

Imaging of Serotonin Mechanisms in Epilepsy

Harry T. Chugani, MD and Diane C. Chugani, PhD

Carman and Ann Adams Department of Pediatrics, Departments of Neurology and Radiology, and the PET Center, Children's Hospital of Michigan, Wayne State University School of Medicine, Detroit, Michigan

Advances in positron emission tomography (PET) techniques have allowed the measurement and imaging of neurotransmitter synthesis, transport, and receptor binding to be performed in vivo. With regard to epileptic disorders, imaging of neurotransmitter systems not only assists in the identification of epileptic foci for surgical treatment, but also provides insights into the basic mechanisms of human epilepsy. Recent investigative interest in epilepsy has focused on PET imaging of tryptophan metabolism, via the serotonin and kynurenine pathways, as well as on imaging of serotonin receptors. This review summarizes advances in PET imaging and how these techniques can be applied clinically for epilepsy treatment.

Evidence of a Role for Serotonin in Epilepsy

The general recognition that serotonin plays a role in epileptic mechanisms is based on several lines of evidence from studies in both animal models of epilepsy and humans. For example, in the genetically epilepsy-prone rat (GEPR) model of generalized epilepsy, a decrease is found in brain concentration of serotonin (1) as well as decreased V_{max} for [3H]serotonin uptake by synaptosomes and tryptophan hydroxylase activity (2). Indeed, pharmacologic treatments that facilitate serotonergic neurotransmission inhibit seizures in many animal models of epilepsy, including the GEPR rat, maximal electroshock model, pentylenetetrazol administration, kindling, and bicuculline microinjections in the anterior piriform cortex (area tempestas) (2). Conversely, reduction of brain serotonin concentrations leads to an increase in seizure susceptibility in animal models of epilepsy (3,4) as well as in humans (5,6). In human brain tissue surgically removed for seizure control, the level of 5-hydroxyindole acetic acid (5-HIAA), which is a breakdown

product of serotonin, was found to be higher in actively spiking temporal cortex as compared with normal tissue (7,8). Finally, increased serotonin immunoreactivity has been reported in human epileptic brain tissue resected for the control of epilepsy (9). These findings provided the background and rationale for applying PET scanning of serotonin neurotransmission in patients with epilepsy.

α -[^{11}C]Methyl-L-tryptophan (AMT) PET Scanning

Diksic et al. (10,11) proposed that PET scanning with the tryptophan analogue α -[^{11}C]methyl-L-tryptophan (AMT) could be used to measure serotonin synthesis in human brain. Under normal circumstances in the brain, the amino acid L-tryptophan is either incorporated into protein or metabolized to serotonin. AMT, in contrast, is not incorporated into protein; Diksic et al. demonstrated that this feature makes it an ideal tracer for the measurement of brain serotonin synthesis (10,11). Furthermore, the serotonin analogue α -methyl-serotonin, which is converted from the administered AMT, is not a substrate for the degradative enzyme monoamine oxidase, thus allowing sufficient time for PET imaging of α -[^{11}C]methyl-serotonin before its gradual clearance and ^{11}C decay (half-life, 20 minutes). Shoaf et al. (12) showed that very little AMT is converted to α -[^{11}C]methyl-serotonin during this time period and suggested that AMT was merely a measure of tryptophan transport. In contrast, Chugani et al. (13) demonstrated that the unidirectional uptake of AMT in different brain regions exhibited the same rank order as that for serotonin content and proposed that the unidirectional uptake rate constant (K-complex) for AMT is a suitable index of serotonin synthesis in human brain.

Studies involving interictal application of AMT-PET to patients with epilepsy found *increased* uptake of AMT in the region of the epileptic focus, as indicated by ictal EEG recordings and glucose PET hypometabolism (H.T. Chugani, November, 1996). Based on the observation of an increased signal in the interictal state, it was hypothesized that patients with tuberous sclerosis and epilepsy might show increased AMT-PET uptake in the region of epileptogenic tubers but not in nonepileptogenic ones. This proved to be the case (see Figure 1), and in 1998, increased interictal AMT uptake evidenced on PET scanning in or surrounding epileptogenic tubers from eight of nine children with tuberous sclerosis and intractable epilepsy was demonstrated (14). Several of these children showed increased AMT uptake in more than one tuber. Subsequently, additional results were reported from a study of 258 cortical tubers in 18 children with tuberous sclerosis (15). In this study, uptake

