CHAPTER

40

The Epilepsies: Phenotypes and Mechanisms

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OUTLINE

EPILEPSY IS A COMMON NEUROLOGICAL DISORDER

The epilepsies constitute a common, serious neurological disorder in humans, affecting approximately 60 million people worldwide. Well in excess of 40 distinct epileptic syndromes have been identified to date. Current treatment is only symptomatic except in uncommon instances when surgical treatment is possible. While available antiseizure medications target ion channels such as the γ-aminobutyric acid $(GABA)_A$ receptor and voltage-activated sodium (Na^+) channels, current research seeks to elucidate the cellular and molecular mechanisms by which a normal brain becomes epileptic. Hopefully, this research will lead to the identification of new targets for which small molecules can be identified and used to prevent or limit progression of epilepsy.

TERMINOLOGY AND CLASSIFICATION

The term *seizure* denotes a fleeting change of behavior caused by the disordered, synchronous, and rhythmic firing of populations of neurons. The term *epilepsy* denotes a disorder of brain function expressed as the periodic and unpredictable occurrence of seizures. Pharmacological agents in current clinical use inhibit epileptic seizures, and thus are referred

TABLE 40-1 Classification of Partial Epileptic Seizures

Partial Seizure	Features	Antiseizure drugs
Simple Partial	Phenotype determined by cortical region activated (e.g., if motor cortex representing left thumb is activated, then left thumb jerking results). Consciousness is preserved.	Carbamazepine, phenytoin, valproate, gabapentin, lacosamide, lamotrigine, levetiracetam, pregabalin, tiagabine, topiramate, zonisamide
Complex Partial	Impaired consciousness lasting sec to min, often associated with automatisms such as lip smacking.	Carbamazepine, phenytoin, valproate, gabapentin, lacosamide, lamotrigine, levetiracetam, pregabalin, tiagabine, topiramate, vigabatrin, zonisamide
Partial with secondary generalization	Simple or partial complex seizure evolves into a tonic-clonic seizure with loss of consciousness. There are sustained muscular contractions (tonic) followed by periods of relaxation (clonic) lasting 1–2 min in duration.	Carbamazepine, phenytoin, phenobarbital, valproate, gabapentin, lamotrigine, levetiracetam, pregabalin, tiagabine, topiramate, zonisamide

TABLE 40-2 Classification of Generalized Epileptic Seizures

Generalized Seizure	Features	Antiseizure drugs
Absence	Abrupt loss of consciousness associated with staring and cessation of activities, normally lasting less than 30 sec.	Ethosuximide, valproate, lamotrigine
Myoclonic	Brief muscular contraction, either focal or generalized in nature.	Valproate
Tonic—clonic	Sustained muscular contractions (tonic), followed by periods of relaxation (clonic) 1–2 min in duration.	Carbamazepine, phenobarbital, phenytoin, primidone, valproate, topiramate

to as antiseizure drugs. It is currently unknown, though, whether any of these agents has any prophylactic value in preventing the development of epilepsy (epileptogenesis). Other commonly used terms used by clinicians to describe individual EEG patterns include electroencephalographic (EEG) descriptors such as ictal (seizure-like) and interictal (between seizures).

Seizures are thought to arise from the cerebral cortex, and not from other central nervous system (CNS) structures such as the thalamus, brainstem, or cerebellum. Epileptic seizures have been classified as partial seizures, which begin focally in a cortical site, and generalized seizures, which involve discharges from both hemispheres widely from the outset (Commission on Classification and Terminology of the International League Against Epilepsy, 1981). The behavioral manifestations of a seizure are determined by the functions normally served by the cortical site at which the seizure arises. For example, a seizure involving motor cortex is associated with the clonic jerking of the body part controlled by this region of cortex. A simple partial seizure is associated with preservation of consciousness, whereas a complex partial seizure is associated with impairment of consciousness. The majority of complex partial seizures originate from the temporal lobe (see Table 40-1). Examples of *generalized* seizures include absence, myoclonic, and tonic–clonic seizures (see Table 40-2). The type of epileptic seizure, diagnosed both by clinical and EEG methodology, is one determinant of the drug selected for therapy, as different antiseizure medications often demonstrate varying abilities to control different seizure phenotypes.

Apart from this epileptic seizure classification, an additional classification specifies epileptic syndromes, which are a cluster of symptoms frequently occurring together. This classification includes seizure type, etiology, age of onset, and other factors (Commission on Classification and Terminology of the International League Against Epilepsy, 1989).

The epileptic syndromes have been categorized into partial *versus* generalized epilepsies. The partial epilepsies account for roughly 60% of all epilepsies. The etiology commonly consists of a lesion in some part of the cortex, such as a tumor, developmental malformation, damage due to trauma or stroke, etc. Such lesions are often evident on brain imaging studies such as magnetic resonance imaging. Alternatively, the etiology may be genetic (see Table 40-3). The generalized epilepsies are characterized by one or more generalized seizure types (listed in Table 40-2). These account for approximately 40% of all epilepsies and are thought to have a genetic etiology. The most common generalized epilepsy is juvenile myoclonic epilepsy (JME), accounting for approximately 10% of all epileptic syndromes. The age of onset is in the early teens, and the condition is characterized typically by myoclonic, tonic—clonic, and often absence seizures. Like most generalized epilepsies, JME is usually due to the inheritance of multiple susceptibility genes; often, there is a familial clustering of cases, but the pattern of inheritance is not Mendelian.

Disrupting the delicate balance of inhibitory and excitatory synaptic transmission can trigger the disordered, synchronous firing of neurons that underlies a seizure

More than a century ago, John Hughlings Jackson, an extraordinarily insightful clinician, proposed that seizures were caused by "occasional, sudden, excessive, rapid and local discharges of gray matter," and a generalized convulsion resulted when normal brain tissue was invaded by the seizure

