Epilepsy is one of the most common neurological disorders, affecting 0.5%–1.0% of the population. Almost one-third of epilepsy patients do not respond to medical treatment and develop intractable seizures. Nuclear imaging modalities such as $^{18}$F-labeled fluoro-2-deoxyglucose–positron emission tomography ($^{18}$F-FDG-PET) and perfusion single photon emission computed tomography (SPECT) are useful in the diagnosis and evaluation of epilepsy. The main role of such modalities in clinical epilepsy is focus detection in patients with intractable epilepsy. They enable us to detect the focal lesion as abnormal uptake of nuclear tracers, and are especially useful in MRI–negative patients or those with multiple abnormal regions that are suspected to be epileptogenic. However, some patients still have multi-imaging–negative focal epilepsy. Thus, the development of other tracers for more precise detection of foci is desirable.
Introduction

Nuclear imaging of the brain is a traditional but still growing tool in clinical and basic epileptology. Its conventional role in clinical epilepsy is primarily focus detection in patients with intractable focal epilepsy. It thus enables the detection of the focal lesion as abnormal uptake of nuclear tracers, even in patients with no visible abnormalities on high-resolution MRI [1]. Over 30% of patients with epilepsy still have intractable seizures despite treatment with newer anti-epileptic drugs [2]. Surgery may be beneficial to patients with such drug-resistant epilepsy, and accurate localization of the epileptogenic zone is of paramount importance for complete and safe resection [3]. In particular, interictal $^{18}$F-labeled fluoro-2-deoxyglucose–positron emission tomography ($^{18}$F-FDG-PET) and ictal perfusion single photon emission computed tomography (SPECT) have been conventionally used in presurgical evaluation [3].

Meanwhile, recent developments in nuclear imaging have enabled us to visualize various molecular structures of the brain in epilepsy. For instance, there have been reports on abnormal distributions of central benzodiazepine receptors [4-6], serotonin receptors, and $\alpha$-methyl-L-tryptophan [7-9] within epileptogenic foci. More recently, abnormalities in glutamate receptors, which play a crucial role in excitatory neurotransmission, have been visualized in temporal lobe epilepsy (TLE) [10]. Thus, the development of nuclear neuroimaging is ongoing and it is expected to reveal further neural mechanisms in epilepsy and exhibit clinical utility.

In this review, we revisit the conventional roles of nuclear imaging in epilepsy and shed light on recent progress.

| Targeted pathway                     | Tracer                          | Uptake pattern                      |
|--------------------------------------|---------------------------------|-------------------------------------|
| PET                                  | Glucose metabolism              | $^{18}$F-FDG                         |
|                                      | $^{11}$C-flumazenil             | Interictal decrease; ictal increase |
|                                      | $^{11}$C-$\alpha$-methyl-L-tryptophan | Interictal increase                |
|                                      | $^{18}$F-FCWAY, $^{18}$F-MPPF  | Interictal decrease                 |
|                                      | Acetylcholine receptors         | $^{18}$F-FA85380                    |
|                                      | Dopamine receptors              | $^{18}$F-fallypride, $^{11}$C-SCH23390 |
|                                      | Histamine receptors             | $^{11}$C-doxepin                    |
|                                      | $N$-methyl-$D$-aspartic acid receptors | Interictal decrease               |
|                                      | Glutamate acid receptors        | $^{11}$C-ketamine                    |
|                                      | SPECT                           | $^{99m}$Tc-ECD, $^{99m}$Tc-HMPAO        |
|                                      | Blood perfusion                 | $^{123}$I-iomazenil                  |
|                                      | Benzdiazepine receptor          | Interictal decrease; ictal increase |

FCWAY = trans-4-fluoro-$N$-2-[4-(2-methoxyphenyl) piperazin-1-yl] ethyl-$N$-(2-pyridyl) cyclohexanecarboxamide; MPPF = 4-$^{18}$F-fluoro-$N$-2-[4-(2-methoxyphenyl)-l-piperazinyl]ethyl-$N$-(2-pyridyl) benzamide; AMPA = $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
Role of Nuclear Medicine

The PET and SPECT radiotracers used to detect epileptogenic foci are summarized in Table 1. While several molecular imaging tracers have been shown to be useful, 18F-FDG-PET and perfusion SPECT remain the mainstay of nuclear imaging for intractable epilepsy. Perfusion SPECT is useful considering its wide availability, reasonable cost, relatively simple procedures, and suitability for ictal assessment [11]. Meanwhile, 18F-FDG-PET provides better images than SPECT due to its higher resolution [11]. In the following sections, we discuss 18F-FDG-PET, perfusion SPECT, and other tracers.

