Postoperative Changes in Cerebral Metabolism in Temporal Lobe Epilepsy

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Background: Fludeoxyglucose F 18 positron emission tomography (18F-FDG-PET) can detect focal metabolic abnormalities ipsilateral to the seizure focus in 80% of patients with temporal lobe epilepsy (TLE). Regions outside the epileptogenic zone can also be affected. We hypothesized that these remote regions might show altered metabolism, tending to return toward normal values, after surgery.

Design: Interictal preoperative and postoperative 18F-FDG-PET metabolism were compared in patients with refractory TLE. Based on pathological findings, disease was classified in the following 3 groups: mesial temporal sclerosis, mass lesions, and no pathological diagnosis. Quantitative PET data analysis was performed using the region-of-interest template previously described. Global normalization was used to adjust for the effect of antiepileptic medication changes. Data were analyzed by Wilcoxon signed rank test and analysis of variance.

Setting: The Clinical Epilepsy Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health.

Results: Preoperatively, in all groups, cerebral metabolic rate for glucose was decreased ipsilateral to the resection site in inferior lateral temporal, inferior mesial temporal, and inferior frontal areas and thalamus. Postoperatively, in all groups, cerebral metabolic rate for glucose increased in ipsilateral inferior frontal area and thalamus. In the mesial temporal sclerosis group, we found a statistically significant increase in the contralateral thalamus.

Conclusion: Temporal lobe epilepsy is associated with extensive preoperative decreased metabolism in inferior lateral temporal, inferior mesial temporal, and inferior frontal areas and thalamus. Seizures may have a reversible effect on brain areas connected with, but remote from, the epileptogenic cortex.

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SUBJECTS AND METHODS

PATIENT POPULATION

Patients for this study were selected among referrals to the Clinical Epilepsy Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health (NIH), Bethesda, Md, for presurgical evaluation of medically refractory epilepsy and met the following selection criteria: (1) long-term video electroencephalographic (EEG) monitoring; (2) preoperative PET; (3) ATL resection; and (4) histopathological examination of the resected tissue. From this group, 22 patients underwent a postoperative PET study after the NIH institutional review board granted approval and the patients had given informed consent.

PATIENT EVALUATION

All patients underwent continuous audiovisual EEG monitoring until at least 3 typical seizures were recorded. Preoperative magnetic resonance imaging scans were obtained in all patients 6 months to 1 year before surgery. All the patients underwent preoperative and postoperative 18F-FDG-PET. Sphenoidal electrodes were implanted in 7 patients and subdural electrodes in 9 for additional localization. Post-surgical outcome was classified according to Engel.14

PET DATA ACQUISITION AND ANALYSIS

All 18F-FDG-PET scans were performed on a scanner (SC2; Scanditronix AB, Uppsala, Sweden) with a full-width half-maximum axial and in-plane resolution of 5.5 mm. Scans were performed in patients who had no seizure activity in the previous 24-hour period and after a 4-hour fast in the awake resting state with eyes patched and ears plugged. A thermoplastic head mask minimized the patient’s movements. All tomographic images were oriented parallel to the canthomeatal plane. After transmission scanning for attenuation correction using a combination of germanium 68 and gallium 68 on a rotating pin source, 185 MBq of 18F-FDG was injected and PET images were acquired after a 30-minute uptake period. The EEG recording was obtained and patients were observed to exclude seizure activity during 18F-FDG uptake. Radial arterial sampling was obtained to perform quantitation of CMRglc.15

RESULTS

DEMOGRAPHICS

We studied 22 patients (10 women and 12 men) with a mean age of 31.1 ± 1.1 years (range, 22-40 years). Mean epilepsy duration was 22.9 ± 1.8 years (range, 3-38 years). All the patients had complex partial seizures. Magnetic resonance imaging revealed findings consistent with hippocampal sclerosis or atrophy in 8 patients and mass lesions in 3, and was unremarkable or demonstrated nonspecific findings in the remainder (Table). All 9 patients who underwent intracranial EEG monitoring for further seizure localization had electrode placement in the temporal and ipsilateral IF areas. In 6 of them, seizure propagation was observed in IF regions.

SURGERY AND PATHOLOGICAL FINDINGS

All patients underwent a standard ATL by the same neurosurgeon (C.K.), with additional tailoring by means of intraoperative electrocorticography. The hippocampus was resected in all but 1 patient. Twelve of 22 patients underwent right ATL; the remainder, left ATL. Pathological examination revealed findings consistent with MTS in 16 patients, mass lesions in 3 patients (mixed glioma, cavernous angioma, and ganglioglioma), and no specific findings in another 3 patients (Table).
FOLLOW-UP AND OUTCOME

At the time of postoperative PET scan, 8 of 22 patients were receiving the same antiepileptic drug (AED); 7 of 22 patients were receiving the same number, but a different combination, of AEDs; 5 patients were taking fewer AEDs; and only 2 were not receiving AEDs (Table).

