Cerebral Metabolism of the Remote Area after Epilepsy Surgery

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Abstract

To clarify whether epilepsy surgery improves cerebral metabolism, pre- and postoperative positron emission tomography (PET) scans were performed, with special reference to hypometabolism outside the resected epileptogenic zones in nine patients (8 males, 1 female) with medically intractable complex partial seizures and multiple hypometabolic zones. Seven patients underwent unilateral anterior temporal lobectomy, one patient underwent selective amygdalohippocampectomy, and one patient underwent parieto-occipital cortical resection and anterior temporal lobectomy. PET scans were obtained at least 6 months after surgery. Eight patients became seizure-free, and one patient had fewer than three seizures per year. Four patients showed improved glucose metabolism in the formerly hypometabolic zones, which were remote to the surgical site and ipsilateral to the epileptogenic foci. Five patients, who showed bilateral temporal hypometabolism preoperatively, had contralateral temporal hypometabolism after surgery. The relative glucose uptake in four of these patients showed increased metabolism of the adjacent lobes ipsilateral to the surgical site. The lobes that showed increased glucose metabolism after surgery were mostly frontal. Hypometabolism is reversible in the ipsilateral remote area, and may be caused by inhibition via the intercortical pathway. Contralateral temporal hypometabolic zones that persist after surgery may be caused by a different mechanism, and neither indicate the presence of seizure foci nor affect the seizure outcome.

Key words: cerebral metabolism, positron emission tomography, epilepsy surgery

Introduction

Positron emission tomography (PET) with $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) has been used to evaluate patients with partial epilepsy since the late 1970s. Interictal PET scans detect one or more zones of glucose hypometabolism. These zones correlate well with the location of the epileptogenic lesion demonstrated by electroencephalography (EEG) and the pathological abnormalities in patients with temporal lobe epilepsy. PET is used to lateralize and/or localize the epileptogenic foci before surgery. However, the true pathogenesis of glucose hypometabolism has not been determined. The causes of hypometabolism include structural damage, such as mesial temporal sclerosis, which is seen most often in patients with temporal lobe epilepsy. The loss of neuronal cells can result in decreased glucose utilization, but the degree of hypometabolism does not correlate with the severity of the lesion.

PET scans show unilateral temporal hypometabolism in about 80% of patients with temporal lobe epilepsy. The area of
hypometabolism is not confined to the mesial temporo-limbic lobe, but usually occurs in the entire temporal lobe and ipsilateral extratemporal sites.\(^8,10,26,30\) Patients with partial epilepsy of neocortical origin often show much larger hypometabolic zones than the epileptogenic lesion\(^8,10,17,28,29\); therefore, there may be functional suppression of glucose utilization in regions outside the epileptogenic lesion.\(^8,10,24,26\)

Since functional suppression may be reversible, it is important to know whether this metabolic alteration is reversible after epilepsy surgery. This is difficult to prove because the lesions are resected surgically and postoperative PET scans are meaningless. However, the fate of hypometabolism outside the surgical site, i.e., remote area, can be evaluated by postoperative PET.

We evaluated the pre- and postoperative PET scans of patients who had medically intractable complex partial seizures and whose preoperative scans identified areas of hypometabolism that were remote to the epileptogenic lesion or zone. We also evaluated the correlation between PET and EEG findings.

### Clinical Materials and Methods

1. **Patient population**

Between January 1991 and March 1994, 33 patients with intractable complex partial epilepsy who were treated at the University of Cincinnati Medical Center underwent preoperative PET scans. We evaluated nine of these patients (8 males and 1 female) who showed multiple and remote hypometabolic zones on preoperative interictal PET scans. The nine patients ranged in age at surgery from 7 to 54 years. The duration of seizures ranged from 6 to 53 years. Three patients had febrile convulsions in their early childhood, and three had meningitis. None had a history of significant head injury (Table 1). Thirty-three PET scans were reviewed, revealing two with normal findings, 11 with unilateral temporal lobe hypometabolic zones, 11 with extratemporal hypometabolic zones, and nine with multiple and remote hypometabolic zones.

2. **Pretreatment evaluations**

For the Phase I evaluation, all patients underwent video-EEG monitoring with scalp and sphenoidal electrodes to record four or more habitual seizures, and spontaneous or sleep-related seizures. A detailed neurological examination was also performed.

