
Increased In Vivo Expression of an Inflammatory Marker in Temporal Lobe Epilepsy

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Animal studies and clinical observations suggest that epilepsy is associated with inflammation. Translocator protein (TSPO) (18 kDa), a marker of inflammation, is increased in vitro in surgical samples from patients with temporal lobe epilepsy. TSPO can be measured in the living human brain with PET and the novel radioligand ¹¹C-PBR28. In this study, we sought to determine whether in vivo expression of TSPO is increased ipsilateral to the seizure focus in patients with temporal lobe epilepsy. **Methods:** Sixteen patients with unilateral temporal lobe epilepsy and 30 healthy subjects were studied with ¹¹C-PBR28 PET and MRI. Uptake of radioactivity after injection of ¹¹C-PBR28 was measured from regions of interest drawn bilaterally onto MR images. Brain uptake from ipsilateral and contralateral hemispheres was compared using a paired-samples *t* test. **Results:** We found that brain uptake was higher ipsilateral to the seizure focus in the hippocampus, parahippocampal gyrus, amygdala, fusiform gyrus, and choroid plexus but not in other brain regions. This asymmetry was more pronounced in patients with hippocampal sclerosis than in those without. **Conclusion:** We found increased uptake of radioactivity after injection of ¹¹C-PBR28 ipsilateral to the seizure focus in patients with temporal lobe epilepsy, suggesting increased expression of TSPO. Studies in larger samples are required to confirm this finding and determine the clinical utility of imaging TSPO in temporal lobe epilepsy.

Key Words: positron emission tomography; translocator protein 18 kDa; epilepsy; inflammation

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Inflammation may contribute to the pathophysiology of epilepsy. Animal studies have found that proinflammatory cytokines are increased in rodent models of epilepsy and that seizure frequency correlates with activation of these cytokines (1–3). Human studies have found increased expression of proinflammatory markers in neurosurgical sam-

ples from patients with focal epilepsy (2,4–6), and a recent metaanalysis suggests an association between epilepsy and a genetic functional polymorphism that causes increased production of the proinflammatory cytokine interleukin-1 β (7).

Translocator protein (TSPO) (18 kDa) is a marker of inflammation (8,9). Basal expression of TSPO is low, but in inflammation, activated microglia and astrocytes overexpress TSPO (10). TSPO expression is increased in vitro in surgical samples from patients with temporal lobe epilepsy (11,12). In these samples, increased TSPO colocalizes with hippocampal sclerosis (12), a lesion associated with neuronal loss and glial proliferation.

TSPO expression has been measured in vivo with PET using the radioligand ¹¹C-(R)-PK11195 (13). However, results from studies with ¹¹C-(R)-PK11195 have not been consistent. Increased uptake of radioactivity after injection of ¹¹C-(R)-PK11195 was reported in 2 cases of Rasmussen encephalitis (13) and 1 case of intractable seizures due to encephalopathy of unknown origin (14) but not in 3 stable patients with temporal lobe epilepsy and hippocampal sclerosis (13). Unfortunately, ¹¹C-(R)-PK11195 has a low ratio of specific-to-nonspecific binding (15) and may therefore lack sufficient sensitivity to detect increased TSPO in temporal lobe epilepsy. We recently developed ¹¹C-PBR28 as an improved PET radioligand for TSPO (16). ¹¹C-PBR28 has a higher ratio of specific-to-nonspecific binding than ¹¹C-(R)-PK11195 (15) and may have sufficient sensitivity to detect increased TSPO in temporal lobe epilepsy.

To determine whether ¹¹C-PBR28 could detect increased TSPO, we scanned 16 patients with temporal lobe epilepsy. Because we expected increased TSPO to be associated with the seizure focus, we compared uptake in brain regions ipsilateral and contralateral to the focus in these patients as well as in right and left hemisphere regions in 30 healthy subjects.

