Effects of seizures on developmental processes in the immature brain

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Infants and children are at a high risk for seizures compared with adults. Although most seizures in children are benign and result in no long-term consequences, increasing experimental animal data strongly suggest that frequent or prolonged seizures in the developing brain result in long-lasting sequelae. Such seizures may intervene with developmental programmes and lead to inadequate construction of cortical networks rather than induction of neuronal cell loss. As a consequence, the deleterious actions of seizures are strongly age dependent: seizures have different effects on immature or migrating neurons endowed with few synapses and more developed neurons that express hundreds of functional synapses. This differential effect is even more important in human beings and subhuman primates who have an extended brain development period. Seizures also beget seizures during maturation and result in a replay of development programmes, which suggests that epileptogenesis recapitulates ontogenesis. Therefore, to understand seizures and their consequences in the developing brain, it is essential to determine how neuronal activity modulates the main steps of cortical formation. In this Review, we present basic developmental principles obtained from animal studies and examine the long-lasting consequences of epilepsy.

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Introduction

During the first few months of life, children are at a particularly high risk for seizures, with the largest number of new-onset seizure disorders occurring during this time.[1,2] During the birthing process, the infant is at risk for insults that can result in seizures. These insults include birth trauma, hypoxic-ischaemic insults, perinatal acquired infections, intracranial haemorrhages, and metabolic disturbances. In addition to being at a high risk for brain insults, substantial evidence suggests that the immature brain is more susceptible to seizures than the mature brain.[3–5]

Any attempt to discuss seizures in the developing brain is problematic because of the intrinsic heterogeneity of developing neurons and the inherent difficulty of finding basic common rules that transcend differences between species and developmental stages. Thus, although two adjacent adult pyramidal neurons might look identical, in utero these same two neurons can differ substantially, with one having many synapses and the other no dendrites or active synapses. This is particularly true for primate and human neurons; because of the long gestation period. Nevertheless, recent animal studies have led to advances in answering three essential questions: why seizures are more common during early life than adulthood; how early-life seizures lead to persistent deleterious effects; and why the effects of seizures are age dependent? The main emphasis of this Review is to examine how frequent or severe early-life seizures modify the development of neuronal circuits, thereby increasing the risk for subsequent seizures and adverse behavioural outcome. Not all seizures, particularly those that are infrequent or brief, are harmful. However, it is important to think about the adverse effects of seizures on brain development so that potential interventions can be considered.

In this Review, we concentrate on these issues and stress how they will improve our understanding of epilepsy in the developing brain. Animal models can only give a limited view of the complexity of human clinical data, but electroencephalographic, molecular, and morphological features of epilepsies can usually transcend interspecies differences.

High incidence of seizures in developing brain

The propensity for seizures or seizure-like activity in the immature brain has been shown in several experimental models, including kainic acid,[6,7] electrical stimulation,[8] hypoxia,[9] penicillin,[10] picrotoxin,[11] $GABA_B$ receptor antagonists,[12] and increased extracellular potassium.[13,14] The underlying mechanisms responsible for the increased excitability in the immature brain are not completely understood but are age dependent. Immature neurons and networks tend to generate periodic discharge and this facilitates the generation of pathological and pathogenic oscillations. This tendency of immature neurons to oscilliate is due to their high input resistance, which helps the generation of action potentials and increases excitability. In addition, during the early postnatal period, a time when the immature brain is highly susceptible to seizures,[14,15] GABA exerts a paradoxical excitatory action in all animal species and brain structures including primates (in utero); this suggests that this mechanism has been preserved throughout evolution.[16] In rats, GABA has a depolarising effect up to about day 14 (postnatal)[14] and until the third trimester in primates.[17] Immature neurons are enriched with a high intracellular concentration of chloride, which leads to an efflux of chloride instead of an influx when GABA receptors are activated.[18,19] The lack of efficient GABAergic inhibition increases excitability and can facilitate synchronicity.[13,14] The delayed maturation of postsynaptic G protein mediated $GABA_B$ mediated inhibition will also contribute to augment neuronal excitability. The prolonged NMDA-mediated excitatory postsynaptic currents in immature versus adult neurons

