In Vivo Hippocampal Metabolic Dysfunction in Human Temporal Lobe Epilepsy

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Background: The nature of functional metabolic disturbances in mesial temporal lobe epilepsy remains unclear.

Objectives: To compare in vivo measures of hippocampal metabolic abnormalities in mesial temporal lobe epilepsy, as acquired with fludeoxyglucose F 18 positron emission tomography and proton magnetic resonance spectroscopic imaging, and to determine the relationship between N-acetylaspartate (NAA) disturbances and well-established derangements of glucose metabolism.

Design: Measures of hippocampal glucose metabolism from fludeoxyglucose F 18 positron emission tomography were normalized to whole brain counts to provide a glucose uptake metabolic index. Proton magnetic resonance spectroscopic imaging was performed at 4.1 T, and measures of creatinine/NAA ratio were made from mostly hippocampal-only voxels. Direct comparisons and correlation analysis of measures were performed.

Setting: Presurgical evaluations for treatment of intractable epilepsy.

Patients: Twenty-nine patients between July 1994 and June 1996 who were candidates for anterior-medial temporal lobectomy at the epilepsy centers of the University of Alabama at Birmingham and Vanderbilt University schools of medicine were studied.

Results: The mean ipsilateral hippocampal glucose metabolic index (0.85) was normal, while the contralateral metabolic index (0.95) was nearly significant for an abnormally elevated measure. The mean ipsilateral hippocampal creatinine/NAA (1.26) was abnormally elevated; the mean contralateral creatinine/NAA (0.88) was normal. Hippocampal glucose and creatinine/NAA measures did not correlate; asymmetry measures also did not correlate.

Conclusions: Hippocampal metabolic disturbances in mesial temporal lobe epilepsy as measured by fludeoxyglucose F 18 positron emission tomography vs proton magnetic resonance spectroscopic imaging reflect different mechanisms of biochemical dysfunction. This lack of correlation is hypothesized to reflect a differential effect of varying degrees of disturbed cellular energy metabolism on mechanisms of glucose use and biosynthesis of NAA.

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(3) to elucidate any significant differences between hippocampal glucose and NAA measures that may exist. We hypothesized that, although FDG uptake and the relative concentration of NAA may indirectly reflect the same underlying causes of neuronal loss and dysfunction in hippocampi of MTLE, the degree of abnormality for each measure was not correlated. We based this on the understanding that, although neuronal metabolic energy disturbances may affect glucose uptake and NAA concentrations, the biochemical mechanisms leading to the changes in each metabolic intermediate are different.

**METHODS**

**PATIENTS**

Twenty-nine patients between July 1994 and June 1996 who were candidates for anterior-medial temporal lobectomy at the epilepsy centers of the University of Alabama at Birmingham and Vanderbilt University schools of medicine and who were able to complete PET and MRSI examinations were studied. For both procedures, informed consent was obtained according to the guidelines of the universities’ institutional review boards. Surgical candidates were excluded if structural imaging revealed pathologic conditions other than evidence for mesial temporal sclerosis. Magnetic resonance imaging evidence of mesial temporal sclerosis was not required. Diagnosis and lateralization of MTLE were based on inpatient interictal and ictal electroencephalographic findings and video monitoring with or without sphenoidal electrodes.

Of the 29 patients in the study, 19 were female. The mean age at evaluation was 34 years (range, 15-44 years). The mean age at seizure onset was 16 years (range, 2-36 years). Nineteen patients had their seizures lateralized to the left temporal lobe and 10 to the right temporal lobe. Twenty-three patients had anterior-medial temporal lobectomy (mean outcome follow-up, >4 years): 17 (74%) are seizure free (Engel class I) and 6 (26%) are not seizure free (Engel class II-IV). Histopathologic examination of hippocampal tissue showed a variable degree of astrogliosis and neuronal cell loss in all cases.

**CONTROL SUBJECTS**

Separate control subjects were studied for PET and MRSI normative data.

Positron emission tomographic scans were performed in 10 neurologically normal subjects (6 women), with a mean age of 31 years (range, 24-37 years). Magnetic resonance spectroscopic imaging studies were performed in 20 normal volunteers (9 women), with a mean age of 35 years (range, 23-50 years).