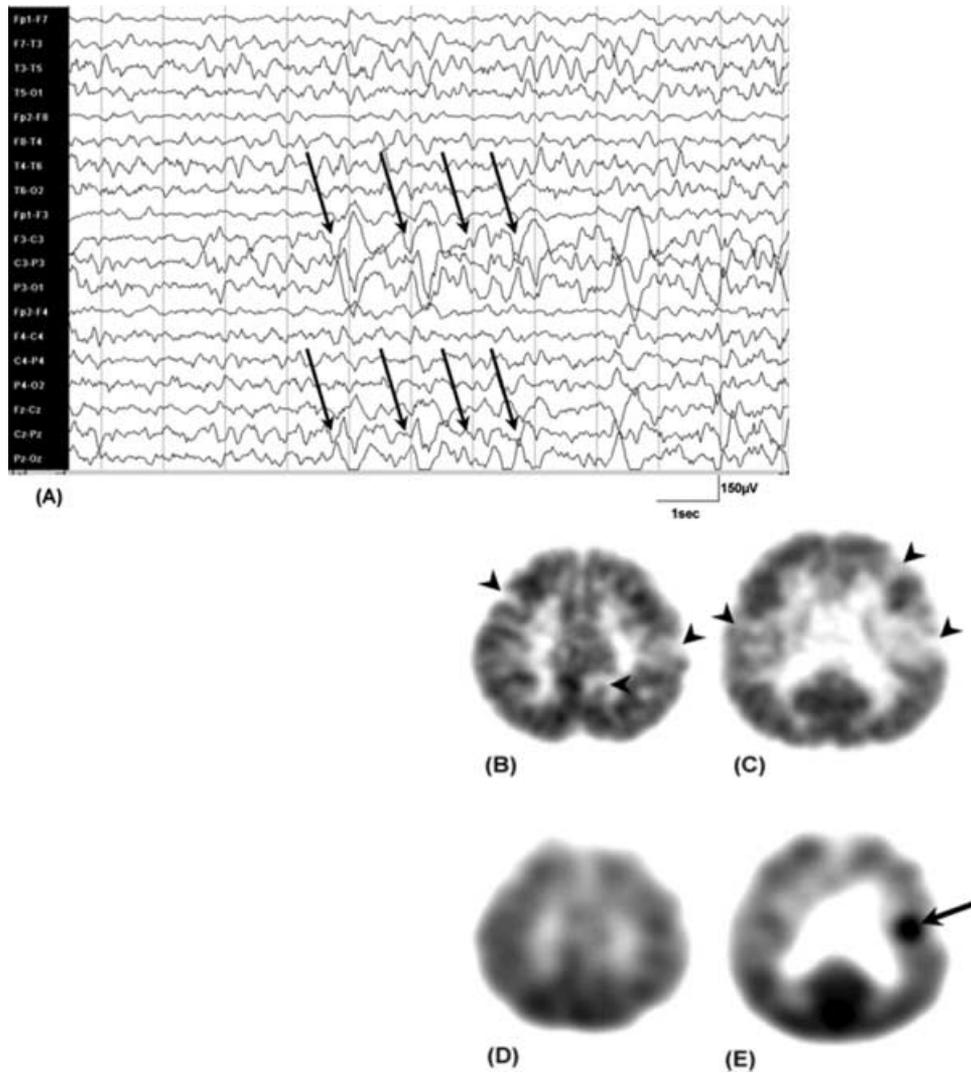


FIGURE 1. Scalp ictal EEG (A) versus [^{18}F]fluorodeoxyglucose (FDG) (B, C) and AMT (D, E) PET scans in a 1-year-old boy with tuberous sclerosis complex and uncontrolled focal seizures. Scalp ictal EEG recording (A) showed sustained, irregular rhythmic slow-wave activity in the left parietal-central region, involving midline electrodes (with the highest amplitude at C3–P3). Interictal FDG PET scan (B, C) showed multifocal nodular hypometabolic regions, including the left inferior and medial parietal regions (designated by arrowheads). Based on the ictal EEG and FDG PET findings, possible epileptogenicity in the left medial parietal region could not be ruled out. A single area of increased AMT uptake (D, E) is detected in the left inferior lateral parietal region (arrow).

ratios were calculated between the AMT uptake in tubers and the uptake in normal cortex (tuber/normal cortex). Receiver operator characteristics analysis was performed to determine the optimal uptake ratio for detecting presumed epileptogenic tubers, as confirmed by EEG recordings, and indicated that a tuber uptake ratio of 0.98 resulted in a specificity of 0.91. It should be pointed out that most tubers appear as a region of *decreased* AMT uptake (similar to hypometabolism on glucose metabolism PET) and when compared with normal cortex, have a ratio less than 1.0. In other words, the receiver operator characteristics analysis showed that cortical tubers with AMT uptake greater than or equal to that of normal cortex are significantly

related to epileptiform activity in that lobe. Therefore, interictal AMT-PET improved the detection of potentially epileptogenic tubers in patients with tuberous sclerosis being evaluated for epilepsy surgery. These findings were replicated by Fedi et al. (16), who reported an increased AMT uptake in the epileptic tuber in four of eight patients studied.

