Posttraumatic Epilepsy
Clinical Challenges, Mechanisms and the Future of Translation

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Disclosures and Disclaimers

• Royalties from PMPH Press for “Advanced Treatment of Epilepsy” Eds. JW Wheless, LJ Willmore and RA Brumback

• Member of Editorial Board “Metabolic Brain Disease”

• CME rules: Nothing to declare

• Your favorite model or mechanism may not be mentioned
Then, Now and the Future

Risk factors
Models and Mechanisms
Translation
Risk Factors
Factors Predicting Risk

- Closed head injury (no fracture) 4.1%
- Depressed skull fracture 16.0%
- Hematoma 28.5%
- Depressed skull fracture 46.6%
  (+) 24 hours posttraumatic amnesia

Wound Characteristics

- Early Hematoma
- Retained metal fragments
- Cortical laceration
- Moderate brain volume loss
  - Prevalence 45-53%


- Left parietal lobe lesion
- Retained ferric metal fragments

Prediction of Risk

- Acute injury to 1 year 104/137 patients
- Low GCS, early seizures, solitary CT lesion
  - EEG focus 1 month post injury
- Greater percentage with PTE compared to those without epilepsy had MRI hyperintense areas including hemosiderin
- Gliosis around hemosiderin facilitated PTE
  - “...the combination of gliosis around hemosiderin spots seems to facilitate rather than protect against PTE.”

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  - “...the combination of gliosis around hemosiderin spots seems to facilitate rather than protect against PTE.”

MRI Prediction of Risk

- Gradient-echo T2-weighted FLAIR
  - Hypointensity: Hemosiderin
  - Hyperintensity: Gliosis

- Hemosiderin with incomplete wall of gliosis

- Incomplete wall evolving to complete wall

- sSDH-c 39% probability at 60 months
  - Subdural-Contusion: Surgical care (sSDH-c)

- Gliosis or hemosiderin alone: no risk

Messori et al. Predicting posttraumatic epilepsy with MRI: Prospective longitudinal morphologic study in adults. Epilepsia 46 (9) 1472-1481, 2005
MRI Prediction of Risk

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Risk Factors by 24 months

- Highest risk factors: Multiple or bilateral contusions, sSDH, early seizures, intracranial procedures, midline shift

- Cortical contusions:
  - Multiple contusions: 25.2%
  - Single contusion: 8.2%
  - No Contusion 5.9%

Risk Factors by 24 months

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Risk Factors

Complex, non-linear and multifactorial

- Trauma dose
- Genetic substrate
- Pressure wave and cavitation
- Shearing injury
- Hemorrhage
- Free radical biochemistry
- Lipid peroxidation
- Immune responses
- Inflammation
- Cell death
- Gliosis

Epilepsia 31:s67-73, 1990
Models and Mechanisms
Development of Models

- **Cortical freezing** 1883

- **Alumina** 1942

- **Cortical Isolation** 1959

- **Cobalt metal** 1960
Development of Models

- **Kindling** 1969

- **Iron-Blood products** 1978

- **Fluid Percussion** 1992
Kainate
Chemical Convulsants
Models and Mechanisms

- Electrical
- Chemical
- Mechanical

- Synaptic reorganization
- Plasticity
- Cell proliferation
- Molecular changes
AES 2011
Key Word Survey

- Trauma 23
- Pilocarpine 9
- Kainate 5
Models and Mechanisms

- Electrical
- Chemical
- Mechanical

- Synaptic reorganization
- Plasticity
- Cell proliferation
- Molecular changes
Partial Cortical Isolation
Cortical Slab

Partial Cortical Isolation

Physiology

- Altered GABAergic inhibitory mechanisms
- Enhanced Excitatory Connectivity
  - Increase in frequency of EPSCs
  - Increased probability of glutamate release


Prince DA et al. Epilepsy following cortical injury: Cellular and molecular mechanisms as targets for potential prophylaxis. Epilepsia 50 (Suppl 2) 30-40, 2009
Partial Cortical Isolation
Fast Spiking Interneurons (FS)