**FDG-PET STUDIES**

All PET scans were performed at Vanderbilt University on an ECAT 933/08/16 (Siemens Gammasonics, Knoxville, Tenn). The effective in-plane resolution was 6.5 × 6.5 × 8.0 mm. Fifteen tomographic planes were obtained simultaneously, with a scanning time of 17 minutes. Before emission scans, a transmission scan was obtained and a measured attenuation correction was performed.

All images were reoriented to the midline of the brain to be parallel to the anterior commissure–posterior commissure line. The Talairach and Tournoux atlas was used for anatomic localization. Hippocampal regions of interest were manually drawn on axial plane 12 ([Figure 1](#) and [Figure 2](#)). Raw counts for individual regions of interest were normalized to whole brain counts (all slices except those that include predominantly temporal lobe regions) to provide a unitless FDG metabolic index that could be compared across subjects.

**MRI STUDIES**

Magnetic resonance imaging studies were performed at the University of Alabama at Birmingham using a standard protocol in an MRI scanner (ACS Unit; Philips, Best, the Netherlands) operating at a field strength of 1.5 T. All patients and controls were studied using the same temporal lobe protocol. For volumetric studies, a volume acquisition (3-dimensional) of the entire brain was acquired using a T1-weighted sequence with an echo time of 6.1 milliseconds, a repetition time of 20.0 milliseconds, a field of view of 23.0 cm, and a flip angle of 28° in a plane perpendicular to the long axis of the hippocampus (1.5-mm-thick slices, 0 gap).
All 1H-MRSI studies were performed at the University of Alabama at Birmingham before electrode implantation or surgical resection and with approval by the institutional review board. Magnetic resonance spectroscopic imaging data were acquired using a 4.1-T whole body imaging–spectroscopy system and quadrature-driven tunable matchable head coil. Sagittal scout images were acquired using a segmented (8 encodes per inversion pulse) inversion recovery gradient echo sequence (repetition time/inversion recovery delay/echo time, 2500/1000/13 milliseconds). The details of MRSI acquisition and metabolite analysis have been previously published.

RESULTS

The Table shows the mean values of normalized FDG uptake and creatinine/NAA (Cr/NAA) measured in the hippocampus of normal controls and patients.

**HIPPOCAMPAL ABNORMALITIES**

**Group Data**

The mean normalized hippocampal FDG uptake measures for left and right hippocampi were 0.89 and 0.91, respectively. Both values were within normal limits and just slightly greater than the normal mean of 0.88. The mean ipsilateral uptake was 0.85; the contralateral mean uptake was 0.95. Neither value was abnormal (outside the range of 2 SDs); however, the contralateral value was nearly significant for an abnormally elevated measure. The mean asymmetry (ipsilateral minus contralateral, asymmetry index=11.64%) was significantly greater than the mean of the controls, the direction of asymmetry reflecting a significant relative ipsilateral decrease in glucose uptake. The mean hippocampal Cr/NAA for left and right hippocampi was 1.04 and 1.10, respectively. Both values were abnormally high. The mean ipsilateral Cr/NAA was 1.26; the contralateral measure was 0.88. The ipsilateral value was highly abnormal, while the contralateral value was normal. The mean asymmetry (ipsilateral minus contralateral, asymmetry index=59.69%) was markedly abnormal, the direction of asymmetry reflecting a significant relative ipsilateral decrease in NAA.

**Individual Patients**

Ten (34%) of the 29 patients had abnormally decreased ipsilateral hippocampal FDG uptake, while 8 (28%) had abnormally elevated contralateral uptake. Eighteen patients (62%) had significantly asymmetric (asymmetry index >9%) hippocampal uptake. All lateralizing asymmetry was concordant with electroencephalographic lateralization.

Twenty-three patients (79%) had abnormally increased ipsilateral hippocampal Cr/NAA, while 8 patients (28%) had abnormally increased contralateral hippocampal Cr/NAA. Twenty-six patients (90%) had significantly asymmetric (asymmetry index >12%) hippocampal Cr/NAA values. Lateralizing asymmetry was discordant with electroencephalographic findings in 3 patients.

**GLUCOSE–Cr/NAA CORRELATION**

When all hippocampi were examined (N=58), no correlation was found between normalized hippocampal FDG uptake and Cr/NAA values (r=-0.009, P=.95). When ipsilateral and contralateral measures were examined separately, neither ipsilateral (r=-0.12, P=.55) nor contralateral (r=0.25, P=.19) metabolic indexes correlated. The hippocampal FDG and Cr/NAA asymmetry measures (larger-smaller and ipsilateral-contralateral) did not correlate (r=0.11, P=.59 and r=-0.07, P=.74); however, left-right asymmetry was strongly correlated (r=-0.51, P=.005).

