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Developmental Seizures Induced by Common Early-Life Insults: Short- and Long-Term Effects on Seizure Susceptibility

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Abstract

The immature brain is highly susceptible to seizures induced by a variety of insults, including hypoxia, fever, and trauma. Unlike early life epilepsy associated with congenital dysplasias or genetic abnormalities, insults induce a hyperexcitable state in a previously normal brain. Here we evaluate the epileptogenic effects of seizure-inducing stimuli on the developing brain, and the age and regional specificity of these effects.

Keywords

epilepsy; neonatal; childhood; animal models; hypoxia; febrile seizure; temporal lobe epilepsy; brain slices

INTRODUCTION

The majority of human seizures occur early in life, and many developmental seizures occur only during discrete windows of development. Understanding the mechanisms and consequences of these early-life seizures, including the features that distinguish them from seizures in the fully mature brain, is fundamentally important for delineating the consequences of seizures on structural and functional integrity of the developing central nervous system. Importantly, most early-life seizures are not genetically determined, and the majority of seizures occurring during infancy and early childhood are not spontaneous but are triggered by fever [Shinnar, 1998], hypoxia [Jensen et al., 1991; Westmark et al., 1995], or trauma [Dinner, 1993]. These triggered or provoked seizures, rapid and transient enhancements of neuronal excitability induced by stressful proconvulsant stimuli, demonstrate an exquisite age specificity. Hypoxia-related seizures occur primarily in neonates [Jensen et al., 1991, 1998; Volpe, 1995], febrile seizures are exclusive to infancy and childhood, and early traumatic seizures are more common in children [Jennett and Lewin, 1960].

The fundamental questions about provoked early-life seizures include the mechanisms of their generation by proconvulsant stimuli and the role of normal brain maturation in regulating neuronal excitability and threshold to the generation of these seizures. Another important issue is whether these seizures, by themselves, influence neuronal functional integrity, seizure susceptibility, and cognitive outcome. Human studies have failed to resolve these critical issues. For example, perinatal hypoxia has been variably associated

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with the development of epilepsy in later life [Bergamasco et al., 1984; Nelson and Ellenberg, 1986]. Early-life seizures in the setting of hypoxic encephalopathy occur in patients with multisystem failure and represent a heterogeneous population, confounding outcome studies. However, in infants undergoing cardiac bypass surgery for repair of congenital heart defects, electroencephalographic monitoring revealed a high incidence of postoperative epileptiform events [Bellinger et al., 1995]. Electroencephalographic (EEG) abnormalities were the major predictor of subsequent structural abnormalities on magnetic resonance imaging (MRI) [Bellinger et al., 1995].

Similarly, in the case of short seizures provoked by fever (simple febrile seizures), prospective epidemiological studies have demonstrated a benign outcome, without cognitive dysfunction [Verity et al., 1998] or subsequent epilepsy [Shinnar, 1998]. However, the relationship between prolonged febrile seizures and temporal lobe epilepsy (TLE) has been a subject of conflicting data and interpretation. Patients with intractable TLE, reported in retrospective risk factor analyses, have a high incidence (30%–60%) of a history of prolonged febrile seizures [Cendes et al., 1993; French et al., 1993]. These numbers far exceed the 3%–5% incidence of febrile seizures in the general population. This correlation has been interpreted as causal, i.e., that febrile seizures produce temporal lobe injury and spontaneous seizures [Falconer et al., 1964; French et al., 1993]. Indeed, even prospective studies, when carried long term, have suggested increased incidence of TLE in adulthood after early-life prolonged febrile seizures [Annegers et al., 1987]. While it has been proposed that prolonged febrile seizures predispose to TLE via seizure-induced injury to temporal lobe structures, an alternative hypothesis suggests that a pre-existing lesion, structural or functional, genetic or acquired, may be the cause of both the prolonged febrile seizure and the subsequent TLE [Shinnar 1998; Lewis, 1999]. Put differently, prolonged febrile seizures in the human may be a marker of already existing TLE that is unmasked by fever [Verity and Golding, 1991; Shinnar, 1998]. In support of this supposition, the increased likelihood of TLE after prolonged febrile seizures is far more evident in individuals with preexisting brain abnormalities compared with those with normal neurological status and neuroimaging studies [Maytal and Shinnar, 1990]. As evident from these data, these types of questions are difficult to address in human studies. Animal models permit controlled, prospective investigations, as well as the use of interventions and dissection of mechanisms. This chapter describes recent discoveries resulting from the use of animal models of hypoxic and febrile seizures in infant rats. They document the acute and long-term consequences of these seizures on neuronal excitability and structural integrity in the hippocampal-limbic circuit.

