127

TEMPORAL LOBE EPILEPSY: RENEWED EMPHASIS ON EXTRAHIPPOCAMPAL AREAS

ROBERT SCHWARCZ
HELEN E. SCHARFMAN
EDWARD H. BERTRAM

Epilepsy is a chronic condition characterized by spontaneously recurring seizures. Although often viewed and discussed as a single clinical entity, epilepsy is a symptom of several disorders that affect the brain. The variety of causes is quite extensive and includes tumors, congenital malformations, genetic alterations in receptors or channels, and acquired structural abnormalities such as those following trauma or infection. Some of the epilepsies with inborn causes, such as rolandic epilepsy, are self-limited and benign, whereas others are progressive (1). The seizures in some forms of epilepsy may arise from the entire brain at one time, whereas in other forms they start in a particular region or focus. Any region of the brain can serve as a seizure focus, but seizure onset is commonly observed in the temporal lobe. Although there are multiple causes for epilepsy originating in the temporal lobe, the most common form is the *mesial temporal lobe epilepsy syndrome* (MTLE), sometimes also termed *limbic epilepsy* because of the apparent involvement of one or more limbic brain regions (2).

MTLE has been recognized as a distinct entity for many years. The common clinical pattern during the seizure episode includes staring and lack of responsiveness, frequently accompanied by automatisms of hand activity and mastication. There is often (but not always) a history of prolonged febrile convulsions in early childhood and common pathologic features of atrophy and neuronal loss in the hippocampus, a structure located on the medial border of the temporal lobe. Seizure onset is frequently detected in the hippocampus when EEG depth recordings are made directly from this area in patients undergoing evaluation for surgical treatment of uncontrolled seizures. Removal of the hippocampus (together with adjacent structures) often successfully controls seizures in ''intractable'' patients whose seizures do not respond to medication (2). For these reasons, a general consensus has developed that the hippocampus is the key to understanding and treating limbic epilepsy, and much of the research directed at MTLE has focused on this area of the brain. However, there is increasing evidence that other structures of the limbic system, such as the amygdala, parts of the neocortex, and the entorhinal cortex, which is a phylogenetically older part of the cortex that controls the information flow into and from the hippocampus (3), also play important roles in the initiation and propagation of seizures in MTLE.

Support for the involvement of nonhippocampal limbic sites in MTLE comes from a variety of sources. As reviewed in this chapter, extrahippocampal areas frequently show pathologic structural changes on histologic examination. Intracranial recordings from patients undergoing evaluation for therapeutic epilepsy surgery often present with a pattern of diffuse limbic onset without a regional predilection (4, 5). Imaging studies have also indicated that there is atrophy or metabolic change in medial temporal structures other than the hippocampus, as well as in subcortical structures with limbic connections (6–8). Surgical results have suggested that it is necessary to remove more than the hippocampus to achieve successful outcome (9,10). Finally, there is ample evidence from a variety of animal models of limbic epilepsy that extrahippocampal sites participate in epileptogenesis, demonstrate anatomic and neuropathologic changes, and show alterations in cellular physiology. In many instances, changes in these regions are greater than those seen in the hippocampus.

The advent of new imaging techniques, the development of several useful new animal models of limbic epilepsy that closely parallel the human condition, and improved means

Robert Schwarcz: Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, Maryland.
Helen E. Scharfman: Neurology Research Center, Helen Hayes Hospital, West Haverstraw, New York.
Edward H. Bertram: Department of Neurology, University of Virginia Medical Center, Charlottesville, Virginia.

for studying neuronal physiology *in vivo* and *in vitro* have provided new opportunities to explore the role and fate of extrahippocampal brain regions in MTLE. In this chapter, we review current knowledge of the neuropathology, physiology, anatomy, and neurochemistry of MTLE and compare the hippocampus with extrahippocampal limbic regions. In closing, we briefly explore how new research directions resulting from recent data may lead to novel and improved treatments of MTLE.

NEUROPATHOLOGY

Hippocampus

The notion of a central role of the hippocampus in MTLE can be traced to a highly influential review article by Sommer, which was published toward the end of the nineteenth century (11). As a young physician at the 'insane asylum'' in Allenberg, Germany, Sommer reviewed the anamneses and corresponding neuropathologic features of 90 patients with epilepsy, only five of whom had been patients at his institution. After pointing out that ''there can be no question that epileptic symptoms are frequently associated with a disease of the Ammon's horn,'' as others had suggested before, he made the ground-breaking observation that patients presented with a preferential degeneration of a band of pyramidal cells termed the CA1 subfield (the *Sommer sector*) of the hippocampus proper (12). With astounding foresight, he concluded that the cell loss was a consequence of prolonged seizure activity and that both head trauma and developmental malformations ought to be considered etiologically important factors in epilepsy. Sommer also noted that neurodegenerative changes in patients with epilepsy are frequently detected in areas surrounding the hippocampus, namely, in the subiculum and in the temporal and occipital cortices. He remarked that ''it is not unlikely that a single underlying defect spreading through several anatomically linked brain areas accounts for the various clinical manifestations of the epileptic syndrome.''

During the first half of the twentieth century, Sommer's pioneering insights and predictions were confirmed and refined by many investigators studying brain pathology post mortem. This period was increasingly dominated by the question whether ''idiopathic'' seizure activity causes neurodegeneration or, conversely, epilepsy occurs only as a sequela of brain damage. The chicken-egg debate, which has not been entirely resolved to this day, was accompanied by uncertainties about the nature of putatively epileptogenic insults, such as respiratory difficulties and asphyxia, infectious diseases leading to encephalitis, and, in particular, vascular abnormalities (13). The advent, in the 1930s, of surgical interventions for the treatment of MTLE revolutionized clinical management of the disease and at the same time provided invaluable information for research purposes (14).

Histologic analysis of excised brain tissue and correlations between the nature of removed temporal lobe structures and surgical outcome unequivocally established the centrality of the hippocampus and associated ''limbic'' brain regions in MTLE *(psychomotor epilepsy).* By the 1950s, support had developed among leading epilepsy researchers for the concepts that MTLE (a) was a ''network'' disorder, caused by abnormal interactions between a limited number of highly interconnected areas within the temporal lobe, and (b) in many cases originated in, and could be treated by removal of, extrahippocampal structures (15). Thus, irrespective of the cellular and molecular events underlying epileptogenesis and the eventual development of spontaneously recurring seizures, which soon were to become the focal points of epilepsy research, brain structures such as the entorhinal and perirhinal cortices and the amygdala were viewed as the critical components of the seizure network.

Studies of the hippocampus of patients with MTLE that used more recent neuroanatomic techniques revealed several signature abnormalities, which, alone or in concert, are suspected to play a critical role in the pathophysiology of the disease. These changes are often seen in conjunction with pronounced neurodegeneration in area CA1 and in the so-called end folium, which includes polymorphic neurons in the hilus of the dentate gyrus and proximal ''CA4'' pyramidal cells (16) (Fig. 127.1A).

Probably the most reliable changes occur in glial cells, which increase in size and number (astrocytes) or change their shape to resemble phagocytotic macrophages (microglia) more closely (17–19). Because of their special biochemical and biophysical properties, these abnormal glial cells are believed to play an active role in the disease process, either by containing or actively enhancing seizure spread (see later).

Of particular interest is the sprouting of mossy fiber axons of surviving excitatory granule cells, which can be visualized by Timm staining or by immunohistochemistry using antibodies against the neuropeptide dynorphin (20). It is often assumed that the new, sprouted fiber network, which has been shown to form recurrent excitatory connections with preexisting neurons (21), may predispose the region to hyperexcitability (22). However, axons also sprout from surviving inhibitory neurons (23), and these novel axons have been proposed to impede chronic hippocampal hyperexcitability (24).