will promote the generation of network-driven events.[20] These properties also underline the propensity of immature networks to generate early network-driven patterns such as giant depolarising potentials.[18,19] The curve that depicts the incidence of seizures and the excitatory to inhibitory shift of GABA's effect shows excellent correlation. This shift also corresponds with the disappearance of giant depolarising potentials, which indicates that physiologically relevant oscillations are replaced by more adult patterns when GABAergic synapses are inhibited. At more developed stages, the transient exuberant formation of excitatory synapses may also contribute to increased excitability.[21–23]

Children are at high risk for seizures during the first few months and years of life.[24] In addition to insults that may occur, several neonatal disorders can present initially with seizures. For example, congenital brain anomalies, inborn errors of metabolism, and genetic disorders can lead to recurrent seizures during the neonatal period. However, the increased risk of seizures in young brains is not only due to these causative factors but is also related to the lower seizure threshold of the immature brain.

Febrile seizures provide an excellent example of the increased susceptibility for seizures in immature brains. Fever, which rarely results in seizures in adults, causes seizures in 1–14% of infants and children worldwide, thus constituting the most common seizure type in the developing brain.[24] Although febrile seizures are typically quite benign, children with febrile seizures have a fivefold excess of afebrile seizures compared with unaffected children; 7% of children who have a febrile seizure will have an afebrile seizure by age 25 years.[25] A small percentage of children with prolonged febrile seizures eventually develop mesial temporal lobe epilepsy.[26,27] However, it is still unclear whether prolonged febrile seizures are a cause of temporal lobe epilepsy or a marker for other processes, such as genetically driven factors.[28,29] The concentration of proinflammatory cytokines is increased during febrile seizures[30,31] and these may play a part in febrile-seizure-induced changes in the brain.

Rodent models of hyperthermic seizures have been used to model febrile seizures.[32–34] Prolonged hyperthermic seizures in 10-day-old rats are associated with long-term enhancement of hippocampal excitability, and spontaneous seizures devlop in some of the rats.[35] This increased seizure susceptibility is not associated with cell loss.[33] However, it should be noted that the hyperthermic seizures studied by Dube and colleagues[35] were prolonged, lasting more than 20 min, and corresponded with complex febrile seizures in human beings. The finding that prolonged hyperthermic seizures are necessary for persistent excessive hippocampal excitability corresponds with clinical studies showing that prolonged (complex) febrile seizures are a risk factor for temporal lobe epilepsy.[26] Similarly, if the rat brain is predisposed to seizures by a cortical malformation, the sequelae of hyperthermic seizures are more pronounced.[34]

Experimental hyperthermic seizures are associated with long-term slowed kinetics of the hyperpolarisation-activated depolarising current, which is mediated through the hyperpolarisation-activated cyclic nucleotide-gated (HCN) cation channel.[36] These currents contribute to various physiological functions, including cardiac and neuronal pacemaker activity, the setting of resting potentials, input conductance and length constants, and dendritic integration. Hyperthermic seizures induce a coordinated reduction of HCN1 mRNA and increase HCN2 expression, thus changing the neuronal HCN phenotype, which favours the formation of slow-kinetic HCN2-encoded channels.[37] Long-term modulation of HCN expression may critically contribute to the increased hippocampal excitability after neonatal seizures.

Taken together, these results suggest that prolonged febrile seizures cause permanent changes in the brain, probably resulting in long-standing increased excitability. Whether similar changes occur in the human brain is not clear.

Maturation of cortical networks

During the development of cortical networks, there is a sequential shift from an ensemble of immature cells with little or no organised communication devices to an active network composed of neurons with thousands of active synapses. This shift is mediated by a series of events that includes both intrinsic and extrinsic factors. Like other insults, seizures can modify these pathways and this leads to persistent deleterious effects. Therefore, it is essential to identify these developmental events and the effects of aberrant activity on these pathways.

