Traumatic brain injury from blunt force impact propagates a pressure wave through the skull causing cavitation within the neuropil and rotational forces that result in structural damage with cortical laceration and contusion. Whether trauma is civilian or military, the severity of the injury correlates with the likelihood for a person to develop epilepsy. However, specific mechanisms and risk factors for development of posttraumatic epilepsy (PTE) remain unknown. Head trauma and the complication of PTE are major public health problems. Prophylaxis has failed because trials were not based upon the fundamental mechanisms that initiate epileptogenesis. Animal models suggest mechanisms of epileptogenesis and even rational interventions. However, the critical challenge is to design screening of interventions, establish efficacy in a broad range of animal models, and then determine whether a severely injured patient can withstand the burden of the side effects of agents that have utility in animals.

**Risk Factors**

Severity of the injury as manifest by duration of unconsciousness, neurologic deficits, and hemorrhage tends to predict the development of PTE in adults and allows a crude prediction of the likelihood to develop posttraumatic epilepsy (PTE) (1). Predictive factors associated with epilepsy risk among those injured in combat included cortical involvement, a moderate volume of brain tissue loss, intracerebral hematoma, and retained metal fragments that are ferric metal in composition (2, 3). Other studies reported prolonged posttraumatic amnesia, the presence of a cortical laceration occurring with a depressed skull fracture with dural laceration, and intracerebral hematoma in patients liable to develop PTE. Englander et al. (4) found the highest risk for late posttraumatic seizures in those patients with multiple or bilateral contusions, subdural hematoma requiring surgery, an early posttraumatic seizure, multiple cranial surgical procedures, and a large midline shift associated with the injury.

Seizures originate in cortical regions but mesiotemporal origins have been reported (2, 5). Swartz et al. found 21 patients, with trauma as a risk factor for epilepsy, from a sequence of 200 undergoing temporal lobectomy (6). While histopathological inspection showed gliosis in all of the 21 neocortical tissue specimens and hemosiderin deposition in 8/21 (38%), cell loss was found in 14/21 (67%); mild loss in 9/21 (43%). They speculate that blood from trauma-induced hemorrhage results in “peroxidation-induced tissue damage,” which couples with hippocampal injury related to percussion that produces seizures (7–9). With penetrating injury, seizures tend to originate from the adjacent injured cortex. Severe trauma tends to be associated with multiple lesions and prolonged unconsciousness (10). Overall, posttraumatic epilepsy tends to occur in patients with neocortical injury with hemispheric or diffuse lesions (10).

Messori et al. (11, 12) evaluated MRI images of 135 patients with traumatic brain injury obtained from 4 to 6 months after injury. Patterns of gliosis were identified as incompletely surrounding an area of hemosiderin, walling the area completely with gliosis, or a region of hemosiderin without any gliotic reaction. Of the 20 patients (14.8%) developing PTE, two had isolated hemosiderin only, while gliosis associated with hemosiderin was associated with development of seizures. Hemosiderin with incomplete surrounding by glia had the greatest probability for the development of PTE (11). Histopathological studies of traumatized brain show hemosiderin deposition, formation of axonal retraction balls, reactive gliosis, Wallerian degeneration, and microglial star formation within cystic white-matter lesions. Iron-filled macrophages, ferruginated neurons, and astroglial cells surround the focus of seizure discharge (13).

Injury results in neuronal destruction and proliferation of glia that may be associated with hemosiderin deposition (11).
Tissue around the area of direct brain trauma is the locus of intense fibrillary astrocitic reactions. These glial accumulations may contain diffuse iron particles in layers II–V and calciﬁcations as well (14). The effect of glial changes may have an important role in the generation of seizures (15). Diffuse axonal injury can alter or modify functional relationships between neural structures that may facilitate the initiation of PTE (16, 17). A consistent finding in one series was neuronal loss in hippocampal hilar regions and changes in temporal neocortical regions (6).

Animal Models
Designing an animal model that reﬂects the components of trauma leading to spontaneous seizures is a challenge. Commonly used systems have included focal injection of blood components into regions of the neuropil, application of ﬂuid percussion through a craniectomy in rodents, undercutting the isocortex, and amygdalar kindling. For a model to be reﬂective of events initiated by trauma to the brain, there must be some resemblance to the processes that can occur to humans. For this reason, chemically induced status epilepticus, which tends to cause chronic and recurrent seizures along with hippocampal histopathological changes, is useful but may not allow study of the longitudinal processes that are initiated by trauma.

