CHAPTER

36

Excitation–Inhibition Epilepsies

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OUTLINE

36.1 INTRODUCTION

Epilepsy affects more than 50 million people across the world, making it the second most common neurological disorder (Hauser et al., 1993). Children in particular are at high risk for seizures, and 5 out of every 1000 children will develop epilepsy in any given year. Known risk factors can account for only 25–45% of cases of early-life epilepsy, including congenital malformations of the central nervous system (CNS), moderate to severe head trauma, CNS infections, hypoxic–ischemic encephalopathy, inherited metabolic conditions, and genetic predisposition (Cowan, 2002).

To begin the discussion of epilepsy research, it is important to define the terms *epilepsy* and *epileptogenesis*. *Epilepsy*

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is a neurological disorder that is characterized by recurrent spontaneous seizures. *Epileptogenesis* is defined as the process during which changes occur in the brain after a precipitating injury or insult that results in the development of spontaneous recurrent seizure activity or epilepsy. The time period between the initial insult and the onset of epilepsy is referred to as the latent period. Much of the research in epilepsy is geared toward understanding the underlying molecular mechanisms associated with epileptogenesis. It is important to elucidate the underlying mechanisms of epileptogenesis both to identify better treatments for existing epilepsy and to develop new therapies to prevent epilepsy, as well as the associated neurocognitive disorders that afflict many individuals with epilepsy (LaFrance et al., 2008).

Although epilepsy is defined by the presence of recurrent seizures, it is often associated with cognitive or behavioral dysfunction, particularly in children, among whom 30% of epilepsy patients will have comorbid autism, intellectual or developmental disabilities, or both (Nolan et al., 2003; Tuchman et al., 2009). Children with epilepsy also show higher rates of attention deficit/hyperactivity disorder, learning disorders, and behavioral problems, as well as depression and anxiety (Beghi et al., 2006; Dunn et al., 2002; Gonzalez-Heydrich et al., 2007; Jones et al., 2007; Laurent and Arzimanoglou, 2006). A number of well-known genetic disorders share epilepsy, intellectual disability, and autism as prominent phenotypic features, including tuberous sclerosis, Rett syndrome, fragile X, Angelman syndrome, and genetic disorders of cortical development/migration with mutations such as aristaless-related homeobox (ARX), DCX, and Lis1 (reviewed in Brooks-Kayal, 2011; Deonna and Roulet, 2006; Guzzetta, 2006; Wolff et al., 2006). Seizures themselves, particularly when occurring during early life, may also produce a variety of cellular and molecular changes in the hippocampus that may contribute to an enhanced risk of cognitive or behavioral dysfunction (reviewed in Brooks-Kayal, 2011). Comorbid changes can be progressive, both over periods of years and over the course of the lifespan, and their severity has been correlated with age of onset, seizure frequency, total number of seizures, and increasing age (Dam, 1990; Hermann et al., 2002, 2003).

36.2 DIFFERENCES BETWEEN THE DEVELOPING AND MATURE BRAIN

To understand the complex effects of seizures on the developing brain, it is imperative to understand the differences between the developing and the adult brain. The functional development of inhibitory and excitatory neurons is an important part of the physiology of the normal developing neonatal brain. Three different types of pyramidal neuronal populations have been identified in the newborn rat hippocampus (Tyzio et al., 1999). These early neurons are described by their responsiveness to the neurotransmitters GABA and glutamate, and the populations consist of silent neurons, neurons that respond to only GABA, and neurons that respond to GABA and glutamate. The silent neurons lack spontaneous or evoked postsynaptic currents (PSCs), even in the presence of toxins that would normally stimulate transmitter release. These neurons have functional $GABA_A$ and glutamate receptors. The neurons that respond to only GABA demonstrate GABA-mediated but not glutamate-mediated PSCs. The neurons that respond to GABA and glutamate demonstrate both GABA-mediated and glutamate-mediated PSCs. These three populations of pyramidal neurons also differ morphologically. The silent neurons have a small soma and an axon with no apical dendrites. The neurons that respond to only GABA are more differentiated and have a larger soma and a small apical dendrite with no basal dendrite. The neurons that respond to GABA and glutamate are even more differentiated and have a basal dendrite and an apical dendrite that reaches the distal part of the stratum lacunosum moleculare (Tyzio et al., 1999).

Even more pertinent to human development is a similar observation made with respect to macaque monkey embryos in utero (Khazipov et al., 2001). In macaque monkeys, neurogenesis is complete in the hippocampus at E165 and morphological differentiation of the hippocampal pyramidal neurons occurs during the second half of gestation. The neurons are highly mature at the time of birth. Embryonic recordings conducted in the second half of gestation from embryonic day (E) 85 to E154 demonstrated that at E85 the CA1 pyramidal neurons were silent, with some neurons that respond to only GABA starting to form. At E105, the proportion of these neurons that respond to only GABA had increased and penetrated deeper into the stratum radiatum with a small proportion of neurons that respond to GABA and glutamate. From E119 and onward, the recorded pyramidal neurons exhibited both GABAergic and glutamatergic PSCs. The ability of $GABA_A$ receptor antagonist bicuculline to initiate epileptiform activity during various stages of development also was studied. At mid-gestation, epileptiform activity was not seen after the administration of the $GABA_A$ antagonists bicuculline but was observed at E105–109, which coincides with the appearance of neurons that respond to only GABA with axonal collaterals and the appearance of spines and glutamatergic PSCs. The occurrence and severity of the epileptiform events coincided with the development of the pyramidal neurons and the increase in the number of spines. Therefore, in primates, maturation of GABAergic and glutamatergic neurotransmission emerges early in utero. The CA1 pyramidal neurons are initially silent and then mature and differentiate to acquire morphological and physiological properties needed to generate

network-driven epileptiform activities well before birth. Early hippocampal development is conserved throughout mammalian development. The steps in hippocampal development seem to be similar in rodents and primates but occur at a faster rate in primates (Khazipov et al., 2001).

The first synapses of the principal neurons in the hippocampus are formed on the apical dendrites (Dupuy and Houser, 1997; Rozenberg et al., 1989). Glutamatergic synapses are formed after the maturity of their postsynaptic target, whereas GABAergic synapses are formed between the axons of GABA neurons and the dendrites of pyramidal neurons. Inhibitory neurons play an important role in normal development of the neocortex and in regulating the critical period. The critical period is defined as a window of time during which experience provides input that is essential for normal development and permanently alters function (Hensch, 2005). During the critical period of rodent visual cortex development, GABA release is important for ocular dominance plasticity (Fagiolini and Hensch, 2000; Hensch et al., 1998). Enhanced inhibition with administration of benzodiazepines just after eye opening is able to accelerate the onset of the critical period (Fagiolini and Hensch, 2000; Fagiolini et al., 2004; Iwai et al., 2003). Tonic GABA release is sufficient to trigger the completion of the critical period even with the complete absence of visual input (Hensch, 2005).

36.2.1 GABAergic Neurotransmission

GABA and glutamate receptors undergo dramatic changes over the course of postnatal development (Figure 36.1). GABAergic neurotransmission provides very important functions in the brain that differ between immature and mature neurons (Ben-Ari, 2002). GABA is a neurotransmitter that acts in an excitatory manner in the immature brain, while acting in an inhibitory manner in the mature brain (Ben-Ari et al., 1989) and is tied to the temporally regulated expression of K^+–Cl^--coupled cotransporter (KCC2) (Rivera et al., 1999). There is also a developmentally regulated shift in the expression of GABA receptor subunits (Brooks-Kayal and Pritchett, 1993; Brooks-Kayal et al., 2001; Fritschy et al., 1999; Wisden et al., 1992).

Ben-Ari et al. first reported that GABA functioned as a depolarizing, or excitatory, neurotransmitter in young neurons from neonatal hippocampal slices, unlike those of adults (Ben-Ari et al., 1989). In disassociated

