ELSEVIER

Seminars in
NUCLEAR
MEDICINE

Neuronuclear Assessment of Patients With Epilepsy

Karolien Goffin, MD,* Stefanie Dedeurwaerdere, PhD,† Koen Van Laere, MD, PhD, DSc,* and Wim Van Paesschen, MD, PhD‡

Epilepsy is a common chronic neurological disorder that is controlled with medication in approximately 70% of cases. When partial seizures are recurrent despite the use of antiepileptic drugs, resection of the epileptogenic cortex may be considered. Nuclear medicine plays an important role in the presurgical assessment of patients with refractory epilepsy. Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) techniques are used to determine the seizure onset zone, which needs to be resected to render a patient seizure free. Correct localization of the ictal onset zone with the use of SPECT or PET is associated with a better surgical outcome. Ictal perfusion SPECT imaging with ^{99m}Tc-ethyl cysteinate dimer (ECD) or ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO) enables one to detect the seizure onset zone in a majority of cases, especially in patients with temporal lobe epilepsy. Interictal SPECT imaging, which is more widely available, is unreliable to determine the ictal onset zone and is usually only used for comparison with ictal SPECT images. Assessment of the ictal onset zone using subtracted ictal and interictal studies, overlayed on structural imaging has proven to be more sensitive and more specific compared with visual assessment. Video-electroencephalography monitoring in combination with ictal SPECT imaging, however, is only available in specialized centers. It is important to inject the perfusion tracer as early as possible after the beginning of a seizure and to be aware of patterns of seizure propagation. Interictal ^{18}F-fluorodeoxyglucose (FDG)-PET is routinely used to detect brain areas of hypometabolism, which usually encompass, but tend to be larger than, the seizure onset zone. Also, for assessment of FDG-PET, it is advisable to use an automated technique comparing the patient's images to a normal database in addition to visual interpretation of the images, since automated techniques have proven to be more accurate. In view of the thickness of the cortical ribbon, which may be below the resolution of the PET camera, posthoc partial volume correction or PET reconstruction incorporating the anatomical information of magnetic resonance imaging (MRI), may be useful for optimal assessment of glucose metabolism. Perfusion SPECT and interictal FDG-PET are able to demonstrate areas of abnormal perfusion and metabolism at a distance from the ictal onset zone, which may be associated with cognitive and psychiatric comorbidities, and may represent the functional deficit zone in epilepsy. Part of the functional deficit zone is a dynamic seizure-related process, which may resolve with cessation of seizures. In recent years, novel PET tracers have been developed to visualize not only glucose metabolism but also a wide variety of specific receptor systems. In patients with epilepsy, changes in the γ-amino-butyric acid$_A$ receptor, opioid receptor, 5-HT$_{1A}$ serotonin receptor, nicotinic acetylcholine receptor systems, and others have been described. Because these tracers are not widely available and the superiority of studying these receptor systems over glucose metabolism in the presurgical evaluation of patients with refractory epilepsy remains to be proven, their use in clinical practice is limited at the moment. Finally, advances in small animal PET scanning allow the in vivo study of the process of epileptogenesis, starting from an initial brain insult to the development of seizures, in animal models of epilepsy. Potential new therapeutic targets may be discovered using this translational approach.
Semin Nucl Med 38:227-239

*Division of Nuclear Medicine, University Hospital Leuven, Leuven, Belgium.
†Department of Medicine, University of Melbourne, Parkville, Australia.
‡Department of Neurology, University Hospital Leuven, Leuven, Belgium.

Address reprint requests to Wim Van Paesschen, Department of Neurology, University Hospital Leuven Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium. E-mail: Wim.Vanpaesschen@uz.kuleuven.be

0001-2998/08/$-see front matter
doi:10.1053/j.semnuclmed.2008.02.004

Epilepsy is a common chronic neurological disorder that is characterized by recurrent, unprovoked seizures[1] and affects approximately 3% of the population during their lifetime.[2] After the first seizure, about 80% of patients experience another seizure within the first 3 years.[3] About 60-70% of patients experience focal or partial seizures, and 30-40% generalized seizures.[4] Epilepsy is controlled with medication in approximately 70% of cases. When seizures are medically intractable, resection of the epileptogenic cortex may be considered.

In this review, we will address the role of radionuclide functional imaging techniques incorporating single-photon emission computed tomography (SPECT) and positron emission tomography (PET) in localizing the ictal onset zone, seizure propagation pathways, and functional deficit zone in patients with intractable partial epilepsy who are candidates for epilepsy surgery. We will also focus on novel developments in PET and SPECT methodology and radioligands, including specific neuroreceptor targets, and will describe possible advantages of these developments when assessing patients with epilepsy. Finally, we will discuss the potential of translational imaging using small animal microPET/microSPECT studies in rodent models of epilepsy.

Presurgical Assessment of Patients With Refractory Epilepsy

A presurgical evaluation starts with a complete seizure history, physical and neurological examination, routine scalp electroencephalography (EEG), and high-resolution magnetic resonance imaging (MRI) of the brain to assess structural abnormalities.[5] These investigations are complemented by video-EEG monitoring, which allows evaluation of the clinical features of seizures, interictal and ictal EEG, ictal SPECT injection, interictal ^{18}F-fluorodeoxyglucose (FDG)-PET, and neuropsychological examination. The presurgical evaluation of patients with refractory partial epilepsy is used to determine whether a patient has a single epileptogenic focus and to localize the epileptogenic zone. The epileptogenic zone is the cortical region that is indispensable for the generation of seizures and that has to be removed to render a patient seizure free. The epileptogenic zone is a theoretical construct, which is defined in terms of different cortical zones.[6] The seizure-onset zone is the region in which the seizures actually originate. Ictal SPECT is the only imaging modality that can define in a reliable and consistent manner the ictal onset zone. The symptomatogenic zone is the (sub)cortical region producing ictal symptoms. The epileptogenic lesion can be visualized on morphological imaging such as magnetic resonance imaging (MRI). The functional deficit zone is the part of the cortex with an abnormal function in-between seizures, due to morphological or functional factors, or both.[7] Interictal FDG-PET is probably the best imaging method to assess the functional deficit zone. Epilepsy surgery has the best results if the different cortical zones are concordant, ie, point toward the same cortical region, provided that there is no overlap with eloquent cortex. The nature of the epileptic lesion and the completeness of the resection are important prognostic factors. Surgery renders up to 60-90% of patients with unilateral temporal lobe epilepsy (TLE)[8] seizure free and up to 70% of patients with a focal cortical malformation.[9]

Ictal and Interictal Perfusion SPECT Imaging

Ictal SPECT perfusion requires video-EEG monitoring and is therefore only available in tertiary care hospitals with an epilepsy surgery program in combination with a dedicated nuclear medicine department. Ictal SPECT is the only imaging modality that is able to visualize the ictal onset zone in routine clinical practice. During epileptic activity, a hyperperfusion of the seizure onset zone occurs because of an autoregulatory response to the local neuronal hyperactivity. For ictal SPECT perfusion imaging, mostly ^{99m}Tc-labeled compounds are used, such as ^{99m}Tc-ethyl cysteinate dimer (ECD) or ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO). They are characterized by fast (first tens of seconds) cerebral uptake proportional to blood flow and trapping into brain cells by intracellular conversion to polar metabolites[10,11] resulting in a static image which remains stable (ie, little regional redistribution or washout) up to 4 hours after injection. Thus, when such perfusion SPECT tracer is injected intravenously immediately after the start of a seizure, this hyperperfusion at the ictal onset zone can be captured and the ictal SPECT images, therefore, reflect the perfusion changes in the early phase of the seizure.

The accuracy of ictal SPECT analysis is greatest when comparing the ictal perfusion images to interictal perfusion data. Methodologically, this can be done by traditional side-by-side visual evaluation, but computer-aided voxel-based coregistration techniques such as subtraction ictal SPECT coregistered to MRI (SISCOM)[12] and ictal-interictal SPECT difference image,[13] are fast, accurate, and are routinely available.

For SISCOM analysis, interictal and ictal SPECT scans are coregistered using an automatic registration algorithm based on mutual information,[14] and the interictal image is then subtracted from the ictal. The difference image is smoothed and transformed into a z-score map using the mean and the standard deviation of the differences in all brain voxels. The mean image of the ictal and interictal coregistered images can be used for coregistration to the patient's MRI. The same transformation is then applied to the z-map. For the functional overlay different thresholds can be used to assess probable differences and locations of propagated seizure activity.

The interpretation of automatically generated SISCOM data often is easy and straightforward.[12] SISCOM analysis has been shown to be more sensitive and specific in the detection of the epileptic onset zone than visual assessment and provides an objective way to study individual propagation patterns,[12,15] especially in extratemporal epilepsies and when fast seizure propagation after an early tracer injection is present.

