

mGluR5 PET Imaging Using ^{18}F -FPEB in Medically Refractory Epilepsy Patients

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Abstract

Introduction: mGluR5 availability in medically refractory epilepsy patients compared to healthy controls (HC) using the PET agent ^{18}F -FPEB was assessed.

Methods: Five epilepsy patients (mean age: 33.6; SD: 13.04); (4F, 1M) and 8 HC (mean age: 24.4; SD of 4.8); (5 M, 3 F) were studied with a High-Resolution Research Tomography and a bolus/infusion technique. Volume of distribution corrected for plasma free fraction values (V_T/f_p) was determined from equilibrium data in different brain regions including the seizure onset zone (SOZ), which was determined at an epilepsy surgical conference.

Results: A trend towards global decreases in ^{18}F -FPEB V_T/f_p was noted. Significant decreases were seen in the frontal lobes, and limbic structures: The amygdala, hippocampi, and thalami compared to HC. No significant differences were found between SOZ and a contralateral mirror region.

Conclusion: ^{18}F -FPEB human imaging of the mGluR5 system in refractory epilepsy showed significant decreases in the frontal lobes and limbic structures.

Keywords: ^{18}F -FPEB; mGluR5; Medically refractory epilepsy; Surgical epilepsy; Seizure onset zone

Introduction

Epilepsy is a chronic debilitating condition. It has a significant socioeconomic impact as well as a prominent cost burden [1,2]. The CDC estimates that about 2.9 million people in the United States have epilepsy. Medical treatment has not been shown to impact clinical outcomes or cost-effectiveness [3]. Surgical epilepsy techniques play a major role in patient's refractory to antiepileptic drugs (AEDs), which represents at least one third of patients. Surgery is also helpful in cases of significant AED side effects and potential teratogenicity. These groups of patients are termed medically refractory epilepsy patients. Their lives are negatively impacted at multiple levels, with decreased independent living, limited financial independence, driving restrictions, neuropsychological impairment, and overall decreased well-being. These described cases have failed medical treatment may therefore benefit from respective surgical alternatives. Since the late 1800's, surgery for epilepsy has been shown to be successful in seizure control. Surgical success is dependent on the preoperative localization of the seizure-onset zone (SOZ) [4]. This is challenging even in centers with extensive experience and advanced expertise. Nuclear medicine techniques have been proven to be useful in delineating the SOZ through detecting changes in blood flow on SPECT images [5]. Additionally, PET imaging of glucose metabolism, central benzodiazepine receptors and serotonin availability has also been shown to impact surgery planning and outcomes. PET has better identified the SOZ necessary to be resected than MRI [6-9]. However current techniques are suboptimal and all have their limitations. mGluR5, a subtype of metabotropic glutamate receptors, plays a role as an excitatory regulator of synaptic transmission and plasticity [10]. Animal studies have implicated the group mGluR subtypes (mGluR1/5) in having pro-convulsive effects and especially mGluR5 in TLE [11], ictally and post-ictally [11-13], and in epileptic seizure models [14-16]. We performed first in human epilepsy PET imaging of mGluR5 using ^{18}F -FPEB, thus imaging the

glutamate system, an immediate driver of seizures. We hypothesize that there would be major changes in the mGluR5 system in epilepsy, and conjectured that it might be useful in identifying the SOZ.

Materials and Methods

Study population

Epilepsy patients with severe medically refractory disease whom were being evaluated for surgical resection of the SOZ and underwent intracranial electrocorticography (IEC). These patients had no MRI contraindication, and were medically stable.

HC subjects were men and women aged 21-70 years, with no history of epilepsy or other neurological disorders and no current or past uncontrolled medical conditions. These subjects also had a normal brain MRI.

