In vivo activation of endocannabinoid system in temporal lobe epilepsy with hippocampal sclerosis

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The endocannabinoid system modulates neuronal excitability, protects neurons against hyperexcitability and is involved in epileptogenesis in animal models of mesial temporal lobe epilepsy with hippocampal sclerosis. We performed in vivo positron emission tomography imaging of the type 1 cannabinoid receptor in patients with mesial temporal lobe epilepsy with hippocampal sclerosis. Twelve patients with refractory mesial temporal lobe epilepsy due to hippocampal sclerosis received a [18F]MK-9470 scan to assess type 1 cannabinoid receptor availability in vivo. Parametric modified standard uptake values were used as quantitative measure of type 1 cannabinoid receptor availability and images were spatially normalized to standard space. Voxel-based analysis was performed comparing patients with hippocampal sclerosis to controls and correlations between type 1 cannabinoid receptor status and seizure characteristics were done using volumes of interest. Type 1 cannabinoid receptor positron emission tomography was co-registered with subtraction ictal single photon emission computed tomography co-registered to magnetic resonance imaging of a complex partial seizure (n = 9). An increased type 1 cannabinoid receptor availability in the ipsilateral temporal lobe was observed, which correlated negatively with the latency since last seizure before scanning and positively to the number of seizures in the month before scanning. A decreased type 1 cannabinoid receptor availability was present in the superior insular cortex, ipsilateral more than contralateral. The ipsilateral insular region displayed a mild ictal hyperperfusion in the transition zone of subtraction ictal single photon emission computed tomography co-registered to magnetic resonance imaging temporal lobe hyperperfusion-frontal lobe hypoperfusion during complex partial seizures. Type 1 cannabinoid receptor availability showed opposite changes in different brain regions that are involved during complex partial seizures in refractory mesial temporal lobe epilepsy with hippocampal sclerosis. The increase in type 1 cannabinoid receptor availability at the seizure onset zone might be a protective mechanism of neurons against hyperexcitability and seizure activity, or contribute to the process of epileptogenesis, or both. The decreased type 1 cannabinoid receptor availability in the insula may play a role in surround inhibition and prevention of seizure propagation.

Keywords: type 1 cannabinoid receptor; hippocampal sclerosis; epilepsy; [18F]MK-9470; positron emission tomography

Abbreviations: CB1R = type 1 cannabinoid receptor; SISCOM = subtraction ictal single photon emission computed tomography co-registered to MRI
Introduction

Epilepsy affects ~3% of the population during their lifetime (Hauser, 1975) and can be successfully treated using anti-epileptic drugs in ~70% of patients. New potent anti-epileptic drugs are therefore still needed. A small group of patients with refractory partial epilepsy can be treated with surgical removal of the epileptogenic zone. In order to perform surgery, the seizure onset zone needs to be identified clearly taking results of clinical and interictal EEG, dedicated MRI, subtraction ictal PET and neuropsychological testing into account (Goffin et al., 2008). Despite this multitude of tests, it is not possible to reliably delineate the seizure onset zone in some patients. To help these patients, new diagnostic tools to improve the detection of the seizure onset zone are important.

Type 1 cannabinoid receptors (CB1Rs) are expressed in high concentrations in the CNS, where they are not only present on neurons, but also in lower concentrations on microglia, astrocytes and oligodendrocytes (Di Marzo et al., 1998). CB1Rs, located mainly on presynaptic nerve terminals, modulate neuronal excitability through suppression of the release of other neurotransmitters, for example glutamate, GABA and dopamine (Wilson and Nicoll, 2002).

The endocannabinoid system provides ‘on-demand’ protection against hyperexcitability and acute seizures and is neuroprotective against excitotoxicity via a CB1R-dependent mechanism (Marsicano et al., 2003). In animal models of mesial temporal lobe epilepsy due to hippocampal sclerosis, CB1R-agonists have a strong anti-epileptic effect (Wallace et al., 2003). In humans, the effect of CB1R-agonists in epilepsy is less clear and not well studied. Conroy and colleagues (1998) suggested that cannabis may have anti-epileptic effects, but others found it ineffective or proconvulsant (Gordon and Devinsky, 2001; Lutz, 2004).