MATERIALS AND METHODS

Subjects

Sixteen patients (8 men, 8 women; mean age \pm SD, 36 \pm 10 y; mean body weight \pm SD, 72 \pm 15 kg) with temporal lobe epilepsy were recruited by the Clinical Epilepsy Section at the National Institute of Neurologic Disorders and Stroke (Table 1). Clinical

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TABLE 1
Demographic and Clinical Information of Patients with Temporal Lobe Epilepsy

Patient no.	Age (y)	Sex	Handedness	Epilepsy duration (y)	Complex partial seizures	Generalized tonic-clonic seizures	Electroencephalography	MRI
1	39	M	Left	29	Occasional	2x/childhood	Right temporal	Negative
2	61	M	Right	16	Rare	Occasional	Right temporal	Right MTS
3	30	M	Right	16	Occasional	Occasional	Left parasagittal/temporal	Negative
4	39	M	Right	28	Occasional	Rare	Left temporal/frontal	Right MTS
5	28	M	Right	13	Rare	2x/lifetime	Left posterior occipital/parietal	Left MTS
6	41	F	Right	3	Rare	Rare	Left anterior temporal	Negative
7	39	F	Right	39	Occasional	Rare	Left temporal	Left MTS
8	36	M	Right	36	Frequent	Occasional	Left temporal	Left MTS
9	33	F	Right	4	Rare	Rare	Left temporal	Left hippocampal malrotation
10	26	F	Right	13	Occasional	Rare	Right temporal	Right MTS
11	41	F	Right	34	Frequent	Rare	Left temporal/frontal	Negative
12	21	F	Left	7	Occasional	1x/lifetime	Left temporal/frontal	Negative
13	41	F	Left	10	Occasional	Occasional	Left anterior midtemporal	Left MTS
14	48	M	Right	7	Occasional	Occasional	Left temporal	Negative
15	22	M	Right	1	Rare	Rare	Left anterior temporal	Left MTS
16	37	F	Right	5	Occasional	Rare	Right temporal	Right MTS

Frequent = >1x/wk; MTS = mesial temporal sclerosis; occasional = 1x/mo - 1x/wk; rare = <1x/mo.

and diagnostic evaluation included detailed medical history, physical examination, laboratory tests of blood and urine, electrocardiogram, ictal videoelectroencephalography, and clinical MRI of the brain. Patients were excluded if they had serious medical conditions (other than epilepsy), had a history of alcohol or drug use disorder, or were pregnant. For each patient, seizure lateralization was based on the presence of unilateral hippocampal sclerosis on MRI or on the presence of lateralizing ictal electroencephalography findings if sclerosis was not present on MRI. In addition to the patients presented here, 1 female patient was recruited but had to be excluded because she had negligible binding of ¹¹C-PBR28 to TSPO in the brain (15,17) (see the "Discussion" section).

To examine physiologic asymmetry in ¹¹C-PBR28 uptake, 2 cohorts of healthy subjects were analyzed: 7 healthy subjects were scanned with the High-Resolution Research Tomograph (HRRT) PET scanner (Siemens Medical Solutions) (4 men, 3 women; mean age ± SD, 45 ± 11 y; mean body weight ± SD, 75 ± 18 kg), and 23 subjects were scanned with the Advance PET scanner (GE Healthcare) (14 men, 9 women; mean age ± SD, 48 ± 17 y; mean body weight ± SD, 78 ± 14 kg). Subjects underwent detailed medical history, physical examination, laboratory tests of blood and urine, and electrocardiogram for excluding serious medical conditions, illicit drug use, and pregnancy.

The subjects' consents were obtained according to the Declaration of Helsinki. The Institutional Review Board of the National Institute of Mental Health/National Institute of Neurological Disorders and Stroke approved the protocol and the consent forms.

MRI

All subjects underwent brain MRI as part of their evaluation. Healthy subjects underwent MRI either at 1.5 T or 3 T and patients with temporal lobe epilepsy at 3 T. The MRI scans included clinical coronal and axial T1-weighted, T2-weighted, and fluid attenuation inversion recovery sequences. A high-resolution 3-dimensional T1-weighted sequence was obtained for anatomic reference for PET image analyses. The presence or absence of hippocampal sclerosis was determined by an experienced neuro-radiologist.

