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EDITORIAL

Critical Issues of Developmental Seizure Disorders

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1. Introduction

There are multiple causes of seizures. Certain seizures occur in response to environmental changes, such as hypoglycemia or high fever. The term reactive seizures, as proposed by Engel (1989), may be appropriate since it suggests the transient nature of these seizures and the lack of recurrence if the appropriate trigger factor is avoided. Epileptic seizures, on the other hand, occur at unpredictable intervals in the absence of any clearly identifiable triggers. Epileptic seizures may be the result of structural brain abnormalities; the term lesional or symptomatic epilepsy has been proposed. When a lesion is not detectable, the epileptic seizure is considered to be idiopathic in origin. However, the failure to detect a lesion may be also related to the availability of high-resolution tests. As technology improves, the number of idiopathic cases may decrease. The term cryptogenic epilepsy has been proposed for the latter (Commission 1989). Genetic factors may also play an important role by either predisposing the occurrence of specific brain anomalies that can induce seizures or by altering the predisposition of an individual to seizures *per se* as is the case of absence seizures or other genetic epileptic syndromes.

Seizures and epilepsy, defined as recurrent unprovoked seizures, are developmental events. The incidence of seizures is highest during the first few years of life (Hauser and Kurland 1975). Are these developmental seizures a reflection of a window of increased epileptogenicity or a marker of the underlying dysfunction? Probably both factors are operating. Human neonatal seizures may be the most applicable example. Neonatal seizures are most often associated with severe insults to the brain. Older patients suffering the same degree of injury may not survive the injury and if they do, seizures may not be prominent. Therefore, neonatal seizures may occur because the immature brain is more susceptible to seizures than the adult brain in response to intense environmental stressors such hypoxia-ischaemia or bleeding (Tuchman and Moshé 1990).

There are several questions that can be raised concerning developmental seizure disorders: 1. How does development influence epileptogenicity? 2. How do seizures affect development? 3. Should antiepileptic treatment be age-specific? 4. What is the effect of treatment on development? To answer these questions, it may be appropriate to study these issues in animal

models of epilepsy in which the investigator has better control of many contributing factors.

The international classification divides epileptic seizures into two principal types: partial (focal) and generalized (Gastaut *et al.* 1975). These two seizure types differ substantially in clinical and EEG patterns as well as in terms of therapy. Therefore, we will discuss each seizure type separately, although there may be overlapping mechanisms of epileptogenesis.

2. How does development influence epileptogenicity?

2.1. Seizure models

2.1.1. *Partial (focal) seizures* begin with local alterations and the generation of the "epileptic focus". As ictal activity propagates away from the original site to involve other structures, a secondary generalized seizure emerges. Finally the seizure stops. Thus, focal epileptogenesis can be separated into three interconnected events: 1) creation of the focus; 2) seizure propagation and 3) arrest of seizures.

Studies on focal seizure models have found that there is an increased susceptibility to focal seizures during the second and third postnatal week of the rat (i.e. at ages roughly corresponding to human infants and young children (Gottlieb *et al.* 1977). Such increased epileptogenicity has been described in amygdala kindling (Moshé 1981), hippocampal kindling (Haas *et al.* 1990, Michelson *et al.* 1989) and hippocampal electrical stimulations (Velíšek and Mareš 1991). Similar data have been already known from the experiments in neocortical focal epileptogenesis in anaesthetized immature rats (Mareš 1973) and in focal electrically-induced neocortical afterdischarges (Mareš *et al.* 1980). Thus the results from the experiments with focal epileptogenesis suggest that the increased susceptibility to seizures in the early development is not restricted to a single structure, but probably represents a widespread phenomenon.