Imaging protocol

^{18}F -FPEB was prepared in accordance with procedures and quality specifications contained in the local Drug Master File (DMF) approved by the Yale-New Haven Hospital Radioactive Drug Research Committee (YNHH RDRC). The study was approved by local IRB and all subjects were consented. PET scans were performed on a High-

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Resolution Research Tomograph (HRRT) at the Yale University PET Center. ¹⁸F-FPEB images were acquired for 2 hours. Motion correction was performed dynamically with measurements from the Vicra (NDI Systems, Waterloo, Ontario) using a dedicated list-mode reconstruction algorithm. PET scans were acquired after administration of ≤ 5 mCi of ¹⁸F-FPEB. A bolus plus constant infusion (B/I) technique was used, as it showed the least inter-subject variability [17,18]. Dynamic images were reconstructed with corrections for attenuation, normalization, random events, scatter, dead time, and motion. The volume of distribution (V_T) was determined at equilibrium and normalized by plasma free fraction (V_T/f_p) to correct for individual and group differences in f_p . Values were obtained in predefined ROIs from the AAL template: hippocampi, parahippocampal gyri, amygdala, thalami, basal ganglia, cingulate gyrus, and insula, and cerebellum, temporal, parietal, occipital and frontal cortices [19]. A rigid PET-MR co-registration was performed from the PET data to the subject's MR, followed by a nonlinear registration to the MR (AAL) template.

Defining the SOZ

Based on various clinical and imaging variables, during a weekly epilepsy multidisciplinary surgical conference, a plan for IEC grid implantation was outlined (the conference was blinded to the ¹⁸F-FPEB results), followed by the patient being admitted to an inpatient epilepsy monitoring unit, withdrawal of antiepileptic medications and later on surgery. Depth electrodes were stereo tactically implanted using MRI guidance and a computerized planning system and subdural strip and grid electrodes were implanted under visual guidance. On average, more than 200 electrode contacts were implanted per patient. To determine the location of the electrodes used for IEC, individual contacts were identified on a postoperative CT scan. This scan was co-registered to a post-operative MRI scan using a 6-parameter rigid transformation, and the post-operative MRI scan was then co-registered with a pre-operative MRI scan using a nonlinear transformation to account for the distortion of the brain caused by craniotomy [20,21]. The intracranial EEG (electroencephalogram) was reviewed and the SOZ coordinates (electrode contacts) were then derived from a grid. These coordinates allowed us to draw multiple ROIs on the pre-operative MRI, as shown

in Figure 1. These coordinates were derived in subjects 1 through 3 from IEC grid analysis, and from an MRI where a lesion concordant with clinical semiology was felt to be the SOZ in subjects 4 and 5. The coordinates were then transformed onto the patient's ¹⁸F-FPEB scan, via the PET-MR registration, to estimate mean V_T/f_p in the SOZ. These coordinates were also mirrored onto the contralateral side for each subject, for comparison to the ipsilateral values. In addition, a HC average (AVG) image dataset (Figure 2) was derived from the 8 HC subjects co-registered via the MR atlas registration. Each SOZ region was applied to the HC AVG for comparison purposes.

Statistical analysis and hypotheses

We hypothesized that there would be decreases in V_T/f_p in epilepsy subjects when compared to healthy controls. This hypothesis was formulated taking into consideration published data [14-16]. A one tailed, unpaired t-test (unequal variances) with alpha=0.05 was used to assess significance. Given the pilot nature of this study, no correction for multiple comparisons was performed.

Results

We performed ¹⁸F-FPEB scans in 5 epilepsy subjects (mean age of 33.6 ± 13.0); (4F, 1M). The mean age of our HC population was 24.4 ± 4.8 , with 5 M and 3 F. mGluR5 age and sex effects were not felt to be significant [22]. Our patient cohort included 3 temporal lobe epilepsy and 2 extra-temporal lobe epilepsy patients. Average epilepsy duration was 10 years (5-44). On average, patients were placed on 5 different antiepileptic medications to control their seizures. The insula, followed by the temporal lobe had the highest ¹⁸F-FPEB uptake and the cerebellum was noted to have the lowest [17]. Overall, V_T/f_p values were lower in the epilepsy patients than in controls (Figure 3). These decreases were statistically significant in the frontal lobe and in the limbic structures: amygdala, hippocampus and thalamus (Table 1). No significant differences were noted when SOZ values were compared to a mirror region on the contralateral side in each subject (Figure 4). Comparing the SOZ values to the respective HC V_T/f_p mean values, in 4/5 cases, the patient SOZ values were lower than the mean control value.