We evaluated seizure outcome at the time of the postoperative PET study based on the classification by Engel.14 Patient follow-up ranged from 10 to 112 months. Seven patients with MTS were seizure free (class IA); 2 patients had rare simple partial seizures (class IB). Six patients had rare complex partial seizures since surgery (class IIB), and 1 patient did not have any appreciable change in seizure frequency (class IV). All patients with mass lesions or no specific pathological findings became seizure free (class IA) (Table).

PET RESULTS

Patients underwent preoperative 18F-FDG-PET 1 month to 40 months before surgery (mean, 14.6 ± 2.4 months). Postoperative PET was performed within 10 to 112 months after surgery (mean, 65.8 ± 5.4 months) (Table). Preoperative CMRglc was reduced in ILT, IMT, IF, and thalamus (Figure 1). An asymmetry was seen in 14 of patients in ILT, 5 in IMT, 4 in IF, and 3 in thalamus. In the MTS group (n=16), metabolism was reduced in the ipsilateral ILT (P<.001), IMT (P<.01), and IF (P<.002) (Figure 1). Postoperatively, there was a profound decrease in ILT and IMT CMRglc because tissue was resected in each patient group. In the remaining cortex, there was a nonsignificant increase in CMRglc in ipsilateral IF (P=.06 for MTS group). A modest increase in metabolism in ipsilateral thalamus was also observed in all groups (Figure 2).

*EEG indicates electroencephalogram; PET, positron emission tomography; MRI, magnetic resonance imaging; Med 1, medication during preoperative PET; Med 2, medication during postoperative PET; L, left; R, right; Inf, inferior; Temp, temporal; Ant, anterior; Med, medial; Hem, hemisphere; Bil, bilateral; Fr, frontal; Hc, hippocampal; incr, increase; T2, on T2-weighted images; A, atrophy; Ni, normal; Hc S, Hc sclerosis; and No, no specific finding.

†Described using classification by Engel.14

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Patient Characteristics

<table>
<thead>
<tr>
<th>Patient No./Sex/Age at Surgery, y</th>
<th>Ictal EEG</th>
<th>PET Before/After Surgery, mo</th>
<th>MRI Findings</th>
<th>Surgery Site/Pathological Finding</th>
<th>Outcome†</th>
<th>Med 1</th>
<th>Med 2</th>
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*EEG indicates electroencephalogram; PET, positron emission tomography; MRI, magnetic resonance imaging; Med 1, medication during preoperative PET; Med 2, medication during postoperative PET; L, left; R, right; Inf, inferior; Temp, temporal; Ant, anterior; Med, medial; Hem, hemisphere; Bil, bilateral; Fr, frontal; Hc, hippocampal; incr, increase; T2, on T2-weighted images; A, atrophy; Ni, normal; Hc S, Hc sclerosis; and No, no specific finding.

†Described using classification by Engel.14
There was a significant increase in CMRglc in contralateral thalamus in the MTS group \( (P = .02) \) (Figure 3). Compared with preoperative PET studies, asymmetry in IF lobes and thalamus was found in 2 and 9 patients, respectively.

We did not find any significant change in postoperative metabolism in parietal or occipital areas.

Age, epilepsy duration, time interval between surgery and postoperative PET study, surgical outcome, and resection site did not affect the change in metabolism postoperatively (ANOVA). No correlation was detected between change in metabolism and time interval between PET scans. In the ANOVA, pathological features were a factor in the increased CMRglc in contralateral IMT \( (P < .001) \) and showed a trend to influence ipsilateral IF metabolism \( (P = .09) \).

Temporal lobe epilepsy is associated with extensive preoperative hypometabolism involving medial and lateral temporal as well as IF areas and thalamus ipsilateral to the seizure focus. Although some previous studies suggested that PET might be less sensitive for patients who did not have MTS,\(^{13}\) we found that all pathological groups exhibited the same extensive preoperative hypometabolism. Hajek et al\(^ {13} \) observed decreased metabolism confined to the mesial and polar regions preoperatively solely in patients with MTS. However, Khan and coinvestigators\(^ {19} \) from the same group recently described extensive reduction in temporal glucose uptake ipsilateral to the focus in patients with tumors, in addition to ipsilateral thalamic hypometabolism regardless of pathological features.

After surgery, we found increased ipsilateral IF and bilateral thalamic metabolism, although the changes were not always statistically significant. Hajek et al\(^ {13} \) demonstrated increased metabolism postoperatively in ipsilateral and contralateral hemispheres in the MTS group, but did not observe any statistically significant specific regional increases. We found a tendency toward increased bilateral IF CMRglc in all patients and significantly increased contralateral thalamic metabolism in patients with MTS. Variation in extent of resection could account for some of the differences between these studies. Akimura et al\(^ {13} \) reported that epilepsy surgery led to increased metabolism mostly in the ipsilateral frontal lobe.

For this study we used all patients as their own controls in evaluating changes in metabolism before and after surgery. In addition, the time interval between surgery and follow-up PET scan had no effect on results. This suggests that methodological factors did not influence our study. Indeed, the longer mean interval between surgery and postoperative PET suggests that the results we found are more likely to reflect physiological stability.