Because surgical outcome after resection of the presumed epileptic focus is the ultimate criterion with which to verify accurate delineation of the epileptogenic zone, the surgical outcome of 17 children with tuberous sclerosis, in whom AMT-PET was used to assist in identification of epileptic foci during presurgical evaluation, was analyzed next (17). Fourteen of the

17 patients underwent two-stage surgery with subdural grid electrodes placement, followed by focal cortical resection or lobectomy. One-stage resective surgery was performed in the remaining three patients, who showed an extensive tuber occupying an entire hemisphere or large calcified tubers remote from the primary motor cortex. Patients with one-stage surgery underwent intraoperative electrocorticography to define the extent of resection. Comparison between EEG and AMT-PET findings showed that the tuber with the highest uptake was located in an ictal EEG onset region in each patient. Tubers with AMT uptake 1.08 or more (at least 8% increase) were all in seizure-onset regions. In three patients, increased tuber AMT uptake correctly detected additional areas with seizure onset not found on ictal scalp EEG, but confirmed by intracranial EEG.

In a study of epilepsy patients whose MRI scans showed either cortical dysplasia or normal findings, Fedi et al. (18) reported increased AMT uptake in 60% of the patients with cortical dysplasia and 30% of patients with normal MRIs. Juhász et al. (19) demonstrated that objectively identified cortical areas of increased AMT uptake on PET were highly specific for the lobe of seizure onset both in patients with normal MRI and in those with malformations of cortical development. Interestingly, a precise spatial comparison of AMT-PET abnormalities with intracranial EEG recordings found that cortex *adjacent* to the region with increased AMT uptake is most often the site of seizure onset, although parts of the region with increased AMT uptake itself also were commonly epileptogenic (15,17).

AMT-PET scanning also has been applied to identify residual epileptogenic cortex after a failed epilepsy surgery (20). In such cases, glucose metabolism PET is not useful because of the extensive diaschisis (i.e., widespread hypometabolism) resulting from the surgery. AMT uptake was increased in cortical regions concordant with seizure-onset zones, as shown on EEG; however, the sensitivity of AMT-PET in identifying residual epileptogenic cortex was only 43% (10 of 23 patients). Nevertheless, this finding represents an important advance in the evaluation for a second surgery of these very difficult patients. The AMT-PET study should not be performed within the first 2 months after the first surgery because of the potential for false-positive results due to inflammatory changes associated with the surgery. Clearly, more sensitive neuroimaging methods are required to identify residual epileptic tissue in surgical failures.

Natsume et al. (21) explored the role of serotonin synthesis in patients with temporal lobe epilepsy by using AMT-PET. The investigators reported increased AMT uptake in the hippocampus ipsilateral to the seizure focus in patients with normal hippocampal volumes but not in patients with hippocampal atrophy. When examining the relation between the results of AMT-PET to those of glucose metabolism PET in temporal lobe epilepsy, Natsume et al. found that decreased glucose metabolism in the lateral temporal and frontal lobes correlated

with an increase in the regional unidirectional uptake rate constant for AMT in the hippocampus. Conversely, they reported that higher ipsilateral lenticular nucleus and cingulate cortex glucose metabolism was correlated with increased hippocampal AMT K-complex. These interesting data may be relevant to seizure-induced hippocampal reorganization and neurogenesis in temporal lobe epilepsy (22).

Increased AMT uptake by the hippocampus may represent increased serotonergic innervation of the area. Brain-derived neurotrophic factor (BDNF) mRNA and protein are increased in the hippocampus after seizures in patients with temporal lobe epilepsy and in some animal models of epilepsy (23). Because infusion of BDNF into rat brain increases sprouting of serotonergic fibers (24), the increased AMT uptake in hippocampus may be the result of serotonergic fiber sprouting induced by BDNF with chronic seizure activity. Furthermore, evidence suggests that serotonin is a regulator of neurogenesis in the dentate gyrus (25). Depletion of serotonin decreases neurogenesis, whereas treatments that increase serotonin in the hippocampus increase neurogenesis. Thus, increased neurogenesis in the patients showing increased AMT uptake in hippocampus may account for the normal hippocampal volume in these subjects. Increased serotonin release in the hippocampus might also result in agonist-mediated downregulation of 5-HT_{1A} receptors in the hippocampus, thus providing a potential mechanism for the decreased binding of [¹⁸F]FCWAY in hippocampus, as reported by Toczek et al. (26). Finally, decreased hippocampal volume and decreased 5-HT_{1A} binding in the raphe and in the mesiotemporal cortex also have been reported in patients with depression (27), and a study of the relation between decreased 5-HT_{1A} receptor binding and hippocampal atrophy may provide new insights into the high incidence of depression in patients with temporal lobe epilepsy (28).

