Feature Article

Cellular and Molecular Basis of Epilepsy

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The epilepsies comprise a remarkably diverse collection of disorders that affect 1% of the population in the United States (Hauser and Hesdorffer, 1990). Current therapy is symptomatic. Available drugs reduce seizure frequency in the majority of patients, but only 40% are free of seizures despite optimal treatment (Elwes et al., 1984; Mattson et al., 1985). Neither an effective prophylaxis nor a cure of any of these disorders is available except neurosurgical resection of epileptic tissue in selected instances. There is hope that understanding the cellular and molecular mechanisms of the epilepsies will lead to improved therapies as well as new insights into brain structure and function.

Because of the inherent diversity of the epilepsies and their models and the wide range of techniques used for investigating their cellular and molecular basis, I focused on selected models and issues, attempted to bring some coherency to the findings, and sought to draw conclusions that may be generally relevant to epilepsy. I made a special effort to show how investigations of the epilepsies with methods from diverse disciplines can be complementary and mutually reinforcing. By use of the tools of electrophysiology it was initially demonstrated that the epilepsies are disorders of neuronal excitability, which were subsequently characterized in populations of neurons, in individual neurons, and single ion channels. Advances in molecular biology and molecular genetics have elucidated the molecular mechanism of a familial epilepsy. I have attempted to show how these diverse approaches can be mutually reinforcing and explain how electrophysiologic insights into the mechanisms of seizures induced by high K^+ provide a plausible connection between the genotype and phenotype in a familial epilepsy. Throughout my account I have addressed the potential therapeutic implications of discerning the underlying mechanisms.

The first topic considered is the terminology and classification of epileptic seizures. Next, I address the cellular mechanisms of seizures induced in tissue slices isolated from *normal* brain. This provides a framework for considering mechanisms that underlie the enduring predisposition of a brain to exhibit a seizure in the absence of an overt extrinsic stimulus. Finally, I present ways

of utilizing genetics for the study of epilepsy in animals and humans.

Terminology and epileptic seizure classification

The term “seizure” refers to a transient change of behavior due to the disordered, synchronous, and rhythmic firing of populations of CNS neurons. The term “epilepsy” refers to a disorder of brain function characterized by the periodic and unpredictable occurrence of seizures. Seizures can be “nonepileptic” when evoked in a normal brain by treatments such as electroshock or chemical convulsants or “epileptic” when occurring without apparent provocation.

Seizures are thought to arise at cortical sites. Epileptic seizures have been classified into *partial* seizures which begin focally at a cortical site, and *generalized* seizures, which entail widespread involvement of the cortex of both hemispheres from the outset (Commission, 1981). The behavioral manifestations of a seizure are determined by the functions normally served by the cortical region at which the seizure arises. For example, a seizure arising in the motor cortex is manifest as clonic jerking of the body part controlled by the cortical region of origin. A *simple* partial seizure is associated with preservation of consciousness. A *complex* partial seizure is associated with impairment of consciousness. The majority of complex partial seizures originate in the temporal lobes. Absence, myoclonic, and tonic-clonic are examples of *generalized* seizures. An absence seizure is characterized by the abrupt cessation of ongoing activities associated with a blank stare lasting a few to 30 sec and followed by an abrupt return to normal behavior. A myoclonic seizure consists of a brief, shock-like contraction of muscles, which may be confined to part of one extremity or may be generalized. A tonic seizure consists of sustained muscle contractions, whereas a clonic seizure consists of muscle contractions alternating with periods of muscle relaxation; a tonic-clonic seizure usually involves muscle groups throughout the body, is associated with loss of consciousness, and typically lasts 30–60 sec. A given patient often exhibits multiple kinds of seizures in different seizure episodes. In addition to this seizure classification, a more recent classification species *epileptic syndromes*, which refer to clusters of symptoms frequently occurring together and include such factors as seizure types, etiology, and age of seizure onset (Commission, 1989).

Other commonly used terms include the adjectival modifiers “ictal” (seizure-like) and “interictal” (between seizure). Electroencephalograms (EEG) taken from humans or experimental animals during seizures reveal distinctive abnormalities, termed “electrographic seizures.” EEG patterns recorded from neocortex during tonic seizures differ from those recorded during clonic

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seizures. Similarities of abnormal electrical patterns recorded during seizures in cortex *in vivo* (Matsumoto and Ajmone-Marsan, 1964a,b) and from brain slices *in vitro* have led some investigators to use the terms “tonic” and “clonic” when referring to distinct forms of electrographic seizures (Traynelis and Dingledine, 1988). The term “status epilepticus” is used to describe very prolonged seizures or seizures occurring so frequently that there is no recovery between attacks.

Cellular mechanisms of partial seizures: insights from the high K⁺ model

Cellular electrophysiologic studies of epilepsy over roughly two decades beginning in the mid-1960s centered on elucidating the mechanisms underlying the depolarization shift (DS), the intracellular correlate of the interictal “spike.” The interictal spike is a sharp waveform identified in the EEG of patients with epilepsy. It is asymptomatic, in that it is not accompanied by any detectable change in the patient’s behavior but it is often localized in the brain region in which seizures originate in a given patient. The DS consists of a large depolarization of the neuronal membrane associated with a burst of action potentials. In most cortical neurons, the DS is generated by a large excitatory synaptic current that can be enhanced by activation of voltage-regulated intrinsic membrane currents (Johnston and Brown, 1981; Prince and Connors, 1984; Dichter and Ayala, 1987). Although the mechanisms generating the DS are increasingly understood, it remains unclear whether the interictal spike (“burst”) triggers a seizure, inhibits a seizure, or is an epiphenomenon with respect to seizure occurrence. The quest for the mechanisms of DS generation set the stage for an inquiry into the cellular mechanisms underlying a seizure.

Several *in vitro* models of seizures were developed in the past decade, using brain slices in which many synaptic connections are preserved. Most of these models have been developed in hippocampal slices by altering the ionic composition of the bathing media, including low Ca²⁺ (Jefferys and Haas, 1982; Taylor and Dudek, 1982), zero Mg²⁺ (Anderson et al., 1986), or elevated K⁺ (Traynelis and Dingledine, 1988). Exposure of olfactory cortical slices to the K⁺ channel blocker 4-aminopyridine (Galvan et al., 1982) and hippocampal or neocortical slices of newborn rats to GABA_A antagonists at elevated K⁺ (Swann and Brady, 1984; Hablitz, 1987) also evokes seizures. Electrical stimulation of hippocampal slices evokes seizures (Somjen, 1984; Stasheff et al., 1985). Spontaneous seizures and spreading depression—seizure-like events with intense cell firing and profound depolarization—have been found in slices of immature rabbit hippocampus (Haglund and Schwartzkroin, 1984). The diverse methods of evoking seizures in rat and rabbit hippocampus suggest that diverse mechanisms might also trigger seizures in humans.