### Table 1  Summary of nine patients who underwent surgery for medically intractable complex partial seizures

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/Sex</th>
<th>Duration (yrs)</th>
<th>Precipitating factors</th>
<th>MR imaging</th>
<th>EEG focus Phase I</th>
<th>EEG focus Phase II</th>
<th>Surgery</th>
<th>Histology</th>
<th>Outcome Class*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32/M</td>
<td>17</td>
<td>meningitis at 8 months old</td>
<td>mild T2 hyperdense in lt temporal lobe</td>
<td>lt mesial temporal lobe</td>
<td>NA</td>
<td>lt ATL</td>
<td>MTS</td>
<td>I</td>
</tr>
<tr>
<td>2</td>
<td>35/F</td>
<td>26</td>
<td>meningitis at 1 year old febrile convulsions</td>
<td>It hippocampal atrophy</td>
<td>nonlateralizing</td>
<td>lt amygdala, no rt spike independent epileptic activity, onset: rt</td>
<td>lt ATL</td>
<td>MTS</td>
<td>I</td>
</tr>
<tr>
<td>3</td>
<td>34/M</td>
<td>11</td>
<td>meningitis at 1 year old febrile convulsions</td>
<td>WNL</td>
<td>rt medial temporal</td>
<td>rt amygdalo-hippocampectomy</td>
<td>MTS</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>18/M</td>
<td>17</td>
<td>meningitis at 1 year old febrile convulsions</td>
<td>WNL</td>
<td>rt medial temporal</td>
<td>NA</td>
<td>rt ATL</td>
<td>MTS</td>
<td>I</td>
</tr>
<tr>
<td>5</td>
<td>54/M</td>
<td>53</td>
<td>meningitis at 1 year old febrile convulsions</td>
<td>lt hippocampal atrophy</td>
<td>N/A</td>
<td>N/A</td>
<td>rt ATL</td>
<td>MTS</td>
<td>II</td>
</tr>
<tr>
<td>6</td>
<td>14/M</td>
<td>13</td>
<td>meningitis at 1 year old febrile convulsions</td>
<td>lt temporal tumor</td>
<td>lt medial temporal, no rt spike</td>
<td>lt lateral temporal</td>
<td>N/A</td>
<td>rt ATL</td>
<td>I</td>
</tr>
<tr>
<td>7</td>
<td>34/M</td>
<td>13</td>
<td>meningitis at 1 year old febrile convulsions</td>
<td>WNL</td>
<td>rt temporal</td>
<td>rt temporal</td>
<td>N/A</td>
<td>rt ATL</td>
<td>I</td>
</tr>
<tr>
<td>8</td>
<td>7/M</td>
<td>22</td>
<td>meningitis at 6 months old</td>
<td>WNL</td>
<td>lt parieto-occipital, lt amygdala</td>
<td>lt parieto-occipital, lt amygdala</td>
<td>MTS</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>28/M</td>
<td>22</td>
<td>meningitis at 6 months old</td>
<td>WNL</td>
<td>lt mesial temporal</td>
<td>NA</td>
<td>rt ATL</td>
<td>MTS</td>
<td>I</td>
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</table>

and routine EEG and magnetic resonance (MR) imaging. Five patients were scanned with a 1.5-tesla magnet and four patients were scanned with a 1.0-tesla magnet. Scan sequences generally included 5-mm spin-echo axial or coronal T2-weighted images and 5-mm coronal T1-weighted images. Two patient scans included a 1.5-mm coronal gradient echo sequence. For this study, the MR images were reevaluated by a neuroradiologist blinded to the results of EEG and PET, noting hippocampal atrophy and signal intensity change. We also performed neuropsychological testing to determine any dysfunctional areas.

Three of nine patients underwent Phase II evaluation with stereotactic depth electrode implantation or subdural electrode implantation to confirm seizure foci. PET studies were performed prior to these evaluations.

III. Surgical procedures
All operations were performed under general anesthesia with the guidance of intraoperative electrocorticography and acute depth electrode recording. Seven patients (Cases 1, 2, 4-7, and 9) underwent unilateral anterior temporal lobectomy. The extent of resection was tailored to the results of intraoperative electrocorticography or Phase II monitoring. The resection included the entire amygdala and more than 1.5 cm of the anterior hippocampus. Resection of the lateral temporal cortex was about 4 cm on the left side and about 6.0 cm on the right side. Case 3 underwent selective amygdalohippocampectomy on the right side using the transsylvian approach. Case 8 had a left anterior temporal lobectomy and an ipsilateral parieto-occipital corticectomy.