Extrahippocampal Areas

Triggered by new information about the anatomic interconnections in the normal brain and by the results of noninvasive imaging studies of MTLE patients (see later), the 1990s also witnessed a renewed interest in the neuropathology of extrahippocampal temporal lobe lesions in MTLE. As mentioned earlier, lesions in the parahippocampal region or the amygdala, in particular, had been considered among the defining hallmarks of MTLE in earlier days, but they were

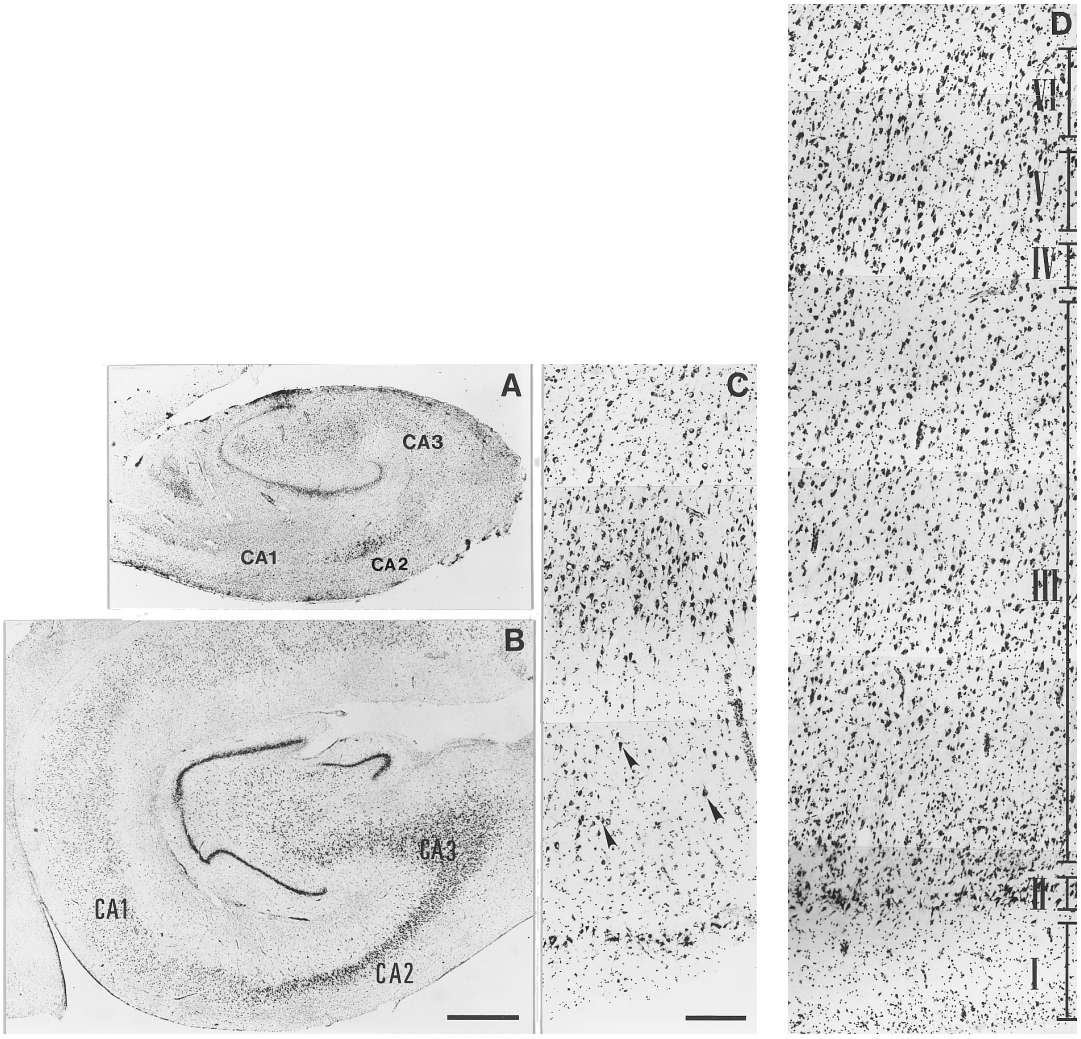

FIGURE 127.1. **A** and **B:** Nissl-stained coronal sections through the rostral portion of the hippocampus taken from a patient with MTLE **(A)** and a control subject **(B).** Note the pronounced neuronal loss and gliosis in areas CA1 and CA3 in the patient with epilepsy. Moreover, the epileptic hippocampus is substantially reduced in size compared with the control. **C** and **D:** High magnification of portions of the olfactory field of the entorhinal cortex from a patient with MTLE **(C)** and a control subject **(D).** Note the substantially reduced width of layers I to III of the entorhinal cortex of the patient with epilepsy. *Arrowheads* in **C** indicate surviving neurons. I to VI, layers of the entorhinal cortex. Scale bars: 1.5 mm in **B** and also in **A;** 200 μm in **C** and also in **D.** (From Du F, Whetsell WO Jr, Abou-Khalil B, et al. Preferential neuronal loss in layer III of the entorhinal cortex in patients with temporal lobe epilepsy. *Epilepsy Res* 1993;16:223–233, with permission.)

less appreciated during a more than 20-year hiatus, ranging essentially from the landmark publication of Margerison and Corsellis (16) to the equally influential monograph of Bruton (25).

In the entorhinal cortex, neuropathologic changes are most readily observed in the superficial layers of the anterior portion of this six-layered parahippocampal structure. Patients frequently present with a characteristic pattern of neuronal loss and associated gliosis, with layer III being preferentially affected and layer II showing pronounced disorganization and some cell loss (26) (Fig. 127.1C). Neuron loss in layer III of the rostral entorhinal cortex can reach dramatic proportions, with only a few, probably γ-aminobutyric acid (GABA)–ergic, cells surviving. This lesion is almost singularly responsible for the substantial tissue shrinkage often described in the epileptic entorhinal cortex (15,26). Because pyramidal cells of layer III normally give rise to the monosynaptic "temporoammonic" pathway to area CA1 of the hippocampus (27), their degeneration in MTLE may lead to deafferentation-induced changes in hippocampal excitability, and such changes have indeed been observed in animals (28). Neuropathologic changes in layer

II of the entorhinal cortex, the origin of the major input to the granule cells of the dentate gyrus (the "perforant path"), may also contribute to hippocampal hyperexcitability in MTLE.

Neuronal loss and gliosis in the amygdala are frequently seen in MTLE and often occur in conjunction with lesions in other parts of the limbic system (29,30). Although the pattern of cell loss has so far not been analyzed in great detail, degenerative events appear primarily to affect the ventromedial aspects of the lateral amygdaloid nucleus and the parvicellular region of the basal nucleus (31). Based on published studies, this relatively restricted damage not only impedes processing of sensory information in intraamygdaloid circuits, but may also account for the impairment of memory processing in MTLE by interrupting information flow to the hippocampal formation (31,32).

It is likely that neuropathologic changes also occur in other areas that are connected to the reverberating seizure network underlying MTLE (33). These structures, which include the thalamus (34), have been shown to be atrophied in patients, but the precise nature and distribution of the degenerative changes, as well as their relation to the pathophysiology of MTLE, have not been elucidated to date.

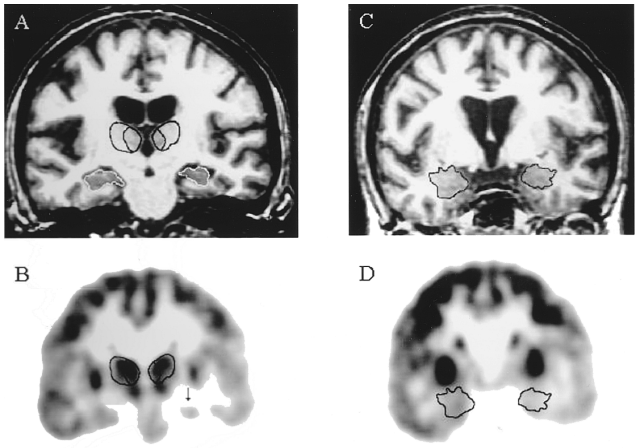

FIGURE 127.2. Imaging studies illustrating changes in extrahippocampal brain regions in MTLE. MRI scans (**A** and **C**) and fluorodeoxyglucose PET scans (**B** and **D**) in a patient with left MTLE. The demarcations on the two sets of scans represent the co-registration of the two techniques so comparable sites are illustrated in the two studies. **A** and **B** show changes in hippocampus (*circled in white* in MRI, indicated with an *arrow* in the PET scan) and thalamus *(outlined in black)* with the medial dorsal nucleus indicated separately in **A**. MRI demonstrates atrophy in the left hippocampus and the left mediodorsal nucleus, and PET shows hypometabolism specific to the temporal lobe and the medial dorsal thalamus. **C** and **D** show atrophy in the left amygdala. The left brain hemisphere corresponds to the right side of the images. (Micrographs courtesy of Drs. C. Juhász and H. Chugani, Wayne State University, Detroit, MI.)

IN VIVO IMAGING

Structural and functional neuroimaging techniques provide noninvasive means to identify brain abnormalities and have thus become indispensable tools to guide therapeutic interventions in neurologic and psychiatric diseases. These methods have also been, and continue to be, of critical importance for the generation and testing of hypotheses related to pathogenesis and disease progression. In the case of MTLE, techniques such as computed tomography, measurements of regional glucose use and receptor densities by positron emission tomography, single photon emission computed tomography measuring regional cerebral blood flow, and, more recently, volumetric and functional magnetic resonance imaging are now widely used—often in concert—to complement classic EEG and neuropsychological patient evaluation. Imaging test results are increasingly used for diagnostic purposes and, specifically, to provide guidance for neurosurgical procedures.