While valuable lessons have been learned from each of these models, seizures induced in hippocampal slices by artificially imposed elevated levels of K⁺ (Traynelis and Dingledine, 1988) are of particular interest (Fig. 1). Elevated concentrations of K⁺ (10–12 mM compared to normal of 3 mM) have been identified during seizures recorded in cats *in vivo* (Moody et al., 1974; Fisher et al., 1976; Lothman and Somjen, 1976), but whether the elevated K⁺ is the cause and/or the consequence of the seizures long remained controversial (Lux et al., 1986). Support for a causal role for elevations of K⁺ in seizure initiation recently emerged from the work of Traynelis and Dingledine (1988), who demonstrated that bathing hippocampal slices from adult rats in solutions containing 8.5 mM K⁺ is sufficient to trigger

recurrent seizures in the CA1 pyramidal cells of the hippocampus in roughly 20% of slices (Fig. 1*b*). The seizures occur in the CA1, but not CA3, region of hippocampus as evident in field potential recordings (Fig. 1*a,c*). The seizure consists of a tonic phase, lasting up to 10 sec, evident in a prolonged depolarization and sustained high-frequency firing of CA1 pyramidal cells, paralleled by a negative extracellular potential in the cell layer (Fig. 1*c*). The tonic phase is followed by a clonic phase, lasting about 10–80 sec, which consists of brief bursts of action potentials riding on a relatively brief depolarization. Since the concentration of 8.5 mM K⁺ is well within the range of elevated K⁺ concentrations described during seizures *in vivo* (Moody et al., 1974; Fisher et al., 1976; Lothman and Somjen, 1976), it seems reasonable to infer that the rise of K⁺ somehow initiated and/or prolonged the seizure.

In addition to implicating K⁺ in generation of seizures, Traynelis and Dingledine (1988) demonstrated that interictal bursts can trigger a seizure. Both the tonic and clonic phases of the electrographic seizures in CA1 neurons are synaptically activated by the brief, synchronous interictal bursts of CA3 neurons. Knife cuts between CA3 and CA1 transected the Shaffer collateral axons through which the CA3 neurons synaptically activate CA1 neurons (note wiring diagram of circuit in Fig. 1*a*). The knife cuts abolished the seizures in CA1, but the seizures were restored by electrical stimulation on the CA1 side of the knife cut, stimulations that activated the cut axons and mimicked the interictal bursts. These data demonstrate that the interictal bursts of CA3 neurons are necessary for seizure initiation in CA1. The fact that seizures could be evoked by electrical stimulation of CA1 distal to the knife cut implied that no change intrinsic to the soma and dendrites of CA3 neurons is necessary to initiate a seizure. The absence of an increase in interictal burst frequency or intensity in CA3 preceding seizure onset in the intact slice further indicated that some change intrinsic to CA1 must render it more sensitive to a given synaptic input.

How might elevated K⁺ cause a seizure? What factor(s) governs the transition from an interictal to an ictal state? Several observations by Traynelis and Dingledine (1988, 1989) shed light on these questions. (1) During the 30–60 sec preceding a seizure, both glia and pyramidal cells in CA1 depolarized, consistent with accumulation of even higher concentrations of K⁺. (2) A competitive NMDA receptor antagonist blocks seizures, indicating that synaptic activation of NMDA receptors is necessary. (3) The electrical resistance in CA1 increases during the 20 sec prior to seizure onset, consistent with shrinkage of the extracellular space. (4) Media rendered hyperosmotic by addition of compounds restricted to the extracellular space decreased electrical resistance and abolished the seizures, suggesting that expansion of extracellular space blocks seizures.

On the basis of these findings Traynelis and Dingledine (1988) proposed that multiple synaptic and nonsynaptic factors interact in a positive feedback loop to precipitate a seizure (Fig. 2). This hypothesis is an extension of earlier ideas advanced by Green (1964), Fetzinger and Ranck (1970), Dichter et al. (1972), Yaari et al. (1986), and others. The fundamental idea is that the artificially imposed elevation of K⁺ evokes multiple consequences, which interact to increase the number and/or synchrony of CA1 pyramidal cells firing in response to an interictal burst of CA3 cells (Fig. 2). The increased firing of CA1 pyramidal cells leads to further increases of K⁺ in CA1 and this cycle becomes regenerative until the threshold for a seizure (denoted by broken arrow) is exceeded. The multiple consequences of the rise in baseline K⁺ are depicted in the five boxes receiving

Schematic Representation of Typical Recording Electrodes

Figure 1. *a*, Schematic depicts sites of recording electrodes in pyramidal cell layers of CA3 and CA1 regions of rat hippocampal slice. The axon collateral of the neuron in CA3c is a Schaffer collateral that evokes an EPSP in the dendrite of the neuron in CA1b. Also depicted is a recurrent inhibitory loop whereby the axon collateral of the CA1b pyramidal cell excites the GABAergic basket cell, which in turn projects to and inhibits the CA1b pyramidal cell. This schematic is intentionally simplified and deletes many important connections including feedforward inhibitory circuits. *b*, Spontaneous seizures evident in field potential recordings from CA1 region of hippocampal slice bathed in media containing 8.5 mM K^+ . *A*, Occurrence of spontaneous seizures, denoted by vertical lines superimposed on the horizontal line. *B–H*, Progressively greater expansions of selected portions of record in *A*, highlighting the tonic (*G*) and clonic (*H*) components. *c*, Simultaneous field potential (CA3 and CA1) and intracellular (CA1 pyramidal cell) recordings during spontaneous seizure lasting approximately 35 sec. Interictal events occur repetitively in CA3 while seizure occurs in CA1 but not in CA3. The abrupt depolarization of approximately 10 mV recorded in the CA1 pyramidal cell at seizure onset is associated with a slow negative shift in the CA1 field potential; high-frequency firing of individual and population action potentials is evident in the intracellular and field potential recordings, respectively. From Traynelis and Dingledine (1988).