Injection of Blood Products
Traumatic contusion and intracerebral hemorrhage result in focal encephalomalacia and hemosiderin deposition (8, 18). Iron liberated from hemoglobin and transferrin, sequestered as hemosiderin, is a prominent histopathological feature of human posttraumatic epilepsy (13). Addition of iron salts or heme compounds to solutions containing polysaturated fatty acids (PUFA) or to suspensions of subcellular organelles results in the formation of highly reactive free radical oxidants, including perferryl ions, superoxide radicals, singlet oxygen, and hydroxyl radicals (9, 19–21). Free radicals react with methylene groups adjacent to double bonds of PUFA and lipids within cellular membranes, causing hydrogen abstraction and subsequent propagation of peroxidation reactions (20). Inorganic iron salts, hematin, and hemoproteins will stimulate peroxidation of lipids of microsomes and mitochondria as well as change cellular thiodisulfide function (22, 23).

Kindling
Manipulation of amygdalar nuclear complexes changes rodent behaviors by kindling that can be induced with such methods as electrical stimulation (24, 25) or by chemical injections (26). Although most paradigms cause animals to have stimulus-dependent seizures, some manipulations do induce spontaneous kindled behaviors, albeit in a small percentage of animals (27). Phenobarbital and 2-deoxyglucose have been proposed as protective in this model (28, 29).

Lateral Fluid Percussion
Measured mechanical force is delivered to rat brain through a craniectomy (30). This method is attractive in that the process initiating the injury response is mechanical in nature. Latency to the occurrence of spontaneous seizures is present in some surviving rodents. Histopathological assessment shows hemorrhage is extensive with isocortical encephalomalacia at the site of impact along with substantial ipsilateral hippocampal atrophy. Mossy ﬁber sprouting is observed within the inner molecular layer of the dentate gyrus (30). Initial lesions show “...focal contusion, blood-brain barrier disruption, altered cerebral metabolism...subdural hematoma, [and] intraparenchymal and subarachnoid hemorrhage...” that raises the question of the role of hemorrhage (30).

Partial Cortical Isolation
Partial isolation of a neocortical island with intact circulation from the pia allows for the development of hyperexcitability and mimics epileptogenesis (31). Cortical regions are reorganized, and this model allows longitudinal assessment and serves as a platform for evaluation of methods for interruption of epileptogenesis (32). Detection of spontaneous events depends upon physiological recording techniques (31). Altered GABAergic inhibitory mechanisms and enhanced excitatory connectivity with increased frequency of EPSCs and probability of glutamate release are reported (33). Fast-spiking interneurons are known to have high density of Na⁺ ATPase; immunoreactivity is decreased in the undercut lesions. Brain-derived neurotrophic factor (BDNF) from pyramidal cells acting at tyrosine kinase receptor B (TrkB) maintain connectivity; reduced TrkB immunoreactivity is observed on the fast-spiking interneurons. Administration of a mimetic at the TrkB receptor, BD-2-4, demonstrates potential rescue of interneurons, suggesting a method for interruption of epileptogenesis (33).

Prevention, Prophylaxis, and Neuroprotection
From the first availability of antiepileptic drugs, physicians have attempted to administer those medications to patients with head trauma with the hope that there would be an effect on epileptogenesis. Prophylaxis is defined as a process of guarding against the development of a specific disease by a treatment or action that affects pathogenesis.

Penry et al. (34), in a prospective, placebo-controlled assessment, administered phenytoin and phenobarbital to patients with head injuries in a double-blind fashion. Seizure probability in the treated group was 21%, with a probability of 13% in controls. They concluded that no signiﬁcant difference was detected between the treatment and control groups, suggesting that anticonvulsant administration had no effect on the development of posttraumatic epilepsy in the treated patients.

Temkin et al. (35) treated 404 patients with severe head trauma who received an intravenous loading dose of either phenytoin or placebo. Serum levels were measured at regular intervals, blood levels of drug were maintained in the therapeutic range, and evaluations were blinded. At 1 year, no difference in incidence of PTE was found between the treatment and control groups. But phenytoin prevented seizures during the acute period up to 3 weeks after injury. By 2 years, PTE had occurred in 27.5% of phenytoin-treated patients and in 21.1% of controls. Valproate had some efficacy in animals but failed as a prophylactic drug in a controlled clinical trial in humans with head trauma (36). Magnesium sulfate was tried as well and was ineffective (37).
Are Models Helping?

There is an accumulation of reports of trials in animals that have failed. For a detailed review see Pitkanen (38). Of concern is the potential that an effective intervention might fail in an inappropriate animal model. Conversely, large-scale clinical trials have failed because of faulty understanding of epileptogenesis; why would a drug that controls seizures be thought to have an impact on epileptogenesis? While kindling is a useful tool that has yielded advances in understanding of brain function and response, evidence of such a mechanism in humans remains elusive. Gowers is oft quoted, but his critical observation that severe epilepsy occurs within the context of a severe brain lesion is overlooked (39). Would a severely injured patient be able to withstand the treatment? One should consider several approaches.

