Epilepsy

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As surgical treatments for adult and pediatric forms of epilepsy have become more refined, methods for noninvasive localization of epileptogenic foci have become increasingly important. Detection of focal brain metabolic or flow abnormalities is now well recognized as an essential step in the presurgical evaluation of many patients with epilepsy. Positron emission tomography (PET) scanning is most beneficial when used in the context of the total clinical evaluation of patients, including scalp EEG, invasive EEG, neuropsychologic testing, etc. Metabolic PET studies also give insight into pathophysiologic mechanisms of epilepsy. The dynamic nature of the interictal hypometabolism observed with ^{18}[F]FDG in some patients suggests that excitatory or inhibitory neurotransmitters and their receptors may be involved. An exciting current application of PET scanning is the use of tracers for neurotransmitter receptors in the study of epilepsy patients. Mu and non-mu opiate receptors have been extensively studied and are beginning to give new insights into this disorder. Increased labeling of mu receptors in temporal neocortex using ^{11}C-carfentanil has been demonstrated and, in some patients, supplements the clinical localization information from ^{18}[F]FDG studies. Increased mu opiate receptor number or affinity is thought to play a role in anticonvulsant mechanisms. Specificity of increased mu receptors is supported by the absence of significant changes in non-mu opiate receptors. Other brain receptors are also of interest for future studies, particularly those for excitatory neurotransmitters. Combined studies of flow, metabolism, and neuroreceptors may elucidate the factors responsible for initiation and termination of seizures, thus improving patient treatment.

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Epilepsy has received renewed interest during the last decade as surgical and medical therapies have improved and pathophysiologic mechanisms have become better understood. The benefits of surgical treatment of adult and pediatric forms of medically refractory epilepsy are increasingly recognized, particularly as criteria for patient selection are refined. In this context, the role of position emission tomography (PET) scanning in identifying patients with focal blood flow or metabolic abnormalities has greatly aided surgical planning and helped to elucidate mechanisms involved in human epilepsy. To understand the place of PET scanning in the total treatment of patients with intractable epilepsy, an appreciation of clinical, EEG, and other criteria for patient selection is required.

Epilepsy is a set of clinical disorders characterized by excessive and uncontrolled electrical activity in the brain (*1*). Such electrical activity may be subclinical and therefore detectable only by electrical tests such as the EEG, or it may result in a clinical seizure. Manifestations of seizures depend upon several factors, including age of the patient, wake/sleep/intentional state of the patient, the presence of medications, and the brain site where abnormal electrical activity originates (*2*). Epilepsy may be considered a state of spontaneously recurrent seizures.

Epilepsy is one of the most prevalent serious neurologic conditions, affecting between 0.5% and 1% of the American population (*3*). Any condition that injures the brain may produce a seizure focus. Such injuries may result from significant trauma, tumor, stroke, hemorrhage, infection, or developmental abnormalities. Generalized or multi-focal seizure disorders may be produced by metabolic causes such as hypoxia, hypoglycemia, hyponatremia, drug or alcohol withdrawal, stimulant drugs, hypocalcemia, hypomagnesemia, hypothyroidism, uremia, diffuse vasculitis, demyelinating disease, and many other medical and neurologic conditions (*2*). The particular etiologies tend to be age-dependent.

Seizures present a diverse clinical spectrum, with differing pathophysiology. Table 1 lists a version of the International Classification of Seizures (*4*).

Partial (focal) seizures are those resulting from an abnormal electrical discharge in one part of the brain. Partial seizures may be simple, indicating no change in consciousness, or complex, indicating decrease or loss of consciousness. An example of a simple partial seizure might be a focal motor seizure in the right hand, arm and face, with complete preservation of awareness. Complex partial seizures have been called by many terms (*5*), most notably "psychomotor", "temporal," or "limbic" seizures. These seizures are the most prevalent type in adults. Many complex partial seizures begin with an aura or a warning of the seizure. This warning may consist of gastrointestinal discomfort, a sense of flushing or heat, perceptual distor-

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TABLE 1
International Classification of Seizures

Partial (Focal) Onset
Simple (without alteration of consciousness)
Motor
Sensory
Autonomic-visceral
Cognitive
Mixed
Complex (with alteration of consciousness)
Secondarily Generalized
Primarily Generalized
Tonic-clonic (grand mal)
Absence (petit mal)
Myoclonic
Tonic
Clonic
Atonic
Unclassified

tions, or cognitive alterations. Such auras are actually simple partial onsets to complex partial seizures. During a complex partial seizure, by definition, awareness and memory are blunted. The patient frequently performs automatisms such as lip smacking, hand rubbing, or aimless fumbling. Duration of partial seizures varies from approximately 10 sec to 10 min.

