**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. Postoperatively, we found increased IF and thalamic metabolism. Seizures may have a reversible effect on brain areas connected with, but remote from, the epileptogenic cortex.
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 meet 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

A standard region of interest (ROI) template was placed on the scan planes using a previously described method.16 We measured absolute regional CMRglc values in milligrams per minute per 100 g in 64 ROIs grouped into 6 pairs anatomic areas (inferior lateral temporal [ILT], inferior temporal [IMT], IF, occipital, parietal, and thalamus). A previous study found good interrater agreement (κ = 0.86; P < .001) for repeated measures using our template.17 For this study, we used metabolic rates normalized to global mean glucose utilization to correct for regional changes due to medication effect. Normalized values were calculated by dividing regional metabolic rate by mean global metabolic rate (where rates are given in milligrams per minute per 100 g). For preoperative studies, the difference in metabolism was expressed as ipsilateral ROI minus contralateral ROI. Postoperative changes were expressed as postoperative ipsilateral ROI minus preoperative ipsilateral ROI and postoperative contralateral ROI minus preoperative contralateral ROI. We also calculated the asymmetry index for each ROI as the difference between the left and right normalized regional values divided by their mean:

\[
\frac{(L-R)/(L+R)/2}{},
\]

where L indicates left and R, right. Regional hypometabolism was defined as an absolute asymmetry index greater than 0.15. This value represents 2 SDs from the mean absolute asymmetry index for healthy controls.17

STATISTICAL ANALYSIS

We performed analysis of variance (ANOVA) to determine the effect of age, epilepsy duration, time interval between surgery and postoperative PET study, seizure outcome, resection site, and abnormalities on the change in CMRglc from preoperative to postoperative PET scan for each ROI separately.

Due to the small sample size of groups with mass lesions (n = 6) and no specific findings (n = 6), we performed further statistical analysis only in the MTS group. We used Wilcoxon signed rank tests to compare regions ipsilateral and contralateral to the resection site in the preoperative PET studies and to compare homologous regions between preoperative and postoperative PET studies. All data are expressed as mean ± SEM. The significance level was set at .05.

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 angiomia, 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. 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 $^{18}$F-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).

**PET RESULTS**

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tween change in metabolism and time interval between
operatively (ANOVA). No correlation was detected be-
gery and postoperative PET study, surgical outcome, and
operative metabolism in parietal or occipital areas.

Compared with preoperative PET studies, asymmetry in
IP lobes and thalamus was found in 2 and 9 patients, re-

There was a significant increase in CMRglc in contra-
lateral 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, re-

We did not find any significant change in postop-
erative metabolism in parietal or occipital areas.

Age, epilepsy duration, time interval between sur-
gery and postoperative PET study, surgical outcome, and
resection site did not affect the change in metabolism post-
operatively (ANOVA). No correlation was detected be-
tween 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).

COMMENT

Temporal lobe epilepsy is associated with extensive preop-
erative hypometabolism involving medial and lateral
temporal as well as IF areas and thalamus ipsilateral to
the seizure focus. Although some previous studies sug-
gested that PET might be less sensitive for patients who
did not have MTS,19 we found that all pathological groups
exhibited the same extensive preoperative hypometab-
olism. Hajek et al13 observed decreased metabolism con-
fined to the mesial and polar regions preoperatively solely
in patients with MTS. However, Khan and coinvestiga-
tors19 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 fea-
tures.

After surgery, we found increased ipsilateral IF and
bilateral thalamic metabolism, although the changes were
not always statistically significant. Hajek et al13 demon-
strated increased metabolism postoperatively in ipsilat-
eral and contralateral hemispheres in the MTS group, but
did not observe any statistically significant specific re-
gional increases. We found a tendency toward in-
creased bilateral IF CMRglc in all patients and signifi-
cantly increased contralateral thalamic metabolism in
patients with MTS. Variation in extent of resection could
account for some of the differences between these stud-
ies. Akimura et al13 reported that epilepsy surgery led to
increased metabolism mostly in the ipsilateral frontal lobe.

For this study we used all patients as their own con-
trols in evaluating changes in metabolism before and af-
after surgery. In addition, the time interval between sur-
gery 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 sur-
gery and follow-up PET suggests that the results we
found are more likely to reflect physiological stability.

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

Phenobarbital sodium, phenytoin sodium, carba-
mazepine, and valproic acid led to variable reductions

Figure 1. Comparison of ipsilateral and contralateral with seizure focus metabolism in preoperative positron emission tomography studies in each patient group. Values in y-axis represent difference in normalized values of glucose metabolism; error bars, SEM. Reduced metabolism was observed in all regions of interest in all patient groups. In the mesial temporal sclerosis (MTS) group (n=16), statistically significant reductions were noted in inferior lateral temporal (ILT) (asterisk; P < .001), inferior medial temporal (IMT) (dagger; P = .002), and inferior frontal (IF) regions (double dagger; P = .002). Th indicates thalamus.

Figure 2. Comparison of preoperative and postoperative positron emission tomography studies ipsilateral to seizure focus. Values in y-axis represent change in normalized values of glucose metabolism; error bars, SEM. Postoperatively, reduced metabolism was demonstrated in remnant inferior lateral temporal (ILT) and remnant inferior medial temporal (IMT) areas in all patient groups and reached statistical significance in the mesial temporal sclerosis (MTS) group (asterisk; P < .001). Increased metabolism was noted in the inferior frontal (IF) region in all patient groups. There was a trend for significance in the mesial gliosis group (P = .06). A modest increase in thalamic metabolism was observed in all 3 groups. Th indicates thalamus.
Cerebral blood flow (CBF) has been studied as well. Futagi et al. 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%). 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. 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.

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 γ-aminobutyric acid, the drugs produce. Usually, the doses are much higher than those used clinically; single doses of valproic acid in baboons did not affect CBF at all.

Epileptogenic human hippocampus is characterized by synaptic inhibition in synchronously firing epileptic neurons during interictal periods, decreased excitatory synaptic input, and reduced efferent output to surrounding projection areas, 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 predominate. Positron emission tomography studies have consistently demonstrated hypometabolism in frontal regions ipsilateral to epileptogenic temporal lobe zone. Intracranial EEG recordings support the view that orbitofrontal cortex is a preferential pathway for mesial temporal seizure propagation. Prefrontal cortex probably receives afferent input from the amygdala, hypothalamus, and mamillary bodies by means of anterior thalamus and projects to posterior cingulate, hippocampus, and amygdala through the association cortex. 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. Functional fluctuations in this region may be associated with postoperative affective symptoms.

Campbell formation, amygdala, and entorhinal cortex. 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. Thalamic involvement in seizure initiation and propagation has been confirmed in humans by neuroimaging studies that showed hyperperfusion ictally, and decreased CBF and metabolism interictally. Thalamic atrophy, neuronal loss, and gliosis have been described in a few patients with TLE, and there is a significant correlation between resected hippocampal cell densities and CMRglc in thalamus bilaterally. 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 affrent 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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REFERENCES


