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Epileptogenesis in Childhood

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Introduction

Although 'epilepsy' is referred to as a single disorder, other articles in this encyclopedia highlight that there are many types of epilepsies, involving different neuronal circuits. In addition, these epilepsies are a result of many differing causes and mechanisms. In some instances, the reason for the development of the spontaneous seizures (i.e., epilepsy) relates to abnormal brain structure (malformation) that can be local or generalized. In others, mutations of ion channel genes or of other genes confer a genetic basis of the epilepsy. In still other cases, infection, trauma, and probably also some very long febrile seizures provoke epileptogenesis, the process of epilepsy generation, in a brain that otherwise would not develop epilepsy without this insult. Commonly, the timing of epilepsy onset is during the first decade in humans, even though the responsible mutation, malformation, or other insult may be congenital or occur much earlier in postnatal life. Why do the first seizures that herald the onset of epilepsy occur in infancy and childhood?

Background

Basis of Susceptibility of the Early Postnatal Brain to Seizures

During the first months to years in humans, and the comparable first days and weeks in rodents, several factors coalesce to render the brain, and particularly the limbic circuit, susceptible to the occurrence of single and recurrent seizures. Much of the information about the mechanisms that contribute to this fact has arisen from rodent animal models, and it is therefore important to realize that direct comparison of the developmental stages between human and rodent brain are inexact. For examples, the gestation and postnatal development of rodents are much shorter, and rats reach puberty at ~6 weeks and adulthood at about two months of age. Comparative anatomy suggests that in rats and mice, cortical neuron birth and migration are completed shortly after birth, and brain growth takes place largely within the first 2–3 weeks of life. Particularly considering hippocampal development, a newborn rat pup's developmental stage is comparable to that of a premature baby, a rat at 5–7 days of age has similar development to that of a full-term newborn, and at 3 weeks that of an older child.

During the first postnatal week, excitatory neurotransmitter development and maturation precedes that of inhibition, mainly because activation of the $GABA_A$ receptor by endogenous γ-aminobutyric acid (GABA) produces depolarization. This is a result of the immature state of chloride transporters, resulting in higher intracellular chloride. In addition, expression of certain glutamate receptor subunits 'overshoots' adult levels during the first two postnatal weeks. This combination increases relative excitatory synaptic transmission, promoting hyperexcitability and the susceptibility to seizures.

The unique developmental profile of neurotransmitter expression is accompanied by similar age-specific expression patterns of neuropeptide modulators and intrinsic neuronal ion channels. Like 'classical' neurotransmitters, neuropeptides are released from neurons and can influence the excitability of a neuronal network, acting typically via metabotropic receptors at postsynaptic or presynaptic sites. Inhibitory neuropeptides, including for example neuropeptide y (NPY), are expressed in cortex and hippocampus in humans (and rodents), and reduce network excitability and seizure susceptibility. NPY levels are relatively low in early postnatal hippocampus, which may contribute to the enhanced susceptibility to seizures. In contrast, the excitatory peptide corticotropin-releasing hormone (CRH), and its major receptor, CRFR1, are expressed in developing hippocampus at levels higher than in the adult. This is particularly true during the second postnatal week in the rodents, a developmental epoch characterized by high susceptibility to seizures. CRH increases network excitability by reducing afterhyperpolarizations.

In addition to age-dependent expression patterns of glutamate, GABA, and neuropeptides, and hence in synaptic neurotransmission, developmental expression patterns of ion channels govern age-specific intrinsic properties of neurons, promoting network excitability. Even minor changes in the function of these channels, resulting from mutations or altered expression levels, may promote seizures and epilepsy. For example, mutations in 3 of the 13 known sodium channel genes in mammals (*NaV*1.1, *NaV*1.2, β1) have been associated with epileptic phenotypes, typically arising during infancy or early childhood, and often disappearing later in life. Potassium channels are particularly important during the developmental period when GABA is depolarizing, because they are among the few cellular components that promote repolarization. Indeed, dysfunction of two members of the voltage-gated potassium channels, KCNQ2 and KCNQ3, that carry the

M-current lead to benign familial neonatal convulsions, seizures that occur during the first days and weeks of life, and disappear later. For the Ca^{2+}-channels, age-specific contribution of the CaV2.1-subunit to seizure susceptibility has been delineated in mice. In thalamic neurons of the neonatal mouse, either N- or P/Q-type channels support neurotransmitter release. However, later in life, this function is taken over exclusively by the P/Q-type channels, formed by CaV2.1 subunits, so that dysfunction of these channels provokes seizure vulnerability.