Figure 2. This schematic depicts a hypothesis of how synaptic and nonsynaptic factors might interact to initiate a seizure evoked by elevated K^+ in CA1 pyramidal cells (see text for elaboration). From Traynelis and Dingledine (1988).

arrows in the left side of Figure 2 and are italicized in the following text. The elevated K^+ produces a positive shift in the reversal potential of K^+ , *partially depolarizing the membrane* (Alger et al., 1983). The partial depolarization of the membrane shifts the membrane potential *closer to spike (action potential) threshold*. The positive shift of the reversal potential of K^+ diminishes the K^+ efflux at a given membrane potential, which impacts on several ionic conductances that regulate the excitability of the CA1 pyramidal cells. The GABA-mediated *IPSP* triggered by activation of the basket cell–recurrent inhibitory feedback to the CA1 pyramidal cell (Fig. 1) consists of both short-latency GABA_A receptor–mediated (chloride) (Dingledine and Gjerstad, 1980) and long-latency GABA_B receptor–mediated (potassium) components (Dutar and Nicoll, 1988; Solis and Nicoll, 1992). The diminished K^+ efflux at a given membrane potential would reduce the GABA_B component of the *IPSP* because this is mediated by K^+ efflux (Dutar and Nicoll, 1988; Solis and Nicoll, 1992). The elevated K^+ would reduce the short-latency (GABA_A) component of the *IPSP*, probably due to a positive shift in the chloride reversal potential (Chamberlin and Dingledine, 1988). After a prolonged burst discharge, hippocampal neurons also exhibit a large afterhyperpolarization (*burst AHP*) that limits repetitive firing; the *AHP* is thought to be generated by a Ca^{2+} –dependent K^+ conductance (Alger and Nicoll, 1980). Diminished K^+ efflux would reduce the amplitude of the *burst AHP* and limit its effectiveness. Finally, the increased K^+ would be expected to induce *swelling of neurons* through reducing K^+ efflux (Dietzel et al., 1980) and *swelling of glia* by uptake of ions and water (Kimelberg et al., 1982; Kimelberg and Frangakis, 1985); the expected reduction of extracellular space could increase neuronal synchronization due to ephaptic interactions.

Each of the various consequences listed in the preceding paragraph can directly, and in some instances indirectly, increase the number and/or synchrony of CA1 pyramidal cells firing in response to a synaptic input arising from an interictal burst of CA3 neurons. The *NMDA* subtype of glutamate receptor is subject to a voltage-dependent block by Mg^{2+} (Mayer et al., 1984; Nowak et al., 1984) and could mediate some of the indirect effects alluded to above. The *depolarization*, together with attenuation of the *IPSPs* and *AHP* could promote NMDA receptor activation through relief of the Mg^{2+} block and result in a larger and prolonged membrane depolarization (Dingledine et al., 1990), further increasing the response of CA1 pyramidal

cells to an excitatory synaptic input. The *swelling of neurons and glia* would be expected to shrink the extracellular space (Nicholson, 1983; Lux et al., 1986; Hablitz and Heinemann, 1989) and enhance transients of K^+ and other extracellular ions simply by reducing the volume entered by an ion translocated from inside the cell. The reduced extracellular space should also increase ephaptic potentials by bringing the somata of CA1 pyramidal cells into closer proximity; the field effects of these potentials could be sufficient to depolarize neighboring neurons beyond their spike threshold and contribute to synchronous bursting of populations of CA1 pyramidal cells even in the absence of synaptic activity (Jefferys, 1981; Jefferys and Haas, 1982; Snow and Dudek, 1984; Taylor and Dudek, 1984). Ultimately, these factors combine to form a threshold at which an interictal burst arriving from CA3 cells triggers the intense tonic depolarization of the population of CA1 pyramidal cells, initiating the seizure. Importantly, this positive feedback model itself is hypothetical, although many of the components have been experimentally demonstrated.

Two additional lines of evidence implicate a causal role of elevated K^+ in the interictal–ictal transition. First, seizures are induced in the CA1 region of hippocampal slices perfused with low Ca^{2+} (<0.2 mM) bathing solutions (Yaari et al., 1986). Although it is unlikely that such low Ca^{2+} concentrations normally occur *in vivo*, striking reductions of Ca^{2+} to 0.7 mM do occur during seizures *in vivo* (Heinemann et al., 1977). Following removal of Ca^{2+} , K^+ content gradually increases in the CA1 pyramidal cell layer, presumably due to the increased firing consequent to loss of Ca^{2+} –dependent inhibitory and membrane-stabilizing mechanisms. Spontaneous seizures occur when the K^+ concentration reaches approximately 0.5 mM above the initial 5 mM baseline. Pressure ejection of K^+ into CA1 stratum pyramidale in concentrations sufficient to raise K^+ approximately 0.5 mM reliably triggers seizures.

Further evidence for a causal role of K^+ emerged from work on spreading depression (SD), a form of intense neuronal depolarization and firing pattern analogous to seizures (Haglund and Schwartzkroin, 1990). The CA1, but not the CA3, region of immature (8–12 d postnatal) rabbit hippocampus has a propensity for SD (Haglund and Schwartzkroin, 1984), which is paralleled by a lower level of Na,K-ATPase, higher baseline levels of K^+ , and a lower threshold for K^+ –induced SD episodes. Importantly, a single application of the Na,K-ATPase inhibitor ouabain to the CA3 region triggered a slow rise of K^+ and

converted the CA3 region to an SD-prone region like the CA1 region. These findings indicate that impaired ability to regulate K^+ is an important determinant of the propensity of the CA1 region of immature hippocampus for SD. Haglund and Schwartzkroin (1990) presented an elaboration of the model of Traynelis and Dingledine (1988), which underscored the importance of Na,K-ATPase in regulation of seizure susceptibility.

The convincing evidence for the causal role of K^+ in seizure expression in these models raises the question as to how generally applicable are these findings. Stated differently, to what extent do mechanisms operative under these conditions contribute to seizures in other models? What is the specific human condition(s) for which these models are informative? Finally, do the mechanisms underlying seizures evoked in tissue from normal brain provide clues to the mechanisms of the hyperexcitability in an epileptic brain?

Mechanisms of temporal lobe epilepsy

Thus far, studies of the cellular mechanisms of seizures have not directly addressed the critical problem of *epilepsy per se*, namely, the cellular and molecular basis of the development and lasting predisposition for seizures. The single most common form of epileptic syndrome is complex partial epilepsy, accounting for approximately 40% of all cases of epilepsy (Hauser and Kurland, 1975). Complex partial epilepsy is manifest by complex partial seizures with or without associated simple partial and tonic-clonic seizures (Commission, 1989). In the majority of probands, complex partial epilepsy appears to arise from an abnormality intrinsic to the temporal lobe, because its surgical resection virtually eliminates epileptic seizures in 80–90% of patients who are refractory to conventional medical therapy (Spencer et al., 1982; Cahan et al., 1984; Dodrill et al., 1986; Walczak et al., 1990).