HYPOXIA-INDUCED SEIZURES

The incidence of seizures is highest in the first year of life, with an even higher incidence in the first few weeks of life [Aicardi and Chevrie, 1970]. Hypoxic encephalopathy is the most common cause of neonatal seizures [Volpe, 1989, 1995]. Perinatal hypoxia can occur in the setting of asphyxia complicating a difficult labor and delivery, sepsis, respiratory distress of the newborn, extracorporeal membrane oxygenation, and perioperatively in infants undergoing cardiac bypass for repair of congenital cardiac defects. Seizures in the setting of hypoxic encephalopathy in the newborn can be prolonged and refractory to conventional anticonvulsants. Furthermore, an association between early-life hypoxia-induced seizures and a higher incidence of later-life epilepsy has been suggested by some clinical studies [Bergamasco et al., 1984] but not others. Specific features of hypoxic seizures that are associated with abnormal outcome have yet to be defined by clinical studies, largely due to the variable presentation of these infants suffering from multisystem effects of hypoxia or other concurrent disease.

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Clinical experience raises several important questions amenable for laboratory study in model systems. First, what features of normal maturation render the neonatal brain so highly susceptible to seizures, and then specifically to seizures induced by hypoxia? Second, does the fact that these seizures are so difficult to suppress pharmacologically imply that their mechanism may be different from that of seizures in the adult or older child? Third, can significant and discrete effects of hypoxic seizures be demonstrated on subsequent brain maturation, seizure susceptibility, and cognitive outcome? Animal models can be suitable for the study of such questions if they mimic the age dependence of the phenomenon and have measurable acute and long-term effects that are observed in the human.

EXPERIMENTAL MODEL OF HYPOXIA-INDUCED SEIZURES

In the case of hypoxia-induced seizures, the immature rat seems to respond with tonic-clonic seizures when exposed to brief episodes of global hypoxia (4% oxygen for 15 min) while the mature rat does not exhibit any behavioral or electroencephalographic epileptiform response to the same hypoxic stimulus. The window for this susceptibility seems to be quite narrow, with rats aged P10–12 exhibiting the greatest susceptibility to hypoxia-induced seizures, and younger (P5–7) or older (P15–60) rats have no seizures [Jensen et al., 1991]. Furthermore, the rats exposed to hypoxia at P10 go on to develop increased seizure susceptibility in later life [Jensen et al., 1991, 1992], in the absence of cognitive side effects. Seizure severity during hypoxia correlated with increases in seizure susceptibility in later life [Jensen et al., 1992]. The seizures seem to emanate from both neocortex and hippocampus, but not other limbic structures such as the amygdala and piriform cortex [Jensen and Wang, 1996]. However, histologic studies show no evidence of cell death in either hippocampus or neocortex either hours or weeks following the events [Jensen and Wang, 1996]. The lack of cell death is a familiar observation in the case of seizures in the developing rodent brain. Many investigators have reported the surprising paradox of the heightened seizure susceptibility of the immature rodent brain across a number of models, yet either no damage or only minimal cellular injury can be demonstrated even after prolonged seizures in the immature brain [Albala et al., 1984; Stafstrom et al., 1992; Wasterlain, 1997; Holmes et al., 1998; Sankar et al., 1998; Toth et al., 1998].

To study whether hypoxia induces long-term functional changes intrinsic to neuronal networks in the absence of significant cell death, electrophysiological recordings were made from hippocampal slices removed from rats either acutely following hypoxia at P10 or from adults with prior hypoxia at P10 [Jensen et al., 1998]. In both cases, effects of hypoxia were observed that supported the in vivo observations that perinatal hypoxia increased network excitability and seizure susceptibility. Slices removed from P10 rats following hypoxia-induced seizures exhibited significantly enhanced long-term potentiation in area CA1 compared with slices from littermate controls [Jensen et al., 1998]. Similarly, slices removed from hypoxic pups demonstrated enhanced kindling in areas CA1 and CA3 compared with littermate controls [Jensen et al., 1998]. These changes were in the absence of alterations in paired pulse facilitation or inhibition, suggesting a functional modification of the postsynaptic response. These studies indicated that in the absence of any overt morphologic damage or neuronal death, hippocampal network excitability was functionally altered both acutely and in the long term by a brief episode of seizures during a critical window of development.