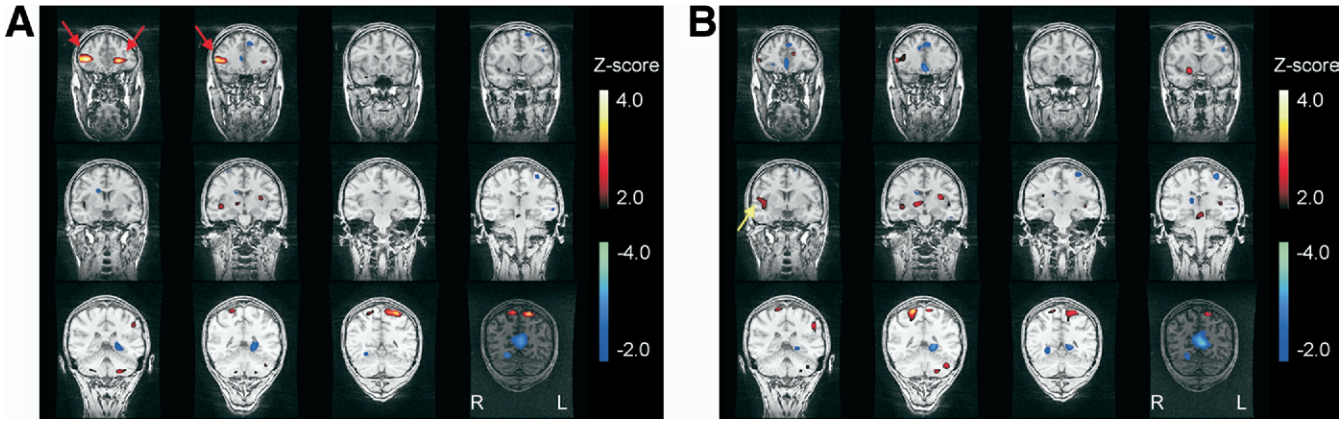

Figure 1 SISCOM images before (A) and after (B) correction for movement during scanning. The foci of ictal hyperperfusion present bilaterally over the inferofrontal cortex (red arrows) on SISCOM (A) were the result of a movement artifact during acquisition and thus false positive. These findings were discordant with the electroclinical suspicion of an ictal onset zone in the right temporal neocortex in this patient with refractory partial epilepsy and normal MRI scan of the brain. All her seizures began with buzzing in the ears, followed by paraesthesia in the left limbs. After movement correction, these clusters were no longer present. A cluster of ictal hyperperfusion was present in the right insular to high temporal cortex (yellow arrow in B), which is concordant with the hypothesis of ictal onset in the right temporal neocortex. The largest and most intense cluster in the right parietal lobe at the midline could be explained by propagation. The referring neurologist planned further depth-EEG studies. The ictal SPECT injection was given during a complex partial seizure that lasted around 200 seconds, with initiation of the injection 18 seconds after seizure onset.

Careful quality control of registration (eg, assessment of acquisition movement artifacts, registration errors) and subtraction is important to avoid false positive and false negative results (Fig. 1), and the result of the SISCOM analysis has to be concordant with the result of visual comparison of the ictal and interictal images, and other data of the presurgical evaluation. Furthermore, SISCOM may be false negative because of the subclinical seizure activity at the moment of tracer injection of interictal SPECT imaging.[16] EEG monitoring during the interictal injection, therefore, should be routinely performed.

When interpreting ictal perfusion data, it is usually assumed that the cluster of the largest and most intense ictal hyperperfusion represents the ictal onset zone.[17] A meta-analysis of SPECT brain imaging in patients with TLE showed a sensitivity of ictal SPECT localization of 0.97, relative to diagnostic evaluation without imaging, while this was only 0.44 for interictal SPECT localization.[18] Interictal SPECT perfusion imaging on its own, therefore, seems to be inefficient in localizing the seizure onset zone and should only be used as a baseline perfusion measure in the comparison of ictal perfusion images.

Ictal perfusion SPECT imaging has a limited temporal resolution. After intravenous injection into an arm vein, it takes 15 to 20 seconds for the tracer to reach the brain.[19] Therefore, the ictal brain perfusion image displays not only the ictal onset zone, but also areas of seizure propagation. It is, therefore, important to be aware of propagation patterns when interpreting ictal perfusion brain SPECT studies and thus to have knowledge of the moment of tracer injection relative to the start of the seizure, the type of seizure, and the ictal EEG recording. In patients with TLE, propagation of seizure activity to the contralateral temporal lobe, and ipsilateral insula, basal ganglia, and frontal lobe often occurs,[20] but also propagation to the parieto-occipital region has been described.[21]

In epilepsy originating from single focal dysplastic lesions (FDLs) that are capable of being visualized on MRI, we reported 3 different ictal perfusion patterns. The first pattern is characterized by the largest and most intense hyperperfusion at the FDL and is most often found with very early injection, representing the ictal onset zone before seizure propagation occurs. The second pattern is characterized by an "hourglass pattern," with the least-intense lobule overlapping with the FDL and the most intense at a distance, representing propagation. Thirdly, a variant of the second pattern exists and shows a more complicated, multilobulated propagation pattern that is most often found in frontal lobe seizures with fast seizure propagation, at relatively later ictal injection times.[15] An example of such seizure propagation from a FDL is shown in Figure 2. Furthermore, it has been demonstrated that in a majority of patients with frontal lobe epilepsy, the largest and most intense cluster of ictal hyperperfusion comprises not only the ictal onset zone, but also other brain regions.[22]

The importance of early tracer injection after the beginning of the seizure cannot be overemphasized. It has been shown that an injection delay of less than 20 seconds is significantly correlated with a correct localization.[16] With early injections, the largest and most intense cluster is more likely to represent the seizure onset zone, and not seizure propagation.

Perfusion changes after the termination of a seizure can be assessed by injection of the tracer in the early postictal (1-60 seconds after seizure termination) or in the late postictal phase (1-10 minutes after seizure termination). The postictal phase is characterized by a postictal switch, when hyperperfusion at the seizure onset zone changes into hypoperfusion.

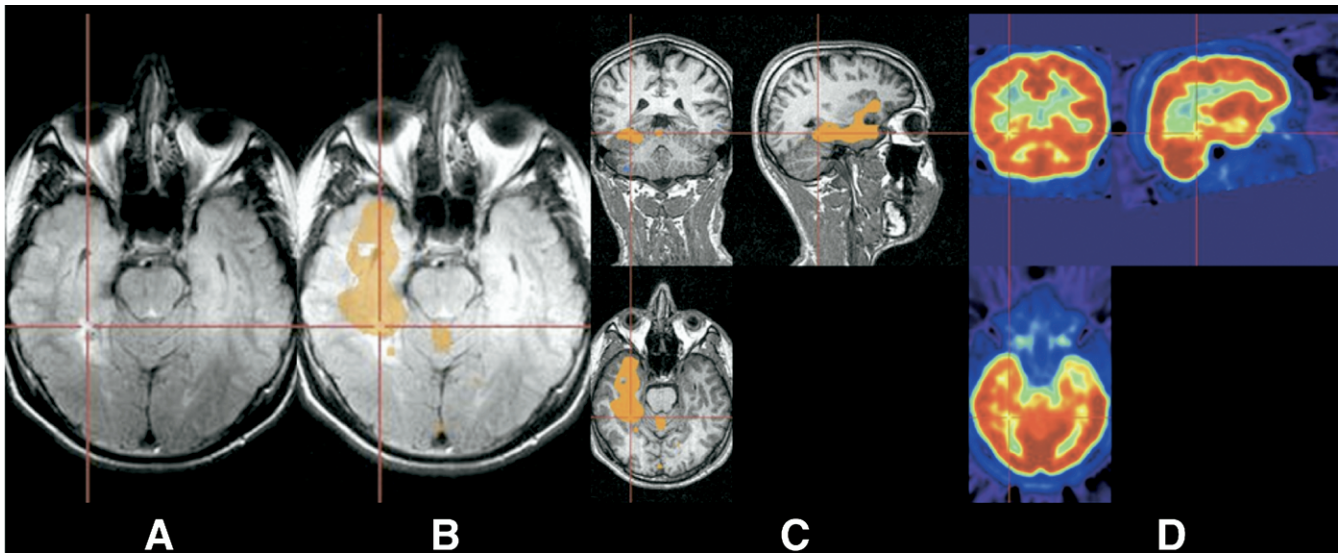

Figure 2 Ictal SPECT and interictal FDG-PET in focal cortical dysplasia. (A) FLAIR showed a focal dysplastic lesion in the right temporal lobe (red cross). (B and C) SISCOM showed a cluster of hyperperfusion of complex configuration in the right temporal and frontal lobe, partially overlapping the focal dysplastic lesion. The ictal SPECT injection was given during a complex partial seizure that lasted 178 seconds, with initiation of the injection 50 seconds after seizure onset. Taking all the data of the presurgical evaluation into consideration, our interpretation of the SISCOM was that the ictal onset zone was in the focal dysplastic lesion with propagation toward the ipsilateral anterior temporal and frontal lobe. (D) FDG-PET showed asymmetric temporal lobe hypometabolism, which was more pronounced on the left. This result was consistent with memory impairment for both verbal and visual material, and illustrates that FDG-PET hypometabolism may be useful in the delineation of the functional deficit zone. Patient underwent epilepsy surgery, and the focal dysplastic lesion was removed. Anatomopathological examination confirmed the presence of focal cortical dysplasia without balloon cells. All images (A-D) were coregistered.

This postictal switch occurs about 60 seconds after the seizure termination. When tracer injection is performed in the first 100 seconds after the end of the seizure, there is still a hyperperfusion present in more than 60% of patients, whereas hypoperfusion can be found in all patients when the tracer is injected later than 100 seconds after seizure termination.[23] In patients with TLE, early postictal SPECT had a sensitivity of 75% in localizing the seizure onset zone.[18] According to McNally and colleagues, postictal SPECT with injections performed soon after seizures is very poor at localizing a single region based on either perfusion increases or decreases, often because changes were similar in multiple brain regions.[13] An example of a localizing postictal SPECT image with SISCOM analysis is shown in Figure 3.