- High density of NaK ATPase
  - Immunoreactivity decreased in undercut lesions
- BDNF from pyramidal cells
  - Acting at TrkB Receptors-maintains connectivity
- Reduced TrkB immunoreactivity on FS
- Preventive: Activation of TrkB receptors “...in injured tissue might ‘rescue’ inhibitory neurons...”
  - BDNF from pyramidal cells-TrkB receptor effect
    - Key to maintenance of IH neurons on pyramidal cells
  - BD2-4 mimetic at TrkB receptor-increase ATPase
Partial Cortical Isolation

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Fluid Percussion

- Models moderate to severe CHI in humans
- Produces “... FOCAL CONTUSION, BBB disruption, altered cerebral metabolism, altered blood flow, subdural hematoma, intraparenchymal and subarachnoid HEMORRHAGE, axonal injury...”
- Edema and extent of hemorrhage related to trauma dose “...at 1 month...frank cavitation....”

Mortality 30-40 %; 43-50% of survivors develop spontaneous seizures
Lateral Fluid Percussion

- Surge of extracellular glutamate immediately after injury by lateral fluid percussion in *rat*  

- Trauma to *Human* cortex
  - Microdialysis
    - Acute ICU seizures - Glutamate increases  

- Glutamate transporters GLAST and GLT-1 are down-regulated  
Lateral Fluid Percussion

• Surge of extracellular glutamate immediately after injury by lateral fluid percussion in rodents

• Trauma to Human cortex
  • Microdialysis
    – Acute ICU seizures-Glutamate increases

• Glutamate transporters GLAST and GLT-1 are down-regulated
FIG. 3. Cumulative late seizure incidence as a function of subdural hematoma and surgery to evacuate it.

Amygdalar Injection of FeCl₃ Causes Spontaneous Recurrent Seizures

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Received January 9, 1998; accepted for publication June 4, 1998
Generation of Free Radicals
Haber-Weiss Reactions

\[ 2O_2 + NADPH \rightarrow NADP^+ + H^+ + 2O_2^\cdot \]

\[ 2O_2^\cdot + 2H^+ \rightarrow H_2O_2 + O_2 \]

\[ Fe^{++} + H_2O_2 \rightarrow Fe^{+++} + OH^- + HO\cdot (\ast) \]

\[ Fe^{+++}O_2 + LOOH \rightarrow Fe^{+++}OH^- + LOO\cdot \]

Aisen P. Some physicochemical aspects of iron metabolism. In “Iron Metabolism”
Ciba Foundation Symposium 51 Elsevier Amsterdam 1977

*Fenton’s reagent: Potent oxidant in biological systems
Generation of Free Radicals

Haber-Weiss Reactions

\[ 2\text{O}_2 + \text{NADPH} \rightarrow \text{NADP}^+ + \text{H}^+ + 2\text{O}_2^\bullet \]
\[ 2\text{O}_2^\bullet + 2\text{H}^+ \rightarrow \text{H}_2\text{O}_2 + \text{O}_2 \]
\[ \text{Fe}^{++} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{+++} + \text{OH}^- + \text{HO}_.(\ast) \]
\[ \text{Fe}^{+++}\text{O}_2 + \text{LOOH} \rightarrow \text{Fe}^{+++}\text{OH}^- + \text{LOO}. \]

Aisen P. Some physicochemical aspects of iron metabolism. In “Iron Metabolism”
Ciba Foundation Symposium 51 Elsevier Amsterdam 1977

*Fenton’s reagent: Potent oxidant in biological systems
Formation of superoxide radicals after FeCl₃ injection into rat isocortex

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(Accepted June 14th, 1983)

Key words: iron — electron spin resonance — superoxide — isocortex

Fig. 1. Formation of oxygen free radicals 5 and 15 min after the intracortical injection of 5 μl of either 100 mM FeCl₃ (shaded bars), or 0.9% acidified saline (open bars). Measurements of the formation of nitro blue formazan were obtained from the injected left hemisphere(A), and from the contralateral homotopic cortex(B). Values are means ± S.D. for 7 saline-injected rats, and 13 FeCl₃-injected rats. * = P < 0.01; ** = P < 0.05.

Fig. 2. ESR signals obtained from whole brain from rats injected with saline (○) or 5 μl of 100 mM FeCl₃ (●) into the left isocortex between 5 and 30 min after injection. A: G of 2.26, for protein-bound copper. B: G of 6.00 for iron-methemoglobin. n = 4 animals for each data point, as mean ± S.D. * = P < 0.01.
In Vivo Lipid Peroxidation in Rat Brain Following Intracortical Fe²⁺ Injection

William J. Triggs and L. James Willmore

Neurology Service, Veterans Administration Hospital and Department of Neurology, University of Florida College of Medicine, Gainesville, Florida, and The University of Texas Medical School, Houston, Texas, U.S.A.

