Emerging Concepts in the Pathogenesis of Epilepsy and Epileptogenesis

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Recent studies of the problem of ictogenesis, or the ways that seizures develop in an already hyperexcitable brain, are leading to paradigm-shifting concepts that may lead to exciting new therapies for seizures. Research on the equally important area of epileptogenesis, or the ways that a normal brain becomes epileptic, is also expanding, but comparable research into translation of laboratory findings into successful clinical interventions for those at high risk needs to be developed.


ICTOGENESIS, THE DISTRIBUTED NATURE OF SEIZURE FOCI, AND SEIZURE PREDICTION

For more than a century, the concept of the epileptic focus, and of the seizures that arise from such brain regions, consisted of a vague notion of one area of the brain that was “injured,” or at least abnormally excitable, that was relatively discrete, and that, if removed, would render the patient seizure free. In addition, it was thought that the seizure was an abrupt and sudden event, either confined to the abnormal region or spreading throughout the brain. It is becoming more apparent from research in several laboratories, partly based on new technologies, that an epileptic region of the brain more likely consists of multiple small distributed hyperexcitable networks. More interesting, perhaps, is that a variety of electrophysiologic changes may be occurring frequently in these regions that move the brain into different seizure probability states that may wax and wane before clinical seizures develop. These abnormal electrical events may include microseizures, or seizurelike electrophysiologic events, which occur frequently in these small regions; clinical seizures may result when these microseizures slowly enlarge, begin to coalesce, and engage more and more of the normal brain in surrounding regions. The implications of this new hy-
receptors, as well as other proteins, compared with their press many different genes that encode ion channels and these spikes in more distant regions. The UCLA group called oscillations seemed to be associated with the regions from high-frequency epileptiform discharges “chronic epileptogenesis requires development of a network of pathologically interconnected neuron clusters.” Although not a radical departure from some previous thinking, this work focused the attention of the field on the concept of a more distributed network rather than on a more homogeneous epileptic area.

At the neocortical level, in patients with injuries or dysplasias, similar phenomena can be found at the anatomical and electrophysiologic levels. Often, these are more difficult to localize or identify because the cellular structure of the neocortex is more complex than that of the hippocampus, and the lesions tend to be more distributed. These concepts have now been taken to a new level by studies using microelectrode recordings from human epileptic regions. This can be done using surface grids and specialized electrodes in the neocortex or using microwire recordings from deep structures. In work originating from the Mayo Clinic, performed by Worrell and Stead in collaboration with Litt at the University of Pennsylvania, brief seizure-like discharges were recorded frequently from several microelectrodes within localized epileptic regions of the cortex, but in only 1 microelectrode at a time. These discharges are never seen with macroelectroencephalographic electrodes, and they seem to occur in very discrete regions. They are often seen in only 1 of a series of closely spaced microelectrodes, a result that indicates a very limited spatial distribution. Although much more data are needed, a hypothesis emerging from these discoveries is that microseizures occur frequently in hyperexcitable regions of the neocortex or hippocampus and that these events are often brief and self-limited. A hypothesis in development based on these observations suggests that a full-blown, clinically detectable seizure develops when these microseizures begin to enlarge, coalesce, and eventually reach critical mass. Whether there are behavioral consequences of these small localized events remains to be seen, but it is an intriguing issue regarding so many of the problems that patients with epilepsy have that seem distinct from the seizures they experience.

What factors are likely to be responsible for these events and their expansion? Undoubtedly, inhibition plays a role in confining the seizure-like events, both in time and space, according to a hypothesis first presented in the 1960s. Experiments performed by the UCLA group illustrate how

Figure 1. Normal human hippocampus (A) and hippocampal sclerosis (B), a indicates neuronal loss and gliosis; and b, granule cell dispersion. Not illustrated in this Nissl stain is extensive axon sprouting by surviving neurons in the granule cell layer and elsewhere and major changes in gene expression in surviving neurons and glia in the injured regions. Original images used with permission from Robert Sloviter, PhD.
fast ripple discharges in a hippocampal slice taken from an epileptic rat are localized (red) at baseline, but, when synaptic, γ-aminobutyric acid–mediated inhibition is reduced, the fast ripples spread throughout the slice and the interictal discharges increase in size.14 These data support some long-standing hypotheses about ictogenesis also based on the balance between excitation and inhibition in small localized cortical circuits.13,15

How does this phenomenon occur physiologically, without the addition of receptor antagonists? In an epileptic region, there is an excitatory center where some of the principal cells tend to fire in abnormal high-frequency bursts. These bursts are likely due, at least in part, to enhanced recurrent excitatory connections. These neurons also typically synapse onto inhibitory interneurons, which have widely distributed local connections and inhibit surrounding regions. When the excitatory neurons fire too aggressively, interesting phenomena occur, all of which are part of the normal functioning of the vertebrate brain. Excitatory synapses are facilitated with repetitive stimulation, producing stronger activation of recurrent excitatory circuits. Simultaneously, repetitive stimulation of inhibitory synapses produces a decline in synaptic strength.16-18 This combination of enhanced positive feedback and diminished negative feedback results in an “explosive” situation, and seizure activity is produced. This can occur in small, highly localized regions, such as those sampled by 1 microwire as discussed previously herein; in larger surrounding regions; or even at distances from the hyperexcitable region. This is the likely mechanism by which seizures develop and spread rapidly throughout the brain.