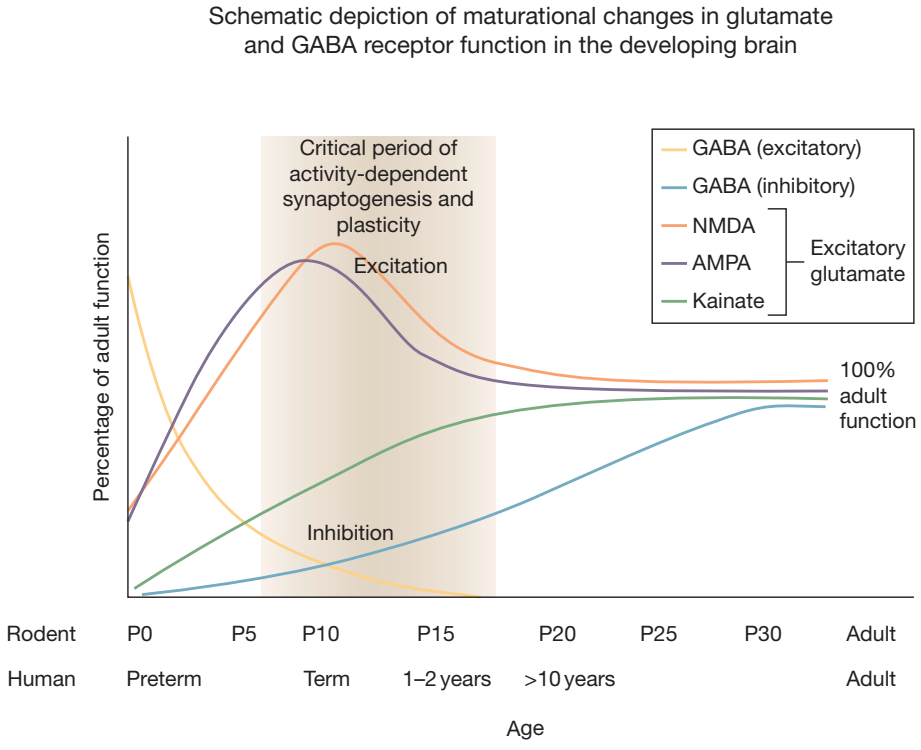


FIGURE 36.1 Equivalent developmental periods are displayed for rats and humans on the top and bottom *x*-axes, respectively. Activation of GABA receptors is depolarizing in rats early in the first postnatal week and in humans up to and including the neonatal period. Functional inhibition, however, is gradually reached over development in rats and humans. Before full maturation of GABA-mediated inhibition, the NMDA and AMPA subtypes of glutamate receptors peak between the first and second postnatal weeks in rats and in the neonatal period in humans. Kainate receptor binding is initially low and gradually rises to adult levels by the fourth postnatal week. Abbreviations: AMPA, -amino-3-hydroxy-5-methyl-4-isoxazole propionate; GABA, γ-aminobutyric acid; NMDA, *N*-methyl-D-aspartate; P, postnatal day. *Reprinted with permission of John Wiley & Sons, Inc. Neonatal seizures.* Annals of Neurology *62(2): 2007, 112–120* © *2007 Wiley-Liss, Inc., A Wiley Company.*

embryonic spinal cord neurons, the opening of a single GABA channel is enough to trigger a sodium action potential (Serafini et al., 1995). The activation of GABA receptors also has the ability to generate calcium currents by directly activating voltage-dependent calcium channels (Fukuda et al., 1998; Leinekugel et al., 1995, 1997). The developmental shift in GABA function has been observed in a wide range of species and has been accepted as a general rule that has been conserved throughout vertebrate evolution. Glutamatergic neurons, which are the main excitatory neurons in the adult brain, are formed after GABAergic neurons (Ben-Ari et al., 1989). Thus, in the immature brain, GABA release and activation of $GABA_A$ receptors initiate depolarization and increased concentration of calcium, whereas glutamate serves this function in the adult brain (Ben-Ari, 2002).

$GABA_A$ receptor activity is sufficient to drive synchronous neuronal activity and can be inhibited by $GABA_A$ receptor blockade (Ben-Ari et al., 1989). In cultured hippocampal slices from young rats, elevated extracellular potassium-induced ictal-like epileptiform activity was blocked by $GABA_A$ receptor antagonists, bicuculline and gabazine, and increased in frequency and duration by $GABA_A$ receptor agonists, isoguvacine and muscimol (Dzhala and Staley, 2003). This exacerbation of epileptiform activity with $GABA_A$ receptor agonists and blockade with $GABA_A$ receptor antagonists is opposite to that seen in adult rats.

36.2.1.1 *Chloride Gradient*

To understand the implications of the chloride gradient on GABAergic transmission, it is important to compare the influx and efflux of chloride ions in neonatal and mature neurons. In neonatal hippocampal slices, Ben-Ari et al. used electrochemical methods to observe an increase in chloride ions in neonatal hippocampal neurons as compared to the adult (Ben-Ari et al., 1989). The increase in chloride concentration by 20–40 mM is sufficient to shift the function of GABA from inhibition in the adult to excitation in the neonate (Ben-Ari, 2002). There are two main families of chloride transporters responsible for influx and efflux of chloride ions in neurons. The chloride gradient is driven by the Na^+–K^+–$2Cl^-$ cotransporter (NKCC1), which imports two ions of chloride for every ion of sodium and potassium exported, and KCC2, which exports one ion of potassium and chloride. Therefore, the activation of NKCC1 allows for the accumulation of intracellular chloride and the activation of KCC2 decreases the concentration of intracellular chloride. NKCC1 is expressed at early developmental stages and is responsible for the high intracellular chloride concentration inside immature neurons (Fukuda et al., 1998). Expression of KCC2 mRNA levels slowly increases to adult levels at 2 weeks postnatally in various brain regions, which coincides with the functional maturation of these areas. The transfection of immature hippocampal neurons with KCC2 caused an early switch of GABA function from excitatory to inhibitory. GABA also remains excitatory in mice that lack KCC2 expression (Rivera et al., 1999). Thus, the key transporter implicated in the developmentally regulated switch from the excitatory to the inhibitory effects of GABA is KCC2 (Figure 36.2).

The developmental shift from excitatory to inhibitory GABAergic currents is regulated by GABA itself (Ganguly et al., 2001). Blocking $GABA_A$ receptors with bicuculline and picrotoxin prevented KCC2 increases and GABA remained excitatory. The developmental

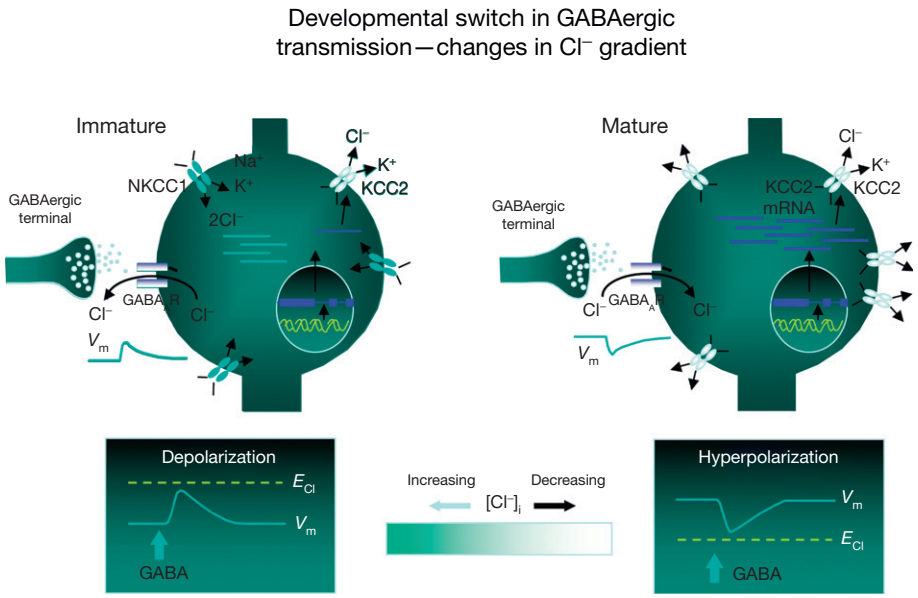


FIGURE 36.2 This schematic illustrates how the developmental shift in the chloride gradient (Cl^-) affects GABAergic transmission in the immature and mature brain. $GABA_{AR}$, $GABA_A$ receptor; KCC2, transports Cl^- out of the cell; NKCC1, transports Cl^- into the cell; mRNA, messenger RNA; V_m, membrane voltage; E_{Cl}, chloride equilibrium potential. *Reprinted from Brooks-Kayal AR (2005) Rearranging receptors.* Epilepsia *46(supplement 7): 29–38, with permission.*

shift is independent of action potentials, since tetrodotoxin, a sodium channel blocker, had no effect on the shift from excitation to inhibition. Therefore, an action potential-independent quantal release of GABA resulting in miniature PSCs is sufficient to cause the expression of KCC2 and reduce $[Ca^{2+}]_i$ and appears to be required. Blocking glutamate activity had no effect on the developmental shift of GABA (Ganguly et al., 2001). Taken together, the studies demonstrate that the shift in GABA function from excitatory to inhibitory is primarily caused by the temporally regulated expression of KCC2 which is downstream of $GABA_A$ receptor activation.

36.2.1.2 GABA Receptor Subunit Changes

There are three main GABA subtypes: $GABA_A$, $GABA_B$, and $GABA_C$. $GABA_A$ receptors are ligand-gated ion channels composed of heterogeneous pentameric protein complexes. The pentameric receptors are formed by various combinations of different subunits: α, β, γ, δ, ε, π, and θ. The various combinations of GABA subunits bestow certain physiological characteristics as well as pharmacological properties. $GABA_A$ receptors are typically located postsynaptically and mediate fast synaptic inhibition in the adult brain and excitation in the developing brain. The $GABA_A$ receptors are primarily anion selective, and typically gate chloride ions but, in certain conditions, gate bicarbonate ions as well. $GABA_A$ receptors are typically composed of two α subunits, two β subunits, and one γ subunit. The γ subunit can be replaced by a δ, an ε, a θ, or a π subunit, depending on the neuronal subtype and subcellular localization of the receptor (McKernan and Whiting, 1996; Rudolph and Möhler, 2004). $GABA_B$ receptors are G-protein-coupled metabotropic receptors that are located both presynaptically and postsynaptically and exhibit longer-duration slow inhibitory currents through K^+ and Ca^{2+} channels. $GABA_B$ receptors are composed of a heterodimer consisting of $GABA_{B1}$ and $GABA_{B2}$. The molecular diversity seen in the $GABA_B$ receptors arises from the splice variants of the $GABA_{B1a}$ and $GABA_{B1b}$ subunit isoforms (Bettler and Tiao, 2006; Couve et al., 2000). $GABA_A$ and $GABA_B$ receptors are distributed across the CNS (Bowery et al., 1987).