FIG 1. Formation of lipid-soluble fluorescence in rat isocortex assayed in chloroform-methanol extracts of homogenates obtained from the injected hemisphere between 5 and 120 min after subpial injection of 10 µl containing 100 mmol/L FeCl₂ (▲), 100 mmol/L CoCl₂ (●), and 0.9% NaCl (○). Fluorescence was measured at excitation of 370 nm and emission of 430 nm. Each data point is the mean ± SD for at least 4 animals. Significant accumulation of lipid-soluble fluorescence (p < 0.001) was found at 120 min after injection of FeCl₂.
Hemin
Hemoglobin
Iron-free hematoprotein porphyrin

Fig. 1. Formation of lipid-soluble fluorescence in rat amygdala assayed in chloroform-methanol extracts obtained from the site of injection of microliter volumes of hemoglobin (●), hemin (○) and iron-free hematoprotein porphyrin (△). Injection of equal volumes of rodent plasma, and assay of the uninjected, contralateral amygdala served as controls. The iron moiety appeared to be necessary for the initiation of lipid peroxidation.
Midori Hiramatsu, PhD
Neuroscientist
Yagamata Technoplex
Yuto Ueda MD PhD
Associate Professor
Department of Psychiatry
Miyazaki University
School of Medicine
Glutamate: Epileptic foci

- Human hippocampal sclerosis
- Slow rate of Glutamate-Glutamine cycling
- Decreased glutamine content
- Increased glutamate content


Human hippocampus

- Microdialysis
  - Seizure-associated glutamate release increased
  - Slow postictal glutamate clearance
Glutamate and Seizures

- Decreased quantity of glial glutamate transporters in hippocampal tissue from humans with MTS

- Failure of glial glutamate detoxification
  - Slow clearance from synapses
    - Petroff OAC et al. Glutamate-glutamine cycling in the epileptic human hippocampus. Epilepsia 43:703-710, 2002
Glutamate: Epilepsy Models

• **Kindling**: Elevated tissue levels of glutamate

• **Kainate**: Prolonged clearance and elevated tissue levels of glutamate
Chronic Seizures and Glutamate Regulation

• **A**: Control glutamate levels

• **B**: Increased levels and prolongation of return to baseline in *kainate* rats

Glial Transporters

- **GLAST (EAAT-1)**
  - Glutamate-Aspartate Transporter
- **GLT-1 (EAAT-2)**
  - Glutamate Transporter-1
- 80% of high-affinity glutamate transport by glial transporters
- Responsible for most synaptic inactivation
Neuronal Transporter

- **EAAC1 (EAAT3)**
- **EAAT4**
- Abundant in neurons
  - Hippocampus, cerebellum, basal ganglia
- Bi-directional movement of Glutamate
- Glutamate-glutamine-GABA shunt

Crino PB et al. Increased expression of the neuronal glutamate transporter (EAAT3/EAAC1) in hippocampal and neocortical epilepsy. Epilepsia 43 (3) 211-218, 2002
Extracellular Glutamate

• Controlled by transporters

  – Prevent excitotoxicity

  – Avert neural injury from seizures
Glutamate Transporters

- Localization of Transporters
  - Synaptic terminals
  - Perisynaptic astroglial processes
Gene Knockout

Glial glutamate transporters

• Results in neuronal excitotoxicity

• Exacerbation of brain injury and seizures

• Loss of hippocampal GABA with knockdown of EAAC1
Transporters During Epileptogenesis
Amygdalar blood product
Kainate amygdala

- Timed samples 5 days, 15 days, 30 days
- Hippocampal tissue
  - Northern, Western, *In situ*
- Glutamate transporters
  - GLAST, GLT-1, EAAC1
- GABA transporters
  - GAT-1 through GAT-4
Epileptogenesis: Collapse of Glutamate Regulation

- Northern and Western blotting: Kainate
- EAA transporters
- Microdialysis: Interictal Glutamate increased
- Ictal: Prolonged increase in glutamate
- Glial transporters down-regulated
Sequential changes in glutamate transporter protein levels during Fe³⁺-induced epileptogenesis