The other major category of seizures is primary generalized seizures (*6*). These appear to start bilaterally in the brain and show no clinical focal onset. The pathophysiology remains uncertain, but it is presumed that subcortical synchronization mechanisms are relevant. One type of generalized seizure is the generalized tonic-clonic seizure, formerly called "grand mal." During the tonic stage, there is stiffening and during the clonic stage, rhythmical jerking. Consciousness is lost immediately in generalized tonic-clonic seizures. Another type of generalized seizure is the primary generalized absence seizure, previously known as "petit mal" (*7*). This is predominantly a disease of childhood onset, including staring for several seconds. Consciousness is partially blunted during generalized absence seizures, but motor activity is usually fairly mild. Other generalized seizure types such as atonic drop attacks, myoclonic jerking, and mixed forms may occur. Any partial seizure may generalize secondarily via synaptic and extrasynaptic pathways of the brain.

A seizure is also referred to as an "ictus." The time between seizures is called "interictal," and immediately after a seizure, "postictal." Electrical abnormalities are usually recorded during a seizure and may or may not be recorded in the interictal stage. When such electrical abnormalities do occur, discoverable by scalp or invasive EEG, they represent synchronous discharge of a group of neurons. Both excitatory and inhibitory electrochemical brain processes are detectable in the scalp EEG (*8*).

Considerable research has been devoted to an understanding of the basic mechanisms of epilepsies (*9*). Seizures result when there is an imbalance between excitatory and inhibitory processes in the brain. Excitatory processes are especially dependent upon the excitatory postsynaptic potential, mediated by a variety of excitatory neurotransmitters (*10*). The most important of these is glutamic acid (*11*). Additional excitatory processes occur at a membrane level secondary to voltage-dependent channels in membranes that govern transmembrane flow of ions. The regenerative Hodgkins-Huxley sodium channel is one example; the voltage-dependent calcium channel is another (*12*). The most important inhibitory process in the brain is the inhibitory postsynaptic potential (IPSP). Gamma-amino-butyric acid (GABA) is the primary inhibitory neurotransmitter in the forebrain (*13*). Certain intrinsic membrane channels give rise to inhibitory currents in some neurons that control excess excitation (*14*). Furthermore, metabolic pumps may subserve inhibitory functions. Over 100 endogenous neuroactive compounds influence the ongoing balance between brain excitation and inhibition (*15*). The mechanism of many of these is mediated by neuroreceptor systems on pre- or postsynaptic cells. Several of the neuromodulators exert effects through membrane or cytosolic second-messenger systems (*16*).

Study of epileptic mechanisms is dependent upon animal models of the epilepsies (*17*). These models can be produced with manipulations (such as pharmacologic antagonists) for GABAergic inhibition, or conversely by providing excess analogs of excitatory transmitters, such as glutamate. Unfortunately, no animal model completely depicts the clinical disorder. For example, brain tissue density of GABAergic terminals may be increased in one model of epilepsy (*18*) and decreased in another (*19*). It is therefore important to study the human disorder and the abnormalities associated with clinical epilepsy. PET scanning plays a role in this area of study.

DIAGNOSIS AND MEDICAL TREATMENT

The key to the diagnosis of epilepsy is the elicitation of a history of stereotyped episodes involving alteration of sensory or motor function, behavior, or consciousness. It is very helpful to document abnormal brain electrical activity (*20*), but this is not always possible. Figure 1 illustrates a rhythmical ictal discharge arising from the left temporal region in scalp EEG recorded at the start of a complex partial seizure, observed during prolonged video-EEG monitoring. Such a discharge would likely be associated with confusion and automatic behaviors. Rhythmic ictal activity can spread from one region of the brain to another (Fig. 2). This may cause various regions anatomically remote from the initial site of seizure origin to become metabolically active—an important factor for meaningful interpretation of PET scans.

Physical findings between seizures are only occasionally helpful, at times indicating a developmental or acquired neurologic disorder of a type associated with epilepsy.

