Published in final edited form as:
Neurosci Lett. 2011 June 27; 497(3): 251–256. doi:10.1016/j.neulet.2011.03.010.

Human clinical trials in antiepileptogenesis

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Abstract

Blocking the development of epilepsy (epileptogenesis) is a fundamental research area with the potential to provide large benefits to patients by avoiding the medical and social consequences that occur with epilepsy and lifelong therapy. Human clinical trials attempting to prevent epilepsy (antiepileptogenesis) have been few and universally unsuccessful to date. In this article, we review data about possible pathophysiological mechanisms underlying epileptogenesis, discuss potential interventions, and summarize prior antiepileptogenesis trials. Elements of ideal trials designs for successful antiepileptogenic intervention are suggested.

Keywords

Epileptogenesis; clinical trials; humans; antiepileptogenesis; seizure; prophylaxis

Introduction

There is a widely quoted phrase somewhat adapted from the Hippocratic oath that all physicians take before entering their profession: “First, do no harm.” Rarely, does anyone ask, “What is second?” In many areas of medicine, emphasis is placed on diagnosing and treating illness. This is particularly true in epilepsy. Unfortunately, what should be “second” is preventing illness, so that it becomes unnecessary to diagnose or treat that which does not exist in the first place. For the most part, preventing epilepsy in those with known risk has not been possible. In order for this unacceptable situation to be corrected, we need to understand the mechanisms by which epilepsy develops in an injured or genetically susceptible brain, demonstrate in some preclinical model that the process can be prevented, and then demonstrate in a well designed clinical trial that the proposed preventive strategy is effective and safe.

Epilepsy affects more than 45 million people worldwide. In the US, the prevalence of epilepsy is approximately 6 to 8 per 1000 people, and the incidence is approximately 26 to 40 per 100,000 person-years [10]. Treatment of epilepsy has focused on preventing recurrence of seizures after the onset of epilepsy. Surgical cure is an option for some

medication-refractory patients, but even then the treatment may be onerous and is usually delayed sufficiently that there often is irreparable biological and psychosocial comorbidity, even if the patient becomes seizure free [1]. In all, approximately 40% of patients that develop epilepsy continue to have life-long seizures [25]. It is common for antiepileptic drugs (AED) to have side effects, with those effects being highest among patients who need a large number and high dosage of AEDs [7]. Avoiding all of this whenever possible is a major advantage to individuals destined to develop epilepsy.

In this article, we will review the concept of epileptogenesis as it relates to man. We will review clinical trials of epileptogenesis prevention and describe steps for creation of future trials of antiepileptogenesis in humans. Special emphasis will be placed on the prevention of epilepsy development after symptomatic brain insults.

Definitions

Epilepsy: chronic disorder of the nervous system characterized by recurrent unproved seizures; there should at least two or more seizures greater than 24 hours apart [16].

Acute (or early) symptomatic seizures: seizures that occur soon after a brain insult. Usually, this time period is specified as 1-2 weeks after the insult. Some authors use 7 days as the cutoff; some use 2 weeks. These are provoked seizures. The pathophysiology that underlies these provoked seizures (e.g. neuronal calcium influx, cerebral edema, intracranial blood effects, and metabolic disorders) likely differs substantially from that which contributes to the development of epilepsy.

Late seizures: seizures that occur after the 1-2 week time period after a brain insult. If no new CNS insult or new systemic disorder (e.g. drug withdrawal, eclampsia, toxins) occur during this “later” time period, these seizures are unprovoked [18].

Antiepileptic: prevents or reduces epileptic seizures.

Neuroprotective: prevents neuronal injury. An antiepileptic may be neuroprotective if seizures are injurious or if the compound has an additional protective activity independent of its antiepileptic activity.

Antiepileptogenic: prevents or slows the process of developing epilepsy. An antiepileptic might be antiepileptogenic if the seizures it blocks are themselves epileptogenic. A neuroprotective compound might be antiepileptogenic if injury leads to epilepsy. Alternatively, some compounds might have antiepileptogenic activity without either blocking seizures or preventing injury [6].