Supplementary information by coregistration of ictal SPECT, SISCOM, and MRI can be gained by multimodal automated registration, because these different imaging modalities provide complementary information, resulting from the specific strengths of each modality.[24] An example of multimodality imaging in the presurgical workup of a patient can be seen in Figure 4.

Interictal Glucose Metabolism Imaging With FDG-PET

Brain glucose metabolism, as a measure of neural activity, can be studied with FDG-PET scanning. FDG, because it is glucose analog, is taken up into the cells and is phosphorylated by hexokinase. Unlike glucose, FDG cannot be further metabolized and accumulates in the cell, thereby representing the regional metabolic rate of glucose consumption (rCMRglu) of the tissue.

Methodology

FDG-PET usually is evaluated visually. In addition, a pixel-wise comparison of the patient's image to an age-matched reference database can be performed in an automated way and provides an objective evaluation of the changes in glucose metabolism with a reduction in observer variability. Such an automated analysis is especially useful in patients with extratemporal epilepsy.[25] In patients with TLE, automated quantification of the maximal metabolic asymmetry in the temporal lobes has been reported to enhance predictive accuracy for seizure-free postsurgical outcomes.[26]

Absolute glucose metabolism measures in patients with epilepsy can identify global reductions in metabolism of around 10-30% as the result of antiepileptic drugs.[27,28] Quantitative FDG-PET studies are time-consuming, require arterial sampling, and are usually only performed in a research setting. However, quantitative FDG-PET studies may be possible in a clinical setting using the simplified kinetic method described by Hunter and colleagues.[29] In this method, a single venous blood sample to determine the blood glucose level and blood ^{18}F-FDG activity at the moment of PET scanning is sufficient to calculate the absolute brain glucose metabolism.

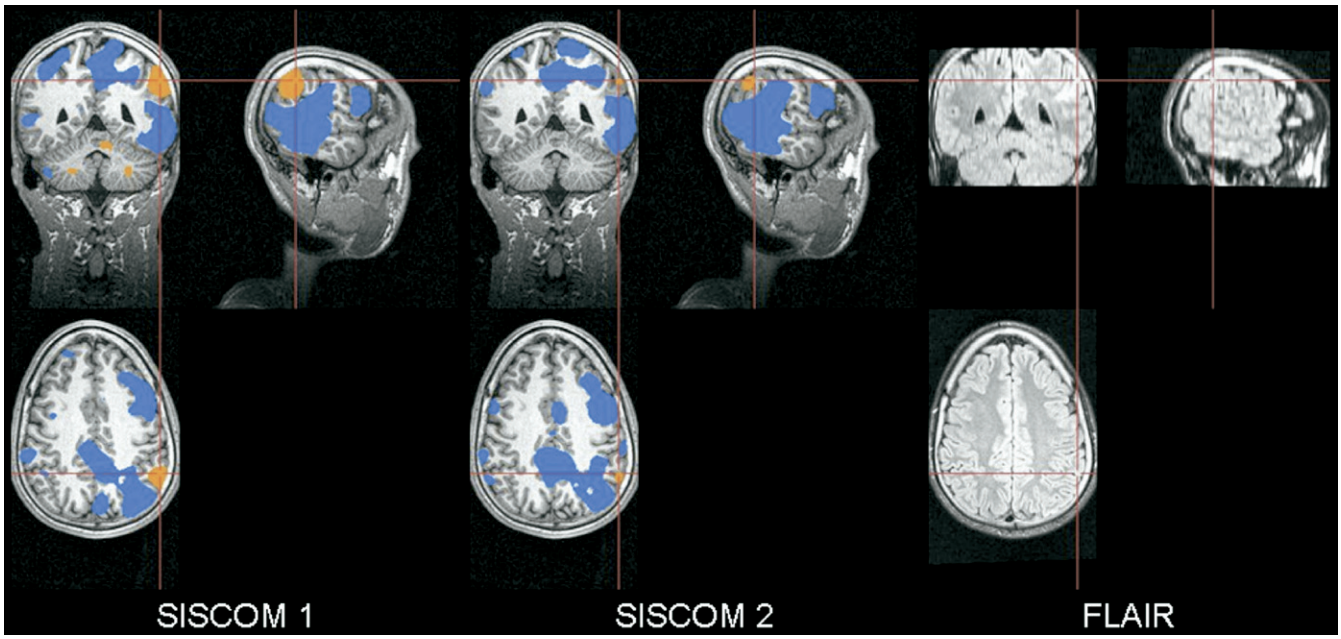

Figure 3 Localizing postictal SISCOM. Threshold: >+2 SD: orange, <−1 SD: blue. Patient had refractory partial epilepsy as the result of a focal dysplastic lesion in the left parietal lobe, which was visible as a hyperintense lesion on FLAIR (red cross). The patient had 2 ictal SPECTs. The first injection was given 5 seconds after the end of a complex partial seizure that lasted 16 seconds, and the second 11 seconds after one that lasted 25 seconds. The largest and most hyperintense cluster partially overlapped the focal dysplastic lesion in both studies (red crosses in SISCOM 1 and 2). Notice the large areas of hypoperfusion surrounding the ictal onset zone, which is not seen in ictal SISCOMs, which is consistent with the hypothesis of "surround inhibition."[43] All images were coregistered.

Measuring small brain structures, such as the cortical ribbon, may lead to an underestimation of the tracer activity due to limits in resolution (approximately 4-5 mm for most current PET scanners). This partial volume effect can lead to spurious hypometabolic regions, resulting in an increased amount of false-positive predicted hypometabolic regions. Moreover, if the finite spatial resolution of the imaging system is not accounted for, a possible spillover of activity to neighboring regions can occur, leading to a misinterpretation of the extent of hypometabolic regions. Several algorithms are available for partial volume correction, both post-hoc (eg, partial volume effect–out[30]) or during reconstruction, for instance, an anatomy-based maximum-a posteriori iterative reconstruction algorithm.[31] We have shown that partial volume correction improves the detection accuracy of small hypometabolic lesions in FDG-PET images of the brain in a human observer study, compared with postsmoothed maximum-likelihood reconstruction.[32]

Clinical Applications

Localization of Epileptogenic Focus. Interictal brain FDG-PET scanning can provide useful localizing information with regards to the epileptogenic focus. Classically, the brain region with the most profound hypometabolism is considered to contain the epileptogenic zone. Using this hypothesis, Lee and coauthors found an overall diagnostic sensitivity of 44% for FDG-PET in detecting the area of seizure onset in a group of patients with different forms of refractory partial epilepsy and normal MRI findings.[33] FDG-PET localization accuracy was greatest in patients with neocortical TLE. Indeed, an area of interictal temporal lobe hypometabolism ipsilateral to the side of the seizure focus can be found in 60 to 90% of patients with TLE[25,34,35] even without structural lesion on MRI (Fig. 5). In extratemporal epilepsy, literature review resulted in a detection rate of hypometabolism relevant to the focus in around 67% of patients.[35] In the same patient group, the sensitivity of FDG-PET in detecting the epileptogenic focus increased from 30-40% to 67% with the use of 3-dimensional stereotactic surface projections instead of visual assessment.[25]

The use of FDG-PET enabled researchers to detect the epileptogenic zone in more than 90% of children with focal cortical dysplasia[36] and provided information additional to that obtained with other investigations regarding the epileptogenic zone in 77% of children with refractory epilepsy and changed management in 50% of patients.[37]

Surgical Outcomes. Lobar localization of the ictal focus by FDG-PET correlates significantly with a seizure free surgical outcome.[33,38] When using multiple techniques to assess the seizure onset zone, concordance between 2 or more presurgical evaluations has been shown to significantly correlate with a seizure-free outcome.[33]

Also the extent of hypometabolism can help to predict whether a good surgical outcome can be achieved or not: in patients with TLE, unilateral temporal hypometabolism is correlated with a better surgical outcome than more extended hypometabolism. It has been demonstrated that more than 75% of patients with TLE and hypometabolism selective