Other disorders are often mistaken for epilepsy, includ-

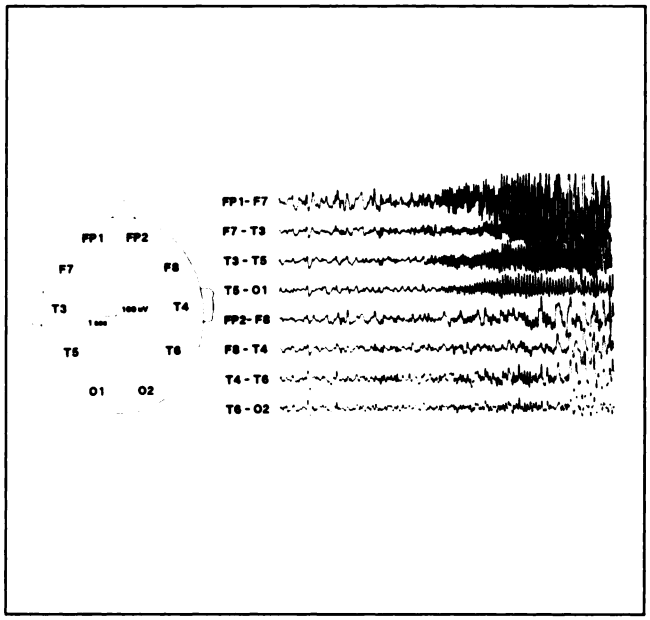

FIGURE 1. An EEG tracing recorded from scalp during continuous monitoring to illustrate rhythmical spiking at the start of a complex partial seizure. For purposes of visual clarity, only 8 of 32 channels are shown. Abnormal activity begins with irregular 2–3 per second slow activity in the left fronto-temporal region (top channel), followed by rhythmical spiking, spreading to neighboring areas. The patient exhibited concurrent staring, fumbling, and confusion. Electrode nomenclature in this and following figures is in accordance with the international 10–20 electrode system.

ing syncope, cerebrovascular disease, complicated migraine headaches, cardiac arrhythmias, hypoglycemia, vertigo, sleep disorders, intermittent movement disorders, and a wide variety of psychologic processes (*21,22*). In the absence of direct clinical and EEG evidence, the diagnosis of epilepsy is based primarily on history and the exclusion of other conditions that may imitate epilepsy.

Approximately twenty anticonvulsant drugs are available to suppress seizures in people suffering from epilepsy (*23*). These medications do not cure the underlying process of epilepsy but only suppress the seizures. More than two out of three patients can be satisfactorily controlled with existing anticonvulsant medications (*24*). The remainder are therapeutic failures because of continued seizures or unacceptable side effects of the medications. Some of these individuals are candidates for epilepsy surgery to ablate the seizure focus.

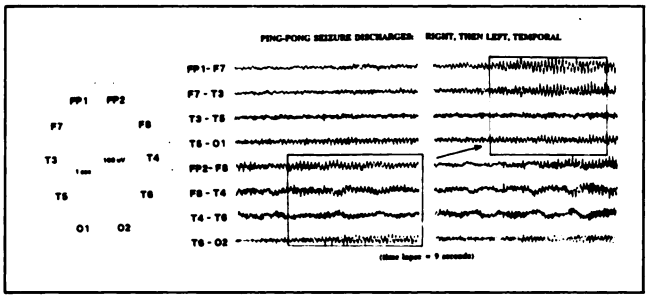

FIGURE 2. Abnormal rhythmical activity spreading from right to left temporal regions during the evolution of a seizure. This common pattern can complicate interpretation of metabolic localization studies.

EPILEPSY IN CHILDREN

Epilepsy is common in children. Idiopathic epilepsy usually begins in childhood or adolescence (*3,25*). Certain seizure types, e.g., generalized tonic-clonic (grand mal) seizures, secondarily generalized seizures, and complex partial seizures, occur in all age groups. Other seizure types specifically occur in the pediatric age group (*26*). Among these are neonatal seizures (*27*), febrile seizures (*28*), infantile spasms of West (*29*), and most primary absence (petit mal) seizures (*30*). The Lennox-Gastaut syndrome is primarily, but not exclusively, a disease of children. This syndrome is characterized by the presence of multiple seizure types, including atonic drop attacks, with variable degrees of mental retardation and slow spike-wave patterns on the EEG (*31,32*).