IV. PET methods
All PET studies were performed using the same scanner during the interictal state. Resolutions were approximately 5.5-mm in-plane. Sections were obtained parallel to the canthomeatal line. Patients received intravenous injections of 5.1 to 10.3 mCi of [18F]FDG. Forty minutes later, 31 contiguous slices (3.4-mm thick) of the brain were obtained. Postoperative PET scans using the same method were obtained at least 6 months after surgery (mean 17 months). Patients received the same antiepileptic medications at the time of the pre- and postoperative PET scans. The pre- and postoperative PET scans were evaluated and compared visually by at least two observers. PET data were analyzed semiquantitatively for all nine patients. All patients received the same anticonvulsants at therapeutic concentrations at the time of the pre- and postoperative PET scans.

V. Postoperative follow-up
Patients were re-evaluated 3 and 6 months after surgery and then every year. They were also evaluated at the time of postoperative PET, which were performed at least 6 months after surgery. The follow-up period ranged from 1 to 4.5 years. All patients had postoperative EEG with 21-channel bipolar and referential recordings at the same time as PET. The pre- and postoperative EEGs were compared.

Postoperative seizure outcome was classified as: Class I, free of disabling seizures; Class II, less than three seizures per year; Class III, worthwhile improvement with an 80% reduction in disabling seizures; Class IV, no worthwhile improvement.

Patients continued to receive antiepileptic drugs for at least 2 years after surgery, even if they became seizure-free.

Results
The pathology specimens showed mesial temporal sclerosis in five patients, gliosis in two, ganglioglioma in one, and normal in one.

Eight patients became Class I and one became Class II after surgery. Five of six patients who had bilateral temporal hypometabolism were Class I, and the other one was Class II. No patient had postoperative complications.

The results of PET and scalp EEG with 21-channel bipolar and referential recordings are shown in Table 2. In five patients (Cases 1, 2, and 4-6), preoperative PET scans showed bilateral temporal hypometabolism, which was more intense in the temporal lobe ipsilateral to the EEG foci. Case 3 showed cerebellar and bilateral temporal hypometabolism. Case 7 showed unilateral temporal and ipsilateral parietal hypometabolism. Cases 8 and 9 had unilateral frontal, parietal, and temporal hypometabolism. Three patients (Cases 4, 7, and 8) showed improved glucose metabolism of the formerly hypometabolic regions, which were extratemporal and ipsilateral to the epileptogenic foci. The other five patients (Cases 1-3, 5, and 6) showed bilateral temporal hypometabolism in the preoperative PET scans with intense hypometabolism ipsilateral to the epileptogenic foci; their postoperative PET scans still showed hypometabolism contralateral to the resected temporal lobe.

Relative glucose uptake was calculated in three patients (Cases 2, 4, and 6) who showed increased metabolism of the adjacent lobes ipsilateral to the surgical site. Case 2 showed increased metabolism.
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Table 2 Pre- and postoperative results of positron emission tomography (PET) and scalp electroencephalography (EEG) with 21-channel bipolar and referential recordings