Preparation of ¹¹C-PBR28

¹¹C-PBR28 was synthesized as previously described (16). Synthesis was performed in accordance with Investigational New Drug application 76,441. A copy of the application is available at <http://pdsp.med.unc.edu/snidd/>. ¹¹C-PBR28 was synthesized with high radiochemical purity (>99%) and had a specific activity at the time of injection of 126 ± 77 GBq/μmol for patients with temporal lobe epilepsy, 64 ± 30 GBq/μmol for healthy subjects scanned with the HRRT camera, and 114 ± 68 GBq/μmol for healthy subjects scanned with the Advance camera.

Image Acquisition

After intravenous injection of ¹¹C-PBR28 (684 ± 48 MBq for patients with temporal lobe epilepsy, 492 ± 64 MBq for healthy subjects scanned with the HRRT camera, and 637 ± 82 MBq for healthy subjects scanned with the Advance camera), PET images were acquired using the HRRT or the Advance as previously described (18) for 120 min. All patients with temporal lobe epilepsy were scanned on the HRRT. We had a total of 7 healthy subjects scanned on the HRRT. To examine a larger sample for potential asymmetry, we used a set of 23 healthy subjects studied on the Advance scanner. Although the spatial resolution (~7 mm) of the

Advance is less than half that of the HRRT (~3 mm), and reconstruction methods are different, the Advance scanner provided similar measures of asymmetry. Voxel volume was about 1.8 mm³ in HRRT images and about 8 mm³ in normalized Advance images.

Image Analysis

T1-weighted MR images were coregistered to averaged (0–120 min) PET images using SPM2 (19) running on MATLAB (version 7.2.0.232; The MathWorks). Hippocampi and amygdalae were then manually delineated using PMOD (version 3.0; PMOD Technologies Ltd.) on axial coregistered T1-weighted MR images and regional time–activity curves extracted from the dynamic PET images. The hippocampal regions included cornua ammonis, dentate gyrus, and fimbriae. Anatomic criteria for delineating the hippocampi were adopted from published guidelines (20,21), and accuracy was inspected using all 3 orthogonal projections. The volume of this region was about 2.9 cm³ in the affected hippocampus in patients with epilepsy and 3.4 cm³ in the unaffected hippocampus in patients with epilepsy and about 3.9 and 3.6 cm³ in the right and left hippocampus, respectively, in healthy subjects scanned with the HRRT camera. For regions outside the mesial temporal region, we used the Automated Anatomical Labeling template of volumes of interest (22) implemented in PMOD. For this analysis, PET images were spatially normalized using the ligand-specific normalization template. This template had been created using data PET images from 7 healthy subjects and normalization parameters derived from MR images. For healthy subjects from the Advance camera, we used the Automated Anatomical Labeling template for all brain regions. Data from the Automated Anatomical Labeling template were consolidated by volume-weighted averaging into the following volumes of interest: cerebellum, fusiform gyrus, occipital cortex, parahippocampal gyrus, parietal cortex, prefrontal cortex, lateral temporal cortex, striatum, and thalamus.

Measurement of Brain Uptake

As a primary evaluation, we measured decay-corrected brain uptake of radioactivity after injection of ¹¹C-PBR28 from the hippocampus ipsilateral to the seizure focus, delineated on coregistered MR images, and compared it with that from the hippocampus contralateral to the seizure focus. To avoid confounding effects of delivery of radioligand into brain, we defined brain uptake as the average of standardized uptake values (SUVs) from 60 to 120 min (SUV_{60–120}). SUVs were calculated as radioactivity concentration divided by injected dose per body mass.