The major finding of this work was the lack of individual and group correlation between in vivo hippocampal glucose uptake and Cr/NAA concentration in patients with MTLE. Also notable was that the sensitivity of detecting ipsilateral hippocampal abnormality of Cr/NAA concentration (79%) was much greater than that of hippocampal FDG uptake (34%).

The absence of an association between hippocampal FDG uptake and NAA concentration has 2 explanations, which are not mutually exclusive: (1) the differences in sensitivity between the techniques are incongruent over the range of abnormality and (2) the underlying mechanisms for these disturbances are different, whether or not they are directly or indirectly related to the same pathogenesis. This is not necessarily an unexpected finding, yet prior FDG-PET and MRSI studies have suggested that glucose and NAA disturbances may be related. At the same time, these studies acknowledge the complementary nature of epilepsy lateralization provided by the different modalities. Furthermore, the high sensitivity of FDG-PET lateralization, which may parallel that demonstrated with 1H MRSI, reflects much more extensive temporal lobe metabolic disturbances, specifically as seen in the extrahippocampal regions of the temporal pole and anterior-lateral neocortex. In contrast, our findings involving measures predominantly from the hippocampus reveal that abnormal NAA concentration is detected with a greater sensitivity compared with abnormal glucose metabolism.

In further contrast between glucose uptake and NAA disturbances, contralateral hippocampal FDG uptake appears to change in a direction opposite that of the rela-

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**Table**

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<tr>
<th>Controls</th>
<th>Patients</th>
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<tbody>
<tr>
<td></td>
<td>Right</td>
</tr>
<tr>
<td>FDG MI</td>
<td>0.86 ± 0.05</td>
</tr>
<tr>
<td>Cr/NAA</td>
<td>0.99 ± 0.16</td>
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*Data are given as mean ± SD. Metabolic index (MI) is calculated as hippocampal counts divided by whole brain counts, excluding the temporal lobes. Ipsilateral indicates ipsilateral to the side of the seizure onset; contralateral, contralateral to the side of the seizure onset. †Greater than 2 SDs above the mean of normal controls.
tive concentration of NAA. Our normalized measures of hippocampal-specific FDG uptake are comparable to those measured by Rubin et al., who found increased mesial basal temporal metabolic indexes. We did not find abnormally elevated ipsilateral hippocampal glucose metabolism; however, our mean value was normal (not abnormally low). Although our contralateral hippocampal metabolic measurement with FDG was not outside 2 SDs of normal, it was nearly so in the direction of being elevated. Therefore, if actual FDG uptake in the hippocampus is normal or elevated, it should not be expected that hippocampal glucose metabolism would correlate with the established expectation of relative decreases in NAA concentration of the same region.

This observed difference in apparent direction of contralateral abnormality is of particular interest. Proton magnetic resonance spectroscopic temporal lobe epilepsy studies have consistently demonstrated a high sensitivity to detect abnormally low measures of NAA in the contralateral mesial temporal lobe regions. The high sensitivity has been explained by the likelihood of contralateral cryptic hippocampal sclerosis, as reported in one autopsy series. However, this simple explanation does not hold up after demonstration that contralateral decreases in NAA measures are reversible, as seen in patients who became seizure free after surgery. This important finding has emphasized the functional or dynamic component of NAA measurement—most important, that it is not simply a measure of irreversible neuronal loss. Of separate issue in the examination of relationships between PET measurement of glucose uptake and 1H MRSI measurement of NAA is the problem that the basic mechanisms responsible for these disturbances in MTLE remain unclear. Glucose is effectively the sole energy substrate for the human brain, and its uptake as measured by FDG-PET is believed to predominantly reflect synaptic activity. Neuronal loss in mesial temporal sclerosis may affect glucose metabolism, but increased synaptic activity (excitatory and inhibitory) and energy associated with synaptic reorganization may unpredictably offset the net glucose use in sclerotic hippocampi. In contrast, the measurement of decreased NAA may reflect multiple causes, including a decrease in neuronal cell density, neuronal or axonal shrinkage with a relative increase in tissue water, or metabolic dysfunction. The latter may reflect a decrease in NAA synthesis, an increase in its catabolism, or a combination of both.