Models

Animal models to investigate mechanisms of epileptogenesis and the critical period for application of specific therapies to prevent epileptogenesis are particularly important. Models based on kindling, prolonged hyperthermia-induced seizures, post-status epilepticus, traumatic brain injury (TBI) and cortical dysplasias produced by tuberous sclerosis have provided a wealth of information about the cellular and biochemical changes that occur during epileptogenesis. However, they have not yet stimulated effective therapies for human antiepileptogenic interventions. These investigations remain important, and the reader is referred to other sections in this issue and other excellent reviews for more information [12].

Postulated Antiepileptogenic Interventions

Unless a key universal epileptogenic cascade can be identified, it is likely that different epilepsies will require different preventative strategies. Several different categories of interventions hold promise for blocking epileptogenesis. Traditional antiepileptic drugs have been the most commonly used in human clinical trials and will remain the most investigated interventions to block epileptogenesis due to their safety and efficacy as seizure suppressing agents. Their use in these studies is based on the unproven hypothesis that intractable epilepsy may be a consequence of recurrent seizures early in the epileptogenic process. Anti-inflammatory agents have also been posited as antiepileptogenic interventions. The blood-brain barrier disruption after cerebral insult may allow efficacy of these agents [40]. Intriguingly, antagonists of the mammalian target of rapamycin (mTOR) pathway have shown promise in tuberous sclerosis models and in post-status models. Trials of seizure treatment and epilepsy modification are underway in patients with epilepsy that is symptomatic of an mTOR pathway dysfunction (e.g. tuberous sclerosis)[43]. Some groups have found that plant products such as resveratrol, found in red wine, and curcumin, found in the spice turmeric, have shown promise in animal models for blocking seizure development after different brain insults [42]. Even device interventions have been proposed, and transcranial magnetic stimulation (TMS) has been shown to decrease the number of EEG interictal spikes [23] which may or may not be directly relevant to the epileptogenic process. Applying this therapy in the acute period after the brain insult, and periodically afterwards, may be an antiepileptogenic intervention.

In a genetic model of epilepsy in rats (WAG/Rij rats), Blumenfeld has demonstrated that epileptogenesis can be blocked by administration of the anti-seizure drug, ethosuximide, before the onset of the typical spike-wave discharges that these rats develop after birth. Furthermore, the drug can be discontinued and the generalized seizures do not develop [3].

Epileptogenesis

Epileptogenesis is often viewed in different phases. The latent interval exists from the time of brain insult until the development of recurrent spontaneous seizures. Different pathologic mechanisms that have been reliably associated with epilepsy have been observed in this latent period, and they may be the subject of antiepileptogenic interventions. Glutamatergic enhancement has been observed in kindling models associated with mossy fiber sprouting [35]. GABAergic disruption has also been observed in refractory seizure development [2, 32]. Additionally, cell loss, gliosis, axonal sprouting, increased expression of intermediate-early genes (c-fos and c-jun), growth factors, inflammatory mediators, network reorganization and changes in voltage-gated ion currents and excitotoxic antibodies have all been described in animal models of epileptogenesis [5, 30].

The critical period for epileptogenesis differs depending on the model; in some animal models it is suggested to occur well past the first clinical seizure [41]. One inciting event may be sufficient, or multiple “hits” may be required for the development of epilepsy [8]. Factors that have been shown to modulate progression to epilepsy include family history of seizures, age, gender, existing organic brain disease, and psychiatric comorbidity [11, 15, 20]. Thus, these variables should be reliably assessed in patients participating in the antiepileptogenic trials because they may be important in identifying differences in response to interventions due to biologic difference associated with these variables.

A subtle variation of the concept of antiepileptogenesis would use these agents to attempt to reverse or attenuate the progression of epileptogenesis to try to decrease seizure frequency, increase response to AEDs, or change epilepsy from refractory to controllable. This concept of disease modification after the latent period is a form of antiepileptogenesis, but the

biology underlying this might differ substantially from that which leads to the development of even the first seizure. This type of disease modification would be valuable but is outside the scope of this article.