In light of the in vitro result suggesting alterations in the postsynaptic response, it is possible that the epileptogenic effects of hypoxia may be mediated by alterations in receptor-mediated events. Given the enhancement in LTP and kindling, both known to be mediated by glutamate receptors, the effect of glutamate receptor blockade on hypoxia in vivo might indicate a subtype-specific dependence of the effects of hypoxia. Glutamate is the major

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excitatory neurotransmitter in the brain, and there are several subtypes of glutamate receptors. Gamma-amino-butyric acid (GABA) is the major inhibitory neurotransmitter in the brain, and many conventional anticonvulsant drugs, such as the benzodiazepines, are thought to exert their effects through facilitation of GABAergic inhibition. Animals exposed to hypoxia at P10 were pretreated with saline, the benzodiazepine lorazepam, MK-801, an antagonist of the NMDA subtype of glutamate receptors, or NBQX, an antagonist of the AMPA/kainate glutamate receptor subtypes. Both the acute and long-term epileptogenic effects of hypoxia were blocked by NBQX but not by MK-801 or lorazepam [Jensen et al., 1995]. These results suggested that in addition to age and regional dependence of the effects of hypoxia, there appeared to be pharmacological specificity. These observations indicate that mechanisms of epileptogenesis during early postnatal life may be significantly different from those in adulthood. In addition, the lack of effect of agents such as lorazepam that are effective in adults suggests that these different mechanisms may be a basis for the refractory nature of these seizures to conventional anticonvulsants.

In summary, early-life seizures induced by hypoxia seem to have a discrete age dependence, regional predilection, and pharmacologic specificity. Furthermore, despite the fact that hypoxic seizures do not induce neuronal death, they result in long-term changes in seizure susceptibility. The increased seizure susceptibility suggests that more subtle functional alterations in network excitability have occurred during development in response to the hypoxic insult.

FEBRILE SEIZURES

Febrile seizures are the most common seizure type during early life. They involve 3% to 5% of infants and young children throughout the world and affect 600,000 individuals per year in the United States alone.

AGE SPECIFICITY OF FEBRILE SEIZURES

Febrile seizures are seen almost exclusively in infants and young children [Verity et al., 1985; Berg et al., 1992]. The susceptibility to the convulsant effects of hyperthermia decreases dramatically with age in the human [Fishman, 1979], indicating that febrile seizures constitute a prevalent form of developmental seizures. Thus, studies of these seizures, aside from having high clinical relevance, may also provide insights into the mechanisms governing inhibition and excitation early in postnatal life.

The major issues concerning the relationship of febrile seizures and adult TLE have been mentioned previously. While prospective epidemiological studies have not shown a progression of febrile seizures to TLE, retrospective analyses of adults with TLE document a high prevalence (30%–50%) of a history of febrile seizures during early childhood, suggesting an etiological role for these seizures in the development of TLE. Neuronal injury and death induced by febrile seizures has been suggested as a mechanism for the development of mesial temporal sclerosis, the pathological hallmark of TLE. An alternative mechanism for the correlation of febrile seizures and TLE involves preexisting neuronal injury triggering both the febrile seizures and the subsequent TLE. Because these questions regarding the causal relationship of prolonged febrile seizures and TLE are difficult to resolve in human studies, animal models, permitting induction of febrile seizures, prospective studies, and interventions addressed at dissecting out their mechanisms and consequences have been proposed.

A model of prolonged febrile seizures in the immature rat has been developed and characterized using animals during a brain development age generally equivalent to that of the human infant and young child. It should be noted that in the rat, as in the human, the

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susceptibility to the convulsant effect of hyperthermia is highly age specific and declines between the 11th and the 17th day of life [Hjeresen and Diaz, 1988]. The rat model of hyperthermic seizures employs 10- to 11-day-old rats. Though precise correlation of rat and human neurodevelopmental profiles is problematic, brain growth and myelination evidence suggests that the first 2 weeks of postnatal development in the rat corresponds to the transition from infancy to childhood in the human [Gottlieb et al., 1977]. Rat brain development during the period of 10 to 15 postnatal days best corresponds to the stage of brain development at which human infants are most susceptible to febrile seizures [Dobbing and Sands, 1973; Gottlieb et al., 1977]. The model uses mildly heated air to raise core (and brain) temperature to that consistent with high fever in the human. Based on findings in more than 200 animals, seizures occur at a threshold temperature of 40.9°C. Hyperthermia (defined as temperature >39°C) is maintained for 30 min, and seizure duration averages 22 min. These seizures would therefore be considered febrile status epilepticus (SE) according to the definition of the International League Against Epilepsy. Mortality related to these prolonged hyperthermic seizures has been nil, and the animals can therefore be studied both acutely and long term.