There are significant spatiotemporal differences in the subunit expression of $GABA_A$ receptors. Alpha$_2$, α_3, and α_5 subunits peak early in development and stabilize or decline, whereas the expression of α_1 and γ_2 is at low levels early in development and increases to adult levels (Fritschy et al., 1994; Wisden et al., 1992). In rats, there is a greater than twofold increase in mRNA expression of α_1, α_4, and γ_2 from postnatal day (P)7 to adulthood and a tenfold decrease in the expression of α_5 mRNA during the same period (Brooks-Kayal et al., 2001). Developmentally regulated changes in $GABA_A$ receptor subunit composition have also been observed in humans. Between the 36th week of gestation and adulthood, there is a threefold increase in the expression of α_1 mRNA levels in the cortex and cerebellum (Brooks-Kayal and Pritchett, 1993). There are also spatiotemporal differences in the subunit expression of $GABA_B$ receptors. In rodents, the presynaptic subunit of $GABA_B$, $GABA_{B1a}$, is high at birth and progressively declines to adult levels by P14 (Fritschy et al., 1999). However, the postsynaptic $GABA_B$ subunit, $GABA_{B1b}$, is low at birth, progressively increases in the first two postnatal weeks, and then declines to adult levels (McLean et al., 1996). There is some presynaptic $GABA_B$ receptor activity at birth, but no postsynaptic activity until the second or third postnatal week (Fukuda et al., 1993; Gaiarsa et al., 1995).

36.2.2 Glutamatergic Neurotransmission

Excitation outweighs inhibition during the first few years of life in the cerebral cortex and limbic structures in humans and rodents (Fox et al., 1996; Huttenlocher et al., 1982). Glutamate receptors are the main excitatory receptors in the adult brain and are divided into two main classes: ionotropic and metabotropic. Most pertinent to the discussion on developmental epilepsies is the ionotropic class of glutamate receptors. These ionotropic glutamate receptors activate cation-selective ion channels permeable to Na^+, K^+, and Ca^{2+} possessing varying degrees of permeability and blockade by the divalent cation Mg^{2+} (Mayer and Westbrook, 1987). There are three main types of ionotropic glutamate receptors: α-amino-3-hydroxyl-5-methyl-4-isoxazolepropionate (AMPA), kainate, and *N*-methyl-D-aspartic acid (NMDA) (Mayer, 2005). NMDA receptors are mainly located postsynaptically, require glycine as a coagonist, and have a voltage-dependent magnesium blockade that must be released before agonist binding can open the channel to allow gating of calcium and sodium. NMDA receptors are composed of an obligatory NR1 subunit with a combination of NR2A, NR2B, NR2C, and/or NR3A subunits (Lau and Zukin, 2007). AMPA receptors are typically located on the postsynaptic membrane and are composed of various combinations of GluR1, GluR2, GluR3, and/or GluR4 (Shepherd and Huganir, 2007). Kainate receptors are located presynaptically and postsynaptically on both neurons and glia. Kainate receptors are almost exclusively composed of various combinations of GluR5, GluR6, GluR7, KA1, and/or KA2 and gate sodium (Pinheiro and Mulle, 2006). NMDA receptors are always permeable to calcium ions, whereas AMPA and kainate receptors are selectively permeable to divalent cations depending on their subunit compositions. When AMPA receptors contain low levels of GluR2 or lack it

entirely, the receptors are calcium-permeable (Shepherd and Huganir, 2007). When kainate receptors have low levels of GluR5 or GluR6 or lack these subunits altogether, they allow increased gating of calcium ions (Pinheiro and Mulle, 2006).

The expression of glutamate receptor subunits is spatially and developmentally regulated and has important functional implications. In the mature brain, NR2A is present in almost all areas of the brain, while NR2B is located in the forebrain, NR2C is limited to the cerebellum, and NR2D is restricted to the thalamus and subthalamus (Monyer et al., 1994). In the immature brain, NMDA receptors have high levels of NR2B, NR2D, and NR3A subunits. Elevated levels of NR2B subunits extend current decay times, and the high levels of NR2D and NR3A reduce NMDA receptor sensitivity to magnesium ions (Lau and Zukin, 2007). The increased expression of the NR2B, NR2D, and NR3A subunits is implicated in increased NMDA receptor-mediated calcium influx, lower threshold for seizures, and excitotoxic hypoxic–ischemic injury during development (Rakhade and Jensen, 2009). AMPA receptor subunit composition is also developmentally regulated. The immature rat brain has lower GluR2 expression and a higher prevalence of GluR2 subunit-deficient receptors, which causes an increased calcium and sodium influx. When GluR2 is present in the receptor, AMPA receptors primarily gate sodium (Kumar et al., 2002; Sanchez and Jensen, 2001). In the developing human brain, there is a relative deficiency in GluR2 subunit-expressing AMPA receptors in cortical neurons during term and the early postnatal period. There is a direct correlation between the expression of GluR2-deficient AMPA receptors and vulnerability to hypoxic/ischemic injury (Talos et al., 2006a,b).

36.2.2.1 GABA, NMDA, and AMPA

In the developing brain, GABAergic and glutamatergic synapses work in conjunction with each other. Early glutamatergic neurotransmission is solely NMDA-receptor mediated, without any significant contribution of AMPA receptors (Durand et al., 1996; Isaac et al., 1997; Wu et al., 1996). Voltage-dependent Mg^{2+} blockade of NMDA receptors takes place in both neonates and adults (Khazipov et al., 1995; Swann et al., 1999); however, the degree varies across development, since NMDA receptors containing NR2D and NR3A are expressed in immature neurons and are less sensitive to Mg^{2+} blockade (Lau and Zukin, 2007). In the CA1 region of the hippocampus, the first glutamatergic synapses formed at P2 are silent at resting potential; however, the proportion of silent synapses progressively decreases from P2 to P5 (Durand et al., 1996; Liao and Malinow, 1996). Typically, the activation of AMPA receptors is sufficient to remove the Mg^{2+} blockade of NMDA channels in adult neurons, resulting in their activation. However, in neonatal hippocampal slices, AMPA activation is not sufficient to remove Mg^{2+} blockade of NMDA channels (Liao and Malinow, 1996); instead, $GABA_A$ receptor activation serves this role (Leinekugel et al., 1995). The opposite is true in the adult brain, where $GABA_A$ receptor activation prevents the activation of NMDA receptors, thereby inhibiting NMDA-dependent forms of synaptic plasticity (Artola and Singer, 1987; Wigström and Gustafsson, 1983). GABA-dependent activation of P2–P5 CA3 pyramidal neurons by the $GABA_A$ receptor agonist, isoguvacine, is sufficient to remove the voltage-dependent Mg^{2+} blockade of NMDA receptors, thereby increasing the affinity of NMDA channels for magnesium and increasing calcium ion influx (Leinekugel et al., 1995). Therefore, in the developing brain, $GABA_A$ receptor activation acts synergistically with NMDA receptor activation, providing the same function that AMPA receptors offer in the adult brain.

36.3 EXPERIMENTAL MODELS OF DEVELOPMENTAL EPILEPSY

Epilepsy is a very complex disease with many different causes and pathologies; therefore, it is important to develop research models that try to mimic the various types of human epilepsies. Many of the research models of seizures and epilepsy have been thoroughly reviewed (Pitkänen et al., 2005; Table 36.1).

36.3.1 Environmental/Perfusion

36.3.1.1 Hypoxia

The most common cause of neonatal seizures is hypoxic encephalopathy (Aicardi and Chevrie, 1970; Hauser et al., 1993). The neonatal rodent hypoxia model has been utilized to elucidate how global hypoxia in neonates leads to increased susceptibility to seizures later in life. Humans and rodents have a similar age-dependent susceptibility to hypoxia-induced seizures early in life, which can cause long-term susceptibility to seizure and neuronal death. P9–P12 Long–Evans rats demonstrate a high susceptibility to hypoxia-induced seizures, with a peak in P10 pups. Sprague–Dawley rats exhibit peak seizures at P8–P9 (Owens et al., 1997). Similar windows of susceptibility are also seen in mice. The hypoxia model uses a brief 15-min exposure to a graded global hypoxia (7–4% O_2) by altering the levels of O_2 and N_2 in an airtight chamber. The acute hypoxia-induced seizures lead to a long-term increase in the susceptibility to seizures, which is usually ascertained through the use of threshold doses of various chemoconvulsants,

TABLE 36.1 Animal Models of Neonatal Seizures and Epilepsy

		Human condition	
		Acute model	Recurrent spontaneous seizures (epilepsy)
Age	Experimental model		
Neonatal			
P0–P5	Flurothyl	Neonatal seizures	No
P3–P7	Hypoxic ischemia	Hypoxic–ischemic encephalopathy and perinatal stroke	Yes
Adolescent			
P8–12	Hypoxia	Hypoxic encephalopathy	Yes
P7–P14	Hypoxic ischemia	Hypoxic–ischemic encephalopathy and perinatal stroke	Yes
P10–P11	Hyperthermia	Febrile seizures	Yes
P10	Tetanus toxin single dose	Complex partial seizures	Yes
P10–P12	Tetanus toxin continuous infusion	Infantile spasms	Yes
P7–P10	Lithium–pilocarpine	Neonatal seizures	No
P12–P20	Lithium–pilocarpine	Neonatal seizures	Yes*
P7–P10	Kainate	Neonatal seizures	No
P20–Adult	Kainate	Neonatal seizures	Yes[a]

[a]*The increase in rate of epilepsy development directly correlates with the age.*

including pentylenetetrazol (PTZ), flurothyl, and kainate (Jensen et al., 1992; Rakhade et al., 2008b), as well as to spontaneous epileptiform/ictal EEG discharges in a subset of exposed animals (Rakhade et al., 2008a).