Yuto Ueda, L. James Willmore

© Department of Psychiatry, Miyazaki Medical College, Miyazaki-Gun, Kihara 5200, Kyotake-cho, Miyazaki 889-1692, Japan
b Saint Louis University School of Medicine 1407 S. Grand Blvd St. Louis MO 63104 USA

Fig. 3. Sequential changes in the levels of glutamate transporters, GLAST, GLUT-1 and EAAC-1. *P < 0.05, **P < 0.01 compared to the level of 0 days at each protein in the ipsilateral side, # P < 0.05, ## P < 0.01 is about contralateral side (F value of GLAST for SIDE effect; F_{1,43} = 0.346, P = 0.559, for TIME effect F_{4,43} = 118.540, P = 0.0001; F value of EAAC-1 for SIDE effect; F_{1,43} = 0.852, P = 0.3613, for TIME effect F_{4,43} = 21.699, P = 0.0001; F value of GLUT-1 for SIDE effect; F_{1,43} = 4.548, P = 0.0387, for TIME effect F_{4,43} = 22.702, P = 0.0001).
Gene Network Analysis

- Amygdala iron: Partial seizures
- Agilent Whole Rat Genome 4X44K G4131F microarray
- 41,012 rat cDNA probes
- **Upregulated**
  - Networks: Interleukin 1β and IL1R1
  - Genes: SPOCK2, CDH1, KCNJ13, SOSTDC1, DSG2, LRRC17
- **Down regulated**
  - Chemokine receptor 1
- **Inflammation and Immune System**
Prophylaxis
Disruption of Epileptogenesis
## Prophylaxis: Open Studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Control</th>
<th>Treated</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoff and Hoff</td>
<td>1947</td>
<td>38%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Birkmayer</td>
<td>1951</td>
<td>51</td>
<td>6</td>
<td></td>
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<tr>
<td>Wohns and Wyler</td>
<td>1979</td>
<td>50</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Young et al</td>
<td>1979</td>
<td>---</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Servit and Musil</td>
<td>1981</td>
<td>25</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Glotzner et al</td>
<td>1983</td>
<td>29</td>
<td>12.5%*</td>
<td>CBZ-Early seizures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>27</td>
<td>22</td>
<td></td>
</tr>
</tbody>
</table>

*CBZ-Early seizures*
### Prophylaxis: Randomized controlled trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Control</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penry et al</td>
<td>PHT/PB</td>
<td>13%</td>
<td>23%</td>
</tr>
<tr>
<td>Young et al</td>
<td>PHT</td>
<td>10.8</td>
<td>12.9</td>
</tr>
<tr>
<td>Temkin et al</td>
<td>PHT</td>
<td>21.1</td>
<td>27.5</td>
</tr>
<tr>
<td>Temkin et al</td>
<td>VPA</td>
<td>-----</td>
<td>24% §</td>
</tr>
<tr>
<td>Temkin et al</td>
<td>MgSO₄</td>
<td>52</td>
<td>55*</td>
</tr>
</tbody>
</table>

PHT mortality 7.5%   VPA mortality 13.4% §

*Composite primary outcome: mortality, seizures, functional measures and NP testing
Candidates for Translation

- Antioxidants - Prevents lipid injury
- β-lactam antibiotics - Upregulates transporters
- BD 2-4 - Stimulates TrkB receptor
- 2-deoxyglucose - Disrupts sprouting
- β-carboline alkaloid - Upregulates transporters
- Minocyclin - Anti-inflammatory
- Rapamycin - Cell signaling
- Minozac - Suppress pro-inflammatory cytokine up-regulation
- Rimonabant - Cannabinoid 1 receptor antagonist
- Resveratrol - Toll-like receptor antagonist
AES 2011
Key Word Survey

- mTOR 11
- Rapamycin 3
- BDNF 1
- Erythropoietin 1
- Resveratrol 1
Candidates for Translation

- **Antioxidants**

- **β-lactam antibiotics**
  - Rothstein JD et al. β-lactam antibiotics offer neuroprotection by increasing glutamate transporter expression. Nature 433:73-77, 2005

- **BD 2-4**

- **2-deoxyglucose**

- **β-carboline alkaloid: harmine**

- **Minocyclin**
  - Foresti ML et al. Role of glia in epilepsy-associated neuropathology, neuroinflammantion and neurogenesis Brain Res Rev 66:115-122, 2011 [chemical]
Candidates for Translation

