

A POTENTIAL ROLE FOR α -METHYL-L-TRYPTOPHAN PET IN SEIZURE LOCALIZATION IN PATIENTS WITH INTRACTABLE EPILEPSY

α -[¹¹C]Methyl-L-tryptophan and Glucose Metabolism in Patients with Temporal Lobe Epilepsy

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OBJECTIVE: To determine whether metabolism in the brain serotonergic system, including the kynurenine pathway, is involved in temporal lobe epilepsy (TLE).

METHODS: The authors studied 14 patients with intractable TLE with positron emission tomography (PET) by using [α]-[¹¹C]methyl-L-tryptophan ([α]-MTrp) and 2-[¹⁸F]fluorodeoxyglucose (FDG) and compared results with 21 healthy control subjects who had [α]-MTrp PET studies. Seven patients had unilateral hippocampal atrophy (HA), and seven had normal hippocampal volumes (NV). The regional uptake constants (K^*) for [α]-MTrp and regional FDG uptake were calculated in regions with high serotonergic innervation, including the hippocampus, amygdala, lateral temporal lobe, frontal lobe, thalamus, lenticular nucleus, and cingulate cortex.

RESULTS: A significant increase of [α]-MTrp uptake was observed in the hippocampus ipsilateral to the seizure focus in seven TLE patients with NV compared with seven patients with HA as well as with healthy controls. In patients with TLE, glucose utilization in the lateral temporal lobe ipsilateral to the seizure focus was correlated negatively with K^* for [α]-MTrp in the ipsilateral hippocampus and positively with K^* in the ipsilateral lenticular nucleus and cingulate cortex. Glucose utilization in the frontal lobe ipsilateral to the seizure shows a reduction in the glucose utilization that relates to the increase in the [α]-MTrp uptake in the ipsilateral lateral temporal lobe.

CONCLUSIONS: This study demonstrates dysfunction of the serotonergic system, which could include metabolism through the kynurenine pathway in TLE pa-

tients with normal hippocampal volumes. [α]-MTrp PET studies might be useful for lateralizing the epileptic focus in TLE patients with normal hippocampal volumes.

Alpha-Methyl-L-tryptophan PET Detects Epileptogenic Cortex in Children with Intractable Epilepsy

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BACKGROUND: In children with tuberous sclerosis, the positron emission tomography (PET) tracer [α][¹¹C]methyl-L-tryptophan (AMT) has been shown to be selectively taken up by epileptogenic tubers, thus allowing differentiation from nonepileptogenic tubers in the interictal state.

OBJECTIVE: To determine whether cortical areas showing increased AMT uptake in children without tuberous sclerosis complex with intractable neocortical epilepsy indicate the epileptogenic zone, and to assess the relative contributions of AMT and 2-deoxy-2-[¹⁸F]fluoro-D-glucose (FDG) PET abnormalities to the localization of epileptogenic cortical regions.

METHODS: Areas of increased AMT and decreased FDG uptake were marked objectively as regions with abnormal asymmetry by using in-house-written software in 27 children who underwent comprehensive evaluation for resective epilepsy surgery. The marked PET abnormalities were compared with the locations of scalp and subdural EEG epileptiform abnormalities, as well as histology and surgical outcome.

RESULTS: Focal cortical increases of AMT uptake were found in 15 patients. The lobar sensitivity (39.0%) of AMT-PET for seizure onset was lower, but its specificity (100%) was higher ($P < 0.0001$) than that of hypometabolism on FDG-PET (sensitivity, 73.2%; specificity, 62.7%). AMT-PET abnormalities were smaller than corresponding FDG-PET hypometabolic regions

($P = 0.002$), and increased AMT uptake occurred in two patients with nonlocalizing FDG-PET. Histologically verified cortical developmental malformations were associated with increased AMT uptake ($P = 0.044$). Subdural electrodes adjacent to the area of increased AMT uptake were most often involved in seizure onset.

CONCLUSIONS: Focal increase of cortical AMT uptake in children is less sensitive but more specific for the lobe of seizure onset than is the corresponding FDG-PET hypometabolism, and it is often associated with epileptogenic cortical developmental malformations. AMT-PET can assist placement of subdural electrodes even when MRI and FDG-PET fail to provide adequate localizing information. Cortical areas adjacent to increased AMT uptake should be carefully addressed by intracranial EEG because these regions often show a high degree of epileptogenicity.

PET Imaging of 5-HT_{1A}-Receptor Binding in Patients with Temporal Lobe Epilepsy

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BACKGROUND: Activation of central serotonin (5-HT)_{1A} receptors, found in high density in brainstem raphe, hippocampus, and temporal neocortex, exerts an anticonvulsant effect in various experimental seizure models. To test the hypothesis that 5-HT_{1A}-receptor binding is reduced in human epileptic foci, positron emission tomography (PET) imaging was performed by using the radioligand [¹⁸F]*trans*-4-fluoro-*N*-2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl-(2-pyridyl)cyclohexanecarboxamide ([¹⁸F]FCWAY), a selective 5-HT_{1A}-receptor antagonist, in patients with temporal lobe epilepsy and normal controls.