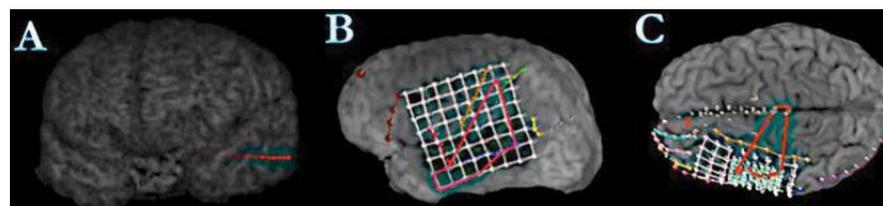


Figure 1: Examples of 3D IEC grid display overlaid on MRI for 3 subjects: red lines correspond to SOZ coordinates.

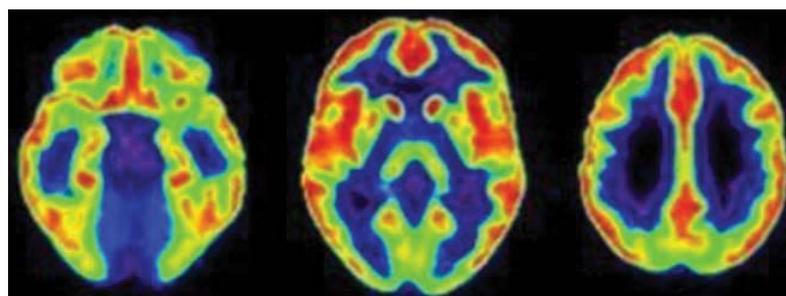


Figure 2: ¹⁸F-FPEB healthy control average PET image.

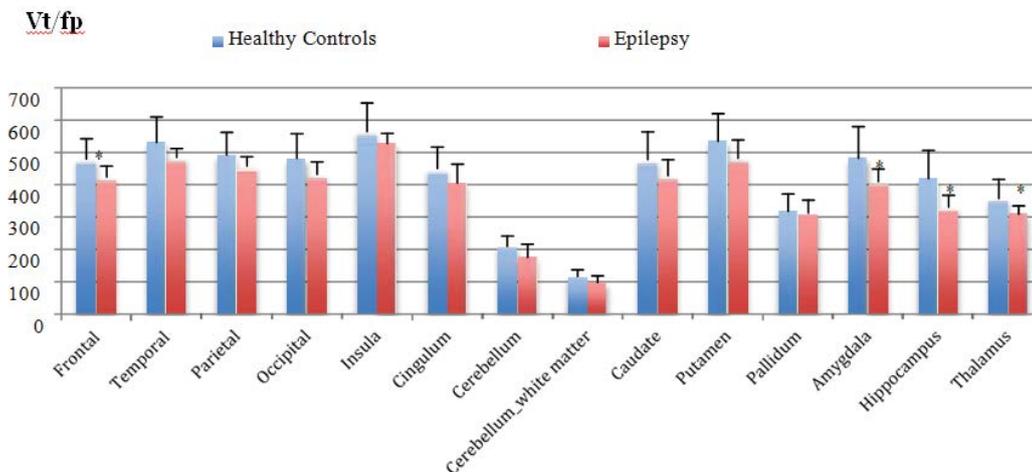


Figure 3: Group differences in mGluR5 availability. *Significant decreases in VT/fp were found in the frontal lobes (p=0.029) and limbic system: amygdala, hippocampus and thalamus (p=0.046, 0.014, 0.033 respectively).

ROI	Brain Structure	p value
1	Frontal	0.029*
2	Temporal	0.082
3	Parietal	0.122
4	Occipital	0.077
5	Insula	0.153
6	Cingulum	0.113
7	Cerebellum	0.076
8	Cerebellum white matter	0.065
9	Caudate	0.104
10	Pallidum	0.425
11	Putamen	0.059
12	Amygdala	0.046*
13	Hippocampus	0.014*
14	Thalamus	0.033*

*Significant p values

Table 1: t-test analysis of 5 PET and 8 HC subjects showing significant decreases in the frontal lobe, amygdala, hippocampus and thalamus.

