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
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 groundbreaking 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 phagocytic 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
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 \( \gamma \)-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.

**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 stim-
ulations required to achieve this plateau depends on several
factors, such as the frequency and duration of focal stimula-
tion and the temporal interval between stimuli (42). In addi-
tion, however, the site of stimulation is critical for the de-
velopment of kindling. Studies of several limbic sites, as well
as comparisons of neocortical and subcortical regions, dem-
onstrated that some extrahippocampal sites, for example,
the amygdala, achieve the fully kindled state much faster
than the hippocampus (43). In addition, focal pharma-
ologic manipulations revealed that both the development and
the expression of kindling are significantly influenced by
certain subcortical structures, including the midline thala-
mus 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, be-
cause 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 at-
tenuate 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 kin-
dling model will eventually also provide a better definition
of the molecular events that underlie the progressive length-
ening 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 spon-
taneous seizures. Since the 1980s, the development of ani-
mal 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 stimu-
lation 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 in-
termittently 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. Sec-
ond, 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 histopath-
ologic 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 condi-
tion, 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 projec-
tion and interneurons, are often found in many limbic sites
associated with MTLE. In some cases, the synaptically me-
diated responses in these neurons show prolonged excitatory
depolarizations with multiple superimposed action poten-
tials (23,56,57) (Fig. 127.3). Underlying these profound
changes are multiple presynaptic and postsynaptic altera-
tions 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 physi-
ology (58,59). These changes are necessarily complex be-
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 deficit 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 co-localized 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 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 dependence and allows channel opening at central neurons even at normal, hyperpolarized membrane potentials. The physiologic action of magnesium, an endogenous modulator of the NMDA receptor, greatly reduces the receptor’s voltage dependence 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 prognocussive 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
A 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. Amg, amygdala; DG, dentate gyrus; EC, entorhinal cortex; HC, hippocampus.

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 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.

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Chapter 127: Temporal Lobe Epilepsy


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