- **Rapamycin**

- **Minozac**
  - Suppressor of pro-inflammatory cytokine up-regulation

- **Rimonabant (SR141716A)**
  - Cannabinoid 1 receptor antagonist

- **Resveratrol**
  - Toll-like receptor (TLR3) antagonist
Rapamycin

- Macrolide antibiotic
- *Streptomyces hygroscopicus*-soil from Rapa Nui
- Regulatory effects on cell growth, proliferation and inflammation
- Inhibits mTOR
  - (mammalian target of rapamycin)
- Use to prevent transplant rejection
  - Aphthous ulcers, hyperlipidemia, infections
Effects

• **Tsc1\(^{GFAP}\) CKO Pretreatment**
  - conditional knock-out TSC mouse
  - Seizures controlled while treated


• **Suppression of sprouting GABAergic synaptic reorganization** [chemical SE]


• **Blocks seizure progression in NS-Pten conditional knockout mice** [genetic]

Sunnen CN et al. Inhibition of the mammalian target of rapamycin blocks epilepsy progression in NS-Pten conditional knockout mice. Epilepsia 52:2065-2075, 2011
Potential for Translation

BDNF-mediated TrkB Signaling

- Delays hippocampal-amygdala kindling
  - Lamert et al 1995
- Strengthens GABAergic inhibition
  - Palma et al 2005
- Fibroblast GF 2 and BDNF attenuates epileptogenesis associated with inflammation
  - Bovolenta et al 2010
- HOWEVER, increased TrkB signaling promoted epileptogenesis in KA model

Of Interest

- FK506 (immunosuppression) [electrical stim amygdala]
- Parecoxib (COX-2 inhibitor) [chemical SE]
- SC58236 (COX-2 inhibitor) [electrical stim]
- α4 integrin specific mAb (cell adhesion prevention) [chemical]
- Erythropoietin (anti: apoptosis, oxidant, inflammatory) [chemical]
- FGF-2 and BDNF (neurotropins) [chemical]
- Levetiracetam (AED) [genetic]
- Ethosuximide (AED) [genetic]
- Atipamezole (α2-adrenergic antagonist) [electrical]

Pitkänen A. Therapeutic approaches to epileptogenesis-Hope on the horizon. Epilepsia 51 (suppl 3) 2-17, 2010
[dl]-\( \alpha \) tocopherol
Effect of [dl]-α-tocopherol on FeCl₂-induced lipid peroxidation in rat amygdala

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Abstract

Peroxidative injury of neural membrane lipids can be initiated by iron-containing blood products, chelated ferrous or ferric ions, and low valence iron in aqueous solution. Lipid peroxidation was measured following focal injection of 3 μl of 100 mM FeCl₂ into rat amygdala. Acute parenteral administration of [dl]-α-tocopherol as the alcohol limited the quantity of peroxidation products generated. These data suggest a potential role for α-tocopherol administration in limiting brain injury responses.

Key words: Lipid peroxidation; α-Tocopherol; Brain injury; Iron; Rat
## Table 1
Lipid peroxidation after tocopherol treatment

<table>
<thead>
<tr>
<th>Agent</th>
<th>Treatment mg/kg</th>
<th>Route</th>
<th>Ipsilateral amygdala</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocopherol</td>
<td>100</td>
<td>s.c.</td>
<td>820 ± 65 (6)</td>
<td>23 ± 4 (4)</td>
</tr>
<tr>
<td>Acetate</td>
<td>100</td>
<td>s.c.</td>
<td>837 ± 22 (6)</td>
<td>740 ± 12 (5)</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>s.c.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>i.v.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tocopherol</td>
<td>100</td>
<td>s.c.</td>
<td>243 ± 11&lt;sup&gt;a&lt;/sup&gt; (5)</td>
<td>47.6 ± 11 (6)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>100</td>
<td>i.v.</td>
<td>370 ± 64&lt;sup&gt;a&lt;/sup&gt; (8)</td>
<td>751 ± 62 (6)</td>
</tr>
</tbody>
</table>

Quantitated in units of lipid-soluble fluorescence per gram wet tissue weight. Animals were treated with tocopherol or tocopherol acetate (subcutaneous, s.c.; intravenous, i.v.) at the time of injection of 3 μl of 100 mM FeCl<sub>3</sub> into the amygdala. Animals were killed 4 h after injection and fluorescence was measured in chloroform methanol extracts of tissue from the injection site. Values are mean ± S.D. Number of rats (n). Injection control indicates untreated animals used to measure the rate of peroxidation induced by the quantity of FeCl<sub>3</sub> injected. Contralateral amygdala assay served as internal control.