36.3.1.2 *Hypoxic Ischemia*

Neonatal seizures also occur after hypoxic–ischemic encephalopathy and perinatal stroke modeled by the hypoxic–ischemic rodent model of neonatal seizures. Typically, this method is used with P3–P14 rodents by ligating a cerebral artery, usually a unilateral carotid or middle cerebral artery. After ligation, the rodents are allowed to recover and are then subjected to 15–30 min of hypoxia (8% O_2) (Jensen et al., 1994; Rice et al., 1981; Vannucci et al., 1999). Similar to the hypoxia model, the hypoxic–ischemic model results in long-term increases in seizure susceptibility as assessed by injections of chemoconvulsants, as well as emergence of epilepsy later in life (Wirrell et al., 2001; Yager et al., 2002).

36.3.1.3 *Hyperthermia*

The most common type of seizure in infants and young children is febrile seizures, with a prevalence of 2.3–4%. Simple febrile seizures are short and generalized and occur with high fevers in infants and young children from ~3 months to 5 years of age, peaking between 6 months and 2 years of age. Complex febrile seizures are prolonged or focal seizures or seizures that recur within a single febrile episode. Although the majority of simple febrile seizures are benign, complex prolonged febrile seizures have been associated with an increased risk of later epilepsy development (Cowan, 2002; Hauser, 1994). The model for prolonged febrile seizures was first developed in the immature rat (Baram et al., 1997; Toth et al., 1998) and then adapted for mice (Dubé et al., 2005). The febrile seizure model induces hyperthermia to produce prolonged seizures. The core temperature of P10–11 rats or P14–15 mice is increased gradually and maintained at hyperthermia (40–42 °C) for 30 min, with the animal's core temperature being tightly regulated. The rodents are then allowed to recover for 1 h. In this model, approximately 24% of rats go on to develop spontaneous temporal lobe seizures in adulthood. If the duration of hyperthermia is increased to 64 min, then 45% of rats develop spontaneous seizures in adulthood (Dubé et al., 2010).

36.3.2 Toxin

36.3.2.1 *Tetanus Toxin*

The ability of tetanus toxin to induce chronic epilepsy was first described by Roux and Borrel (1898). The modern form of the tetanus toxin model of epilepsy involves stereotaxic injection of minute amounts of tetanus toxin into the brain to create an epileptic focus that spontaneously discharges. After interhippocampal infusion of tetanus toxin in P10 rats, anywhere from one to seven seizures are typically observed during the first week, with each seizure lasting from a few seconds to several minutes. The seizure frequency usually peaks on day two and declines over the week following infusion (Benke and Swann, 2004). When the immature rats become adults, they can exhibit unprovoked seizures, typically with a low prevalence (Lee et al., 1995).

36.3.3 Chemoconvulsant

36.3.3.1 *Lithium–Pilocarpine*

The lithium–pilocarpine model is a variation of the pilocarpine model used in adults. Honchar et al. determined that systemic activation of the cholinergic system in lithium-treated rats induced seizures (Honchar et al., 1983). Typically, lithium is administered 24 h before administration of pilocarpine. The pretreatment with lithium greatly decreases the amount of pilocarpine needed to

induce status epilepticus (SE). There are two dosing regimens, the first with a high dose of pilocarpine (25–60 mg kg^{-1}) 24 h after lithium treatment and the other with divided doses (10 mg kg^{-1}) administered 24 h after lithium treatment every 30 min until SE is induced (Glien et al., 2001). In P12 rats, 25% of the rats experience spontaneous electrographic seizures of limbic onset (i.e., temporal lobe epilepsy (TLE)) 3 months after SE (Kubová et al., 2004). By P20, this percentage increases to 67% (Raol et al., 2003).

36.3.3.2 *Kainate*

The seizure-inducing properties of kainate were first reported by Nadler et al. (1978). The kainate model is another useful model of TLE, because the rats experience an episode of SE on the order of hours after injection with kainate, followed by days to weeks of a seizure-free latent period, finally ending with progressive recurrent spontaneous seizures, typically when SE occurs in rodents ≥P20. Spontaneous recurrent seizures do not develop in P0 and P5 kainate-induced rats (Stafstrom et al., 1992). There are two main dosing regimens for kainate-induced SE, one using a single high dose (Meier et al., 1992) and the other using repetitive low doses (Meier and Dudek, 1996).

36.3.3.3 *Flurothyl*

Flurothyl is an inhaled GABAergic antagonist that induces seizures within minutes (Truitt et al., 1960). This method can be used to induce seizures up to five times per day (Cha et al., 2002; Holmes et al., 1998). Seizures are arrested within 30 s of returning the rats to room air; therefore, it is a useful model to study the effect of recurrent seizures. Continuous exposure to flurothyl is able to produce SE (Sperber et al., 1999). Immature rats (P0–P5) that receive recurrent flurothyl seizures do not go on to develop spontaneous recurrent seizures; however, the rats do have a reduced seizure threshold later in life (Holmes et al., 1998; Sogawa et al., 2001).

36.3.4 Kindling

The phenomenon of kindling was first described by Graham Goddard (1967). Goddard studied the effect of repeated hippocampal electrical stimulation on learning in rats. The small electrical insults led progressively to greater severity of seizures and resulted in a permanent increase in seizure susceptibility (Goddard et al., 1969). Kindling is initiated by periodic insults that result in network synchronization that are accompanied by behavioral seizures. There are two main methods of kindling, electrical and chemical. The electrical model of kindling uses repetitive electrical stimulation to various brain centers including the amygdala, perforant pathway, dorsal hippocampus, olfactory bulb, and perirhinal cortex. Chemical kindling utilizes repetitive administration of chemical agents that evoke repetitive epileptic spiking such as carbacol, acetylcholine, bicuculline, lidocaine, cocaine, and PTZ.

36.3.5 Infantile Spasms Models

Infantile spasms are a severe form of developmental epilepsy that begins between 3 and 12 months of age and has numerous etiologies, including a wide range of acquired and congenital causes (Frost and Hrachovy, 2005). Infantile spasms are associated with specific and unique electroencephalogram (EEG) findings, consisting of chaotic, high-voltage slow background activity intermixed with multifocal spikes and generalized slow waves (hypsarrhythmia), followed by generalized voltage attenuation during the spasm seizures. Only a few medications are effective for infantile spasms (glucocorticoids, adrenocorticotropic hormone, and vigabatrin), and the outcome of infantile spasms is usually poor, with other seizure types occurring after the first year of life and severely abnormal neurological development. The prognosis is especially poor in cases where delay is noted prior to the onset of spasms and the spasms do not disappear with therapy (Stafstrom, 2009). Recently, several animal models have been developed that recapitulate many of the features of infantile spasms, including the NMDA model (Kábová et al., 1999), the tetrodotoxin infusion model (Lee et al., 2008), and the multiple injury model (Scantlebury and Moshé, 2006). In addition, two genetic models of infantile spasms have been developed, the ARX model and the Ts65Dn Down syndrome model, which are discussed later. These new models should provide insights that will improve the understanding, treatment, and prevention of this devastating early-childhood epilepsy syndrome.

36.3.6 Genetic

In humans, mutations in the X-linked ARX gene are linked to structural brain abnormalities, including lissencephaly and abnormal migration of inhibitory interneurons, and neurological deficits, including severe intellectual disability and early-life epilepsy (known as an infantile epileptic encephalopathy). Conditional ARX knockouts exhibit behavioral and electrographic early-life seizures resembling infantile spasms (Marsh et al., 2009; Price et al., 2009). The administration of $GABA_B$ agonists to a mouse model of Down syndrome Ts65Dn mice between 1 week and 2 months old causes them to develop clusters of extensor spasms, which resemble infantile spasms, accompanied by polyspike-wave bursts and electrodecremental responses on EEG (Cortez et al., 2009).

Transgenic mice with mutations in KCNQ3 are known to develop seizures within the first 2 weeks of life. Mutations of KCNQ2 and KCNQ3 are linked to benign familial neonatal convulsions in humans (Castaldo et al., 2002). $K_v1.1$ knockouts exhibit a seizure-sensitive predisposition at P10, demonstrating an increase in early-life seizure susceptibility. Mutations in KCNA1, the human homolog of $K_v1.1$, can lead to episodic ataxia and seizures in humans (Rho et al., 1999). There are many other genetic mouse models with genes that are implicated in human early-life seizures, including SCN2A, SCN1B, and KCNQ2, to name a few. However, these mouse models do not demonstrate early-life seizures but rather develop seizures later in life (Chen et al., 2004; Kearney et al., 2001; Peters et al., 2005).