Risk of Epilepsy Development (RED syndrome)

The Risk of Epilepsy Development (RED) syndrome is a condition that recognizes that a variety of neurologic conditions precede the process of development of later unprovoked seizures [8]. This syndrome was created to better identify patients at high risk for epilepsy development so that therapies can be targeted for primary disease prevention. The intent is to focus on research leading to therapies for primary prevention of unprovoked seizures and the onset of epilepsy. An apt analogy is the treatment of cardiovascular risk factors for the primary prevention of stroke and myocardial infarction.

Epidemiologic studies have identified several cerebral insults or neurologic conditions with substantial risk for the development of epilepsy. These include TBI, intracranial hemorrhage, brain tumors, craniotomy, cerebral palsy, intrapartum hypoxia, and status epilepticus. In addition, most forms of genetically determined epilepsy develop well after birth. Thus, individuals with various forms of inherited epilepsy could also be considered to have the RED syndrome. The absolute risk of epilepsy development after specific cerebral insults varies according to risk modifying characteristics, most notably patient age, severity of the insult and other comorbid CNS conditions. The risk also depends on the outcome assessment used (i.e. follow-up period, seizure classification of acute vs. late and provoked vs. unprovoked). For example, a prior review of studies has suggested the absolute risk of epilepsy development after certain insults as follows: greater than 25-30% over two years in moderate-severe TBI; 5-15% over ten years in stroke; 5-10% over fifteen years in CNS infections [17].

The risk of epilepsy after a single unprovoked late seizure after certain brain insults is high. In a Rochester, MN population-based study of 148 patients with brain insults, subsequent 10-year epilepsy risk was high after a single unprovoked seizure after mild-severe TBI (47% 10 year epilepsy risk), stroke (72% risk), and CNS infections (64% risk) [21]. In another study, 86% of patients with moderate-severe TBI and a single late unprovoked seizure went on to have epilepsy in two years of follow-up [14]. These data support the hypothesis that by the time a single unprovoked late seizure has occurred in a patient with certain brain insults, much of the pathologic process to create a high likelihood for epilepsy has already occurred.

In addition, acute symptomatic status epilepticus at time of initial seizure confers greater risk for future unprovoked seizures than acute symptomatic seizures, with a 41% versus 13% risk for future unprovoked seizures at 10 years [19]. The impact of acute symptomatic subclinical seizures detected via EEG monitoring in some patients after acute brain injury needs to be assessed for its impact in epileptogenesis [17]. Although neonatal seizures often do not immediately progress to chronic epilepsy, they do cause increased susceptibility to seizures and risk of epilepsy later in life [31]. In human infants, hypoxia is the most common cause of seizures [22]. It is theorized that hypoxia is first hit in a multi-hit process leading to epileptogenesis [12].

Past Clinical Trials in Epileptogenesis

A number of human clinical trials have been conducted in preventing epilepsy development in subjects at risk for epilepsy, but only a few of these have been randomized, double blind placebo controlled studies. These trials have generally included patients with brain injuries or brain tumors, and all have failed to discover useful preventative treatments. A landmark human clinical trial showed that phenytoin administration after moderate to severe TBI does

not decrease the chance of unprovoked seizures after the first week of brain injury. In this well-executed blinded placebo-controlled trial, patients were randomized to phenytoin or placebo within 24 hrs after TBI. Half of the 323 patients continued to receive phenytoin for one year while the placebo group continued on placebo. Patients were subsequently followed for one additional year for a total of 2 years of observation. There was no significant difference in late seizures in the first year (21.5% of phenytoin group and 15.7% of placebo group) or in the second year (27.5% of phenytoin group and 21.1% of control group, risk ratio 1.20, 95% CI 0.71-2.02) [36]. The point estimate for seizure reduction actually non-significantly favored the control group. A second study done by the same group investigated 1-week phenytoin vs. 1-week valproate vs. 6-months of valproate administration after TBI (the first 2 arms received placebo until 6 months after active drug arm cessation); this study also failed to show antiepileptogenic effects. Valproate treatment for 6 months was associated with a non-significant increase in late seizure rate [37]. Other placebo-controlled trials in epilepsy prevention after initial febrile seizures (diazepam, phenobarbital), brain tumor discovery (valproate, phenytoin), craniotomy (phenytoin), and traumatic brain injury (carbamazepine, phenobarbital) have also proven unsuccessful [38]. Non-AED interventions after TBI have also proven unsuccessful in blocking epileptogenesis. Administration of magnesium sulfate in the first five days after moderate to severe TBI was not associated with a significant change in late seizures over the following 6 months compared to placebo in a randomized controlled trial of 500 total patients [39]. Well-powered, randomized, placebo-controlled trials in this area continue to be relatively scarce, and at the time of writing this chapter, the authors are unaware of any such ongoing trials.