METHODS: Magnetic resonance imaging (MRI) and PET were performed by using [¹⁵O]water and [¹⁸F]FCWAY in 10 controls and in 12 patients with temporal lobe epilepsy confirmed on ictal video-EEG; patients also underwent [¹⁸F]fluorodeoxyglucose PET. By using quantitative PET image analysis, regional values were obtained for [¹⁸F]FCWAY volume of distribution (*V*), cerebral blood flow (CBF), and glucose cerebral metabolic rate (CMR-glc). Hippocampal volume (HV) also was measured with MRI. [¹⁸F]FCWAY *V* PET and MR measures were compared within patients and controls by using paired *t* tests;

grouped comparisons were made with two-sample *t* tests.

RESULTS: Lower [¹⁸F]FCWAY *V* was found ipsilateral than contralateral to the epileptic focus in inferior medial (IMT) and lateral (ILT) temporal regions of patients (ILT, 47.4 ± 6.1 vs. 61.8 ± 6.1 ; $P < 0.01$; IMT, 52 ± 4.6 vs. 67.0 ± 6.0 ; $P < 0.01$). [¹⁸F]FCWAY *V* was 29% lower in raphe and 34% lower in the ipsilateral thalamic region of patients than in controls. In ILT, mean [¹⁸F]FCWAY *V* asymmetry index (AI) was significantly greater than mean CBF and mean CMR-glc AI. Mean [¹⁸F]FCWAY *V* AI in IMT was greater than mean HV AI, but the difference was not significant.

CONCLUSIONS: These findings support the hypothesis of reduced serotonin-receptor binding in temporal lobe epileptic foci.

COMMENTARY

Serotonin has long been implicated in the pathophysiology of epilepsy (1). Experimental models of epilepsy suggest an inhibitory role. Research has demonstrated that application of exogenous serotonin decreases neuronal firing rates in the CA1 region of the hippocampus of genetically epilepsy-prone rats, using either *in vitro* hippocampal slice preparations or with an *in vivo* model of intrahippocampal kainic acid-induced seizures in the freely moving rat. Furthermore, serotonin receptors are abundant in human brain regions implicated in epilepsy, including the hippocampus, temporal neocortex, and brainstem raphe nuclei. Therefore alterations in the serotonin receptor might logically accompany human epileptogenesis.

In the recent series of independent, but related, positron emission tomography (PET) studies, radioligands that bind selectively to serotonin receptors have been exploited to image human brain regions functionally for purposes of seizure localization. The studies have important pragmatic implications for evaluating patients with medically resistant seizures, especially when anatomic imaging fails to identify a discrete structural lesion (2). In contrast to MRI, 2-deoxy-2[¹⁸F]fluoro-D-glucose (FDG) PET studies can define regions of interictal hypometabolism that are considerably larger than or a greater distance from the primary epileptic focus.

Two recent studies investigated the role of the radioligand α -methyl-L-tryptophan (AMT). In one study, Natsume et al. investigated AMT and FDG uptake in 14 patients with intractable temporal lobe epilepsy and compared the results with those in 21 healthy controls. They found increased AMT uptake in the ipsilateral hippocampus in patients with normal hippocampal volume but not in patients with hippocampal atrophy. In

addition, decreased glucose utilization in the lateral temporal and frontal lobes and increased glucose utilization in the ipsilateral lenticular nucleus and cingulate cortex correlated with increased AMT uptake in ipsilateral hippocampus. In a second study of 27 children with intractable epilepsy, Juhász et al. found that a focal increase in AMT-PET was often associated with epileptogenic cortical malformations. They further observed that AMT-PET was less sensitive but more specific than FDG-PET hypometabolism in identifying the lobe of seizure onset.

In a third study, Toczek et al. used [^{18}F] *trans*-4-fluoro-*N*-2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl)-(2-pyridyl)cyclohexanecarboxamide ([^{18}F]FCWAY), a radioligand that binds specifically to central 5-HT_{1A} receptors, to demonstrate reduced serotonin receptor binding in 13 patients with medically resistant temporal lobe epilepsy. Compared with 10 healthy control volunteers, decreased [^{18}F]FCWAY uptake was noted in ipsilateral inferior medial and lateral temporal cortex, brainstem raphe nuclei, and thalamus of the 13 patients. The reduction in [^{18}F]FCWAY exceeded any reduction in regional cerebral blood flow and hippocampal volume, again suggesting that volume loss is not directly responsible for the observed reduction in serotonin receptors.

How should we interpret these findings? At the very least, the results demonstrate that radioligands that bind to serotonin receptors show great promise for the preoperative evaluation

of epilepsy surgical candidates. Furthermore, AMT-PET studies also reveal that abnormalities of serotonin receptors occur in brain regions distant from the primary epileptic focus. However, the research does not clarify whether decreases in serotonin-induced inhibition are responsible for the hypometabolic regions seen on FDG-PET.

Larger series are clearly needed, and further research is warranted on how the correlation between PET findings and the neurochemical features of resected tissue relates to long-term surgical outcome. Further investigations would likely strengthen the link between abnormalities of serotonin receptors and human epilepsy, while demonstrating that receptor dysfunction can be exploited as a localizing tool. Equally important is the potential contribution of new radioligands to bring understanding to the relation between the widespread serotonin-receptor abnormalities and dysfunctional circuits in human epilepsy.

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