The repertoire of cellular components, including ion channels, transporters, and receptors, that are differentially expressed during development and may influence susceptibility to seizures is constantly enlarging. Recent additions include the chloride transporter NKCC1.

Conceptual and Methodological Considerations

Susceptibility to Seizures Vs. Vulnerability to Epileptogenesis

Although a significant body of information exists that clarifies, or at least is consistent with, the increased likelihood of seizures early in postnatal life, little is known about the basis for the vulnerability to epileptogenesis during this epoch. Indeed, seizure susceptibility is not synonymous with epileptogenesis. An excellent example for this dichotomy involves the consequences of trauma in children and adults. Children are much more likely to experience a seizure in response to even modest trauma, compared with adults. However, the probability of developing posttraumatic epilepsy is at least threefold lower. This example suggests that the developing brain might not be more vulnerable to epileptogenesis compared with that of a mature organism. In this scenario, epileptogenesis might occur more commonly early in life because the incidence of inciting insults, and especially seizures and status epilepticus (SE), is higher. This higher incidence, in turn, is dependent on the factors described earlier.

Age-Specific Epileptogenesis

Epileptogenesis is a term defining a series of complex processes leading to the occurrence of spontaneous seizures. The determinant of epileptogenesis varies widely. The process may arise on an almost purely genetic basis, for example, in the setting of a mutation of a critical gene such as an ion channel. In contrast, environmental input might play a key role in certain epilepsies, such as trauma or stroke. Generally, it is believed that gene–environment interaction underlies the majority of epileptogenic events.

Most of our knowledge of the epileptogenic processes is derived from studies in animals. These have been helpful for both 'genetic' and 'acquired' epilepsies. For example, transgenic mice carrying ion channel mutations, or natural mutations in calcium and other channels, have developed epilepsy, usually around puberty or later. In this case, the effects of the mutation promote seizures, and are typically, but not always, unaccompanied by neuronal death or other anatomical changes. In several animal models, the recurrent spontaneous seizures themselves, i.e., the epilepsy, eventually lead to cell death and often compensatory 'sprouting' of axons of remaining neurons.

Animal models of human epilepsies that do not seem to have strong familial or genetic component, including temporal lobe epilepsy, have often relied on SE as an inciting insult. As described in other chapters, SE leads to loss of neurons in vulnerable brain regions. In the hippocampus, loss of pyramidal cells in areas CA3 and CA1, and loss of neuronal population in the hilus of the dentate gyrus, are typical. The cell loss is classically followed by sprouting of granule cells and other neurons, formation of abnormal circuitry, and – after a latent period – the evolution of spontaneous seizures (i.e., epilepsy). There is considerable evidence that supports the notion that the cell death provoked by the original SE is required for the development of epilepsy.

Recent Results

Seizure-Induced Plasticity May Contribute to Epileptogenesis during Infancy and Childhood

Early in life, however, the story is quite different. In the 1980s it became clear that during the first two weeks of the rodent life, even severe seizures lead to little neuronal death. This finding was originally interpreted to suggest that early postnatal seizures might be benign, and indeed, gross cognitive sequelae as well as epileptogenesis were rare. However, more recently, more refined assessment of cognitive function has suggested that recurrent short seizures or prolonged single seizures might lead to impaired function. Still, the majority of the conventional chemically- and electrically induced SE and prolonged seizures do not seem to result in epileptogenesis.