Increased Serotonin or Other Tryptophan Products?

Two patterns of AMT increase are seen on PET scanning in patients with epilepsy. Some patients show an intense and well-demarcated area of increased AMT uptake, whereas others show a more diffuse pattern of increase without clear borders on the PET scan. Although both patterns may be seen in patients with tuberous sclerosis, the typical pattern is an intense nodular uptake (again, see Figure 1). Given the finding that AMT uptake is increased in the vicinity of epileptogenic tubers but not in nonepileptogenic ones (14), one would expect to find very high levels of serotonin and serotonin markers in the surgically resected brain tissue from these patients that contains the area of intense AMT uptake, but surprisingly, the levels are normal. What was being measured in these regions of very high AMT uptake, if not serotonin? A review of tryptophan metabolism indicates that, in addition to protein synthesis (in which AMT

does not participate) and serotonin synthesis, tryptophan also can be metabolized via the kynurenine pathway. However, under normal circumstances, the concentrations of tryptophan metabolites of this pathway are between 100- and 1,000-fold lower than the concentration of tryptophan in the brain (29). In comparison, the sum of the concentrations of serotonin and its metabolite 5-HIAA is approximately one-fifth the concentration of tryptophan in brain (30). Therefore, the kynurenine pathway is not expected to contribute significantly to the accumulation of AMT in brain under normal circumstances. However, after brain injury or immune activation, induction of the enzyme indoleamine 2,3-dioxygenase metabolizes tryptophan along the kynurenine pathway (29).

Importantly, several metabolites of the kynurenine pathway, including quinolinic acid, kynurenine, and 3-hydroxykynurenine, are convulsants through their action as agonists at *N*-methyl-D-aspartate (NMDA) receptors (31–36). Conversely, kynurenic acid, which is another metabolite in this pathway and is an NMDA antagonist (31), has been reported to suppress epileptiform activity in animal models of epilepsy (37). It has been postulated that metabolites of the kynurenine pathway might play a role in the initiation and maintenance of seizures in human seizure disorders (38,39). Although quinolinic acid concentrations were not increased in the seizure focus as compared with nonfocus brain regions of adults undergoing surgery for temporal lobe epilepsy (39), in patients with tuberous sclerosis, fivefold higher concentrations of quinolinic acid were found in tubers showing elevated AMT accumulation (i.e., epileptogenic tubers) compared with tubers and brain tissue that do not show elevated AMT accumulation (40). These findings suggest that, in at least some cases, the mechanism of epileptogenesis may involve activation of the kynurenine pathway, leading to the production of endogenous convulsants.

Imaging of Serotonin-receptor Binding

A number of studies have used PET to image serotonin 5-HT_{1A} receptors in patients with epilepsy, particularly temporal lobe epilepsy. Toczek et al. (26) reported decreased binding of the PET tracer [¹⁸F]FCWAY to the 5-HT_{1A} receptor in both medial and lateral temporal regions ipsilateral to the epileptic focus as well as in the brainstem of patients with temporal lobe epilepsy. By using PET with [¹¹C]WAY, Savic et al. (41) addressed whether extratemporal abnormalities of 5-HT_{1A} receptors are related to affective symptoms in patients with mesial temporal lobe epilepsy. They found decreased binding not only in the epileptic focus (hippocampus, amygdala) but also in limbic connections such as insula and cingulate, thus suggesting a potential mechanism for affective symptoms in patients with mesial temporal lobe epilepsy. The findings generally were confirmed in a study by Merlet et al. (42). These same in-

vestigators correlated intracranial stereo-EEG recordings with 5-HT_{1A}-receptor binding, measured by using the PET tracer [¹⁸F]MPPF in patients with temporal lobe epilepsy (43). They found that epileptogenic areas as well as areas of seizure propagation showed lower binding than nonepileptogenic areas. These few studies have shown that PET imaging of 5-HT_{1A}-receptor binding may provide important insights into the mechanisms of epilepsy and evaluation of comorbid conditions, such as depression.

Conclusion and Future Perspectives

Until recently, one could not have imagined that a neuroimaging tool could be used to distinguish an epileptic tuber amidst a multitude of tubers in the brains of patients with tuberous sclerosis, to identify residual epileptogenic zones in surgical failures, or to study depression in epilepsy patients. Clearly, these features now can be evaluated with PET, although much more remains to be done to optimize imaging tools for large-scale clinical application. From a basic science perspective, important questions regarding the role of the kynurenine pathway in epilepsy have resurfaced and provide fruitful areas of research, particularly in relation to tuberous sclerosis mutations.

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