What are the implications of all this information? First, at a purely clinical level, the recording of these events may permit enhanced seizure focus localization for resective surgery. Second, as newer, innovative treatments are developed, localization for brain stimulation or local drug delivery can be performed. Third, if seizures are not beginning abruptly but are developing by the increases and regressions of these microseizures, it is possible that seizures can be predicted, safe periods can be identified, and therapy can be directed to patients during high-risk times, possibly by using intelligent closed-loop feedback devices. These therapies can be directed toward disrupting incipient hypersynchrony.

Other recent research10 indicates that seizures do not start abruptly but may develop with a predictable series of changes in brain electrical activity. One example, from Litt’s laboratory, is that multiple dimensions of information can be extracted from intracranial electroencephalograms (without microwire recordings) in various time domains preceding seizures.20 In a more recent study,21 this laboratory, using sophisticated statistical techniques, demonstrated the occurrence of a more probabilistic series of events, with focus on an increasing probability of seizure occurrence rather than on a purely linear “march” toward a seizure. Regions of the brain oscillate between periods of relative quiescence and periods of increasingly higher probabilities, suggesting that a seizure may be imminent.21 All this work is focused on the design of new therapies that will be tied directly to the prediction of seizure occurrence online and the delivery of some form of therapy to disrupt the developing hypersynchrony. The first generation of such devices is currently undergoing clinical testing as both an open-loop stimulation22 and a closed-loop stimulation coupled with early seizure detection.23 As more is learned about localized changes in brain excitability states, it is hoped that closed-loop devices could be activated by the impending increase in excitability rather than the patient having to wait for a seizure to actually begin.

PREVENTION OF EPILEPSY

At this time, attention can be turned from predicting and preventing seizures to predicting and preventing epilepsy. How does the normal human brain develop epilepsy, or hyperexcitability? This is a fundamental scientific and clinical issue. However, unlike the dramatic and paradigm-changing advances discussed so far, the issue of prevention of epilepsy remains problematic.

For this reason, it is appropriate to propose the recognition of a new syndrome: the risk of epilepsy development (RED) syndrome. The RED syndrome recognizes that after a variety of brain “injuries” (eg, trauma, status epilepticus, ischemia, central nervous system infection, and some forms of chronic neurodegeneration), a process has begun that leads to the development of epilepsy, at least in a substantial fraction of individuals. Why is it necessary to invent a new syndrome? Epilepsy seems to be either the only disease known to humankind, or one of very few, in which physicians wait until the disorder develops and then only try to treat the symptoms. Research and treatment strategies for virtually every other disease focus on either prevention or cure, especially prevention. Smokers are not encouraged to continue smoking and then treated for a cough only after they develop lung cancer. Very high cholesterol levels or blood pressure readings are not ignored until heart attacks or strokes occur. When possible, medical therapy focuses on risk reduction and prevention.

Epilepsy prevention has not been a major focus of research despite the fact that epilepsy is a major medical problem. It develops over time, so there is opportunity to intervene, and risk factors can often be identified. So one may ask why the neurology community has not focused more on this issue. Part of the reason is because there is insufficient basic scientific information about intervention strategies. However, there has been a recent dramatic increase in research focusing on the mechanisms of epileptogenesis that parallels the studies described earlier on the mechanisms of ictogenesis.

It is clearly possible to identify patients who are at relatively high risk for epilepsy.24,25 These include individuals with moderate to severe head injury (such as we are seeing in veterans returning from Iraq and Afghanistan); individuals with intracerebral hemorrhage, brain tumors, status epilepticus, and a variety of chronic neurodegenerative diseases; and children with prolonged febrile seizures, dysplastic brains, and who have certain genetic forms of epilepsy but have not yet become symptomatic. However, at the present time, nothing can be done to reduce the risk of epilepsy in these individuals. One can get a sense of the state of clinical investiga-
tion in this area by examining the ClinicalTrials.gov Web site (Figure 2). Most of the major neurologic disorders list many clinical trials in progress, most of which are focused on prevention or direct treatment. The figure includes more than 150 clinical trials in epilepsy, but almost all of them are devoted to symptomatic therapy. There are only 2 clinical trials listed that are trying to prevent epilepsy in high-risk individuals. Both are pilot trials and focus on individuals with traumatic brain injury. It is clear that more work needs to be done in this area.