In recent years, several animal models have shed light on the mechanisms of early-life epileptogenesis. Remarkably, although highly diverse, they provide consistent information. Spontaneous seizures have been reported after early-life experimental prolonged febrile seizures, after tetanus toxin, focal TTX injection, or endothelin-1 injections. In these models, cell death was not prominent and, in contradistinction to the mature brain, does not appear to be required for epileptogenesis. 'Sprouting' and neurogenesis were also not consistently present in the brain of immature rodents that developed epilepsy after these provoking insults. These data suggest that the mechanisms of epileptogenesis during early life require

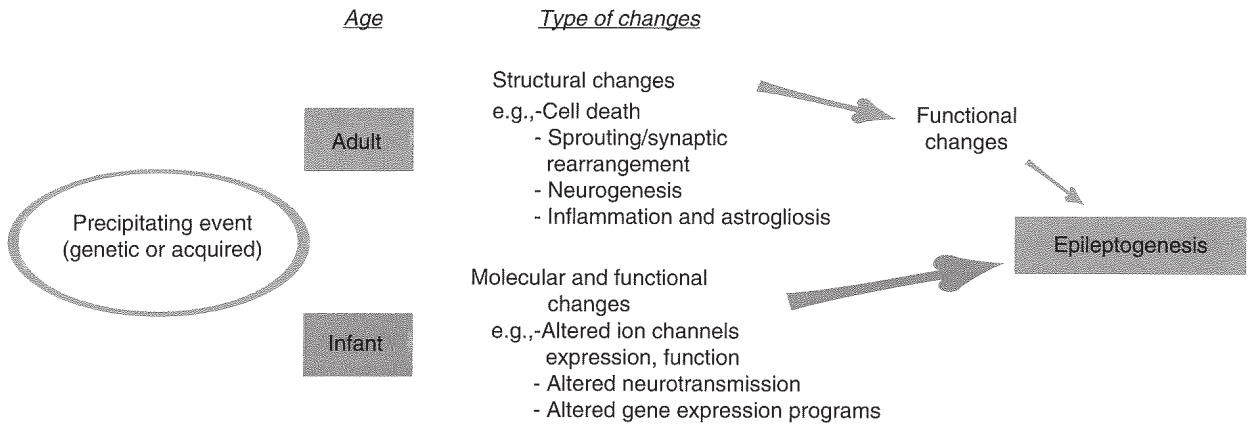

Figure 1 Distinguishing characteristics of epileptogenesis in the mature vs. the immature brain. The schematic shows how an original insult (e.g., genetic mutation of an important gene or severe long seizures) leads to epileptogenesis through different type of processes in immature and adult brain. An adult brain typically requires structural changes such as cell death and sprouting to become epileptic (as best defined in models of acquired epilepsy). In contrast, during childhood, neuroplasticity, often governed by altered programs of gene expression, is a leading mechanism of epileptogenesis.

functional rather than structural changes in neurons and neuronal circuit (**Figure 1**).

Several candidate mechanisms exist for epileptogenesis without cell death, and generally involve enduring changes in expression programs of key genes. Early-life seizures lead to persistent changes in the expression of several $GABA_A$ receptor subunits, which profoundly alter the properties of the receptors, rendering the brain more conducive to 'runaway excitability.' *N*-methyl-D-aspartate (NMDA)- and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)-type glutamate receptors are also changed. The expression of intrinsic ion channels, notably the hyperpolarization-activated ion channels, is also changed, leading to currents that increase the probability of rebound depolarization. Other receptors (e.g., the endocannabinoid receptor type 1) are also modulated long-term. The nature of the regulatory factors that are activated by early-life seizures to orchestrate these coordinate alterations of gene expression programs are not yet known. Altered signaling through the cAMP system and the neuronal suppressor NRSF have been found. One theory proposes that, at least in the case of long experimental febrile seizures, induction of endogenous inflammatory mediators and specifically IL-1β leads to altered gene expression via the NF-kB cascade, and endures long-term.