Antiepileptogenic morbidity

One factor that complicates trials is that the AEDs, especially the older ones, can cause substantial morbidity. Phenytoin caused significant neurobehavioral impairment months after traumatic brain injury compared to patients with similar injury receiving placebo [9]. Post-stroke recovery in animal models has been shown to be impaired by GABA-ergic drugs [13]. Similarly, in a trial where recovery of function after intracerebral hemorrhage was studied, patients on antiepileptic drugs fared more poorly than those not receiving such drugs [28].

Biomarkers

Given the long duration until clinical detection of epileptogenesis after brain injury and the lack of promising results from human antiepileptogenesis trials, development and validation of biomarkers for human epileptogenesis will be extremely important to better detect beneficial effects of interventions. Surface EEG spikes, specific intracranial EEG spike patterns, and intracranial EEG seizures may be present before development of clinical seizures and serve as biomarkers.

High frequency oscillations (HFOs) have been suggested to accompany the process of epileptogenesis from animal data and may be present before seizures [4, 33], and microseizures [34] are being investigated as an epilepsy biomarker. Changes in hippocampal structures and hypometabolism on PET have been associated with worsening of seizures in human case series and could become useful as biomarkers for epileptogenesis. MRI diffusion tensor imaging (DTI) is also being investigated as marker for epilepsy [27]. Each of these promising techniques could be examined during antiepileptogenesis clinical trials to validate whether they would be useful as independent biomarkers.

An Ideal Human Antiepileptogenesis Trial

Selecting the appropriate patient population is the most important factor in designing a study of antiepileptogenesis in humans [Table 1]. The ideal population would be subjects with very high epilepsy risk (high RED scores) to maximize the chance of detecting a difference between the treatment and placebo arms. Further, the risk factor for epilepsy must be readily identifiable in origin and time in order to establish a relatively homogeneous population with a similar starting point. In addition, the latency from insult to onset of seizures must be relatively short. Long trial periods are prohibitively expensive and subject to compromise by non-adherence to therapy, especially if the agent's side effects are not benign.

There are several populations that have high RED scores that could be used [Table 2]. The acquired brain insults with the highest RED scores in the adult population are brain tumors, intracerebral hemorrhage, and traumatic brain injury [17]. Other possible groups include individuals with clearly defined genetic epilepsy syndromes and those with cortical dysplasias such as in tuberous sclerosis. In the past, studies have also included individuals with febrile seizures, cerebral malaria, perinatal asphyxia, craniotomies, and contrast media associated seizures [38].

It is likely that the first successful antiepileptogenesis study with acute, acquired epileptogenic stimuli will be drawn from subjects with either traumatic brain injury or intracerebral hemorrhage. This is because the patient population is easily identifiable, risk of seizures is high, latency to seizures is relatively short, and beginning of RED syndrome is easily calculated. There are a number of important hurdles to deal with in some adult subjects of these disease investigation groups. For example, in a pilot study at The University of Pennsylvania, we found that many people in the civilian population who suffer TBI, especially in inner city environments, are also at high risk for taking illicit drugs and for poor follow-up and adherence. Additionally, planning a trial examining simultaneous neuroprotective and antiepileptogenic agents will require different design and/or greater sample size than typical add-on AED trials for refractory partial seizures. A crossover design or higher samples sizes needed for three or more intervention arms could be considered for simultaneous neuroprotective and antiepileptogenic agents trials given the need to examine the safety and efficacy of agents against placebo and each other. In addition, obtaining traditional informed consent is problematic in any study that requires rapid entry of very ill patients. If the study involves life-saving therapies, informed consent can be provided as community consent or can be waived, but for most antiepileptogenesis trials this will be difficult. On the other hand, if it is not deemed necessary to start treatment very shortly after the TBI or ICH, informed consent will be obtainable from the patient or appropriate family members.