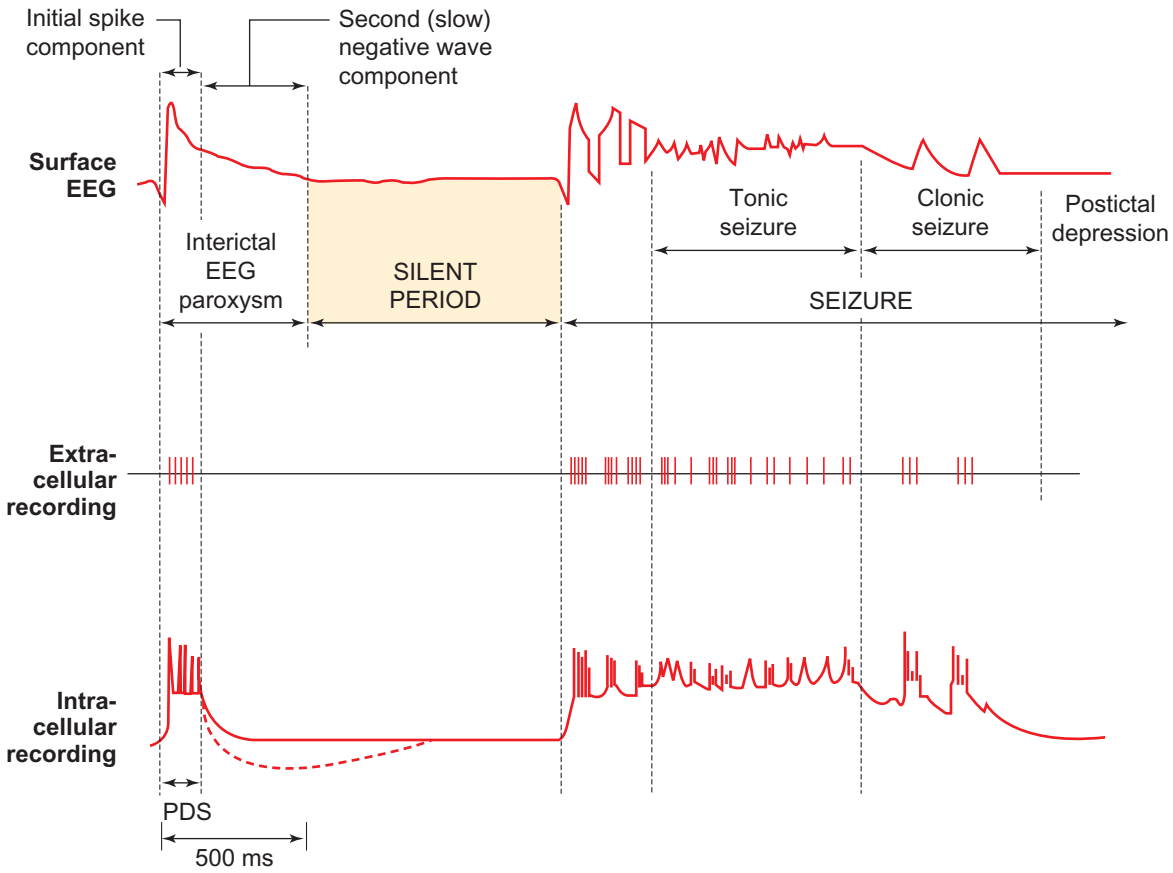

FIGURE 40-1 **Relationship among cortical EEG, extracellular, and intracellular recordings in a seizure focus exposed to a convulsant agent in cortex.** Note the high frequency firing of the neuron in both intracellular and extracellular recordings during the paroxysmal depolarization shift (PDS) (Ayala et al., 1973). Cellular electrophysiological studies of epilepsy over roughly two decades beginning in the mid-1960s were focused on elucidating the mechanisms underlying the DS, the intracellular correlate of the "interictal spike." The interictal spike is a sharp waveform recorded in the EEG of patients with epilepsy; it is asymptomatic in that it is accompanied by no detectable change in a patient's behavior. However, the location of the interictal spike helps localize the brain region from 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, a large excitatory synaptic current that can be enhanced by activation of voltage-regulated intrinsic membrane currents generates the DS.

activity initiated in the abnormal focus. In fact, this prediction provided a valuable framework for current thinking about mechanisms of partial epilepsy. The advent of the EEG in the 1930s permitted the recording of electrical activity from the scalp of humans and demonstrated that the epilepsies are disorders of neuronal excitability.

The pivotal role of synapses in mediating communication among neurons in the mammalian brain suggested that defective synaptic function might lead to an epileptic seizure, with a delicate synaptic balance necessary to maintain the normal state of neurons. That is, a reduction of inhibitory synaptic activity or enhancement of excitatory synaptic activity might be expected to trigger a seizure. Indeed, pharmacological studies of seizures have supported this hypothesis. The neurotransmitters mediating the bulk of synaptic transmission in the mammalian brain are amino acids, with GABA (Ch. 18) and glutamate (Ch. 17) being the principal inhibitory and excitatory neurotransmitters, respectively. Pharmacological studies in normal animals disclosed that injection of either antagonists of the $GABA_A$ receptor or agonists of different glutamate-receptor subtypes (NMDA, AMPA, or kainic acid) triggered seizures in otherwise normal animals *in vivo*. In contrast, pharmacological agents that enhance GABA-mediated synaptic inhibition, such as benzodiazepines, reduce seizure activity. Likewise, glutamate receptor antagonists inhibit seizures in diverse models, including seizures evoked by electroshock or chemical convulsants.

These findings were confirmed and extended by *in vitro* electrophysiological studies of brain slices from normal animals revealing that subtle (e.g., 20%) reductions of inhibitory synaptic function could lead to epileptiform activity.

Importantly, activation of excitatory synapses is often pivotal in the expression of a seizure in distinct models *in vitro.* In addition to these important pharmacological observations, electrophysiological analyses of individual neurons during a partial seizure revealed that neurons undergo a massive depolarization and fire action potentials at high frequencies (Figure 40-1) (Ayala et al., 1973). This pattern of neuronal firing is characteristic of a seizure and is uncommon during physiological neuronal activity, a finding that provides

a plausible explanation for the ability of some antiseizure drugs to inhibit seizures with minimal effect on normal functions of mammalian brain. While synapses are important, the initiation and expression of a seizure can involve a diversity of additional mechanisms, including nonsynaptic mechanisms such as the volume of the extracellular space, and intrinsic properties of a neuron such as voltage-regulated ion channels, including those gating K^+, Na^+, and Ca^{2+} ions (Traynelis & Dingledine, 1988) (see also Ch. 4). Identification of these diverse synaptic and nonsynaptic factors controlling seizures *in vitro* provides potentially valuable pharmacological targets for regulating seizure susceptibility *in vivo* in humans.

Cellular mechanisms underlying hyperexcitability have been analyzed by electrophysiological studies of hippocampal slices isolated from animals with epilepsy

The pharmacological evidence implicating GABAergic and glutamatergic synapses in the expression of seizures both *in vivo* and *in vitro* led to hypotheses as to the mechanism of the enduring hyperexcitability of the epileptic brain. That is, scientists hypothesized that one mechanism accounting for the hyperexcitability of the epileptic brain may be an impaired function of inhibitory synapses and/or enhanced function of excitatory synapses. The availability of animal models of epilepsy provided a powerful tool to test these hypotheses, particularly when *ex vivo* study of hippocampal slices isolated from epileptic animals permitted analysis of synaptic function. Also, the anatomic focus on the properties of an identified population of neurons thought to be important for epilepsy was critical, with the dentate granule cells of hippocampus providing one such anatomic locale. Consideration of the animal models and the rationale for study of the dentate granule cells will be followed by review of the analyses of the synaptic properties of these neurons in epilepsy models.