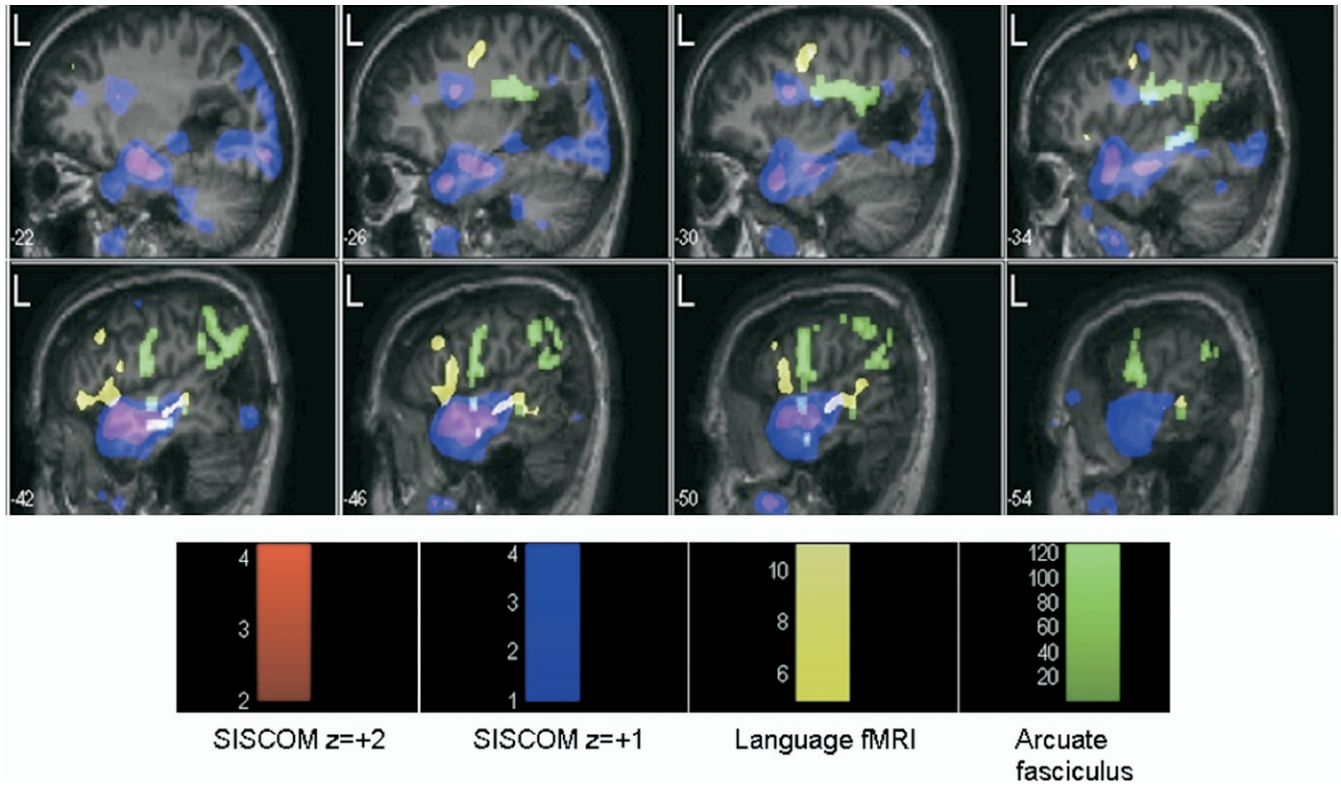

Figure 4 Multimodal imaging in the presurgical evaluation combining 3D MRI, SISCOM, functional MRI (fMRI), and diffusion tensor imaging (DTI): SISCOM thresholded at $z = +2$ (red), SISCOM thresholded at $z = +1$ (blue), language fMRI (yellow), and arcuate fasciculus (green). This right-handed patient developed epilepsy after neurosurgery in the left temporoparietal area for an intraventricular meningioma. (Early) ictal and postictal aphasia were a prominent symptom of her habitual epileptic seizures. SISCOM thresholded at $z = +2$ showed a large cluster of hyperperfusion in the left anterior temporal lobe, at $z = +1$ a larger area also involving more posterior brain regions surrounding the surgical resection site. These findings are consistent with an ictal onset zone surrounding the surgical resection site with fast ictal propagation into the left temporal lobe. fMRI showed left lateralized language functions. The arcuate fasciculus was immediately anterior to the resection site, probably coinciding with the ictal onset zone. She was not offered surgery.

to the ipsilateral temporal cortex were completely seizure free after surgery. In contrast, 45% of patients with extratemporal cortical hypometabolism confined to the ipsilateral cerebral hemisphere and only 20% of patients with hypometabolism in the contralateral cerebral cortex were completely seizure free after surgery.[39] Lin and coauthors predicted seizure free outcome in patients with TLE using quantification of the maximal metabolic asymmetry in the 20% most asymmetric temporal left–right pixel pairs and found that those patients with greater maximal asymmetry had a significantly decreased chance of achieving seizure-free status after surgery than those with lower degrees of asymmetry,[26] in subject groups with generally unilateral temporal hypometabolism.

Functional Deficit Zone and Surround Inhibition

Hypometabolism on FDG-PET has been ascribed to factors such as neuronal loss, diaschisis, inhibitory processes, reduction in synaptic density, or decreased blood–brain barrier glucose transporter activity.[40-42] Recent studies have, however, provided new insights into its pathophysiology. In partial epilepsy, the hypometabolism on PET is often more extensive than the pathological abnormality.[35] In patients with TLE, hypometabolism in the ipsilateral temporal lobe is often associated with hypometabolism in the ipsilateral orbitofrontal and prefrontal cortex. This frontal hypometabolism can even be more pronounced than the temporal hypometabolism (Fig. 6).[43] We speculate that this frontal hypometabolism can be attributed to surround inhibition in the areas of seizure propagation, which has the purpose to act as a dynamic defense mechanism against this seizure propagation. This frontal hypometabolism may be responsible for the deficits in executive function that are often observed in patients with TLE. Resting hypometabolism in the frontal lobe can predict executive dysfunction in patients with epilepsy.[44] Depression, often present in patients with TLE, is also associated with hypometabolism in the frontal lobe.[45]

The frontal hypometabolism on PET in mesial TLE is a dynamic seizure-related process.[43] Patients with a greater frequency of seizures suffer from more severe cognitive impairment that correlates with glucose hypometabolism in the prefrontal cortices.[46] Longitudinal changes in cortical glucose hypometabolism have been reported in children with refractory epilepsy when 2 sequential FDG-PET scans performed 7 to 44 months apart were compared. The change in seizure frequency between 2 PET scans correlated positively

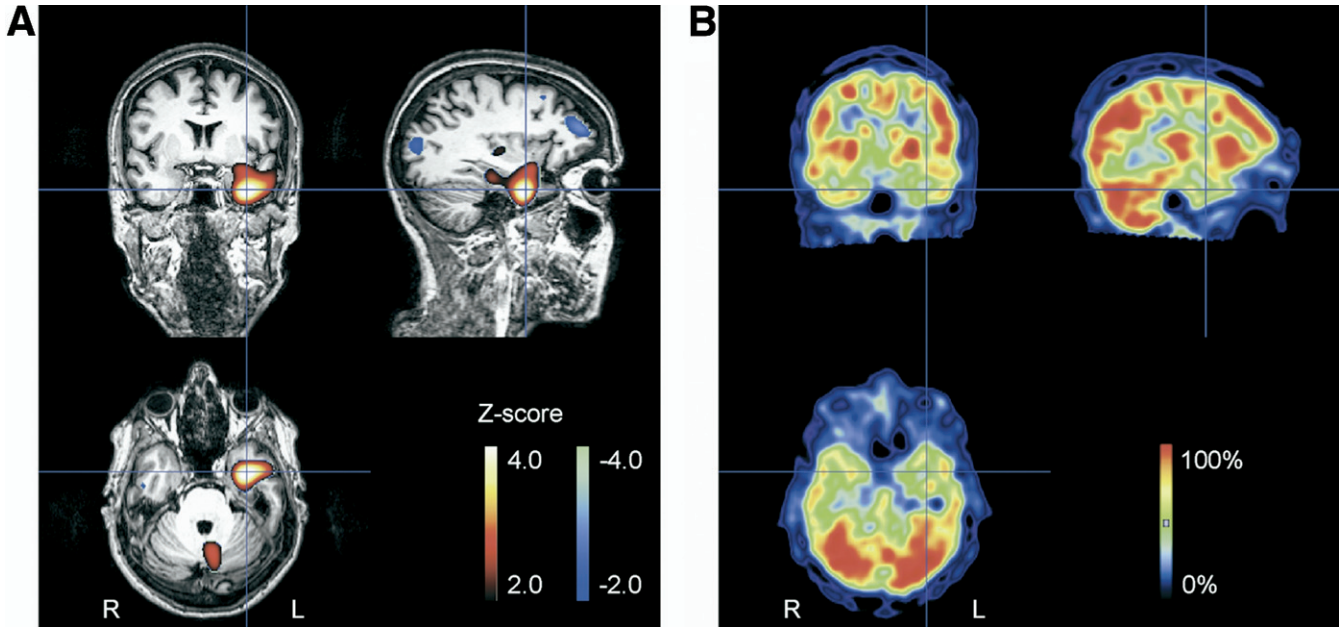

Figure 5 SISCOM (A) and FDG-PET (B) images of a 42-year-old patient with left TLE and normal MRI. SISCOM analysis showed a large cluster of ictal hyperperfusion located at the left temporal lobe (indicated by the blue cross). The ictal SPECT injection was given during a complex partial seizure that lasted 67 seconds, with initiation of the injection 35 seconds after seizure onset. FDG-PET showed a subtle hypometabolism in the same area. All images were coregistered. These functional imaging data were concordant with electroclinical and neuropsychological data, and were considered an important argument to proceed to surgery. Patient underwent a neocortical temporal lobectomy including amygdala, but with sparing of the hippocampus. She has remained seizure free. Neuropathological examination did not reveal an epileptic lesion.

with the change in the extent of cortical glucose hypometabolism. There was enlargement in the area of hypometabolism on the second PET scan when the seizure frequency was persistent or increased. On the other hand, the area of hypometabolism decreased with improved seizure control.[47] Similar results were found when comparing pre- and postoperative FDG-PET scans in patients with TLE caused by hippocampal sclerosis (HS) who were rendered seizure free after surgery. Increases in metabolism were observed after surgery in the propagation pathways of ictal and interictal epileptic discharges, such as temporal stem white matter, inferior precentral gyrus, and anterior cingulate gyrus in the ipsilateral hemisphere. The hypometabolism in these areas was likely to be functional, seizure-related, and reversible. Decreased metabolism was found postsurgically in brain structures with afferents from resected temporal structures.[48] We provided anecdotal evidence that patients with cognitive impairment associated with frontal lobe hypometabolism as the result of ongoing parietal lobe seizures recovered more than 1 year after remission of seizures and that this recovery was associated with the resolution of hypometabolism.[49]

Imaging of Specific Neurotransmitter Systems

Apart from studies investigating changes in glucose metabolism or perfusion as indirect markers of neural activity, neurochemical characterization of the different cortical zones in the epileptic brain with the use of specific receptor ligands is also of high interest. Several of these receptor systems represent existing or possible therapeutic targets. The lack of studies demonstrating the clinical usefulness of the assessment of these receptor systems and their superiority over ictal perfusion SPECT and brain FDG-PET imaging in epilepsy, and the continuous availability of FDG and SPECT perfusion tracers in nuclear medicine departments, has limited the use of these other tracers to research studies in patients with epilepsy.

