Epileptogenesis in the Dysplastic Brain: A Revival of Familiar Themes

Scott C. Baraban, Ph.D.

Department of Neurological Surgery and The Graduate Program in Neuroscience, University of California, San Francisco, San Francisco, California

Brain malformations are now widely recognized in many forms of epilepsy. To investigate how malformed brain regions participate in the generation of seizure activity researchers have focused on animal models. Here we describe recent advances in this field.

The dysplastic (or malformed) brain wherein an identifiable structural abnormality results in a medically intractable form of epilepsy (3) provides an ideal system in which to examine mechanisms of epileptogenesis. Of particular interest is an examination of the properties of dysplastic tissue because clinical–pathological studies have established that surgical resection of these regions has therapeutic benefit (27,40,41). To study dysplastic tissue in detail, it would be helpful to have a readily available animal model. Fortunately, in the case of dysplasia-associated epilepsies, several such models already exist (Table 1; and Fig. 1). The majority of the early work on these models was devoted to detailed descriptions of the anatomical features of a malformed rodent brain. More recently, investigators have turned their attention to mechanisms of epileptogenesis.

Two long-standing hypotheses have recently re-emerged in the context of dysplasia-associated epilepsies. First, epileptogenesis results from an alteration in the synaptic properties of a group of interconnected neurons. Second, abnormal intrinsic neuronal properties—ion channel mutations, for example—result in an epileptic focus. Now, these two hypotheses are joined by an additional, although not entirely novel, concept (e.g., altered glial activity contributes to epileptogenesis). As is

the case for many, if not all, hypotheses, considerable experimental evidence exists to support each of these possibilities.

We already know that a common feature in each dysplasia model is some form of hyperexcitability associated with the structural malformation (6,23,28,52). Now, recent articles by Castro et al. (18), Zhu and Roper (62), and Bordey et al. (15) report on specific intrinsic, synaptic, or glial deficits in the malformed brain that may underlie (or directly contribute) to epileptogenesis. These latter studies have important clinical implications for how we may design novel syndrome-specific treatment options for dysplasia-associated epilepsies. It is also clear from recent studies that much remains to be learned about the dysplastic brain. Here an update on some recent progress in understanding epileptogenesis in the dysplastic brain and a few speculations on where this field may be headed are provided.

Intrinsic Properties of Dysplastic Neurons

Originating with work by Hans Berger over a half century ago, epilepsy has been linked with the abnormal paroxysmal discharge of individual neurons (11). Through observations of electroencephalographic activity, A.A. Ward Jr. and others (43,45,59) proposed the idea of an “epileptic neuron” giving rise to abnormal patterns of burst discharge. These studies led to investigations of the neuronal membrane properties responsible for generation of paroxysmal depolarizations in acute and chronic forms of seizure activity. It is now clear that membrane-bound ion channels, in particular K^+ , Na^+ , and Ca^{2+} , play a key role in generating burst activity and that a “pacemaker” group of neurons (CA2/CA3 pyramidal neurons in hippocampus or layers IV/V pyramidal neurons in neocortex) can act as a site of seizure initiation (42,46). The concept of an epileptic neuron with pathological ion channel expression/function is further supported by recent demonstrations of a Na^+ -channel mutation (*SCN1*) in generalized epilepsy with febrile convulsions and a K^+ (*KCNQ*)-channel abnormality in benign familial neonatal convulsions (12,58). This concept of an “epileptic neuron” has been revisited in the recent analysis of animal models of dysplasia.

One of the most salient clinical findings regarding the dysplastic brain is that abnormal electrical discharge is observed in the malformed brain region, and surgical removal of these regions leads to a reduction or elimination of seizures (38,40,41,48). Consistent with these clinical observations, isolated nodular heterotopia in the MAM model are capable of independent burst generation when a heterotopia minislice is perfused with

Address correspondence to Dr. Scott C. Baraban at Box 0520, Department of Neurological Surgery, 513 Parnassus Avenue, UCSF, San Francisco, CA 94143; E-mail: baraban@itsa.ucsf.edu

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FIGURE 1 Rodent models of cortical dysplasia. Band heterotopia or “double cortex” in the TISH rat brain stained with cresyl violet (**TISH**). Granule cell dispersion in the *p35* mutant mouse brain stained with cresyl violet (**p35**). Nodular heterotopia in the MAM rat brain stained with cresyl violet (**MAM**). Layer I neuronal ectopia in the NZB autoimmune mouse brain stained with cresyl violet. Cortical microgyrus in the freeze-lesion rat brain stained with cresyl violet (**FL**). Cortical dysplasia in the irradiated rat brain stained with an antibody to NeuN, a neuron-specific protein (**Irradiated**). Arrowheads in each panel indicate malformations. Abbreviations: CX, cortex; HC, hippocampus.