Improvements in the spatial resolution of most imaging techniques have made it possible to study regional brain abnormalities in MTLE with increasing accuracy. In early studies, hypometabolism and decreases in cerebral blood flow in the temporal lobe were demonstrated even when no structural damage was detectable by computed tomography. These methods were unable to localize the changes and to provide quantitative data adequately (8,35), but results obtained by magnetic resonance imaging are remarkably informative on both counts. Thus, using various modifications of the technique, it became feasible to visualize hippocampal atrophy in MTLE (36,37) (Fig. 127.2A). In the 1990s, magnetic resonance imaging studies also revealed shrinkage in other areas of the seizure circuit, namely, the amygdala (38,39), the entorhinal cortex (40), and the thalamus (6), findings demonstrating that the extrahippocampal changes in tissue volume known to exist in many MTLE patients can be visualized noninvasively (Fig. 127.2B–D). Further methodologic developments are likely to permit the imaging of increasingly smaller lesions and thereby to shed light on the roles of other extrahippocampal brain areas in the pathophysiology of MTLE.

STUDIES IN EXPERIMENTAL ANIMALS

Kindling

Kindling, a phenomenon first described in 1969 (41), has become a major research tool to study seizures involving the limbic system. In this model, a single site in the brain is stimulated electrically with sufficient intensity to induce an electrical after-discharge, but hardly any behavioral changes. With repeated focal stimulations for days or weeks, there is a gradual lengthening of the after-discharge, and behavioral seizures develop. During the seizure, the animal's behavior progresses to the point of a full convulsion. After a number of stimulations, the seizures reach a plateau of

consistent duration and behavioral severity, at which point the animal is considered fully kindled. The number of stimulations required to achieve this plateau depends on several factors, such as the frequency and duration of focal stimulation and the temporal interval between stimuli (42). In addition, however, the site of stimulation is critical for the development of kindling. Studies of several limbic sites, as well as comparisons of neocortical and subcortical regions, demonstrated that some extrahippocampal sites, for example, the amygdala, achieve the fully kindled state much faster than the hippocampus (43). In addition, focal pharmacologic manipulations revealed that both the development and the expression of kindling are significantly influenced by certain subcortical structures, including the midline thalamus and the substantia nigra (44,45).

The variable rates of kindling from different stimulation sites suggest that some regions are more *epileptogenic,* that is, more able to generate and support seizure activity than other sites. An alternative explanation is that the areas with more rapid rates of kindling are ''closer'' to the pathways of secondary generalization. This implies that seizure activity spreads by gradual recruitment of adjacent cortex (similar to the classic *jacksonian march*), exemplified by the proposed role of the perirhinal cortex as the major route from the limbic system to the neocortex (46). However, this idea is confounded by the observation that seizures can appear simultaneously at sites that have few direct interactions (e.g., hippocampus and amygdala) (33). Taken together, these findings therefore suggest the existence of a subcortical ''control center,'' for example, the midline thalamic region, with direct connections to several of the limbic sites involved (Fig. 127.4B).

The effect of pharmacologic intervention on the rate of kindling has been of great interest to epilepsy research, because drugs that prolong or abolish kindling acquisition could ameliorate or prevent the development of chronic epilepsy, that is, act as antiepileptogenic agents. Indeed, agents such as phenobarbital, carbamazepine, and several *N*-methyl-D-aspartate (NMDA)–receptor antagonists attenuate the kindling rate, whereas other commonly used antiepileptic compounds, such as phenytoin, do not have such an effect (47). This clinically relevant use of the kindling model will eventually also provide a better definition of the molecular events that underlie the progressive lengthening of seizure activity on repetitive stimulation.

Animal Models of MTLE

The kindling model has been, and continues to be, valuable for our understanding of the role of particular brain regions in the generation and propagation of seizures. However, with a few exceptions, kindled animals do not develop spontaneous seizures. Since the 1980s, the development of animal models with recurrent, spontaneous convulsions has therefore become a major focus of epilepsy research. These models are commonly based on an inciting event of limbic status epilepticus that is precipitated by various methods, including the systemic administration of chemoconvulsants (e.g., pilocarpine or kainate) (48,49), focal microinjection of a chemoconvulsant (e.g., kainate) in a limbic brain region (50), or focal, prolonged (up to 90 minutes) electrical stimulation of a limbic structure (hippocampus, perforant path, amygdala) (51–53). In all these models, the animals recover after status epilepticus and, after a latent period of weeks to months, develop spontaneous seizures that continue intermittently throughout the animals' lives.

These rat models parallel the human condition in several noteworthy ways. First, seizures appear spontaneously and, like the seizures of human MTLE, have a clear predilection to occur during daytime hours. This pattern suggests that the seizures are likely to be under subcortical influence. Second, as in the case of human MTLE, there is a latent period during which a previously nonepileptic brain evolves into one that generates recurring seizures. Third, the histopathologic changes in chronically epileptic animals, such as gliosis and neuronal loss in the hippocampus, amygdala, entorhinal cortex, and medial dorsal thalamus, closely resemble those seen in the human condition. Finally, the EEG patterns and the locations of seizure onset are similar in human MTLE and in these animal models, a finding suggesting similarities in the underlying pathophysiology (Fig. 127.3).

For these reasons, rat models of MTLE have become increasingly important for the study of limbic epilepsy. The animals offer several important advantages, which largely offset the limitations of the rodent brain, that is, its small size and less developed cortical architecture. Rats are not only relatively inexpensive and easy to manipulate, but allow well-controlled, multidisciplinary studies that can be readily compared across laboratories. The availability of ''MTLE-like'' animals also makes it possible to study the progression of events that eventually result in a chronic epileptic condition, that is, to assess the silent, latent period between status epilepticus and the first spontaneous limbic seizure. Finally, these animal models provide opportunities to test innovative clinical interventions for the treatment and possible cure of MTLE (54,55).

These models of limbic epilepsy have been exploited to test novel concepts related to the pathophysiology of MTLE. For example, hyperexcitable neurons, both projection and interneurons, are often found in many limbic sites associated with MTLE. In some cases, the synaptically mediated responses in these neurons show prolonged excitatory depolarizations with multiple superimposed action potentials (23,56,57) (Fig. 127.3). Underlying these profound changes are multiple presynaptic and postsynaptic alterations in neurotransmitter receptors and ion channels. Judged by physiologic criteria, there is evidence that changes in both inhibitory and excitatory receptors, namely GABA and glutamate receptors, contribute to the abnormal physiology (58,59). These changes are necessarily complex be-