Excitatory actions of GABA on immature neurons

GABA, which provides most of the inhibitory drive in adult networks, is initially excitatory because there is a larger intracellular concentration of chloride in immature neurons than in mature ones (figure 1).[18,19,38] The shift from a depolarising to a hyperpolarising intracellular chloride concentration occurs in an extended period and this depends on the age and developmental stage of the neuron. The shift is mediated by a delayed expression of a chloride co-transporter (KCC2) that extrudes chloride to establish adult concentrations of intracellular chloride. Depolarisation of immature neurons with GABA is sufficient to generate sodium action potentials and remove the voltage-dependent magnesium-ion blockade of NMDA channels and activate voltage-dependent calcium channels; this leads to a large influx of calcium that in turn triggers long-term changes of synaptic efficacy.

This maturation is dynamic and the expression of the co-transporter, KCC2, is activity dependent and down regulated by seizures and other insults.[39–42] In addition, drugs that interfere with the transport of chloride have an antiepileptogenic effect.[43] After recurrent seizures in vitro, GABA exerts an excitatory action; this indicates

that there is a permanent shift back to the immature state with seizures and a halt of developmental trends.[7] This action is preserved for the life of an in vitro preparation (days); however it is not known whether this is a permanent action. In tissue from human adults with epilepsy,[44] there is a shift to excitatory GABA in some neurons years after seizures, raising the possibility that epileptogenesis recapitulates ontogenesis. Therefore, seizures can reduce the threshold for further seizures via permanent modification of the intracellular chloride concentration and therefore the effects of GABAergic transmission. How seizures can induce such long-lasting consequences on GABA's effects is still to be explained. One study[45] has reported an association between KCC2 and density of GABAergic synapses, suggesting that the intracellular chloride concentration may affect the efficacy of GABAergic inhibition in postsynaptic neurons. Clearly, the control of intracellular chloride concentration is an essential step that links developmental trends and the pathogenic effects of seizures.

GABAergic synapses are formed before glutamatergic synapses

Studies that use both GABA receptor antagonists and neuronal reconstruction showed that GABAergic synapses are formed first and glutamate synapses subsequently.[19,46] This applies to neonatal rodents[47] and in utero primate central neurons.[16] GABA also has an important trophic role in the modulation of dendrite extension and neuronal arborisation.[48,49] Because of the intrinsic heterogeneity of neurons during early development, the actions of GABAergic drugs on different neurons will vary. Thus, seizures in early life may differentially affect neurons with only GABA synapses and those with both GABA and glutamate synapses with different long-term changes of synaptic efficacy.

There are two additional fundamental properties of immature networks to consider: GABA transporters mature after glutamate transporters and this leads to a greater diffusion of GABA that can act as a neuromodulator at distant sites.[50] Conversely, the extracellular concentration of glutamate is controlled tightly even before synapses are formed. Thus, in-vitro and in-vivo administration of a glutamate-transport inhibitor generates oscillations and long-lasting seizures at birth in rats[51]—with electroencephalograms that are reminiscent of the suppression bursts associated with epileptic encephalopathies.[52] A mutation in glutamate mitochondrial transport in a familial form of encephalopathy was shown recently;[53] and even before synapses are formed, there is tonic release of GABA that modulates migration of immature neurons and neuronal precursors. Inhibition of GABA receptors slows neuronal migration in vitro, which indicates the possible consequences of drugs that act on GABA receptors in utero, including antiepileptic drugs.[54]

