REVIEW ARTICLE

The Developing Nervous System: A Series of Review Articles

The following article is the second in our series on the developmental biology of the nervous system and its relation to diseases and disorders that are found in newborn infants and children. This article, by Gregory Holmes and Yehezkiel Ben-Ari, discusses the pathophysiology of epileptic seizures in the developing brain and the long-term consequences that may result from seizures that occur in the immature brain.

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The Neurobiology and Consequences of Epilepsy in the Developing Brain

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ABSTRACT

Epilepsy is a disorder in which the balance between cerebral excitability and inhibition is tipped toward uncontrolled excitability. There is now clear evidence that there are distinct differences between the immature and mature brain in the pathophysiology and consequences of seizures. Both the enhanced excitability of the immature brain compared with the mature brain and the unique pathologic consequences of seizures are related to the sequential development and expression of essential signaling pathways. Although the immature brain is less vulnerable than the mature brain to seizure-induced cell death, seizures in the developing brain can result in irreversible alterations in neuronal connectivity. Developing novel strategies to treat and avert the consequences of seizures in children will require further

understanding of the unique mechanisms of seizure initiation and propagation in the immature brain. (*Pediatr Res* 49: 320–325, 2001)

Abbreviations

AMPS, α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)
EPSP, excitatory postsynaptic potentials
GABA, γ -aminobutyric acid
GDPs, giant depolarizing potentials
KA, kainic acid
NMDA, *N*-methyl-d-aspartate
PDS, paroxysmal depolarization shift

As originally described by J. Hughlings Jackson in 1870, a seizure is an “excessive discharge of nerve tissue on muscle” (1). Jackson went on to say that “this discharge occurs in all degrees, it occurs with all sorts of conditions of ill health, at all ages, and

under innumerable circumstances.” These comments by Jackson are as true now as they were 130 years ago. Epileptic seizures are one of the most common, and frightening, neurologic conditions that occur in children. The incidence of seizures in children is significantly higher than in adults, with the highest incidence during the first year of life (2). Although there are many common features of the disorder across age groups, it has become clear that there are also significant differences between young children and adults in both the pathogenesis and consequences of epilepsy.

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Partial seizures, the most common seizure type to occur in both children and adults, will be reviewed in this article. The pathogenesis and consequences of recurrent brief seizures and status epilepticus will be reviewed. The mechanisms of generalized seizures, such as absences, are quite different and will not be reviewed here. Interested readers are referred to a review article by Snead (3).

Basic mechanisms of partial seizures. The core physiologic feature of epileptic seizures is hyperexcitability of CNS neurons. When a sufficient number of neurons synchronously depolarize and generate action potentials, a seizure begins. Both the location of the initial event and the propagation pattern of the discharge will determine the behavioral changes that occur. The hallmark of this synchronous discharge of neurons in the epileptic focus is the PDS, which is a large and sustained depolarization of the neuron. During a PDS, the cell membrane near the soma undergoes a high-voltage (approximately 10–15 mV) and long (100–200 ms) depolarization. This depolarization is much longer than the depolarization seen with normal EPSP, in which the duration is in the range of 10–16 ms. This long depolarization has the effect of generating a train of action potentials that are conducted away from the soma along the axon of the neuron. The PDS would correspond to a spike on the EEG (Fig. 1). The PDS is followed by a large hyperpolarization, which serves to limit the duration of inter-

ictal paroxysms. This hyperpolarization is generated by current through a number of ionic channels, including GABA and Ca^{2+} -activated K^{+} channels. During a seizure, the epileptic neurons undergo a prolonged depolarization with continuous bursts of action potentials without an intervening repolarization. The behavioral correlate of this prolonged depolarization is the tonic phase of the seizure. An EEG recorded at this time on the surface of the brain would demonstrate continuous spikes. During the next stage, large inhibitory potentials occur and alternate with recurrent rhythmic PDS. This pattern coincides with the clonic stage of the seizure. During this stage of the seizure, generalized spike-and-wave discharges would be present on the EEG.