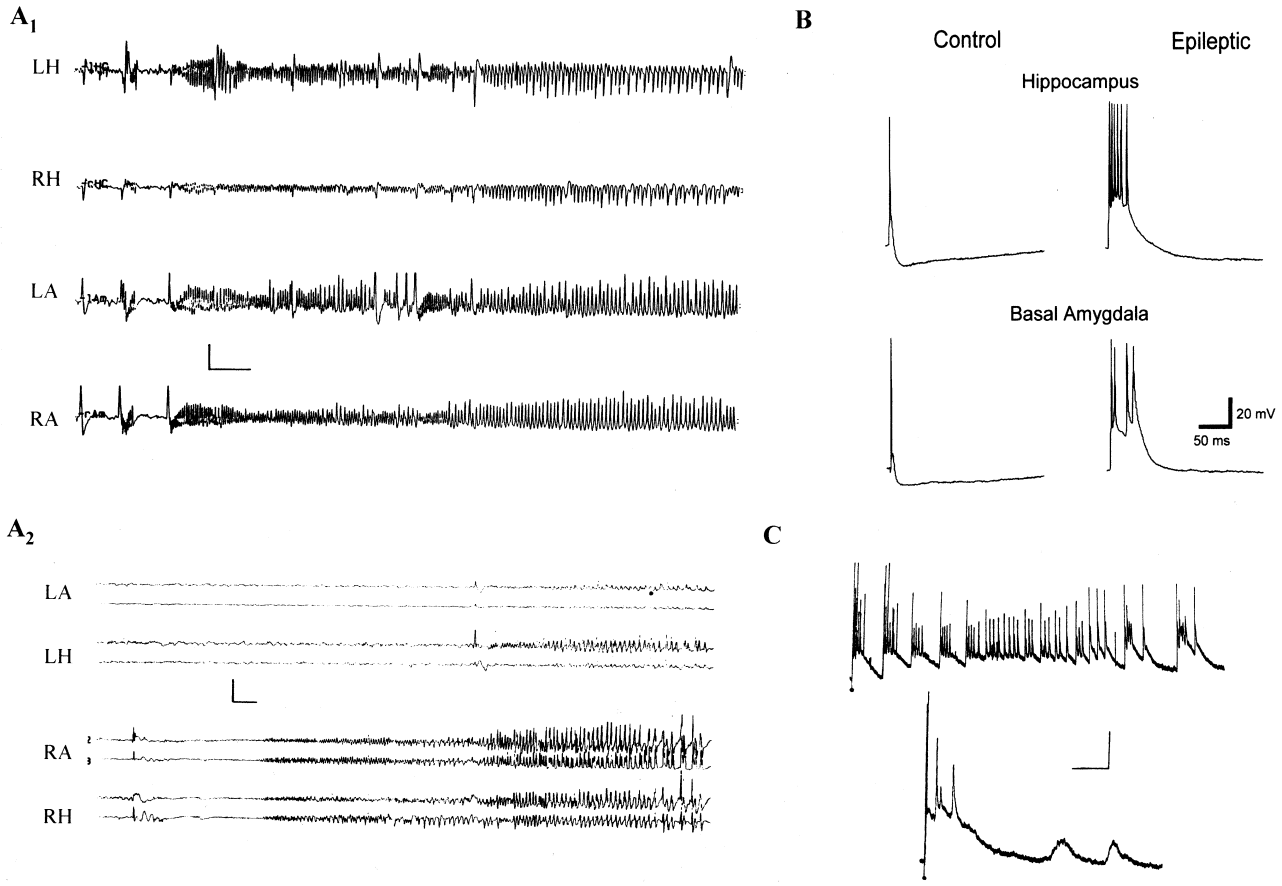

FIGURE 127.3. Seizures in human MTLE and in rat models of MTLE: illustrations of altered neuronal physiology. Chronic epilepsy in animals was induced by prolonged electrical stimulation or chemoconvulsants (see text). **A:** Bilateral recordings from hippocampus (LH, RH) and amygdala (LA, RA) in rat (A1) and human (A2). Both sites are involved at the onset, a finding suggesting a synchronizing pulse from an external site. The human recording shows a later but regionally simultaneous onset on the left hemisphere. This time difference is not seen in rats, probably as a result of stronger interhemispheric connections. **B:** Intracellular recordings from hippocampal and amygdalar neurons in normal and epileptic rats. At both sites, after a brief (0.1-ms) electrical pulse, the neurons from the epileptic animals show prolonged depolarization with multiple superimposed action potentials as compared with normal controls. **C:** Intracellular recordings from the entorhinal cortex of epileptic rats, also illustrating the prolonged depolarizations and multiple superimposed action potentials. Overall, this figure emphasizes the changes throughout the limbic system in nonhippocampal regions.

cause they reflect a composite picture of receptors and receptor subunits and their reactive up-regulation or down-regulation (60–62). In addition, the models also involve many other biochemical changes in one or more parts of the limbic seizure network. This ever-increasing list includes ions, enzymes, hormones and their receptors, and a host of other chemical entities. In most instances, however, the possible functional significance of these changes has so far not been elucidated.

Experimental MTLE also provides an opportunity to evaluate the existence and functional significance of synaptic rearrangements, which occur in response to epileptogenic insults or neuronal damage and may be involved in the development of spontaneously recurring seizures (20–24, 63). The prototype for this process, the sprouting of mossy fibers originating from hippocampal granule cells, has garnered substantial attention, in part because of the seeming simplicity of the new circuit and the easily visualized anatomic change (64). Because the animal models of MTLE show extensive neuronal loss in multiple brain areas, it is quite likely that seizure-related synaptic and circuit rearrangements also occur in extrahippocampal regions (65).

CURRENT CONCEPTS OF EPILEPTOGENESIS: MOLECULES AND MECHANISMS

Neurotransmitters

A long-standing theme in epilepsy research has been the role of the major inhibitory neurotransmitter, GABA, in

both epileptogenesis and chronic epilepsy. Defects of the GABA system have been implicated since the 1970s, when a loss of GABA neurons was suspected to underlie seizures (66), but physiologic studies in animal models of epilepsy did not necessarily reveal a reduction in GABAergic inhibition (67). Other studies proposed a specific defect in the excitability of otherwise normal ("dormant") GABAergic neurons resulting from their deafferentation (68). This hypothesis is still rather controversial, attesting to the complexity of GABAergic neurotransmission (63). However, it seems unlikely that a single deficit in the GABAergic systems of the brain underlies limbic epilepsy.

More recent studies have expanded our understanding of GABAergic transmission. For example, we now have a greatly improved view of GABAergic inhibitory neurons *(interneurons).* These cells are morphologically heterogeneous, have diverse connections, and contain different colocalized transmitters (69). Thus, many GABAergic neurons also contain the peptides neuropeptide Y and somatostatin or calcium-binding proteins such as parvalbumin or calretinin. Although many anatomic studies have focused exclusively on the hippocampus and the neocortex, some common themes also seem to apply to other sites, such as the entorhinal and the perirhinal cortex. The physiologic characteristics of these different cells and their respective roles in epileptogenesis in both hippocampus and extrahippocampal areas will need to be elaborated in the future. These studies must also be complemented by a detailed molecular and functional analysis of GABA receptors and GABA transporters (70,71).

Because MTLE is frequently conceptualized as the result of an imbalance between excitation and inhibition in the brain, the abundant excitatory neurotransmitter glutamate is also likely to play an important role in the pathophysiology of MTLE. Indeed, both ionotropic [NMDA, 2-amino-(3-hydroxy-5-methylisoxazol-4-yl) propanoate (AMPA) and kainate] and metabotropic (i.e., G-protein–coupled) glutamate receptors have been implicated in epileptogenesis and chronic epilepsy (44,48,50,58,61,62). For example, a decrease in magnesium, an endogenous modulator of the NMDA receptor, greatly reduces the receptor's voltage dependency and allows channel opening at central neurons even at normal, hyperpolarized membrane potentials. The result is spontaneous epileptiform activity (72). NMDA-receptor subunit composition changes in response to seizure activity and may be responsible for the increase in excitability that often follows an initial seizure (61,62). Such changes occur in MTLE as well as in relevant animal models and are seen both in the hippocampus, so far the most thoroughly investigated brain region, and in extrahippocampal areas such as the entorhinal cortex (56).

Blockade of AMPA or kainate receptors is one of the most effective means to reduce epileptiform activity. These receptors, which mediate most fast excitatory neurotransmission, are also composed of an array of subunits, which assemble to form distinct receptor subtypes (73). Receptor compositions are abnormal in epileptic brain tissue of both humans and animals (60,61), although their role in epileptogenesis is currently unclear. This not only suggests that AMPA and kainate receptors are involved in spontaneously recurrent seizure activity but also offers promising new ideas for antiepileptic drug development (74).

Pharmacologic manipulation of metabotropic glutamate receptors and interference with the function of glutamate transporters, a group of several distinct proteins that control the extracellular concentration of glutamate in the brain, too, have profound consequences on neuronal excitability. These sites are therefore under careful scrutiny both for their potential role in epileptogenesis and as novel therapeutic targets (75,76).

A considerable body of evidence suggests that other classic neurotransmitters, such as monoamines and acetylcholine, also play critical roles in MTLE, and that the proconvulsant or anticonvulsant effects of these agents manifest themselves in several regions of the epileptic network. Drugs that selectively influence, for example, noradrenergic or cholinergic neurotransmission are therefore useful experimental tools and of potential benefit in the treatment of MTLE (77,78).

Neuromodulators: Neuropeptides, Growth Factors, Cytokines

Neuropeptides have long constituted an enigma to neuroscientists. They are present in many different brain areas, where they are localized in various neuronal types, often in cells expressing GABA as a neurotransmitter (69), yet their physiologic function remains obscure. Some of these agents, such as neuropeptide Y and dynorphin, show increased or reduced brain content after prolonged seizure activity (20, 79). Physiologic studies have demonstrated that neuropeptide Y has an inhibitory action, suppressing neurotransmission in single hippocampal cells and seizures *in vivo.* It is therefore conceivable that neuropeptide Y, portrayed here as a prototype of a relatively large group of neuroactive peptides, plays an important role as an endogenous modulator of seizure generation and in epilepsy. Its physiologic actions, as well as its chemical and anatomic changes in MTLE, are not confined to the hippocampus but also affect other parts of the seizure network (79).