convulsant agents e.g., 4-AP or bicuculline (8). This finding recalls early slice studies in which an isolated CA3 “tissue prism” containing as few as 1000 neurons was shown to sustain spontaneous epileptic bursts (36). A search for neurons with pacemaker or “epileptic” properties in the MAM model revealed that hippocampal heterotopiae consist largely of burster-type neurons (5,56) and periventricular heterotopic neurons exhibit “excessive” burst discharge properties (54). Now, Castro et al. (18) using a combination of molecular and physiological approaches, have identified an interesting ion channel abnormality on heterotopic neurons in the MAM model. Although normotopic pyramidal neurons in hippocampal slices from MAM animals and CA1 pyramidal neurons from control animals possess a voltage-activated fast, transient K^+ current (I_A) and the associated expression of *Kv4.2* channel subunits, heterotopic pyramidal neurons lack I_A and *Kv4.2* channels. A loss of this potassium current is a likely mechanism through which heterotopic neurons can generate abnormal discharge activity. Ion channel abnormalities that could be considered evidence of an “epileptic neuron” have not been identified for any of the other animal models of dysplasia, although future studies will undoubtedly explore this possibility.

Synaptic Function in the Dysplastic Brain

A bursting discharge pattern in individual neurons, with clear evidence of hyperexcitability, does not constitute epileptic ac-

tivity. Indeed, it is well established that discharges of many neurons need to become synchronized in order to generate the abnormal electrical activity seen on EEG, and as H. Jasper eloquently surmised, “Epilepsies can never be achieved by considering properties of single cells alone” (29,30).

Over the last half century, a tremendous amount of progress has been made in identifying the excitatory, inhibitory, and nonsynaptic mechanisms that underlie neuronal synchronization and seizure propagation. Because a major part of the synaptic circuitry of the brain is devoted to controlling excitation, it is not surprising that a loss of inhibition can play a key role in epileptogenesis. In fact, a classic feature of many epileptic conditions is a decrease in the efficacy of inhibitory synaptic transmission. This can be achieved through a loss of subpopulations of inhibitory interneurons (20), alteration in GABA reuptake systems (22), or a change in GABA receptor subunit expression (34). Now, Zhu and Roper (62), using sensitive voltage-clamp recording techniques, have identified impairment in GABAergic synaptic transmission in the dysplastic cortex of irradiated rats. Specifically, the frequency of spontaneous inhibitory postsynaptic currents is decreased by ~70% for dysplastic pyramidal neurons in comparison with control layers II/III or layer V pyramidal neurons. The authors also reported a decrease in the amplitude of evoked inhibitory postsynaptic currents and a loss of paired-pulse depression in dysplastic brain slices. These findings are consistent with earlier work describing a reduction in the density of parvalbu-

TABLE 1 Animal Models Featuring Clinically-Relevant Structural Abnormalities

Rodent Model	Malformation	Reference
Postnatal freeze-lesion (FL) rats	Polymicrogyria	(21,28)
<i>In utero</i> gamma irradiation rats	Nodular heterotopia	(26,52)
	Loss of lamination	
	Cortical dysplasia	
	Periventricular heterotopia	
<i>In utero</i> methylazoxymethanol exposure (MAM) rats	Nodular heterotopia	(5,19)
	Loss of lamination	
	Cortical dysplasia	
	Periventricular heterotopia	
<i>In utero</i> BCNU exposure rats	Nodular heterotopia	(10)
	Loss of lamination	
	Cortical dysplasia	
<i>In utero</i> cocaine exposure rats	Microdysgenesis	(7)
Ihara rats	Microdysgenesis	(2)
	Heterotopia	
Ibotenate injection rats	Periventricular heterotopia	(35)
	Band heterotopia	
Telencephalic internal structural heterotopia (TISH) rats	Band heterotopia	(32)
Shaking rat Kawasaki (SRK)	Loss of lamination	(1)
	Cortical dysplasia	
<i>p35</i> knockout mice	Granule cell dispersion	(17,31)
<i>Flathead (fh/fh)</i> mutant mice	Lissencephaly	(50,55)
	Hydrocephaly	
<i>Lis1</i> heterozygote mice	Cortical disorganization	(23)
	Loss of lamination	
<i>Otx1</i> heterozygote mice	Cortical disorganization	(4)
<i>Emx-1</i> knockout mice	Agenesis of the corpus callosum	(49)
NXSM and NZB autoimmune mice	Neocortical ectopia	(24,57)
Eker rats/ <i>TSC</i> heterozygote mice	Cortical tubers	(37,39)
	Abnormal giant cells	