Future Directions

Although much has been learned from these studies and others about the pathways that convert a normal developing brain into an epileptic brain, many questions remain unanswered. For example, following a given insult, such as hypoxia, trauma, or complex febrile seizure, an individual rat or human may or may not develop epilepsy. The ability to predict who will develop epilepsy after an initiating event would be highly beneficial, because it will enable targeting of future interventions to the population at risk. Current and future studies aim to determine genetic and acquired susceptibility to epileptogenesis. In parallel, investigators are attempting to define 'biomarkers' of the epileptogenic process. Molecular arrays, or fingerprints, at mRNA or protein levels are under investigation. In addition, imaging methods (including MRI) are being used to examine whether changes visible in vulnerable brain areas denote regions that are undergoing changes conducive to the development of epilepsy at a later date.

In summary, significant evidence supports the independence of epileptogenesis in childhood from the need for cell death. However, relatively little is known about the nature and basis of the functional neuronal changes (neuroplasticity) that promote the epileptogenic process early in life. Future studies should help clarify these processes and, optimally, predict in advance who will develop epilepsy, and enable intervention and prevention of this disorder.

See also: **Epileptogenesis**: Multi-Hit Mechanisms Involved in Epileptogenesis: Role of Early-Life Seizures; **Glutamate**: Glutamate-Mediated Excitation and Mechanisms of Epileptogenesis in the Immature Brain; **Oscillatory Activity**: Seizures Beget Seizures in the Developing Brain: Central Role of GABA and High Frequency Oscillations; **Pediatric Epilepsy**: Animal Models of Catastrophic Epilepsies of Childhood; Animal Models of Infant-Onset Epileptic Encephalopathy; Cellular, Molecular and Behavioral Consequences of Early-Life Seizures; Developmental Aspects of Seizures; Seizure-Induced Injury and the Two-Hit Hypothesis.

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Hippocampal EEG in the Neonatal Rat: Development of Normal and Pathological Activity

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Introduction

Children are particularly susceptible to seizures during the first few months of postnatal life. During this period, a clinician may examine a child's background (nonparoxysmal) EEG activity for abnormal patterns that might predict pathological outcomes. In this context, 'abnormal' background EEG patterns (e.g., abnormalities of amplitude and frequency) are defined in relation to 'normal' age-specific patterns, which change continuously across this period as the complexity of the EEG increases.

The most common cause of seizures during the neonatal period is hypoxic–ischemic encephalopathy (HIE). To study the age-dependence of vulnerability to HIE and its associated neurological damage, an animal model was developed by Jensen and her colleagues. This experimental model involves the exposure of neonatal rats to graded global hypoxia in an airtight chamber. Studies utilizing this paradigm have reported age-dependent effects in the developing neocortex and hippocampus, with seizure being most readily induced at approximately postnatal day (P)10. The model therefore appears to capture a period of heightened seizure susceptibility in the neonatal rat that is analogous to that of the human infant. Yet, if the prognostic background EEG correlates of the HIE-like state in rats are to be properly studied, we need to better understand what 'normal' background activity entails.

Recent work in our laboratory has systematically assessed the development of the 'normal' hippocampal EEG across the first three postnatal weeks in unanesthetized rats. In addition, we have correlated the developmental changes in spontaneous activity with the age-dependent emergence of evoked pathological activity. In this article, we describe our findings, with special emphasis on the dramatic changes occurring during the second postnatal week.

Background

In rats, peak susceptibility to hippocampal seizures occurs during the second postnatal week. The increased excitability of the hippocampus during this period appears to be attributable to several factors. One of the more extensively studied of these factors is the ontogenetic shift in intracellular Cl^- concentration, which causes $GABA_A$ receptor activation to transition from having a depolarizing effect to a hyperpolarizing effect on the cell. This shift occurs as the Cl^- accumulating cotransporter NKCC1 is down-regulated, and the Cl^- extruding cotransporter KCC2 is up-regulated. A separate factor thought to contribute to the increased excitability of the neonatal hippocampus is that the effects of the excitatory neurotransmitter glutamate are potentiated by a transient up-regulation of AMPA and NMDA receptors. In addition, electrical coupling between neurons appears to be more abundant during the second