Many animal models of epilepsy have been identified (Schwartzkroin, 1993). Two of the most commonly studied models are the "kindling" and "status epilepticus" models. Kindling is a model of temporal lobe epilepsy (TLE) that is induced by the periodic administration of brief, low-intensity electrical stimulation of the amygdala or other limbic structures. Described by Graham Goddard and his colleagues (Goddard et al., 1969), initial stimulations evoke a brief electrical seizure recorded on EEG without behavioral change, but repeated (e.g., 10 to 20) stimulations result in progressive intensification of seizures, culminating in tonic–clonic seizures. Once established, the enhanced sensitivity to electrical stimulation persists for the life of the animal. Despite the lifelong propensity to express intense seizures in response to low-intensity stimulation, spontaneous seizures or a truly epileptic condition do not occur until approximately 100 stimulation-evoked seizures have occurred. The ease of control of kindling induction (i.e., stimulations administered at the investigator's convenience), its graded onset, and the ease of quantifying epileptogenesis (number of stimulations required to evoke tonic–clonic seizures) simplify study of early stages of epileptogenesis with this model.

A variety of models exist in which epilepsy arises weeks after an episode of status epilepticus, a state of continuous seizures lasting hours.

Whether triggered by chemoconvulsants (e.g., pilocarpine or kainic acid) or continuous electrical stimulation, the fleeting episode of status epilepticus is followed in the coming weeks by the onset of spontaneous seizures (Lemos & Cavalheiro, 1995; Longo & Mello, 1998), an intriguing parallel to the scenario of complicated febrile seizures in young children followed by the emergence of spontaneous seizures years later. In contrast to the limited or absent neuronal loss characteristic of the kindling model, overt destruction of hippocampal neurons occurs in both the pilocarpine and kainate models, mimicking characteristics of hippocampal sclerosis observed in many humans with medically refractory TLE. Indeed, the discovery that complicated febrile seizures are followed by and thus are almost certainly one cause of hippocampal sclerosis in young children establishes yet another commonality between these models and the human condition (VanLandingham et al., 1998).

Normally the dentate granule cells of hippocampus limit excessive activation of their targets, the CA3 pyramidal cells

Insight into the structural and functional properties of diverse populations of principal neurons of the hippocampus and its connections have provided a context for considering how the function of these neurons underlies normal behaviors such as learning and memory as well as the hyperexcitability of TLE. The extensive recurrent excitatory synaptic connections among CA3 pyramidal neurons, together with the propensity of individual CA3 pyramidal neurons to fire action potentials in a bursting pattern, explained the propensity of these neurons to exhibit seizures (Traub et al., 1989). Given this propensity, it became clear that the principal afferents of the CA3 pyramidal cells, the dentate granule cells, must function as a gatekeeper to limit the activation of the CA3 pyramidal cells and their subsequent explosion into seizure activity (Lothman et al., 1992). The uniqueness of the innervation of their targets by the granule cells underscores their function as gatekeepers. That is, excitatory principal neurons (e.g., CA3 pyramidal cell innervation of its targets in CA1) of mammalian forebrain typically innervate other excitatory neurons directly in great quantitative preference to inhibitory interneurons (Henze et al., 2002). In stark contrast, the dentate granule cells innervate approximately 10 inhibitory interneurons for every one CA3 pyramidal neuron; these inhibitory interneurons mediate feedforward inhibition of the CA3 pyramidal neurons, thus underlying the net inhibitory effect and tight control of CA3 pyramidal cell firing by the dentate granule cells (Buzsaki et al., 2004). Using deoxyglucose autoradiography studies, the dentate granule cells did indeed appear to function as a barrier for invasion of hippocampus by seizure activity *in vivo* (Collins et al., 1983). These findings led to the hypothesis that compromise of the normal barrier function of the granule cells permits activation of the CA3 pyramidal cells and recruitment of the hippocampal circuit into seizure activity, thereby contributing to the hyperexcitability of TLE.

Analyses of afferents of dentate granule cells from epileptic animals reveal abnormal inhibitory and excitatory synaptic input

Selectively enhanced function of excitatory synapses using NMDA receptors has been identified in afferents of the dentate granule cells in hippocampal slices isolated from kindled animals (Kohr & Mody, 1994).

In the pilocarpine model, net reductions of inhibitory synaptic transmission mediated by $GABA_A$ receptors have been demonstrated in dentate granule cells; this may be due in part to altered responses to GABA by $GABA_A$ receptors, which in turn may be due to altered subunit composition of the $GABA_A$ receptor (Gibbs et al., 1997). Not surprisingly, the reality is substantially more complex than described here. Paradoxically, enhanced function of $GABA_A$ synaptic input has been identified in the dentate granule cells in slices isolated from kindled animals, most likely underlying a compensatory response aimed at preventing emergence of spontaneous seizures in these animals (Buhl et al., 1996). An alternative possibility is that this enhanced GABA input contributes to hyperexcitability. Proper function of GABAergic circuits requires tight maintenance of intracellular chloride levels below extracellular levels; thus, when GABA binds to its receptor, the receptor undergoes a conformational change that allows chloride ions to flow down a gradient into the cell, resulting in hyperpolarization (Ch. 18). This regulation of intracellular chloride is largely mediated by KCC2, a K^+/Cl^- cotransporter (Ch. 3). In the pilocarpine model, reductions in KCC2 protein levels (and a corresponding shift in the driving force of Cl^-) have been identified. Elevated intracellular chloride levels disrupt the efficacy of GABA signaling by leading to a smaller hyperpolarization (or even depolarization) when the $GABA_A$ receptor is activated, compromising the function of inhibitory circuits. Indeed, depolarizing responses effected by synaptic $GABA_A$ receptors have been identified in hippocampal neurons in slices prepared from temporal lobes surgically excised for treatment of epilepsy (Huberfeld et al., 2007).

Axonal and dendritic sprouting lead to abnormal recurrent excitatory synaptic circuits among the dentate granule cells in epileptic brain

Repeated seizures have been demonstrated to result in a structural reorganization of hippocampal circuitry, a reorganization that increases substantially in the presence of cell death as occurs often in temporal lobe epilepsy. The best-described structural reorganization is that in which axons of the excitatory granule cells sprout and reinnervate themselves and/or their neighbors through recurrent collaterals, forming a feed-forward excitatory loop coined "mossy fiber sprouting" (Nadler, 2003). More recently, sprouting of basilar dendrites of the granule cells has also been identified and these provide additional targets for the sprouted axons (Ribak et al., 2004). The recurrent axonal collaterals are readily identified experimentally in various seizure models and in the human condition using the Timm's stain. The fact that networks of recurrent excitatory synapses represent an efficient substrate for initiation and propagation of seizure activity underscores the appeal of the idea that this reorganized granule cell synaptic network may contribute to the hyperexcitability of TLE. Functional evidence for the presence of recurrent excitatory synapses has emerged from synaptic physiological studies of slices in the pilocarpine model. Nonetheless, the extent to which this reorganized network of dentate granule cells contributes to the hyperexcitability of the epileptic brain is uncertain at present.

While alterations in dentate granule synaptic physiology and anatomy provide a snapshot to begin to understand how a normal brain changes to an "epileptic" brain, the dentate granule cells represent only one small piece of the complex puzzle of how a normal brain becomes epileptic. A myriad of changes have been reported to occur in neurons elsewhere in the hippocampus and other regions of the brain. Not all of these changes involve excitatory or inhibitory synapses. For example, the defective inactivation of voltage-gated sodium channels has been identified in CA1 pyramidal neurons in slices isolated from the kindling model (Gorter et al., 2002). Therefore, when one begins to assess the hyperexcitability of the epileptic brain, it is imperative to view these alterations on a global platform, and not just localized to a single population of neurons, in order to appreciate the vast complexities that are involved.