The logistics of any such trial must also be carefully designed. As mentioned, time to first treatment will have a significant effect on patient recruitment. Duration of therapy is also critical, and will depend on data from animal experiments as well as the potential toxicity of the treatment and its level of convenience.

Despite these impediments, clinical trials of antiepileptogenesis after TBI have been completed with very good study designs and adequate patient accrual, demonstrating the feasibility of studies of this kind in TBI.

Other patient populations are strong possibilities, but suffer from some drawbacks. Patients with slow-growing brain tumors have a high risk for epilepsy. Unfortunately, many of these patients actually present with seizures, so it is possible that an intervention could completely miss window to intervene in the epileptogenic biology. Similarly, even in those without clinical seizures, it would not be known if the process of epileptogenesis had been

proceeding for some time before treatment began. In addition, the variable nature of the progressive tumor will provide a significant issue for data analysis.

Patients with genetic diseases may be a viable population for future studies. The advantage of this population is that the group could be quite homogenous and the risk of epilepsy could be estimated relatively precisely. The main drawbacks would be the relative rarity of the appropriate syndromes, the potentially long and differing latency to seizures, and the variable penetrance that many of these genetic disorders demonstrate. A genetic disorder that produces epileptogenic cortical dysplasias, such as tuberous sclerosis, may be another good candidate for antiepileptogenesis studies, as it would provide a relatively homogeneous population with high risk of developing partial onset epilepsy.

The outcome of any study will be clinical appearance of late onset seizures, which is a process best measured over years. In trials of other long-latency diseases, one main strategy is to use biomarkers to shorten the trial. Certainly a validated surrogate marker for epileptogenesis would be very useful, but this, unfortunately, is not yet available. There has been considerable effort in the field to find epilepsy biomarkers including work in imaging and neurophysiology. One emerging possibility is the potential for implantable electrodes to monitor subclinical seizures or spikes [24]. Additionally, it is possible that some clinical characteristics comprising a biomarker could be evaluated early in the RED syndrome. Some examples of these possible clinical biomarkers are common epilepsy comorbidities like memory problems, mood problems, and personality changes. Even if a valid surrogate marker is never found, a good biomarker could help with other elements of trial design such as selection of the correct dose of the investigational agent. Barring the emergence of a reliable biomarker, a trial should also follow epilepsy characteristics that may be modified by antiepileptogenic therapy. These include the seizure frequency, the type of seizure, duration of seizure, duration and severity of postical dysfunction, and refractoriness.

As mentioned above, it is important to be mindful that neuroprotection against seizures is not necessarily synonymous with neuroprotection against loss of properly functioning brain tissue. The two processes might be opposed to each other in some circumstances, so rigorous methods for following patient safety must be met as well. Including stopping criteria dependent on significant clinical differences in recovery from brain injury, such as physical, cognitive, and behavioral outcomes should be considered.

A study of antiepileptogenesis must be able to differentiate anti-seizure effect (e.g. symptomatic therapy) from antipepileptogenic effect. A standard approach would be to establish a finite treatment period and follow patients during the treatment and for a defined period after treatment cessation. Following the subjects after this stop date will yield either a continued reduction in development of seizures compared to baseline (a success), or a merging of the two arms (a failure).

Conclusion

Preventing epilepsy in those known to be at risk should be a very high priority for the medical community and epilepsy specialists in particular. Curing epilepsy once it develops or stopping existing seizures with medications or devices will also continue to be crucial. In order for us to develop the ability to prevent epileptogenesis, we will need to understand the process better and to employ appropriate animal models to test therapeutic hypotheses. However, it needs to be recognized that even if a therapy is discovered that works well in animal models, it will take a substantial effort and probably a decade to organize clinical trials that can demonstrate efficacy and safety in human patients. This process can be shortened by devoting appropriate efforts in advance of the preclinical breakthrough to