Before further discussion of any putative hypothesis or interpretation of our findings, limitations of the work, mostly regarding methods, must be emphasized. In a region as small as the hippocampus, partial volume effects compromise our measurements from PET and 1H MRSI. As such, it is difficult to determine whether estimates of the hippocampal gray matter component in the different measures were roughly equal (with respect to proportion and distribution of instrument sampling). If the measures are grossly unequal, then tests of correlation will not be valid. We attempted to minimize partial volume effects by designating contours of the PET hippocampal regions of interest clearly within the outer margins of the hippocampal tracer activity. For 1H MRSI, the exclusion of voxels not involving hippocampal tissue and high resolution provided by the improved signal to noise from our 4.1-T magnet allowed maximal measurement of predominantly hippocampal gray matter and minimized the partial volume effect as much as possible without tissue segmentation.

Another issue is our assumption that the measure of Cr/NAA is a reliable measure of NAA change. Although it is ideal to measure the actual concentration of NAA, the methods are particularly complex and not always practical. Fortunately, prior work that measured the concentration of hippocampal creatinine in MTLE showed that it was not significantly different from the mean of control subjects. Therefore, until efficient and reliable measures of actual concentration of NAA become more routine, relative values such as the measure of NAA to Cr or NAA to (choline plus Cr) remain commonly used practical measures of relative NAA change.

Our hypothesis that these measures of metabolic disturbance were not related was based mainly on the expectation that mechanisms underlying interictal changes in glucose uptake and relative NAA concentration have a differential dependence on the neuronal cellular energy state. It would be expected that, in the progression of disturbed neuronal energy maintenance, NAA concentration would decrease at a time when glucose uptake would not. This would occur early, at a time when mitochondrial function is compromised but when other mechanisms of cellular energy maintenance are preserved. N-acetylaspartate synthesis by the mitochondrial enzyme L-aspartate N-acetyltransferase is dependent on the mitochondrial concentration of acetyl coenzyme A. When the tricarboxylic acid cycle is operating normally, sufficient acetyl coenzyme A should be produced for normal synthesis of NAA. When mitochondrial enzymes—either the enzyme complexes of oxidative phosphorylation or the regulated pyruvate dehydrogenase complex—begin to dysfunction, acetyl coenzyme A production would diminish such that NAA synthesis is affected. Early in this process of dysfunction, before occurrence of cellular energy failure, glucose uptake would remain normal or elevated, because glycolysis would still be functioning to maintain cellular energy charge. Such a proposed explanation, although without many of the mechanistic details elucidated, allows for the disassociation between glucose uptake and NAA measures in MTLE, as well as their reversibility or dynamic nature and the possibility for a normal or relative net increase in glucose metabolism. Furthermore, preliminary work with phosphorus P 31 MRSI shows no net change in energy charge occurring in the interictal state, based on the observation that the adenosine triphosphate concentration does not change significantly. Finally, 1H MRSI studies of lactate provide evidence that an elevation of lactate may exist interictally in epileptogenic tissue, supporting the possibility that some degree of anaerobic glycolysis may occur in an attempt to maintain cellular energy charge.

Two important questions remain: (1) What pathogenesis associated with epilepsy causes glucose hypometabolism that is reversible without irreversible neuronal injury or death? and (2) What causes reversible neuronal cellular dysfunction in and around epileptogenic tissue? The first may in part be simply explained by net changes in regional neuronal synaptic activity. This is an impor-
tant variable that appears to be mostly independent of NAA changes, for neuronal activity changes associated with seizures and the postictal state appear to cause no significant change in MRSI measures of NAA. The second question remains unanswered on 2 levels: (1) What might be responsible for long-term decreased interictal neuronal synaptic activity? and (2) What might be the cause of reversible mitochondrial dysfunction? In vitro rat brain studies show decreased concentration of NAA (due to decreased synthesis) with inhibition of mitochondrial respiratory chain enzymes, including inhibition that is not to such a degree that the cells become irreversibly injured. Further supporting a hypothesis that proposes dysfunctional mitochondrial synthesis of NAA as a cause for its decreased measure in epileptic tissue is evidence from human PET and MRSI investigations of mitochondrial encephalomyelopathies that demonstrates a connection between chronic defects in oxidative phosphorylation and epileptogenesis. Moreover, recent work provides direct evidence that mitochondrial dysfunction exists in epileptic tissue of human temporal lobe epilepsy.

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