2.1.2. *Generalized (primary generalized) seizures* involve at least two phases: 1) seizure onset sometimes with further propagation and 2) seizure arrest. These seizures are not unifocal. It is not known, however, whether these seizures are indeed generalized or they have a multifocal origin. Generalized seizures are also developmentally bound. The increase in seizure susceptibility may not be restricted to the second and third postnatal week of the rat. Rat pups have rather lower thresholds for generalized seizures than adult rats without a prominent window, e.g. seizures induced by isonicotinehydrazide (Mareš and Trojan 1991). However, in the most common model of generalized seizures induced by systemic pentylenetetrazol, the lowest CD_{50}, as well as the most rapid onset of seizures were found during the second and third postnatal week of the rat (Velíšek *et al.* 1992). Similar data are available on bicuculline- and picrotoxin-induced seizures (de Feo *et al.* 1985, Mareš and Trojan 1991, Vernadakis and Woodbury 1969, Zouhar *et al.* 1989). Usually in pups, the increased susceptibility to generalized seizures probably involves most, if not all, brain structures. In the seizure model induced by the excitatory amino acid analogue N-methyl-D-aspartate (NMDA) there is two order of magnitude difference between the CD_{50} of young pups and adult rats (Mareš and Velíšek 1992). Because of the highest density of NMDA receptors in CA1 area of the hippocampus and a spectrum of automatisms observed in this model, it is not clear whether NMDA-induced seizures represent a model of primary or secondarily generalized seizures. This issue has been clarified in kainic acid (KA) induced seizures which originate either in the hippocampus of adult rats or in the hippocampus or neocortex of rat pups (Albala *et al.* 1984). In KA-induced seizures there is an order of magnitude difference between effective doses for pups and adult rats (Albala *et al.* 1984, Cherubini *et al.* 1983, Tremblay *et al.* 1984, Velíšková *et al.* 1988).

2.2. Possible underlying mechanisms

Several factors have been implicated in the creation of the epileptic focus. It has been suggested that a seizure may be the result of an abrupt, excessive neuronal discharge (Swann and Brady 1984), due to a focal imbalance between excitation and inhibition (Michelson and Lothman 1989). This imbalance may as well play a role in generalized seizures.

2.2.1. *Excitation*

One possibility is that there is an abundance of excitatory postsynaptic potentials bombarding neurons, thus overwhelming inhibitory postsynaptic potentials. Swann *et al.* (1988) have presented data indicating that, early in life, there is a temporary augmentation in excitability due to the abundance of recurrent excitatory synapses located primarily in the basilar dendritic layer of the CA3 pyramidal neurons. This finding may be associated with increased density of NMDA binding sites in the immature hippocampus (Tremblay *et al.* 1988). With maturation, as these synapses disappear, the capacity of the adult CA3 neurons to develop epileptiform discharges is reduced. Another critical factor may be the presence of many interacting neurons participating in a network of recurrent excitation (Swann *et al.* 1988). The number of neurons involved in recurrent excitatory circuits becomes small in adulthood (Miles and Wong 1987). Lastly, there is evidence implying that, in the immature animal, the voltage dependency of NMDA receptors is regulated by extracellular calcium rather than by magnesium as in adults (Brady *et al.* 1991). This

difference may also lead to additional increases in excitability by augmenting excitatory amino acid-mediated neurotransmission. There are reports describing both an increased sensitivity of NMDA receptors to an agonist and increased number of these receptors in several brain regions in young compared to adult animals (Hamon and Heinemann 1988, Insel *et al.* 1990, Tremblay *et al.* 1988, Tsumoto *et al.* 1987). Hamon and Heineman (1988) have reported that, during the critical period for epileptogenesis (second and third postnatal week in the rat), the apical dendrites of CA1 pyramidal neurons become more sensitive to NMDA. This is manifested by large influxes of calcium. With maturation, the sensitivity of the same apical dendrites to NMDA decreases and is similar to that present before the critical period. During the same critical period, there are also increases in neocortical excitability as a result of transient expression of powerful polysynaptic NMDA-mediated events (Luhmann and Prince 1989). It is possible that this transient expression of NMDA receptors in the synaptic transmission represents a more generalized phenomenon and may be responsible, in part, for the pronounced susceptibility to the development of epileptiform discharges.