Several peptides and small proteins with no previously recognized relevance to epilepsy may also turn out to play a role in epileptogenesis. Examples include growth factors and cytokines, which have been shown to be neuroactive in various test systems. Thus, various members of the neurotrophin family, including nerve growth factor, brain-derived growth factor (BDNF), and others, for example, neurotrophin 3 and neurotrophin 4/5, influence neurotransmission, although their effects vary widely in both qualitative and quantitative terms (80). All reports of these neuroactive effects are so far based on exogenously applied neurotrophins; that is, the results could be compromised by the finding

that the concentrations used for experimentation exceeded physiologic levels. Still, it is certainly of interest that the brain concentration of some neurotrophins, such as BDNF, increases dramatically after seizures, whereas others, such as neurotrophin 3, decrease. The high-affinity trk receptors and low-affinity p75 receptors for neurotrophins also appear to change after seizures, setting the stage for potentially important, interactive roles of the various neurotrophins in epileptogenesis and epilepsy (80). Because normal expression and seizure-induced changes of these putative neuromodulators occur throughout the limbic system, critical seizure-related effects may not only take place in the hippocampus, where most studies have been performed to date. For example, potent effects of BDNF in the entorhinal cortex have been described (81).

Cytokines were originally characterized as mediators of inflammatory responses and were discussed as messengers of the immune system. However, some of these compounds, for example, interleukin 1 (IL-1), IL-6, and tumor necrosis factor-α, are expressed in the brain, influence neuronal activity, and therefore have potential links to seizure mechanisms. In particular, the mRNA for IL-1β and IL-6, as well as IL receptors, is increased by seizures (82). Moreover, IL-1α is elevated in tissue from patients with epilepsy (83). Finally, the finding that cytokines are expressed and released by microglia underscores the role of nonneuronal cells in epilepsy (see later).

Neuron-Glia Interactions

The importance of glia to neuronal function has been appreciated since the early period of neuroscience research. Yet to this day, the interrelationship of glia and neurons continues to unfold. Besides other roles in brain physiology, glial cells may play a significant role in the modulation of seizure phenomena. Thus, both astrocytes and microglial cells, the two major glial cell types in the brain, are rapidly activated by seizure activity in the limbic system (84). It is currently unclear, however, whether this cellular reaction has proconvulsive or anticonvulsive effects. Astrocytes have the ability to buffer extracellular potassium and can avidly accumulate the excitatory amino acid glutamate (76). Moreover, astrocytes increase the production and release of the endogenous neuroinhibitory and anticonvulsant compound kynurenate, possibly as an early defensive response to seizures (85). These and many conceptually related data indicate a protective function of astrocytes in epileptogenesis and, perhaps, in chronic epilepsy. Conversely, both astrocytes and microglia also synthesize endogenous proconvulsive agents such as quinolinate (86) and cytokines (87), which may exacerbate seizure activity during any stage of the epileptic process.

Of possible relevance to their role in epilepsy, glial cells in limbic brain areas are heterogeneous with regard to both structure and function. For example, both the electrophysiologic properties and the histochemical staining pattern of astrocytes in area CA1 of the hippocampus differ from those in area CA3 (88). Similar differences are likely to exist in other brain areas as well, adding another layer of complexity to the study of neuron-glia interactions as they pertain to mechanisms of epileptogenesis and chronic epilepsy.

Seizure-Induced Changes in Gene Expression

Prolonged seizure activity, especially episodes of status epilepticus, often has dramatic effects on gene expression, inducing a bewildering array of new genes in the brain. The expression of a variety of proteins and peptides is increased, whereas that of others is reduced. These changes involve neurotransmitters, neuromodulators and their receptors, growth factors, cytokines, and additional classes of compounds. A popular hypothesis to explain these changes is that seizures induce, or influence the expression of, genes that are normally expressed during development. Sequelae of seizures may therefore mimic or, to use a more teleologic term, *recapitulate* development. Examples include the seizure-induced up-regulation of growth factors and proteins that are involved in synaptogenesis (89). Other investigators have proposed, again arguing teleologically, that seizure-induced changes merely constitute compensatory mechanisms of the adult brain, that is, attempts of the system to counter a potentially dangerous increase in excitability or impending cellular damage. This implies the up-regulation of systems that inhibit neuronal activity. Indeed, seizures lead to changed expression of glutamate decarboxylase, the enzyme responsible for GABA synthesis, and GABA receptors (71,90).

Conversely, seizure-induced changes in gene expression may be part of the development of the epileptic state. Thus, a first seizure may induce gene expression of substances that will contribute to further hyperexcitability. One example is the neurotrophin BDNF, which is normally expressed in dentate gyrus granule cells and, to a lesser extent, other areas of the hippocampus and other brain regions (91). After a single seizure, BDNF message, protein, and the high-affinity trkB receptor all increase in granule cells (92,93). Because BDNF enhances neuronal activity in the hippocampus, the increase in expression could have functional consequences; that is, it could lead to a reduction in seizure threshold. BDNF also has effects on neuronal structure and could thus contribute to structural changes occurring after seizures that, in turn, increase susceptibility to seizures (81, 94). Because BDNF, and other neurotrophins and neuromodulators, are expressed in extrahippocampal regions, this hyperexcitability may also occur in these areas.

Synaptic Reorganization

As mentioned above, seizures induce many genes in the brain. These genes express a variety of different proteins,

which often closely resemble or duplicate those that are preferentially expressed during brain development. It is therefore hardly surprising that growth and synaptic reorganization occur as a consequence of seizure activity. In experimental animals, this phenomenon has been studied in great detail in the hippocampus, although it can also be observed in extrahippocampal areas such as the entorhinal cortex (65) and the neocortex (95). In the hippocampus, mossy fiber axons of dentate granule cells grow new collaterals that innervate an abnormal lamina *(mossy fiber sprouting)* (96). It has been suggested that these connections are functional (97,98), but opinions are still divided on whether and to what extent they contribute to the precipitation of spontaneously recurring seizures (20–24).

Neurogenesis

Confirmation of neurogenesis in the adult mammalian nervous system has galvanized interest in the potential role of newly born cells in the mature brain. This issue may be of particular relevance to the study of epilepsy because neurogenesis is stimulated in adult animals after seizures. This has been documented in some detail in the hippocampus, where an increase in newly born dentate granule cells was detected in response to single seizures (99), kindling (100), or status epilepticus (101). In rats treated with pilocarpine, newly born granule cells develop intrinsic electrophysiologic properties that are identical to normal granule cells. However, the integration of these cells into the host circuitry appears to be different from adult granule cells, because they become synchronized with epileptiform activity in the CA3 cell layer (102). These studies indicate that cells born in response to seizures can become fully functioning neurons and may develop abnormal electrical activity.

More recent studies, although still somewhat controversial, have demonstrated that neurogenesis in the adult brain can also occur in the neocortex (103). Moreover, many newly born cells, possibly neurons, can also be detected in the entorhinal cortex of pilocarpine-treated rats (104). Rather than an isolated, region-specific phenomenon, the birth of new neurons in response to seizures may therefore take place in several parts of the limbic system and possibly elsewhere. Alone or together, these cells may eventually cause enhanced excitability and may decrease seizure threshold. It is tempting to speculate that this may underlie the heightened excitability in patients with cortical dysplasias, which can arise as a result of aberrant migration of newly born cells.

Transgenic Animals

The availability of transgenic mice has provided exciting new research opportunities for the study of MTLE. Thus, targeted genetic manipulation has permitted the detailed examination of the effects of changes in one specific gene product. This selectivity is particularly important in the study of epileptic phenomena, which are associated with many concurrent molecular and cellular changes. Transgenics may be engineered to overexpress or delete a given gene product, and recent techniques have made it possible to modify gene expression conditionally, that is, in a brain region– or age-specific fashion (105).

To name only one of several relevant examples, BDNF transgenics show increased excitability and, in some cases, exhibit spontaneous seizures. BDNF overexpression in these animals is most obvious in mossy fiber axons of dentate gyrus granule cells, and excitability is indeed increased in the postsynaptic targets of mossy fibers. However, BDNF is also overexpressed in other limbic regions such as the entorhinal cortex, and these areas, too, are hyperexcitable (94). These and qualitatively similar results from other genetically manipulated animals illustrate the value of this novel experimental approach for delineating the respective roles of the hippocampus and extrahippocampal areas in epileptogenesis and chronic epilepsy.

MTLE AS A NETWORK DISEASE: IMPLICATIONS FOR FURTHER RESEARCH AND THERAPY

As briefly reviewed here, the available data indicate that both the hippocampus and interconnected extrahippocampal limbic regions play a role in the pathophysiology of MTLE (Fig. 127.4). Methodologic advances, ranging from novel and improved *in vivo* imaging techniques and neurosurgical approaches to increasingly sophisticated assessments of cellular physiology and chemistry, have resulted in a refinement of nineteenth-century concepts without fundamentally altering the major premises of Sommer and his contemporaries. In humans, any of a number of primary insults, such as severe febrile convulsions during childhood, head trauma, infections, tumors, or developmental malformations, have been proposed to be epileptogenic, leading to MTLE after a characteristic latency period. Studies in several new animal models have shown that these pathogenic injuries preferentially affect one or more limbic brain areas, including, but not necessarily limited to, hippocampus, entorhinal cortex, amygdala, thalamus, and neocortical regions. This neuronal injury or degeneration may constitute a major factor in the establishment of epileptogenic circuits within the limbic system and may cause further structural and functional changes. Eventually, after a ''silent'' interval characterized by functionally significant yet currently still unspecified changes, a hyperexcitable epileptogenic circuit develops, resulting in MTLE.