Mesial temporal lobe epilepsy due to hippocampal sclerosis is often preceded by an initial precipitating injury (Mathern et al., 1999), such as a prolonged febrile convulsion, cerebral trauma or meningoencephalitis. The time between initial precipitating injury and onset of habitual epileptic seizures is called the silent period or latent interval. Epileptogenesis refers to a process in which an initial brain-damaging insult triggers a cascade of molecular and cellular changes that eventually lead to occurrence of spontaneous seizures. In animal models of mesial temporal lobe epilepsy due to hippocampal sclerosis, the endocannabinoid system has been implicated in the process of epileptogenesis (Goffin et al., 2009), and early administration of CB1R-antagonists was anti-epileptogenic and prevented the development of epilepsy (Chen et al., 2007).

In patients with mesial temporal lobe epilepsy due to hippocampal sclerosis, only in vitro studies have been performed to date, demonstrating a decreased level of CB1R messenger RNA in the sclerotic hippocampus (Ludanyi et al., 2008). In this article, we have used [18F]MK-9470, a radioligand with high affinity and specificity for the CB1R (Burns et al., 2007), and PET imaging in a cross-sectional study. The aim was to assess CB1R availability in patients with mesial temporal lobe epilepsy due to hippocampal sclerosis in vivo, to correlate CB1R availability with clinical data and to determine the potential role of CB1R imaging as a supplementary tool in identifying the seizure onset zone during presurgical evaluation.

Materials and methods

Patient characteristics

A total of 12 patients with refractory mesial temporal lobe epilepsy due to hippocampal sclerosis (seven males, five females; age range 28–70 years) were included. The seizure onset zone was defined using a combination of seizure semiology, ictal and interictal EEG, optimized MRI, ictal and interictal brain perfusion single photon emission computed tomography imaging and SISCOM analysis (n = 9) (Table 1).

A population of 50 Caucasian volunteers (25 female, 25 male; age range 18–69 years) from a previous study was available as the control group (Van Laere et al., 2008).

The study was approved by the local Ethics Committee and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects prior to the study.

Radiotracer characteristics and preparation

[18F]MK-9470 (Merck Research Laboratories, West Point, PA, USA) is an inverse agonist with high selectivity and specificity for the human CB1R (Burns et al., 2007). The precursor for tracer synthesis was obtained from MRL and labelling was performed on-site using [18F]-ethylbromide. The final product was obtained after high-performance liquid chromatography separation and had a radiochemical purity >95%. Specific activity was higher than 200 GBq/μmol. The tracer was administered in a sterile solution of 5 mM sodium acetate buffer, pH 5.5 containing 6% ethanol.

Imaging procedure

All patients were fasted for at least 4 h prior to PET imaging. Subjects received on average 306 MBq (range 233–362 MBq) of [18F]MK-9470 in slow intravenous injection under standardized injection circumstances (supine, low ambient noise, dimly lit room). Starting 90 min after injection, a dynamic PET emission scan was started in 3D mode (HR+, Siemens, Germany), consisting of six frames with frame duration of 300 s. Total scan duration was 30 min. The subject’s head was placed in a head holder and fixed using a vacuum mask to avoid excessive head movement. Images were reconstructed using a 3DRP algorithm including scatter and measured attenuation correction (68Ge source).