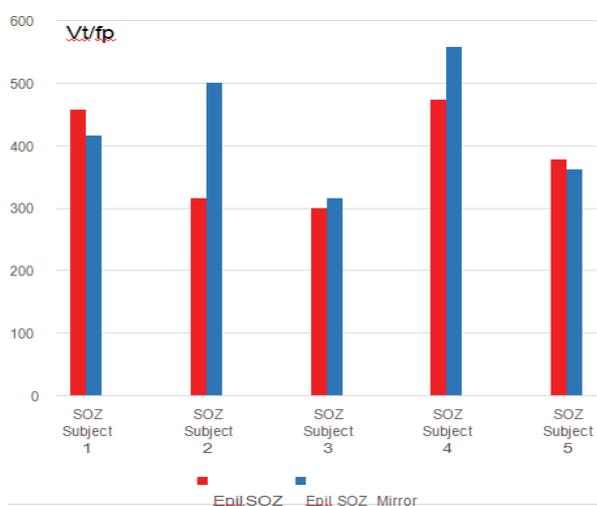


Figure 4: mGluR5 distribution volume V_T (mL/cm³) normalized by plasma free fraction (f_p) as measured on an FPEB scan in the SOZ of epilepsy subjects compared to contralateral mirror region.

Discussion

The current clinical standard uses FDG PET to assess glucose metabolism distribution in the brain of epilepsy patients. FDG PET identifies indirect secondary changes of the disease and neuronal dysfunction in these patients. It evaluates the functional deficit zone, and rarely the irritative zone, or even the seizure onset zone; it has a high spatial resolution but has a limited temporal resolution. It can also be at times limited by a non-localizing study as well as frequent hypo metabolism extending beyond the SOZ, to the propagation zone and other connected regions. In our study we evaluated mGluR5 which is part of the glutamate system -a direct driver of seizures- using a novel PET agent ¹⁸F-FPEB. We demonstrated changes in mGluR5 bio distribution in a group of medically refractory epilepsy patients using this PET tracer ¹⁸F-FPEB. When compared to a cohort of healthy controls, statistically significant regional decreases and a trend for whole brain decrease in ¹⁸F-FPEB V_T/f_p was noted. Since these patients have severe long-standing refractory epilepsy, it is unclear if these changes would be seen in well-controlled epilepsy patients. This may be due to down regulation of mGluR5 receptors in severe human epilepsy, concordant with preclinical models of epilepsy [14-16]. In contrast, resected tissue from TLE showed increased mGluR5 immunoreactivity, although expression was inversely related to seizure frequency [23]. Another factor that affects *in vivo* measurements is increased extracellular glutamate; although ¹⁸F-FPEB does not bind directly to mGluR5, glutamate release has been associated with lower PET tracer signal [24-26]. We found significant decreases in ¹⁸F-FPEB uptake in the frontal lobe and several limbic structures: amygdala, hippocampi, and thalami. This may be evidence of the role of these structures in the propagation of seizures, the epileptogenic network, or the chronicity of seizures [16]. Limbic system involvement in epilepsy has also been described in preclinical models and in humans with metabolic and serotonergic PET probes. On the other hand ¹⁸F-FPEB has also been shown by Ceccarrini et al. [27] to be decreased in limbic structures in alcohol dependent patients and described as a potential biomarker for the assessment of the recovery of these patients [27,28]. In a group of PTSD patients Davis et al. and Holmes et al. [29,30] stated increases in FPEB were noted in the frontal and limbic system but not in patients with major depression [29-31]. Dang et al. in another study in Parkinson's disease (PD) patients showed that average ¹⁸F-FPEB BPND values were slightly more than 20% higher in PD than healthy

volunteers in several mesocortical regions, including the bilateral putamen, hippocampus, and amygdala [32]. Additionally Fatemi et al. [33] identified significantly higher ¹⁸F-FPEB binding potential in the post central gyrus and cerebellum of individuals with autism [33]. In essence, in our study we evaluated ¹⁸F-FPEB a novel radiotracer targeting the mGluR5 system that can be used to noninvasively evaluate the glutamate system, a direct driver of seizures. Its use in the pre-surgical phase of severe refractory epilepsy or in other epilepsy circumstances requires further study.

Conclusion

¹⁸F-FPEB human imaging of the mGluR5 system in refractory epilepsy is feasible. Significant decreases in the frontal lobes and limbic structures were found. Further studies with extracellular glutamate micro dialysis and postsurgical histological specimen correlations are needed.

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