36.4 SEIZURE-INDUCED CHANGES IN THE BRAIN

The changes in the brain due to seizures can be divided into three overlapping temporal groups: acute, subacute, and chronic. Acute changes are those changes that occur in the brain within the first few minutes to days after a seizure. The subacute changes take place from hours to weeks with the chronic changes taking place over weeks to months. The acute changes that occur are activation of immediate early genes (IEGs), posttranslational protein modifications, and changes to ion channel activity. The subacute changes in the brain include neuronal death, activation of neurotrophic factors, inflammation, neurogenesis, and alterations in transcription factors. The chronic changes include mossy fiber sprouting, dendritic plasticity, and increased susceptibility to recurrent seizures (Rakhade and Jensen, 2009).

36.4.1 Acute

36.4.1.1 Immediate Early Genes

IEGs are genes that are rapidly transcribed in response to cellular stimuli, such as neuronal activity, and are implicated in synaptic plasticity and synaptogenesis. Many IEGs are transcription factors and DNA-binding proteins and have the ability to activate specialized signaling cascades. Repeated synaptic activity induces IEG activation which leads to depolarization and opening of NMDA receptor channels. The calcium influx following NMDA receptor activation can cause activation of kinase cascades that result in phosphorylation of specific transcription factors such as cyclic-AMP response element-binding protein (CREB) and CREB-binding protein (CBP) (Greer and Greenberg, 2008). CREB is a bZIP transcription factor that is activated when phosphorylated at its Ser133 site. The phosphorylated CREB (pCREB) then translocates into the nucleus and dimerizes and binds to the promoter consensus sequence TGACGTCA, which is known as the cAMP response element (CRE) motif. pCREB along with CBP, a chromatin regulator, has the ability to upregulate transcription of target genes (Lonze and Ginty, 2002). The upregulated IEGs can activate secondary response genes that have the ability to modulate synaptic activity (Greer and Greenberg, 2008). IEGs, including *Fos*, *Jun*, *EGr1*, *Egr4*, *Homer1*, *Nurr77*, *Arc*, and *CREB*, have been identified as activated in adult animal models of epilepsy (Herdegen and Leah, 1998), some as early as 30 min after seizure induction (Honkaniemi and Sharp, 1999). IEG activation has also been seen in the developing brain, but to a lesser degree. *Fos* and *Jun* activation has been seen in hypoxia-induced seizures and lithium–pilocarpine SE models (Dubé et al., 1998; Jensen et al., 1993). Activation of *Fos* differs based on age and mode of seizure induction. PTZ- and flurothyl-induced seizures show similar patterns of *Fos* activation in the amygdala, piriform cortex, and hypothalamus, but patterns in the cortex vary based on the age of the rat. *Fos* activation in adults is seen in the superficial layers of the cortex, whereas in P10 rats the activation is seen in the deep layers of the neocortex. Hypoxia-induced seizures demonstrated that *Fos* activation is confined to layer VI of the neocortex and is rarely involved in the limbic structures as seen with chemoconvulsant models (Jensen et al., 1993).

36.4.1.2 Ion Channel and Receptor Posttranscriptional Regulation

The calcium influx after a seizure has the ability to activate phosphatases and kinases that alter ion channel and neurotransmitter receptor function. The calcium-calmodulin-activated phosphatase, calcineurin, can lead to $GABA_A$ receptor endocytosis, decreased inhibitory postsynaptic potential frequency, and reduced network inhibition after early-life hypoxia-induced seizures (Sanchez et al., 2005) and adult pilocarpine-induced SE *in vivo* (Kurz et al., 2001). The same observation of calcineurin-regulated $GABA_A$ receptor-mediated synaptic inhibition has also been seen in neuronal culture and whole hippocampal slices (Khalilov et al., 2003). Seizure-induced calcineurin activation causes dephosphorylation and endocytosis of $GABA_A$ receptors (Blair et al., 2004; Sanchez et al., 2005) and $K_v2.1$ channels (Bernard et al., 2004). Pretreatment with FK506, a calcineurin inhibitor, reversed SE-induced dephosphorylation of $GABA_A$ receptor 2/3 subunits. Calcineurin-mediated dephosphorylation and endocytosis of $GABA_A$ receptors reduce their inhibitory function and may contribute to neuronal excitability in the hippocampus after seizures and epileptogenesis (Wang et al., 2009).

Glutamate receptors contain kinase phosphorylation sites that can be activated by seizures in the developing

brain. Within minutes after a seizure in juvenile rats, protein kinase C activity and calcium–calmodulin-dependent kinase II activity cause an increase in phosphorylation of Ser831 on GluR1 and Ser880 on GluR2 subunits of the AMPA receptor. Protein kinase A activity and phosphorylation of Ser845 on GluR1 are also observed (Rakhade et al., 2008a,b). The phosphorylation of Ser831 on GluR1 is known to increase channel conductance and phosphorylation of Ser845 on GluR1 increases open-channel probability (Shepherd and Huganir, 2007), which can lead to AMPA receptor-mediated potentiation (Rakhade et al., 2008a,b). The administration of AMPA receptor antagonists 48 h after a seizure is sufficient to prevent kinase activation, phosphorylation of Ser831 and Ser845 on GluR1, altered AMPA receptor activity, and increased seizure susceptibility later in life (Rakhade et al., 2008a,b). Increased phosphorylation of Ser880 on GluR2 is known to cause endocytosis of GluR2 subunit and increased Ca^{2+} permeability (Shepherd and Huganir, 2007). Activation of cellular sarcoma kinases can induce phosphorylation of NR2A and NR2B receptor subunits in NMDA receptors in the hypoxic–ischemic model of developmental epilepsy (Jiang et al., 2008).

36.4.2 Subacute

36.4.2.1 Neuronal Death

Adult models of epilepsy have shown progressive loss of CA3 and CA1 neurons via necrosis and apoptosis in the hippocampus in response to electrical or chemoconvulsant stimulation (Henshall and Murphy, 2008; Henshall and Simon, 2005). Models of early-life seizures have failed to demonstrate neuronal loss in the amygdala, hippocampus, or temporal cortical regions of animals younger than 2 weeks of age (Holopainen, 2008). There is limited neuronal death seen in the hippocampal neurons of immature brains in the flurothyl-induced seizure model (Wasterlain et al., 2002) and in the febrile seizure model (Toth et al., 1998). In the lithium–pilocarpine model, regional and age-related differences in neuronal cell loss have been demonstrated. In P14 and P21 rats exposed to lithium–pilocarpine-induced seizures, few damaged neurons were seen in the CA1 region of the hippocampus, whereas some neuronal damage was observed in the hilar and CA3 regions at P14, with extensive damage at P21 in some, but not all, animals (Raol et al., 2003; Sankar et al., 1998). The damage is thought to be mediated via necrosis, as demonstrated by eosinophilic cell infiltration, and apoptosis, as demonstrated by terminal deoxynucleotidyl transferase-mediated biotinylated UTP nick end labeling (TUNEL) stain. A direct relationship between age and vulnerability of neurons in the amygdala and dentate gyrus was also observed (Sankar et al., 1998). Interestingly, the degree of cell loss did not correlate with the risk of later development of epilepsy (Raol et al., 2003). Some variability in neuronal death in chemoconvulsant models has been seen with different routes of administration. Intracerebroventricular (i.c.v.) delivery of kainic acid causes more severe acute and progressive damage than an intraperitoneal (i.p.) route of delivery. Administration of kainic acid in P7 rats i.c.v. causes a dose-dependent acute neuronal loss in the CA3 region of the hippocampus with apoptosis seen in CA3 and CA1 as demonstrated by electron microscopy and TUNEL staining (Humphrey et al., 2002). However, kainic-acid-induced SE in P9 rats delivered by i.p. did not produce neuronal damage (Rizzi et al., 2003).

There is another population of neurons, the subplate neurons, that is susceptible to neuronal loss in the hypoxic–ischemic model of developmental epilepsies (McQuillen et al., 2003). The subplate neurons are located in the deep gray matter proper of the neocortex and become interstitial neurons of the subcortical white matter during the prenatal and neonatal periods. They are important for normal maturation of cortical networks, such as the visual cortex (Kanold et al., 2003; Kostovic and Rakic, 1980; Rakic, 1977). Subplate neurons also possess high levels of NMDA and AMPA receptors (Talos et al., 2006a,b) but lack oxidative stress defense mechanisms, making them especially susceptible to hypoxic–ischemic insults (McQuillen et al., 2003). Administration of antioxidants, such as erythropoietin, after acute hypoxia increased the latency of seizures, reduced the duration of seizures, protected against hippocampal cell loss, and decreased apoptosis in P10 rats (Mikati et al., 2007).