Image processing and data analysis

Correction for motion between frames was performed using the realignment module in SPM2 (Wellcome Department of Cognitive Neuroscience, London, UK). Modified standardized uptake value images of [18F]MK-9470 binding were calculated using PMOD version 2.7 (PMOD Inc., Zurich, Switzerland) where the activity concentration at each voxel was divided by the amount of tracer injected and normalized to the subject’s weight (kg); modified standardized uptake
### Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Number</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Initial precipitating injury</th>
<th>Age at onset (years)</th>
<th>Number of seizures in month before scanning</th>
<th>Latency since last seizure before scanning (days)</th>
<th>MRI</th>
<th>Interictal EEG</th>
<th>Ictal EEG</th>
<th>SISCOM</th>
<th>FDG PET</th>
<th>Relative CB1R in temporal lobe cluster</th>
<th>Outcome surgery</th>
<th>Pathology</th>
<th>Antiepileptic drugs</th>
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<tbody>
<tr>
<td>1</td>
<td>28</td>
<td>F</td>
<td>Febrile seizures</td>
<td>6</td>
<td>2</td>
<td>26</td>
<td>HS R</td>
<td>Temporal R</td>
<td>Temporal R</td>
<td>Temporal R</td>
<td>Temporal R</td>
<td>0.92</td>
<td>Engel I</td>
<td>HS</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>M</td>
<td>Limbic encephalitis</td>
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<td>M</td>
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<td>Temporal R</td>
<td>1.16</td>
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<td>Febrile seizures</td>
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<td>HS L</td>
<td>Temporal L</td>
<td>Temporal L</td>
<td>Temporal L</td>
<td>Temporal L</td>
<td>0.99</td>
<td>Engel II</td>
<td>HS</td>
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<tr>
<td>10</td>
<td>46</td>
<td>M</td>
<td></td>
<td>1</td>
<td>8</td>
<td>1.3</td>
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<td>Temporal R</td>
<td>Temporal R</td>
<td>Temporal R</td>
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<td></td>
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<td>Carbamazepine, vigabatrin, levetiracetam</td>
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<tr>
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<td>55</td>
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<td></td>
<td>35</td>
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<td>HS R</td>
<td>Temporal R</td>
<td>Temporal R</td>
<td>Temporal R</td>
<td>Temporal R</td>
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</tr>
<tr>
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<td>28</td>
<td>M</td>
<td></td>
<td>13</td>
<td>4</td>
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<td>HS L</td>
<td>Temporal L</td>
<td>Temporal L</td>
<td>Temporal L</td>
<td>Temporal L</td>
<td>1.03</td>
<td>Engel II</td>
<td>HS</td>
<td>Carbamazepine, levetiracetam</td>
</tr>
</tbody>
</table>

F = female; FDG = 2-[18F]-fluoro-2-deoxy-D-glucose; HS = hippocampal sclerosis; L = left; M = male; R = right.
value = \{activity \times (weight \text{ (kg)} + 70 \text{ kg})/2\}/injected dose (Sanabria-Bohorquez et al., 2010). [\textsuperscript{18}F]MK-9470 modified standardized uptake value images were co-registered to the subject’s magnetic resonance image. The images of patients with hippocampal sclerosis on the right and left side were combined for analysis by left–right reversing images from patients with left-sided hippocampal sclerosis, in order to show the epileptogenic zone on the same (right) side in all patients. For this, PET and magnetic resonance images were co-registered and then flipped. Afterwards these images were spatially normalized to an in-house created CB1R template (Van Laere et al., 2008) in standard Montreal Neurological Institute (MNI) space in SPM2 using non-linear warping (7 \times 9 \times 7 basis functions, 16 iterations). For further analyses, data were smoothed with a Gaussian kernel with a full-width at half-maximum of 10 mm.

Statistical parametric mapping analysis was performed comparing patients to controls in a categorical subject design with age and gender as nuisance variables, since CB1R availability is different for males and females and shows an age dependency (Van Laere et al., 2008). Proportional scaling was used and a relative analysis threshold of 80% of the mean was set to exclude non-grey matter activity. Data were explored using \( P_{\text{height}} < 0.001 \) (uncorrected). Clusters of significantly different CB1R binding were used as volumes of interest for further correlation analyses. Average modified standardized uptake values within the cluster volumes of interest were determined using Pmod and were normalized to the uptake in the whole brain.

Relative CB1R availability in the cluster volumes of interest was correlated with the latency since last seizure before scanning and the number of seizures in the month before scanning using a Spearman’s correlation analysis (Statistica, version 9; Statsoft Inc., Tulsa, USA). Descriptive statistics and normality testing of the evaluated variables are shown in Table 2.

To evaluate the CB1R availability in individual patients, a Z-score map was created comparing the individual patient to controls. Z-score maps were explored at a threshold level of \( \geq 2 \) SD compared to controls.