Epileptogenesis is the process by which a normal brain becomes epileptic

The very complexity of understanding mechanisms underlying the hyperexcitability of the epileptic brain has contributed to enhanced emphasis in attempts to prevent development of epilepsy, that is, epileptogenesis. Interestingly, many forms of partial epilepsy are characterized by a seizure-free interval lasting months to years between the occurrence of the causative insult and the emergence of epilepsy; termed the "latent period," this provides a valuable window of opportunity during which pharmacologic intervention might be implemented in high-risk individuals so that development of epilepsy could be prevented.

Mesial temporal lobe epilepsy (MTLE) is the most highly prevalent form of partial epilepsy, and is a progressive disorder in about one-third of MTLE patients. This is manifested as continued presence of seizures in spite of anticonvulsant therapy (Cascino, 2009; Berg et al., 2006) and destruction of cortical gray matter (Bernhardt et al., 2009). While the precise cause or causes of progression in MTLE have not been identified, an attractive hypothesis is that recurrent seizures themselves may drive the progression of MTLE—in other words, "seizures beget seizures." The fact that induction of repeated seizures alone is sufficient to produce progressively more severe spontaneously occurring seizures and death of hippocampal neurons supports this idea (Pinel & Rovner, 1978; Sayin et al., 2003; Kotloski et al., 2002). Also, consistent with this hypothesis, a progressive increase in spontaneous seizure frequency has been observed in a number of animal models following a diversity of epileptogenic insults (Noè et al., 2008; Williams et al., 2009; Kadam et al., 2010).

Identifying molecular mechanisms of epileptogenesis will provide new targets for developing small molecules to prevent epilepsy

Understanding the cellular mechanisms of epileptogenesis in molecular terms will hopefully lead to identification of molecular targets for which small molecules might be identified for the prevention of epilepsy. Studies of the kindling model established the critical role of pathological activity in the pathogenesis of partial epilepsy. This led to the question as to what molecular consequences of pathologic activity might mediate the transformation of a normal brain to an epileptic brain. In turn, this led to a focus on neurotrophins such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) that have been implicated in transducing fleeting experiences into lasting changes in phenotypes (see Ch. 29). In fact, seizures produce striking increases in the expression of BDNF. Indeed, enhanced activation of the tyrosine kinase receptor of BDNF, TrkB, occurs in multiple models of epileptogenesis (He et al., 2004). BDNF somehow contributes to epileptogenesis in the kindling model because epileptogenesis is partially inhibited in mice in which one or both

TARGETS OF RESEARCH INTO PREVENTING EPILEPTOGENESIS

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Mesial temporal lobe epilepsy (MTLE) is the most common form of partial epilepsy. Interestingly, up to two-thirds of MTLE patients exhibit a history of complicated febrile seizures, preceding the emergence of MTLE. The clinical study of these febrile seizures has revealed that these seizures are associated with MRI (magnetic resonance imaging) evidence of acute swelling of the hippocampus, which subsequently becomes sclerotic. This hippocampal sclerosis, referred to as Ammon's horn sclerosis, is frequently associated with MTLE. It is therefore thought that this period of intense febrile seizures leads, in the short term, to Ammon's horn sclerosis and, in the long term, to MTLE.

The hypothesis that early complicated febrile seizures cause epilepsy has led to intense research into the mechanisms by which "seizures beget seizures." With a greater understanding of the cellular and molecular mechanisms that underlie this process, it may be possible to identify therapeutic targets that can prevent the progression to epilepsy after febrile seizures have occurred.

Epileptogenesis research, utilizing a number of animal models, seeks to understand these mechanisms and to identify such targets. For example, there are multiple animal models in which chemically induced status epilepticus in mice or rats leads to the emergence of spontaneous recurrent seizures, which mirrors the development of MTLE following complicated febrile seizures in humans (Williams et al., 2009).

Using a number of cellular and molecular approaches to study these animal models, researchers have identified molecules that play important roles in this process and that may therefore be attractive therapeutic targets for preventing epileptogenesis following seizures.

The mammalian target of rapamycin (mTOR) is one such target that has been identified in recent years in research using animal models of epileptogenesis. The mTOR signaling pathway has been found to be upregulated after the chemical induction of status epilepticus in mice and rats. In addition, increased activation of the mTOR pathway is observed in patients with Tuberous Sclerosis Complex (TSC), a genetically caused epilepsy syndrome (see also Box 28). Treatment of mice or rats with the mTOR inhibitor rapamycin following status epilepticus has been found to significantly attenuate the appearance of hallmarks of TLE, including mossy fiber sprouting (Buckmaster & Lew, 2011). Rapamycin-induced reductions in the subsequent emergence of spontaneous recurrent seizures have been observed in some but not all of these studies (Buckmaster & Lew, 2011; Zeng et al., 2009).

In addition, the brain-derived neurotrophic factor (BDNF)-TrkB (see in Ch. 29) signaling pathway has been implicated in epileptogenesis in numerous animal studies. Levels of BDNF, which activates its receptor TrkB, have been found to increase following seizures. Indeed, seizure-induced TrkB activation has been observed in the mossy fiber pathway (Danzer et al., 2004). It is thought that TrkB activation is pro-epileptogenic, because mice lacking TrkB in forebrain neurons are unable to undergo epileptogenesis in the kindling model of epileptogenesis (He et al., 2004). Consequently, selective inhibitors of TrkB may be effective anti-epileptogenic agents.

This research will be greatly assisted by the availability of small molecule libraries that can be screened for favorable interactions with targets identified in animal studies of epileptogenesis. It is hoped that these lines of research will lead to clinical trials for methods of therapeutic intervention after status epilepticus, but before the development of spontaneous recurrent seizures.

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alleles of the BDNF gene have been eliminated. By contrast, epileptogenesis in the kindling model is prevented altogether in mice in which both alleles of the TrkB gene are eliminated (He et al., 2004), providing the first genetic or pharmacological perturbation that is *required* for epileptogenesis in this model. These findings focus the search for mechanisms of epileptogenesis on structural and functional consequences of TrkB activation. One way in which TrkB activation is thought to promote epileptogenesis is by regulating the expression of KCC2. Elevated neuronal activity has been found to result in BDNF- and TrkB-dependent reductions in KCC2 protein, leading to intracellular chloride accumulation and compromised function of GABA systems. This activity-dependent regulation of KCC2 by TrkB requires signaling through the PLCγ1 pathway, rather than the Shc pathway (see discussion of TrkB signaling pathways in Ch. 26). Consistent with this idea, epileptogenesis is inhibited in genetically modified mice in which TrkB activation of PLCγ1 is eliminated. By contrast, epileptogenesis develops as in wild-type animals in genetically modified mice in which TrkB activation of Shc signaling is eliminated (He et al., 2010). Collectively, these findings implicate TrkB and its PLCγ1 signaling pathways as highly attractive targets for development of small molecule inhibitors for the prevention of epilepsy.