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Preoperative EEG</th>
<th>PET</th>
<th>Postoperative EEG</th>
<th>PET</th>
<th>Anticonvulsants</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lt inferior F spike, lt PT slow</td>
<td>bil T hypo (lt &gt; rt)</td>
<td>no spike, lt T slow</td>
<td>unchanged (rt T)</td>
<td>Tegretal, Depakote</td>
</tr>
<tr>
<td>2</td>
<td>generalized slow</td>
<td>bil T hypo (lt &gt; rt)</td>
<td>normal</td>
<td>improved (lt FT), rt T hypo</td>
<td>Depakote, Dilantin, Depakote, Myoline</td>
</tr>
<tr>
<td>3</td>
<td>rt T slow</td>
<td>bil T and cerebellar hypo</td>
<td>rt T slow</td>
<td>unchanged (lt T)</td>
<td>Myoline, Depakote</td>
</tr>
<tr>
<td>4</td>
<td>rt T spike, rare lt T spike</td>
<td>bil T hypo (lt &gt; rt)</td>
<td>normal</td>
<td>unchanged (lt T)</td>
<td>Tegretal, Clonopin</td>
</tr>
<tr>
<td>5</td>
<td>generalized slow, lt IPDA</td>
<td>bil T hypo (lt &gt; rt)</td>
<td>moderate lt T slow</td>
<td>improved (lt FTP), rt T hypo</td>
<td>Tegretal, Depakote</td>
</tr>
<tr>
<td>6</td>
<td>normal</td>
<td>bil T hypo (lt &gt; rt)</td>
<td>paroxysmal spikes in bil hemispheres</td>
<td>improved (lt F, basal ganglia, thalamus), rt T hypo</td>
<td>Tegretal, Depakote</td>
</tr>
<tr>
<td>7</td>
<td>rt F spike, rt FT slow</td>
<td>rt TP hypo</td>
<td>mild rt FT slow</td>
<td>improved (rt P)</td>
<td>Tegretal, Dilantin, Tegretal</td>
</tr>
<tr>
<td>8</td>
<td>lt CTP spike, lt PT PPDA</td>
<td>lt hemisphere hypo</td>
<td>decreased spike, decreased slow</td>
<td>improved (lt F)</td>
<td>Tegretal, Depakote</td>
</tr>
<tr>
<td>9</td>
<td>rt FTP spike, rt FT IPDA</td>
<td>rt hemisphere hypo</td>
<td>rt T IPDA, rare lt T IPDA</td>
<td>improved (rt FP)</td>
<td>Tegretal</td>
</tr>
</tbody>
</table>


(3.5%) in the ipsilateral frontal and parietal lobes following anterior temporal lobectomy. Case 4 showed increased metabolism in the ipsilateral frontal and parietal lobes (9%) after anterior temporal lobectomy; the contralateral temporal lobe remained hypometabolic. Case 6 showed increased metabolism in the ipsilateral frontal lobe, basal ganglia, and thalamus (3.5%), and hypometabolism in the contralateral temporal lobe. Overall, six of nine patients showed increased cerebral metabolism and five patients had increased metabolism in the frontal lobe ipsilateral to the surgical site.

Retrospective study of MR images by a neuroradiologist who was blinded to the study revealed unilateral mesial temporal abnormality in four patients. Two patients had hippocampal atrophy, one had increased T2 density, and one had a tumor ipsilateral to the surgical site. The other two patients had no significant change in the mesial temporal structure. Postoperative EEG revealed diminished or decreased epileptogenic activity remote to the surgical sites in five patients (Cases 1, 4, and 7–9) (Table 2). Four patients (Cases 2, 5, 8, and 9) showed decreased slow activities such as intermittent delta activities. Decreased epileptiform activities and slow waves seen on postoperative EEG correlated well with improved metabolism shown by postoperative PET. Patients with contralateral temporal lobe hypometabolism (Cases 1–6) showed no apparent epileptogenic activities in the temporal regions. One patient (Case 6) showed paroxysmal spikes in the bilateral hemispheres that were not seen on the preoperative EEG. One patient (Case 3) showed no significant EEG changes.

Illustrative Cases

Case 1: A 32-year-old ambidextrous male had meningitis at age 8 months and had experienced complex partial seizures since age 17 years that were intractable to all antiepileptic drugs. Neuropsychological testing demonstrated a full-scale intelligence quotient (IQ) (revised Wechsler Adult Intelligence Scale) of 98, with no evidence of lateralized or localized dysfunction. The finger tapping, Boston Naming, and memory tests were nonlateralizing. MR imaging was interpreted initially within normal limits, but a blind review revealed left mesial temporal sclerosis. The 21-channel referential and bipolar recordings with sphenoidal electrodes were normal. Prolonged video EEG monitoring demonstrated six complex partial seizures that began with motor activity, including rhythmic right-hand grasping followed by left-hand grasping, nonspecific leg movements, and altered consciousness. The patient showed postictal language disturbance for more than 7 minutes. EEG onset typically showed semirhythmic, slow activity primarily in the left frontotemporal region. In each seizure, a rhythmic, sharply contoured theta-alpha discharge was seen primarily from the left sphenoidal electrode within 30 seconds of seizure onset. No such activities were seen on the right side. Preoperative interictal PET scans demonstrated hypometabolism of both tem-
Fig. 1 Case 1. Preoperative positron emission tomography (PET) scans (upper panel) showing hypometabolic zones in the bilateral temporal lobes, more intense in the left temporal lobe than in the right. Postoperative PET scans (lower panel) revealing a defect in the left temporal lobe. The right temporal lobe has decreased metabolism compared with the gray matter of the cerebral hemispheres. Glucose metabolism elsewhere in the brain is normal.