36.4.2.2 Neurotrophic Factors

Neurotrophic factors are important mediators of normal synaptogenesis and are expressed at higher amounts during postnatal development than in the adult (Greer and Greenberg, 2008). Early-life seizures in animal models have been shown to increase neurotrophic factor expression (Tandon et al., 1999). Chronic intrahippocampal injection of brain-derived neurotrophic factor (BDNF) results in spontaneous limbic seizures through TrkB signaling in adult animals, suggesting that BDNF is sufficient to produce epileptogenesis (Scharfman et al., 2002). Mice with a conditional knockout of TrkB in neurons have been shown to be protected from epileptogenesis (McNamara et al., 2006). In the adult rat kindling model, BDNF/TrkB activation suppresses the surface expression of KCC2, thereby suppressing chloride-dependent fast GABAergic inhibition (Rivera et al., 2002). However, BDNF has also been demonstrated to play a neuroprotective role during seizures in immature brains. During kainate-induced seizures in P19 rats, BDNF concentrations increase twofold and the administration of antisense oligodeoxynucleotides

specific to BNDF increased seizure duration and loss of CA1 and CA3 pyramidal cells and hilar interneurons. The neuronal loss was determined not to be dependent on seizure duration (Tandon et al., 1999).

36.4.2.3 *Inflammation*

The inflammatory processes that occur after seizures in the adult brain are important contributors to neuronal cell death (Kunz and Oliw, 2001); however, the role of inflammatory processes in the developing brain is less well understood. SE-induced glial activation and cytokine transcription are age-dependent. At P9, there is very little increase in the activation of glia and cytokine induction after kainate-induced seizures. At P15, immunostaining of microglia and astrocytes increased, as did IL-1β mRNA expression and CA3 neuronal injury. At P21, the immunostaining of microglia and astrocytes was significantly increased, as were IL-1β, TNF-α, IL-6, and Ra (endogenous IL-1 receptor antagonist). The neuronal injury in CA1 and CA3 was also significantly increased (Rizzi et al., 2003). The precise mechanism of neuronal death is poorly understood; however, increase in cytokine expression may play a role. One possible mechanism may involve IL-1β, as IL-1β is known to initiate phosphorylation of NMDA receptors (Viviani et al., 2003), thereby altering the receptor channel-gating properties to favor Ca^{2+} influx (Ali and Salter, 2001). In the rodent model of prolonged febrile seizure, hippocampal levels of IL-1β were significantly elevated after prolonged febrile seizures for a period of over 24 h. Chronically, IL-1β levels were elevated only in the subset of rats that developed spontaneous limbic seizures after febrile SE, consistent with a role for this inflammatory mediator in epileptogenesis (Dubé et al., 2010).

Microglia are a glial cell type that reside in the brain and spinal cord and function, in a manner similar to macrophages, as active immune defense for the CNS. Microglia reach maximal density in the brain during early development in humans (Billiards et al., 2006) and rodents (Dalmau et al., 2003). In addition to the phagocytic role of microglia, they are able to produce neurotrophic molecules, cytokines, and chemokines (Kim and de Vellis, 2005). Microglia are also involved in classical complement cascade-mediated CNS synapse elimination in the developing brain (Stevens et al., 2007). Seizures can directly activate microglia that trigger a cytokine-mediated inflammatory response, as well as complement factors and major histocompatibility class factors (Vezzani et al., 2008). In adult rats, the administration of the microglial inactivators minocyclin and doxycycline has been shown to protect against neuronal death in the kainate-induced SE model (Heo et al., 2006). This observation could not be reproduced in juvenile rat kainate-induced seizures because of the lack of neuronal cell loss during the second postnatal week in this model (Holopainen, 2008).

Cytokine activation can induce two main developmentally regulated inflammatory pathways: inducible nitric oxide synthesis (iNOS) (Romero et al., 1996) and/or the cyclooxygenase (COX) pathway (Tocco et al., 1997). COX-2 is the rate-limiting enzyme for conversion of arachidonic acid to prostaglandins. The enzyme is upregulated in response to seizures and may contribute to SE-induced CA3 hippocampal neuron damage in adult rats (Kawaguchi et al., 2005; Tu and Bazan, 2003). The expression of COX-2 markedly increases between P7 and P14 and reaches adult levels at P21 (Tocco et al., 1997). The developmentally regulated nature of COX-2 expression may in part explain the age-dependent effect of inflammation and neuronal death. In P9 rats, iNOS and COX-2 were upregulated after NMDA injection-induced excitotoxic shock. iNOS was observed in infiltrated neutrophils and in ramified protoplasmic astrocytes closely associated with blood vessels, whereas COX-2 was observed in active microglial and neuronal cells (Acarin et al., 2002). In P21 KA-induced rats, two phases were seen after seizure induction. The first phase occurs within 30 min, is localized to the hippocampus, and is caused by kainic acid receptor activation. Pretreatment with a selective COX-2 inhibitor, NS398, is able to inhibit the inflammatory process almost entirely. The late phase of the inflammatory process seems to be due to prolonged COX-2 expression localized to the hippocampus (Yoshikawa et al., 2006). Pretreatment with celecoxib, a selective COX-2 inhibitor, in flurothyl-induced P7 rats is able to delay signs of seizure and attenuate COX-2 expression (Kim and Jang, 2006). Interestingly, inflammatory mediators can affect neuronal function by altering activity-dependent long-term synaptic plasticity, neuronal excitability, and synaptic transmission in CA1 pyramidal neurons (Chen and Bazan, 2005).

36.4.2.4 *Alteration in Transcription of Receptors*

In addition to acute changes in posttranslational regulation of ion channels and neurotransmitter receptors, seizures can induce transcriptional changes in GABA and glutamate receptors (Holopainen, 2008). Kainate-induced seizures in P9 rats are sufficient to alter the normal maturation of $GABA_A$ receptor expression by altering region-selective expression of α_1, α_2 β_3, and γ_2 subunit mRNAs in the hippocampus that can last up to a week (Laurén et al., 2005). In addition to acute and subacute changes in $GABA_A$ receptor composition in young rats, long-term alterations in $GABA_A$ receptor α_1 subunit mRNA and protein expression persisted up to 3 months in the dentate gyrus of the hippocampus in SE-induced P10 and P20 rats (Raol et al., 2006; Zhang et al., 2004). The shifting role of $GABA_A$ receptors

from excitatory to inhibitory in the developing brain is demonstrated when seizures generated by functional excitatory GABAergic synapses cause fast oscillations that are necessary to transform normal network activity to an epileptic network (Khazipov et al., 2004). Interestingly, in the immature brain, inhibition of $GABA_A$ receptors can prevent long-lasting sequelae of seizures, whereas in the adult brain $GABA_A$ receptor inhibition leads to high-frequency seizures (Khalilov et al., 2005).

Seizures also affect the expression of both ionotropic and metabotropic glutamate receptor subunits. Downregulation of kainate receptors in the CA3 and dentate gyrus was observed in recurrent kainate-induced seizures in P12 rats (Tandon et al., 2002). In addition, elevation of $mGluR1_\alpha$ protein expression was seen in the inhibitory interneurons of the CA1 stratum oriens–alveus, amygdala, and piriform cortex of the same kainate-induced model. This change in $mGluR1_\alpha$ expression may induce synchrony of the limbic network suppression that can prevent further seizure propagation (Avallone et al., 2006). There is a decrease in GluR2 protein levels at P10 after lithium–pilocarpine (Zhang et al., 2004) and hypoxia-induced seizures (Sanchez et al., 2001). The decrease in GluR2 levels could be explained by excitotoxicity, which activates the repressor element 1-silencing transcription factor that suppresses GluR2 promoter activity, leading to AMPA receptor-mediated neuronal death (Calderone et al., 2003). Ionotropic glutamate receptors such as NMDA receptors are responsible for the excitotoxicity seen with prolonged receptor activation and Ca^{2+} influx in seizure-related neuronal death in adult rats (Furukawa et al., 1997).

Pilocarpine-induced SE in P14 rats showed increased AMPA GluR2 and kainate KA2 subunit mRNAs with decreases in AMPA GluR3 and kainate GluR6 mRNAs, but only in mature dentate granule cell neurons. In the study, immature dentate granule cells showed a decrease only in kainate GluR6 mRNA levels (Porter et al., 2006). These changes to kainate receptor subunits may play a role in the altered kainate receptor conductance and dentate granule cell excitability seen in chronic epilepsy (Epsztein et al., 2005). At P7, a single kainate-induced seizure has the ability to cause a long-term decrease in expression of GluR1 and NR2A subunits and an increase in PSD-95, a primary subsynaptic scaffold, in CA1 (Cornejo et al., 2007).