This concept of epileptogenesis and chronic limbic epilepsy has several ramifications for the treatment of MTLE. First, it is possible that the development of an epileptic circuit will be inhibited if the multiple changes in limbic

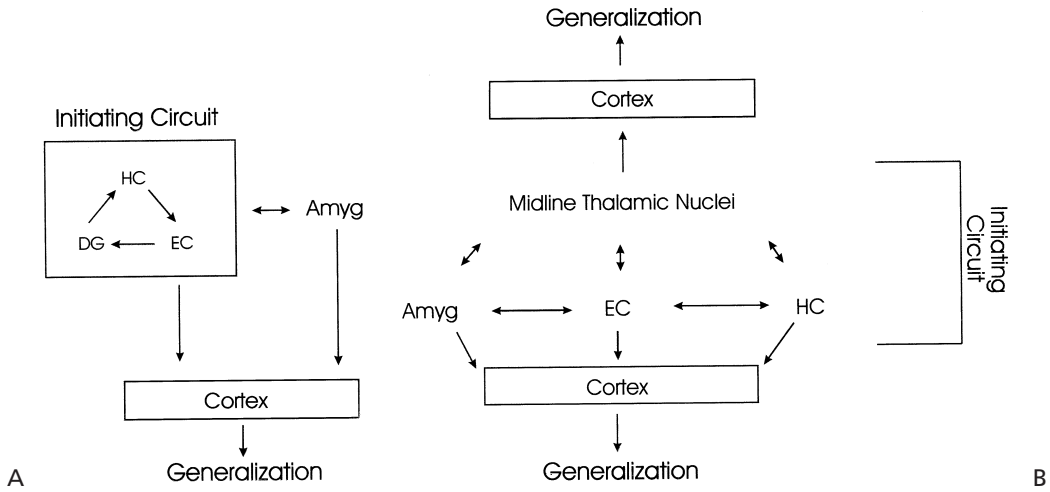

FIGURE 127.4. Schematic representation of the functional anatomy underlying MTLE. **A:** In the conventional model, seizures originate in a reverberating loop consisting of entorhinal cortex, dentate gyrus, and area CA1 of the hippocampus. At some point, seizure activity spreads to the amygdala and other adjacent areas before involving the neocortex and resulting in secondary generalization. **B:** Newer studies suggest an alternative model, in which several limbic sites initially interact with one another independently. Because of their reciprocal connections to all these regions, the midline thalamic nuclei constitute part of the initiating circuit, acting as a subcortical synchronizing site. Generalization can occur through gradual recruitment of adjacent neocortex or through the thalamus, which secondarily recruits the neocortex. Amyg, amygdala; DG, dentate gyrus; EC, entorhinal cortex; HC, hippocampus.

circuitry that follow the initial insult are minimized. Second, it raises the possibility that hippocampal or extrahippocampal interventions during the "silent" period may prevent the evolution of spontaneously recurring seizures. Third, it indicates that any of a number of limbic brain areas, or even certain neuronal populations within a given region, could conceivably be targeted for surgical or pharmacologic intervention.

Although the pathophysiologically important role of extrahippocampal brain regions in MTLE is supported by the successful outcome of various surgical interventions in patients with medically intractable epilepsy (5,9,10,14–16), several critical questions need to be resolved before the therapeutic approaches listed earlier can be adequately evaluated in clinical settings. For example, we need to clarify whether neuronal death, gliosis, and synaptic reorganizations promote or attenuate seizure evolution and whether, on the cellular level, pharmacologic or genetic manipulation of receptors and ion channels can influence the development of chronic hyperexcitability. Because circuit disruption is widespread throughout the limbic system, we need to elaborate those subcortical structures that are particularly effective in controlling seizure spread and generalization. Other studies will decipher cell- and region-specific and time-dependent changes in the composition of neurotransmitter receptors and of other proteins that determine the action of endogenous neuroactive agents. These analyses must be complemented by examining shifts in the concentration of endogenous neuromodulators that can alter neuronal excitability. To optimize the development of novel strategies for the treatment of MTLE, these molecular studies should be performed in parallel in extrahippocampal areas and in the hippocampal region whenever possible. This approach should eventually provide significant advances in the therapy of this debilitating disorder.

ACKNOWLEDGMENTS

Work described in this article was in part supported by United States Public Health Service grants NS 16102, NS 25605, and NS 37562. We are grateful to Drs. C. Juhasz and H. Chugani (Wayne State University, Detroit, MI) for providing the micrographs shown in Fig. 127.2.

REFERENCES

1. Wyllie E. *The treatment of epilepsy: principles and practice.* Philadelphia: Lea & Febiger, 1993.
2. Engel J, ed. *Surgical treatment of the epilepsies.* New York: Raven, 1993.
3. Lopes Da Silva FH, Witter MP, Boeijinga PH, et al. Anatomic organization and physiology of the limbic cortex. *Physiol Rev* 1990;70:453–511.
4. So NK. Depth electrode studies in mesial temporal epilepsy. In: Lüders H, ed. *Epilepsy surgery.* New York: Raven, 1991: 371–384.