γ-Amino-Butyric Acid (GABA) Receptor

GABA is the main inhibitory neurotransmitter in the brain and maintains the inhibitory tone that counterbalances neuronal excitation. Evidence from experimental and clinical studies indicates that GABA plays an important role in the mechanism and treatment of epilepsy.[50]

GABA acts on 2 types of receptors: $GABA_A$ and $GABA_B$. Imaging of the $GABA_A$ receptor can be done using either ^{11}C- or ^{18}F-labeled flumazenil (FMZ). The use of FMZ in patients with epilepsy has the disadvantage that FMZ binding is affected by several antiepileptic drugs that are often used in clinical practice, such as benzodiazepines, barbiturates, and vigabatrin, thereby limiting its clinical use.

^{11}C-labeled FMZ binding was found to be abnormal in gray and white matter in the brain of 75% of patients with different types of refractory neocortical focal epilepsy and normal MRI. Focal increases as well as decreases in ^{11}C-la-

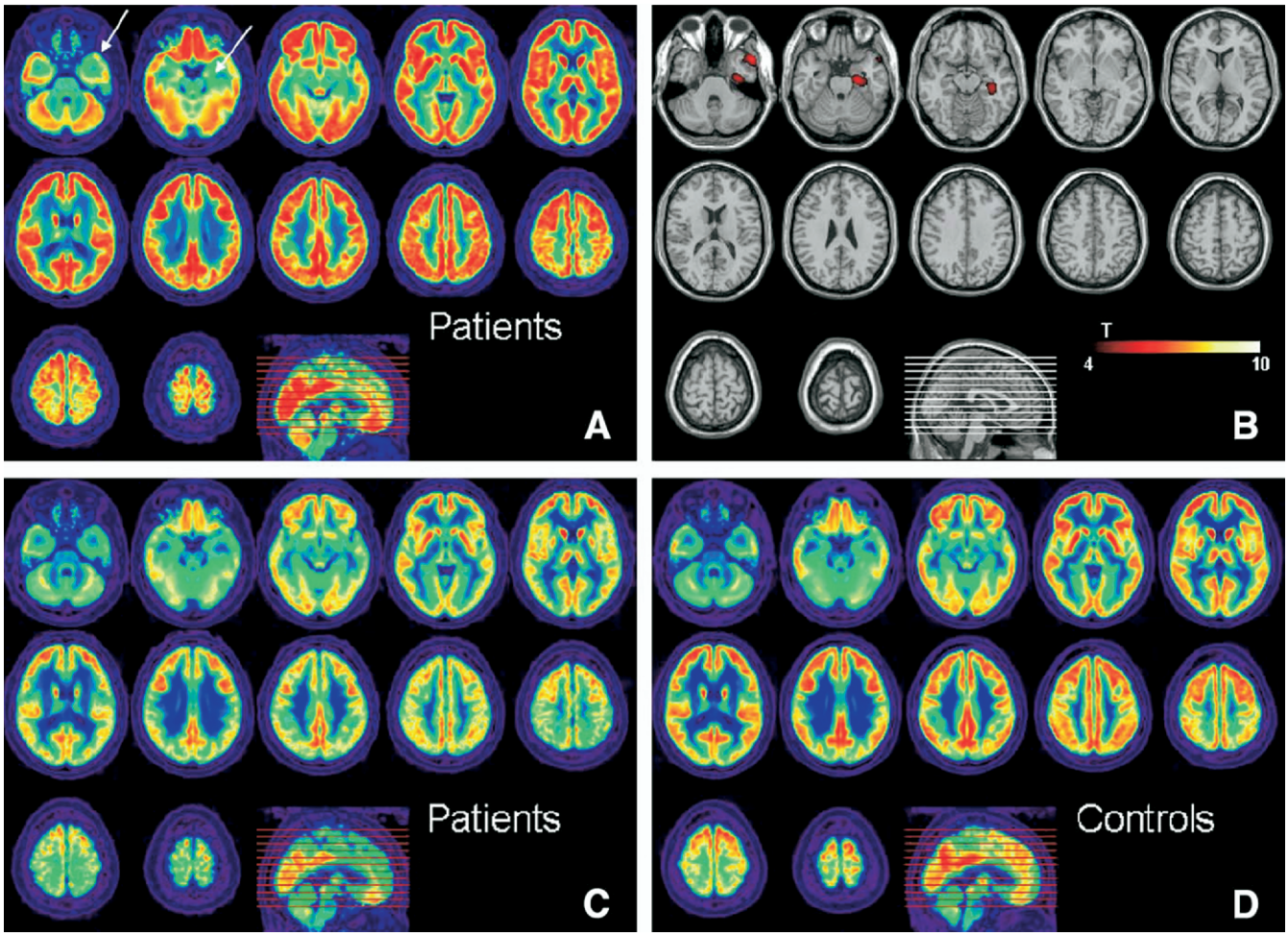

Figure 6 Frontal lobe hypometabolism in mesial TLE with HS. (A) Mean image of the normalized FDG-PET across a group of patients with TLE caused by HS shows that the ipsilateral temporal lobe (white arrows) is more hypometabolic than the contralateral side, and appears to be the most hypometabolic region in the brain. (B) SPM T-map (uncorrected $P < 0.001$) shown on the MRI of a single subject in MNI space confirms that a significant asymmetry in interhemispheric metabolism is only found in the temporal lobes. (C and D) Mean images of the normalized FDG-PET across patients with TLE (C) and controls (D), displayed using the same color table, show a striking hypometabolism in the fronto-parietal lobes in patients compared with controls. The hypometabolism in the epileptic temporal lobe, on the other hand, is less striking than the changes in the extratemporal regions. (Reprinted with permission from Nelissen et al.[43])

beled FMZ binding or a combination of both were reported. In a subgroup of patients, the increases in FMZ binding were periventricular, in locations where periventricular nodular heterotopia is often present. In patients with parietal lobe epilepsy, there were frontal and parietal increases in FMZ binding in gray and white matter. Decreases in FMZ binding were present in the cingulate gyrus in patients with occipital lobe epilepsy.[51]

In a group of patients with TLE who underwent a routine presurgical evaluation, FMZ-PET was able to localize the onset zone of seizures in a majority of patients. In those patients who had a lesion on MRI, the changes in FMZ binding were concordant with this lesion. When MRI showed a normal or ambiguous result, FMZ uptake was abnormal and concordant with the electrophysiological localization of the epileptic focus. Remote abnormalities on FMZ-PET were present in 90% of patients and were associated with early age of seizure onset and long duration of epilepsy.[52]

In patients with unilateral HS, preoperative ^{11}C-labeled FMZ-PET detected decreased binding in the affected hippocampus,[53] and this in vivo binding correlated with ex vivo FMZ-autoradiography.[54] Increases of FMZ binding in periventricular white matter in patients with unilateral HS, possibly reflecting the number of neuronal cell bodies in the white matter, correlated with a poorer outcome after epilepsy surgery.[55] Hammers and colleagues reported that full quantification with an image-independent input produces the best results in the evaluation of FMZ-PET.[56] Implementing research PET methodologies of the highest standards into routine clinical practice will remain a challenge.

The changes that can be seen in FMZ binding are, as is the case for the changes in glucose metabolism, dynamic. A test-retest FMZ-PET study in patients with TLE revealed a significant effect of the duration of the interictal period on FMZ binding with lower maximal FMZ binding related to shorter interictal periods.[57]

The recent development of ^{18}F-labeled FMZ may make the study of the central benzodiazepine receptors more widely available because the tracer has a longer half life and the need of an on-site cyclotron can be eliminated.[58]

Opioid Receptor

There is growing evidence for the existence of an endogenous anticonvulsant mechanism in humans modulated by an anticonvulsant substance with opioid characteristics. Endogenous opioids are thought to play a dynamic role in the termination of seizures,[59] because high-frequency firing is required for their endogenous release.[60]

Interictal PET studies in patients with TLE that use ^{11}C-carfentanil,[61,62] which is selective for the μ-opioid peptide receptor, or ^{11}C-methylnaltrindole,[63] which is selective for the δ-opioid peptide receptor, have shown increased binding in the lateral temporal neocortex on the side of the epileptogenic focus in patients with TLE.