36.4.2.5 Neurogenesis

Increased neurogenesis has been seen in autopsy specimens and tissue biopsies from pediatric epilepsy surgery patients (Takei et al., 2007). Timing of the seizure insult plays a very important role in seizure-induced neurogenesis. There is a significant decrease in the neurogenesis observed in the granule cell layer of the dentate gyrus following a series of 25 flurothyl-induced seizures at P0–P4 as determined via 5-bromo-2′-deoxyuridine-5′-monophosphate (BrdU) and NeuN co-labeling (McCabe et al., 2001; Schmid et al., 1999). The decrease in BrdU labeling continued for 6 days after the last seizure. A single flurothyl-induced seizure showed no difference in BrdU-labeled cells when compared to controls. Adult rats that were subjected to a series of 25 flurothyl-induced seizures showed a marked increase in dentate gyrus neurogenesis when compared to controls (McCabe et al., 2001). Between 1 and 4 weeks of age, chemoconvulsant-induced seizures cause long-term increases in dentate granule cells after flurothyl-induced seizures (Holmes et al., 1998) and lithium–pilocarpine-induced seizures (Porter et al., 2004; Sankar et al., 2000). Lithium- and pilocarpine-induced SE rats at P20 showed a sixfold increase in BrdU labeling 8 days after SE induction in the dentate gyrus, which decreased to a threefold increase 3 weeks after induction. In addition to increased neurogenesis, an increase in apoptosis was observed in the same samples as determined by a threefold increase in TUNEL staining 8 days after induction as compared to controls. Only a subset of the newborn cells actually went on to become mature neurons as demonstrated by NeuN staining (Porter et al., 2004). The number of episodes of SE and type of chemoconvulsant also have important implications for neurogenesis. One or two episodes of kainate-induced seizures showed no difference at P6 and P9 in BrdU labeling in the dentate gyrus when compared to controls. However, three episodes of kainate-induced seizures demonstrated a decrease in BrdU labeling in the dentate gyrus at P6, P9, and P13 at 48 h after seizure. No difference in cell death or apoptosis was observed in the kainate-induced SE rats when compared to controls; however, the newly born cells demonstrate irregular morphology (Liu, 2003). Alterations in neurogenesis may have a significant functional impact on normal brain development since 80% of granule cells develop after birth, and about half develop after P5 in normal rat brain development (Bayer, 1980).

36.4.3 Chronic

36.4.3.1 Sprouting

In adult rodent models of epilepsy and chronic epileptic foci removed from adult and older pediatric patients, hippocampal granule cell mossy fibers 'sprout' aberrant collaterals to the inner molecular layer of the dentate gyrus, forming monosynaptic connections and a positive feedback loop that may contribute to the seizure focus (Williams et al., 2007). The degree and localization of mossy fiber sprouting differ greatly with age (Holmes et al., 1998, 1999; Liu et al., 1999). In neonatal seizures, much of the sprouting is minimal and located in the CA3 (Holmes et al., 1998, 1999). The adult has a greater

amount of sprouting, which is localized to the supragranular region and results from cell loss in the hilus and CA3 (Liu et al., 1999). The pattern of mossy fiber sprouting in early-life seizures is distinct from adult patterns in that the mossy fiber synapses terminate on the basal dendrites in the CA3 region and the stratum oriens (Holmes et al., 1999). There is some controversy regarding the effect of sprouting on epileptogenesis. Early studies have demonstrated that direct infusion of the protein inhibitor cyclohexamide was able to block pilocarpine- and kainate-induced mossy fiber sprouting in adult rats but not epileptogenesis (Longo and Mello, 1997). However, more recent studies have demonstrated that direct infusion of cyclohexamide to the dentate gyrus of adult rats spanning the period of pilocarpine treatment was unable to block mossy fiber sprouting or epileptogenesis (Toyoda and Buckmaster, 2005; Williams et al., 2002). The mechanism of mossy fiber sprouting is still unclear. Some hypothesize that the sprouting is caused by hyperexcitability; however, recent studies do not support this hypothesis. In adults, blocking L-type calcium channels and sodium channels is unable to stop mossy fiber sprouting in the pilocarpine model (Buckmaster, 2004; Ingram et al., 2009). However, in P14 mice, pilocarpine-induced L-type calcium channel blockade was able to inhibit mossy fiber sprouting (Ikegaya et al., 2000). Early treatment with rapamycin, an inhibitor of the mammalian target of rapamycin, was able to decrease seizure susceptibility in a transgenic mouse model of tuberous sclerosis (Meikle et al., 2008) and block mossy fiber sprouting in the pilocarpine model only with constant infusion, as the sprouting developed again after the cessation of infusion (Buckmaster et al., 2009).

36.5 TREATMENTS

The most challenging aspect of pediatric epilepsy treatment is to identify drugs that can protect against seizures while allowing normal functioning and development of the nervous system. Bromide was the first effective epilepsy treatment. Bromides act by augmenting $GABA_A$ receptor-mediated inhibition by increasing $GABA_A$-mediated currents due to a threefold increase in receptor permeability to Br^- over Cl^- (Bormann et al., 1987; Gallagher et al., 1978). Bromide has been replaced with less toxic antiepileptic drugs (AEDs), some of which target the same GABAergic pathway. Many newer AEDs work through non-GABAergic pathways or possess mixed mechanisms of action. The three main mechanisms of AEDs include enhancement of synaptic inhibition, reduction of synaptic excitation, or modulation of voltage-gated ion channels. Molecular targets of AEDs include voltage-gated sodium channels, voltage-gated calcium channels, GABAergic neurotransmission, and glutamatergic neurotransmission (Rogawski and Löscher, 2004; Table 36.2).

Methods of AED discovery have been recently reviewed by Bialer and White (2010). It is important to note that AED drug testing is typically studied in the adult rat brain. Drugs that pass this first level of screening are then studied in models of epilepsy, typically first in adult models and only later (if at all) in developmental epilepsies. There are three main types of drug-testing modalities used currently: maximal electroshock, subcutaneous PTZ injection, and electric kindling. The maximal electroshock modality utilizes electrical pulses delivered via ear clips or corneal electrodes to cause tonic extension of the hind limbs. If the administration of the drug inhibits the extension of the hind limbs, then the potential AED is thought to prevent the spread of seizure activity through neural tissue and is useful in screening AEDs effective against generalized tonic–clonic seizures. In the subcutaneous PTZ injection, animals are evaluated for clonic seizures. The effectiveness of a drug is determined by its ability to suppress these clonic seizures, making the model useful for finding AEDs effective against generalized myoclonic seizures. The drug discovery model of electrical kindling uses corneal electrodes to deliver 6 Hz electrical signals to induce complex partial seizures. Animals that do not display a clonic phase and automatisms are thought to be protected, making this method useful in screening drugs effective against partial seizures (Bialer et al., 2002; Holmes and Zhao, 2008). Unfortunately, these methods are not always accurate in their predictive efficacy. Levitacetam failed the subcutaneous PTZ and maximal electroshock models, but has proven to be a very effective AED (Klitgaard et al., 1998; Löscher et al., 1998). Therefore, new models of drug screening will be important in the future discovery of effective AEDs, especially for pediatric epilepsies.

36.5.1 GABA

36.5.1.1 Phenobarbital

Phenobarbital is a positive allosteric modulator of $GABA_A$ receptors that works by increasing channel-opening probability (Macdonald and Olsen, 1994). In addition to its primary GABAergic effect, phenobarbital can also block sodium channels and T-type calcium channels (Ffrench-Mullen et al., 1993). Phenobarbital is currently used as a first-line therapy for pediatric seizures but is mostly ineffective due to the shift in chloride gradient previously described. The effects of prenatal exposure to phenobarbital on CNS development have been studied extensively (Fishman and Yanai, 1983; Yanai et al., 1979) and have been reviewed (Kaindl et al., 2006). Perinatal and early-life exposure to phenobarbital can reduce brain

TABLE 36.2 Antiepileptic Drugs Used to Treat Neonatal Seizures and Pediatric Epilepsies

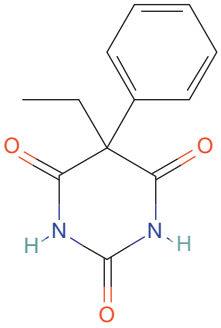
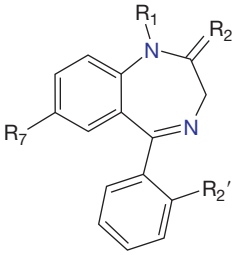
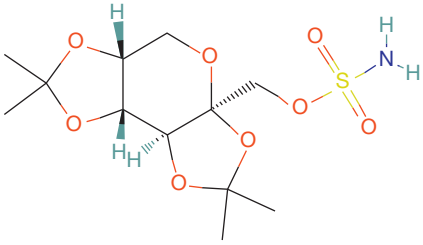
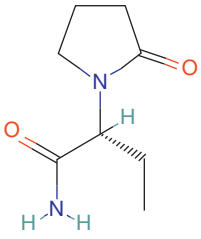
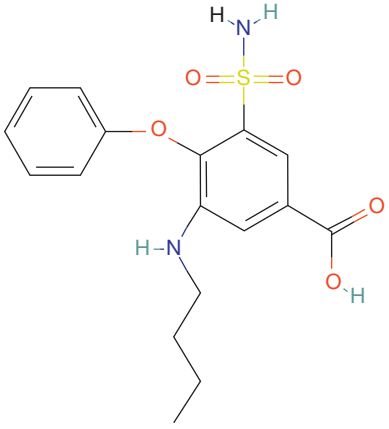
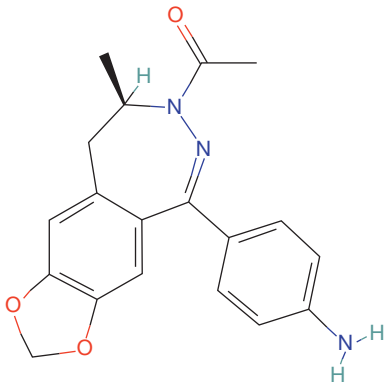
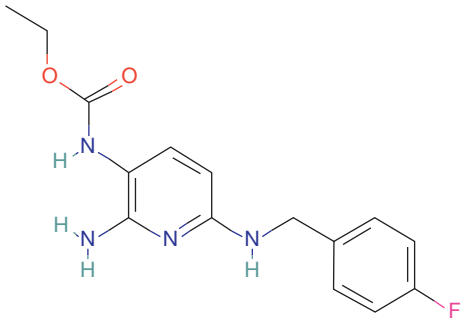
Structure	Drug	Primary effect	Site of action
	Phenobarbital	Enhances inhibition	GABA(A) – Mature brain
	Benzodiazepines	Enhances inhibition	GABA(A) – Mature brain
	Topiramate	Decreases excitation and enhances inhibition	Voltage-dependent sodium channels, Calcium channels, AMPA, and Kainate receptors/ GABA(A)
	Levetiracetam	Decreases excitation and enhances inhibition	Calcium channels, and SV2A/ GABA(A)
	Bumetanide	Enhances inhibition	NKCC1 (chloride gradient)