The prognosis of most childhood epilepsy is very good; unfortunately, this is not the case for children with infantile spasms and the Lennox-Gastaut syndrome. Medical therapy for Lennox-Gastaut syndrome is often ineffective. Surgical therapy is also difficult, because electrical discharges and brain abnormalities are usually diffuse, and a single focus cannot be found. PET scanning recently has been shown to play a role in localization of the predominant regions of cortical dysfunction in children with intractable seizure disorders (*33–35*).

EPILEPSY SURGERY

If electrical abnormalities associated with seizures originate in a well-circumscribed and consistent region of brain, and if this region of brain is susceptible to removal without major postoperative deficits, then seizure surgery can be curative (*36*). Several hundred patients undergo epilepsy surgery in the United States each year, although the number of potential candidates for such surgery has been estimated to be as high as 20,000–100,000 (*37*). The most important and most commonly performed procedure is anterior temporal lobectomy in treatment of complex partial (temporal lobe) seizures (*38*). Operations can also be performed on frontal, parietal, or occipital lobes when testing discloses well-localized seizure foci in these regions. In some neuroradiologic studies, such as CT scans, MRIs and angiograms can demonstrate an underlying structural lesion, such as increased white matter signal on MRI or a region of atrophy (*39,40*). This can serve as a pointer to the surgical approach. Unfortunately, in many cases no lesion is visible and the localization of the focus has to rely upon electrodiagnostic studies. Occasionally, lesions are not helpful in localization of a seizure focus because the processes generating the lesion and the seizure are inde-

pendent, or because the seizure focus is in a limited region of the boundary of the lesion. Electrodiagnostic studies are critical in such cases to localize the seizure focus.

Electrodiagnosis of epilepsy may be accomplished with scalp EEG recordings; however, scalp recordings may fail to demonstrate a clear-cut seizure focus in as many as 20%–40% of patients who ultimately are found to be good surgical candidates (*41*). Therefore, special techniques are often used to localize the seizure focus (*42*). The approach varies among different institutions. Some institutions favor extensive use of scalp recording with extra electrodes to enhance spatial resolution; some insert epidural electrodes or strips of electrodes bilaterally to obtain cleaner and more accurate EEG recordings; and others employ depth wires implanted into deep frontal or temporal regions, either unilaterally or bilaterally, to map seizure foci. A relatively new approach is employment of subdural stimulating-recording grids (*43–45*). These grids are sheets of disk electrodes in flexible plastic, designed to be fitted directly over the surface of the brain. Subdural electrodes allow precise recording of seizure topography, provided that the grid is placed over the general location of the seizure focus. Electrical stimulation can also be performed via the grid to map underlying functional regions of the cortex related to sensory motor activity, language, and other higher cognitive functions (*43*).

A 1986 meeting in California (*36*) and a recent NIH consensus conference (*46*) disclosed the variability in approach to treating patients for epilepsy surgery among different centers. At the Johns Hopkins Epilepsy Center, we recommend the following approach. First, we must be convinced from the clinical history that the patient is suffering from seizures and not one of the imitators of epilepsy. Furthermore, the seizures should be severe enough to disrupt their lives. No specific number of seizures serves as a criterion for whether a patient is a surgical candidate. Those individuals untroubled by daily complex partial seizures are not candidates for surgery, whereas others may have complex partial seizures every few months, yet feel great distress at the resulting limitations (e.g., the ability to drive, employment and social relationships), and justifiably seek surgery.

Before consideration of surgery, studies should be performed to look for underlying lesions or metabolic causes that would require independent treatment. Medical therapy should be managed according to standard principles (*47*) and shown to be ineffective in controlling the seizures. Medication therapy is generally considered preferable to surgical therapy, unless it does not work or results in unacceptable toxicity, because the risk is less than that of surgical therapy. General cognitive and psychosocial evaluation should be performed to demonstrate that the patient is likely to benefit from surgery and that widespread disturbances of brain function are not present, making local resection less likely to be curative.

If an individual is considering seizure surgery, then the seizure focus must be localized. The first approach is interictal scalp EEG. Epileptiform spikes and sharp waves usually correlate with the site of origin of the seizures, but not always. It is therefore useful to monitor the patient with continuous video-EEG monitoring to observe the EEG pattern during several typical seizures. Ideally, five or more seizures should be recorded over a span of time in order to determine whether the seizures begin at one or several foci or are apparently generalized from the start. Computer analysis of the EEG helps to detect patterns and map the spatial distribution of EEG abnormalities (*42*). Video correlation can ensure that the patient's symptomatic seizures are treatable and may also give independent clues to help localize where the seizure begins. If, for example, the right hand starts twitching early in the seizure, then it is suggested that the focus is likely to begin in the left motor cortex. More than one scalp recording session may be necessary over a period of a few days or weeks to localize the seizure focus.