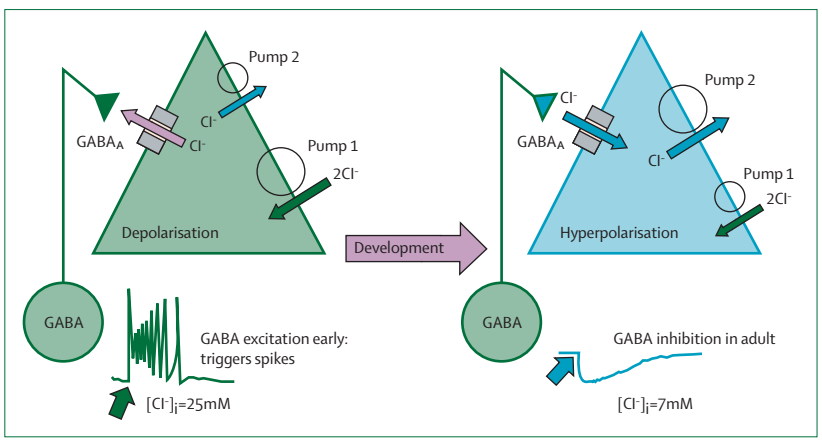

Figure 1: **Excitatory actions of GABA and developmental alterations of the intracellular concentration of chloride**
The diagram shows early operation of a co-transporter that imports and augments the chloride ion concentration in immature neurons, whereas the extruding co-transporter is not efficient. This leads to a higher concentration of chloride ions at an early stage and an efflux of chloride when GABA receptors are activated. Green represents the immature neuron and blue represents the mature neuron. $[cl^-]_i$=intracellular concentration of chloride.

A primitive oscillation pattern in developing networks

By contrast to adult networks, which have a plethora of behaviourally relevant oscillations, immature networks initially show a single primitive pattern of giant depolarising potentials that is present in all developing networks and animal species, including in-utero primates and premature infants.[16,18,19,55] This is the only activity in the developing hippocampus until the end of the first postnatal week when it disappears in parallel with GABA's excitatory to inhibitory shift. In other species studied, the switch occurs at different stages: early in structures that develop first, such as the spinal cord, and even within the same structure the shift will depend on the postmitotic age of the neuron.[49] Studies in rodent hippocampal slices indicate that the lowest threshold for seizure generation occurs around the second postnatal week (figure 2), a time when two factors converge: a massive shift of less excitatory actions due to GABA (but not yet fullly efficient as hyperpolarising or inhibitory); and the formation of glutamatergic synapses, which can facilitate the propagation of seizures. The strong correlation between the disappearance of this primitive ocillatory pattern and the GABA shift together with the low seizure threshold reinforces the importance of the GABA shift.[56]

The deleterious consequences of seizures strongly depend on the developmental stage at which they occur. If, as present results suggest, the crucial factor in an efficient chloride removal is the expression of the KCC2 co-transporter, then immature neurons that have few synapses will accumulate chloride more readily and show long-lasting consequences of seizures. Seizures may also interfere with the construction of cortical maps; this will have particularly deleterious effects considering the large degree of plasticity of neurons at that stage.[55] Key factors in the modulation of seizures include NMDA receptors

and voltage-gated calcium currents, which together control intracellular calcium and the activation of genes, and the expression of neuronal phenotypes and neuronal excitability.

Differences between developing and adult networks

Animal studies have shown that the pathophysiological consequences of both status epilepticus and recurrent seizures in the developing brain differ substantially from those of the mature brain.[57]

In adult animals, status epilepticus causes neuronal loss in the hippocampal regions CA1, CA3, and the dentate hilus.[58] In addition to cell death, prolonged seizures in the adult brain lead to synaptic reorganisation with aberrant growth (sprouting) of granule cell axons (the so-called mossy fibres) in the supragranular zone of the fascia and infrapyramidale region of CA3.[59,60] Sprouting and neosynapse formation occur in other brain regions, notably the CA1 pyramidal neurons, where newly formed synapses result in an increased frequency of glutamatergic spontaneous synaptic currents[61] and the formation of new aberrant kainatergic synapses on targets of mossy fibres.[62] Additionally, status epilepticus in adult rats results in long-term deficits in learning, memory, and behaviour.[63–65] By contrast, young animals, less than two weeks of age, are less vulnerable than mature animals to cell loss in the hippocampus after a prolonged seizure (figure 3).[6,66–68] Cell loss in the hippocampus, as a result of status epilepticus, is unlikely to occur until after age 2 weeks.[67,69] Reactive plasticity of mossy fibres, a signature of adult temporal lobe epilepsies, is less prominent in young animals.[70,71] Although the hippocampus seems to be preserved after prolonged seizures, thalamic lesions have been reported after prolonged seizures.[72]