### Results

There were no differences in global CB1R availability between patients with mesial temporal lobe epilepsy due to hippocampal sclerosis [modified standardized uptake value 1.07 \pm 0.24 (mean \pm SD)] and controls (1.19 \pm 0.20; \( P = 0.13 \)).

In a voxel-based statistical parametric mapping group analysis, comparing patients with mesial temporal lobe epilepsy due to hippocampal sclerosis to controls, we found an increased CB1R availability in the ipsilateral temporal lobe extending from the inferotemporal to the mid- and superior temporal cortex (Fig. 1).

### Table 2

Descriptive statistics and normality testing of the evaluated variables

<table>
<thead>
<tr>
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<th>Median</th>
<th>IQR</th>
<th>Shapiro–Wilk's W test, ( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CB1R availability in ipsilateral temporal lobe</td>
<td>0.98</td>
<td>0.07</td>
<td>0.02</td>
</tr>
<tr>
<td>Latency since last seizure (days)</td>
<td>8.50</td>
<td>48.98</td>
<td>0.002</td>
</tr>
<tr>
<td>Number of seizures in last month</td>
<td>3.00</td>
<td>4.50</td>
<td>0.27</td>
</tr>
</tbody>
</table>

IQR = interquartile range.

### Figure 1

Statistical parametric mapping results showing average differences in the relative CB1R availability in patients with mesial temporal lobe epilepsy due to hippocampal sclerosis compared to healthy volunteers. Serial axial (top two rows) and coronal (bottom row) brain sections show an increase in CB1R availability in patients with mesial temporal lobe epilepsy due to hippocampal sclerosis in the ipsilateral temporal lobe extending from inferotemporal to mid-temporal and superior temporal cortex (yellow/red) and a decrease in the ipsilateral and contralateral superior insular cortex (green/blue). Significance at the voxel level is shown with a \( t \)-statistic colour scale. Results are projected on a spatially normalized T1-weighted magnetic resonance imaging template. L = left; R = right.
The CB1R availability was decreased in patients with mesial temporal lobe epilepsy due to hippocampal sclerosis in the ipsilateral and to a lesser extent the contralateral superior insular cortex (Fig. 1). A detailed description of the cluster characteristics and of the coordinates of the peak cluster locations is given in Table 3.

Evaluation of SISCOM images demonstrated that in the ipsilateral temporal lobe cluster, brain perfusion was increased during a seizure (average $Z$-score $= 2.29$, range $0.90–3.45$). An increased ictal perfusion was also found in the ipsilateral superior insular lobe cluster, but this was less pronounced (average $Z$-score $= 0.73$, range $0.33–1.43$). In the contralateral superior insular lobe cluster, ictal perfusion was decreased slightly on average, but variable between patients (average $Z$-score $= -0.18$, range $-1.03$ to $0.85$).

Correlation analysis using the cluster volumes of interest from the statistical parametric mapping analysis showed a positive correlation between relative CB1R availability in the ipsilateral temporal lobe and the number of seizures in the month before scanning ($P = 0.04$, $r = 0.60$) and a negative correlation with the latency since last seizure before scanning ($P = 0.04$, $r = -0.60$) (Fig. 2). There was no significant correlation between the relative CB1R availability in the ipsi- or contralateral superior insular cortex and the latency since the last seizure before scanning or the number of seizures in the month before scanning.

Individual comparison of patients to controls using $Z$-score maps demonstrated a cluster of significantly increased CB1R availability ($> 2$ SD) in the ipsilateral temporal lobe in six of 12 patients. These six patients were scanned within 2 days of their last seizure (range $0.2–2$ days). An example of such an individual $Z$-score map can be seen in Fig. 3. The cluster of individually increased CB1R availability in the ipsilateral temporal lobe coincides with the seizure onset zone, as presented by the relative ictal hyperperfusion in the patient's SISCOM image.