18F FDG PET

18F-FDG-PET is useful for measuring cerebral glucose metabolism related to neuronal and synaptic activity. In the interictal state, the epileptogenic zone is typically seen as a region of reduced radiotracer uptake (hypometabolism) (Figure 1). Although the exact cause of hypometabolism has not yet been clarified, possible associations of hypometabolism with neuronal loss, mossy fiber abnormalities, and neuroinflammation have been proposed [12]. Cortical hypometabolism seems to be related to seizure duration, frequency, and severity. Interictal hypometabolism may involve seizure propagation pathways, the contralateral mirror region, and functional suppression. In addition to the cortex, hypometabolism can also be found in the ipsilateral thalamus and striatum and in the contralateral cerebellum (diaschisis) [1]. However, because the hypometabolic regions often extend beyond the presumed epileptogenic zone, 18F-FDG-PET alone cannot be used to determine the extent of surgical re-

Figure 1. A 27-year-old man with TLE and right hippocampal sclerosis. (A) A coronal T2-weighted image shows right hippocampal atrophy (arrow). (B) An interictal 18F-FDG-PET MRI fusion image shows hypometabolism in the medial and lateral sides of the right temporal cortex (arrows).
section. Thus, concordance among multimodal examinations, including other imaging findings and electrophysiological data, is important. The sensitivity for focus detection is reported to be 85-90% in TLE and 45-92% (generally up to 55%) in extra-TLE [1]. The higher sensitivity of $^{18}$F-FDG-PET compared to interictal/ictal SPECT may be due to higher resolution of PET than SPECT as well as the uncoupling of cerebral blood flow (CBF) and glucose metabolism [12, 13]. $^{18}$F-FDG-PET is useful for detecting the focus in MRI-negative patients. Previous work has shown comparable surgical outcomes between MRI-negative/PET-positive TLE patients and those with hippocampal sclerosis [14]. A commonly used reading technique for $^{18}$F-FDG-PET involving visual inspection is evaluation of hemispheric asymmetry versus the normal FDG brain pattern. Although statistical analyses such as three-dimensional stereotactic surface projection and easy Z-score imaging can boost the diagnostic power, these analyses are limited to facilities that possess normal database of $^{18}$F-FDG-PET. $^{18}$F-FDG-PET/MRI fusion image can also improve the detection of epileptogenic foci, especially “bottom of sulcus” type of small focal cortical dysplasia located in the deep sulcus and sometimes difficult to detect on MRI or $^{18}$F-FDG-PET images (Figure 2) [15]. The great advantage of $^{18}$F-FDG-PET/MRI fusion image is its simplicity since it can be obtained easily using 3D T1-weighted MRI image performed in routine clinical practice.

**Perfusion SPECT**

Perfusion SPECT is used to measure CBF related to the electrical status of the brain. The commonly used perfusion SPECT tracers are $^{123}$I-N-isopropyl-iodoamphetamine ($^{123}$I-IMP), $^{99m}$Tc-ethyl cysteinate dimer ($^{99m}$Tc-ECD) and $^{99m}$Tc-hexamethyl-propyleneamine.

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**Figure 2.** A 5-year-old girl with “bottom of sulcus” focal cortical dysplasia type IIb in the right frontal lobe. (A) A coronal FLAIR image shows blurring of the gray-white matter junction and transmantle sign (arrow), which is high intensity signal band directing to the lateral ventricle. (B) It may be difficult to detect localized hypometabolism (arrow) on $^{18}$F-FDG-PET image in the deep sulcus with one look. (C) $^{18}$F-FDG-PET MRI fusion image increases the diagnostic ability because it clearly shows hypometabolism in the corresponding cortex (arrow).
oxime (99mTc-HMPAO). Interictal SPECT detects a wide region of hypoperfusion including the epileptogenic focus, but the sensitivity of detecting the epileptogenic focus is relatively low in TLE [1]. In contrast, ictal SPECT can often correctly detect localized ictal hyperperfusion in the epileptogenic focus both in TLE (70-90%) and extra-TLE (66%) [1]. Thus, the seizure focus is commonly diagnosed by assessing ictal hyperperfusion. 99mTc-based tracers remain fixed in the brain for many hours, preserving the CBF as it was at the time of injection. Given the evidence of dynamic changes in CBF during seizures in ictal SPECT, the injection time is critical [16]. Ideally, the injection should start within 15 s of seizure onset. This is because 99mTc-based tracers take 15 to 30 s to reach the brain and the switch from ictal hyperperfusion to hypoperfusion can occur in less than 1 to 2 minutes. 123I-IMP is not suited for ictal imaging because it takes about 10 minutes to determine the tracer distribution in the brain, and the distribution changes thereafter.

The main role of interictal SPECT is to help the evaluation of ictal SPECT using subtraction of ictal SPECT coregistered to MRI (SISCOM) by supplying baseline CBF. SISCOM subtracts the interictal SPECT images from ictal SPECT images and identifies areas of regional activation in the brain during seizures by fusing functional information with structural anatomy. A previous study of inter-rater agreement between SISCOM and visual inspection of ictal SPECT revealed a better outcome for SISCOM (84.3% vs 41.2%, \(\kappa = 0.83\) vs 0.26; \(p < 0.0001\)) [17]. Moreover, concordance between SISCOM localization and the resected region predicts the postsurgical improvement in seizure outcome. Compared with 18F-FDG-PET, SISCOM appears to be more sensitive to detect seizure foci [18]. Moreover, because statistically significant CBF changes can be objectively detected, it is also useful for the evaluation of postoperative recurrence (Figure 3).