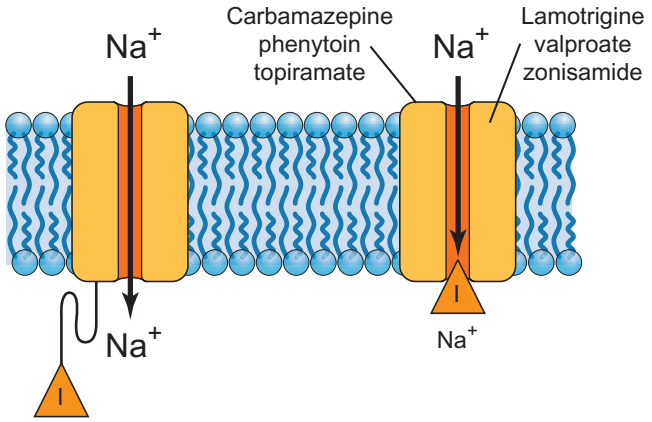

FIGURE 40-2 **Antiseizure Na^+ channel inactivation.** Some antiseizure drugs work mechanistically by prolonging the inactivation of the Na^+ channel, thereby reducing the ability of neurons to fire at high frequencies. Antiseizure drugs known to promote inactivation of this channel include carbamazepine, phenytoin, topiramate, lamotrigine, valproate, and zonisamide. Note that the inactivated channel appears to remain open but is blocked by the inactivation gate (I) at the pore.

MECHANISMS OF ANTISEIZURE DRUGS

Insights into the mechanisms of action of medications effective against partial seizures (Macdonald & Greenfield, 1997) emerged from electrophysiological studies of reduced preparations, such as CNS neurons maintained in primary culture. The experimental control and accessibility available in these models combined with use of clinically relevant concentrations led to clarification of the mechanisms of various antiseizure medications. Although difficult to prove that a given antiseizure drug effect observed *in vitro* is the mechanism by which a drug acts *in vivo* to inhibit a seizure, there is a strong likelihood that the putative mechanisms identified in the laboratory underlie actions *in vivo* in humans. To date, most antiseizure drugs target voltage-gated sodium channels or synapses that employ $GABA_A$ receptors.

Many antiseizure drugs act on voltage-gated sodium channels to limit high-frequency, but not low-frequency, firing of neurons

As described earlier, electrophysiological analyses of individual neurons during a partial seizure demonstrate that neurons undergo depolarization and fire action potentials at high frequencies (Figure 40-1). This pattern of neuronal firing is the hallmark of a seizure and is rare during physiological activity. Therefore, the selective inhibition of this high-frequency firing pattern would be expected to reduce seizures, hopefully with minimal unwanted effects. Carbamazepine, lamotrigine, phenytoin, and valproic acid modulate high-frequency firing at concentrations known to be effective in the limitation of seizures in humans (Macdonald & Greenfield, 1997). The mechanism by which the drugs limit high-frequency firing involves slowing the recovery of voltage-gated Na^+ channels from inactivation, also termed a use-dependent blockade (Figure 40-2).

Stated differently, depolarization-triggered opening of the Na^+ channels in the axonal membrane of a neuron is required for an action potential; after opening, the channels spontaneously close, a process termed inactivation (see Ch. 4). This inactivation is thought to mediate the refractory period—the brief period following an action potential during which it is not possible to evoke another action potential. Upon recovery from inactivation, the Na^+ channels are poised to participate in generation of another action potential. Because firing at a slow rate permits sufficient time for Na^+ channels to recover from inactivation, inactivation has little or no effect on low-frequency firing. However, reducing the rate of recovery of Na^+ channels from inactivation would limit the ability of a neuron to fire at high frequencies, an effect that most probably underlies the effects of carbamazepine, lacosamide, lamotrigine, phenytoin, rufinamide, topiramate, valproic acid, and zonisamide against partial seizures.

Other antiseizure drugs enhance GABA-mediated synaptic inhibition

Insights into mechanisms of seizures suggest that enhancing GABA-mediated synaptic inhibition, particularly $GABA_A$ inhibition, would reduce neuronal excitability and therefore raise the seizure threshold. Several drugs are thought to inhibit seizures by regulating GABA-mediated synaptic inhibition through an action at distinct sites of the synapse (Macdonald & Greenfield, 1997). The principal postsynaptic receptor of synaptically released GABA is the $GABA_A$ receptor (see Ch. 18). Activation of the $GABA_A$ receptor effects inhibition of the postsynaptic cell by increasing the flow of Cl^- ions into the cell, which tends to hyperpolarize the neuron. It is worth noting, however, that in the presence of elevated

intracellular chloride levels, a drug that acts by enhancing GABA function might be ineffective, with the inward driving force of chloride being reduced or eliminated. Clinically relevant concentrations of both benzodiazepines and barbiturates can enhance $GABA_A$ receptor–mediated inhibition through distinct actions on the $GABA_A$ receptor (Figure 40-3) (Macdonald & Greenfield, 1997). This mechanism probably underlies the effectiveness of these compounds against partial and tonic–clonic seizures in humans. At higher concentrations, such as might be used for status epilepticus, these drugs also can inhibit high-frequency firing of action potentials. γ-vinyl GABA (vigabatrin) is thought to exert its antiseizure action by irreversibly inhibiting an enzyme that degrades GABA, GABA transaminase; this probably leads to increased amounts of GABA available for synaptic release (Macdonald & Greenfield, 1997). A third mechanism of enhancing GABA-mediated synaptic inhibition is thought to underlie the antiseizure mechanism of tiagabine; tiagabine inhibits the GABA transporter, GAT-1, and reduces neuronal and glial uptake of GABA (Macdonald & Greenfield, 1997) (Figure 40-3).

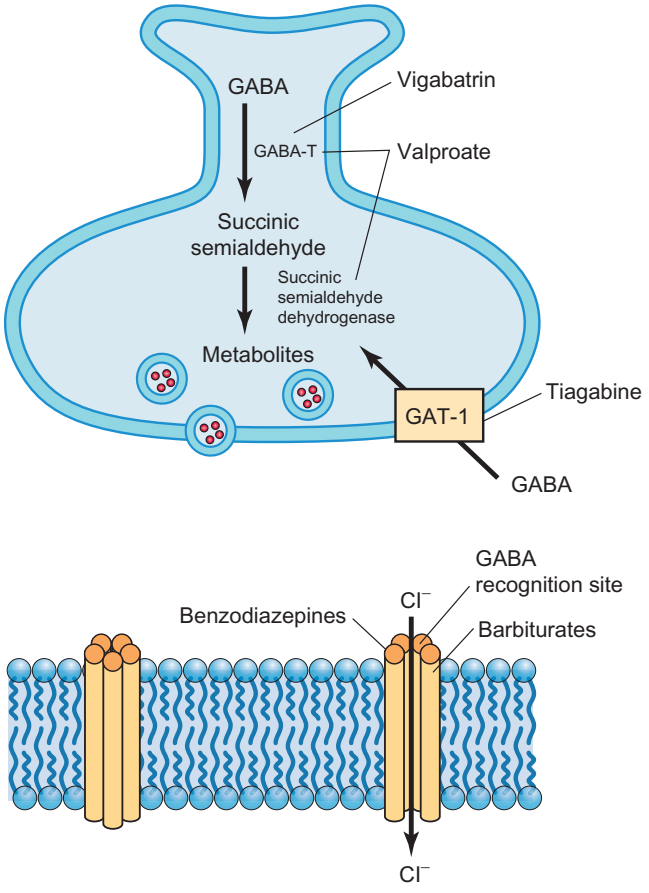

FIGURE 40-3 **Increased GABAergic transmission mediated by antiseizure drugs.** Some antiseizure drugs mediate the increased opening of $GABA_A$ receptors in turn increasing membrane hyperpolarization, e.g., benzodiazepines and barbiturates. Others inhibit GABA reuptake (tiagabine) or the degradation of synaptically released GABA (vigabatrin).