### Table 3

<table>
<thead>
<tr>
<th>Cluster level</th>
<th>Voxel level</th>
<th>MNI peak coordinates and structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{\text{corrected}}$</td>
<td>$k_E$ (mm$^3$)</td>
<td>$T$</td>
</tr>
<tr>
<td>HS $&gt;$ HV</td>
<td>$&lt; 0.001$</td>
<td>10 768</td>
</tr>
<tr>
<td>HS $&lt;$ HV</td>
<td>$&lt; 0.001$</td>
<td>13 160</td>
</tr>
<tr>
<td>0.03</td>
<td>3208</td>
<td>5.27</td>
</tr>
</tbody>
</table>

HS = hippocampal sclerosis; HV = healthy volunteers; $k_E$ = cluster extent.

### Discussion

In this article, we demonstrate that the endocannabinoid system in general and the CB1R more specifically show alterations in spatial relationship to the epileptogenic zone and in temporal relationship to seizures, suggesting a role in the pathophysiology of seizures. In patients with mesial temporal lobe epilepsy due to hippocampal sclerosis, we detected an increased CB1R availability in close
A longitudinal [11C]flumazenil PET design, Bouvard and co-workers repeated PET scans in the same patient is required. Using a longitudinal [11C]diprenorphine PET design, Hammers et al. (2007) demonstrated that in patients with mesial temporal lobe epilepsy, who often have some degree of neocortical atrophy in addition to the hippocampal atrophy (Bernhardt et al., 2010). Absence of partial volume correction in our study probably underestimated the detected increase in CB1R availability. In vitro, Ludanyi et al. (2008) have demonstrated a decreased level of CB1R messenger RNA and of CB1R density in the resected sclerotic hippocampus of patients who underwent epilepsy surgery.

Methodologically, quantification of CB1R availability was done using the brain radioactivity uptake parameter standardized uptake value, which does not incorporate the plasma input curve. CB1R standardized uptake values correlate to fractional uptake rate values, which represent CB1R density (Sanabria-Bohorquez et al., 2010). In order to reduce the influence of a subject’s weight on quantitative measurements (Thie et al., 2007), we used modified standardized uptake values in the evaluation of the endocannabinoid system in patients that show the best correlation with fractional uptake rate values. Since only regional differences were found between epilepsy and control groups, it is unlikely that this would be a confound.

In the hippocampus, CB1Rs are present on both excitatory glutamatergic neurons and inhibitory GABA-ergic interneurons (Hoffman and Lupica, 2000; Hoffman et al., 2010). Although PET imaging allows for in vivo imaging of CB1R in humans with epilepsy, it is unable to allocate the subpopulation of neurons on which this increased number of CB1Rs is present. The detected increased CB1R availability in epilepsy can, therefore, be interpreted in several ways. It may represent an acute on-demand activation of CB1Rs on glutamatergic neurons as an anti-epileptic and neuroprotective mechanism, or a long-term upregulation of CB1Rs on GABA-ergic neurons, which renders the epileptogenic zone hyperexcitable and vulnerable to epileptic seizures, or a combination of both.

In the first hypothesis, the increased number of CB1Rs would mainly be present on glutamatergic nerve endings, which can be

Figure 3 CB1R Z-score map (top row) and SISCOM (bottom row) of Patient 10 with right-sided hippocampal sclerosis. Serial axial brain sections show CB1R availability (yellow/red) in the right temporal lobe. This cluster coincides with the seizure onset zone, represented by the relative ictal hyperperfusion present in the patient’s SISCOM image (yellow/red). Significance at the voxel level is shown with a Z-statistic colour scale. Results are projected on the patient’s spatially normalized T1-weighted magnetic resonance image. L = left; R = right.
seen as a mechanism, induced by seizures, in order to protect neurons against hyperexcitability, further seizure activity and excitotoxicity (Marsicano et al., 2003). Cannabinoid action would thus result in increased depolarization-induced suppression of excitation. It has been shown that in the hippocampus, depolarization-induced suppression of inhibition is the prominent cannabinoid-induced phenomenon in basic conditions and plays an important role in normal brain functions. When high-frequency action potentials occur, as is the case during a seizure, depolarization-induced suppression of inhibition is abolished completely (Foldy et al., 2006) and a switch takes place towards depolarization-induced suppression of excitation (Ohno-Shosaku et al., 2002). In several animal models, it has been demonstrated that an increase of the endocannabinoid tone by administration of exogenous cannabinoid agonists has anticonvulsant properties (Wallace et al., 2001, 2002; Blair et al., 2006; Deshpande et al., 2007; Naderi et al., 2008).