Invasive recordings are necessary in some patients. Depth wires, epidural, or subdural grids can help to define the region of electrical abnormality, but require craniotomy and associated risks. With depth wires, a few percent of the patients will have minor hemorrhage or infection, and a smaller number will have a more serious complication (*37*). Subdural grids can cause cerebral edema and in approximately 4% of cases significant infection requiring prolonged antibiotic therapy (*43*). Because of the risks of invasive electrodes, noninvasive techniques to localize a seizure focus, such as PET, are of great importance, and may obviate the need for invasive techniques in some cases (*48*).

PET SCANNING IN EPILEPSY

Early in the last decade, the UCLA group (*49*) observed decreased glucose metabolism in the region of a temporal seizure focus, using fluorine-18-fluorodeoxyglucose (FDG) as a marker of glucose metabolism. These findings were subsequently supported by larger studies (*50–57*). It has been observed that the hypometabolic regions defined by PET are generally larger than the area identified as the seizure focus with invasive electrical recordings, reflecting secondary inhibition of surrounding areas by the seizure focus, a larger disease process leading to the seizures, or a loss of neuronal tissue. A PET scan obtained during a complex partial or secondarily generalized seizure often demonstrates hypermetabolic activity at the focus. PET scans during generalized spike and wave discharges have been found by some groups to give variable results with either increased, decreased, or unchanged metabolism, possibly because a postictal hypometabolic period is averaged over time with the hypermetabolic ictal period (*58*). PET studies may have a role to play in elucidating mechanisms of certain developmental disorders (*33*).

PET abnormalities identify only the approximate region of a seizure focus, and not necessarily the specific area that

gives rise to the abnormal discharge. Hypometabolism may be greatest in lateral neocortex, even when depth EEG indicates that the seizures originate in the mesial temporal lobe (*59*). A recent study showed that ipsilateral thalamic and, to a lesser extent, frontal, parietal, and basal ganglia hypometabolism may be present in temporal lobe epilepsy (*60*). Thus, PET may perform a useful function in the presurgical evaluation to distinguish temporal from extra-temporal seizure foci, and to identify laterality of seizure origin, but it is not as accurate as electrodes in providing a "micro-map" of the region to be resected.

Children are particularly amenable to surgical treatment of epilepsy due to the enhanced plasticity of the developing brain. Accordingly, functions subserved by the resected regions are much more easily taken over by remaining tissue than in the adult brain. The effectiveness of seizure surgery for intractable epilepsy in childhood and the role of PET are well documented (*35,60–67*). In comparison with other noninvasive modalities such as x-ray CT, MRI, and scalp EEG, PET provides more accurate localization of seizure foci as identified by neuropathology and intraoperative corticography. Indeed, there is good correlation between the hypometabolic areas seen on PET and intraoperative corticography (*65*). PET is also useful in assessing the functional integrity of brain tissue beyond the region of potential resection. The functional reorganization taking place during postsurgical recovery may also be monitored. Although PET provides much needed information in childhood seizure disorders, it must still be used in conjunction with x-ray CT, MRI, and EEG when identifying surgical candidates.

We forego invasive recordings in adult subjects when: scalp EEG interictally and ictally shows consistent focus in one temporal lobe anteriorly, no lesion evident in other regions by MRI, neuropsychology and cognitive testing consistent with the suspected side of origin, and when an FDG scan localizes a hypermetabolic region interictally to the suspected epileptic focus. This approach is consistent with the results of a recent retrospective study in 153 patients with medically intractable epilepsy (*67*). This large study compared results from invasive and surface EEG and FDG-PET scanning, evaluating sensitivity and specificity of each with regard to lateralization and localization of seizure foci. It concluded that the risks of invasive electrode monitoring for anterior temporal lobectomy could not be justified when specific criteria for focal scalp-spenoidal ictal EEG onsets are met and when localized hypometabolism is observed that predominantly involves the same temporal lobe. If features are inconsistent, then a form of invasive recording must be seriously considered.