Other antiseizure drugs regulate a subset of voltage-gated calcium currents

In contrast to partial seizures, which arise from localized regions of the cerebral cortex, the "absence" or "petit mal" form of generalized-onset seizures arises from the reciprocal firing of the thalamus and cerebral cortex (Huguenard, 1999). Although a detailed consideration of the mechanisms is beyond the scope of this chapter, many of the structural and functional properties of thalamus and cortex that underlie the generalized spike-and-wave discharges of petit mal or absence seizures have been clarified in the past decade (Huguenard, 1999). The EEG hallmark of an absence seizure is generalized spike-and-wave discharges at a frequency of 3 Hz. These bilaterally synchronous spike-and-wave discharges, recorded locally from electrodes in both the thalamus and the neocortex, represent oscillations between thalamus and cortex. Correlative EEG and intracellular recordings reveal that the EEG spikes are associated with the firing of action potentials and that the following slow wave is associated with prolonged inhibition. These reverberatory, low-frequency rhythms are made possible by a combination of factors, including reciprocal excitatory synaptic connections between the cortex and thalamus as well as intrinsic properties of neurons in the thalamus, most importantly the low-threshold calcium current or I_T (Huguenard, 1999). The expression of I_T in thalamic neurons is critical to the generation of the 3 Hz spike and waves. In contrast to its small size in most cortical and hippocampal pyramidal neurons, the thalamic I_T is of large amplitude, with bursts of action potentials superimposed on this current. Thus the I_T serves an amplifying role in thalamic oscillations, with each oscillation being the three-per-second spike and wave of the absence seizure. Importantly, the principal mechanism by which some anti-absence seizure drugs (ethosuximide, valproic acid) are thought to act is by inhibition of the I_T (Kelly et al., 1990) (Figure 40-4).

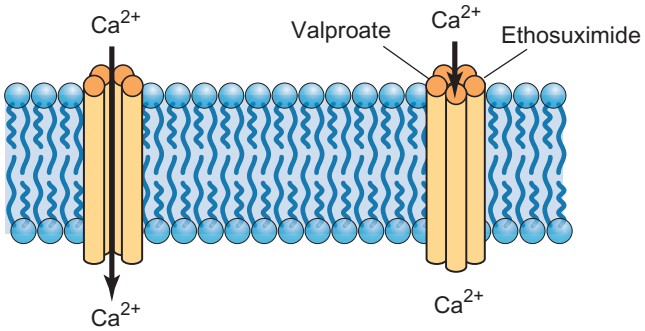

FIGURE 40-4 **Antiseizure mediated reduction of I_T.** Certain antiseizure drugs reduce the flow of calcium through T-type Ca^{2+} channels (ethosuximide, valproate), thereby reducing the pacemaker current that underlies spike-wave discharges of generalized absence epilepsy.

GENETICS OF EPILEPSY

Many forms of epilepsy have genetic determinants

Progress in molecular biology and molecular genetics has fueled discovery of genes causing epilepsy in humans and mice in the past 10–15 years (McNamara, 1999). Overall, perhaps 50–60% of all human epilepsies have genetic determinants. However, only a small fraction (less than 5%) of the epilepsies are inherited in a Mendelian pattern in which the cause can be traced to a single mutant gene. The gene(s) causing a Mendelian form are typically found to be responsible for a single or a few pedigrees, but not for the common forms of human epilepsy such as most cases of JME or childhood absence epilepsy (CAE). Disorders like JME and CAE appear to be caused by simultaneous inheritance of two or more susceptibility genes interacting with environmental factors (Noebels, 2003), a scenario similar to late onset Alzheimer's disease (AD), in which apolipoptotein E isoforms powerfully influence risk but alone are not sufficient to produce AD. By analogy to the rare pedigrees of AD that are inherited in a Mendelian pattern (like the mutation in amyloid precursor protein in a Swedish pedigree), a single JME pedigree was identified in which a mutation of the α_1 subunit of a $GABA_A$ receptor was causal (Cossette et al., 2002). In contrast to apoliprotein E and AD, a single gene that confers susceptibility to the common forms of epilepsy like JME has not been identified and may not exist.

Tables 40-3 and 40-4 list the genes responsible for idiopathic and symptomatic epilepsies in humans, respectively. Table 40-5 lists genes identified to cause epilepsy in mice.

Several themes emerge from this immense information. As noted above in descriptions of epilepsy syndromes, the idiopathic epilepsies affect individuals who are otherwise normal and in whom no structural cause has been identified. Perhaps the most remarkable feature of the genetic causes of the idiopathic epilepsies is that the vast majority of these genes encode an ion channel gated by voltage or a neurotransmitter. These include channels permeable to Ca^{2+}, Na^+, K^+, and Cl^-, as well as channels gated by GABA and acetylcholine. This is of particular interest because several other episodic disorders involving other organs also are caused by mutations of genes encoding ion channels. For example, episodic disorders of the heart (cardiac arrhythmias), skeletal muscle (periodic paralyses, see Ch.44), cerebellum (episodic ataxia), vasculature (familial hemiplegic migraine), and other organs all have been linked to mutant genes encoding a component of an ion channel (Ptacek, 1997). In none of these episodic disorders is it understood what triggers an event or what terminates the event. The sole gene that does not encode an ion channel is partial epilepsy with auditory features, in which the gene encoding "leucine-rich glioma inactivated" (LGI1) is responsible; loss of both of these alleles is associated with enhanced progression of glial tumors (Kalachikov et al., 2002). This gene was recently reported to play a role in the maturation of excitatory synapses; mice with mutated LGI1 exhibited excessive glutamatergic transmission and were more susceptible to seizures than wild-type control mice (Zhou et al., 2009).

Except for JME, each of these idiopathic syndromes is rare, and these forms, taken together, likely account for well less than 1% of all of the human epilepsies. The GABRA1 mutation identified in JME involved a single pedigree and was not evident in multiple sporadic cases of JME. It is rarely clear how the genotype leads to the phenotype of epilepsy. Identification of the genes permits engineering mutant mice that, it is hoped, will exhibit epilepsy. Substantial progress is being made in characterizing mutant mouse models with mutations engineered to mimic those found in humans with epilepsy. One example is $K_v1.1$ null mutant mice, which exhibit complex partial and secondarily generalized tonic–clonic seizures—forms of seizures similar to those in some humans carrying mutations that are likely haploinsufficient (Rho et al., 1999).