5. Spencer DD, Spencer SS. Hippocampal resections and the use of human tissue in defining temporal lobe epilepsy syndromes. *Hippocampus* 1994;4:243–249.
6. Juhász C, Nagy F, Watson C, et al. Glucose and [^{14}C]flumazenil positron emission tomography abnormalities of thalamic nuclei in temporal lobe epilepsy. *Neurology* 1999;53:2037–2045.
7. Sperling MR, Gur RC, Alavi A, et al. Subcortical metabolic alterations in partial epilepsy. *Epilepsia* 1990;31:145-155.
8. Theodore WH, Brooks R, Margolin R, et al. Positron emission tomography in generalized seizures. *Neurology* 1985;35: 684–690.
9. Siegel AM, Wieser HG, Wichmann W, et al. Relationships between MR-imaged total amount of tissue removed, resection scores of specific mediobasal limbic subcompartments and clinical outcome following selective amygdalohippocampectomy. *Epilepsy Res* 1990;6:56–65.
10. Parrent AG, Blume WT. Stereotactic amygdalohippocampotomy for the treatment of medial temporal lobe epilepsy. *Epilepsia* 1999;40:1408–1416.
11. Sommer W. Erkrankung des Ammonshorns als aetiologisches Moment der Epilepsie. *Arch Psychiatr Nervenkrankh* 1880;10: 631–675.
12. Lorente de Nó R. Studies on the structure of the cerebral cortex. *J Psychol Neurol* 1933;45:381–438.
13. Zimmerman HM. The histopathology of convulsive disorders of children. *J Pediatr* 1938;13:839–890.
14. Penfield W, Baldwin M. Temporal lobe seizures and the technic of subtotal temporal lobectomy. *Ann Surg* 1952;136:625–634.
15. Gastaut H. Colloque sur les problemes d'anatomie normale et pathologique posés par les décharges épileptiques. *Acta Med Belg* 1956:5–66.
16. Margerison JH, Corsellis JAN. Epilepsy and the temporal lobes: a clinical, electroencephalographic and neuropathological study of the brain in epilepsy, with particular reference to the temporal lobes. *Brain* 1966;89:499–530.
17. O'Connor ER, Sontheimer H, Spencer DD, et al. Astrocytes from human hippocampal epileptogenic foci exhibit action potential-like responses. *Epilepsia* 1998;39:347–354.
18. Krishman B, Armstrong DL, Grossman RG, et al. Glial cell nuclear hypertrophy in complex partial seizures. *J Neuropathol Exp Neurol* 1994;53:502–507.
19. Beach TG, Woodhurst WB, MacDonald DB, et al. Reactive microglia in hippocampal sclerosis associated with human temporal lobe epilepsy. *Neurosci Lett* 1995;191:27–30.
20. Houser CR, Miyashiro JE, Swartz BE, et al. Altered patterns of dynorphin immunoreactivity suggest mossy fiber reorganization in human hippocampal epilepsy. *J Neurosci* 1990;10: 267–282.
21. Okazaki MM, Evenson DA, Nadler JV. Hippocampal mossy fiber sprouting and synapse formation after status epilepticus in rats: visualization after retrograde transport of biocytin. *J Comparative Neurology* 1995;352:515–534.
22. Wuarin JP, Dudek FE. Electrographic seizures and new recurrent excitatory circuits in the dentate gyrus of hippocampal slices from kainate-treated epileptic rats. *J Neurosci* 1996;16: 4438–4448.
23. Davenport CJ, Brown WJ, Babb TL. Sprouting of GABAergic and mossy fiber axons in dentate gyrus following intrahippocampal kainate in the rat. *Exp Neurol* 1990;109:180–190.
24. Sloviter RS. Possible functional consequences of synaptic reorganization in the dentate gyrus of kainate-treated rats. *Neurosci Lett* 1992;137:91–96.
25. Bruton CJ. The neuropathology of temporal lobe epilepsy. *Maudsley monograph no. 31.* Oxford: Oxford University Press, 1988.
26. Du F, Whetsell WO Jr, Abou-Khalil B, et al. Preferential neuronal loss in layer III of the entorhinal cortex in patients with temporal lobe epilepsy. *Epilepsy Res* 1993;16:223–233.
27. Witter MP, Griffioen AW, Jorritsma-Byham B, et al. Entorhinal projections to the hippocampal CA1 region in the rat: an underestimated pathway. *Neurosci Lett* 1988;85:193–198.
28. Scharfman HE, Goodman JH, Du F, et al. Chronic changes in synaptic responses of entorhinal and hippocampal neurons after entorhinal cortical cell loss produced by intracortical amino-oxyacetic acid (AOAA) injection: an *in vitro* and *in vivo* study in the rat. *J Neurophysiol* 1998;80:3031–3046.
29. Cavanagh JB, Meyer A. Aetiological aspects of Ammon's horn sclerosis associated with temporal lobe epilepsy. *BMJ* 1956;2: 1403–1407.
30. Hudson LP, Monoz DG, Miller L, et al. Amgdaloid sclerosis in temporal lobe epilepsy. *Ann Neurol* 1993;33:622–631.
31. Pitkänen A, Tuunanen J, Kalviainen R, et al. Amygdala damage in experimental and human temporal lobe epilepsy. *Epilepsy Res* 1998;32:233–253.
32. Cahill L, Haier RJ, Fallon J, et al. Amygdala activity at encoding correlated with long-term, free recall of emotional information. *Proc Natl Acad Sci USA* 1996;93:8016–8021.
33. Bertram EH. Functional anatomy of spontaneous seizures in a rat model of limbic epilepsy. *Epilepsia* 1997;38:95–105.
34. De Carli C, Hatta J, Fazilat S, et al. Extratemporal atrophy in patients with complex partial seizures of left temporal origin. *Ann Neurol* 1998;43:41–45.
35. Engel J Jr, Kuhl DE, Phelps ME, et al. Interictal cerebral glucose metabolism in partial epilepsy and its relation to EEG changes. *Ann Neurol* 1982;12:510–517.
36. Berkovic SF, Andermann F, Olivier A, et al. Hippocampal sclerosis in temporal lobe epilepsy demonstrated by magnetic resonance imaging. *Ann Neurol* 1991;29:175–182.
37. Lencz T, McCarthy G, Bronen RA, et al. Quantitative magnetic resonance imaging in temporal lobe epilepsy: relationship to neuropathology and neuropsychological function. *Ann Neurol* 1992;31:629–637.
38. Cendes F, Andermann F, Gloor P, et al. Atrophy of mesial structures in patients with temporal lobe epilepsy: cause or consequence of repeated seizures? *Ann Neurol* 1993;34:795–801.
39. Van Paesschen W, Connelly A, Johnson CL, et al. The amygdala and intractable temporal lobe epilepsy: a quantitative magnetic resonance imaging study. *Neurology* 1996;47:1021–1031.
40. Bernasconi N, Bernasconi A, Andermann F, et al. Entorhinal cortex in temporal lobe epilepsy. *Neurology* 1999;52:1870–1876.
41. Goddard GV, McIntyre DC, Leech CK. A permanent change in brain function resulting from daily electrical stimulation. *Exp Neurol* 1969;25:295–330.
42. Lothman EW, Williamson JK. Rapid kindling with recurrent hipocampal seizures: effect of stimulus frequency and train duration. *Epilepsy Res* 1993;14:209–220.
43. Racine R. Kindling: the first decade. *Neurosurgery* 1978;3: 234–252.
44. Hirayasu Y, Wada JA. *N*-methyl-D-aspartate injection into the massa intermedia facilitates development of limbic kindling in rats. *Epilepsia* 1992;33:965–970.
45. Gale K. Subcortical structures and pathways involved in convulsive seizure generation. *J Clin Neurophysiol* 1992;9:264–277.
46. McIntyre DC, Kelly ME, Dufresne C. FAST and SLOW amygdala kindling rat strains: comparison of amygdala, hippocampal, piriform and perirhinal cortex kindling. *Epilepsy Res* 1999;35: 197–209.
47. Löscher W. Animal models of intractable epilepsy. *Prog Neurobiol* 1997;53:239–258.
48. Ben-Ari Y. Limbic seizure and brain damage produced by kainic