<sup>a</sup> P < 0.01, [dl]-α-tocopherol alcohol compared to either acetate or injection control.
Candidates for Translation

- Antioxidants
- β-lactam antibiotics
- BD 2-4
- 2-deoxyglucose
- β-carboline alkaloid
- Minocyclin
- Rapamycin
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- FK506-immunosuppression
- Parecoxib (COX-2 inhibitor)
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- α4 integrin specific mAb
- Erythropoietin
- FGF-2 and BDNF (neurotropins)
- Levetiracetam
- Ethosuximide
- Atipamezole
Failed Neuroprotection Trials

- Aptiganel-NMDA blocker-Aes
- Citicoline-Lipid protector-Failed
- Clomethiazole-GABA agonist-Failed
- Dextrorphan NMDA antagonist-Failed
- Enlimobab-anti-inflammatory-Increased mortality
- Flunarizine-Ca^{++} blocker-Failed
- Fosphenytoin-Na^{+} effect-Failed
- Lubeluzole-non-NMDA antagonist-Failed
- Nimodipine-Ca^{++} blocker-failed ischemia, okay SAH
- Piracetam-cAMP-Failed
- Remacemide-NMDA antagonist-Failed protection
- Tirilazide-Lipid peroxidation-Failed
- ZK-200775-AMPA antagonist-XS sedation
Epilepsy Research Benchmarks

Area I

• Prevent epilepsy and its progression
  –B. Identify underlying mechanisms of epileptogenesis
  –E. Develop new animal models to study epileptogenesis
  –F. Test the efficacy of prevention strategies
Acknowledgments

- Norman Bass MD
  - Fellowship director and mentor
- Jay Rubin MD
  - Student in my laboratory
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  - Student and colleague in my laboratory
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- Yuto Ueda MD PhD
  - Postdoctoral fellow in my laboratory
  - Colleague and collaborator
- John Willmore
  - Eldest son and CEO BizIntel
  - Translations from French and German
Akitane Mori, MD PhD
Chairman Emeritus
Department of Neurobiology
Okayama College of Medicine
Okayama, Japan
Summary

Humans
Trauma dose and hemorrhage
Dysfunction in glutamate regulation

Models
Kindling, kainate, PTZ, Lateral Fluid Percussion, Amygdalar iron
Down-regulation of glutamate transporters
Epileptogenesis

- Immediate early gene expression
- Molecular changes
  - Expression of BDNF, TrkB, GluR1-2, NR2B
- Free radicals-lipid peroxidation
- Plasticity
- Neurogenesis
- Dyslamination
- Altered glutamate receptor subunits
- Altered glutamate transport
- Excitation-inhibition
- Gliosis
- Altered signaling pathway regulation

Sutula et al. J Neuroscience 1992
Prediction of risk

- Trauma - No deficit 7%
- Loss of consciousness 10%
- Structural injury - Dura intact 39%
- No deficit - Dural laceration 20%
- LOC - Dural laceration 51%
- Structural injury - Brain Laceration 58%

Caveness, WF. Epilepsy, a product of trauma in our time. Epilepsia 17: 207-215, 1976
Prediction of risk

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Antiperoxidant pretreatment and iron-induced epileptiform discharges in the rat: EEG and histopathologic studies

L. James Willmore, M.D., and Jay J. Rubin, B.S., B.A.


Phenytoin Prophylaxis

- Identification of effect: 1938
  - Merritt and Putnam

- First report of use for prophylaxis:

Risk Factors

Trauma dose
- Pressure wave
- Cavitation
- Shearing
- Hemorrhage
GLAST: Chronic Seizures

- Amygdala: FeCl\textsuperscript{3+}
- Spontaneous chronic seizures: Kindled S4 by +15d and +30 d
- Western Blot:
  - GLAST reduced in bilateral hippocampal regions
- Impaired glial glutamate transport