Histologic abnormalities of the resected tissues provided clues to the pathogenesis of the disorder. The most common abnormality observed is termed “Ammon’s horn sclerosis,” a pattern observed in roughly 50% of resected specimens (Bruton, 1988), characterized by striking loss of the principal neurons of hippocampus, accompanied by gliosis. An additional 15–20% of specimens contain a presumed epileptogenic lesion, such as a neoplasm or a vascular anomaly (Bruton, 1988).

Ammon’s horn sclerosis: cause and/or consequence of temporal lobe epilepsy?

Approximately 50 years following identification of Ammon’s horn sclerosis (synonymous with hippocampal sclerosis) in post-mortem studies of patients afflicted with epilepsy (Bouchet and Cazauveilh, 1825), Sommer (1880) suggested that hippocampal sclerosis caused epilepsy. Later that same year Pfleger concluded that the neuronal necrosis arose from the local circulatory or metabolic disturbances related to the seizures (Meldrum and Corsellis, 1984). Work in the 1970s and early 1980s demonstrated that status epilepticus was sufficient to cause hippocampal sclerosis (Olney, 1984), presumably through pathologic activation of glutamate receptors (Sloviter, 1983; Sloviter and Dempster, 1985; Olney, 1986; Fariello et al., 1989). The fact that resection of sclerotic hippocampus ordinarily results in dramatic improvement or cure of the epileptic condition suggested that a sclerotic hippocampus causes epilepsy. Such afflicted individuals often have a history of repeated or intense febrile seizures or status epilepticus in childhood, followed by the later development of temporal lobe epilepsy (Sagar and Oxbury, 1987;

Bruton, 1988). Thus, it seems plausible that intense seizures can cause hippocampal sclerosis, but once developed, the hippocampal sclerosis can itself cause epilepsy.

How might neuronal death and ensuing morphologic rearrangements lead to focal hyperexcitability in the hippocampus and the subsequent emergence of epilepsy? A leading hypothesis through the mid-1980s was that death of GABAergic interneurons resulted in attenuation or elimination of GABA-mediated inhibition, resulting in pathologic hyperexcitability of the principal neuronal populations in the hippocampus. However, detailed immunocytochemical studies of the sclerotic hippocampus isolated from experimental models and humans have revised thinking about mechanisms of the hyperexcitability. Sloviter (1987) demonstrated that presumptive GABAergic neurons are *more* resistant to seizure-induced neuronal death than other hippocampal neurons. By contrast, mossy cells and somatostatin-containing neurons in the dentate hilus, the region between the blades of the granule cell layers, are highly sensitive to seizure-induced cell death. The preferential preservation of GABA-immunoreactive cells was confirmed in specimens from humans with epilepsy (Babb et al., 1989). The mossy cells constitute the most numerous neuron type in the dentate hilus (Amaral, 1978), receive synaptic input from both dentate granule cells and the perforant path (Scharfman and Schwartzkroin, 1990), project to stratum moleculare of the dentate gyrus through both associational and commissural projections (Zimmer et al., 1983; Ribak et al., 1985), and are presumably excitatory (Buzsáki and Eidelberg, 1981; Fischer et al., 1986; Schwartzkroin et al., 1990).

The finding that repeated, intense seizures cause a loss of recurrent, GABA-mediated inhibition of the dentate granule cells *in vivo* was consistent with the idea that synaptic disinhibition contributed to the hyperexcitability, yet the preferential preservation of GABAergic neurons was paradoxical. This paradox led Sloviter (1991) to propose the “dormant basket cell hypothesis” (Fig. 3). This hypothesis holds that the seizure-induced death of excitatory neurons in the hilus, perhaps the mossy cells, removes an excitatory input to the GABAergic basket cells, resulting in a disinhibition because the basket cells lie dormant without their usual activation by mossy cells. Once initiated, a partial loss of this inhibition combined with excitatory synaptic input due to otherwise normal stimuli is postulated to lead to excessive firing of the granule cells, progression of the cell death, and emergence of an epileptic condition years after the initial insult.

An alternative hypothesis holds that hyperexcitability of the dentate granule cells is a consequence of a pathologic rearrangement of neuronal circuitry in which the excitatory granule cells innervate themselves, resulting in a recurrent excitatory circuit (Nadler et al., 1980; Tauck and Nadler, 1985). This rearrangement would be attributable to the synapse elimination resulting from death of neurons like the mossy cells that normally project to the proximal third of the dendrites of the granule cells (the supragranular area). The eliminated synapses would be replaced by the mossy fiber axons of the granule cells themselves. The mossy fiber axons contain high concentrations of zinc and can be readily identified by a Timm stain, thereby facilitating detection of axonal rearrangements of these neurons. A consistent increase in this projection in the supragranular layer of the dentate gyrus has been identified with Timm staining following seizures induced by the glutamate receptor agonist kainate (Tauck and Nadler, 1985), in kindling (Sutula et al., 1988; Cavazos et al., 1991), and in specimens from humans with epilepsy (Sutula

Dormant Basket Cell Hypothesis

Figure 3. Schematics of alternative hypotheses explaining increased excitability of dentate granule cells in epilepsy models. *Bottom portion* contains typical field potential recordings from dentate hilus following two single shocks (denoted by *arrows*) of perforant path at 40 msec interval. In normal animal the first shock evokes an upward-going event reflecting EPSP interrupted by sharp downgoing event reflecting synchronous action potentials of populations of granule cells; the second shock fails to trigger the action potentials, presumed to be due at least in part to recurrent inhibition active during this time. In epileptic animal, both the first and second shocks evoke multiple population action potentials. *Top left* depicts an intentional oversimplification of circuitry in which the mossy cells (*M*) provide excitatory input to both the GABAergic basket cells (*B*) and the granule cells (*G*). *Top right* depicts how removal of the excitatory input to the basket cells due to seizure-induced death of the mossy cells is postulated to result in dormancy of the basket cells and increased response of granule cells to excitatory synaptic input. *Middle left* depicts circuitry in normal animal as in *top left*. *Middle right* depicts the formation of recurrent excitatory synapse (autapse) of granule cell axon onto its own dendrite, following removal of mossy cell input due to seizure-induced death; formation of the excitatory autapse is postulated to account for the increased response of granule cells to excitatory synaptic input. An early draft of part of this schematic was received through the courtesy of Dr. R. Sloviter.