TABLE 36.2 Antiepileptic Drugs Used to Treat Neonatal Seizures and Pediatric Epilepsies—cont'd

Structure	Drug	Primary effect	Site of action
	Talampanel	Decreases excitation	AMPA receptors
	Flupirtine	Decreases excitation and enhances inhibition	NMDA receptors/KCNQ channels

weight in infant rats, with reductions in DNA, RNA, protein, cholesterol, neuronal number, and neurogenesis occurring, as well as enhanced apoptosis and alterations in gene expression (Bittigau et al., 2002; Diaz and Schain, 1978; Pick and Yanai, 1985; Raol et al., 2005; Stefovska et al., 2008; Yanai et al., 1989). Behavioral studies evaluating the morphological and neurochemical effects of perinatal and early-life exposure to phenobarbital, including deficits in various spatial-learning tasks and memory (Mikati et al., 1994; Pick and Yanai, 1985; Rogel-Fuchs et al., 1992; Yanai et al., 1989). Perinatal exposure to phenobarbital also increased aggression and activity levels in neonatal rats (Diaz and Schain, 1978; File and Wilks, 1990). Phenobarbital also has effects on synaptogenesis and myelination. The administration of phenobarbital to neonatal rats resulted in persistent abnormalities in mitochondria, myelin sheaths, and lamellar inclusion bodies in the cerebellum when compared to controls (Fishman et al., 1989).

36.5.1.2 *Benzodiazepines*

Benzodiazepines are first-line drugs in the treatment of SE. The actions of benzodiazepines are mediated by allosterically modulating $GABA_A$ receptors that contain the γ_2 with the α1, α2, α3, and α5 subunits (Rudolph et al., 1999; Smith, 2001), increasing $GABA_A$ receptor currents (Bai et al., 2001). Behavioral deficits have been attributed to the effects of benzodiazepines on memory, possibly due to an alteration in attention (Pereira et al., 1989). The administration of a single dose of diazepam to P11 rats caused a significant decrease in cell proliferation (Pawlikowski et al., 1987). Diazepam and clonazepam administration to P7 rats caused widespread apoptotic neurodegeneration, which is associated with reduced expression of neurotrophins and other prosurvival proteins (Bittigau et al., 2002). Diazepam administration from P10 to P40 in rats permanently altered the expression of genes for GABA receptor subunits, GABA transporters, and GABA-synthesizing enzymes in hippocampal dentate granule neurons (Raol et al., 2005). Diazepam also affects cell proliferation, cell differentiation, and myelination making it less than ideal for treating pediatric epilepsies (Stefovska et al., 2008).

36.5.2 Non-GABA

36.5.2.1 *Topiramate*

Topiramate works through many pharmacological mechanisms including modulation of voltage-dependent sodium channels, modulation of calcium channels, enhancement of the effect of GABA on $GABA_A$ receptors,

and modulation of AMPA and kainate receptors, all of which have been demonstrated to possess possible neuroprotective qualities. The administration of topiramate before hypoxia-induced seizures suppressed acute seizures in a dose-dependent manner. In addition to blocking acute seizures, topiramate administration was also able to eliminate the long-term susceptibility to kainate-induced seizures and the seizure-induced neuronal injury observed after acute hypoxia (Koh and Jensen, 2001). In lithium–pilocarpine-induced seizures in P20 rats, topiramate treatment resulted in an improved visuospatial performance in the water maze test when compared to saline-treated controls; however, no differences were found in histological examination of the hippocampus. The administration of topiramate in seizure-free neonatal rats resulted in no difference in water maze or histological studies (Cha et al., 2002). Topiramate demonstrates no neurotoxicity to the developing brain at anticonvulsant doses in P7 rats, in stark contrast to phenobarbital (Glier et al., 2004). The administration of topiramate to cultured fetal rat hippocampal and cortical neurons showed an increase in neurite outgrowth (Smith-Swintosky et al., 2001).

36.5.2.2 *Levetiracetam*

The mechanism of levetiracetam is not fully understood. The drug can block N-type calcium channels and reverse the inhibition by negative allosteric modulators such as zinc and beta-carbolines on neuronal GABA and glycine-gated currents (Rigo et al., 2002). Another pharmacological function distinct to levetiracetam is its binding to synaptic protein SV2A (Lynch et al., 2004). Recent studies have determined that SV2A is an important broad-spectrum anticonvulsant target (Kaminski et al., 2008). More studies are needed to elucidate the role of SV2A in ictal events. The administration of levetiracetam resulted in no deficits in visuospatial memory as observed via water maze testing in amygdala-kindled rats (Lamberty et al., 2000). In neonatal rats, levetiracetam resulted in no neurotoxicity when administered from P0 to P7 and analyzed from 2 to 5 days after administration (Manthey et al., 2005). Levetiracetam is effective in treating tonic convulsions and absence-like seizures in spontaneously epileptic rats during drug administration for up to 8 days after final administration, possibly demonstrating an antiepileptogenic effect (Ji-qun et al., 2005). Levetiracetam administration resulted in no alteration in hippocampal cell proliferation; however, significant effects in protein expression associated with the cytoskeleton, energy metabolism, neurotransmission, signal transduction, myelination, and stress response were observed (Paulson et al., 2010).

36.5.2.3 *Bumetanide*

Bumetanide is a well-known loop diuretic that is a specific inhibitor of NKCC1. Since enhanced expression of NKCC1 relative to KCC2 is responsible for the excitatory actions of GABA in the developing brain, it is easy to hypothesize that inhibiting NKCC1 would result in decreased excitatory actions of GABA. Dzahla et al. demonstrated the ability of bumetanide to shift the chloride gradient in immature neurons, suppress the epileptiform activity in hippocampal slices, and attenuate electrographic seizures in neonatal rats *in vivo* (Dzhala et al., 2005). Recent *in vitro* studies have shown that bumetanide can enhance the efficacy of phenobarbital in a neonatal seizure model. In the study, phenobarbital alone was able to abolish recurrent seizures in only 30% of the hippocampal slices, whereas the administration of bumetanide with phenobarbital was able to abolish recurrent seizures in 70% of the hippocampal slices. In addition to preventing recurrent seizures, the coadministration of bumetanide and phenobarbital also reduced the frequency, duration, and power of seizures in the remaining 30% (Dzhala et al., 2008). Bumetanide is able to block focal epileptic seizures in immature rat hippocampus, but is not able to prevent the formation of an epileptogenic mirror focus *in vitro* (Nardou et al., 2009).

36.5.2.4 *Talampanel*

Talampanel is a noncompetitive antagonist of the AMPA receptor and possesses anticonvulsant and neuroprotective properties. Talampanel administration to P10 rats in the hypoxia-induced seizure model suppressed seizures in a dose-dependent manner. Pretreatment of P10 rats before hypoxia prevented increases in seizure-induced neuronal injury later in life (Aujla et al., 2009). Talampanel is also neuroprotective in the CA1 region of the hippocampus in the fluid percussion traumatic brain injury model when administered within 30 min of injury but not when administered at 3 h (Belayev et al., 2001).

36.5.2.5 *Flupirtine*

Flupirtine, a selective neuronal potassium channel opener, activates KCNQ channels (G-protein-regulated inward rectifying K^+ channels) and stabilizes the resting membrane potential. Flupirtine also works via NMDA receptor antagonism by enhancing Mg^{2+} blockade (Kornhuber et al., 1999). The anticonvulsant properties of flupirtine have only recently been studied. Flupirtine proved successful in completely suppressing seizures in the flurothyl model of neonatal seizures and in preventing electrographic and behavioral seizures in the kainic-acid-induced SE model in P10 rats (Raol et al., 2009). Further studies are necessary to determine the long-term effects of flupirtine treatment of neonatal seizures.

36.6 CONCLUSION

Epilepsy is a very complex disease that affects millions of people worldwide. There are many different types of epilepsy, with various animal models used to elucidate the molecular mechanisms of epileptogenesis. The developing brain is especially sensitive to seizures and epilepsy due to the early enhancement of excitation in the immature brain. The acute and chronic effects of SE are quite complicated and include alterations in ion channels and neurotransmitter receptors, neuronal death, neurotrophin expression, inflammation, and mossy fiber sprouting. Since the development of the human brain is quite dynamic, the same therapeutic modalities used in adults have proved unsuccessful in controlling neonatal seizures. Newer therapeutics that act via novel mechanisms and are more effective in the developing brain are needed in order to treat those suffering from neonatal seizures and pediatric epilepsies adequately.

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