Although the PDS has been useful in increasing our understanding of cellular physiology in epilepsy, the PDS can be recorded in only a limited number of models. However, in virtually all animal models of epilepsy there is some form of cellular “burst” discharge. Presumably, it is this enhanced cell excitability, or decreased inhibition, and synchrony that are responsible for both the “epileptic” EEG pattern and behavioral change. Although it is clear that seizures begin at the cellular level, epilepsy is a disorder of a network of neurons that synchronously discharge together.

The mechanisms responsible for the transition from interictal to ictal activity are not entirely understood. Factors such as

Figure 1. Diagram of cellular events corresponding to behavioral and electroencephalographic changes during the interictal and ictal periods. The *bottom diagram* demonstrates the PDS, a large and prolonged depolarization with generation of action potential spikes (*arrow*) (V_m is the voltage across the membrane). The *horizontal bars* at the bottom of the figure represent the period during which the particular channel is open (g_{Na^+} , $g_{\text{Ca}^{2+}}$, g_{K^+} refer to conductances of the ions across the membrane), the beginning of the bar indicates the opening of the channel and the end of the bar its closure. At the onset of the PDS, the AMPA channel opens, which allows Na^+ to enter the cell and begin the process of depolarization. The NMDA channel then opens allowing both Na^+ and Ca^{2+} to enter. Following depolarization, there is opening of the K^+ and activation of GABA channels with Cl^- entering the cell. Both the influx of Cl^- and efflux of K^+ lead to hyperpolarization on the cell. The PDS corresponds to a spike or sharp wave on the EEG (*top of diagram*). During an actual seizure (ictus), there is a failure of adequate inhibitory mechanisms and no hyperpolarization following the PDS occurs. This prolonged depolarization with action potentials corresponds to the tonic phase of the seizure. When inhibition is reinitiated, there are brief periods of depolarization following by hyperpolarization. This period corresponds to the clonic phase of the seizure. Modified from Kandel ER, Schwartz JH, Jessell TM 2000 *Principles of Neural Science*, 4th Ed. McGraw-Hill, with permission.

a change in the ionic microenvironment of the epileptic focus, decreases in GABAergic function, increases in synaptic excitation, alteration in K^+ or Ca^{2+} currents, or changes in the extracellular ion concentrations may trigger the prolonged depolarization. Even less is known about why seizures stop. Seizures may end when there is activation of inhibitory circuits in the neuronal network or changes in the ionic environment, such as reduction of extracellular K^+ , elimination of intracellular Ca^{2+} , or reduced release of glutamate.

Seizures, brain damage and plasticity in the adult brain. It has long been known that severe seizures are associated with brain damage and cell loss in children. Studies using animal models have enabled investigators to determine some of the mechanisms involved and their long-term consequences on the network. Although seizures can induce changes in multiple areas of the brain, the hippocampus has been particularly well studied inasmuch as this is the brain area that is frequently the most vulnerable to seizure-induced injury. In the adult animal, status epilepticus causes neuronal loss in hippocampal fields CA1, CA3, dentate granule cell layer, and the dentate hilus (4–8). Cellular damage occurs from excessive excitatory neurotransmitter release, which activates NMDA receptors and voltage-activated Ca^{2+} channels, allowing Ca^{2+} to enter the cell. Ca^{2+} and other ionic changes result in a cascade of biochemical changes eventually resulting in cell death (9). High Ca^{2+} leads to generation of reactive oxygen species *via* activation of nitric oxide synthase, uncouples oxidative phosphorylation in mitochondria, and activates a large range of enzymes, such as lipases, proteases, endonucleases, and other catabolic enzymes that collectively have adverse consequences for cell function (10).