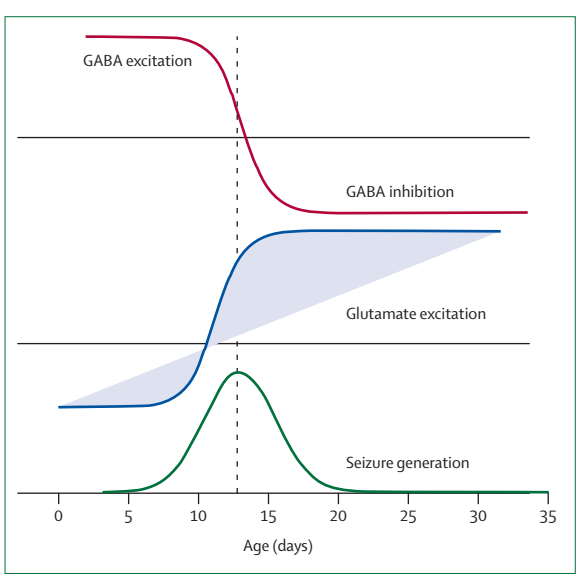

Figure 2: **Developmental shifts in the threshold of seizure generation**
In hippocampal slices, seizures are more readily generated around the second postnatal week. This corresponds to the peak shift of the actions of GABA—when GABA is less excitatory but not yet inhibitory—but the density of glutamatergic synapses is close to that of adults. Therefore, seizures will be readily generated and propagate as a result of a relatively dense glutamate network.

Resistance to other insults parallels the relative resistance of the immature brain to seizure-induced damage. Immature hippocampal neurons are also less sensitive to anoxic insults and respond to synaptic stimuli in a fully anoxic environment for longer durations than adult neurons.[73] Several factors make the immature brain less susceptible to seizure-induced changes than the mature brain.[57] The immature brain seems to be less vulnerable to the toxic effects of glutamate than the mature brain.[74–76] This is probably the result of the lower calcium ion entry in the immature brain. This relative resistance may be due to the smaller density of active synapses, lower energy consumption, and the relative immaturity of biochemical cascades that lead to cell death after insults. Additional protective factors probably include: high concentrations of brain-derived neurotrophic factor in newborn brains;[77] reduced proinflammatory cytokines associated with seizures in young rats;[78] and better maintenance of GABA synthesis during status epilepticus in the immature rather than the mature brain.[79] Neonatal seizures are also associated with reduced oxidative stress compared with adult seizures.[80] High concentrations of the mitochondrial uncoupling protein (UCP2), which are basally increased in neonatal brains by the fat-rich diet of maternal milk, seem to reduce the formation of reactive oxygen species and protect the mitochondria from seizure-induced damage.[81]

Behavioural effects of status epilepticus are also associated with the age of the animal at the time of the event; adult animals that survive status epilepticus have substantial deficits in learning, memory, and behaviour; whereas, young rats (<2 weeks of age) after status epilepticus had fewer deficits in learning, memory, and behaviour.[65] Similarly, spontaneous seizures after status epilepticus are more likely to occur in adult animals with status epilepticus than in young animals.[82]

Changes in glutamate and GABA receptors have also been reported after status epilepticus in young animals.[83,84] GluR2 mRNA expression and protein concentrations are reduced in the dentate gyrus after lithium or pilocarpine-induced status epilepticus,[84] and in the neocortex and hippocampus after hypoxia-induced seizures[85] in young rats. The excitatory amino acid carrier 1 (EAAC1) protein is increased in the dentate gyrus after status epilepticus.[84] Zhang and colleagues[83] reported that status epilepticus in young rats resulted in an increase in α1 subunit expression of the $GABA_A$ receptor. However, these changes in the α1 subunit were the opposite of those seen in adult rats with status epilepticus.[86,87]