Fig. 2 Case 8. Seizure focus localization. Preoperative magnetic resonance (MR) images showing no apparent abnormal findings (left column). Preoperative positron emission tomography (PET) scans showing hypometabolism in the left frontal, parietal, and temporal lobes (center left column). Postoperative MR images showing tissue defects after surgery (center right column). Postoperative PET scans revealing significantly improved metabolism in the left frontal and parietal lobes (right column).

Case 8: A 7-year-old left-handed boy began to experience complex partial seizures at age 9 months. The cause was unknown. Anticonvulsant therapy failed to control his seizures. His full-scale IQ (Wechsler Intelligence Scale for Children) was 70. MR imaging showed no apparent abnormality (Fig. 2 left column). Routine EEG showed a persistent focus of polymorphic delta activity in the left parietotemporal region and frequent spike and wave discharges in the left centrotemporal region. Prolonged video-EEG monitoring showed ictal epileptic discharges arising from the left posterior temporoparietal region. Preoperative interictal PET scans showed a large area of decreased glucose metabolism in the left posterior parietal, occipital, and temporal regions, as well as the left frontal lobe (Fig. 2 center left column). Phase II monitoring with depth and subdural electrodes showed continuous spike and slow wave activities in the left amygdala and parieto-occipital lobe.

The left anterior temporal lobe and part of the left
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parieto-occipital cortex were resected through the left temporoparieto-occipital craniotomy (Fig. 2 center right column). Pathology indicated nonspecific chronic gliosis without evidence of tumor. Interictal PET scans obtained 10 months after surgery revealed normal glucose metabolism in the left frontal and left perietal lobes (Fig. 2 right column). Postoperative EEG also showed a significant decrease in the left central, temporal, and parietal spikes and frontotemporal intermittent polymorphic delta activities (Fig. 3). He has been seizure-free since surgery for more than 2 years and is progressing in school.

Discussion

Hypometabolism is reversible in the ipsilateral remote area and may be caused by functional suppression via the intercortical pathway. Contralateral temporal hypometabolic zones that persist after surgery may be caused by a different and irreversible mechanism and do not indicate the presence of an epileptogenic focus.

Preoperative PET is used to determine the later-
quantitative analysis. A high prevalence of thalamic hypometabolism was not detected by our methods. Our findings revealed a relatively high prevalence of bilateral temporal lobe hypometabolism compared with other series. The temporal lobe might be asymmetrically sectioned by PET causing overestimation or underestimation of glucose metabolism. This problem can be overcome with a higher resolution PET scanner and careful positioning of the patient. The presence of bilateral temporal hypometabolism also suggests the presence of secondary epileptogenesis or kindling. However, we could not detect the presence of apparent mirror foci on preoperative EEGs of the patients with bilateral temporal hypometabolism. Only one patient (Case 3) showed independent epileptiform activities that were revealed by depth electrode monitoring in the bilateral mesial temporal lobes.

Antiepileptic drugs might cause bilateral temporal hypometabolism. Phenobarbital and phenytoin are generally considered to cause global depression of glucose metabolism. Cases 2, 3, and 5 were receiving phenobarbital or phenytoin; however, hypometabolism was apparent in the temporal lobe compared with the ipsilateral frontal, parietal, or occipital lobes. It is unlikely that these drugs caused functional and selective depression of the temporal lobe. Case 3 showed a high plasma concentration of phenytoin (30 µg/dl) at the time of PET; therefore, hypometabolism of the cerebellum, which persisted after surgery, may be due to the phenytoin effect.

II. Possible causes of interictal glucose hypometabolism

Improved temporal lobe function was achieved after resection of the ipsilateral parietal lobe. Glucose metabolism of the brain worsened in one patient and improved in another patient after amygdalohippocampectomy. Postoperative hypometabolism of striate cortex was associated with hemianopsia. These previous reports, including a variety of operative methods, show there are no consistent findings for postoperative PET.