A second example consists of mice with only one functional allele of *SCN1A*, which display spontaneous clonic and tonic–clonic seizures.

Spontaneous (and putatively loss-of-function) mutations in *SCN1A*, which encodes the α subunit of the highly expressed voltage-gated Na^+ channel $Na_v1.1$, have been associated with severe myoclonic epilepsy of infancy in humans.

TABLE 40-3 Idiopathic Human Epilepsies: Genes and Syndromes

Syndrome	Gene
Autosomal dominant nocturnal frontal lobe epilepsy, 1	Nicotinic receptor subunit: α_4
Autosomal dominant nocturnal frontal lobe epilepsy, 3	Nicotinic receptor subunit: β_2
Autosomal dominant nocturnal frontal lobe epilepsy	Nicotinic receptor subunit: α_2
Benign neonatal epilepsy, type 1	K^+ channel subunit: KCNQ2
Benign neonatal epilepsy, type 2	K^+ channel subunit: KCNQ3
GEFS +, severe myoclonic epilepsy of infancy (SMEI)	Na^+ channel subunit: $Na_V1.1$
Febrile and afebrile seizures, benign familial neonatal–infantile seizures	Na^+ channel subunit: $Na_V1.2$
GEFS +	Na^+ channel subunit: β_1
Generalized epilepsy with febrile seizures plus (GEFS +), childhood absence epilepsy	$GABA_A$ receptor: γ_2
Juvenile myoclonic epilepsy	$GABA_A$ receptor: α_1
GEFS +	$GABA_A$ receptor: δ
Partial Epilepsy with auditory features	Leucine-rich, glioma-inactivated 1
Childhood absence epilepsy	Ca^{2+} channel subunit: $Ca_v3.2$
Juvenile myoclonic epilepsy	Ca^{2+} channel subunit: β_4
Juvenile myoclonic epilepsy	EF-hand domain containing 1
Benign familial infantile seizures with familial hemiplegic migraine	ATPase, Na^+/K^+ transporting, α_2 polypeptide

Heterozygous *SCN1A* knockout mice (*SCN1A*$^{+/-}$ mice) are epileptic and have provided clues to the mechanism by which *SCN1A* mutation gives rise to seizures. Interestingly, inhibitory interneurons in *SCN1A*$^{+/-}$ mice exhibited deficiencies in action potential firing, while pyramidal neurons were unaffected (Yu et al., 2006). Impaired activity in inhibitory populations of neurons, presumably leading to reduced GABA release, is a plausible mechanism that could give rise to seizures in humans with only one functional allele of *SCN1A*. Indeed, $Na_v1.1$ expression was recently reported to be highly enriched in parvalbumin-expressing, basket-type interneurons, and is required for these inhibitory cells to generate normal spike output (Ogiwara et al., 2007).

Third, mice with a triplet repeat expansion in *ARX* exhibit spontaneous seizures and spasm-like myoclonus, mirroring the phenotype of humans with such a mutation.

In this mouse model of infantile spasms, researchers uncovered a selective reduction in the number of certain

TABLE 40-4 Symptomatic Human Epilepsies: Genes and Syndromes

Syndrome	Inheritance pattern	Gene
Miller–Dieker Syndrome	De novo	Platelet-activating factor acetylhydrolase
Unverricht–Lundborg disease	Autosomal recessive	Cystatin B
Myoclonic epilepsy with ragged red fibers (MERRF)	Mitochondrial	$tRNA^{lys}$
Batten disease	Autosomal recessive	CLN3
Angelman syndrome	Mostly de novo	UBE3A
Lafora disease	Autosomal recessive	EPM2A, EPM2B
Subcortical band heterotopia	X-linked	Doublecortin
Periventricular nodular heteropia	X-linked	Filamin
Lissencephalic cortical neuronal migration defect	X-linked	Reelin
X-linked lissencephaly with abnormal genitalia (XLAG)	X-linked	Aristaless-related homeobox
Rett's syndrome	X-linked	MECP2
Cerebral cavernous malformations	Autosomal dominant	KRIT1
Infantile neuronal ceroid lipofuscinosis (CLN1)	Autosomal recessive	Palmitooylprotein thioesterase
Late infantile neuronal ceroid lipofuscinosis (CLN2)	Autosomal recessive	Pepstatin-insensitive lysosomal peptidase
Juvenile Gaucher's disease	Autosomal recessive	Glucocerebrosidase
Sialidosis I	Autosomal recessive	α-neurominidase
Sialidosis II	Autosomal recessive	Stabilizing protein of the α-neurominidase-β-galactosidase complex
Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke like episodes (MELAS)	Mitochondrial	tRNA (leu)
Dentatorubalpallidoluysian atrophy (DRPLA)	Autosomal dominant	CAG trinucleotide repeat
Acanthocytosis	Autosomal recessive	Chorein
Holoprosencephaly	De novo	Sonic hedgehog homolog
Polyhydramnios, megalencephaly, and symptomatic epilepsy (PMSE)	Autosomal recessive	STE20-related kinase adaptor α
Alpers' Disease	Autosomal recessive	Mitochondrial DNA polymerase: γ subunit
Microcephaly with polymicrogyria and corpus callosum agenesis	Autosomal recessive	Eomesodermin
Primary microcephaly	Autosomal recessive	Microcephalin, cyclin-dependent kinase 5 regulatory associated protein 2, abnormal spindle-like microcephaly associated protein
Microcephaly, early-onset seizures, and developmental delay (MCSZ)	Autosomal recessive	Polynucleotide kinase 3′-phosphatase

types of inhibitory interneurons (Price et al., 2009). The loss of some inhibitory function may underlie epilepsy in mice and humans with mutations in *ARX*. These mice, along with other strains, will provide tools vital to determining how the genotype leads to the phenotype.

Apart from determining steps, if any, between expression of a mutant ion channel and emergence of epileptic seizures, in some instances the mutant channels suggest some intriguing molecular targets for development of antiseizure drugs acting by novel mechanisms.

For example, the mutations of the K^+ channel (KCNQ2 and KCNQ3) underlie a slowly inactivating K^+ current and mediate spike frequency adaptation. These channels provide a novel molecular target for development of antiseizure drugs. In addition, impaired inhibition in $SCN1A^{+/-}$ mice suggested that drugs that enhance GABA systems might be useful in treating severe myoclonic epilepsy of infancy. Indeed, such a drug has been found to reduce seizures in these patients (Chiron. 2007). These results highlight the benefits that may be gained from studying animal models that closely mirror the human condition.

Table 40-4 lists a number of symptomatic epilepsies of humans for which mutant genes have been identified.