In summary, substantial data from rodents suggest that prolonged seizures result in far less cell loss in young rats (<2 weeks) than seizures of similar duration

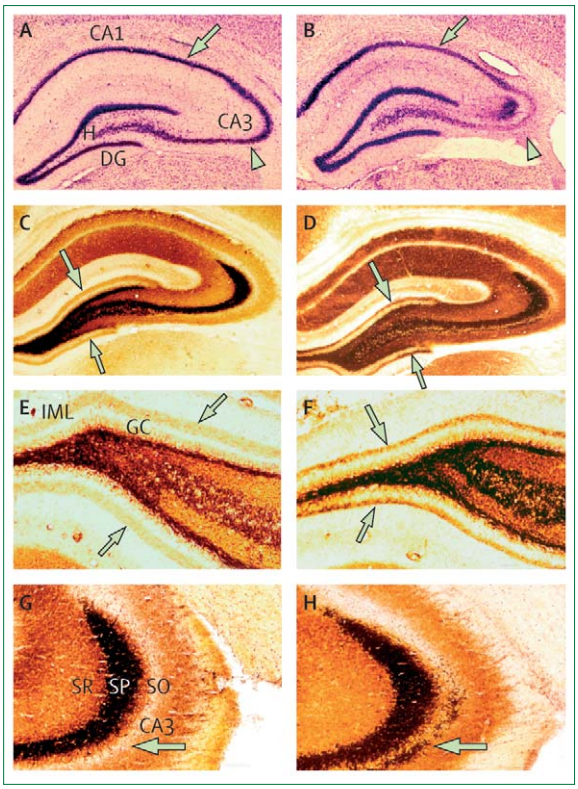

Figure 3: **Histological lesions in the hippocampus of rats in status epilepticus at age 10 days (immature), left column, or age 60 days (mature), right column**
In both animals status epilepticus was induced with the chemoconvulsant pilocarpine. A,B: stained with thionin. There is extensive cell loss in CA3 (arrowheads), CA1 (arrows), and the hilus (H) in the mature, but not immature brain. The granule cells in the dentate gyrus (DG) are spared from extensive cell loss in both age groups. C–H: hippocampus was stained with Timm. Timm staining is used to stain zinc, which is concentrated in the mossy fibres. C,D: sprouting of mossy fibres in the supragranular region in the adult, but not immature rat (arrows). E,F: higher magnification of the supragranular region showing Timm stained granules in the inner molecular layer (IML) of the granule cell (GC) layer. G,H: mossy fibre sprouting in CA3 of the mature, but not immature rat. Usually the terminals of the mossy fibres are in the stratum radiatum (SR). However, in mature rats with status epilepticus sprouting into the stratum pyramidale (SP) occurs (arrows; SO=stratum oriens). Calibration: A–D=100 μm; E–H=50 μm.

in adult brains. This reduced susceptibility to cell loss is probably due to the decreased vulnerability of immature neurons to glutamate toxicity. However, the lack of seizure-induced cell loss does not mean that prolonged seizures do not permanently alter the immature brain. Changes in glutamate and GABA subunit configuration and altered expression are just a few of the changes that occur after status epilepticus. A challenge for scientists is to determine which of these changes are harmful.

Recurrent seizures

As with prolonged seizures, recurrent seizures in infants and children can be harmful.[88,89] Several studies have shown that recurrent seizures during early development can result in long-term morphological and behavioural changes.[90–92]

Neonatal seizures induced in rats by the inhalant flurotyl at days 1–5 caused impairment of visual spatial memory in the Morris water maze—a measure of visual-spatial memory.[93] When recurrent seizures were induced by flurotyl in animals at day 15–20, impairment of auditory discrimination was also reported.[94] These morphological, behavioural, and physiological changes occur in the absence of any discernible cell loss.[95] Although cell loss does not occur after recurrent seizures in immature rats, recurrent seizures can adversely affect neurogenesis.[96] After a series of neonatal seizures, rats have a substantial reduction in the number of newly formed granular cells in the dentate gyrus and hilus compared with control animals. In comparison, adult rats that undergo a series of 25-flurotyl-induced seizures had a notable increase in neurogenesis compared with controls. This study indicates that after recurrent seizures in the neonatal rat, there is a reduction in newly formed granule cells.