The question can be raised as to why early in the development, excitation is so powerful rendering the brain more susceptible to seizures. Axonal sprouting, functional connections and neuronal survival are established (and maintained) during this period. Only those neurons that are most active can survive in this highly competitive environment. Therefore, the frequency of excitatory postsynaptic potentials and firing of action potentials may decide whether a neuron would reach its target, establish functional connection and survive the competition (Cotman 1978). This demand may set a high general level of excitability.

2.2.2. *Inhibition*

Another explanation may be that, early in life, both focal and global inhibitory processes are absent or weak. Although the markers of the most abundant inhibitory transmitter GABA are present already in the fetus, the levels of GABA are low early postnatally and they reach adult values at 4 weeks of age in the rat (Coyle and Enna 1976). A similar developmental profile has been found in the concentration of GABA receptors (Madtes 1987). The uptake of GABA is highest at 15 days of age in the rat and decreases to adulthood (Coyle and Enna 1976), thus increasing the half-time of GABA in the synaptic cleft. The developmental changes in seizure susceptibility that occur in the CA1 hippocampal subfield may be an example of delayed maturation of inhibitory events (Schwartzkroin 1982, Schwartzkroin 1984, Schwartzkroin *et al.* 1982, Swann *et al.* 1988a,b, Swann *et al.* 1990). Both orthodromic and antidromic stimulation produce only depolarizing postsynaptic potentials during the first two weeks of life (Schwartzkroin 1982, Schwartzkroin 1984, Schwartzkroin *et al.* 1982, Swann *et al.* 1988a,b, Swann *et al.* 1990). Hyperpolarizing inhibitory postsynaptic potentials begin to appear at 10-14 days of age (Schwartzkroin 1982, Swann *et al.* 1988a,b). These neurophysiological observations are supported by the anatomical data. Symetric synapses with flattened presynaptic vesicles, that are associated with inhibition in adults, are rare in the CA1 area until 10–18 days of age (Schwartzkroin *et al.* 1982). The period of maximal seizure susceptibility, however, usually occurs during the second and third week postnatally when inhibitory events are already present. At the critical period for epileptogenesis those findings suggest that ictal discharges can be triggered following the application of the GABA antagonist, picrotoxin (Hablitz and Heinemann 1987, 1989, Hablitz *et al.* 1989). Recent finding that microelectrophoretically ejected GABA can produce depolarizations in the dendritic tree of CA3 pyramidal neurons in hippocampal slices from immature animals, could also help to explain the increased developmental seizure susceptibility, at least in some brain regions (Cherubini *et al.* 1990, Michelson and Wong 1991). Another study suggests a sensitive and vulnerable regulation of NMDA-mediated events in developing rat neocortex by the level of GABAergic inhibition, a phenomenon which does not occur in adult neocortex (Luhmann and Prince 1990).

2.2.3. *Other factors*

Several other factors have been proposed to explain the existence of the critical period for epileptogenesis at second and third postnatal week in the rat (Schwartzkroin 1984). Immature neurons have high input resistance and, thus, small currents may lead to large voltage changes. Increases in axonal myelination may provide more effective communication among cells. Electrotonic junctions or ephaptic influences may facilitate neuronal synchronization (this remains speculative). Delayed development of glia may allow for the accumulation of potassium in the extracellular space which may lead to general hyperexcitability (Mutani *et al.* 1984). Thus, while in adult rats, stimulus-induced rises in extracellular potassium ($[K^+]_o$) are limited to about 12 mM, in immature two to three-week-old rats, $[K^+]_o$ may reach 18 mM (Hablitz and Heinemann 1989). These effluxes of potassium may contribute to an easy spread of epileptiform activity.