Small foci of higher uptake appeared on the superior border of the anterior hippocampus (see the “Results” section). These foci

likely represented choroid plexus in the temporal horn of the lateral ventricle. Because choroid plexus in this region is difficult to separate from the hippocampus, we extracted this structure from PET images as follows. We used an automated algorithm to extract 50 contiguous voxels within a 7 × 7 × 7 voxel cube centered on the hottest voxel within the area containing hippocampus and choroid plexus, from a PET image that had been averaged from 10 to 100 min and smoothed with a 3-mm gaussian kernel (full width at half maximum). Time–activity curves within this 50-voxel cluster were then calculated from the dynamic PET images. Finally, time–activity curves for the hippocampus were calculated by removing the area within the cluster from the dynamic image and then applying the region of interest for the whole hippocampus. The 50-voxel cutoff was selected on the basis of visual inspection.

Statistical Analysis

Data were analyzed with SPSS (release 17.0.0 [SPSS Inc.] for Windows [Microsoft]). Brain uptake from ipsilateral and contralateral hemispheres was compared using 2-tailed paired-samples *t* tests, specifically testing the hypothesis of increased uptake ipsilateral to the seizure focus. Similarly, the paired-samples *t* test was used in the healthy subjects to test the hypothesis of physiologically lateralized uptake of ¹¹C-PBR28. In addition, we calculated an absolute asymmetry index for each subject as $200 \times |(\text{left} - \text{right})/(\text{left} + \text{right})|$ and compared these indices between the groups using ANOVA and an independent-samples *t* test. To maintain a hypothesiswise type I error rate of 0.05, observed *P* values were corrected for multiple comparisons using the false discovery rate correction (23).

RESULTS

After injection of ¹¹C-PBR28, a focal area of increased uptake was found in the hippocampal region in both patients and healthy subjects. Uptake in this focus was about 60% higher than that in the hippocampus. This focus occurred in both hemispheres and was anatomically located near the anterior and dorsal hippocampus (Fig. 1). On the basis of our prior imaging studies with ¹¹C-PBR28 in monkeys (24), this focus was likely the choroid plexus in the temporal horn of the lateral ventricle, adjacent to the hippocampus. We confirmed the anatomic identity of the focus of high uptake by examining PET images from 1 healthy subject who, in addition to ¹¹C-PBR28, had previously been scanned with ¹¹C-*N-desmethyl*-loperamide (¹¹C-dLop) (25). ¹¹C-dLop is

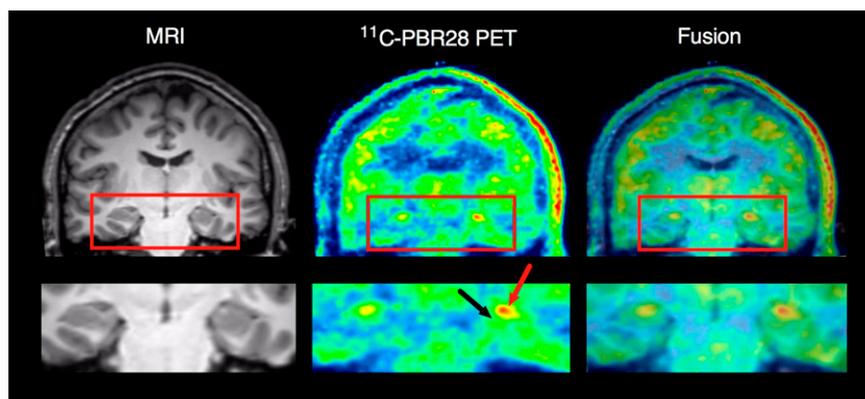


FIGURE 1. Coronal sections of MR, PET, and fused PET/MR images demonstrate distribution of radioactivity in brain after injection of ¹¹C-PBR28 in patient with left-sided temporal lobe epilepsy. PET image is summed from 0 to 120 min. Right side of brain appears on left side of image. Area within red rectangles appears magnified in bottom row. There is higher uptake in ipsilateral than in contralateral side in choroid plexus (red arrow) and hippocampus (black arrow).

a substrate radioligand for P-glycoprotein, or P-gp, which is one of the major transporter molecules at the blood–brain barrier. In normal-brain parenchyma, P-gp blocks the entry of ^{11}C -dLop, but for unknown reasons, ^{11}C -dLop is avidly taken up in the choroid plexus (25). In this subject who underwent both ^{11}C -PBR28 and ^{11}C -dLop imaging, we noted spatial correspondence between the foci of high uptake in both images (Supplemental Fig. 1; supplemental materials are available online only at <http://jnm.snmjournals.org>). Therefore, the foci of high ^{11}C -PBR28 uptake likely represent choroid plexus.