After recurrent seizures, there is extensive synaptic reorganisation of the axons and terminals of the dentate granule cells, with sprouting of mossy fibres in the CA3 hippocampal subfield.[90,91,93] The sprouting in CA3 after neonatal seizures differs substantially from the sprouting reported in adult animals after status epilepticus, which occurs in the supragranular region and is a result of cell loss in the hilus and CA3. Because seizure-induced sprouting occurs in the absence of cell loss and is not secondary to a failure of pruning, the sprouting seems to be a result of excessive excitatory drive. Although the functional significance of the CA3 sprouting is not clear, there is a correlation between degree of mossy-fibre sprouting in CA3 and performance in the Morris water maze; the animals with the most sprouting do worse in the maze than animals with little sprouting.[97]

In summary, recurrent seizures during early development in rodents result in aberrant sprouting in the CA3 and supragranular regions of the hippocampus, reduced neurogenesis, morphological changes in dendritic spines, and changes in glutamate receptor distribution. It is not clear whether these changes have long-term detrimental effects.

Seizures beget seizures: confirming an old concept

One of the strongest indications that seizures can reliably lead to long-lasting effects is the transformation of a naive network by seizures to one that has increased seizure susceptibility. The distinguished neurologist William Gowers[98] noted: "The tendency of the disease [epilepsy] is to self-perpetuation; each attack facilitates the occurrence of another, by increasing the instability of the nerve elements." Direct support for Gowers' idea that seizures beget seizures emerged from the discovery of the kindling model of epilepsy.[99] In the kindling model, repeated focal application of initially subconvulsive electrical stimuli eventually resulted in intense focal and tonic-clonic seizures. Once established, this increased sensitivity to electrical

stimulation persists throughout the animal's lifetime.[100,101] The kindling paradigm is central to our understanding of the associations between synaptic plasticity and hyperactivity as well as the generation and propagation of seizures between brain structures.[100] This paradigm is reminiscent of changes of synaptic efficacy in which electrical stimuli generate a persistent increase in the responses evoked by electrical stimuli.[102] Kindling, like kainate administration, operates at an early developmental stage. Seizures in the immature brain can not only change synaptic efficacy but also affect processes that are only or mainly expressed during development.

Despite the usefulness of in-vivo studies, they are inadequate to control the conditions by which seizures propagate and the mechanisms that induce long-lasting consequences. In other studies, Khazipov and colleagues[7,103,104] developed a triple chamber that accommodated two interconnected intact hippocampi in vitro that allowed the application of different drugs to each hemisphere as well as to their hemispheric connections placed in a third chamber.[104] A persistent epileptogenic mirror focus in a drug-naive hippocampus was formed after repeated applications of kainate or other epileptogenic drugs to the other hippocampus.[7] Although one seizure had no detectable effect, after a few seizures the naive network was transformed to an epileptic condition with unprovoked spontaneous discharges. This transformation was valid for the life of the preparation (up to 2 days). However, preparation of slices from the mirror focus hemisphere generated spontaneous ictal seizures that have never been reported in conventional submerged slices; this indicates that there were some intrinsic changes.[7] Unfortunately, this preparation cannot be used in adult hippocampi; however, similar studies with adult slices and repeated applications of kainate have already shown that recurrent seizures lead to long-lasting transformations of naive networks to networks that show repetitive seizures.[102]