Seizures in the adult brain lead to various forms of synaptic plasticity, including long-term potentiation of synaptic responses, a process that is reminiscent of that occurring in memory processes (11). This is followed by alterations in the cortical network that result in a reduction of seizure threshold. Seizures have been shown to activate hundreds of genes that lead to axonal growth and neosynaptogenesis (reviewed in (12)). Thus, prolonged seizures can cause synaptic reorganization with aberrant growth (sprouting) of granule cell axons (the so-called mossy fibers) in the supragranular zone of the fascia dentata and infrapyramidal region of CA3 in the supragranular zone of the fascia dentata (13, 14) and infrapyramidal region of CA3 (14). Because glutamate is the neurotransmitter of the mossy fibers, it is likely that this sprouting results in an excessive degree of excitation of dentate granule cells and, perhaps more importantly, CA3 pyramidal neurons. A further indication of the role of excitability in the generation of synaptic plasticity is the observation that blocking one of the glutamate subreceptors (NMDA) retards the development of mossy fiber development (15, 16). Sprouting and neosynapse formation occur in other brain regions—notably the CA1 pyramidal neurons, where it has been recently shown that newly formed synapses produce an enhanced frequency of glutamatergic spontaneous synaptic currents (17). Therefore, these alterations appear to be a general response of cortical networks to hyperactivity; the consequences of the seizures far outlasting the effects of the initiating event.

Immature neurons are more susceptible to seizure generation but less vulnerable to its pathologic consequences. It is well recognized that children are at higher risk for seizures than adults. In addition to the higher incidence of epilepsy in children than adults, precipitating factors such as fever are far more likely to induce a seizure in a young child than in an adult. Children also have a significantly higher likelihood of entering remission than adults, further suggesting that the brain becomes less excitable with age. Results from animal studies parallel clinical studies demonstrating that the immature brain is more susceptible to seizures than the adult brain. Kindling, a process in which recurrent electrical stimulations that initially result only in brief electrical discharges and mild behavioral changes but result progressively in more prolonged and intense electrical and behavioral seizures, occurs at all ages. Young animals kindle more rapidly than mature animals (18). In addition, a shorter period of postictal refractoriness in young animals leads to a quick progression through early stages of kindling and results in rapid generalization of seizures (19). Immature rats are more likely to develop seizures with hypoxia than mature rats (20). Similarly, the dosage of the convulsant kainic acid needed to induce seizures in immature animals is significantly lower than that required to induce seizures of similar intensity and duration in the mature rat (21).

Although the threshold for seizure generation is lower in the immature brain than in the adult brain, developing neurons are less vulnerable, in terms of neuronal damage and cell loss, than adult neurons to a wide variety of pathologic insults. For example, immature hippocampal neurons will continue responding to synaptic stimuli in a fully anoxic environment for longer durations than adult ones; likewise, longer anoxic episodes are required to irreversibly destroy neural pathways in young animals (22). Young animals are less vulnerable to cell loss following a prolonged seizure than mature animals (21, 23–28). Likewise, sprouting of mossy fibers is less prominent following prolonged seizures in young animals than seizures of similar duration in older animals (29, 30).

The immature brain appears to be more “resistant” to the toxic effects of glutamate than the mature brain (31–33). Marks *et al.* (33) found that the degree of Ca^{2+} entry into the hippocampal subfield CA1 and subsequent damage was directly related to age. In postnatal d 1–3 neurons glutamate increased intracellular Ca^{2+} minimally, whereas in postnatal d 21–23 neurons glutamate resulted in marked increases in intracellular Ca^{2+} and caused severe swelling of the cell and retraction of dendrites into the soma of the neuron. This relative resistance is thought to be due to the smaller density of active synapses, lower energy consumption, and, in general, the relative immaturity of biochemical cascades that lead to cell death following insults.

Behavioral consequences following status epilepticus are also related to age of the animal at the time of the status; adult animals surviving status epilepticus have significant deficits in learning, memory, and behavior (27) whereas young rats following status epilepticus have fewer deficits in learning, memory, and behavior (27, 34). Likewise, spontaneous seizures following status epilepticus are more likely to occur in older

animals experiencing status epilepticus than in younger animals (35–37).

Why is the immature brain so prone to seizure generation?