In patients, brain uptake was higher in the hippocampus, parahippocampal gyrus, amygdala, fusiform gyrus, and choroid plexus ipsilateral to seizure foci (Table 2; Fig. 2). The increased uptake in the hippocampus ipsilateral to the epileptic focus was more pronounced among patients with (13% \pm 6%, $n = 9$) than without (5% \pm 4%, $n = 7$) hippocampal sclerosis (2-tailed $P = 0.009$) but did not correlate with duration of illness or frequency of seizures. Notably, asymmetry was significant even within patients without hippocampal sclerosis alone ($P = 0.020$, $n = 7$).

We wondered if increased hippocampal uptake ipsilateral to seizure foci in patients was confounded by physiologic asymmetry in brain uptake of ^{11}C -PBR28. No such asymmetry was seen among healthy subjects scanned with the HRRT camera, either in the hippocampus (right 0.1% larger than left; $P = 0.855$) or choroid plexus (right 3.8% smaller than left; $P = 0.163$). However, in the 23 healthy subjects scanned with the Advance camera, uptake was slightly higher in the left hemisphere than in the right hemisphere for the hippocampus (1.9%, $P < 0.01$) and fusiform gyrus (1.5%, $P = 0.02$) but not for the parahippocampal gyrus or amygdala. Although statistically significant, the asymmetry was substantially smaller in healthy subjects (range, -10%

to 11%) than in patients (range, -2% to 26%). Finally, we compared absolute asymmetry indices between patients with epilepsy and healthy subjects scanned with the 2 PET cameras. ANOVA showed a significant difference between the 3 groups ($F_{2,43} = 11.6$, $P < 0.001$). Posthoc contrast showed that patients with epilepsy differed from all healthy subjects ($t = 3.49$, $P = 0.001$) and that healthy subjects scanned with the HRRT camera did not differ from those scanned with the Advance camera ($P = 0.063$). The asymmetry index was 9.4 ± 5.4 in patients with epilepsy ($n = 16$) and 3.9 ± 3.3 in healthy subjects ($n = 30$). This analysis confirmed that the difference between affected and unaffected hippocampus in patients with epilepsy was significantly greater than the difference between the right and left hippocampus in healthy subjects.

The 95% confidence interval for the absolute asymmetry index in the 30 healthy subjects was 2.7–5.1. Four patients of 16 (patients 1, 3, 9, and 14; Table 1) had asymmetry values within the 95% confidence interval of healthy subjects. None of the subjects had hippocampal sclerosis. However, we caution against using lack of significant asymmetry as evidence for lack of inflammation, because increased uptake in the contralateral hemisphere could diminish asymmetry.

Could radioactivity from choroid plexus have contaminated the signal measured from adjacent regions via partial-volume effects? We simulated the spillover based on the spatial resolution of the camera and the distance between choroid plexus and amygdala. We assumed that the images had a resolution of 2.5 mm in full width at half maximum; that the choroid plexus and amygdala were 8 and 12 mm in diameter, respectively; that the choroid plexus and amygdala were separated by 2 mm; and that the SUV_{60-120} was 1.8 in choroid plexus (measured from the affected hemi-

TABLE 2
Uptake of Radioactivity After Injection of ^{11}C -PBR28 in Brain Regions Ipsilateral and Contralateral to Seizure Focus