Our results showed that cerebral glucose hypometabolism improved in the ipsilateral remote area after surgery, but persisted in the contralateral temporal lobe and cerebellum. In eight patients, follow-up results were Class I and the epileptogenic foci appear to have been successfully removed. The causes of hypometabolism included pathological lesions with loss of neurons such as mesial temporal sclerosis. However, the severity of mesial temporal sclerosis did not correlate with the degree of hypometabolism. Cerebral hypometabolism of the ipsilateral remote area diminished after surgery in our patients, indicating the presence of functional suppression, i.e., either decreased afferent activity or increased inhibition. Afferent activity might decrease or be unchanged after surgery, whereas the inhibitory mechanism should diminish after resection of epileptogenic foci.

Remote transneuronal metabolic depression can occur through the reciprocal connections among the hippocampus, amygdala, and cerebral cortex. After removing the epileptogenic foci that cause increased suppression, functional suppression may subside and glucose metabolism may improve. Theoretically, this transneuronal suppression can occur through the interhemispheric connections; however, we could not find reversible depression in the patients with bilateral temporal hypometabolism.

In our cases, other causes independent of the contralateral temporal lobe, such as bilateral mesial temporal sclerosis, were considered. Since approximately 50% of the patients with mesial temporal sclerosis have bilateral lesions, we expect bilateral temporal hypometabolism more often if mesial temporal sclerosis causes hypometabolism. To clarify this, the MR images were re-evaluated by a neuroradiologist blinded to the results of PET and EEG. The presence of bilateral mesial temporal sclerosis was not detected. Because of the lack of a control study, the MR images may look normal if mild atrophy of the hippocampus was equal on both sides. Case 6 had a ganglioglioma of the left temporal lobe. PET scan showed bilateral temporal lobe hypometabolism. His right temporal lobe remained hypometabolic after surgery, whereas the left frontal lobe, basal ganglia, and thalamus showed increased metabolism. Because it is unlikely that he had mesial temporal sclerosis, the cause of contralateral temporal hypometabolism was unknown. Bilateral temporal hypometabolism does not seem to affect the result of surgery; five of six patients had a Class I outcome. It may be difficult to lateralize the seizure focus if patients have bilateral hypometabolic zones, but the priority must be placed on the electrophysiological evaluation.

III. Correlations between EEG and PET

Phase I and/or Phase II studies of these nine patients successfully identified unilateral single- or multiple-seizure foci. The patients with bilateral temporal hypometabolism showed only unilateral seizure foci. Routine scalp EEGs with 21-channel referential and bipolar recordings showed the presence of slow waves or spikes, and correlated well with the hypometabolic zones shown on preoperative PET scans. However, the routine
EEG did not show epileptogenic activity in the contralateral temporal lobe with glucose hypometabolism. As shown in Cases 2, 4, and 7–9, improved glucose metabolism seems to correlate with improvement shown on EEG such as decreased epileptiform activity and slow waves. Case 6 showed paroxysmal spike waves on postoperative EEG, which were not seen on preoperative interictal EEG. The significance of these spikes is unknown because the patient was seizure free and postoperative PET scans showed improved glucose metabolism. Hypometabolism shown by interictal PET does not identify the epileptic nature of the lesion, but indicates the abnormal neuronal activity in an epileptogenic focus. Therefore, postoperative improvement of neuronal activity adjacent to the epileptogenic focus can also be suggested by routine scalp EEG.

IV. Correlation between [18F]FDG PET, 11C-flumazenil PET, and proton MR spectroscopy

The pathophysiology of the interictal hypometabolism in temporal lobe and other epilepsies is unknown and remains an active area of research. Seizures that originate in a small area in the temporal lobe (e.g., hippocampus) often have interictal hypometabolism that involve the entire temporal lobe and sometimes extend over to the adjacent frontal, parietal, and contralateral temporal lobes. Several theories have been advanced. The most commonly accepted is that “Localized neuronal loss in brain structures involved in seizure onset and spread causes reduced metabolic activity locally, and associated diaschisis results in reduced metabolic activity in other structures.” This may not be the full explanation since comparison of preoperative quantified glucose metabolism with quantified neuronal density in surgical specimens has shown that neuronal loss and diaschisis cannot fully account for the hypometabolism. In addition, when pre- and postoperative PET are compared, as in our study, unresected adjacent hypometabolic areas preoperatively showed increased metabolism postoperatively. Multifocal neuronal loss with diaschisis cannot explain the above finding. Therefore, it appears that other factors intrinsic to seizures and epilepsy in addition to structural lesions are the cause of glucose interictal hypometabolism.