There are several anatomic structures that may have a substantial influence on the propagation of seizures, e.g., area tempestas or substantia nigra (Gale 1988). The substantia nigra may play a crucial role in regulating seizure expression, particularly of flurothyl-induced seizures (Moshé *et al.* 1986, Moshé and Albala 1984). The nigral GABAergic transmission may be a key factor responsible for the age-dependent

anticonvulsant action of intranigrally infused GABA agonists (Gale 1992, Moshé and Sperber 1990). In 15-day-old rat pups, intranigral infusions of the $GABA_A$ agonist muscimol are proconvulsant although similar infusions are anticonvulsant in adult rats (Moshé and Albala 1984). The nigral infusions of the $GABA_B$ agonist baclofen have anticonvulsant effects only in 15-day-old rats and no effects in adults (Sperber *et al.* 1989). There are developmental differences in the densities of nigral $GABA_A$ and $GABA_B$ receptors. To explain the developmental differences in the substantia nigra-mediated seizure suppression, we have proposed that there may be age-dependent differences in the composition of subunits of $GABA_A$ receptors (Xu *et al.* 1992).

3. How do seizures affect development?

3.1. Patients

There has been much debate concerning the relationship between temporal lobe epilepsy and seizures early in life. It has been repeatedly discussed whether hippocampal sclerosis is a consequence of convulsions early in life. Retrospective studies indicated a correlation between adult patients with temporal lobe epilepsy (and mesial temporal sclerosis) and the report of seizure onset and status epilepticus in childhood (Falconer 1971, Margerison and Corsellis 1966, Sagar and Oxbury 1987). Recent prospective studies of children with seizures, however, indicate that the risk of seizure recurrence is low following a single unprovoked idiopathic seizure (Shinnar *et al.* 1990) or following status epilepticus without an antecedent injury (Dunn 1988, Maytal and Shinnar 1990, Maytal *et al.* 1989). There is a high incidence of status epilepticus and frequent onset of seizures during childhood (Hauser and Kurland 1975). However, this does not necessarilly indicate that young children are more susceptible to seizure-induced hippocampal damage. Only few papers have delt with this problem. Corsellis and Bruton (1983) observed hippocampal changes in 8 children who died during or following status epilepticus. However, the primary etiology of status epilepticus was not reported. In contrast, Represa *et al.* (1989) reported that hippocampal sclerosis was not observed in children following seizures. From more recent data from epileptic children it appears that hippocampal sclerosis is extremely rare under the age of 6 and uncommon under 12 years of age (Duchowny *et al.* 1992). Even in those cases, in which sclerosis was found, the origin of seizures was in the ipsilateral temporal lobe, but extrahippocampal. Because of problems associated with clinical research, such as obtaining early biopsies, controlling for the age of onset of seizures and presence of prior brain damage, the controversial question can be best addressed in the animal models.

3.2. Laboratory animals

In order to study the long-term consequences of prolonged epileptic seizures, several seizure models have been used. First, a model of seizures induced by kainic acid was employed, then similar experiments were carried out with amygdala kindled seizures and with flurothyl-induced seizures.

Kainic acid (KA) is a glutamate analogue with preferred neurotoxicity towards CA3 hippocampal pyramidal neurons which contain extremely high density of KA receptors (Nadler 1981). Seizures induced by KA propagate rapidly from the hippocampal focus to become generalized clonic seizures in adult rats or tonic-clonic seizures in rat pups (Albala *et al.* 1984, Ben-Ari 1985). Both types of seizures are long-lasting becoming status epilepticus defined as a seizure lasting more than 30 min. Adult rats were subjected to histological examination of the hippocampus two weeks following KA-induced status epilepticus. The Timm stain was used (Timm 1958); this method permits the detection of axonal sprouting and synaptic reorganization, believed to be due to a cell loss. There was an extensive Timm staining in the supragranular layer of the hippocampal dentate gyrus. A similar pattern has been frequently reported previously (Albala *et al.* 1984, Ben-Ari *et al.* 1981, Nitecka *et al.* 1984, Tauck and Nadler 1985) and parallels the hippocampal damage observed in patients with hippocampal sclerosis (Babb and Brown 1987, Falconer *et al.* 1964, Sutula *et al.* 1989). The anatomical reorganization of the synaptic system in the rat hippocampus was accompanied by profound functional changes. During the stimulation of the entorhinal-dentate pathway using paired stimuli (10 ms – 10 s interval) hippocampal slices from KA-treated adult rats demonstrated an enhanced late suppression phase (200–600 ms) (Sperber *et al.* 1991). The experiments were repeated with 5- and 15-day-old rats which were more vulnerable to KA-induced status epilepticus than adult rats. However, no changes either in Timm staining or in perforant path electrophysiology were found (Haas *et al.* 1990). Similar results with KA-induced seizures in immature rats were reported by others (Albala *et al.* 1984, Holmes and Thompson 1988, Nitecka *et al.* 1984). Thus, there is a substantial difference in the seizure-induced neuronal damage after KA treatment between adult and immature rats.