To develop strategies for the prevention of epilepsy, it is necessary to understand the process of epileptogenesis. Initially, a normal brain experiences some form of “injury.” The injury can result from trauma, infection, ischemia, a bout of prolonged seizures (status epilepticus), or the presence of a malformation or mass lesion. Depending on the patient’s age and genetic background, some acute damage occurs, and then, progressive damage often continues. The brain tries to repair itself, but after a latent period of days, weeks, months, or even years, a condition of hyperexcitability develops and seizures begin. The seizures themselves may produce progressive damage, depending on where in the brain they occur and how intense they are. We do not know whether this is a 1-shot event or whether multiple “hits” are necessary for full expression of the epileptic phenotype (Figure 3).

The end product of the epileptogenic process has been analyzed using human brain tissue, mostly via electrophysiologic studies or postmortem or surgical pathologic examinations. The process of epileptogenesis has also been examined in a variety of animal models. The major findings of these studies can be distilled to the types that were discussed earlier: cell loss, axonal sprouting, synaptic reorganization, alterations in the neuronal phenotype, neurogenesis, circuit reorganization, and altered glial function. Each of these can be a therapeutic target, but it must be appreciated that many of these processes may be involved in the attempt of the brain to repair the damage and recover lost function. This is a significant issue for any clinical trial because it is important not to prevent epilepsy at the cost of impairing recovery of function. In fact, several antiseizure agents have been shown to retard recovery of function in models of ischemia and traumatic brain injury.

There are several current hypotheses about approaches to prevention of epilepsy, but there are very few data in this field to build a significant clinical program. One prominent idea is that by protecting the brain from the injury, one can prevent epilepsy. At a gross level this is true: that is, if all damage is prevented, epilepsy is unlikely to occur. However, there are also data from experimental studies that indicate that some forms of partial protection do not, in fact, prevent subsequent epilepsy. Thus, even a logical and sensible hypothesis needs careful experimental and clinical verification.

Examination of the current status of antiepileptogenesis at the clinical level produces disappointing results. This can lead to a nihilistic conclusion that nothing should be done until basic research in animal models indicates more promising pathways. However, if the clinical research in this field is put on hold until that time, without suitable preparation and pilot studies, it will take at least 5 or 10 years to determine whether any laboratory breakthrough is effective in a clinical setting with human patients. An alternative plan would be to begin the process now so that when the laboratory breakthrough becomes available, it will be clear how best to evaluate its effectiveness as a therapy.

It is important to continue to improve the ability to identify those at risk, to begin thinking about treatment before seizures develop, to treat with "safe" therapies, and to examine the outcome. In the process of developing a truly antiepileptogenic therapy, it will be important to distinguish the delay of the onset of symptoms accomplished by using a symptomatic treatment (eg, an antiseizure drug) from the true reduction of the occurrence of the disorder. However, it must also be recognized that effective suppres-
sion of all early seizures, even small ones that are not easily identified using current technologies, may be interfering with the process of epileptogenesis; so, in this case, “symptomatic” antiseizure drug therapy may also be antiepileptogenic. As mentioned, there are currently 2 ongoing pilot studies designed to explore these issues, and there are pioneering studies by Temkin and colleagues at the University of Washington that have led the way in this field.

As these pilot studies are undertaken, it will be useful to examine biomarkers in several domains that might identify those in the high-risk groups who are developing hyperexcitable brains and who might require more aggressive monitoring and intervention. These biomarkers would include electrophysiologic markers, from scalp and, likely, intracranial recordings, where one might look for the appearance of interictal spikes, fast ripples, and microseizures. They would also include imaging biomarkers and, possibly, biochemical biomarkers in serum or cerebrospinal fluid.

The long-term goal in this effort is to “cure” epilepsy by preventing its development in at-risk individuals. To accomplish this, it will be necessary to recognize the RED syndrome, to develop a consensus for the need for clinical trials in antiepileptogenesis, to develop the clinical infrastructure for performing such trials in a network of centers, to develop better clinical trial paradigms, and to partner with those who perform basic research in antiepileptogenesis.

In summary, paradigm-shifting research is altering how we understand the processes by which seizures develop in an already hyperexcitable brain. These new discoveries have great promise to lead to new forms of therapy with long-term intracranial electroencephalographic monitoring, seizure prediction, brain stimulation, local drug delivery, and intelligent implanted closed-loop feedback devices. These are therapies that would have been in the realm of science fiction just a few years ago. In addition to learning how to predict seizures, it is also possible to predict epilepsy, at least with some level of probability. However, just as the field is trying to capitalize on a newly developed ability to predict seizures, a strong focus of basic and clinical research on the important topic of preventing epilepsy in those who are known to be at high risk is needed. In this endeavor, it would be appropriate to raise a RED flag for epilepsy!

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