min- and calbindin-immunoreactive inhibitory interneurons in dysplastic cortex from irradiated rats (53). Studies by Jacobs et al. (28) in the freeze-lesion (FL) polymicrogyria model report similar findings (28), namely a reduction in the number of parvalbumin-immunoreactive interneurons in the area of the microgyrus and a compensatory increase in spontaneous IPSC amplitude (or an increase in mEPSC amplitude; ref. 21) for neurons in the epileptogenic area adjacent to the microgyrus (47). In contrast, Layer I ectopia in NXSM/NZB autoimmune mice do not show an anatomical loss of GABAergic interneurons or a functional change in GABAergic synaptic neurotransmission (24). Early synaptic investigation in *p35* mutant mice, featuring granule cell dispersion, revealed abnormal dentate gyrus field responses, but analysis of specific excitatory and inhibitory synapses has not yet been performed (60). Further detailed examination of synaptic function in malformations will lead to a better understanding of how seizures initiate and propagate in the dysplastic brain.

Glial Changes in the Dysplastic Brain

Glial spatial buffering of extracellular potassium was first presented as an epileptogenic mechanism over 30 years ago. More recently, Barres and others have described the properties of glial voltage-activated K^+ channels and suggested a role for the inwardly rectifying K^+ channel (K_{IR}) in potassium buffering (9,14,15,61). Although reactive gliosis and alterations in sodium channel expression are common features of the epileptic brain (14,44), direct evidence for a pathological change in the spatial buffering capacity of an epileptogenic brain region has not yet been reported.

Early anatomical studies using irradiation or MAM models of dysplasia indicated morphological changes in astrocyte expression in the brains of these animals (8,51). However, no attempts were made to correlate these findings with functional studies. Now, Bordey et al. (13) using an elegant combination of anatomical and electrophysiological techniques, have described the presence of proliferative, BrdU-positive astrocytes in the hy-

perexcitable zone near FL microgyri (13). Perhaps of even greater importance, they went on to study K_{IR} currents on these astrocytes using voltage-clamp techniques. Interestingly, proliferative astrocytes in the FL cortex exhibited a profound reduction in inward potassium current amplitude and increased gap junction coupling. If one equates K_{IR} function with the ability of astrocytes to take up K^+ , then these results suggest that in the core of the FL microgyrus, there is a decreased capacity to spatially buffer extracellular potassium. Such an impairment of glial control of extracellular K^+ could directly contribute to hyperexcitability and generation of ictal discharges in a region of brain malformation. Whether such glial dysfunction contributes to (or is a result of) hyperexcitable firing activity in the dysplastic brain remains to be determined.

Conclusions & Future Directions

In the closing pages of *Basic Mechanisms of the Epilepsies: Molecular and Cellular Approaches* (25), Grisar summarizes a recollection of H. Gastaut that bears repeating here:

Tissot in 1772, who wrote in his Treatise of Epilepsy: To produce epilepsy, two conditions must be met: (1) a disposition of the brain to enter into seizures more easily than in the healthy state (i.e., a genetic defect of neuronal membrane metabolism); and (2) a cause for initiation which activates this disposition (i.e., an acquired lesion such as abnormal glial cells).

Although nearly 300 years have passed since this wonderfully insightful observation, it is once again clear that our understanding of epileptogenesis in the malformed (or “epileptic”) brain hinges on three simple themes: intrinsic, synaptic, and glial. Recent investigations summarized here, whether with specific intention (or not), have revived these long-debated hypotheses. What then does the future hold for basic research related to dysplasia-associated epilepsy? At least one idea emerges from recent work using animal models that mimic identified clinical abnormalities e.g., each dysplastic brain is marked by a specific epileptogenic deficit. At present, deficits appear to be model-specific, although some unifying principles will undoubtedly emerge. Perhaps the same idea holds for clinical forms of dysplasia, namely, each dysplasia-associated syndrome (lissencephaly, focal cortical dysplasia, tuberous sclerosis, etc.) needs to be examined in detail in order to identify syndrome-specific abnormalities that could lead to epileptogenesis. More importantly, recent studies identifying subtle functional, anatomical, and in some cases genetic, defects hold the promise for development of novel treatment strategies for medically intractable dysplasia-associated epilepsies. For example, would over-expression of *Kv4.2* potassium channels into dysplastic neurons *increase* the threshold for generation of seizure activity in the malformed brain? Similarly,

would transfer of K_{IR} functional astrocytes (or astrocyte precursors?) into a microgyrus increase potassium buffering capacity and *prevent* epileptogenesis? These questions, as well as a more complete understanding of other ion channels, postsynaptic receptors, gene expression and synaptic connectivity in regions of malformation, are all relatively unexplored research directions in the field of dysplasia-associated epilepsy.

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