Amygdala kindling represents a model of partial seizures with secondary generalization. Adult rats were kindled until three consecutive stages 5 appeared (Racine 1972). Fifteen-day-old rat pups were stimulated at 15 min intervals until they had severe seizures [stages 6,7] (Sperber *et al.* 1990). After two weeks, histological and electrophysiological examination was performed. The results were similar to those observed with KA-induced seizures. In the adult hippocampus, Timm staining revealed

supragranular sprouting and an increase of late suppression in perforant path paired-pulse paradigm. However, the changes were less pronounced than those observed after KA-induced seizures. In rat pups, there were no hippocampal changes.

Flurothyl-induced seizures represent a model of primary generalized seizures which can culminate into status epilepticus. Other authors have reported neuronal cell loss in area CA4 of the hippocampus after flurothyl-induced status epilepticus (Nevander *et al.* 1985). There was no neuronal loss or synaptic reorganization in the hippocampus of 15-day-old rats after flurothyl-induced status epilepticus (Sperber *et al.* 1992) and in 4-day-old rat pups (Wasterlain and Dwyer 1983).

3.3. Summary

It appears from both clinical and laboratory data that the age of patients or laboratory animals is the crucial variable in the proposed equation "seizures = hippocampal sclerosis". In adult animals or patients, there is very high correlation of both phenomena. This is not the case in young animals or children. However, the less pronounced findings in the kindling model suggest that the seizure type may play a role in the expression of hippocampal damage.

4. Should antiepileptic treatment be age-specific?

There are substantial age-related differences in the seizure susceptibility and in the consequences of seizures. Therefore, it is likely that antiepileptic treatment should be age-specific. There are several examples from human and experimental epileptology demonstrating both qualitative and quantitative differences as a function of age after equivalent antiepileptic treatment. Qualitative differences usually cannot be fully explained by pharmacokinetics. In contrast, quantitative differences are usually caused by developmental changes in the antiepileptic drug kinetics.

4.1. Qualitative differences

Phenytoin is a standard anticonvulsant drug that is used in the treatment of human partial and generalized convulsive seizures (Engel 1989, Woodbury 1980). In early development, phenytoin has been described as having proconvulsant effects (Mareš *et al.* 1983, Vernadakis and Woodbury 1969) which may reflect the phenytoin toxicity described in humans (Dam 1982). Phenytoin overdose was also reported to be convulsant in rats younger than 18 days (Mareš *et al.* 1987). In humans a similar finding was reported in pubescents (Osorio *et al.* 1989). Ongoing research has demonstrated that phenytoin although anticonvulsant in adult rats, loses its anticonvulsant activity in rat pups using the same dosage and pretreatment intervals. However, this may not be the case in humans.

Baclofen is a $GABA_B$ receptor agonist which has been considered as a possible anticonvulsant agent. However, in the flurothyl and pentylenetetrazol seizure models baclofen was found proconvulsant in 9-day-old rat pups, although it had anticonvulsant properties in older age groups (Velíšková *et al.* in press). The results suggest that the treatment of epileptic seizures by baclofen should not be used in infants who roughly correspond with 9-day-old rats in the level of brain development (Gottlieb *et al.* 1977). Exacerbation of spontaneous spike and wave discharges in genetically prone rats has been reported after baclofen (Marescaux *et al.* 1992, Vergnes *et al.* 1984). These discharges are considered to be a model of human absences, an age-dependent epilepsy. In the experimental model, spike and wave discharges appear at a certain level of maturation of the brain (Marescaux *et al.* 1992). Therefore, the action of baclofen is also age-specific and baclofen should be avoided in the treatment of human absences.