Flumazenil is a specific, reversibly bound central benzodiazepine receptor (cBZR) antagonist and 11C-flumazenil is a PET ligand that can be used to measure cBZR density. Many investigators have demonstrated a selective decrease in 11C-flumazenil binding that is confined to the hippocampus, but with more widespread glucose hypometabolism. The most recent study, when corrected for partial volume effect, showed that absolute 11C-flumazenil binding to cBZR was significantly reduced in the sclerosed hippocampus over and above the loss of volume. This suggests that in addition to loss of neurons, there is a diminished number of receptors per neuron, which may reflect functional changes in the epileptogenic zone. In addition, cBZR density was normal in the neocortical temporal lobe and in the rest of the brain. Therefore, neuronal integrity appears to be preserved in the neocortex and the glucose hypometabolism that extends beyond the mesial temporal structures may at least be partially due to diaschisis.

Proton MR spectroscopy has shown that there is a reduction in N-acetyl aspartate (NAA)/choline + creatine and phosphocreatine (CR) ratio in the medial temporal lobe of patients with epilepsy compared with normal subjects. There was a reduction in NAA (located primarily within neurons) and an increase in choline and CR (with higher concentrations in astrocytes). These results are consistent with loss or dysfunction of neurons and possibly gliosis in the affected medial temporal areas. A study of 25 adults with intractable temporal lobe epilepsy showed that NAA/choline + CR ratio was reduced in 88% of the patients on the side of the seizure focus, with 40% having bilateral abnormalities. In patients with bilateral abnormalities, one temporal lobe was judged to be significantly more abnormal than the other, similar to our findings of bilateral glucose hypometabolism. The magnitude of NAA reduction was not only confined to the hippocampus, but also involved adjacent areas, similar to the results of [18F]FDG PET. The cellular mechanisms involved in the reduction of NAA and the increase in choline and CR remain unknown and need further study.

Full understanding of the cause of glucose hypometabolism in the affected temporal lobe and adjacent areas depends on further investigations. Contralateral glucose hypometabolism is less understood compared with ipsilateral hypometabolism. Abnormalities in the unoperated side may not be a prognostic factor for seizure outcome. Patients with left temporal lobe abnormalities verified by MR spectroscopy who underwent right temporal resection had verbal memory deficits. Therefore, contralateral glucose hypometabolism and MR spectroscopy abnormalities may be indicative of the functional integrity of this part of the brain. Whether this is related to the contralateral seizure focus requires further investigation.
V. Can epilepsy surgery improve cerebral glucose metabolism?

Hypometabolism of the ipsilateral remote area became normal after successful surgery; the areas of improvement were mostly in the frontal lobe. The ipsilateral remote area was probably inhibited via the intercortical pathway, and successful resection of epileptogenic foci could improve glucose metabolism. Surgical resection did not change contralateral or cerebellar hypometabolism, suggesting that the metabolic suppression was independent of the epileptogenic foci. Diffuse hypometabolism remained constant after anterior corpus callosotomy. These results seem reasonable because the patients did not undergo resection of the epileptogenic zones, which can cause depression of glucose metabolism. A marked decrease in glucose metabolism of the contralateral hemisphere occurred after hemispherectomy, and the decrease in metabolism may have been caused by the massive degeneration of callosal system, leading to cell soma changes in the intact side due to the severance of axon branches. This is an example of decreased affective activity of the contralateral hemisphere enhanced by hemispherectomy.

Investigation of 25 patients with [(18)F]FDG PET before and after temporal lobe epilepsy indicated an increase of regional cerebral metabolic rate of glucose, both in the ipsilateral and contralateral hemispheres in patients with mesiobasal limbic temporal lobe epilepsy and mesial gliosis. There was no EEG during the PET studies and no postoperative EEG recording to compare with the PET findings. PET uses a neurobiochemical marker, such as [11C]-flumazenil, with a high affinity for BZRs, which is more specific in mesiobasal temporal lobe seizures. PET may become more important in the study of the pathophysiology of epilepsy.