As suggested by the terminology, these epilepsies are symptomatic of some overt underlying disease, some of which begin at various times in the first decade of life or later and are progressive whereas others exhibit catastrophic neurological abnormalities at birth and do not progress further. These diseases include epileptic seizures as a prominent feature but are also associated with additional prominent abnormalities of CNS function, and often structure as well. In contrast to the striking homogeneity with respect to genes encoding ion channels in the idiopathic epilepsies, the genes causing the symptomatic epilepsies are striking in their diversity. The syndromes include genetically determined abnormalities of neuronal migration, segmentation, and patterning as seen in periventricular nodular heteropia, as well as dysregulation of transcription factors as observed in diseases like Rett's syndrome.

Some spontaneous and some engineered mutations of mice result in epilepsy

In parallel to identification of the genes causing human epilepsies, many genes causing epilepsy in mice have been identified (Table 40-5). In most instances, the genes were overexpressed or eliminated and the epileptic phenotype was an unexpected consequence. Genes encoding proteins subserving a component of synaptic function constitute the single

TABLE 40-5 Mouse Epilepsy Genes

Gene	Protein	Human gene (and location)
Induced Mutations		
Npy	Neuropeptide Y	NPY (7pter-q22)
Syn1	Synapsin 1	SYN1 (Xp 11.2)
Syn2	Synapsin 2	SYN2 (3p)
Slc1a (Glt-1)	Glutamate transporter	SLC1A2 (11p13-p12)
Akp2	Tissue-nonspecific alkaline phosphatase	ALPL (1p36.1-p34)
Gad2	Glutamic acid decarboxylase	GAD2 (10p21.3)
Gabrβ3	$GABA_A$ receptor subunit	GABRB3 (15q11.2-q12)
Gabrδ	$GABA_A$ receptor subunit	GABRD (1p)
Gria2	Glutamate receptor subunit 2	GRIA2 (4q32-q33)
Htr2c	Hydroxytryptamine receptor 2c	HTR2C (Xq24)
Kcna1	Voltage gated K^+ channel	KCNA1 (12p13)
Scn1a	Sodium channel type 1 α subunit	SCN1A (2q24.3)
Scn2a	Sodium channel type 2 α subunit	SCN2A1 (2q23-q24.3)
Kcnj6 (Girk2)	Inward-rectifying K^+ channel	KCNJ6 (21q22.2)
Camka	Calcium calmodulin kinase α subunit	CAMKA (5q31.3-q32)
Itrp1	Inositol 1,4,5 triphosphate receptor	ITPR1 (3p26-25)
Gap43	Growth associated protein	GAP43 (3q21-qter)
Cdk5r	Neuronal-specific activator of cyclin kinase	CDK5R (17p)
Otx1	Orthodenticle homolog	OTX1 (p13.3)

(Continued)

TABLE 40-5 (Continued)

Gene	Protein	Human gene (and location)
Jrk	*Jerky*	JH8 (8q24.3)
Pcmt1	Protein L-isoaspartate (D-aspartate) O-methyltransferase	PCMT1 (6q22.3-6q24)
Hex-a	α subunit of β-hexosaminase	HEX-A (15q23-q24)
Hex-b	β subunit of β-hexosaminase	HEX-B (5q13)
Stfb (Cstb)	Cystatin-B	STFB (21q22.3) (CSTB)
Psap	Sphingolipid activator protein	PSAP (10q22.1)
Il6	Cytokine, interleukin 6	IL6 (7p21)
App	Amyloid precursor protein	APP (21q21.2)
Hdh	Huntingtin amino-terminal polyglutamine sequence	HD (4p16.3)
Polyglutamine repeat	146-unit CAG repeat inserted in hprt gene	-
Arx (polyalanine repeat)	Aristaless-related homeobox (Arx plus 7)	ARX (Xp21)
Dlx1	Distal-less homeobox 1	DLX1 (2q32)
Chrna4	Nicotonic acetylcholine receptor α4 subunit	CHRNA4 (20q13.2-q13.3)
Dcx, Dclk2	Doublecortin and doublecortin-like kinase	DCX (Xq22.3-q23), DCLK2 (4q31.23-q31.3)
C1qa	Complement component 1, q subcomponent, A chain	C1QA (1p36.12)
Plcb4	Phospholipase c β4	PLCB4 (20p12)
Pafah1b1 (Lis1)	Platelet-activating factor acetylhydrolase 1b, regulatory subunit 1	PAFAH1B1 (17p13.3)
Adam23	ADAM metallopeptidase domain 23	ADAM23 (2q33)
Kcnq2	Potassium voltage-gated channel, KQT-like subfamily, member 2	KCNQ2 (20q13.3)
Kcnq3	Potassium voltage-gated channel, KQT-like subfamily, member 3	KCNQ3 (8q24)
Bsn	*Bassoon*	BSN (3p21.31)
Pten	Phosphatase and tensin homolog	PTEN (10q23.3)
Cdk5r1 (p35)	Cyclin-dependent kinase 5, regulatory subunit 1	CDK5R1 (17q11.2)
Spontaneous Mutations		
Ccha1a	Calcium channel α 1a subunit (*tottering*)	CACNA1A (19p13.1)
Ccha2a	Calcium channel α 1a subunit (*tottering leaner*)	CACNA1A (19p13.1)
Cchb4	Calcium channel β4 subunit (*tottering leaner*)	CACNB4 (2q22-q23)
Cacng2	Calcium channel γ subunit (*tottering leaner*)	CACNG2 (22q)
Slc9a1	Na^+/H^+ antiporter (slow wave epilepsy)	SLC9A1 (1p36.1-p35)
Kcnj6 (Girk2)	Inwardly rectifying K^+ channel (Weaver)	KCNJ6 (21q22.2)
Itpr1	Inositol 1,4,5 triphosphate receptor 1 (opisthotonus)	ITPR1 (3p26-25)
Cacna2d2	Calcium channel α2δ2 subunit (*ducky*)	CACNA2D2
Atp1a3	Na^+K^+ATPase α3 isoform (*Myshkin*)	ATP1A3 (19q13.31)
Hcn2	Hyperpolarization-activated cyclic nucleotide gated potassium channel 2 (*apathetic*)	HCN2 (19p13.3)

most common subset of mutations in this category (Table 40-5). This is no surprise given the role of synapses in the CNS and the delicate balance that exists between excitation and inhibition. For example, the fact that deletion of a gene encoding a subunit found in the $GABA_A$ receptor or a K^+ channel leads to epilepsy is not surprising. However, the occurrence of an epileptic phenotype in mice carrying null mutations of synapsin 1 was unexpected until this mutation was shown to preferentially compromise the efficacy of inhibitory synaptic transmission (Terada et al., 1999).

Finally, linkage analysis followed by sequencing led to identification of genes in spontaneously arising mutations that had been found to cause epilepsy in mice.

In most of these, the nature of the epilepsy was a generalized spike and wave, mimicking the generalized onset epilepsies like absence. In contrast to absence epilepsy in humans, many of these mutant mouse strains exhibit cerebellar ataxia and often degeneration. Like the idiopathic epilepsies of humans, many of these genes encode ion channels. Interestingly, none of the mutant genes in these mouse strains have been identified as causing a form of absence epilepsy in humans.

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