Mossy Fiber Sprouting Hypothesis

et al., 1989). Tauck and Nadler (1985) described electrophysiologic findings in the dentate gyrus of the hippocampal slices isolated from normal and kainate-treated rats. In slices from normal rats, stimulation of the perforant path input to the granule cells produced an EPSP and population action potential evident in field potential recordings; a second stimulation administered 40 msec later evoked an EPSP but no population action potential, presumably due to the recurrent inhibition active during this time (Fig. 3). In contrast to this paired pulse inhibition observed in slices from normal rats, the second stimulation evoked multiple population action potentials in slices from kainate-treated animals (Fig. 3). This "paired pulse excitation" correlated with the presence of robust sprouting evident in Timm staining and was interpreted to be due to the existence of a functional recurrent excitatory synapse (autapse) (Fig. 3). This interpretation has evoked considerable controversy. Although the presence of the sprouting has been identified by multiple investigators, whether the granule cells themselves alone are the recipients of this anomalous projection is uncertain. Some anatomical evidence suggests that sprouted mossy fibers innervate GABAergic basket cells, which would be expected to *enhance* paired pulse inhibition of the granule cells (Sloviter, 1992). Using field potential recordings *in vivo* in kainate-treated rats, Sloviter (1992) found a reduction of granule cell inhibition and increased excitability *prior* to the development of the sprouting. The development of mossy fiber sprouting into the supragranular layer correlated with restoration of recurrent inhibition, leading Sloviter to propose that the net effect of the sprouting is inhibitory, perhaps because of preferential reinnervation of GABAergic basket cells. Thus, in contrast to the suggestion of Tauck and Nadler (1985), these results suggest that the mossy fiber sprouting represents a compensatory response to the hyperexcitability aimed at limiting seizure activity.

More recent electrophysiologic studies of slices isolated from kainate-treated rats suggest that the interpretations by Tauck and Nadler (1985) as well as Sloviter (1992) may be correct. Cronin et al. (1992) found relatively normal orthodromic and antidromic responses of dentate granule cells in hippocampal slices isolated from kainate-treated rats in normal media. By contrast, hilar stimulation in the presence of the GABA_A receptor antagonist bicuculline resulted in synchronous bursts of granule cells in roughly 25% of slices with robust sprouting but in none of the slices from control animals or from kainate-treated animals without robust sprouting. Cronin et al. (1992) suggested that new local recurrent inhibitory *and* excitatory circuits are formed, and that the excitatory circuits may be normally suppressed, but emerge when synaptic inhibition is blocked.

Although these controversies remain unresolved, the findings raise a constellation of molecular questions. It seems likely that prevention of neuronal injury would preclude this deleterious chain of events culminating in epilepsy. Understanding the molecular mechanism of the seizure-induced death of the exquisitely sensitive mossy cells may provide a clue to pharmacologic interventions aimed at rescuing them following injury. Scharfman and Schwartzkroin (1989) demonstrated that the mechanism of mossy cell injury following intense synaptic activation requires NMDA receptor activation resulting in presumptive rises of Ca²⁺. The Ca²⁺-activated intracellular signaling pathways culminating in neuronal death are obscure. However, expression of the immediate-early gene *c-fos* in some hippocampal neurons destined to die following repeated seizures (Smeyne et al., 1993) suggests that the product of this or related genes may

contribute to cell death. If so, identification of the "death genes" and of the intracellular signals controlling their expression could guide development of pharmacologic approaches. Elucidating the intracellular signaling pathways linking glutamate receptor activation to transcriptional activation of *c-fos* may shed light on these pathways (Bading et al., 1993; Lerea and McNamara, 1993). What is the molecular basis of sprouting? Expression of genes encoding neurotrophins (NGF and brain-derived neurotrophic factor) (Gall and Isackson, 1989; Ernfors et al., 1991) and neurotrophin receptors (TrkB and TrkC) (Bengzon et al., 1993) can be induced in the dentate granule cells and other neurons by seizures and may form part of the molecular machinery responsible for pathological morphologic rearrangements.

Insight into the molecular basis of seizure-induced neuronal death could provide therapies aimed at salvaging neurons following intense seizures in children, thereby preventing initiation of this deleterious sequence of events. Identifying key molecular determinants of the axonal sprouting may permit pharmacologic regulation aimed at enhancing or limiting the sprouting. If the dormant basket cell hypothesis is correct, identification of pharmacologic methods of activating the basket cells may reduce seizure frequency.

Focal lesion as a cause of temporal lobe epilepsy

How might a focal lesion such as a vascular anomaly or slowly growing neoplasm cause temporal lobe epilepsy? Perhaps the focal lesion produces focal hyperexcitability, which itself somehow increases excitability of its synaptically related brain regions and culminates in the epileptic condition. This idea arose from clinical findings that some patients with epilepsy due to a localized lesion developed evidence of two sites of seizure initiation, one in the vicinity of the lesion and another in the contralateral hemisphere (Falconer and Kennedy, 1961; Falconer et al., 1962; Morrell, 1979). The discovery of the kindling phenomenon by Goddard and his colleagues provided a model to investigate this idea (Goddard et al., 1969; McNamara et al., 1993). Kindling refers to a process in which repeated, focal applications of initially subconvulsive electrical stimulations eventually results in intense partial and generalized convulsive seizures. Once established, this increased sensitivity persists for the life of the animal. The necessary condition for induction of kindling is the periodic production of focal electrical seizures (afterdischarge); the electrical stimulus provides a convenient method of triggering focal electrical seizures. The essence of this model is that focal seizures produce a lasting propensity for longer and more widely propagated seizures and a lowered seizure threshold.

A focal vascular anomaly could produce focal hyperexcitability. For example, microhemorrhages occur in the immediate vicinity of small cavernous hemangiomas (Russell and Rubinstein, 1977; Bruton, 1988), thereby depositing iron complexed with hemoglobin into the extracellular space. Focal deposition of iron is sufficient to induce focal electrical seizure activity (Reid and Sypert, 1984), which in turn could "kindle" target structures. This idea is consistent with clinical observations of therapeutically refractory patients in whom surgical removal of both an extrahippocampal temporal lobe lesion such as a tumor or hamartoma and the ipsilateral hippocampus provides more effective relief of seizures than removal of either the lesion or hippocampus alone (Fish et al., 1991; Blume et al., 1993; Cascino et al., 1993).