NEURORECEPTOR IMAGING IN EPILEPSY

Electroencephalography is the mainstay of diagnosis, classification, and lesion identification in epilepsy, as discussed above. Accordingly, abnormal brain electrical activity is the sine qua non of epilepsy. However, few of the molecular, ionic, and cellular processes that underlie the electrical events in human epilepsy are yet known. While PET has advanced our understanding of the basic ictal and interictal blood flow and metabolic events in human epilepsy (*51,64,68,69*), these types of measurements alone are limited in their potential to elucidate the neurochemical mechanisms responsible for initiation and termination of seizures. Metabolic PET imaging has become an established tool for the clinical treatment of seizure patients, but new methods are needed to further improve localization of the epileptogenic foci, predict prognosis following seizure surgery, and stratify patients for various drug therapies.

As metabolic studies in epilepsy have continued to be developed and applied clinically, parallel investigations have provided evidence that a number of excitatory and inhibitory neurotransmitters and their receptors play a role in seizure mechanisms. These studies were carried out initially in experimental models of epilepsy and subsequently applied to human brain tissue from patients treated surgically for epilepsy (*70–75*). Recent advances in PET imaging permit the extension of these types of studies to in vivo measurements in epilepsy patients (*76–81*). Although there are numerous neuroreceptors and their transmitters of interest for PET studies in epilepsy, the majority of studies have been performed to image opiate receptors.

Endogenous Opioids, Opiate Receptors, and Epilepsy

During the last decade a large number of studies have been carried out, using experimental models of epilepsy to investigate anticonvulsant, and in a few cases convulsant, effects of endogenous and exogenous opioid substances (*82,83*). The earliest studies suggested that opioid peptides were endogenous convulsants based on the production of bursts of epileptiform EEG discharges in rat brain *without* true convulsive seizures. Subsequent studies suggested that this effect was the result of presynaptic disinhibition of inhibitory pyramidal interneurons in the rat hippocampus. These observations were found not to generalize to species other than the rat. The consensus of recent studies using the opiate antagonist naloxone is that the endogenous opioids and opiate receptors do not, in fact, play a prominent role in the initiation of seizures.

There is evidence of a role for opioid systems in the suppression of seizures in a variety of experimental models of epilepsy in several species (*82*). Naloxone-reversible, anticonvulsant effects of opioid peptides have been documented in mice, rats, gerbils, rabbits, and baboons by the use of chemical, electrical, and genetic experimental models of human epilepsy. Furthermore, seizures result in the release of an anticonvulsant substance into cerebrospinal fluid (CSF) and the effects of this substance can be reversed by naloxone. Immunoreactivity studies indicate the presence in CSF of a beta-endorphin-like substance and a [MET]enkephalin precursor. Current evidence also

suggests that the anticonvulsant effects of both peptide and nonpeptide opioids can be mediated through mu, delta, or kappa opiate receptors.

The opiate antagonist naloxone affects ictal and interictal EEG activity in human epilepsy patients. Most recently, Molaie and Kadzielawa studied the effect of all-night continuous infusion of 10 mg of naloxone on focal interictal epileptiform discharges in eight patients with complex partial seizures (*84*). Patients with a high baseline level of interictal discharges (n = 5) displayed a 20%–67% increase in interictal discharges during the naloxone infusion. The remaining patients with infrequent interictal discharges demonstrated no effect of naloxone. These human data are consistent with the inhibition by naloxone of an endogenous inhibitory effect of opioid peptides, and the possible existence of an opiate receptor-mediated endogenous anticonvulsant system in human epilepsy. Supporting this notion is the recent study demonstrating increased levels of CSF in enkephlin in epilepsy patients (*85*).

The cumulative evidence suggests that opioid peptides are more involved with the termination of seizures than with seizure initiation or propagation. Further evidence of a role for opioid systems in seizure mechanisms derives from the observation that opiate receptors are also altered following experimental seizures (*86–88*).

Mu-opiate Receptor Imaging Using ^{11}C-Carfentanil

The highly mu-selective opiate agonist carbon-11-(^{11}C) carfentanil has been used to image and quantify mu opiate receptors in normal subjects and those with temporal lobe epilepsy (*89*). Presently, 40 patients with partial complex epilepsy and a unilateral temporal lobe seizure focus have been studied using ^{11}C-carfentanil and FDG. All patients had a diagnosis of idiopathic epilepsy without significant structural abnormalities as demonstrated by contrast-enhanced x-ray computed tomography (CT).