Hammers and coworkers showed that changes in the opioid system are seizure-related. In a longitudinal study, each patient with TLE was scanned twice using the nonsubtype selective opioid receptor PET radioligand ^{11}C-diprenorphine, and one scan was within hours after a seizure. There was an increase of opioid receptor availability found in the temporal pole and fusiform gyrus ipsilateral to the seizure focus; this increase correlated negatively with the time since the last seizure, compatible with an early increase and gradual return to baseline. This study emphasized the possibly important role of the opioid system in seizure control.[64]

5-HT$_{1A}$ Serotonin Receptor

Several lines of evidence suggest that serotonin (5-HT) may also have an anticonvulsant effect through activation of the 5-HT$_{1A}$ receptor[65,66] because activation of this receptor affects the release and activity of other neurotransmitters such as glutamate, dopamine, and GABA. Theodore and coworkers used ^{18}F-FCWAY, a selective 5-HT$_{1A}$ receptor antagonist, to study the receptor in patients with TLE and demonstrated a reduced serotonin receptor binding in temporal lobe epileptic foci.[67] The same group recently showed that there is a relationship between hippocampal 5-HT$_{1A}$ binding and depressive symptoms in patients with TLE.[68] They also showed that these reductions in 5-HT$_{1A}$ receptor binding in mesial temporal structures and insula remained significant after partial volume correction.[69] Using ^{11}C-WAY100635, Ito and coauthors found a decreased 5-HT$_{1A}$ receptor binding predominantly in the ipsilateral mesial temporal lobe structures but also in the contralateral side in patients with nonlesional TLE.[70]

Imaging of Tuberous Sclerosis Using α-[^{11}C]methyl-L-tryptophan (AMT)

Imaging of the serotonin synthesis can be performed using AMT. In patients with tuberous sclerosis, an increased AMT uptake can be found in a subset of epileptogenic tubers consistent with the location of the seizure focus[71,72] thereby detecting those tubers that need to be resected to achieve a seizure free outcome. In this way, AMT-PET imaging can provide independent complementary information regarding the localization of epileptogenic regions in tuberous sclerosis and enhance the confidence of patient selection for successful epilepsy surgery.[73]

Nicotinic Acetylcholine Receptor (nAChR)

nAChRs are ionotropic receptors that form ligand gated ion channels and are opened by the binding of ACh, but also of nicotine. The role of nAChRs in epilepsy has been suggested by the finding of mutations in a subset of genes coding for subunits of the nAChRs in autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). In around 10% of ADNFLE families, mutations were identified in the nAChR α_4 or β_2 subunit, which together compose the main cerebral nAChR. Functional characterization of some mutations suggests that gain of the receptor function might be the basis for epileptogenesis.[74] Picard and coauthors used ^{18}F-F-A-85380 to study the α_4 β_2 nAChRs in vivo in patients with ADNFLE and found a significantly increased nAChR density in the epithalamus, ventral mesencephalon and cerebellum, implicating these structures in the pathophysiology of ADNFLE. On the other hand, the nAChR density was decreased in the right dorsolateral prefrontal region, consistent with a focal epilepsy involving the frontal lobe.[75]

Type-1 Cannabinoid Receptor

In the brain, endogenous and exogenous cannabinoids act on the G-protein-coupled type 1 cannabinoid receptor (CB1R), expressed on neurons, astrocytes, microglia, and oligodendrocytes.[76] CB1 receptors, located mainly on the presynaptic nerve terminal, mediate mixed inhibitory-disinhibitory effects on neurotransmission through suppression of the release of other neurotransmitters, for example glutamate, GABA and dopamine.[77]

Several lines of evidence point toward a link between the endocannabinoid system and mechanisms involved in generation and cessation of epileptic seizures. The endocannabinoid system would provide an "on-demand" protection against acute excitotoxicity in neurons of the central nervous system and would contribute to a signaling system that protects neurons against the consequences of abnormal discharge activity.[78] In humans, cannabis may act as an anticonvulsant in the treatment of partial and secondarily generalized seizures,[79] although prospective and randomized studies are lacking. In rodent models of epilepsy, administration of cannabinoids is protective against seizures[80,81] and affects seizure frequency and duration. Endocannabinoid and CB1R levels are increased in these epileptic animals.[82]

In vivo visualization of the CB1R has been possible since the development of specific ligands for this receptor. ^{18}F-MK-9470, a selective, high-affinity, inverse agonist for the CB1R has the potential to be a valuable, noninvasive research tool for the in vivo study of CB1R biology and pharmacology in a variety of neuropsychiatric disorders in humans.[83]

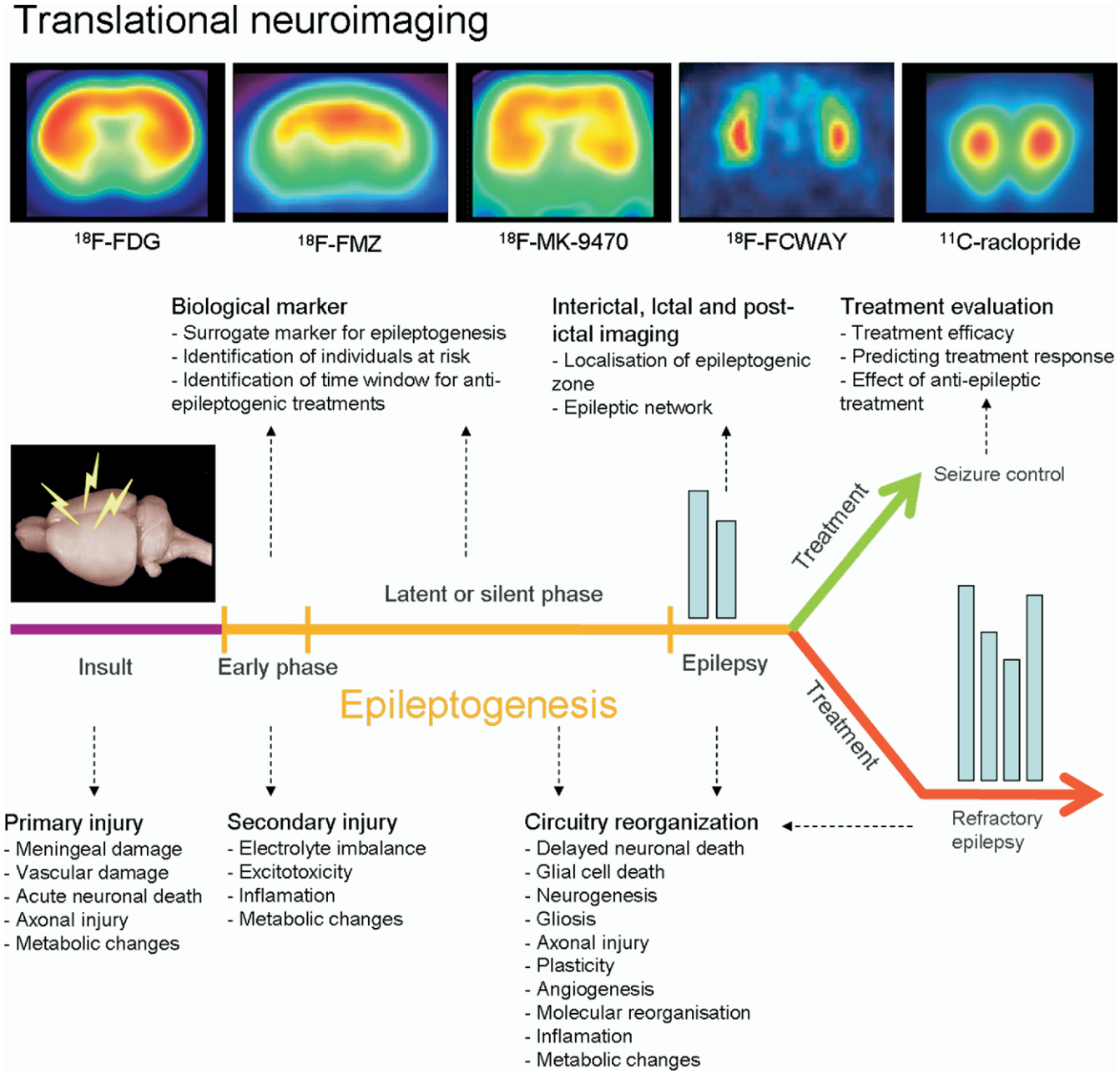

Figure 7 Overview of saPET applications in epilepsy research. Coronal views of PET images through the hippocampus of the rat brain with ^{18}F-FDG (glucose metabolism; top row, first image); ^{18}F-FMZ ($GABA_A$ receptor system; top row, second image); ^{18}F-MK-9470 (CB1 receptor system; top row, third image); and ^{18}F-FCWAY ($5\text{-}HT_{1A}$ serotonin receptor system; top row, fourth image) after inhibition of defluorination with miconazole treatment. (Reprinted by permission from the Society of Nuclear Medicine from Tipre et al.[89]). ^{11}C-raclopride (dopamine D_2 receptor system; top row, fifth image), section through the striatum. Description of the possible imaging milestones during the process of epileptogenesis and the development of epilepsy and outline of some of the neurobiological alterations during this time window (bottom row).

Small Animal Imaging: Translational Research

The use of animal models in epilepsy research enables the investigation of a wide range of neurobiological processes during the development, onset, and progression of the disease in laboratory-controlled conditions. Complex molecular events can be unraveled with the use of specific interventions to pinpoint certain mechanisms. Neuroimaging in vivo allows preclinical research to be conducted in a noninvasive and longitudinal manner, facilitating translation of knowledge from bench side to clinical applications.

In animal models, epileptogenesis is generally induced by a precipitating insult (genetic or acquired) that initiates a cascade of processes that transform a normal to a hyperexcitable epileptic brain, resulting in the occurrence of recurrent

spontaneous seizures after a latent or silent period (Fig. 7). A multitude of alterations have been described to occur during the insult, in the first hours and days immediately after the initial insult and during the silent period, such as cell death, gliosis, inflammation, mossy fiber sprouting, neurogenesis, and synaptogenesis.[84] When spontaneous seizures develop, these recurrent insults are likely to affect the brain, for example, induction of protective mechanisms and rewiring of the neuronal circuits, in addition to ongoing epileptogenic processes.