One hypothesis that accounts for the hyperexcitability of the brain is that it is due to structural rearrangements exemplified by sprouting of the mossy fiber axons of the dentate granule cells similar to that described above in the kainate model (Sutula et al., 1988). An alternative hypothesis attributes the hyperexcitability to enhanced function of a subpopulation of glutamatergic synapses using NMDA receptors. Systemic administration of NMDA receptor antagonists suppress kindled seizures (McNamara et al., 1988). Intracellular recordings in hippocampal slices from kindled animals disclose enhanced participation of NMDA receptors in the perforant path–granule cell EPSP (Mody and Heinemann, 1987). Morrisett et al. (1989) demonstrated a selective and long-lasting increased sensitivity of hippocampal neurons to NMDA in slices isolated from kindled animals. Martin et al. (1992) used a grease gap technique to show that CA3 pyramidal neurons in particular exhibited a striking and long-lasting increase in the sensitivity to NMDA-evoked depolarization. The increased sensitivity was evident in slices removed either one day or one month after the last seizure. The molecular basis of the increased sensitivity to NMDA may be the expression of a novel subtype of NMDA receptor. That is, a striking increase (150%) in number of NMDA receptors detected by binding of an NMDA antagonist, ^3H -CPP, has been identified in membranes isolated from the CA3 region of hippocampus of kindled animals (J.E. Kraus, G.C. Yeh, D.W. Bonhaus, J.V. Nadler, and J.O. McNamara, unpublished observations). This is a “novel” NMDA receptor since it is not recognized by another NMDA antagonist, ^3H -CGS 17555. The expression of this novel NMDA receptor may underlie the increased sensitivity to NMDA since the direction, locale, and time course of increased numbers of NMDA receptors coincide with the enhanced sensitivity to NMDA-evoked depolarization (Yeh et al., 1989; Martin et al., 1992; Kraus et al., in press).

The lasting, increased NMDA sensitivity of CA3 pyramidal cells of the kindled hippocampus might enhance the responsiveness to synaptically released glutamate and lead to initiation and/or enhanced propagation of a seizure. Computer modeling of the properties of a network of CA3 pyramidal neurons indicates that an increased conductance of a Ca^{2+} channel (as might be produced by a novel NMDA receptor) in the apical dendrites would increase the likelihood of an interictal burst becoming prolonged as in a seizure (Traub et al., 1993). Identifying the molecular nature of this novel NMDA receptor and ascertaining its cellular and subcellular locale will help determine whether and how the synaptic physiology of CA3 pyramidal cells is modified. This in turn will facilitate elucidating the role of this novel receptor in the hyperexcitability of the CA3 pyramidal cells in the kindled hippocampus (King et al., 1985) and how the CA3 pyramidal cells might contribute to the hyperexcitability of the kindled brain.

Genetic approaches to epilepsy

Included among the more than 40 individual epileptic syndromes described in humans (Commission, 1989) are at least eight familial forms in which genetic determinants appear to be prominently involved. In contrast to the intensive investigations aimed at elucidating the cellular mechanisms of epileptiform activity over the past three decades, the application of modern techniques of human genetics to the study of epilepsy is in its infancy. Insights into the genetics of epilepsy have emerged from studies of twins and linkage analyses of pedigrees with familial epilepsies (Dichter and Buchalter, 1993).

Twin studies of familial epilepsies. Analyses of childhood ab-

sence epilepsy (CAE), juvenile absence epilepsy (JAE), and juvenile myoclonic epilepsy (JME) in monozygotic (MZ) and dizygotic (DZ) twins have provided clues to the genetic basis of these disorders. CAE is characterized by absence seizures with or without tonic-clonic seizures beginning between the ages of 3 and 10. Affected individuals usually have a normal intellect and no other neurologic deficits. JAE is similar to CAE except for a later age of onset (10–14 years) (Janz, 1985; Delgado-Escueta et al., 1990), frequency of spike-wave discharge on EEG (CAE, 2.5–3.5 Hz; JAE, >3.5 Hz; Janz, 1985; Dooze and Baier, 1989; Delgado-Escueta et al., 1990), and frequency of absence seizures (CAE, many per day; JAE, <1/d; Janz, 1985). JME is characterized by myoclonic and tonic-clonic seizures with absence seizures in approximately 30% (Commission, 1989). Seizures are especially common shortly after awakening. Onset of seizures occurs in adolescence and the disorder is lifelong.

Berkovic et al. (1993) studied 245 twin pairs in which one or both twins have seizures. Twenty pairs of MZ twins were identified in which at least one twin had CAE, JAE, or JME. Thirteen of the 20 twins (65%) were concordant for epilepsy. In each instance, the twins exhibited the identical syndrome; stated differently, the epilepsies were “syndromically faithful.” Each of the seven “unaffected” twins exhibited an abnormal EEG; 21 pairs of DZ twins were identified in which at least one twin had CAE, JAE, or JME; 5 of the 21 pairs (24%) were concordant for epilepsy. In contrast to the MZ twins, four of the five pairs of DZ twins concordant for epilepsy exhibited *different* epilepsy syndromes; that is, the epilepsies in DZ twins were usually “syndromically unfaithful.” The presence of CAE and other epilepsy syndromes in families in which the proband exhibited JME (Greenberg and Delgado-Escueta, 1993) is consistent with these observations in DZ twins. The studies of Berkovic et al. (1993) replicate a number of the earlier findings by Lennox (1951) and Metrakos and Metrakos (1961).

Several conclusions can be drawn from these observations. The high concordance rate in MZ twins in comparison to DZ twins implicates a strong genetic determinant. The disorders exhibit a high penetrance, since at least 65% of MZ pairs are concordant for epilepsy. The inheritance of a given disorder does not follow a simple Mendelian pattern (i.e., autosomal dominant or recessive, X-linked, etc.) in view of the lack of syndromic fidelity among DZ twins. The lack of Mendelian patterns of inheritance together with syndromic fidelity among MZ but not DZ twins leads us to favor the idea that multiple but overlapping genes underlie each disorder; that is, inheritance of a given gene(s) predisposes an individual to multiple forms of these disorders but inheritance of a different gene(s) predisposes an individual to one specific disorder. Interactions between genetic predisposition and environmental factors could also contribute to expression of these disorders.