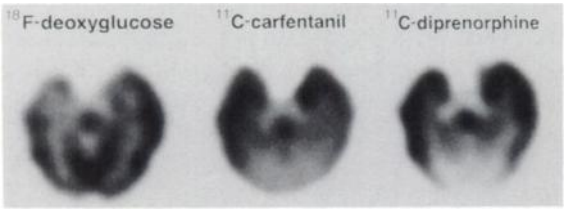

FIGURE 3. Carbon-11-carfentanil, ^{11}C-diprenorphine, and [^{18}F] FDG PET images in a 26-yr-old right-handed woman with left-sided temporal lobe seizures. In the CFN study (left image), a 70% increase in mu opiate receptor binding in the mid- and posterior temporal neocortex and a 40% decrease in binding in the amygdala are present in the left temporal lobe ipsilateral to the EEG focus. In the DPN study (center image), there is a 15% increase in binding in the left temporal cortex compared to the contralateral side, but this increase was not statistically significant in the analysis of all patients. In the FDG study (right image), there is diffuse hypometabolism (~30%) involving the amygdala and temporal neocortex in the electrically abnormal left temporal lobe.

Results from these studies demonstrate a significantly elevated mu opiate receptor binding in the temporal neocortex ipsilateral to the seizure focus (Fig. 3). The mean elevation is about 35% compared to the contralateral temporal lobe, although values range from little or no asymmetry to as much as a two-fold elevation in the ipsilateral cortex. In the first reported series of patients, mu opiate receptor binding in the amygdala was not significantly different in EEG focus and nonfocus temporal lobes, although some patients did show reduced binding in the ipsilateral cortex (*89*). The second series of patients (n = 1) were studied following MRI-based localization of the amygdala (*90*) and did demonstrate significantly reduced amygdala binding (*91*).

The increases in mu receptor binding in the temporal neocortex, as opposed to mesial temporal lobe structures from which seizures are thought to originate, suggest activation of an endogenous anticonvulsant mechanism involving endogenous opioids. Thus, elevated opiate receptors may serve to limit the propagation of seizures from their sites of origin. We have not found a correlation between increased opiate receptor binding and clinical parameters such as seizure frequency, age of onset, and disease duration. The observation that the opiate system is primarily involved in the termination of seizures in experimental models suggests that the duration of individual seizures would be an important parameter to correlate with changes in mu opiate receptor binding. Unfortunately, the duration of individual seizures is difficult to document outside the context of 24-hr-a-day monitoring. The subset of patients with a history of status epilepticus would be predicted to have normal or reduced mu opiate receptor binding; this hypothesis is to be tested in future studies.

In our most recent series of patients, mu opiate receptor binding in the amygdala was significantly reduced in many subjects. Whether this change reflects damage and cellular loss in the amygdala or abnormal regulatory mechanisms is yet unknown. Conceivably, decreased opiate-mediated inhibitory processes in the amygdala could facilitate generation and propagation of seizure activity.

Elevated ^{11}C-carfentanil binding is commonly observed in regions of reduced glucose utilization demonstrated by [^{18}F]FDG (*89*). In 34 patients studied with ^{11}C-carfentanil and [^{18}F]FDG, the reduced metabolism ipsilateral to the temporal lobe seizure focus was observed in only 68%. In the remaining 32% of patients with nondiagnostic FDG scans, a significant number displayed increased ^{11}C-carfentanil binding ipsilateral to the seizure focus. Accordingly, the combined use of [^{18}F]FDG and ^{11}C-carfentanil resulted in an overall sensitivity in correctly lateralizing the seizure focus of 93% in this preliminary series. The sensitivity of ^{11}C-carfentanil alone was similar to that of [^{18}F]FDG. These results demonstrate the potential complementary role of metabolic and receptor imaging studies in seizure lateralization.

Mu and Non-Mu Opiate Receptor Imaging Using ^{11}C-Carfentanil and ^{11}C-Diprenorphine

Mu, delta, and kappa opiate receptors each play a role in anticonvulsant mechanisms; it is therefore of interest to know if non-mu (i.e., delta or kappa) opiate receptors are altered in human epilepsy. Is non-mu opiate receptor binding elevated in temporal neocortex, similar to mu opiate receptor binding, or does a different pattern of change exist? Since mu, delta, and kappa opiate receptors are present in different nerve cell populations, as evidenced by their differential distribution within cortical layers and various amygdala nuclei, one might not expect parallel changes among these three opiate receptor subtypes.