Brain region	Brain uptake (SUV_{60-120})		Difference	Effect size	P
	Ipsilateral	Contralateral			
Hippocampus	1.15 \pm 0.4	1.04 \pm 0.4	+10%	0.29	0.00007*
Parahippocampal gyrus	1.02 \pm 0.4	0.94 \pm 0.3	+8%	0.23	0.0007*
Amygdala	1.16 \pm 0.4	1.09 \pm 0.4	+8%	0.18	0.002*
Fusiform gyrus	1.01 \pm 0.5	0.97 \pm 0.4	+4%	0.08	0.002*
Choroid plexus	1.81 \pm 0.7	1.58 \pm 0.6	+16%	0.36	0.016*
Occipital cortex	1.11 \pm 0.5	1.09 \pm 0.5	+1%	0.04	0.190
Striatum	0.87 \pm 0.4	0.85 \pm 0.4	+2%	0.05	0.227
Thalamus	1.13 \pm 0.5	1.12 \pm 0.5	+1%	0.03	0.373
Lateral temporal cortex	1.05 \pm 0.5	1.03 \pm 0.4	+1%	0.04	0.441
Parietal cortex	0.95 \pm 0.4	0.94 \pm 0.4	+1%	0.03	0.539
Prefrontal cortex	0.98 \pm 0.4	0.99 \pm 0.4	-1%	-0.02	0.545
Cerebellum	1.41 \pm 0.6	1.42 \pm 0.5	-1%	-0.02	0.951

*Statistically significant, and survives false discovery rate correction for multiple comparisons.

Hippocampal values do not include contributions from choroid plexus, which was subtracted from total hippocampal volume using automated clustering algorithm (see “Results” section). P values are uncorrected from 2-tailed paired-samples t test. Brain uptake values are mean \pm SD.

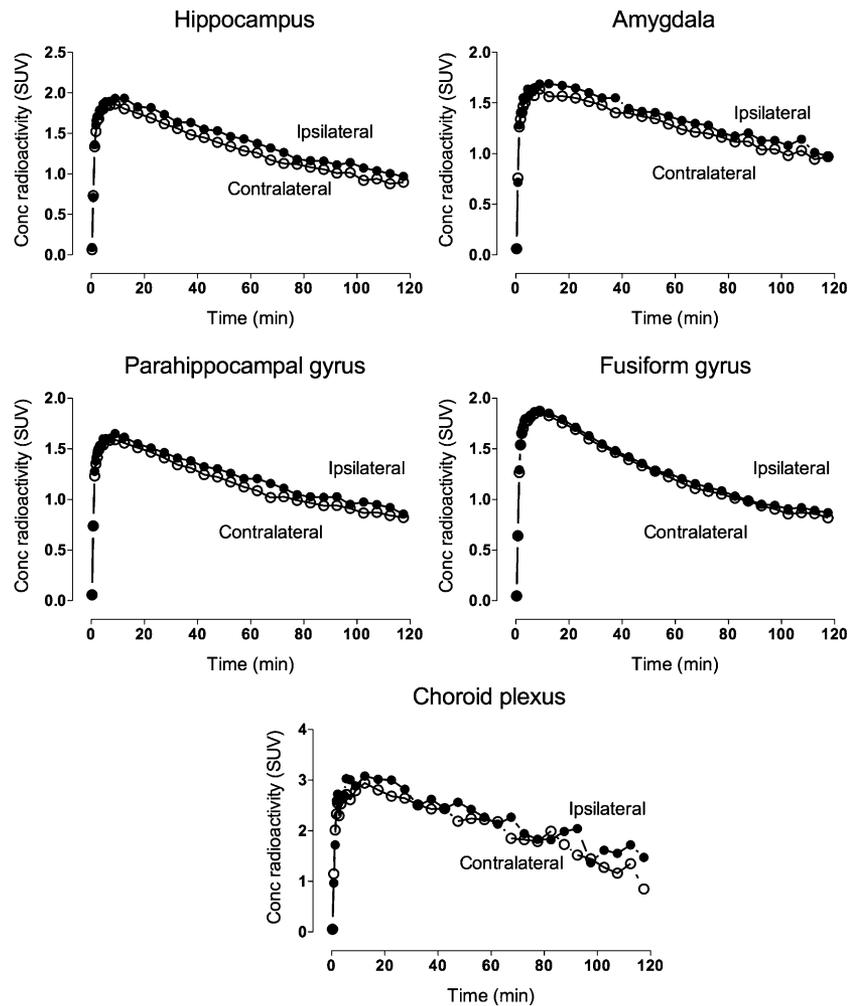


FIGURE 2. Uptake of radioactivity after injection of ^{11}C -PBR28 ipsilateral and contralateral to seizure focus in brain regions that showed significant asymmetry. Values are mean of all 16 patients.