acid: mechanisms and relevance to human temporal lobe epilepsy. *Neuroscience* 1985;14:375–403.
49. Cavalheiro EA, Leite JP, Bortolotto ZA, et al. Long-term effects of pilocarpine in rats: structural damage of the brain triggers kindling and spontaneous recurrent seizures. *Epilepsia* 1991;32: 778–782.
50. Wilson CL, Maidment NT, Shomer MH, et al. Comparison of seizure related amino acid release in human epileptic hippocampus versus a chronic, kainate rat model of hippocampal epilepsy. *Epilepsy Res* 1996;26:245–254.
51. Lothman EW, Bertram EH, Kapur J, et al. Recurrent spontaneous hippocampal seizures in the rat as a chronic sequela to limbic status epilepticus. *Epilepsy Res* 1990;6:110–118.
52. Nissinen J, Halonen T, Koivisto E, et al. A new model of chronic temporal lobe epilepsy induced by electrical stimulation of the amygdala in rat. *Epilepsy Res* 2000;38:177–205.
53. Mazarati AM, Wasterlain CG, Sankar R, et al. Self-sustaining status epilepticus after brief electrical stimulation of the perforant path. *Brain Res* 1998;801:251–253.
54. Leite JP, Cavalheiro EA. Effects of conventional antiepileptic drugs in a model of spontaneous recurrent seizures in rats. *Epilepsy Res* 1995;20:93–104.
55. Bertram, EH, Riddick G. Model of chronic spontaneous limbic seizures can be used for testing antiepileptic drugs. *Epilepsia* 1993;34(suppl 6):12.
56. Fountain NB, Bear J, Bertram EH III, et al. Responses of deep entorhinal cortex are epileptiform in an electrogenic rat model of chronic temporal lobe epilepsy. *J Neurophysiol* 1998;80: 230–240.
57. Scharfman HE. Hyperexcitability of entorhinal cortex and hippocampus after application of amino-oxyacetic acid (AOAA) to medial entorhinal cortex in combined entorhinal and hippocampal slices. *J Neurophysiol* 1997;76:2986–3001.
58. Bradford HF. Glutamate, GABA and epilepsy. *Prog Neurobiol* 1995;47:477–511.
59. Mangan P, Bertram E. Shortened duration GABA A receptor mediated synaptic potentials underlie enhanced CA1 excitability in a chronic model of temporal lobe epilepsy. *Neuroscience* 1997; 80:1101–1111.
60. de Lanerolle NC, Eid T, von Campe G, et al. Glutamate receptor subunits GluR1 and GluR2/3 distribution shows reorganization in the human epileptogenic hippocampus. *Eur J Neurosci* 1998;10:1687–1703.
61. Zilles K, Qu MS, Kohling R, et al. Ionotropic glutamate and GABA receptors in human epileptic neocortical tissue: quantitative *in vitro* receptor autoradiography. *Neuroscience* 1999;94: 1051–1061.
62. Musshof U, Schünke U, Köhling R, et al. Alternative splicing of the NMDAR1 glutamate receptor subunit in human temporal lobe epilepsy. *Mol Brain Res* 2000;76:377–384.
63. Bernard C, Esclapez M, Hirsch JC, et al. Interneurones are not so dormant in temporal lobe epilepsy: a critical reappraisal of the dormant basket cell hypothesis. *Epilepsy Res* 1998;32:93–103.
64. Tauck DL, Nadler JV. Evidence of functional mossy fiber sprouting in hippocampal formation of kainic acid treated rats. *J Neurosci* 1985;5:1016–1022.
65. Eid T, Schwarcz R, Ottersen OP. Ultrastructure and immunocytochemical distribution of GABA in layer III of the rat medial cortex following aminoxyacetic acid-induced seizures. *Exp Brain Res* 1999;125:463–475.
66. Ribak CE. Morphological, biochemical and immunocytochemical changes of the cortical GABAergic system in epileptic foci. In: Ward AA, Penry JK, Purpura DP, eds. *Epilepsy.* New York: Raven, 1983:109–129.
67. Prince DA, Jacobs KM, Salin PA, et al. Chronic focal neocortical epileptogenesis: does disinhibition play a role? *Can J Physiol Pharmacol* 1997;75:500–507.
68. Sloviter RS. Permanently altered hippocampal structure, excitability, and inhibition after experimental status epilepticus in the rat: the ''dormant basket cell'' hypothesis and its possible relevance to temporal lobe epilepsy. *Hippocampus* 1991;1: 41–66.
69. Freund TF, Buzsaki G. Interneurons of the hippocampus. *Hippocampus* 1996;6:347–470.
70. Kapur J, Coulter DA. Experimental status epilepticus alters γ-aminobutyric acid type A receptor function in CA1 pyramidal neurons. *Ann Neurol* 1995;38:893–900.
71. Sperk G, Schwarzer C, Tsunashima K, et al. Expression of GABA A receptor subunits in the hippocampus of the rat after kainic acid-induced seizures. *Epilepsy Res* 1998;32:129–139.
72. Stanton PK, Jones RSG, Mody I, et al. Epileptiform activity induced by lowering extracellular $[Mg^{2+}]$ in combined hippocampal-entorhinal cortex slices: modulation by receptors for norepinephrine and *N*-methyl-D-aspartate. *Epilepsy Res* 1987;1: 53–62.
73. Seeburg PH. The TINS/TIPS lecture The molecular biology of mammalian glutamate receptor channels. *Trends Neurosci* 1993;16:359–365.
74. Swedberg MDB, Jacobsen P, Honoré T. Anticonvulsant, anxiolytic and discriminative effects of the AMPA antagonist 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(f)quinoxaline (NBQX). *J Pharmacol Exp Ther* 1995;274:1113–1121.
75. Aronica EM, Gorter JA, Paupard M-C, et al. Status epilepticus-induced alterations in metabotropic glutamate receptor expression in young and adult rats. *J Neurosci* 1997;17:8588–8595.
76. Tessler S, Danbolt NC, Faull RLM, et al. Expression of the glutamate transporters in human temporal lobe epilepsy. *Neuroscience* 1999;88:1083–1091.
77. Nagao T, Alonso A, Avoli M. Epileptiform activity induced by pilocarpine in the rat hippocampal/entorhinal slice preparation. *Neuroscience* 1996;72:399–408.
78. Cavalheiro EA, Fernandes MJ, Turski L, et al. Spontaneous recurrent seizures in rats: amino acid and monamine determination in the hippocampus. *Epilepsia* 1994;35:1–11.
79. Vezzani A, Sperk G, Colmers WF. Neuropeptide Y: emerging evidence for a functional role in seizure modulation. *Trends Neurosc* 1999;22:25–30.
80. Lindvall O, Kokaia Z, Bengzon J, et al. Neurotrophins and brain insults. *Trends Neurosci* 1994;17:490–496.
81. Scharfman HE. Hyperexcitability in combined entorhinal/hippocampal slices of adult rat after exposure to brain-derived neurotrophic factor. *J Neurophysiol* 1997;78:1082–1095.
82. Minami M, Kuraishi Y, Satoh M. Effects of kainic acid on messenger RNA levels of IL1 IL6, TNFα, and Lif in the rat brain. *Biochem Biophys Res Commun* 1991;176:593–598.
83. Sheng JG, Boop FA, Mrak RE, et al. Increased neuronal β-amyloid precursor protein expression in human temporal lobe epilepsy: association with interleukin 1 immunoreactivity. *J Neurochem* 1994;63:1872–1879.
84. Steward O, Torre ER, Tomasulo R, et al. Neuronal activity upregulates astroglial gene expression. *Proc Natl Acad Sci USA* 1991;88:6819–6823.
85. Wu H-Q, Schwarcz R. Seizure activity causes elevation of endogenous extracellular kynurenic acid in the rat brain. *Brain Res Bull* 1996;39:155–162.
86. Okuno E, Köhler C, Schwarcz R. Rat 3-hydroxyanthranilic acid oxygenase: purification from the liver and immunocytochemical localization in the brain. *J Neurochem* 1987;49:771–780.
87. Vezzani A, Conti M, Luigi AD, et al. Interleukin 1 immunoreactivity and microglia are enhanced in the rat hippocampus by

focal kainate application: functional evidence for enhancement of electrographic seizures. *J Neurosci* 1999;19:5054–5065.
88. D'Ambrosio R, Wenzel J, Schwartzkroin PA, et al. Functional specialization and topographic segregation of hippocampal astrocytes. *J Neurosci* 1998;18:4425–4438.
89. Liu M, Pleasure SJ, Collins AE, et al. Loss of β2/NeuroD leads to malformation of the dentate gyrus and epilepsy. *Proc Natl Acad Sci USA* 2000;97:865–870.
90. Schwarzer C, Sperk G. Hippocampal granule cells empress glutamic acid decarboxylase-67 after limbic seizures in the rat. *Neuroscience* 1995;69:705–709.
91. Yan Q, Rosenfeld RD, Matheson CR, et al. Expression of brain-derived neurotrophic factor protein in the adult rat central nervous system. *Neuroscience* 1997;78:431–448.
92. Schmidt-Kastner R, Humpel C, Wetmore C, et al. Cellular hybridization for BDNF, trkB, and NGF mRNAs and BDNF-immunoreactivity in rat forebrain after pilocarpine induced status epilepticus. *Exp Brain Res* 1996;107:331–347.
93. Gall CM. Seizure-induced changes in neurotrophin expression: implications for epilepsy. *Exp Neurol* 1993;124:150–166.
94. Croll SD, Suri C, Compton DL, et al. Brain-derived neurotrophic factor (BDNF) transgenic mice exhibit passive avoidance deficits, increased seizure severity, and *in vitro* hyperexcitability in the hippocampus and entorhinal cortex. *Neuroscience* 1999;93:1491–1506.
95. Salin P, Tseng GF, Hoffman S, et al. Axonal sprouting in layer V pyramidal neurons of chronically injured cerebral cortex. *J Neurosci* 1995;12:8234–8245.
96. Sugino T, Nozaki K, Tokime T, et al. 3-Nitropropionic acid induces poly (ADP-ribosyl)ation and apoptosis related gene expression in the striatum *in vivo*. *Neurosci Lett* 1997;237:121–124.
97. Buckmaster PS, Dudek FE. Neuron loss, granule cell axon reorganization, and functional changes in the dentate gyrus of epileptic kainate-treated rats. *J Comp Neurol* 1997;385:385–404.
98. Esclapez M, Hirsch JC, Ben-Ari Y, et al. Newly formed excitatory pathways provide a substrate for hyperexcitability in experimental temporal lobe epilepsy. *J Comp Neurol* 1999;408:449–460.
99. Bengzon J, Kokaia Z, Elmer E, et al. Apoptosis and proliferation of dentate gyrus neurons after single and intermittent limbic seizures. *Proc Natl Acad Sci USA* 1997;94:10432–10437.
100. Gray WP, Sundstrom LE. Kainic acid increases the proliferation of granule cell progenitors in the dentate gyrus of the adult rat. *Brain Res* 1998;790:52–59.
101. Parent JM, Yu TW, Leibowitz RT, et al. Dentate granule cell neurogenesis is increased by seizures and contributes to aberrant network reorganization in the adult rat hippocampus. *J Neurosci* 1997;17:3727–3728.
102. Scharfman HE, Goodman JH. Granule-like neurons at the hilar/CA3 border after status epilepticus and their synchrony with area CA3 pyramidal cells: functional implications of seizure-induced neurogenesis. *J Neurosci* 2000;20:6144–6158.
103. Gould E, Reeves AJ, Graziano MSA, et al. Neurogenesis in the neocortex of adult primates. *Science* 1999;286:548–552.
104. Scharfman HE. Epileptogenesis in the parahippocampal region: parallels with the dentate gyrus. In: Scharfman HE, Witter MP, Schwarcz R, eds. *The parahippocampal region: basic science and clinical implications.* New York: New York Academy of Sciences, 2000:305–327.
105. Tsien JZ, Huerta PT, Tonegawa S. The essential role of hippocampal CA1 NMDA receptor-dependent synaptic plasticity in spatial memory. *Cell* 1996;87:1327–1338.