Linkage analyses of familial epilepsies. Thus far, the chromosomal loci of mutant genes responsible for three familial epileptic syndromes have been identified by linkage analysis. The locus for JME was mapped to chromosome 6p in families identified in California using HLA typing and properdin factor B (Greenberg et al., 1988; Greenberg and Delgado-Escueta, 1993). The maximum LOD (“log of the odds”) score obtained was 3.78 using a recombination fraction of 0.01, assuming autosomal dominant inheritance and 90% penetrance. [Explanations of LOD scores and recombination fractions are beyond the scope of this article, but the reader might consult either Brock (1993) or Davies (1986) for discussions of these concepts.] Individuals were characterized as affected based upon an abnormal EEG

and also if syndromes such as JAE and CAE were expressed. If clinically normal individuals with abnormal EEGs were defined as unaffected, a positive LOD score was not obtained (Greenberg and Delgado-Escueta, 1993). The localization of JME to the same region of 6p was confirmed in 23 families from Berlin by Weissbecker et al. (1991) using HLA serologic markers. The highest LOD score obtained was 3.11, defining affecteds as having JME or other familial epilepsies but not using abnormal EEGs as a criterion. A more recent study of 25 families with JME identified in the United Kingdom and Sweden (Whitehouse et al., 1993) examined linkage with eight polymorphic DNA markers on 6p. No evidence for linkage on 6p was found despite using different models for linkage analysis (either pairwise or multipoint), different patterns of inheritance (autosomal recessive or dominant), or variable penetrance (age-dependent high or low penetrance). These findings may reflect the presence of genetic heterogeneity of the disorder. Alternatively, Whitehouse et al. (1993) also suggest that, because so many models were used in the previous studies of JME, some doubt as to the exact statistical significance of the LOD scores exists.

Of all the known familial epilepsies, only two, benign familial neonatal convulsions (BNFC) and Unverricht-Lundborg syndrome, are inherited in a simple Mendelian pattern. BNFC is a rare disorder characterized by unprovoked tonic, tonic-clonic, and focal clonic seizures in the first postnatal week (Commission, 1989). The pattern of inheritance is autosomal dominant. Approximately 10% of individuals affected with BNFC exhibit seizures later in life. Leppert et al. (1989) established tight linkage (maximum LOD score of 5.64) between two polymorphic markers on chromosome 20q and the disease locus in a single pedigree containing 19 affected individuals spanning five generations. Ryan et al. (1991) and Malafosse et al. (1992) confirmed this localization in additional families. A second locus for BNFC was recently identified on 8q (Lewis et al., 1993) in another large pedigree spanning three generations with 14 affected individuals. A maximum LOD score of 4.43 was obtained with two polymorphic DNA markers. This establishes the genetic heterogeneity of the disorder. The possibility of further genetic heterogeneity is suggested by the finding of an autosomal recessive form of this disorder (Schiffman et al., 1991).

Unverricht-Lundborg syndrome is a form of progressive myoclonic epilepsy inherited in an autosomal recessive pattern with onset between 6 and 15 years of age (Unverricht, 1891; Berkovic et al., 1986). It is characterized by myoclonic and tonic-clonic seizures together with progressive dementia, ataxia, and dysarthria. The prominence of neurologic deficits in addition to epilepsy distinguishes this from CAE, JAE, JME, and other forms of "pure epilepsy." Linkage analyses of 12 pedigrees containing 26 affected individuals using polymorphic DNA markers localized the disorder to chromosome 21q22.3 with a multipoint LOD score of 10.08 (Lehesjoki et al., 1991).

Genetic models of epilepsy in animals. Genetic models of epilepsy have been identified in diverse species including gerbils, mice, rats, and baboons. A diversity of seizure types have also been identified, including photic-induced myoclonic seizures, and spontaneous clonic motor, absence, complex partial, and tonic-clonic seizures. These animal models permit applying genetic analysis to the complex problem of hyperexcitability in the mammalian brain. A specific gene can be identified in the affected animals that controls brain excitability and whose homolog may underlie some forms of epilepsy in humans.

Seventeen single locus (and presumed single gene) mutations associated with epilepsy as a prominent phenotype have been

identified in the mouse (Noebels, 1986). In no instance has the mutant gene responsible for an epileptic phenotype in a mouse been identified at a molecular level. Of the 17 single locus mutations expressing an epileptic phenotype, at least four—tottering, stargazer, mocha, and lethargic—exhibit features characteristic of absence seizures (Noebels, 1986). The momentary behavioral arrest associated with bilaterally synchronous 6–7 Hz spike-wave bursts on the cortical EEG in these mutant mice suggests these represent absence seizures, a suggestion supported by responsiveness to anti-absence drugs such as ethosuximide in the tottering (Heller et al., 1983) and lethargic (Hosford et al., 1992).

Although the absence seizures expressed by these strains are very similar, both genetic and phenotypic heterogeneity is apparent. The chromosomal loci of the mutations of the four strains are distinct: totterer, chromosome 8; stargazer, chromosome 15; mocha, chromosome 10; and lethargic, chromosome 2 (Noebels, 1986; Noebels et al., 1990; Hosford et al., 1992). If the mutant genes underlying these putative models of absence exist as single copies, their distinct chromosomal loci indicate that mutations of at least four different genes can produce an absence seizure phenotype. Moreover, significant phenotypic differences have come to light among these strains. Responsiveness of absence seizures to GABA_B antagonists in lethargic but not totterer mice implies different mechanisms underlying overtly similar seizures (Hosford et al., 1992) as does the sprouting of locus ceruleus axons in the totterer (Noebels, 1984) but not in the stargazer (Noebels et al., 1990). These distinct genotypes may have parallels in human absence epilepsy; perhaps differences in genotypes explain responsiveness of some but not all patients to a particular anti-absence agent or phenotypic differences between childhood and juvenile absence epilepsy.

The recent development of gene knockout technology provides a new and powerful approach to the analysis of the effects of selective elimination of a single gene on the epileptic phenotype. Available evidence suggests that formation of long-term potentiation (LTP) of excitatory synapses is necessary for the development of kindling (Sutula and Steward, 1986, 1987). Formation of LTP is impaired in transgenic mice carrying a null mutation for the gene encoding the α -subunit of calcium/calmodulin kinase II (α -CaMKII) (Silva et al., 1992). It therefore seemed plausible that the development of kindling would be impaired in homozygous mutants ($-/-$) carrying the null mutation of α -CaMKII. To our surprise, we found that the $-/-$ mice exhibited profound hyperexcitability. That is, administration of a single, normally subconvulsive stimulation of the amygdala evoked prolonged, often repeated, and sometimes fatal seizures (Butler et al., 1993). Morphologic study of *unstimulated* mice disclosed extensive sprouting of mossy fibers in the supragranular region of the dentate gyrus of $-/-$ mice in comparison to wild-type mice with intermediate amounts evident in heterozygotes. Together with evidence of profound hyperexcitability, this sprouting suggests that the $-/-$ mice are *epileptic*. If so, this mutation and myoclonic epilepsy and ragged red fiber disease (MERRF) represent the only identified genetic defects that cause epilepsy in mammals. Combining genetic approaches with other methods of investigation should facilitate elucidating the cellular and molecular mechanisms of this phenotype.