Acute studies of hyperthermic seizures in this model have provided important information about the *regional specificity* of febrile seizures: in the human, febrile seizures occur unexpectedly, and therefore only a single EEG study of such seizures is available to the authors' knowledge [Morimoto et al., 1991]. In the rat, the behavioral seizures are principally tonic. However, localizing movements, consisting of chewing and biting of an extremity, occur often, suggesting a limbic origin of these seizures. Bipolar depth electrodes implanted in cortex, amygdala and hippocampus were used to better localize the seizures and have provided evidence that the hyperthermia-induced seizures involve primarily the hippocampus but not the neocortex [Baram et al., 1997; Dubé et al., 2000].

The outcome of febrile seizures, i.e., whether they result in neuronal injury or death, alteration of excitability, susceptibility to subsequent seizures, or the development of spontaneous seizures (epilepsy) have been investigated using this appropriate-age hyperthermic seizure model. For example, the model was used to determine whether prolonged febrile seizures injure and kill neurons. Direct evidence for DNA fragmentation, shown to be associated with several forms of neuronal death, including death induced by kainic acid–induced SE [Pollard et al., 1994], was studied using in situ end labeling. After hyperthermic seizures, only occasional amygdala and hippocampal neurons were labeled in sections derived from rats subjected to hyperthermic seizures and permitted to survive for 1, 4, 8.5, 20, or 48 hr [Toth et al., 1998]. Sections from adult rats subjected to kainic acid–induced SE and allowed a 20-hr survival time, which were run in parallel, contained abundant labeled neurons in hippocampal CA3 and most amygdala nuclei, confirming the validity of the in situ end labeling method. Although neuronal death was not seen, neuronal injury, evident from avid argyrophilia of discrete hippocampal and amygdala regions resulted from the prolonged hyperthermic seizures. Sections from animals sacrificed 24 hr following hyperthermic seizures contained significant populations of silver-stained neurons in hippocampus, including the CA1 and CA3 pyramidal cell layer and occasional granule cells. Importantly, no argyrophilic neurons were apparent in control sections or in sections from animals pretreated with anticonvulsants prior to hyperthermia induction. This indicates that hyperthermia-induced seizures, not hyperthermia per se, led to these physicochemical changes in cellular cytoskeleton [Toth et al., 1998]. Outside the hippocampus, silver-stained neurons were abundant also in the lateral division of the central amygdala nucleus, where more than a third of all cells were involved. The argyrophilia induced by hyperthermic seizures persisted for at least 2 weeks. However, neuronal counts in the highly affected region, the central amygdala nucleus, were similar in all the experimental groups. These

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results do not exclude death of *some* injured neurons but indicate that the majority of hyperthermic seizures–induced argyrophilic neurons do not die and drop out.

A second question that was evaluated was whether prolonged febrile seizures alter hippocampal excitability acutely. Put differently, whether the apparently reversible injury to hippocampal neurons was sufficient to alter their functional properties, thus influencing hippocampal excitability. these questions were addressed both in vivo and in vitro. Collaborative studies [Chen et al., 1999], using intracellular recording in the hippocampal slice, demonstrated profound and long-lasting changes in the excitability of the hippocampal circuit. These changes were clearly evident within a week after the seizures and lasted into adulthood. Specifically, it was determined that hyperthermia-induced seizures (but not hyperthermia alone) in the immature rat caused a selective presynaptic increase in inhibitory synaptic transmission in the hippocampus [Chen et al., 1999]. However, whether the overall effects of these changes on excitability in the limbic circuit were inhibitory or (via enhanced synchronization or disinhibition) promoted excitability was not fully resolved. This question was further clarified using prospective long-term in vivo and in vitro approaches: Rats experiencing hyperthermic seizures— or hyperthermia—alone on postnatal day 10 or 11 were studied during adulthood [Dubé et al., 2000]. Extensive hippocampal EEGs and behavioral monitoring failed to demonstrate spontaneous seizures in adult rats that had experienced hyperthermic seizures during infancy. However, 100% of animals developed hippocampal seizures on systemic administration of a low kainate dose and most progressed to SE. In contrast, only a minority of normothermic and hyperthermic controls had (brief) seizures, none developing SE. In vitro, spontaneous epileptiform discharges were not observed in hippocampal-entorhinal cortex slices derived from either control or experimental groups. However, Schaeffer collateral stimulation induced prolonged, self-sustaining, SE-like discharges exclusively in slices from experimental rats [Dubé et al., 2000]. These data indicate that hyperthermic seizures in the immature rat model of prolonged febrile seizures do not cause spontaneous limbic seizures during adulthood. However, they reduce thresholds to chemical convulsants in vivo and electrical stimulation in vitro, indicating persistent enhancement of limbic excitability that may facilitate the development of epilepsy [Dubé et al., 2000].