Although 13 patients had changes in their AEDs during the postoperative study, these are unlikely to have influenced the results. We measured globally normalized metabolic rates, rather than absolute values. This procedure adjusts regional values for the whole brain mean, removing any global drug effects. Specific regional effects are unlikely to have been important.

Phenobarbital sodium, phenytoin sodium, carbamazepine, and valproic acid led to variable reductions...
in global metabolism, but no consistent regional effects.\textsuperscript{16,20-24} None of our patients were receiving the experimental AED vigabatrin, which reduced mean global CMRglc by 8%. Eight of 28 individual regions, including 3 of 4 inferior temporal regions, had significant reductions; the small number of patients in the study and the variability of the data make the regional differences difficult to interpret.\textsuperscript{25}

Cerebral blood flow (CBF) has been studied as well. Futagi et al\textsuperscript{26} found that carbamazepine, phenobarbital, and valproic acid led to reductions in carotid artery blood flow, again consistent with widespread effects. In a study of valproic acid and CBF, the greatest effect was found in the thalamus (19.8%). However, reductions were found in all regions (global decrease, 16%).\textsuperscript{16} Thus, the effect on the thalamus, which was bilateral, was not much greater than the effect on the rest of the brain. Moreover, CMRglc, which we measured in our study, may be decoupled from CBF in epileptic foci.\textsuperscript{37} Therefore, valproic acid, which had no regional effects on CMRglc, is unlikely to have influenced the results. Occasional global, but not regional, transient CBF increases have been reported.\textsuperscript{28}

A large number of studies have reported that AEDs lead to global, rather than regional, reductions in CBF and CMRglc in animal models, consistent with the effects on neuronal membranes or widespread transmitter systems, such as $\gamma$-aminobutyric acid, the drugs produce.\textsuperscript{29} Usually, the doses are much higher than those used clinically; single doses of valproic acid in baboons did not affect CBF at all.\textsuperscript{30}

Epileptogenic human hippocampus is characterized by synaptic inhibition in synchronously firing epileptic neurons during interictal periods,\textsuperscript{31} decreased excitatory synaptic input,\textsuperscript{32} and reduced efferent output to surrounding projection areas,\textsuperscript{33} which may result in reduced glucose metabolism interictally. In rats, the hippocampal formation projects to medial frontal cortex in a reciprocal manner and inhibitory responses predominated.\textsuperscript{34,35} Positron emission tomography studies have consistently demonstrated hypometabolism in frontal regions ipsilateral to epileptogenic temporal lobe zone.\textsuperscript{3,36} Intracranial EEG recordings support the view that orbitofrontal cortex is a preferable pathway for mesial temporal seizure propagation.\textsuperscript{37} Prefrontal cortex probably receives afferent input from the amygdala, hypothalamus, and mammillary bodies by means of anterior thalamus and projects to posterior cingulate, hippocampus, and amygdala through the association cortex.\textsuperscript{38} In our patient group, 9 patients had subdural temporal frontal grid placement, and in 6 of them we observed temporal IF propagation. The postoperative increase in IF lobe metabolism we found confirms the existence of temporal-frontal interactions and indicates that frontal hypometabolism reflects functional and reversible disturbance after the resection of the primary epileptogenic zone. Inferior frontal hypometabolism has been associated with depressive symptoms in patients with epilepsy and primary affective disorders.\textsuperscript{39} Functional fluctuations in this region may be associated with postoperative affective symptoms.

In the monkey, and perhaps also in man, extensive reciprocal connections exist between thalamus, hippocampal formation, amygdala, and entorhinal cortex.\textsuperscript{40,41} The thalamus plays an important role in seizure initiation by inducing excitatory responses in limbic circuits as well as in seizure spread to nonlimbic sites in rats.\textsuperscript{42} Thalamic involvement in seizure initiation and propagation has been confirmed in humans by neuroimaging studies that showed hyperperfusion ictally, and decreased CBF\textsuperscript{43} and metabolism interictally.\textsuperscript{3-5,18} Thalamic atrophy, neuronal loss, and gliosis have been described in a few patients with TLE,\textsuperscript{34,44} and there is a significant correlation between resected hippocampal cell densities and CMRglc in thalamus bilaterally.\textsuperscript{5} Increased postoperative thalamic glucose metabolism, however, suggests that reduced metabolism reflects, at least in part, a functional disturbance. Reduced efferent output from the mesial temporal structures to the thalamus may be an important synaptic mechanism of dysfacilitation that would result in decreased thalamic neuronal activity and metabolism.

The pattern of mild postoperative metabolic changes we found suggests that hypometabolism detected by PET may be caused by decreased efferent output or afferent input as well as the extent of neuronal loss. The pattern of postoperative changes may depend on the type of surgery performed. Future FDG-PET studies may help to study the effects of varying surgical approaches to TLE.

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