Molecular etiology of an epilepsy (MERRF). The molecular basis of a human epilepsy was elucidated three years ago by Shoffner et al. (1990). MERRF (Tsairis et al., 1973; Fukuhara

et al., 1980; DiMauro et al., 1985; Berkovic et al., 1989; De Vivo, 1993) is a rare familial disease with exclusively maternal inheritance. Epileptic seizures are a prominent manifestation. The epileptic seizures are typically myoclonic, but tonic-clonic, elementary partial, and complex partial seizures also occur (Berkovic et al., 1989). The myopathy is named "ragged red fiber" because of a distinctive disordered appearance of occasional muscle fibers, revealed by a modified Gomori trichrome stain. Although the syndrome is defined by the occurrence of a myopathy identified by histopathology, the clinical manifestations of the myopathy are often mild or absent. Additional clinical features include ataxia, dementia, and hearing loss. The age of onset varies from 3 to 63 years. Perhaps the most striking feature of the disease is that the severity, rate of progression, and manifestations vary enormously, even among members of the same family (Berkovic et al., 1989).

Several lines of evidence indicated that MERRF is due to a mutation of a mitochondrial gene (Shoffner et al., 1990). The maternal inheritance affecting both male and female offspring pointed to a mitochondrial gene, since the oocyte but not sperm contributes cytoplasmic mitochondria to the zygote. It is associated with defects in mitochondrial oxidative phosphorylation (OXPHOS) complexes enriched in proteins encoded by mitochondrial genes, namely, complexes I and IV. The variability of the OXPHOS defect among different tissues is consistent with the random distribution of mitochondria containing wild-type or mutant DNA among cells during organogenesis in embryonic development. Among the potential mitochondrial genes under consideration, Wallace et al. (1988) suspected that MERRF may be due to a mutation of an mtDNA, rRNA, or tRNA gene because the mitochondrial translation products derived from lymphoblastoid cell lines of MERRF patients exhibited a reduction in labeling of high- relative to low-molecular-weight polypeptides. Shoffner et al. (1990) demonstrated that a point mutation, an A to G mutation at nucleotide pair 8344, of a mitochondrial gene encoding a tRNA^{lys} is responsible for the disease. They demonstrated the presence of the mutation in three MERRF pedigrees, its absence in 75 controls, and showed that the mutation was heteroplasmic, that is, that the proportion of wild-type and mutant mtDNA varied within a given tissue among affected relatives.

The mechanism by which the mitochondrial mutant gene produces the pleiotropic phenotypic manifestations of MERRF, in particular the epileptic seizures, is unclear, but it seems likely that an OXPHOS defect is responsible. The direct consequence of this mutation is impaired oxidative phosphorylation and reduced mitochondrial free energy in the form of ATP. This is noteworthy since an estimated 25–50% of brain ATP is devoted to the operation of Na,K-ATPase (Albers et al., 1989), the molecular basis of the Na,K pump that maintains the differential distribution of these monovalent cations across the cell membrane. In view of the pivotal role of elevated K⁺_o in the genesis of seizures and the critical role of reduced Na,K-ATPase in the propensity of the immature rabbit hippocampus to exhibit intense seizure-like episodes (Haglund and Schwartzkroin, 1990), it seems plausible that this genetic defect causes seizures by an impaired regulation of K⁺_o. That is, the impaired Na,K-ATPase activity would result in an elevated K⁺_o and evoke the depolarization of neuronal membranes and other consequences presented in Figure 2. The different types of epileptic seizures affecting different MERRF patients could simply reflect the particular population of neurons in which the mutant mitochondria are

in greater abundance, but the explanation for the predilection for myoclonic seizures remains obscure. Since OXPHOS decays with age in all individuals, an individual with a high percentage of mutant mtDNA could be normal as a child yet profoundly impaired as an adult (Wallace, 1992). Indeed, the unusual variability in age of onset of the disease may be explained by a combination of the percentage of mutant mtDNAs in a given tissue and age (Wallace, 1992).

The demonstration that the molecular etiology of this epilepsy evolves from an OXPHOS defect suggests that a similar etiology may underlie other forms of epilepsy, especially a disorder such as progressive myoclonic epilepsy of Unverricht-Lundborg. Unfortunately the genetics underlying OXPHOS regulation is extremely complex. The mitochondrial genome contains genes encoding 13 OXPHOS proteins and the tRNAs and rRNAs needed for their expression (Wallace, 1992). The remaining 50 OXPHOS proteins, as well as hundreds of genes needed for mitochondrial replication, transcription, and translation, are encoded by nuclear genes.

Concluding remarks

In contrast to a quite homogeneous neurological disorder such as Huntington's disease, the great heterogeneity of disorders labeled as epilepsy is daunting. Yet, the past several years have witnessed remarkable progress in understanding the cellular and molecular mechanisms of the diverse epilepsies. Plausible explanations of the mechanisms of hyperexcitability in acquired epilepsies have emerged, providing hypotheses testable with gene targeting and other methods. Insights into the cellular mechanisms underlying the interictal-ictal transition are emerging from analyses of seizures in brain slices. The molecular etiology of a human epilepsy has been elucidated through a molecular genetic approach. It is increasingly evident that insights derived from approaches to epilepsy as disparate as cellular electrophysiology and molecular genetics are yielding information that is complementary and promises to be mutually reinforcing.

In the future, it seems likely that molecular genetic approaches will elucidate the molecular etiologies of epilepsies in mice. This should expedite discovery of the molecular etiologies of additional familial epilepsies in humans and will lead to development of transgenic models of epilepsy based precisely upon the genetic mechanism of the disease. Investigations of the cellular electrophysiology of these models will facilitate understanding how the mutant gene leads to the epileptic phenotype. Gene targeting approaches will permit testing whether a putative cellular and molecular mechanism identified in reduced preparation is causally linked to the epileptic phenotype in the intact mammalian nervous system. Together, these emerging insights should lead to novel and rational therapies based upon knowledge of disease mechanisms.

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