Although a Z-score of 2 has been pro-

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**Figure 3.** A 4-year-old girl who underwent resection of focal cortical dysplasia type IIa in the left parietal lobe. (A) An axial T2-weighted image obtained 3 years after the surgery to investigate recurrence of epilepsy shows slight blurring of the gray-white matter junction at the surgical margin (arrow). Compared with interictal SPECT (B), it is difficult to detect hyperperfusion at the surgical margin on ictal SPECT (C). However, SISCOM clearly shows the region as having a high Z-score (D). Resection of the lesion in the left parietal lobe localized by SISCOM was subsequently performed, and focal cortical dysplasia type IIa was confirmed pathologically. After the reoperation, the number of seizures decreased.
posed as the traditional criterion, detection of the epileptogenic focus can be difficult when there are multiple areas with $Z$-scores of 2 or more. There have been several attempts to identify the optimal $Z$-score for SISCOM. By searching for the highest $Z$-score area on SISCOM, our group previously demonstrated a new method for identifying epileptogenic foci and found better concordance of this approach with pathology than with MRI [19]. Furthermore, diagnosis using both SISCOM and MRI resulted in higher detection of foci, up to 90%.

### Other Tracers

Other tracers have the potential to evaluate epilepsy. $^{11}$C-flumazenil PET and $^{123}$I-iomazenil SPECT bind to the central benzodiazepine receptor, which is mainly distributed in nerve cells and indirectly acts at GABA receptor. The numbers of benzodiazepine receptors are reduced in the epileptogenic focus. Compared with $^{18}$F-FDG-PET, which usually shows extratemporal hypometabolism related to cognitive function or diaschisis in TLE, $^{11}$C-flumazenil PET may identify a smaller decrease in tracer accumulation [5]. Moreover, it can provide further information on the seizure focus in frontal lobe epilepsy. Although $^{123}$I-iomazenil SPECT is superior to interictal SPECT, the evidence on benzodiazepine receptor imaging is still scarce compared with $^{18}$F-FDG-PET and ictal SPECT [4]. Because it can sometimes be difficult to identify focally reduced receptor binding by visual inspection alone, statistical image analysis can be helpful for more objective and accurate diagnosis.

$^{11}$C-$\alpha$-Methyl-L-tryptophan (AMT) measures tryptophan metabolism. AMT shows increased uptake in the epileptogenic area interictally, in contrast to other tracers which usually show reduced uptake. In terms of focal AMT uptake, unlike MRI-negative patients with focal cortical dysplasia, patients with normal pathology and intractable epilepsy are prone to surgical failure. AMT is useful in patients with tuberous sclerosis and multiple cortical tubers. However, MRI and $^{18}$F-FDG-PET cannot identify epileptogenic tubers [9]. $^{18}$F-FDG-PET shows reduced uptake in all tubers, reflecting abnormal tissues. Ictal SPECT would be helpful, but seizures in children are often brief and difficult to capture. AMT possibly accumulates selectively in the epileptogenic tuber. However, the underlying mechanism is unknown, and evidence is still insufficient.

Other tracers include receptors for serotonin, acetylcholine, dopamine, histamine, $N$-methyl-D-aspartic acid, and other neurotransmitters. Recently, $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors are successfully visualized in the living human brain [10]. Increased $^{11}$C-K-2 uptake in the epileptogenic focus, pathologically confirmed AMPA receptor distribution, was detected in TLE. $^{11}$C-K-2 may be a potential biochemical marker of not only epilepsy, but also neuropsychiatric disorders involving AMPA receptors.

Furthermore, increasing evidence shows the involvement of brain inflammation in the process of epileptogenesis, including microglia activation, dysfunction of the blood–brain barrier and glutamate hyperexcitability [20]. The radioligand-based imaging of neuroinflammatory targets may contribute to lo-
calize the epileptogenic onset zone, especially in treatment–resistant, MRI–negative patients, and improve overall prognosis. PET successfully captures metabolism in the brain using radioactive tracers such as 18-kDa translocator protein (TSPO)–related tracers for immune cells including microglia [21] and (R)-11C-verapamil for the blood–brain barrier [22].

When introducing these new tracers to routine clinical practice, it is necessary to confirm the safety and stability of radiopharmaceuticals in living human brains. In case of 11C-labeled tracers, PET centers that own on-site cyclotron and radiopharmacy facilities are needed, since the short 20-minute half-life of 11C limits its clinical use. Moreover, chemists and other specialized personnel with detailed knowledges are necessary.

**Conclusion**

Epilepsy is a heterogeneous disorder, and the main role of nuclear imaging is the detection of epileptogenic foci in focal epilepsy. Nuclear imaging modalities such as 18F-FDG-PET and ictal SPECT provide crucial information for surgical options in clinical practice and can now help to achieve dramatic improvement or cure in some patients. However, some patients still have multi-imaging–negative focal epilepsy. In addition, even in patients with concordance among imaging examinations, the success rate of surgery is still less than 100%. Thus, more precise detection of foci or novel treatment is desirable.

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**Conflict of Interest**

The authors declare that they have no conflicts of interest.

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