Epilepsy surgery improved the cerebral glucose metabolism remote but ipsilateral to the seizure foci, and appeared to correlate with EEG findings. Persistent contralateral temporal hypometabolism without clinical symptoms or ictal EEG abnormality was found, but the mechanism remains unknown. Continued prospective PET study of the brain before and after epilepsy surgery may provide a better understanding of cerebral metabolism and chronic epilepsy.

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14) Hajek M, Wieser HG, Khan N, Antonini A, Schrott
Postoperative Cerebral Metabolism


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Commentary

Cerebral metabolism of the remote area after epilepsy surgery is a very important issue which is not fully understood. In this paper, the lobes that showed increased metabolism after surgery were mostly frontal, whereas contralateral temporal hypometabolic zones persisted after surgery. The reason for this persistence of hypometabolism in the contralateral temporal zones should be clearly established. Serial follow-up of this hypometabolism is one way to elucidate this persistence of hypometabolism. Therefore, long-term follow-up of cerebral metabolism by PET is mandatory to understand the mechanism or reason of this hypometabolism. In this article, only qualitative data have been presented, but to elucidate the true nature of this hypometabolism quantitative data should be presented. In addition to FDG-PET data, MRS, EEG or MEG dipole data, and neuropsychological data should be also presented to understand the mechanism. The authors should be encouraged to continue this study employing modalities other than FDG-PET to understand the meaning of this temporal hypometabolism. This article has added important evidences about postoperative glucose metabolism in cases of the temporal lobe epilepsy at the level of the
This is an interesting article that gives additional support to the observation that in patients with focal epilepsy cerebral metabolism is altered not only in the epileptogenic zone but also at remote areas ipsi- and contralateral to the focus. Interestingly, it has been shown in this work as also in previous publications, that successful removal of the epileptogenic region leads to normalization of the remote hypometabolic areas. These observations suggest that the remote hypometabolism is not just the consequence of the atrophy of the epileptogenic zone but most probably due to active inhibitory effects secondary to the abnormal epileptiform discharges in the epileptogenic zone.

Dr. Akimura and coworkers did not observe normalization of contralateral hypometabolism in patients with mesial temporal epilepsy. These findings are not in agreement with the studies of Hajek et al. (ref. 14 of this article) who actually reported normalization of the contralateral temporal hypometabolism following successful surgical treatment. The reason for that discrepancy is unclear.

In the presurgical evaluation of patients who are candidates for surgery of epilepsy, it is important to consider the above mentioned remote areas of cortical hypometabolism that may be detected by PET scanning. These remote effects determine that the "functional deficit zone," as measured by PET scanning, will usually overestimate the epileptogenic zone and, therefore, should not be used to define the limits of a surgical resection.

Reference


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Positron emission tomography (PET) has in recent years proved to be a valuable technique in the presurgical assessment of patients with partial epilepsy, in particular temporal lobe epilepsy. Recent PET studies in patients with intractable temporal lobe epilepsy have reported hypometabolism in the temporal and frontal lobes.

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Many studies have discussed the preoperative findings of cerebral blood flow or glucose metabolism in relation to the epileptic focus. However, few studies have examined the important issue of postoperative changes of cerebral metabolism after resection of the epileptogenic area. This article, which analyzed PET scans before and after epilepsy surgery, is very valuable in this sense. I find great interest in that the cerebral glucose metabolism adjacent to the epileptic focus was found to improve after surgery. As many authors indicated, PET generally detects a more extensive hypometabolic area during the interictal phase compared with the electrophysiologically or histopathologically abnormal zone. This discrepancy is suspected to be caused by the surrounding inhibition of adjacent cortices, a well-known phenomenon observed around the epileptic focus. The results of this article confirmed this hypothesis. In addition,
decreased metabolism in the contralateral temporal lobe was observed after temporal lobectomy. This phenomenon was persistent and was not concordant with clinical symptoms or PET findings. The mechanism of this decreased metabolism was not fully discussed in this article. According to the study by Hajek et al. (ref. 14 of this article), in which the glucose metabolism was quantitatively analyzed and 20 patients with mesiobasal limbic temporal lobe epilepsy underwent surgery by amygdalohippocampectomy, this postoperative contralateral temporal hypometabolism is confined only to the mesiobasal areas. This finding was considered to indicate strong interhemispheric connections between both mesial temporal structures. Readers are recommended to read the study by Hajek et al. and come back again to this paper.

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