The enhanced excitability of the immature brain compared with the mature brain, like the pathologic consequences of seizures, is related to the sequential development and expression of essential signaling pathways. Thus, in the adult brain, glutamate is the primary excitatory neurotransmitter and GABA is the principal inhibitory transmitter. Synaptic transmission is mediated by glutamate that is released from the pyramidal neurons and depolarizes and excites the target neurons *via* ionotropic receptors [NMDA (AMPA) and KA]. Although all of the glutamate subreceptors respond to glutamate, they have individual characteristics. The AMPA receptor rapidly responds to glutamate with opening of the channel to allow Na^+ to enter the cell and depolarize the membrane. The NMDA channel has characteristics of both a neurotransmitter or ligand-activated and voltage-sensitive channel. Mg^{2+} sits in the channel blocking the flow of ions. Only with depolarization of the membrane is Mg^{2+} displaced and Na^+ and Ca^{2+} ions are able to cross the channel. The rise of intracellular Ca^{2+} is an essential signal for memory processes, hence NMDA receptor plays an important role in learning and plasticity. Activation of GABA_A and GABA_B results in hyperpolarization of the membrane and a reduction of excitability and action potential generation.

During development, these receptors are not functionally expressed simultaneously, but rather in a sequence of GABA_A -NMDA-AMPA. Recently it was found that, at birth, pyramidal neurons of the CA1 region of the hippocampus are of three types. They are silent (no synaptic currents), express only GABAergic currents, or express GABA and glutamatergic currents (Fig. 2). These three different types of CA1 neurons have different morphologic appearances: silent neurons have a soma and an axon, but no dendrites; GABA only neurons have a soma, axon, and small dendrite; and GABA and glutamate neurons have a soma, axon, and extended apical and basal dendrites.

Figure 2. Example of three types of pyramidal neurons at P0. These three different types of CA1 neurons have different morphologic appearances: silent neurons have a cell body and an axon but no dendrites; GABA-only neurons have a cell body, axon, and small dendrites; and GABA and glutamate neurons have a cell body, axon, and extended apical and basal dendrites. The arrow points to the axons and the arrowhead points to the dendrites. Modified from (38) with permission.

dendrites. GABAergic synapses therefore form before glutamatergic ones, presumably on the apical dendrites of the principal neurons (38). This sequence is of particular importance as GABA provides the main excitatory drive to hippocampal neurons at early stages of postnatal development because of a high Cl^- content in immature neurons. Opening of the Cl^- channels with efflux of Cl^- leads to depolarization of young neurons, rather than the hyperpolarization observed in adults (Fig. 3). Consequently, in the immature brain, GABA_A responses result in Cl^- efflux, depolarization, and subsequent activation of voltage-dependent Na^+ and Ca^{2+} channels (39). The depolarization produced by GABA is sufficient to remove the voltage-dependent Mg^{2+} block from NMDA channels, thereby inducing large Ca^{2+} influx into immature neurons. Initially discovered in the hippocampus, this effect of GABA has now been described in all brain structures studied (40). The effects of GABA include, however, an inhibitory component due to its shunting action. This explains why drugs such as phenobarbital or diazepam that work at the GABA_A receptor do not cause seizures in the immature brain. More recent studies by Ben-Ari *et al.* suggest that in the embryonic monkey GABA is first excitatory, the shift occurring around embryonic

Neonate

Adult

Figure 3. Comparison of excitatory and inhibitory channels in neonate and adult. In the adult, AMPA responds to glutamate by opening and allowing Na^+ to enter cell. With depolarization, Mg^{2+} is displaced from the channel and Na^+ and Ca^{2+} enter the cell. With membrane depolarization, voltage-gated channels (VDNa^+ and VDCa^{2+}) also open. GABA_A and GABA_B , through Cl^- and K^+ ionic flow, serve to hyperpolarize the cell. In the neonate, AMPA receptors, although present, are not functional (designated as white). NMDA channels, because of the block with Mg^{2+} , do not function at normal membrane resting potentials. Because of the higher Cl^- content of the immature brain, GABA activation results in an efflux of Cl^- that serves to depolarize the cell. With depolarization, the NMDA and voltage-gated channels can open. GABA_B (designated white in the neonate's brain), like AMPA, develops later and provides little postsynaptic inhibition in the neonate. Modified from (40) with permission.

d 100–120 (41). These findings suggest that the effects of epileptogenic agents will be strongly age, species, and structure dependent.