In the second hypothesis, the increase represents a long-term upregulation of CB1R on GABA-ergic neurons, which renders the epileptogenic zone hyperexcitable and vulnerable to epileptic seizures. The increased cannabinoid transmission would then result in an increased suppression of inhibition, leading to hyperexcitability. An initial precipitating insult, like complex febrile seizures, might trigger pro-epileptogenic changes in the endocannabinoid system, which after a latent period, result in the development of spontaneous seizures. Chen and colleagues have shown that early administration of CB1R-antagonists during prolonged febrile convulsions may have an anti-epileptogenic effect (Chen et al., 2007). After each seizure, these changes can reoccur and cause worsening of the seizures over time, as is the case in patients with mesial temporal lobe epilepsy due to hippocampal sclerosis (French et al., 1993). More generally, the CB1R upregulation in the epileptogenic zone may then be a hallmark of acquired epilepsies characterized by an initial precipitating injury, of which mesial temporal lobe epilepsy due to hippocampal sclerosis is an example. Further studies of the CB1R availability therefore seem warranted in, for example, patients with acquired epilepsy after a traumatic brain injury.

Despite multiple drug treatment, a group of patients will continue to have frequent seizures. These patients can benefit from surgical resection of the seizure onset zone. In order to perform surgery, this seizure onset zone needs to be identified clearly. Despite the multitude of tests available, reliable detection of the seizure onset zone remains difficult in some patients. CB1R-PET performed within 1 or 2 days after a seizure may be an excellent imaging modality to visualize the seizure onset zone. Further studies are warranted.

In addition to an increased CB1R availability in the ipsilateral temporal lobe, we found a decreased receptor availability in the ipsilateral and contralateral superior insular cortex. Within the ipsilateral insular cortex, we detected an ictal hyperperfusion on the SISCOM images, which was, however, less pronounced than the ictal hyperperfusion in the seizure onset zone itself. In the contralateral insular cortex, the ictal perfusion was slightly decreased on average, but with significant variation between subjects. The superior insular cortex, therefore, is at the border of the transition zone between temporal lobe hyperperfusion-frontal lobe hypoperfusion during complex partial seizures (Van Paesschen et al., 2003). Dense connections exist between temporo-limbic structures and the insular cortex and seizures originating in the temporal lobe often invade the insular cortex (Lindsay et al., 2000). In the insular cortex, CB1Rs are expressed in moderate levels (Van Laere et al., 2008) and are mainly present on GABA-ergic nerve terminals (Hill et al., 2007). A decreased level of CB1Rs on these nerve terminals may thus result in an increased level of inhibition, which might contribute to prevention of seizure propagation. Using interictal 2-[18F]-fluoro-2-deoxy-D-glucose PET imaging and SISCOM during complex partial seizures in patients with mesial temporal lobe epilepsy due to hippocampal sclerosis, we were able to demonstrate that the ipsilateral frontal lobe is characterized by interictal hypometabolism and ictal hypoperfusion. We postulated that there is surround inhibition in the ipsilateral frontal lobe, which is a dynamic defence mechanism against propagation of complex partial seizures in mesial temporal lobe epilepsy due to hippocampal sclerosis (Nelissen et al., 2006). From our data, we speculate that the endocannabinoid system in the insular region plays an important role in this inhibition of seizure propagation in mesial temporal lobe epilepsy due to hippocampal sclerosis. In other areas with frequent seizure propagation, no average group differences in CB1R availability were detected.

Conclusion

In summary, using in vivo [18F]MK-9470 PET imaging, we found a seizure-associated increase in CB1R availability at the seizure onset zone and a decrease in CB1R availability in the insular cortex in patients with mesial temporal lobe epilepsy due to hippocampal sclerosis, suggesting that changes in the endocannabinoid system modify excitability in different ways in the epileptic network in mesial temporal lobe epilepsy due to hippocampal sclerosis. Longitudinal studies and studies in other epilepsy syndromes are important to further elucidate the role of the endocannabinoid system in epilepsy.

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