search for useful biomarkers and to establish clinical protocols that can be refined while the field awaits new basic discoveries. There is a science to designing and implementing innovative clinical trial designs for important unsolved clinical problems and a significant fraction of efforts allotted to antiepileptogenesis needs to be devoted to this aspect of the problem. Moreover, as more attention is paid to preventing epilepsy at the clinical level, it is likely that more efforts will be focused on this important topic at the basic level as well. Pressure from both the patients and the professional care-providers can help stimulate these efforts. Our experience to date indicates that neither the basic nor the clinical research in this area will be easy or quick. However, the rewards of a successful antiepileptogenesis program should be much greater than most have imagined, and the cost-effectiveness of preventing lifetime disabilities and lifetime requirements for intense medical care favor increased funding for these research efforts.

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Table 1

Trial Methodology Key Points & Suggestions

- Population selection
  - Relatively common problem; preferably adult population
  - Relatively high risk (high RED score)
  - Relatively short latency to epilepsy
  - Homogenous etiology
  - Lack of other neurological confounding issues or progressive disease
- Objective epilepsy risk factor definition and examination for all risk factors
  - Neurologic history and physical (including thorough family history for epilepsy susceptibility; neurologic and psychiatric comorbidities)
  - Examination for severity of insult and possible acute symptomatic seizure history and status epilepticus
  - Imaging with attention to region of interest (MRI, DTI, PET)
  - Prolonged EEG (awake and asleep); objective assessment of epileptiform activity
  - Consider MEG in patients with breach artifact for more reliable epileptiform activity assessment [26]
  - Consider chronic intracranial electrodes when they become available
- Consent: allow for rapid consent, surrogate consent, waiver of informed consent
- Therapeutic agent
  - Easy to administer
  - Low side effect profile – safe
  - Can be maintained for sufficient duration as determined by preclinical data
- Treatment initiation timing
  - Depends on cause (suggestion is within 1-3 days from most acute insult types)
- Multiple arms with placebo and varying duration of prophylactic administration
- Periodic AED levels and confirmation of adherence necessary
- Long observation period after epileptogenesis intervention phase has ended; follow up of at least 2 years - 5 years would be better
- Track other epileptogenic hits that may be acquired during follow up period (history, imaging, EEG)
- Sample size and powering
  - Target effect size should depend on expected prevalence of epilepsy given underlying brain insult; consider powering to detect difference of at least 20-50% reduction in patients with new-onset unprovoked seizures [36]
  - Trial should be multicenter given high sample size requirements
- Outcome assessment
  - Seizures: time to first seizure, seizure frequency, refractory epilepsy, provoked or unprovoked seizure, seizure type
    - Blinded neurologist assessment of first seizure description report and ambiguous subsequent seizures
  - Reassessment of biomarkers as stated above
  - Neuropsychogical test scores
  - Functional recovery
  - Traditional trial adverse events

TABLE 2

Factors for and against using each RED syndrome population in a clinical trial to prevent epileptogenesis.

RED Syndrome Population	Pros for trial	Cons for trial
TBI (moderate to severe)	• Patient availability • Epilepsy prevalence • Few years follow-up • Prior trials	• Neurologic sequelae • Variable pathology • Effect of treatment on recovery of function
Stroke - Supratentorial lobar hemorrhage	• Patient availability • Epilepsy prevalence • Few years follow-up • Focal region defined	• Older patients • Neurologic sequelae Effect of treatment on recovery of function
Craniotomy	• Patient availability • Few years follow-up • Focal region defined	• Heterogeneous brain lesions and patient population • EEG breach artifact
Tuberous sclerosis (cortical tubers)	• Focal region defined	• Multi-center • May have multiple lesions
Cortical dysplasia	• Focal region defined	• Some ill-defined lesions • Follow-up period unknown • Heterogeneous population • Patient availability
Post new-onset status epilepticus	• Epilepsy prevalence	• Heterogeneity of insults • Heterogeneity of patients • Patient availability • Multi-center
Brain Tumors	• Patient availability • Focal region defined	• Progressive disease • Variable time to onset of seizures
Complex febrile seizures or febrile status epilepticus	• Epilepsy prevalence • Focal region defined	• Patient availability • Long follow-up period • Multi-center • Special pediatric trial issues