Small animal PET (saPET) and SPECT offer the possibility to map and follow the evolution of pathophysiological processes in epilepsy models in vivo (Fig. 7). However, we have to bear in mind partial volume effects, because of the limited resolution of saPET (1-2 mm) and the small size of the brains of small animals. At present, most animal studies conducted with saPET have used FDG to assess changes in glucose metabolism during seizures and epileptogenesis.[85-87] We have recently reviewed these studies and possible applications of saPET for epilepsy research.[88]

Specific neurobiological changes at several time points can be measured with a range of PET tracers, as mentioned previously (Fig. 7). In addition, the relevance of these alterations as a biomarker for the development of seizures can be studied in follow-up studies, which may give clues for new therapeutic targets. A therapeutic window may be identified creating the opportunity to assess the effects of potential antiepileptogenic treatments. Several tracers could be compared for their validity to identify the epileptogenic zone in a focal epilepsy model. In addition, saPET can be used to appraise the temporary and permanent effects of recurrent seizures on the brain (Fig. 7), which can help in interpreting human imaging data.

Conclusion

Ictal perfusion SPECT and interictal FDG-PET imaging remain important tools in the localization of the ictal onset zone, seizure propagation pathways, and the functional deficit zone in the presurgical evaluation of patients with refractory partial epilepsy. Automated image processing techniques and novel reconstruction techniques help to provide objective results, although careful interpretation by close collaboration between the nuclear medicine and neurology department remains necessary. Imaging of specific receptor systems is likely to become more important in the future and may give us a better understanding of the complex mechanisms that underlie the development and termination of seizures and epilepsy. Also, translational small animal imaging to investigate animal models of epilepsy may prove useful to this cause.

References

1. Fisher RS, van Emde Boas W, Blume W, et al: Epileptic seizures and epilepsy: Definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 46:470-472, 2005
2. Hauser WA, Kurland LT: The epidemiology of epilepsy in Rochester, Minnesota, 1935 through 1967. Epilepsia 16:1-66, 1975
3. Hart YM, Sander JW, Johnson AL, et al: National general practice study of epilepsy: Recurrence after a first seizure. Lancet 336:1271-1274, 1990
4. Commission on Classification and Terminology of the International League Against Epilepsy: Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 22:489-501, 1981
5. Li LM, Fish DR, Sisodiya SM, et al: High resolution magnetic resonance imaging in adults with partial or secondary generalised epilepsy attending a tertiary referral unit. J Neurol Neurosurg Psychiatry 59:384-387, 1995
6. Rosenow F, Lüders H: Presurgical evaluation of epilepsy. Brain 124: 1683-1700, 2001
7. Elger CE, Helmstaedter C, Kurthen M: Chronic epilepsy and cognition. Lancet Neurol 3:663-672, 2004
8. Wiebe S, Blume WT, Girvin JP, et al: A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med 345:311-318, 2001
9. Cohen-Gadol AA, Ozduman K, Bronen RA, et al: Long-term outcome after epilepsy surgery for focal cortical dysplasia. J Neurosurg 101:55-65, 2004
10. Sharp PF, Smith FW, Gemmell HG, et al: Technetium-99m HM-PAO stereoisomers as potential agents for imaging regional cerebral blood flow: Human volunteer studies. J Nucl Med 27:171-177, 1986
11. Vallabhajosula S, Zimmerman RE, Picard M, et al: Technetium-99m ECD: A new brain imaging agent: in vivo kinetics and biodistribution studies in normal human subjects. J Nucl Med 30:599-604, 1989
12. O'Brien TJ, So EL, Mullan BP, et al: Subtraction ictal SPECT co-registered to MRI improves clinical usefulness of SPECT in localizing the surgical seizure focus. Neurology 50:445-454, 1998
13. McNally KA, Paige AL, Varghese G, et al: Localizing value of ictal-interictal SPECT analyzed by SPM (ISAS). Epilepsia 46:1450-1464, 2005
14. Maes F, Collignon A, Vandermeulen D, et al: Multimodality image registration by maximization of mutual information. IEEE Trans Med Imaging 16:187-198, 1997
15. Dupont P, Van Paesschen W, Palmini A, et al: Ictal perfusion patterns associated with single MRI-visible focal dysplastic lesions: implications for the noninvasive delineation of the epileptogenic zone. Epilepsia 47:1550-1557, 2006
16. Lee SK, Lee SY, Yun CH, et al: Ictal SPECT in neocortical epilepsies: Clinical usefulness and factors affecting the pattern of hyperperfusion. Neuroradiology 48:678-684, 2006
17. Van Paesschen W, Dupont P, Sunaert S, et al: The use of SPECT and PET in routine clinical practice in epilepsy. Curr Opin Neurol 20:194-202, 2007
18. Devous MD Sr., Thisted RA, Morgan GF, et al: SPECT brain imaging in epilepsy: A meta-analysis. J Nucl Med 39:285-293, 1998
19. Bartolini A: Regional arm-brain mean transit time in the diagnostic evaluation of patients with cerebral vascular disease. Stroke 12:241-245, 1981
20. Shin WC, Hong SB, Tae WS, et al: Ictal hyperperfusion patterns according to the progression of temporal lobe seizures. Neurology 58:373-380, 2002
21. Amorim BJ, Etchebehere EC, Camargo EE, et al: Statistical voxel-wise analysis of ictal SPECT reveals pattern of abnormal perfusion in patients with temporal lobe epilepsy. Arq Neuropsiquiatr 63:977-983, 2005
22. Fukuda M, Masuda H, Honma J, et al: Ictal SPECT analyzed by three-dimensional stereotactic surface projection in frontal lobe epilepsy patients. Epilepsy Res 68:95-102, 2006
23. Avery RA, Spencer SS, Spanaki MV, et al: Effect of injection time on postictal SPET perfusion changes in medically refractory epilepsy. Eur J Nucl Med 26:830-836, 1999
24. Cherry SR: Multimodality in vivo imaging systems: Twice the power or double the trouble? Annu Rev Biomed Eng 8:35-62, 2006