The other major postsynaptic inhibitory system, the postsynaptic GABA_B, adenosine, and 5-hydroxytryptamine-G protein coupled K⁺ channels, also have a delayed maturation, suggesting that the neonatal circuit operates without transmitter-gated inhibition. In contrast, presynaptic inhibition, mediated by adenosine, GABA_B, or other metabotropic receptors, is fully operational at birth; evidence that the major form of inhibition in the neonatal circuit is the control of transmitter release. If there is interference of these presynaptic controls of inhibition, pronounced seizures may occur. For example, it has recently been demonstrated that caffeine, an adenosine blocker, can be highly epileptogenic during hypoxia in the immature but not the adult rat (42).

In summary, the immature brain is more prone to seizures than the mature brain because of a developmental mismatch between the delicate balance of excitation and inhibition. The depolarizing effects of GABA during early development combined with a delay in postsynaptic inhibitory systems result in a situation in which seizures are easily elicited.

Deleterious effects of seizures to the developing brain. In spite of the relative resistance of immature neurons to epilepsy-induced brain damage, seizures in the developing brain do produce significant and often irreversible alterations of the developing brain. Kindling during the first weeks of life results in lifelong increases in seizure susceptibility (43). Using two models of neonatal seizures, pentylenetetrazol and flurothyl, we recently demonstrated that recurrent seizures during the neonatal period result in subsequent increases in mossy fiber growth in both the supragranular region and CA3 hippocampal subfield (44–46). Recurrent seizures also result in alterations of neuronal pathways activated during seizures (46); animals undergoing a series of seizures have a progressive increase in the extent of neuronal activation as evidenced by early gene activation of *c-fos*. In addition to the anatomical changes, neonatal seizures have also been shown to result in impairment of visual-spatial memory when the animals are tested as adults (44).

The aberrant network set up by recurrent seizures increase brain vulnerability to future injury. Schmid *et al.* (47) produced status epilepticus using either KA or perforant pathway stimulation in adolescent rats with a history of 25 seizures during the first 4 d of life. The authors found no cell loss in animals that had neonatal seizures only. Animals that had neonatal seizures, however, had significantly more severe brain injury following both KA and perforant pathway stimulation than did animals without a history of neonatal seizures. Although the mechanism behind this enhanced susceptibility to injury is not yet known, the study provides further evidence that neonatal seizures alter the brain in a maladaptive manner.

Seizures may perturb a wide range of developmental phenomena that are activity dependent, including cell division, migration, sequential expression of receptors, formation, and probably stabilization of synapses (48). Indeed seizures can modify—slow down or accelerate—a wide range of unique processes that take place during development and are essential

for the correct formation and wiring of the circuitry. The migration of neurons, the arborization of the neurites, the formation of synapses, or the removal of redundant processes are all essential processes that are activity dependent and may be disturbed by seizures. Thus, recurrent activation of NMDA receptors accelerates neuronal migration (49) and may lead to the formation of aberrant connections. In addition, as noted above, most of the receptor proteins or second messenger cascades that have been studied are modified during development, and there are good reasons to believe that aberrant hyperactivity may alter the pattern and sequence of expression. Thus, the expression of AMPA receptors appears to be activity dependent with synchronized activity being required to facilitate its expression, much like plasticity in adult synapses (50). Aberrant episodes of hyperactivity will modify this sequence.

It is known that synaptic activity in the developing brain develops as a result of slow waves of depolarization that spread throughout the brain. Initially described in the hippocampus, GDP have now been observed in every neuronal structure studied (neocortex, retina, thalamus, spinal cord, etc.). GDP are generated by the combined excitatory actions of GABA and glutamate in developing circuits. Studies in intact hippocampi *in vitro* in rodents have shown that, in the rat, epileptogenic discharges can be generated within days of birth (51) and that GDP can be significantly altered by epileptogenic activity (52).

It now appears clear that prolonged or recurrent seizure activity, through activity-dependent mechanisms, can irreversibly alter the way the immature brain develops and forms synapses. These alterations in normal neuronal connectivity can result in long-term consequences in seizure susceptibility, learning and memory, and risk for subsequent seizure-induced injury.

CONCLUSIONS

The highest risk for seizures occurs during the first decade of life. This increased susceptibility to seizures is related to a developmental imbalance between excitatory and inhibitory processes. Although the immature brain is less vulnerable to seizure-induced injury than the mature brain, there are a number of developmental processes that appear to be permanently altered by the seizures.

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