spheres) and 1.09 in amygdala (measured from the unaffected hemisphere). Under these assumptions, the spill-in of radioactivity from choroid plexus constituted less than 0.1% of activity in the nearby amygdala.

DISCUSSION

We imaged patients with temporal lobe epilepsy and healthy subjects with the selective and sensitive TSPO radioligand ^{11}C -PBR28. By comparing ipsilateral and contralateral regions, we found increased uptake of radioactivity in the hippocampal regions near the seizure focus. Our results suggest a neuroinflammatory response on the side of the epileptogenic focus, associated with increased density of reactive astrocytes or activated microglia. Analysis outside the hippocampus suggested that the parahippocampal gyrus, amygdala, fusiform gyrus, and choroid plexus are also affected.

We analyzed hemispheric asymmetry rather than absolute binding levels. This strategy has been used extensively in PET epilepsy studies and has several advantages. It directly tests the main hypothesis of relative increases in TSPO binding in the epileptic focus, compared with contralateral hippocampus, and obviates potential effects of global confounders such as antiepileptic drugs. Our

approach had the disadvantage of not being able to detect alterations that may be bilateral. For example, we clearly found increased TSPO binding in the ipsilateral, compared with the contralateral, hemisphere, but the contralateral hemisphere itself may have elevated binding, compared with that in control subjects. For such an analysis, we would need arterial blood data to measure the absolute binding (i.e., distribution volume) in each hemisphere of both patients and control subjects. Brain uptake values are dependent on how much tracer is available in plasma, and both the metabolism and the plasma protein binding may be different in medicated patients, compared with healthy subjects. Fully quantitative analysis of ^{11}C -PBR28 binding requires arterial catheterization and will be done in the future to determine whether patients with epilepsy have increased TSPO binding only in the hemisphere containing the epileptogenic focus or in both hemispheres.

In contrast to our results, 1 previous study using ^{11}C -(R)-PK11195 did not find a lateralized increase of binding in 3 patients with temporal lobe epilepsy (13). This negative result might have been caused by a small sample size; due to the fact that the patients were seizure-free on stable doses of antiepileptic medications, rather than being evaluated for

uncontrolled epilepsy; or because of the low ratio of specific to nonspecific binding of ^{11}C -(R)-PK11195.

Even with our improved PET ligand, ^{11}C -PBR28, the increase was small, compared with decreased activity reported in PET studies of glucose metabolism (26). However, our results are comparable to increases in opiate receptor binding in temporal lobe epilepsy (27). Furthermore, the TSPO may be increased in only part of the hippocampus. In temporal lobe epilepsy, TSPO expression *in vitro* is most increased in the CA1 subfield of the hippocampus, which also shows the greatest atrophy (11). Thus, partial-volume effects may have prevented us from detecting this pronounced but spatially restricted increase in TSPO expression *in vivo* with PET. Other explanations for the small asymmetry are increased uptake in the contralateral and ipsilateral hemispheres and the possibility that the epileptogenic focus in some patients with temporal lobe epilepsy may be less affected by inflammation than that in others.

In all subjects, we noted foci of higher uptake superior to the anterior part of the hippocampus. These foci likely represented the choroid plexus in the temporal horn of the lateral ventricle, because the choroid plexus is known to have a high density of TSPO in monkeys (24,28). Limited spatial resolution of PET and MRI impeded us from anatomically separating the choroid plexus from the hippocampus. Nevertheless, we confirmed the identity of the focus by comparing the distribution of uptake after injection of ^{11}C -PBR28 with that after injection of ^{11}C -dLop, a substrate radioligand for P-gp that is avidly taken up by the choroid plexus. In a healthy subject who underwent both PET scans, the focus of high uptake in the ^{11}C -PBR28 image corresponded spatially to that in the ^{11}C -dLop image (Supplemental Fig. 1), confirming that the focus in both images represents choroid plexus.