25. Drzezga A, Arnold S, Minoshima S, et al: 18F-FDG PET studies in patients with extratemporal and temporal epilepsy: Evaluation of an observer-independent analysis. J Nucl Med 40:737-746, 1999
26. Lin TW, de Aburto MA, Dahlbom M, et al: Predicting seizure-free status for temporal lobe epilepsy patients undergoing surgery: Prognostic value of quantifying maximal metabolic asymmetry extending over a specified proportion of the temporal lobe. J Nucl Med 48:776-782, 2007
27. Gaillard WD, Zeffiro T, Fazilat S, et al: Effect of valproate on cerebral metabolism and blood flow: An 18F-2-deoxyglucose and 15O water positron emission tomography study. Epilepsia 37:515-521, 1996
28. Theodore WH: Antiepileptic drugs and cerebral glucose metabolism. Epilepsia 29:S48-S55, 1988 (suppl 2)
29. Hunter GJ, Hamberg LM, Alpert NM, et al: Simplified measurement of deoxyglucose utilization rate. J Nucl Med 37:950-955, 1996
30. Quarantelli M, Berkouk K, Prinster A, et al: Integrated software for the analysis of brain PET/SPECT studies with partial-volume-effect correction. J Nucl Med 45:192-201, 2004
31. Baete K, Nuyts J, Van Paesschen W, et al: Anatomical-based FDG-PET reconstruction for the detection of hypo-metabolic regions in epilepsy. IEEE Trans Med Imaging 23:510-519, 2004
32. Baete K, Nuyts J, Van Laere K, et al: Evaluation of anatomy based reconstruction for partial volume correction in brain FDG-PET. Neuroimage 23:305-317, 2004
33. Lee SK, Lee SY, Kim KK, et al: Surgical outcome and prognostic factors of cryptogenic neocortical epilepsy. Ann Neurol 58:525-532, 2005
34. Breier JI, Mullani NA, Thomas AB, et al: Effects of duration of epilepsy on the uncoupling of metabolism and blood flow in complex partial seizures. Neurology 48:1047-1053, 1997
35. Casse R, Rowe CC, Newton M, et al: Positron emission tomography and epilepsy. Mol Imaging Biol 4:338-351, 2002
36. Park CK, Kim SK, Wang KC, et al: Surgical outcome and prognostic factors of pediatric epilepsy caused by cortical dysplasia. Childs Nerv Syst 22:586-592, 2006
37. Ollenberger GP, Byrne AJ, Berlangieri SU, et al: Assessment of the role of FDG PET in the diagnosis and management of children with refractory epilepsy. Eur J Nucl Med Mol Imaging 32:1311-1316, 2005
38. Yun CH, Lee SK, Lee SY, et al: Prognostic factors in neocortical epilepsy surgery: Multivariate analysis. Epilepsia 47:574-579, 2006
39. Choi JY, Kim SJ, Hong SB, et al: Extratemporal hypometabolism on FDG PET in temporal lobe epilepsy as a predictor of seizure outcome after temporal lobectomy. Eur J Nucl Med Mol Imaging 30:581-587, 2003
40. Henry TR, Babb TL, Engel J Jr., et al: Hippocampal neuronal loss and regional hypometabolism in temporal lobe epilepsy. Ann Neurol 36: 925-927, 1994
41. Foldvary N, Lee N, Hanson MW, et al: Correlation of hippocampal neuronal density and FDG-PET in mesial temporal lobe epilepsy. Epilepsia 40:26-29, 1999
42. Cornford EM, Gee MN, Swartz BE, et al: Dynamic [18F]fluorodeoxyglucose positron emission tomography and hypometabolic zones in seizures: Reduced capillary influx. Ann Neurol 43:801-808, 1998
43. Nelissen N, Van Paesschen W, Baete K, et al: Correlations of interictal FDG-PET metabolism and ictal SPECT perfusion changes in human temporal lobe epilepsy with hippocampal sclerosis. Neuroimage 32: 684-695, 2006
44. McDonald CR, Swartz BE, Halgren E, et al: The relationship of regional frontal hypometabolism to executive function: a resting fluorodeoxyglucose PET study of patients with epilepsy and healthy controls. Epilepsy Behav 9:58-67, 2006
45. Salzberg M, Taher T, Davie M, et al: Depression in temporal lobe epilepsy surgery patients: An FDG-PET study. Epilepsia 47:2125-2130, 2006
46. Takaya S, Hanakawa T, Hashikawa K, et al: Prefrontal hypofunction in patients with intractable mesial temporal lobe epilepsy. Neurology 67: 1674-1676, 2006
47. Benedek K, Juhasz C, Chugani DC, et al: Longitudinal changes in cortical glucose hypometabolism in children with intractable epilepsy. J Child Neurol 21:26-31, 2006
48. Joo EY, Hong SB, Han HJ, et al: Postoperative alteration of cerebral glucose metabolism in mesial temporal lobe epilepsy. Brain 128:1802-1810, 2005
49. Van Paesschen W, Porke K, Fannes K, et al: Cognitive deficits during status epilepticus and time course of recovery: A case report. Epilepsia 48:1979-1983, 2007
50. Treiman DM: GABAergic mechanisms in epilepsy. Epilepsia 42:8-12, 2001 (suppl 3)
51. Hammers A, Koepp MJ, Richardson MP, et al: Grey and white matter flumazenil binding in neocortical epilepsy with normal MRI. A PET study of 44 patients. Brain 126:1300-1318, 2003
52. Padma MV, Simkins R, White P, et al: Clinical utility of 11C-flumazenil positron emission tomography in intractable temporal lobe epilepsy. Neurol India 52:457-462, 2004
53. Koepp MJ, Richardson MP, Brooks DJ, et al: Cerebral benzodiazepine receptors in hippocampal sclerosis. An objective in vivo analysis. Brain 119:1677-1687, 1996
54. Koepp MJ, Hand KS, Labbe C, et al: In vivo [11C]flumazenil-PET correlates with ex vivo [3H]flumazenil autoradiography in hippocampal sclerosis. Ann Neurol 43:618-626, 1998
55. Hammers A, Koepp MJ, Brooks DJ, et al: Periventricular white matter flumazenil binding and postoperative outcome in hippocampal sclerosis. Epilepsia 46:944-948, 2005
56. Hammers A, Panagoda P, Heckemann RA, et al: [(11)C]Flumazenil PET in temporal lobe epilepsy: Do we need an arterial input function or kinetic modeling? J Cereb Blood Flow Metab 28:207-216, 2008
57. Bouvard S, Costes N, Bonnefoi F, et al: Seizure-related short-term plasticity of benzodiazepine receptors in partial epilepsy: A [11C]flumazenil-PET study. Brain 128:1330-1343, 2005
58. Chang YS, Jeong JM, Yoon YH, et al: Biological properties of 2′-[18F]fluoroflumazenil for central benzodiazepine receptor imaging. Nucl Med Biol 32:263-268, 2005
59. Tortella FC, Long JB: Endogenous anticonvulsant substance in rat cerebrospinal fluid after a generalized seizure. Science 228:1106-1108, 1985
60. Wagner JJ, Caudle RM, Neumaier JF, et al: Stimulation of endogenous opioid release displaces mu receptor binding in rat hippocampus. Neuroscience 37:45-53, 1990
61. Frost JJ, Mayberg HS, Fisher RS, et al: Mu-opiate receptors measured by positron emission tomography are increased in temporal lobe epilepsy. Ann Neurol 23:231-237, 1988
62. Mayberg HS, Sadzot B, Meltzer CC, et al: Quantification of mu and non-mu opiate receptors in temporal lobe epilepsy using positron emission tomography. Ann Neurol 30:3-11, 1991
63. Madar I, Lesser RP, Krauss G, et al: Imaging of delta- and mu-opioid receptors in temporal lobe epilepsy by positron emission tomography. Ann Neurol 41:358-367, 1997
64. Hammers A, Asselin MC, Hinz R, et al: Upregulation of opioid receptor binding following spontaneous epileptic seizures. Brain 130:1009-1016, 2007
65. Pasini A, Tortorella A, Gale K: Anticonvulsant effect of intranigral fluoxetine. Brain Res 593:287-290, 1992
66. Favale E, Rubino V, Mainardi P, et al: Anticonvulsant effect of fluoxetine in humans. Neurology 45:1926-1927, 1995
67. Toczek MT, Carson RE, Lang L, et al: PET imaging of 5-HT1A receptor binding in patients with temporal lobe epilepsy. Neurology 60:749-756, 2003
68. Theodore WH, Hasler G, Giovacchini G, et al: Reduced hippocampal 5HT1A PET receptor binding and depression in temporal lobe epilepsy. Epilepsia 48:1526-1530, 2007
69. Giovacchini G, Toczek MT, Bonwetsch R, et al: 5-HT 1A receptors are reduced in temporal lobe epilepsy after partial-volume correction. J Nucl Med 46:1128-1135, 2005
70. Ito S, Suhara T, Ito H, et al: Changes in central 5-HT(1A) receptor binding in mesial temporal epilepsy measured by positron emission tomography with [(11)C]WAY100635. Epilepsy Res 73:111-118, 2007

71. Chugani DC, Chugani HT, Muzik O, et al: Imaging epileptogenic tubers in children with tuberous sclerosis complex using alpha-[11C]methyl-L-tryptophan positron emission tomography. Ann Neurol 44: 858-866, 1998
72. Fedi M, Reutens DC, Andermann F, et al: alpha-[11C]-Methyl-L-tryptophan PET identifies the epileptogenic tuber and correlates with interictal spike frequency. Epilepsy Res 52:203-213, 2003
73. Kagawa K, Chugani DC, Asano E, et al: Epilepsy surgery outcome in children with tuberous sclerosis complex evaluated with alpha-[11C]methyl-L-tryptophan positron emission tomography (PET). J Child Neurol 20:429-438, 2005
74. Marini C, Guerrini R: The role of the nicotinic acetylcholine receptors in sleep-related epilepsy. Biochem Pharmacol 74:1308-1314, 2007
75. Picard F, Bruel D, Servent D, et al: Alteration of the in vivo nicotinic receptor density in ADNFLE patients: a PET study. Brain 129:2047-2060, 2006
76. Iversen L: Cannabis and the brain. Brain 126:1252-1270, 2003
77. Wilson RI, Nicoll RA: Endocannabinoid signaling in the brain. Science 296:678-682, 2002
78. Marsicano G, Goodenough S, Monory K, et al: CB1 cannabinoid receptors and on-demand defense against excitotoxicity. Science 302:84-88, 2003
79. Ben Amar M: Cannabinoids in medicine: A review of their therapeutic potential. J Ethnopharmacol 105:1-25, 2006
80. Wallace MJ, Wiley JL, Martin BR, et al: Assessment of the role of CB1 receptors in cannabinoid anticonvulsant effects. Eur J Pharmacol 428: 51-57, 2001
81. Wallace MJ, Martin BR, DeLorenzo RJ: Evidence for a physiological role of endocannabinoids in the modulation of seizure threshold and severity. Eur J Pharmacol 452:295-301, 2002
82. Wallace MJ, Blair RE, Falenski KW, et al: The endogenous cannabinoid system regulates seizure frequency and duration in a model of temporal lobe epilepsy. J Pharmacol Exp Ther 307:129-137, 2003
83. Burns HD, Van Laere K, Sanabria-Bohorquez S, et al: [18F]MK-9470, a positron emission tomography (PET) tracer for in vivo human PET brain imaging of the cannabinoid-1 receptor. Proc Natl Acad Sci U S A 104:9800-9805, 2007
84. Pitkänen A, Kharatishvili I, Karhunen H, et al: Epileptogenesis in experimental models. Epilepsia 48:13-20, 2007 (suppl 2)
85. Kornblum HI, Araujo DM, Annala AJ, et al: In vivo imaging of neuronal activation and plasticity in the rat brain by high resolution positron emission tomography (microPET). Nat Biotechnol 18:655-660, 2000
86. Mirrione MM, Schiffer WK, Siddiq M, et al: PET imaging of glucose metabolism in a mouse model of temporal lobe epilepsy. Synapse 59: 119-121, 2006
87. Jupp B, Williams J, Binns D, et al: Imaging small animal models of epileptogenesis. Neurology Asia 12:51-54, 2007 (suppl 1)
88. Dedeurwaerdere S, Jupp B, O'Brien TJ: Positron emission tomography in basic epilepsy research: a view of the epileptic brain. Epilepsia 48: 56-64, 2007 (suppl 4)
89. Tipre DN, Zoghbi SS, Liow JS, et al: PET imaging of brain 5-HT1A receptors in rat in vivo with 18F-FCWAY and improvement by successful inhibition of radioligand defluorination with miconazole. J Nucl Med 47:345-353, 2006