4.2. Quantitative changes

There are several examples of quantitative changes in the efficacy of treatment of seizures with antiepileptic drugs. Higher doses of barbiturates may be needed in infants and lower in children in comparison to adults (Engel 1989). The difference is due to the functional state of liver enzymatic system responsible for barbiturate degradation, as well as the kidney excretion systems and the maturation of GABA receptors (barbiturate target sites).

Gamma-vinyl GABA (GVG), an irreversible inhibitor of GABA degradation enzyme GABA-transaminase (Jung *et al.* 1977) has some anticonvulsant effects in human epileptics and in laboratory models of epileptic seizures (Engel 1989, Xu *et al.* 1991). In rats, the anticonvulsant effects of GVG are present only after high doses and they are better in 15-day-old rats than in adult animals.

In our recent study on the anticonvulsant action of MK-801 during development, we found that MK-801 was extremely effective in 7-day-old rat pups. At this age, the dose of MK-801 as low as 0.05 mg/kg abolished generalized tonic-clonic pentylenetetrazol-induced seizures. In adult rats, the dose ten times higher (0.5 mg/kg) was necessary for the same effect (Velíšek *et al.* 1991). There are probably no changes in the permeability of blood-brain-barrier for MK-801 during development. The difference in the effective dosage is probably caused by the increased number of receptors involved and higher intrinsic activity of MK-801 early in the development. Thus MK-801 can be an example of pharmacodynamics-based quantitative changes in anticonvulsant drug action (Velíšek and Mareš 1992).

5. What is the effect of treatment on development?

This issue is probably least understood and studied. There are almost no reports available dealing with the effects of long-term treatment with the antiepileptics on the development of nervous system and its function.

It has been postulated that early treatment with ACTH or corticosteroids may improve an outcome of infantile spasms, a seizure type which occurs in infancy and has unfavorable prognosis usually associated with profound mental retardation (Engel 1989, Kellaway *et al.* 1983). However, controlled studies have not been performed.

There may be several negative actions of effective antiepileptics on the developing organism. The best example is the correlation between antiepileptic treatment of mothers during the first trimester of pregnancy and increased incidence of malformations in the fetus. There are reports that in a minority of patients, phenytoin and barbiturates can produce general teratogenic effects (Zhu and Zhou 1989), whereas valproate and carbamazepine, may cause neural tube defects (Engel 1989). The teratogenicity of antiepileptic drugs may be caused by oxidative metabolites, since there are data demonstrating decreased levels of microsomal epoxide hydrolase activity in patients with fetal antiepileptic drug syndrome (Finnell *et al.* 1992). These data should lead to the careful choice of antiepileptic drugs for pregnant epileptic women and to additional studies on the effects of prolonged anticonvulsant therapy on nervous system development.

6. Conclusions

The data reviewed here show that there is a period of increased susceptibility to seizures during the early postnatal development of the rat. This window is probably caused by overwhelming excitation throughout the brain which appears to be physiologic for this stage of development. It has been demonstrated, however, that even severe seizures in rat produce minute or no damage in the hippocampus which is the most vulnerable structure to seizure-induced damage in adult rats. Anticonvulsant therapy also has age-dependent qualitative and quantitative characteristics. There are almost no data on the long-term effects of antiepileptic treatment on brain development. The possibility that aggresive antiepileptic therapy may suppress the excitatory synaptic transmission during a sensitive period and therefore alter brain development needs to be further investigated. Controversely, more studies are needed to show that early intervention improves the long-term outcome irrespective of the underlying condition that is responsible for the seizures and which may have its own intrinsic detrimental effects on the brain.

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