While many animal screenings have failed, there are several showing effect; lack of uniformity of models is a consistent confounding factor in interpretation of an action to be taken in administration to humans. Treatment with minocycline to alter inflammation and neurogenesis has been used in chemical convulsant models (40). Alteration in kindling by 2-deoxyglucose is proposed as well (29). Using a mouse model with closed skull trauma, a suppressor of pro-inflammatory cytokine upregulation prevented susceptibility to provocation with electroconvulsive shock (41). Rapid administration of a cannabinoid-1 receptor antagonist, SR141716A, to head-injured rats prevents seizure susceptibility (42). Resveratrol, a toll-like receptor antagonist, protects rats against epileptogenesis induced by kainate (43). Several models of PTE show injured rats prevents seizure susceptibility (42). Resveratrol, a macrolide antibiotic used to prevent transplant rejection (44) prevents epileptogenesis, or is an antiepileptic drug, in tuberous sclerosis complex in mice (47–49); with trials underway in humans.

Histopathological alterations following injection of aqueous iron into neural tissue can be prevented by pretreatment of animals with alpha-tocopherol and selenium, further supporting the contention that peroxidative reactions are of importance in trauma-induced brain injury responses (50–52). Tocopherol acetate penetrates the brain slowly, but tocopherol in the alcohol form is an effective neuroprotectant in rats (53); this form of the vitamin is not available for human use.

Recently available antiepileptic drugs have been tested for efficacy in neuroprotection. Lamotrigine pretreatment in animals attenuates the elevation of glutamate and aspartate that occurs during reperfusion following experimental ischemia. This attenuation of release of excitatory neurotransmitters by lamotrigine suggests potential for neuroprotective effects (54). Levetiracetam, in the kindling model, did inhibit the pace of kindling in a way similar to antagonists of NMDA receptors (55). When evaluated in focal ischemia, however, levetiracetam had a 33% protective effect by infarct volume, but MK801 pretreatment, considered the standard in receptor blockade, reached 74% reduction in infarct volume, with hypothermia as a confounder of interpretation (56). Topiramate in focal ischemia models reduced infarct volume by 50 to 80%. In global ischemia, cells were protected and behavioral skills preserved. Cellular injury was prevented in electrical limbic status epilepticus (57). Zonisamide was assessed in animal models of ischemia and had neuroprotective properties (58).

Summary

Many questions remain. Animals as surrogates for injury responses in humans have failed to yield useful methods for neuroprotection. Some agents appear to be effective in specific animal models while being ineffective in others. Must studies involve animals other than rodents? Must drugs or compounds pass an entire panel of models before moving on to human use? Must a drug have a “clinical” effect in preventing an animal from developing behavioral seizures or is alteration of physiological thresholds adequate? Large-scale efforts to discover new compounds for treatment of epilepsy have been effective. It is time to launch a discovery process to validate models and move forward with screening of known compounds or development of others that will control epileptogenesis in the injured.

References


Disclosure of Potential Conflicts of Interest

**American Epilepsy Society**

**Epilepsy Currents Journal**

**Instructions**

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. **Identifying information.**
   
Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. **The work under consideration for publication.**
   
   This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. **Relevant financial activities outside the submitted work.**
   
   This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

   Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

   For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. **Other relationships**
   
   Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.
Section #1 Identifying Information

1. Today’s Date: 3/7/12

2. First Name  L. James       Last Name  Willmore    Degree  MD

3. Are you the Main Assigned Author?  ☑ Yes  ☐ No 

If no, enter your name as co-author:

4. Manuscript/Article Title: Posttraumatic Epilepsy: What's Contusion got to do with it?

5. Journal Issue you are submitting for:

Section #2 The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

<table>
<thead>
<tr>
<th>Type</th>
<th>No</th>
<th>Money Paid to You</th>
<th>Money to Your Institution*</th>
<th>Name of Entity</th>
<th>Comments**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Grant</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Consulting fee or honorarium</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Support for travel to meetings for the study or other purposes</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Fees for participating in review activities such as data monitoring boards, statistical analysis, end point committees, and the like</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Payment for writing or reviewing the manuscript</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Provision of writing assistance, medicines, equipment, or administrative support.</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Other</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* This means money that your institution received for your efforts on this study.

** Use this section to provide any needed explanation.
**Section #3 Relevant financial activities outside the submitted work.**
Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the “Add” box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

<table>
<thead>
<tr>
<th>Type of relationship (in alphabetical order)</th>
<th>No</th>
<th>Money Paid to You</th>
<th>Money to Your Institution*</th>
<th>Name of Entity</th>
<th>Comments**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Board membership</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Consultancy</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Employment</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Expert testimony</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Grants/grants pending</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Payment for lectures including service on speakers bureaus</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Payment for manuscript preparation.</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Patents (planned, pending or issued)</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Royalties</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Payment for development of educational presentations</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Stock/stock options</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Travel/accommodations/meeting expenses unrelated to activities listed.**</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Other (err on the side of full disclosure)</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

**Section #4 Other relationships**
Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☑ No other relationships/conditions/circumstances that present a potential conflict of interest.
☐ Yes, the following relationships/conditions/circumstances are present:

Thank you for your assistance.

*Epilepsy Currents* Editorial Board