Thus, these series of studies, using an animal model for *prolonged* febrile seizures provide direct, key, and novel information about their outcome: (1) Prolonged febrile seizures do not kill neurons, but they lead to neuronal injury in the hippocampal formation. (2) The functional properties of a neuronal sub-population are altered profoundly and permanently via a mechanism (presynaptic enhancement of inhibition) not previously described and thus potentially amenable to targeted intervention. (3) Prolonged febrile seizures in the immature rat do not cause spontaneous seizures, i.e., epilepsy, but they lower threshold to excitatory stimuli (chemical or electrical) and thus increase the likelihood of seizures during adulthood.

FACTORS CONTRIBUTING TO THE SUSCEPTIBILITY TO SEIZURES INDUCED BY EARLY-LIFE INSULTS

The susceptibility to seizures in response to pathologic stimuli is clearly higher in the immature brain than in the adult both clinically and in experimental models. In the rat, many models indicate that the window between P10 and P15 represents a period of maturation during which the threshold to several different seizure stimuli is low compared with the adult [Mares et al., 1981; Moshe and Albala, 1983; Holmes and Thompson, 1988; Jensen et al., 1991; Mello et al., 1993; Baram and Hatalski, 1998; Toth et al., 1998]. In the above models, the specific window between P10 and P15 represents a time when a number of factors governing neuronal excitability are developmentally regulated in such a way that excitation predominates over inhibition. Studies in many species indicate that the early

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postnatal period represents a critical window of development for enhanced learning, synaptogenesis, and neuronal plasticity compared with the adult. Excitatory neurotransmission mediated by glutamate receptors is required for these processes and thus has been postulated to be enhanced in the immature brain compared with the adult [Huttenlocher et al., 1982; Fox et al., 1996]. Synaptic density actually undergoes a postnatal overshoot before being "pruned" to adult levels [Rakic et al., 1989]. Before and during this overshoot, excitatory synapses appear to predominate over inhibitory synapses, and, accordingly, the overshoot in synaptic density is paralleled by an overshoot in expression of glutamate receptors [Swann, 1992]. In rat, this overshoot peaks in the second postnatal week, which is roughly analogous to the human term neonate with respect to a number of physiological and biochemical parameters and myelination patterns [Himwich, 1970; Vanier et al., 1971; Mares et al., 1981; Romijin et al., 1991]. Interestingly, at this time, receptors for the inhibitory neurotransmitter GABA are relatively underexpressed compared with the adult [Coyle and Enna, 1976; Palacios et al., 1979; Hosokawa et al., 1994; Du et al., 1996; Anderson et al., 1997; Brooks-Kayal et al., 1998], and before P6 GABA receptors are actually depolarizing due to a reversal of chloride flux compared with the adult [Ben-Ari et al., 1997; Flint et al., 1998]. Several other major components of synaptic transmission are undergoing dramatic changes around this time, including neurotransmitter receptor distribution, density, and subunit composition, neurotransmitter transporter expression, ion channel expression, ion homeostatic mechanisms, and energy metabolism [for a review see Jensen, 1999]. The maturational state of many of these factors promotes excitatory network activity. Hence, the heightened state of excitability and plasticity can be said to be a "double-edged sword" that can also promote pathological changes in network excitability that may persist for life.

As the normal process of maturation may predispose the immature brain to seizures induced by a variety of brain insults, the question remains as to how the injury modifies brain development to result in epileptogenesis. It is clear that many models of seizures in the immature brain result in far less neuronal death compared with the adult, yet long-term seizure susceptibility still results from these early-life insults. One mechanism for the long-term changes is that surviving neurons are functionally altered and that the process of epileptogenesis in the immature brain may utilize processes required for normal plasticity and development that are unique to the developing brain. Future focus on age-specific mechanisms of epileptogenesis in models of insult-induced seizures in the immature brain may lead to a better understanding not only of why the normal developing brain is seizure prone but of how seizures may subsequently modify brain development.

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