Ligands for selectively labeling delta or kappa opiate receptors using PET do not yet exist; however, diprenorphine, a high-affinity weak partial opiate agonist, has high and similar affinity for mu, delta, and kappa opiate receptors. Carbon-11-diprenorphine has been used to localize and quantitate opiate receptor binding in man using PET (*92*). Comparative studies were performed in normal volunteers using ^{11}C-carfentanil and ^{11}C-diprenorphine to evaluate differences in regional binding in relation to the known differences in the localization of opiate receptor subtypes in the brain. Carbon-11-diprenorphine showed much higher labeling of cerebral cortex, cingulate cortex, and basal ganglia compared with ^{11}C-carfentanil, consistent with in vivo labeling of non-mu opiate receptors. Accordingly, non-mu opiate receptor binding can be evaluated in parallel studies conducted in the same individual using ^{11}C-diprenorphine and ^{11}C-carfentanil.

This approach has been applied to 11 patients with unilateral temporal lobe epilepsy who were studied with ^{11}C-carfentanil, ^{11}C-diprenorphine, and [^{18}F]FDG (*91,93*). There was a 35% mean elevation in ^{11}C-carfentanil binding in the temporal neocortex ipsilateral to the seizure focus, corresponding to an average reduction in cerebral metabolism of about 15%. Carbon-11-carfentanil binding and regional metabolism were reduced approximately 10% in the amygdala. In contrast to the elevations in ^{11}C-carfentanil binding, ^{11}C-diprenorphine displayed symmetric binding in all temporal lobe regions in the group analysis. A plausible explanation of this difference is an increase in delta or kappa opiate receptors ipsilateral to the seizure focus. This has also been observed in preliminary studies using ^{18}F-cyclo-foxy, a nonselective opiate antagonist (*94*). This is most likely due to a reduction in kappa opiate receptor binding since delta receptors are normally low in cerebral cortex. Indeed, a number of patients displayed clearly reduced ^{11}C-diprenorphine binding in the ipsilateral temporal cortex. These results suggest a role for kappa or delta opiate receptors in human epilepsy and, more importantly, demonstrate the specificity of increased mu-opiate receptor binding.

Future studies using kappa- or delta-selective PET ligands will further elucidate the role of non-mu opiate receptors in epilepsy and further enhance applications to clinical management of patients with intractable epilepsy. Studies of other receptors are just beginning, but they do represent fertile ground for future studies. For example, a recent study of benzodiazepine receptor binding using ^{11}C-Ro 15-1788 and PET demonstrated a mean reduction in receptor number in the epileptic focus (29%) of 10 patients with idiopathic epilepsy (*95*).

CONCLUSION

Epilepsy is a complex disorder, but PET scanning, a relatively new technology compared with EEG, is beginning to shed light on its nature. PET has demonstrated clinical value for localizing seizure foci and, in some cases, has supplanted the need for invasive EEG monitoring. Nonetheless, the mechanism of hypometabolism interictally remains controversial. Recent anecdotal reports of intrasubject changes in interictal and postictal flow and metabolism suggest that dynamic mechanisms are involved in regulating neural activity, perhaps representing alterations in neurotransmitters and their receptors. However, the interpretation of ligand binding data is not simple in vivo, since they can result from alteration in the number of receptors, affinity, or the occupancy of receptors by endogenous unlabeled compounds. Some of the most important neurotransmitters involved in epilepsy, such as GABA, can presently be investigated by PET only indirectly (i.e., through benzodiazepine binding sites), and tracers for the excitatory amino acids are unavailable. Alteration in receptor number or affinity may be secondary to seizures, or in some way causative, or even an epiphenomenon. Experiments to distinguish these possibilities are difficult in the clinical setting and are best addressed through animal models. Nonetheless, identification of a receptor or other biochemical marker that maps the distribution of interictal or ictal electrical abnormalities would represent a great advance in noninvasive evaluation of patients and planning of seizure surgery. It is uncertain to what extent hypometabolism or receptor changes with PET reflect a long-term history of a seizure focus, and to what extent they are biased by the recent history of seizures. This would be an important issue in patients who have shifting bilateral seizure foci.

PET has proven itself a useful and practical tool to assist the clinician in detecting seizure foci in patients being considered for epilepsy surgery. Further applications of PET will increase our understanding of epilepsy and may ultimately reveal its primary and secondary neurochemical causes.

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