We considered performing partial-volume correction but decided not to do so for several reasons. This correction is commonly performed in pathologic conditions in which both the density of the target and the volume of tissue are decreased. The purpose of partial-volume correction is to determine whether the loss of receptors is proportionate to or disproportionately greater than the loss of tissue. The value of partial-volume correction is uncertain, however, in conditions such as temporal lobe epilepsy in which the density of the target (TSPO) is increased but the volume of tissue is generally decreased. Furthermore, not all tissues in the epileptogenic region have decreased volume. The region with the highest uptake is the choroid plexus, and we do not know whether the volume of this tissue is increased or decreased in the epileptogenic area. Finally, if we had done partial-volume correction—and assuming loss of tissue in the areas in the epileptogenic region—increased TSPO binding in temporal lobe epilepsy would have been even greater after partial-volume correction.

Physiologic asymmetry in the hippocampus and the fusiform gyrus was noted among 23 healthy subjects

scanned with ^{11}C -PBR28 using another PET camera with lower spatial resolution (Advance), such that values from the left hemisphere were less than 2% higher than values from the right hemisphere. Our results are only minimally confounded by this normal asymmetry. First, asymmetry was higher among the patients (range, -2% to 26%) than among healthy subjects (range, -10% to 11%), and patients had significantly higher absolute asymmetry indices. Second, patients showed significant asymmetry in regions that were not asymmetric among healthy subjects, such as the amygdala and parahippocampal gyrus. Finally, 5 of 16 patients (31%) had the epileptogenic focus in the right not in the left hemisphere, which counterbalances for physiologic asymmetry.

Our results are not likely confounded by changes in cerebral blood flow in patients with temporal lobe epilepsy. We measured brain uptake of radioactivity from 60 to 120 min to avoid the early phase of uptake in which the cerebral blood flow has the largest effect. In addition, patients with temporal lobe epilepsy have reduced interictal blood flow ipsilateral to the seizure focus (29), which would only diminish the uptake of radioactivity after injection of ^{11}C -PBR28.

About 10 percent of the approximately 100 subjects we have studied to date show negligible binding of ^{11}C -PBR28 to TSPO in the brain and periphery. PBR28 has a much lower affinity for TSPOs in this subpopulation than in the larger population—about 10-fold lower for binding to membranes of white blood cells (15) and 25-fold lower for binding to human brain tissue (17). In addition to low-affinity binders, Owen et al. (17) identified another group of subjects (~30% of their study sample) that had mixed affinity—that is, a mixture of high- and low-affinity binding (17). For the current study, we excluded 1 patient with low-affinity binding based on PET images of the brain and following the criteria of Kreisl et al. (15). We doubt that *in vivo* imaging with ^{11}C -PBR28 can detect mixed-affinity binders, who may therefore be included in our study. Nevertheless, inclusion of such individuals would not bias the within-subject comparison of ipsilateral and contralateral hemispheres assuming the distribution of mixed-affinity binding is uniform throughout the brain.

CONCLUSION

We found increased uptake of radioactivity after injection of ^{11}C -PBR28 ipsilateral to the seizure focus in patients with temporal lobe epilepsy, suggesting an increased expression of TSPO. Exploratory analysis indicated that the adjacent parahippocampal gyrus, amygdala, fusiform gyrus, and choroid plexus are similarly affected. Future studies in larger samples should confirm this initial observation, establish whether other brain regions are involved, and measure absolute binding values using fully quantitative analysis. TSPO imaging may have utility in studies of the pathophysiology and treatment of temporal lobe epilepsy.

DISCLOSURE STATEMENT

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734.

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