gliosis (3, 4, 7, 13), and they extend findings of high MBH $T_2$ signal in association with obesity in humans (19). Histologically, we found increased density of both astrocyte cell bodies and processes as well as increased microglial cell number in the ARC of HFD-fed mice. $T_2$ relaxation time was significantly correlated with a marker of astrogliosis (GFAP density), but not with microglial density, among the HFD-fed mice, suggesting that the MRI technique we employed may be sensitive primarily to the astrocyte component of the gliosis response. These findings identify $T_2$ relaxation time measured using high-field MRI as a promising quantitative radiological marker of gliosis in the MBH despite the minute size of this brain area. Because MRI is a safe and established tool for human brain imaging, these techniques justify studies that investigate the potential translational value of comparable measurements of gliosis in the MBH of obese humans.

The multiparametric MR approach we used allowed us to assess the utility of two other techniques based on diffusion tensor imaging that also have the potential to detect and quantify gliosis localized to mouse MBH (12). However, unlike the $T_2$ relaxation signal, neither of the diffusion tensor imaging sequences that we employed detected the significant differences in MBH gliosis between groups. There are several possible reasons why diffusion tensor imaging measurements did not show any significant differences. The simplest explanation is that changes in brain microstructural integrity do not occur during HFD feeding in mice. Another possibility relates to the larger voxel size (150 vs. 66 μm for the $T_2$ acquisitions) required for diffusion tensor imaging to reduce acquisition
time. This fact, combined with the use of only two diffusion
gradients ($b$ values of 0 and 1,000 s/mm$^2$), may have limited
our ability to detect small changes in brain microstructure.
Moreover, there were slight differences between ROI sizes for
diffusion tensor imaging and $T_2$ relaxation time that further
complicate direct comparisons among the modalities. There-
fore, it is possible that diffusion tensor imaging will yield
informative data if modified approaches are applied. Ad-
ditional MR approaches to consider in future studies include
1) $T_2$ flair and inversion recovery sequences with white matter
nulling to highlight signal changes and 2) assessment of mag-
netization transfer effects that may provide a measure of white
matter integrity. Further optimization of these methods will not
only enable the acquisition of information that is otherwise
difficult to obtain, such as the ability to monitor dynamic
changes in MBH gliosis over time in individual animals, but
also have important translational implications for performing
comparable studies in humans.

Previous studies (4, 7, 10) as well as our supplementary
histopathological correlations suggest that longer $T_2$ relaxation
time reflects increased glial cell numbers (4, 7), reactive
astrocytosis (10), and/or decreased neuronal populations (4) in
the MBH. The relationship between $T_2$ relaxation time and
increased astrocyte density was particularly strong in the right
MBH among HFD-fed animals, and trends were present among
all animals. These findings suggest a positive correlation be-
tween MBH $T_2$ relaxation times and astrocyte density. In
contrast, there were no consistent relationships between micro-
glial number or staining density and MBH $T_2$ relaxation time
despite the effect of the HFD to increase microglial cell
number in the MBH. Although it is possible that astrocytosis
rather than microgliosis is the primary gliosis component
responsible for prolongation of the $T_2$ relaxation time by HFD
feeding in mice, other factors may also have affected the
correlation between the $T_2$ signal and histopathological end
points. For one, our high-resolution MR sequences achieved 66
$\mu$m in-plane resolution in a 200-$\mu$m-thick slice, whereas the
immunofluorescence sections had sub-$\mu$m resolution in a 14-
$\mu$m-thick section. Thus, the fact that a much larger area of
tissue contributed to the measurement of $T_2$ relaxation time
than to the histological end points undoubtedly contributed to
variability in the statistical correlation between these measure-
ments.

Several additional limitations and challenges remain to be
addressed. In addition to uncertainty regarding the specific cell
types involved in gliosis that increase $T_2$ relaxation time, unmeasured
histological changes in MBH tissue such as edema
or enhanced vascularity could also affect the $T_2$ signal (15, 24).
Finally, the ARC has no distinctive appearance on MRI and is
small, measuring ~500 $\mu$m in maximum height and 1,000 $\mu$m
in maximum bilateral width and extending for 1,580 $\mu$m along
the rostrocaudal axis (16). Therefore, we based our target range
for image acquisition on other anatomic markers for the re-
gions between $-1.46$ and $-1.82$ mm from bregma (16), but
this does not guarantee that our MBH data were acquired from
within the ARC or that tissue from adjacent regions was
excluded from our ROIs. This fact created additional variance
in the measurement and hence, likely reduced the strength of
its correlation with histological end points. Nevertheless,
our data strongly suggest that $T_2$ relaxation time is prolonged in the
MBH but not other brain regions of HFD-fed mice and that this
prolongation is a marker of tissue level changes associated with
gliosis.

In summary, we report that $T_2$ relaxation time as measured
by high-field MRI is a useful, noninvasive tool for assessing
MBH gliosis in mouse models of diet-induced obesity. This
technique may be particularly useful for studies in which
changes in MBH gliosis are measured serially over time to
better define the time course and potential reversibility of
hypothalamic damage in mouse models. MRI is also a safe and
accessible tool that provides an exceptional opportunity to
translate findings from rodent models to humans. Such studies
are critical to establish whether hypothalamic inflammation,
gliosis, and damage in humans, as in rodents (8, 19), is induced
by obesity and/or dietary factors. Ultimately, this information
may help to better understand the role of MBH gliosis in the
pathogenesis of human obesity.

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DISCLOSURES

The authors declare no competing financial interests.

AUTHOR CONTRIBUTIONS

D.L., J.P.T., M.W.S., and E.A.S. contributed to the conception and design
of the research; D.L., J.P.T., K.E.B., S.J.M., M.W.S., and E.A.S. interpreted
the results of the experiments; D.L., J.P.T., K.E.B., S.J.M., M.W.S., and
E.A.S. drafted the manuscript; D.L., J.P.T., K.E.B., S.J.M., M.W.S., and
E.A.S. edited and revised the manuscript; D.L., J.P.T., K.E.B., S.J.M.,
M.W.S., and E.A.S. approved the final version of the manuscript; J.P.T.,
K.E.B., and E.A.S. performed the experiments; J.P.T., K.E.B., S.J.M., and
E.A.S. analyzed the data; K.E.B. and S.J.M. prepared the figures.

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Innovative Methodology

$T_2$ RELAXATION TIME INDICATES HYPOTHALAMIC GLIOSIS

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