Next, we examined the properties of seizures that are needed for the transformation to occur; only seizures that had high-frequency components elicited long-lasting alterations in excitability in the contralateral hippocampus.[105] Seizures with recurrent low-frequency events did not lead to long-lasting consequences. Both GABA and NMDA receptors are needed to generate high-frequency oscillations; blocking either type of receptor alleviates the long-term effects of seizures—ie, the naive hippocampus remains unable to generate spontaneous seizures after several hours of propagated seizures from the other hemisphere. Thus, the synergistic actions of GABA and NMDA receptors[106] are needed to generate high-frequency oscillations. This is perhaps best shown by the finding that co-application of kainate and a GABA receptor antagonist to the same hippocampus prevented the local formation of a mirror focus, even after long-lasting seizures, because these did not contain high-frequency oscillations. By contrast, the other hemisphere did become epileptic because GABA receptors were not blocked there. Therefore, if GABA receptors are blocked, recurrent seizures do not have long-lasting consequences. The time course of postsynaptic currents mediated by GABA and NMDA receptors are complementary in immature neurons. The long-lasting kinetics of NMDA-receptor-mediated currents in immature neurons generates prolonged excitatory postsynaptic currents that help the generation of synapse-driven network activities. Thus, the developing network is ideally organised to produce prolonged currents and thus facilitates the effects of synchronised events. These findings also indicate the massive changes that occur after seizures and emphasise the importance of GABA in the generation of high-frequency oscillations that in turn will lead to pathogenic consequences.

Because very immature networks cannot generate high-frequency oscillations until the density of functional GABA and glutamate synapses is sufficient, the deleterious effects of recurrent seizures, at least those mediated by neuronal activity, will not operate. Other actions of hyperactivity generated by the more developed neurons are due to alterations of essential developmental processes in adjacent less developed neurons. This duality may also explain the plethora and heterogeneity of actions of seizures at an early stage.

Whether the mature brain differs from the immature brain in the development of a mirror focus remains unclear. After about day 12 (postnatal) the triple chamber cannot be used to study the development of the mirror focus because the brain is no longer viable. However, as in immature neurons, in adult slices recurrent seizures need functional NMDA receptors to trigger the cascade of events needed to transform a naive hippocampus to an epileptic one.[102] Whether the oscillations play a similar part is still not known. Future studies will need to incorporate an in-vivo model to compare the physiological factors needed to develop a mirror focus in the immature and mature brain.

Conclusions

Recurrent seizures are more readily generated in immature networks than in adult networks. Although most children with epilepsy do well and eventually outgrow their seizures,[107,108] some will have long-lasting effects. Experimental evidence suggests that the adverse effects of frequent or prolonged seizures at an early stage are primarily due to their interference with developmental programmes rather than cell loss because developing networks are quite resistant to brain damage. This implies that the severity of recurrent seizures will be time dependent. We hypothesise that seizures or brief episodes of hyperactivity that occur when most neurons are migrating with receptors, but few if any functional synapses, will exert different effects than seizures occurring when neurons have many synapses

Search strategy and selection criteria

References for this review were identified by searches of PubMed from 1980 until 2006 in September 2006, with special reference to "maturation of transmitters", "networks", "synapse formation and their relation to seizures" and "adverse effects on brain development". Articles were also identified through searches of the authors' personal files. To limit the references to 100, review articles were reviewed after assessing original articles. Only papers published in English were reviewed.

and a primitive network-driven pattern. The former may interrupt the construction of cortical networks or lead to displaced cells and migration disorders, whereas the latter will change the expression or the operation of functional receptors and synapses and consequently change the threshold of further seizures. Considering developing networks as a single entity in terms of the sequelae of seizures is counterproductive. From a clinical perspective, determining the time dependent effects of seizures in experimental animals will help to extract from the many consequences of seizures, those that are directly harmful. The finding that some seizures beget seizures whereas others do not, raises the possibility that we may be able to identify which components of seizures are detrimental. This will lead to more efficient assessment of the need for aggressive interventions to interrupt seizures.

Contributors

YB-A wrote the first draft and most of the expeirmental data. GH wrote the clinical aspects.

Conflicts of interest

We have no conflicts of interest.

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